MSF HIV/TB clinical guide for primary care

2018

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MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

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Cover photo: A doctor examines a patient in a primary care HIV clinic.
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This is the ninth edition of the *MSF HIV/TB Clinical Guide*. The first edition was developed for use in primary care clinics opened by Médecins Sans Frontières (MSF) in the township of Khayelitsha, Cape Town, South Africa. It successfully became a practical reference tool for nurses and doctors in those clinics and later in the MSF projects located in the rural areas of Lusikisiki in the Eastern Cape and Morija, Lesotho.

Drawing on the experience provided by eight previous editions, the ninth edition has evolved to provide a more comprehensive approach to clinical HIV/TB care in the context of ongoing developments. Based on feedback from clinicians in the field, the content has been substantially revised and updated with additional chapters to meet newly identified needs. South African guidelines have been removed and replaced by those from WHO to allow for wider use internationally.

The primary objective of this book is to provide practical, up-to-date guidelines for the consulting clinician working with patients with HIV in primary care clinics.

- References, both to other sections in the book and to various websites are regularly provided for those who wish to access more detailed information.
- The basic **HIV e-learning course** is designed to match the content of the book, so that the clinician new to HIV and TB can enjoy a more comprehensive learning process: https://samumsf.org/en/training/hiv-tb-clinical-training/hivtb-e-learning-basic-level-online.
- A pdf version of this book can be downloaded from the SAMU website (https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018).
- With the recent development of a separate booklet that provides guidance for clinical approaches to sick inpatients, this guide now focuses purely on the information needs of the outpatient clinician. Where patients have danger signs and need referral, regular reference is made to **MSF HIV/TB Clinical Guide: Hospital Level** (available as a pdf from https://samumsf.org/en/resources/msf-hivtb-clinical-guide-hospital-2018).

Welcome to the ninth edition of the MSF HIV/TB Clinical Guide.

This now-famous image celebrates a bright day in December 2002, when Nelson Mandela came to visit our clinics in Khayelitsha. He came to offer political support, while we were confronted with strong HIV denialism from the national government. He left people in no doubt regarding his personal convictions when, without hesitation, he swiftly put on the HIV-positive T-shirt, an image that made world headlines.

By endorsing this T-shirt, he identified with the political struggle to gain access to ARVs. To have the world's foremost statesman come to a destitute township like Khayelitsha, take off his shirt and don a strongly political T-shirt symbolised in one gesture what we had tried to do for years: make ARV treatment accessible to the poorest and most affected, as close as possible to where they live, in a country still completely divided along socio-economic lines.

This is what *MSF HIV/TB Clinical Guide for Primary Care* is about: it aims at motivating and equipping primary care health staff with the necessary knowledge

'After climbing a great hill, one only finds that there are many more hills to climb.' **Nelson Mandela**

to treat HIV-related conditions and initiate adults, children and pregnant women onto ARVs within their own clinics, even if they have no support available from a specialised health care centre. It aims to support HIV care at the grassroots level.

When we drafted the first edition of this guideline in 2000, we had no idea if we would succeed in such a tremendous challenge. This is the ninth edition and, in the meantime, major progress has been made in Khayelitsha: more than 42 000 on ART, including 3 500 children and a mother-to-child transmission rate reduced to less than 1%.

Similar exponential coverage took place in the region, with an immediate impact on reducing mortality: for example life expectancy increased in KwaZulu-Natal (KZN), a high HIV-burden province in South Africa, from 49.2 years in 2003 to 60.5 years in 2011.

These figures are definitely impressive, but there remain many challenges, some of them new and most of them qualitative: we have to find innovative ways to keep initiated patients in long-term care with undetectable HIV viral loads, and, even more, we need to reduce new infections, particularly in young women, and eliminate vertical transmission (from mother to child during pregnancy or breastfeeding); all of this in the absence of an effective vaccine, probably for the next decade.

This guide is not close to becoming obsolete, as unfortunately AIDS is not 'over': despite impressive ART coverage, we still see late presenters and increasing numbers of treatment failures and re-admissions, with people with advanced opportunistic infections coming to our clinics and hospitals. These patients often require high-level diagnostic and treatment procedures, and for this reason a complement to this guide, aimed at addressing such complex cases referred for hospital care, is now available: *MSF HIV/TB Clinical Guide: Hospital Level.*

'AIDS is a war against humanity', said Nelson Mandela on that day in 2002. In making his symbolic gesture, he offered his own sense of humanity to head the battle, giving us the courage to fight our worst enemies: stigmatisation and ignorance.

Let us together continue on this path, striving together to provide an increased quality of care to people living with HIV.

This guideline is dedicated to the memory of Madiba.

Eric Goemaere, December 2017

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Doctors Without Borders (MSF) distributes antiretroviral (ARV) drugs at the Elia village, Semonkong, Lesotho.

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Appendices, algorithms, figures and tables

Appendices

Algorithms

Figures

Tables

Hospitalisation Survivors project, Democratic Republic of Congo.

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How to use this book

1. For the reader new to HIV, we recommend starting with Chapter 1, noting especially the overview of all the chapters at the end.
2. An e-learning course, available online and free of charge to all can be accessed via the training section in the SAMU website https://samumsf.org/en/training/hiv-tb-clinical-training/hivtb-e-learning-basic-level-online. It is specifically designed to tutor the student in a more interactive way through chapters 1–7, 9 and 12 in this book.
3. Several chapters deal with how diseases related to HIV manifest in different organ systems in the body. These chapters are designed to provide quick and easy access to the information needed in the consulting room.
4. In order to facilitate access to all necessary information and to provide a comprehensive approach to a particular problem (e.g. managing the patient with advanced disease), there is extensive cross-referencing throughout the book.
5. For more detailed information, regular references are given to a variety of websites.
6. The SAMU website is regularly referenced for access to more detailed articles and documents that can be downloaded from the files 'additional resources' and 'updates' at the following site (https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018).
7. HIV medicine, as in most other disciplines, has its own set of abbreviations. A list of abbreviations provides the reader with explanations of these.
8. Interspersed throughout the book are icons and boxes drawing attention to specific information. A key to what each icon represents is provided opposite.

If any omissions or errors are noticed, the editor of this edition welcomes any feedback. Please contact him at ian.proudfoot@joburg.msf.org.

Disclaimer

This guideline has been developed in collaboration with many experts in both academic environments in resource-limited settings in the field. It has drawn from a variety of guidelines, with a particular focus on those from WHO. Protocols are constantly changing as new evidence appears, potentially compromising the future accuracy of some of the recommendations. It is therefore recommended that diagnostic and management decisions are always checked with current national or WHO guidelines.

Drug dosages have been thoroughly checked but some errors may have been overlooked or there may have been recent changes or updates in protocols. Unless otherwise stated, drug dosages are for oral administration and recommendations are for the non-pregnant adult who is not breastfeeding. Please always consult your national formulary or drug manufacturer's information before prescribing medication.

The authors and the publishers do not accept responsibility or legal liability for any errors in the text or for the misuse or misapplication of material in this work.

What the icons mean

Caution/Danger

Important information

Refer the patient to a specialist or hospital

Infomation regarding children, see Chapter 10

Patient support needed, see Chapter 25

Practical tip

Available in the SAMU e-learning course

Refer to a website

Refer to the MSF HIV/TB Guide: Hospital Level*

Refer to your national guidelines

Refer to the WHO guidelines

* The **MSF HIV/TB Clinical Guide: Hospital Level** is available as a pdf at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-hospital-2018

MSF supporting different health centers, Democratic Republic of Congo.

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Abbreviations

3TC	Lamivudine
ABC	Abacavir
ABR	Antibiotic resistance
ADA	Adenosine deaminase (test done on some body fluids to detect TB)
ADC	AIDS-defining cancer
AEB	Accidental exposure to blood
AFASS	Affordable, feasible, accessible, safe and sustainable
AFB	Acid-fast bacilli (usually refers to TB bacillus)
AIDS	Acquired immunodeficiency syndrome
AKI	Acute kidney insult
ALP	Alkaline phosphetone (a liver blood test)
ALT/ALAT	Alanine aminotransferase (a liver blood test)
ANC	Antenatal clinic
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate transaminase (a liver blood test)
ATN	Acute tubular necrosis
ATV	Atazanavir
AZT	Zidovudine (occasionally also written as ‘ZDV’)
BCG	Bacillus Calmette-Guérin (TB vaccine)
bid/bd	Twice daily
BMI	Body mass index (used to classify adults as overweight or underweight)
bOPV	Bivalent oral polio vaccine
BSA	Body surface area (sometimes used to calculate ARV dosages in children)
CAG	Community ART groups
cART	Combined antiretroviral therapy
CCM	Cryptococcal meningitis
CIN	Cervical intraepithelial neoplasia
CKD	Chronic kidney disease
CLAT/CrAg	Test for detection of cryptococcal antigen
CMV	Cytomegalovirus
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
Cr	Creatinine
CrCl	Creatinine clearance (a measure of kidney function)
CRP	C-reactive protein (a blood test that measures inflammation)
CSF	Cerebrospinal fluid
CSW	Commercial sex worker
CToP	Choice on termination of pregnancy
CTX	Cotrimoxazole
CXR	Chest x-ray
d4T	Stavudine
DAA	Directly acting antivirals
DBS	Dry blood spot test
DDI	Didanosine
DILI	Drug-induced liver injury
DLM	Delamanid
DM	Diabetes mellitus
DOT	Directly observed therapy
DR TB	Drug resistant TB
DRESS	Drug reaction with eosinophilia and systemic symptoms
DST	Drug sensitivity/susceptibility testing

DSTB	drug-sensitive/drug-susceptible tuberculosis
DTG	Dolutegravir
DVT	Deep vein thrombosis
EAC	Enhanced adherence counselling
EBV	Epstien Barr virus
EFV	Efavirenz
EID	Early infant diagnosis
ELISA	Enzyme-linked immunosorbent assays
EPI	Expanded Programme on Immunisation
EPTB	Extra-pulmonary tuberculosis
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
ETV	etravirine
FBC	Full blood count
FDC	Fixed drug combination
FNAB	Fine needle aspiration biopsy
FP	Family planning
FQ	Fluoroquinolone
FTC	Emtricitabine
GERD	Gastro-oesophagal reflux disease
GGT	Gamma glutamyl transferase (a liver blood test)
GIT	Gastro-intestinal tract
GORD	Gastro-oesophageal reflux disease
GU	Genital ulcer
H or INH	Isoniazid
HAART	Highly active antiretroviral therapy
HAI	Hospital-acquired infection
Hb	Haemoglobin
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCTZ	hydrochlorthiazide
HCV	Hepatitis C virus
HCW	Healthcare worker
HEU	HIV-exposed but uninfected
HHV-8	Human herpes virus-8
HIV	Human immunodeficiency virus
HIVAN	HIV-associated nephropathy
HPV	Human papilloma virus
HR	Heart rate
HSR	Hypersensitivity reaction
HSV	Herpes simplex virus
HTS	HIV testing services
IC	Infection control
IHD	Ischaemic heart disease
IM	Intramuscular
IMCI	Integrated management of childhood illnesses
INH or H	Isoniazid
INR	International normalized ratio, an indicator of clotting ability
IPT	Isoniazid prophylaxis therapy
IPV	Inactivated polio vaccine
IRIS	Immune reconstitution inflammatory syndrome
ITP	Idiopathic thrombocytopaenic purpura
IUCD	Intra-uterine contraceptive device
IV	Intravenous
IYCF	Infant and young child feeding practices
JVP	Jugular venous pressure
KS	Kaposi's sarcoma
LFT	Liver function test
LIP	Lymphoid interstitial pneumonitis
LLM	Long-lasting method
LMP	Last menstrual period
LP	Lumbar puncture

LPV	Lopinavir
LPV/r; LPV/RTV	Lopinavir/ritonavir (Kaletra® or Aluvia®)
LRTI	Lower respiratory tract infection
LTFU	Lost to follow-up
M&E	Monitoring and evaluation
MAC	Mycobacterium avium complex
MAM	Moderate acute malnutrition
MCH	Maternal and child health
MCS	Microscopy, culture and sensitivities
MCV	Measles-containing vaccine
MDR-TB	Multi-drug resistant tuberculosis
MEC	Medical eligibility criteria
MER	More efficacious regimen
MH	Mental health
MI	Myocardial infarct
MMC	Male medical circumcision
MoH	Ministry of Health
MOTT	Mycobacterium other than tuberculosis
MRSA	Methicillin-resistant staph aureus
MSF	Médecins Sans Frontières (French for 'doctors without borders')
MSM	Men who have sex with men
MTCT	Mother-to-child transmission (of HIV)
MUAC	Mid-upper arm circumference
MVA	Manual vacuum aspiration
NADC	Non-AIDS-defining cancer
NAT	Nucleic acid test
NCD	Non-communicable disease
NNRTI	Non-nucleoside reverse transcriptase inhibitor ('non-nuke')
NRTI	Nucleoside reverse transcriptase inhibitor ('nuke')
NSAID	Nonsteroidal anti-inflammatory drug
NTM	Non-tuberculous mycobacteria
NVP	Nevirapine
OC	Oral contraceptive
OD	Once daily
OI	Opportunistic infection
ORS	Oral rehydration solution
ORT	Oral rehydration therapy
PAC	Post-abortion care
PAP	Papanicolou smear for cervical screening
PAS	P-aminosalicylic acid
PCP	Pneumocystis carinii pneumonia (also known as PJP, pneumocystis jiroveci)
PCR	Polymerase chain reaction (a laboratory test)
PE	Pulmonary embulism
PEP	Post-exposure prophylaxis
PHN	Post-herpetic neuralgia
PI	Protease inhibitor
PID	Pelvic inflammatory disease
PITC	Provider-initiated testing and counselling
PLD	Pegylated liposomal doxorubicin
PLHIV	Person/people living with HIV/AIDS
PML	Progressive multifocal leuco-encephalopathy
PMTCT	Prevention of mother-to-child transmission (of HIV)
PN	Peripheral neuropathy
PO	Per os (by mouth)
POC	Point of care
PPD	Purified protein derivative (used in TB skin testing)
PPE	Papular pruriginous eruption (a common itchy rash)

PrEP	Pre-exposure prophylaxis
prn	As required
PS	Patient support
PT	Pregnancy test
Pt.	Patient
PTB	Pulmonary tuberculosis
PWID	People who inject drugs
qid/qds	Four times a day
QTc	QT interval (corrected)
r	ritonavir (given with another PI, often written as eg; LPV/r)
R or RIF	Rifampicin
RAL	Raltegravir
RBC	Red blood cell
RDT	Rapid diagnostic test
Rfb	Rifabutin
RH	Rifampicin and isoniazid
RHZE	Rifampicin, isoniazid, pyrazinamide and ethambutol
RIF or R	Rifampicin
RNI	Recommended nutrient intake
RPR	Rapid plasma reagin test for syphilis
RPV	Rilpivirine
RR	Respiratory rate
RTV	Ritonavir
RUQ	Right upper quadrant
RUTF	Ready-to-use therapeutic food
SAC	Safe abortion care
SAM	Severe acute malnutrition
SAMU	Southern Africa Medical Unit
SAT	Self-administered therapy
SJS	Stevens-Johnson syndrome
SOL	Space-occupying lesion
SOP	Standard operating procedure
SRH	Sexual and reproductive health
SSRI	Selective serotonine re-uptake inhibitor
Stat	Immediately
STI	Sexually transmitted infection
SV	Sexual violence
TB LAM	TB lipoarabinomanan, a TB test done on urine
TB	Tuberculosis
TBM	Tuberculous meningitis
TCA	Tricyclic antidepressants
TDF	Tenofovir
tds/tid	Three times a day
TENS	Toxic epidermal necrolysis syndrome
ToP	Termination of pregnancy
TPHA	Treponema pallidum haemaglutination assay (syphilis test)
TPV	Tipranavir
TSH	Thyroid stimulating hormone
TST	TB skin testing
TTP	Thrombotic thrombocytopaenia purpura
UPSI	Unprotected sexual intercourse
URTI	Upper respiratory tract infection
UTI	Urinary tract infection
VCT	Voluntary counselling and testing
VDRL	Test for syphilis
VIA	Visual inspection assessment
VL	Viral load
VMMC	Voluntary male medical circumcision
VPD	Vaccine-preventable disease
VZV	Varicella zoster virus
WBC	White blood cell
WHO	World Health Organisation
WHZ	Weight-for-height Z-score
XDR TB	Extensively drug-resistant tuberculosis

CHAPTER 1

HIV overview

Please note that a more comprehensive overview of HIV is provided in Unit 1, modules 1 and 2 of the MSF Southern Africa Medical Unit **(SAMU) HIV/TB E-Learning** (see ‘How to use this book’ on page xx for details).

What exactly is HIV?

Viruses attack different parts of the body. Some viruses, for example, attack the respiratory system, resulting in a cold, while others attack the liver, resulting in hepatitis. How do they know how to do this? It’s all to do with receptors. So, viruses that attack the respiratory system have receptors on them that fit only into receptors on cells that are able to receive them. If the only place where those receptors are found is in the respiratory tract, that’s where the virus will express itself.

Human immunodeficiency virus (HIV) connects only to CD4 receptors, and these are found in very limited places in the body, mainly in the bloodstream, in the cells of the immune system. The main target is a particular subset of lymphocytes called CD4 T cells. These cells produce chemicals that play an important role in the body’s immune response to infection. The other site is the genital tracts of both males and females.

How do people get infected with HIV?

Transmission of HIV is via routes that allow the virus to get in contact with cells of the immune system and genital tracts. People therefore acquire HIV through three main routes:

1. Sexually (anal sex transmission is greater than vaginal transmission, which is greater than oral transmission);
2. From mother to child (pregnancy, delivery and breastfeeding); and
3. Direct contamination of blood (IV drug use, which is less common in sub-Saharan Africa; occupational needle-stick injuries; blood transfusions).

HIV is not transmitted by saliva, tears, sharing of eating utensils or from hugging or shaking hands.

What does HIV actually do in the body?

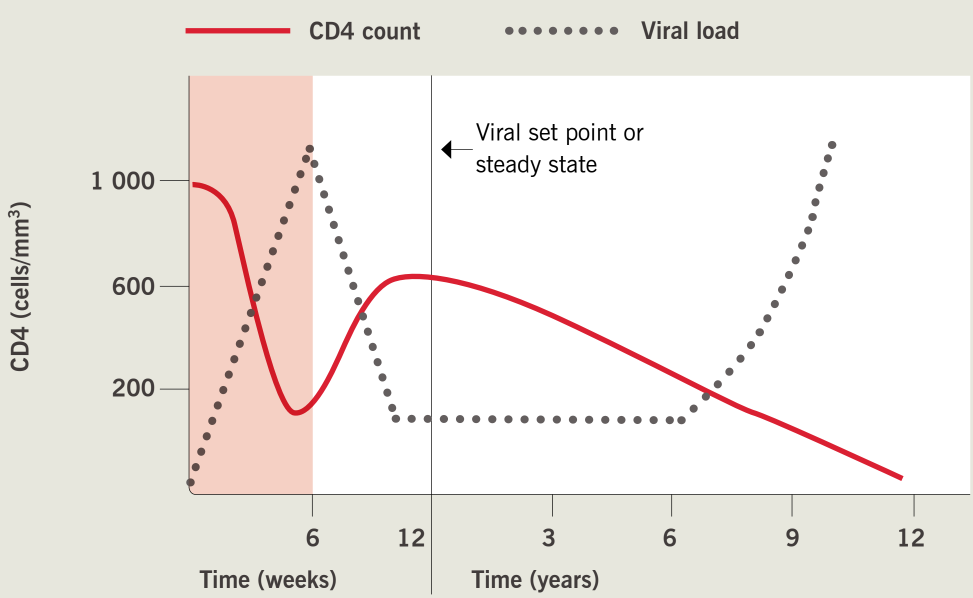
Via the routes mentioned above, HIV finds its way into the bloodstream and into CD4 cells. Once inside the cell it invades the nucleus and re-programmes it to stop producing these immune chemicals and instead to make more HIV. In order to fight infection, the infected CD4 cells continue to multiply as they are designed to; but, because they are now re-programmed to produce the virus, they make more and more virus instead. In effect, they become a factory, producing loads of copies of HIV. (This process will be covered in more detail in **Chapter 2**.)

Over several years from the initial infection, the infected CD4 cells slowly die and the level of HIV rises in the body. As a result of this, the body's immunity is progressively destroyed, resulting in increasingly serious infections from which an untreated person will eventually die.

Natural history of HIV

In broad principle, an infected patient starts with a high CD4 count and a low viral load. The viral load rises progressively, along with a steady drop in the CD4, until the patient dies from a range of serious infections. (In more resource-limited contexts, due a higher rate of opportunistic infections, the terminal decline tends to be shorter by several years.) The detail is a bit more complicated than this.

Figure 1.1 Natural history of untreated HIV



Source: Modified from Fauci AS et al. 1996. Ann Intern Med. 124–654

The first 6–12 weeks

The virus infects the CD4 T cells and invades the nucleus, to 're-programme' it to stop making chemicals involved in the immune response, and instead make more virus. Initially, the CD4 T cells increase their activity as they are designed to, in order to fight infection. However, because they are now re-programmed to produce the virus, this increased activity actually results in multiple copies of HIV. The CD4 T cells 'burn out' from all this activity and die, resulting in a dropping CD4 count. This initial stage of rising viral load and dropping CD4 is reflected in the red zone in Figure 1.1 above. The lowest point that the CD4 drops to is often referred to as the **CD4 nadir**.

Clinically, at this stage the patient may be asymptomatic or may present with an acute viral syndrome similar to glandular fever, with fever and/or rash and/or enlarged lymph nodes. This is referred to as 'acute HIV infection' or 'primary HIV infection'. Because the viral load is very high at this stage, the patient is particularly infectious to others. As the patient is often unaware of being infected, he/she is less likely to use preventative measures, resulting in a much higher risk of HIV transmission.

In this early 'red-zone' stage (see Figure 1.1), a delay in the production of antibodies by other parts of the body's immune system results in the CD4 T cells becoming overpowered by the virus. This production delay has diagnostic implications, because the tests commonly used for HIV rely on the presence of antibodies. In reality, most people show antibodies by about 6 weeks but it can be as long as 3 months. We refer to the time between infection and the presence of HIV antibodies as the **window period**.

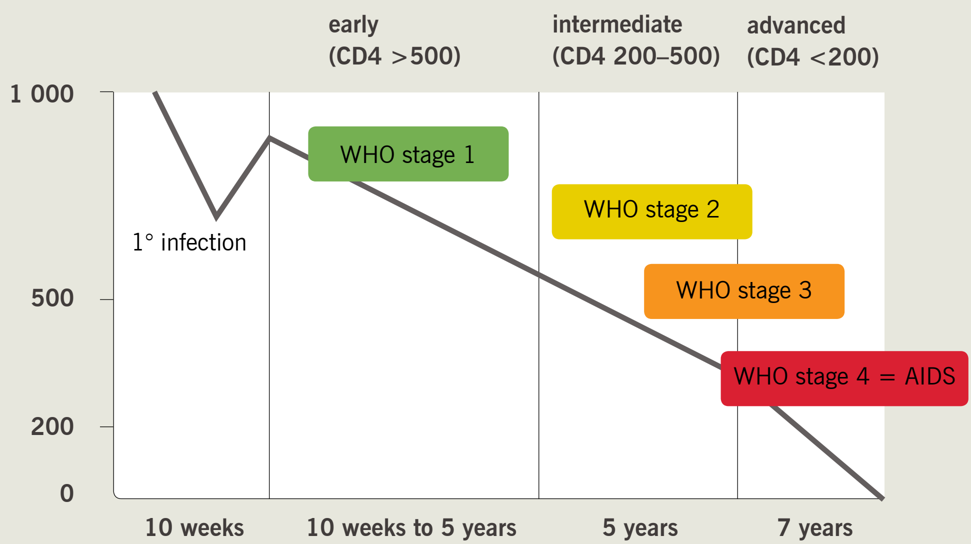
It is very important to inform patients coming for testing that during the window period they may show a negative test, but at the same time be at their most infectious because of the very high viral load. It is standard to recommend that the patient returns for another test 4–6 weeks after a high risk contact. The process of developing antibodies and changing from being HIV negative to positive is referred to as **seroconversion**.

From approximately 3 months, to 7–10 years

After the initial rapid rise in viral load and drop in CD4, the body develops antibodies and starts to fight back against the virus. At this point, the viral load drops a bit and the CD4 count rises. When it has settled, this is referred to as a **steady state** or the **viral set point** (marked on Figure 1.1).

The viral load set point, though frequently not identified at the time, can give an idea of the prognosis. The higher the viral load set point, the poorer the prognosis.

Figure 1.2 Deterioration linked to loss of CD4 cells



Over the next several years, the viral load slowly rises and the CD4 drops, resulting in a progressive worsening of the body's ability to fight infection. Initially, there may be no evidence of infection at all, but, as the immunity drops, more infections start to occur and with increasing severity. WHO has divided this period into four stages, defined by the types of infections that generally occur (Figure 1.2).

Though the WHO stages 1–4 roughly correspond to CD4 levels, it is the diseases and clinical symptoms that determine each stage, not the CD4 count. It is possible to have a patient with a very low CD4 count who is still in clinical stage 1 (i.e. without any identified disease). It is equally possible to have a patient with a CD4 count over 500, who has stage 4 disease defined by specific opportunistic infections (OIs) such as Kaposi's sarcoma or HIV-related nephropathy (see Appendix 1.1 on page 14 for staging details).

This being said, it remains essential to measure CD4 count in all new patients, as well as those suspected of treatment failures, as a low CD4 count (especially <200) will trigger the clinician to look specifically for a range of potentially life-threatening opportunistic infections (see **Chapter 11**).

Table 1.1 Risk of opportunistic infections and other HIV-related conditions by CD4 cell count

Table 1.1 shows the correlation between CD4 and the types of infection that can be anticipated.

CD4 count*	Condition
Any CD4 count	Parotid gland enlargement Herpes zoster (shingles) Pulmonary tuberculosis Bacterial pneumonia Cervical intraepithelial neoplasia (CIN) HIV-related thrombocytopaenia Lymphocytic interstitial pneumonitis (LIP) commonly seen in children Kaposi's sarcoma
<200 cells/μL (when severe OIs begin to appear)*	Oral candidiasis (i.e. thrush) Oesophageal candidiasis Pneumocystis jiroveci pneumonia (PCP) Cryptosporidiosis Lymphoma (non-CNS) HIV-associated dementia Disseminated tuberculosis Isospora infection
<100 cells/μL	Toxoplasmosis Cryptococcal meningitis (CCM) Cytomegalovirus infection Disseminated fungal disease (histoplasmosis, aspergillosis, penicilliosis)
<50 cells/μL	Non-tuberculosis mycobacterial (NTM) infection Lymphoma (CNS) Progressive multifocal leukoencephalopathy (PML)

* Note:

- It is possible to have a patient with a very low CD4 count who is still in clinical stage 1, i.e. without any symptoms.
- There are also a few clinical stage 4 conditions (HIV-related lymphoma, Kaposi's sarcoma, cardiomyopathy, and nephropathy) that may occur at higher CD4 counts.
- While conditions seen at lower CD4 counts are rarely seen with higher CD4 counts, it is possible for any condition seen at higher CD4 counts also to be seen at lower CD4 counts.

Without treatment, the time period from initial infection to death varies from person to person. Some deteriorate rapidly (rapid progressors) and others may take 15–20 years before they start to develop significant OIs, but for most it is 7–10 years. This time period is influenced by a few different factors, including the viral load set point and the presence of OIs, especially TB. When a person is in stages 1–3, we refer to them as being ‘HIV-infected’ and it is only when they reach stage 4 that we say they have ‘AIDS’.

What determines the rate at which an individual progresses to AIDS?

Without treatment, all HIV-infected people will ultimately develop severe infections and die. The rate of progression depends on a variety of factors:

Factors that may cause faster progression, if untreated, include:

- Age less than 5 years
- Age over 40 years
- Presence of other infections, especially tuberculosis
- Possible genetic factors.

It is worth noting that there are two main types of HIV that infect humans, HIV1 and HIV2. HIV1 is the dominant type in sub-Saharan Africa, and, unless mentioned otherwise, is the focus of this book. Please note the following regarding HIV2.

- It is more common in West Africa.
- It is less virulent which may be why an untreated HIV-positive person deteriorates very slowly.
- It is also detected by rapid tests, usually at the same time as HIV1.
- It does not respond to standard first line regimens.

Global HIV epidemic statistics

In light of the above information, it is informative to note the status of the epidemic globally, and particularly in sub-Saharan Africa, where MSF has the bulk of its HIV projects. The UNAIDS 2016 report notes the following changes from 2010 to 2016:

- People living with HIV have increased from 33 to 37 million, of whom 25 million are in sub-Saharan Africa.
- In the 25 countries of West and Central Africa, though the HIV prevalence is <5%, there are 6.6 million people living with HIV. This represents 17.9% of people living with HIV in the whole world*. HIV-related mortality, however, has increased substantially and now represents 42% of all HIV-related deaths in sub-Saharan Africa.

**Le prix de l’oubli* - MSF report 20 April 2016 (English translation: ‘Out of focus’)

- The total number of newly infected people has decreased from 2.2 to 2.1 million, 1.3 million of whom are from sub-Saharan Africa, but this number is slowly plateauing.
- According to the 2016 UNAIDS report, of those living with HIV, those on treatment have increased substantially, from 7 to 19.5 million. Of the 19.5 million PLHIV, 12 million are from sub-Saharan Africa.
- The global mortality rate from HIV has dropped from 1.5 to 1.1 million, but this figure is now also plateauing. The bulk of these deaths (800 000) are from sub-Saharan Africa*.

Summary

HIV is a virus that specifically targets CD4 T lymphocytes, an important component of the body's immune defence mechanism. The virus is spread by three main routes: sexually; from mother-to-child (during pregnancy or via breastfeeding); and by direct entry into the bloodstream (transfusions, IV drug use and occupational needle-stick injuries).

The untreated infected person will experience a slow deterioration in their immunity, eventually developing an overwhelming infection, resulting in death. This process usually takes 7–10 years. We divide immune deterioration into four different stages, determined by the severity of infection. The term 'AIDS' is used to describe stage 4, the final stage of the disease progression.

A broad overview of diagnosis, prevention and treatment

Diagnosis of HIV

The diagnosis can be made either by detecting antibodies to HIV in the bloodstream or saliva or by detecting the actual virus in the blood. In adults and children over 18 months, the standard method of diagnosis is by antibody tests. Remember that, during the window period (up to the first three months after the initial infection with HIV), the antibodies may not have formed yet. This may result in a false negative test.

In children under 18 months, a combination of both antibody tests and tests for the virus itself are used. The infant carries the mother's antibodies for up to 18 months after birth, so a positive antibody test does not necessarily tell us that the baby is infected. This is explained in more detail in **Chapter 10**.

**Le prix de l'oubli* - MSF report 20 April 2016 (English translation: 'Out of focus')

Testing strategies

In its 90:90:90 plan for 2020, WHO set the goal of 90% of all people with diagnosed HIV infection knowing their status, 90% of those patients being on antiretroviral therapy and 90% of those on this therapy achieving viral suppression.

In order to achieve the first 90%, there needs to be extensive testing in a variety of ways. This includes testing by the full range of healthcare workers, especially lay cadres (counsellors and community workers) in the following settings:

- different outpatient sites, such as maternal and child health, vaccination, TB and general outpatient clinics;
- in the community: strategies such as door-to-door, mobile and fixed-site testing, or campaigns targeting index clients, such as relatives and partners; and
- self-testing.

A comprehensive detailing of these strategies, including inpatient testing, is beyond the scope of this clinically oriented book, but this in no way diminishes the importance of these strategies being implemented wherever possible within the broad primary care environment.

Prevention strategies in HIV

Clinicians and programme managers use several different strategies in the management of HIV. These include:

- the HIV-positive person making themselves less infectious to others;
- the HIV-negative person taking precautions to avoid becoming infected with HIV;
- health system contributions to decreasing transmission of HIV; and
- the HIV-positive person taking appropriate medication to decrease the risk of developing OIs.

These are detailed in **Chapter 8**, with specific focus on three key interventions: PrEP, PEP and vaccinations.

Treatment of HIV

The cornerstone in the treatment of HIV is the use of HIV medication. HIV is part of a group of viruses called retroviruses. Drugs used to treat HIV are, therefore, often referred to as antiretrovirals, often abbreviated to ARVs. The most commonly used term for treatment is ART (antiretroviral therapy) but other terms also used are HAART (highly active antiretroviral therapy) or cART (Combined AntiRetroviral Therapy). This topic is covered comprehensively in the next few chapters.

In 2015, the **WHO guidelines** stated that all patients of all ages, regardless of their CD4 count or clinical stage, were eligible to start ART as soon as possible. This means that, from the patient's first visit to the clinic, the healthcare staff are now oriented to starting ART.

WHO guidelines

The critical role of patient support (PS)

The foundation of HIV patient management is getting patients to take their medication correctly, whether ARVs, TB drugs or any other medication important for their optimum health. **Adherence to lifelong treatment is arguably the biggest challenge in the management of HIV today.**

All people, regardless of education and socio-economic status, have concerns and feelings about any illness they may have – along with expectations of what is going to happen to them – and their own personal ways to deal with it. This applies all the more to a disease like HIV, with its devastating consequences, not only for physical health, but also for its psychosocial impact. The degree to which patients' concerns, feelings and behaviours related to their illness are identified and addressed determines the likelihood of people taking their medication correctly.

Patient support to optimise treatment adherence describes the various processes a team of people, comprising mostly clinicians and counsellors, use to attempt to explore and address patients' feelings, concerns and health behaviours. Patient support empowers people in such a way that they take their drugs properly.

Patient support
(see Chapter 25)

The icon alongside weaves the thread of **patient support** throughout this book. Its appearance draws attention to the importance of some aspect of additional support to address potential concerns and optimise adherence of the patient. Even if a clinician does not directly provide the patient support, they should at all times be aware of what is being addressed in the counselling sessions and be prepared to step in, if more qualified help is needed.

Chapter 25: Patient support deals in more detail with the principles of patient support and the essential role that clinicians play in collaborating with counsellors.

Chapter sequencing in this book

Chapters 2–9 are designed to match the knowledge sequence required to manage consultations.

Chapter 2: **Antiviral therapy and eligibility** gives an introduction to ART and details the different drugs used.

Chapter 3: **Initial assessment and ART initiation** guides the clinician through the preparatory history, examination and tests that need to be done in the first few visits to the clinic, and explains the principles of building an ART regimen.

Chapter 4: **ARV side effects** deals with the different side effects of ARVs.

Chapter 5: **Follow-up of the patient on ART and IRIS**, builds on the foundation of the previous chapters, details how to monitor the patient on ART, and provides some guidelines on the diagnosis and management of Immune Reconstitution Inflammatory Syndrome (IRIS).

Chapter 6: **Managing possible ART failure** takes the clinician through the diagnosis and management of a patient with a high viral load.

Chapter 7: **Drug-drug interactions in HIV/TB** explains the important drug-drug interactions in the management of HIV and TB.

Building on the foundation of this core knowledge, **chapters 8–10** cover the use of ART and the management of HIV in three specific settings.

Chapter 8: **Prevention strategies in the HIV-positive patient** includes pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP) and vaccinations.

Chapter 9: **Prevention of mother-to-child transmission of HIV**

Chapter 10: **HIV in children**

The patient who presents with advanced disease – in which TB unfortunately remains a significant cause of mortality – is a significant new focus in HIV management. These two topics are covered in **chapters 11–12**.

Chapter 11: **Advanced disease – ambulatory patient**

Chapter 12: **Drug-sensitive and drug-resistant tuberculosis**

In 2016, WHO issued a guideline for patients with advanced HIV. Defined as 'all adults and adolescents with CD4 count <200 or stage 3 or 4 disease, as well as all HIV-infected children <5 years old', these patients deserve specific clinical management because of their higher risk of mortality (see **Chapter 11**).

HIV affects every organ in the body, either directly or via OIs. **Chapters 13–20** cover the different organ systems affected specifically in the HIV-positive patient.

Chapter 13: **Respiratory disease**

Chapter 14: **Neurological disease**

Chapter 15: **Gastro-intestinal conditions**

Chapter 16: **Liver disease**

Chapter 17: **Renal disease**

Chapter 18: **Haematological conditions**

Chapter 19: **Sexual and reproductive health**

Chapter 20: **Skin diseases**

These are followed by two areas (**chapters 21–22**) not necessarily directly affected by the virus, but certainly needing special attention in the HIV-positive patient.

Chapter 21: **Non-communicable diseases and HIV**

Chapter 22: **Mental health disorders**

Chapters 23–26 cover areas of HIV medicine that draw on or contribute to different aspects of HIV care covered in the rest of the book.

Appendix 1.1 WHO clinical staging of HIV disease in adults, adolescents and children

Adults and adolescents[a]	Children
Clinical stage 1	
Asymptomatic Persistent generalised lymphadenopathy	Asymptomatic Persistent generalised lymphadenopathy
Clinical stage 2	
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Seborrhoeic dermatitis	Unexplained persistent hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Herpes zoster Lineal gingival erythema Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Extensive wart virus infection Extensive molluscum contagiosum Unexplained persistent parotid enlargement
Clinical stage 3	
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than one month Unexplained persistent fever (intermittent or constant for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotising ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10^9/l) and/or chronic thrombocytopaenia (<50 x 10^9/l)	Unexplained moderate malnutrition[b] not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one month) Persistent oral candidiasis (after first 6 weeks of life) Oral hairy leukoplakia Lymph node tuberculosis Pulmonary tuberculosis Severe recurrent bacterial pneumonia Acute necrotising ulcerative gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5x10^9/l) or chronic thrombocytopaenia (<50 x 10^9/l) Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including bronchiectasis

(Source: Adapted from World Health Organisation. 2007. *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children.* www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf)

Adults and adolescents[a]	Children
Clinical stage 4[c]	
HIV wasting syndrome Pneumocystis *(jiroveci)* pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extra-pulmonary tuberculosis Kaposi's sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extra-pulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extra-pulmonary histoplasmosis, coccidioidomycosis) Lymphoma (cerebral or B-cell non-Hodgkin) Symptomatic HIV-associated nephropathy or cardiomyopathy Recurrent septicaemia (including nontyphoidal *Salmonella*) Invasive cervical carcinoma Atypical disseminated leishmaniasis	Unexplained severe wasting, stunting or severe malnutrition[d] not responding to standard therapy Pneumocystis *(jiroveci)* pneumonia Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extra-pulmonary tuberculosis Kaposi's sarcoma Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than one month) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy Extra-pulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis Disseminated endemic mycosis (extra-pulmonary histoplasmosis, coccidioidomycosis, penicilliosis) Cerebral or B-cell non-Hodgkin lymphoma HIV-associated nephropathy or cardiomyopathy

a In the development of this table, adolescents were defined as 15 years or older. For those aged less than 15 years, the clinical staging for children should be used.

b For children younger than 5 years, moderate malnutrition is defined as weight-for-height <-2 z-score or mid-upper arm circumference ≥115 mm to <125 mm.

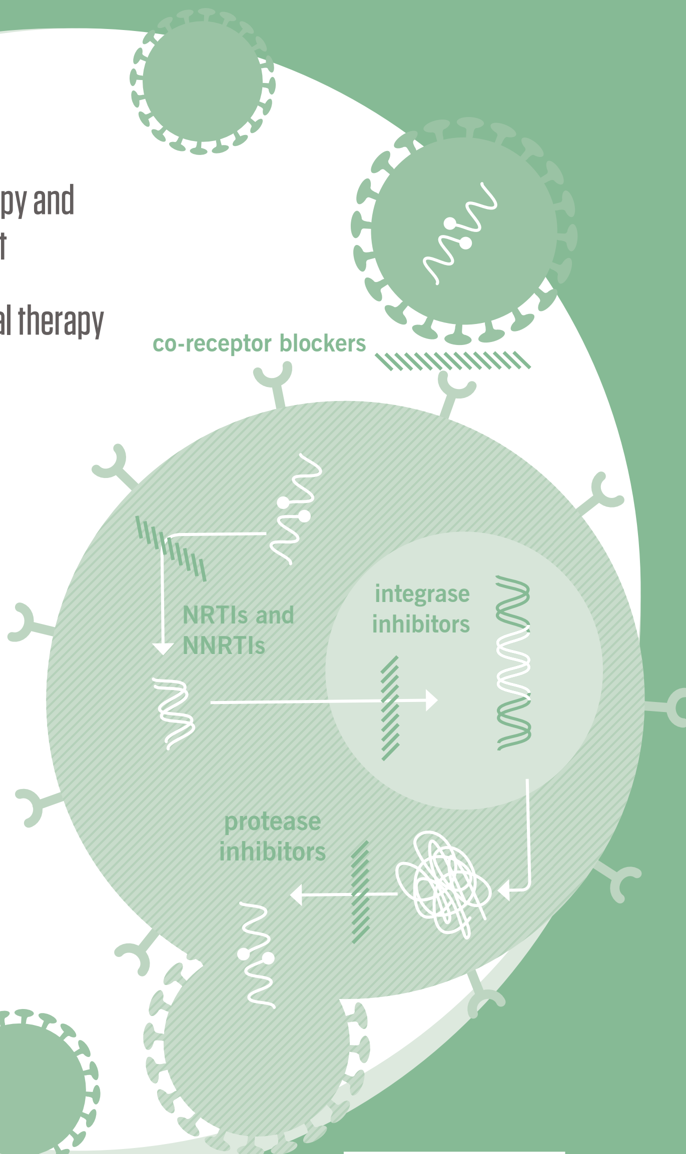
c Some additional specific conditions can be included in regional classifications, such as penicilliosis in Asia, HIV-associated rectovaginal fistula in southern Africa and reactivation of trypanosomiasis in Latin America.

d For children younger than 5 years of age, severe wasting is defined as weight-for-height <-3 z-score; stunting is defined as length-for-age/height-for-age <-2 z-score; and severe acute malnutrition is either weight for height <-3 z-score or mid-upper arm circumference <115 mm or the presence of oedema.

CHAPTER 2

Antiretroviral therapy and eligibility

- Antiretroviral therapy and objectives of treatment
- Eligibility to start antiretroviral therapy
- An introduction to antiretroviral therapy (ART)
- Classification of ARVs
- General principles in using ART
- When ARVs are used for treatment
- The individual drugs and their side effects



Please note that this topic is covered more fully in the **SAMU HIV/TB E-Learning course**. See 'How to use this book' for details.

Antiretroviral therapy and objectives of treatment

ARVs are the standard of care for HIV treatment worldwide. ARVs do not eradicate HIV, but block its ability to reproduce. What this means is that the virus is blocked from converting the CD4 cell into an HIV factory. The CD4 cells stop producing the virus and therefore stop dying. The immune system is then able to recover its strength, resulting in OIs becoming both less frequent and less severe. The infected person's clinical condition markedly improves as a result.

Principle objectives of ART include:

- Prolong life expectancy and improve quality of life: For example, in South Africa, life expectancy increased from 54 to 60 years between 2005 and 2011, largely due to ART scale-up.
- Reduce the amount of virus in the body (HIV viral load): The aim is to reduce the virus's ability to reproduce (viral replication), thereby blocking further replication and CD4 destruction.
- Improve the CD4 count: This will result in immunological improvement, an improvement in the body's ability to fight infection. Such immunological recovery varies from person to person, but the majority of patients improve rapidly in the first few (1–3) months, with a more gradual recovery thereafter. In a small percentage of patients, the CD4 count will not significantly increase, although the immune function may improve.
- Reduce OIs and other HIV-related conditions.
- Reduce transmission of HIV: Studies have shown that HIV-positive patients who are on ART and who have an undetectable viral load (often referred to as being virally suppressed) do not transmit the virus to others (U=U: undetectable = untransmittable).

Eligibility to start antiretroviral therapy

Recent studies have shown that there is considerable benefit in starting ART as soon as possible, even with CD4 cell counts >500. In 2015, WHO, therefore, recommended that all HIV-positive people (adults, adolescents and children) are eligible to start ART at any CD4 count. This means that all patients should ideally start on ART as soon after diagnosis as possible.

This will result in individual benefit in terms of immune protection (fewer OIs, less frequent hospitalisations and fewer deaths) and greater public health benefit, as a result of stopping transmission of the virus.

Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection (WHO, 2016):

- ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 count (strong recommendation, moderate-quality evidence).
- As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤350 cells/mm^3 (strong recommendation, moderate-quality evidence).
- ART should be initiated in all pregnant and breastfeeding women living with HIV, regardless of WHO clinical stage and at any CD4 cell count, and continued lifelong (strong recommendation, moderate-quality evidence)]

Initiation criteria for children and adolescents are covered in **Chapter 10**.

WHO guidelines

Children
(see Chapter 10)

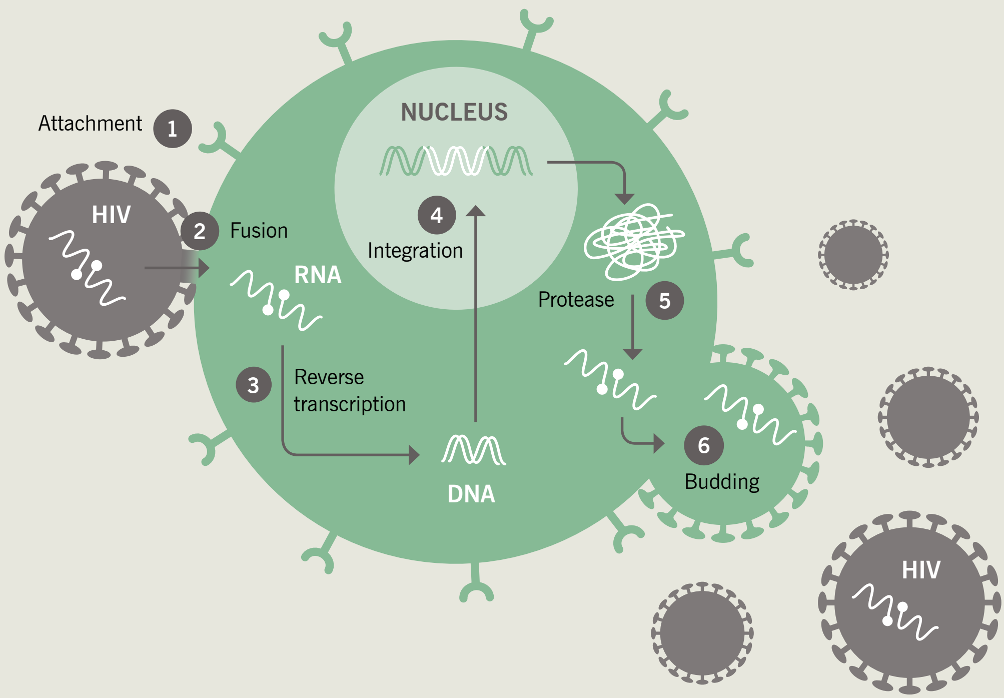
The WHO provides guidance on HIV treatment. The guidance is updated regularly to encompass new scientific evidence that informs the public health response, globally. The WHO, thus, informs national country guidelines, which have to consider cost and implementation challenges.

An introduction to antiretroviral therapy (ART)

Over the last thirty years, much research has been done to try and work out how to interrupt the reproductive cycle of HIV. Currently, there are nine drugs in three different categories in regular use in poorly-resourced countries, with a fourth category currently making its way into everyday use. To understand these different drugs, it will be helpful to look at the HIV life cycle in a bit more detail.

The numbered notes below Figure 2.1 refer to the numbered part of the HIV life cycle. The next paragraph shows in which parts of this cycle the commonly used drugs act, along with those of the newer group now heading into regular use.

Figure 2.1 Lifecycle of HIV



Notes

1. **Attachment:** The first step in the cycle is for the HIV particle to attach to the CD4 cell.
2. **Fusion:** Once attached, the virus then fuses onto the CD4 cell and injects its genetic material into the body of the cell.
3. **Reverse transcription:** The genetic material is in a format called RNA and needs to be converted to another format called DNA so that it can effectively mix with the CD4 cell's genetic material. This conversion of RNA to DNA, called reverse transcription, happens with the help of an enzyme called reverse **transcriptase**.
4. **Integration:** This DNA finds its way into the nucleus of the cell (the programming centre) where it mixes (integrates) with the genetic material of the CD4 cell. This happens with the support of an enzyme called **integrase**. The cell is now re-programmed to stop making chemicals to fight infections and instead make more HIV.
5. The new message heads out into the cell to get the cell machinery to make more HIV. Part of this process of building a new HIV particle involves an enzyme called **protease**.
6. **Budding:** When the new particle is fully formed, it is discharged from the cell into the circulation, a term referred to as 'budding'.

This process repeats itself over and over again, millions of times a day as the CD4 cells are slowly taken over by the HIV. The quest in the laboratories has been and continues to be to find the best drug to interrupt this reproduction cycle and give the body time to restore its immune function.

Classification of ARVs

ARVs are classified according to the sites at which they act. The site numbers in the text below link to the numbers in Figure 2.1.

Site 3: Some ARVs block the action of the reverse transcriptase enzyme. There are two different sub-groups that act at this site:

- Nucleoside or nucleotide reverse transcriptase inhibitors (**NRTIs**), often referred to as '**nucs**':
  - tenofovir (TDF)
  - lamivudine (3TC)
  - zidovudine (AZT)
  - abacavir (ABC)
- Non-nucleoside reverse transcriptase inhibitors (**NNRTIs**), often referred to as '**non-nucs**':
  - efavirenz (EFV)
  - nevirapine (NVP)
  - Also newer, less commonly used drugs: etravirine (ETV) and rilpivirine (RPV)

Site 4: Some ARVs block the action of the integrase enzyme and are called **integrase inhibitors** (referred to as **INSTIs** – integrase strand transfer inhibitors):

- raltegravir (RAL)
- dolutegravir (DTG)

Site 5: Some ARVs block the enzyme (protease) and are called **protease inhibitors** (referred to as **PIs**). The more commonly used ones are:

- lopinavir (LPV)
- ritonavir (R)
- atazanavir (ATV)
- darunavir (DRV)
- tipranavir (TPV)

(Ritonavir is never given alone. The other PIs are never given alone either, but must always be given in combination with ritonavir to make them effective.)

General principles in using ART

ARVs can be given for:

- HIV prevention
    - post-exposure prophylaxis (PEP): e.g. post-rape or high-risk sex (**Chapter 8**)
    - pre-exposure prophylaxis (PrEP): e.g. in those engaging in high-risk sex, such as an HIV-negative, commercial sex worker or partner of an HIV-positive person) (**Chapter 8**)
    - prevention of mother-to-child transmission (PMTCT) (**Chapter 9**)
- HIV treatment

When ARVs are used for treatment

ARVs are never used alone but in regimens consisting of three drugs used in well-established combinations. This is often referred to as 'triple therapy'.

In order to make it as easy as possible for patients to take three pills every day for life, ARVs are often combined in a single tablet, in what is termed a 'fixed drug combination' or 'FDC'. Both the patient and the clinician need to be aware that this one pill actually contains three drugs, each with its own potential side effects.

The details of how to combine these drugs are provided in **Chapter 3**. A combination of three drugs is given to prevent HIV developing resistance to individual ARVs. The same principle operates in the management of TB, where multiple TB drugs are given simultaneously, both to treat the TB and to avoid resistance developing to the drugs.

If resistance to ARVs does develop, it means that those three ARVs won't be effective ever again for that person, even if the ARVs are subsequently taken faithfully, even many years later. The only chance the person then has to lower the HIV 'viral load' is to start taking three new ARVs (known as 'second line' treatment). This is dealt with in detail in **Chapter 6.**

The individual drugs and their side effects

Each of these drugs has its own set of potential side effects, along with the necessary precautions that need to be taken in using them. This will be covered in detail in **Chapter 4**. However, in order to understand some aspects of the first few consultations with an HIV-positive patient, it will be useful to review briefly Appendix 2.1, which provides an overview of the commonly used ARVs.

Consider providing ART education and counselling on the same day a patient is prescribed their ART. We cannot expect patients to take their ARVs as prescribed if they have not understood well why/when/what/how to take them, the possible side effects they may have and how to deal with treatment-related issues. Refer to **Chapter 25** for further details.

Patient support (see Chapter 25)

Appendix 2.1 Classes, drugs and 'need-to-know' facts

Class	ARV	Formulation	Usual adult dose*	Specifics
		*** Paediatric dosages for all of the ARVs can be determined using children's weights – see Tables 10.8–10.10.**		
NRTIs (nucleoside or nucleotide reverse transcriptase inhibitors)	TDF (tenofovir)	300 mg tablets	300 mg OD	Well tolerated but toxic to the kidney in <1% of patients. Active against hepatitis B. Always test for hepatitis B before stopping it (see page 87). CrCl must be >50 ml/min. Contra-indicated in some children. For children <15 years and <40 kg see your national guidelines
	ABC (abacavir)	syrup (20 mg/ml) 300 mg tabs	300 mg twice daily Or 600 mg daily (available as 600 mg in a combination drug with 300 mg 3TC)	Hypersensitivity reaction with fever and rash in 3% of patients (less in those of African descent). No food restrictions. Tablet may not be crushed – see other formulations for children.
	3TC (lamivudine)	syrup (10 mg/ml) 150 mg tabs (also in combo with AZT, d4T and TDF)	150 mg twice daily (or 300 mg OD with TDF)	Well tolerated. Is almost identical to FTC. Used in both first and second line regimens. Active against Hep B.
	FTC (emtricit-abine)	Usually in fixed-dose combination with TDF.	200 mg OD	Well tolerated. Is almost identical to 3TC (used interchangeably). May cause palmar rash.
	AZT (zidovudine)	syrup (10 mg/ml) 100 mg tabs 300 mg AZT (also in combination with 3TC)	300 mg twice daily	Capsules may be opened (children). Anaemia is a common side effect and may be severe. Often causes nausea.
	d4T (stavudine)	syrup (1 mg/ml) 15 mg caps 20 mg caps 30 mg caps	30 mg twice daily for all adults	Is being phased out world-wide due to its long-term toxicity. Is safe to use in the first 4–6 months but after this can start to cause severe toxicities (see Appendix 4.4 for all d4T toxicity details).

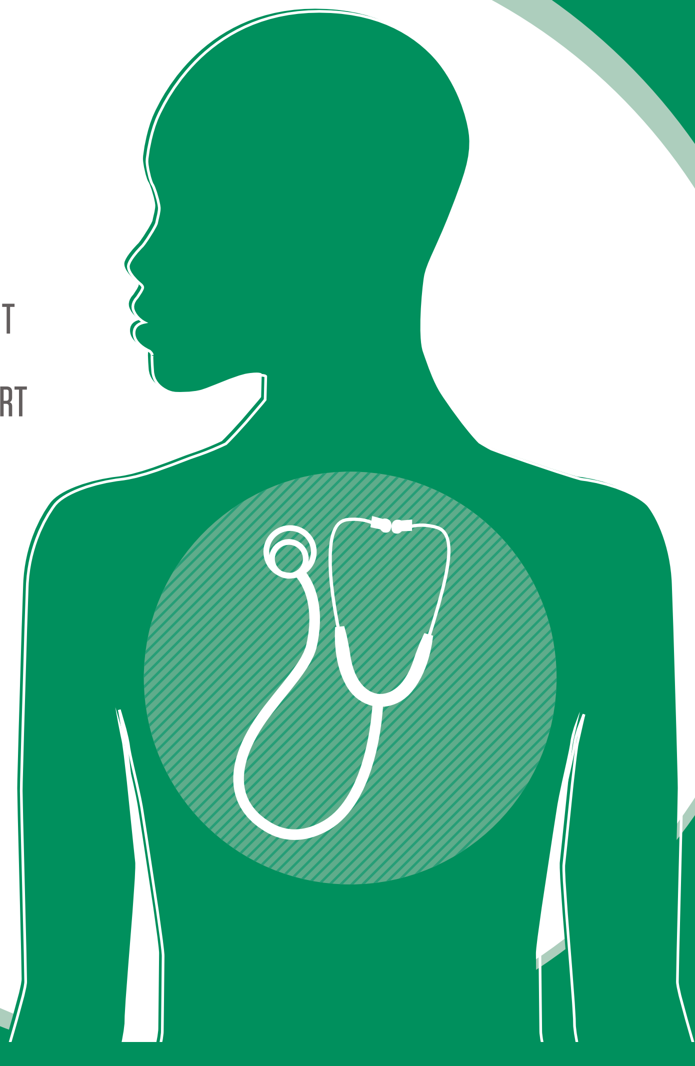
Class	ARV	Formulation	Usual adult dose*	Specifics
		* Paediatric dosages for all of the ARVs can be determined using children's weights – see Tables 10.8–10.10.		
NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors (low genetic barrier to resistance and if present confers class resistance)	NVP (nevirapine)	Syrup (10 mg/ml) 200 mg tabs	200 mg once daily for the first 2 weeks, then 200 mg twice daily.	Tablet may be crushed (children). Contra-indicated in females with CD4 >250 and in males with CD4 >400. Can cause rashes ranging from mild measles-like (morbilliform) to severe Stevens-Johnson Syndrome, which requires hospitalisation and may be fatal. Can cause hepatitis with high ALT levels. This needs urgent attention. Graded introduction of NVP can lessen the impact of the above. Interacts with fluconazole and rifampicin.
	EFV (efavirenz)	50 mg tabs or caps 200 mg tabs or caps 600 mg tabs	600 mg at night if >40 kg. If <40 kg, use 400 mg. NB: if on rifampicin, 600 mg should be prescribed, as the rifampicin induces the metabolism of efavirenz and may drop it to sub-therapeutic blood levels.	Neuropsychiatric side effects are possible, so avoid in shift workers and pre-existing psychiatric conditions. Preferred NNRTI in TB patients. Taken at night to limit side effects. Avoid taking with fatty foods. Capsules may be opened (children). Tablets may not be chewed, divided or crushed. Studies suggests it is safe in the first trimester of pregnancy (WHO 2012). Sometimes causes gynaecomastia.

INSTI (Integrase strand transfer inhibitors)	(RAL) Raltegravir	400 mg tablets	400 mg twice a day	Nausea, diarrhoea and headache. Can cause a hepatitis and a hypersensitivity reaction – both rare.
	(DTG) Dolutegravir	50 mg tablets	50 mg once a day	Insomnia and headache; also some nausea and diarrhoea. Can cause a hepatitis and a hypersensitivity reaction – both rare.

Class	ARV	Formulation	Usual adult dose*	Specifics
		* Paediatric dosages for all of the ARVs can be determined using children's weights – see Tables 10.8–10.10.		
PIs (protease inhibitors)	Kaletra® (lopinavir/ ritonavir or LPV/r)	Syrup (80/20 mg/ml) LPV 133 mg/ RTV 33 mg caps	400/100 mg (= 3 caps) twice daily	Lopinavir is boosted by ritonavir. Capsules must be swallowed whole and not chewed, divided or crushed. Syrup and capsules (not tablets) must be taken with food to enhance absorption and refrigerated until dispensed. Do not open capsules.
	Aluvia® = heat-stable lopinavir/ ritonavir (LPV/r)	Two FDCs LPV 200 mg/ ritonavir 50 mg LPV 100 mg/ ritonavir 25 mg	400/100 mg (= 2 tabs) twice daily	Does not have to be taken with food. Common side effects: nausea, vomiting and diarrhoea. If patient is on rifampicin-containing TB regimen, the dose of LPV/r must either be doubled or 'super-boosted' with additional ritonavir.
	ATV (atazanavir) – always given with ritonavir. see below for FDC info.	150 mg tabs 200 mg tabs	300 mg (2 tabs of 150 mg) OD, together with 1 cap of 100 mg ritonavir (ie 'boosted ATV')	To be stored at <25°C (but keep ritonavir caps in the fridge). Must always be boosted (usually with ritonavir). This is especially important when taken with TDF. Not absorbed well in an alkaline medium: • Don't take with omeprazole. • Take two >2 hours after simple antacids. • Better taken with food due to the acid secretion. ATV can cause a benign jaundice. If normal ALT and no nausea, vomiting or abdominal pain, can continue ATV. Do not give ATV/r with rifampicin. See **Chapter 7, Table 7.2** for detail.
	ATV/r (atazanavir/ ritonavir) – it doesn't require a fridge.	FDC that contains ATV 300 mg and ritonavir 100 mg	1 tablet once a day	See specifics above under details for ATV.
	DRV (darunavir)	600 mg	1 tab twice a day, together with 1 cap of 100 mg ritonavir twice a day (ie 'boosted DRV')	Must always be boosted with ritonavir (100 mg twice a day).
	RTV or r (ritonavir)	100 mg tablet	RTV is never given alone. It is always given in combination with another PI to boost its efficacy.	

CHAPTER 3

Initial assessment and ART initiation



Steps to follow when starting a patient on ART

Initial assessment and ART initiation: Key points

Please note that this topic is covered more fully in the **SAMU HIV/TB E-Learning**. See 'How to use this book' for more details.

As all HIV-positive people are now automatically eligible to start ART, the first consultation is not only an initial evaluation of the patient's overall health status, but also a preparation for the many different aspects of readiness needed to start lifelong medication with potentially toxic drugs.

There are several important steps in this process. With so much information to remember, it is useful to have some sort of reminder for use in our consulting rooms.

Practical tip

Many HIV clinics use **prompted stationery** to ensure that each step is followed. We provide an example of this stationery that can be downloaded and adapted to individual settings and suggest that you use it, either as a checklist during the first consultation or as the actual stationery on which you record your notes. See the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

Steps to follow when starting a patient on ART

The rest of this chapter details the different steps that need to be taken to start a patient on ART.

1. Meet **eligibility criteria** (National Guidelines).
2. Decide **when** to start ART and assess patients' readiness.
3. **Treat** pre-existing conditions and screen for and treat those that may not yet have been detected.
4. Perform the required **tests** before starting.
5. Choose the correct three-drug **regimen**.
6. Provide ART initiation **counselling**.

Step 1. Meet eligibility criteria

WHO guidelines

Eligibility criteria have been covered in **Chapter 2**. In summary, **WHO** now states that 'ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count'.

Step 2. Decide when to start ART

Routine situations

In principle, patients should be started on ART as soon as all the preparatory steps have been taken. The most recent WHO guideline recommends that this should happen within one week.

Fast-tracking the process

Sometimes the process must be speeded up ('fast-tracked'). Patients presenting with a low CD4 count, or who are ill, are at significantly higher risk of mortality. They need a specific package of care, including rapid initiation of ART. This is covered in detail in Chapter 11.

Because of the risk of transmission to the foetus and infant, pregnant and breast-feeding women need specific packages of care. These are detailed in Chapter 9.

Delaying the process

Sometimes the process must be delayed: there is a well-recognised syndrome in patients with HIV who are starting ART, called IRIS, in which the body's rapidly restoring immunity results in the patient temporarily becoming sicker. This condition is seen most commonly in patients with low CD4 counts (usually <200) and can at times cause considerable morbidity, and at times, death.

IRIS has been clearly shown to be associated with certain conditions, and, if appropriate care is taken, the chance of developing IRIS is considerably lessened. IRIS is covered in detail in **Chapter 5**.

In summary, these are the situations in which ART initiation is deliberately delayed:

- Non-neurological TB:
  - If the CD4 is <50, ART is delayed to 2 weeks after starting TB treatment.
  - If the CD4 is >50, ART can be delayed for up to 8 weeks after starting TB treatment. However, in practice, we tend to start ART within the first 4 weeks of starting TB treatment. With CD4 counts closer to 50, we tend to start ART even earlier.
- Neurological TB (meningitis, brain and cord lesions): Regardless of CD4 count, ART is delayed for 4 weeks after starting TB treatment.
- Cryptococcal meningitis: Regardless of CD4 count, ART is delayed until 4 weeks after starting treatment.
- CMV retinopathy: Delay ARV initiation for 2 weeks after beginning of CMV treatment.

Because of the higher risk for serious IRIS in patients with these conditions, it is important to screen all patients for TB and in those with a CD4 count <100 for cryptococcal disease. In addition, in high prevalence areas, the fundi should be examined for signs of cytomegalovirus (CMV) retinopathy (see **Chapter 11**).

Delayed for other reasons

Some countries have not yet implemented WHO's latest guideline of initiating everyone on ART, regardless of CD4 count. Under these circumstances, clinicians need to follow the patients until they meet the existing criteria for initiation.

Specific recommendations for follow-up consultations are to:

- Ensure regular 6-monthly visits to the clinic, checking the CD4 each time and reassessing eligibility to start ART;
- Provide advice on HIV prevention;
- Educate patients about the symptoms of common OIs and advise them to seek medical advice should they show signs of any symptoms developing.
- Ensure that the patient is taking cotrimoxazole (CTX), and, if the patient screens negative for TB, isoniazid (abbreviated as INH) prophylaxis (follow your **national guideline** for both these drugs);
- Check patient's weight and WHO stage at each visit; and
- Continue to screen for and treat all the illnesses mentioned in the next section.
- Patients who do not yet meet local ARV initiation criteria are at high risk of being lost to follow-up before actually starting ART. Good counselling and health education are important.
- Explain to the patient that the healthcare provider will advise the patient to start treatment at their next appointment, but that it is up to the patient to take the final decision.
- Find out whether the patient still has any concerns about starting ART.
- If the patient feels ready, book an appointment for the ART initiation session(s). If the patient does not feel ready, book an appointment for the ART readiness session.

Refer to your national guidelines

Step 3. Treat pre-existing conditions and screen for and treat those that may not yet have been detected

A patient presenting for a first visit to an HIV clinic may well have several conditions needing treatment. These may be:

- HIV-related, resulting from lowered immunity, e.g. conditions in Table 1.1 on page 6.
- Unrelated to HIV, e.g. hypertension, diabetes, epilepsy, etc.

In the busy primary care clinic, history and examination are often of necessity shortened, to focus on the key presenting problems. For the first consultation, however, it really is important to take more time to do a fuller history and examination.

It is not easy to remember the many things to look for in a first consultation. Many clinicians find it helpful to use a checklist or prompted stationery to ensure that nothing is missed. An example of this can be **downloaded** from samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Figure 3.1 shows the key things to look for on examination. The easiest way to cover all this is to do a standard, full examination of all the systems, remembering a few specific places to look (e.g. the mouth for oral candida and Kaposi's sarcoma). In the HIV-positive patient many of these illnesses have greater significance. On page 31 you will find brief notes on the key conditions to look for.

Some HIV clinics have found it **helpful** to set up a small room, where basic observations are done for all new patients and some specific patients who need particular examinations followed up. The routine examinations performed are weight, pulse, blood pressure, respiratory rate, temperature and urine dipstick. This ensures that these are all done at baseline and takes some of the pressure off the busy clinician.

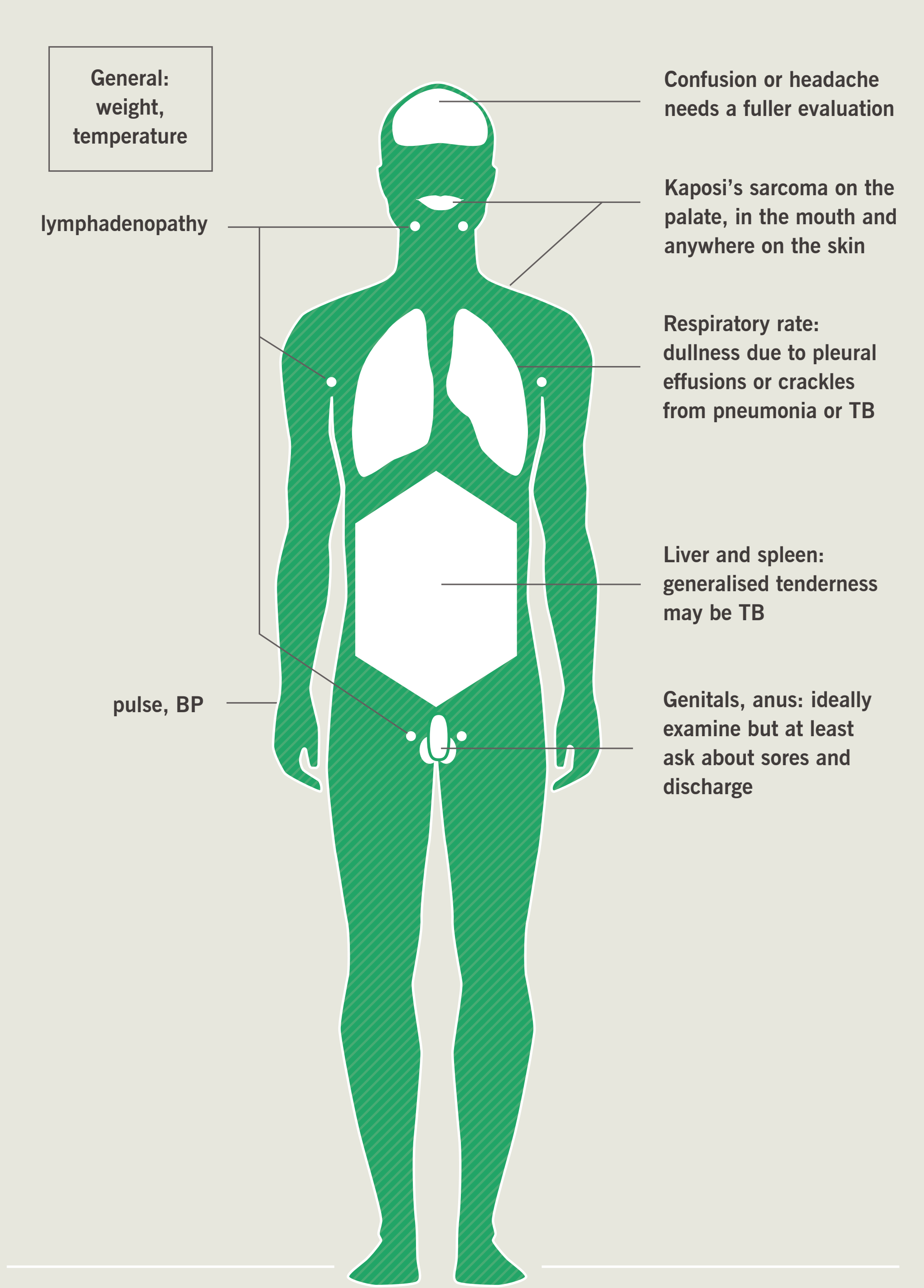
Practical tip

Routine examination at the first consultation

A once-off, full, systemic examination at the first consultation will pick up many different conditions needing attention.

1. General:
   - Look for JACCOL (jaundice, anaemia, clubbing, cyanosis, oedema and lymphadenopathy)
   - In the mouth and on skin for Kaposi's sarcoma
   - Skin for rashes
   - Nails for fungal infection
2. Routine chest, cardiovascular and abdominal examination (key areas highlighted in figure below)
3. Rapid neurological examination. Core need is to test:
   - Global functioning – confusion, abnormal behaviour
   - Neck stiffness
   - Cranial nerves (eye movements, facial movements and sensation)
   - Motor (upper and lower limb strength and symmetry, coordination and viewing patient walking).

Figure 3.1 Conditions often missed in routine examination



Key conditions to look for

Tuberculosis

In some settings, up to 75% of patients with TB are HIV positive. TB is not only associated with a higher morbidity and mortality in HIV-positive patients, but it often presents differently and is more difficult to detect.

The presence of TB also affects the timing of ART initiation, and in addition sometimes influences the choice of ART, due to drug interactions. It is therefore important to look for it actively, not only in the first consultation, but also in subsequent consultations.

In addition, if TB is not detected, the patient should be started on INH prophylaxis.

Sexual and reproductive health

It is critical that any pregnant woman is started on ART as soon as possible. **Pregnancy enquiry and screening** is therefore important.

If the patient is not pregnant, the first consultation is an opportunity not only to **emphasise the importance of condom** use but also to assess current **contraceptive use** and make appropriate recommendations.

Sexually transmitted infections (STIs), via ulcers or inflamed mucosal or epithelial surfaces, both increase the spread of HIV and increase the chance of acquiring it. Routine screening for men and women should therefore include a syphilis test and enquiry regarding genital sores and discharge.

Carcinoma of the cervix is caused by the human papilloma virus (HPV) and is seen far more commonly in HIV-positive women. As with most viral infections, lowered immunity due to HIV results in increased viral activity. With HPV infection, the progression from initial infection to carcinoma of the cervix is significantly speeded up. It is, therefore, important to ensure that all HIV-positive women are adequately **screened for cervical abnormalities** as per your national guideline for HIV-positive people (PAP smear or VIA). This should be much more frequent for HIV-positive people (see **Chapter 19**).

HIV infection, especially in association with other opportunistic infections, frequently results in **poor nutritional status**. Initial assessment of this will therefore help with access to nutritional supplementation (see **Chapter 24**).

Other conditions

An HIV-positive patient may, of course, have the same non-communicable diseases (NCDs) seen in HIV-negative patients. The management of these naturally needs to continue and ideally in a way that avoids repeated clinic visits on different days. The management of these conditions in our HIV-positive patients is of growing importance as life expectancy increases, and is covered more comprehensively in **Chapter 21**.

Other HIV-related conditions

A full history and examination consciously looking for the conditions seen in Table 1.1 on page 6 will complete the illness screening and management process in the first consultation.

Refer to your national guidelines

Step 4. Perform the required tests before starting

WHO makes several recommendations for pre-ART tests. As always, this is the ideal, but is often not possible in poorly resourced countries. Please follow your local **national guidelines**.

Table 3.1 Recommended tests for HIV screening and monitoring and approaches to screening for co-infections and non-communicable diseases

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis	HIV testing (serology for adults and children 18 months or older; PCR for children younger than 18 months) CD4 cell count TB symptom screening	HBV (HBsAg) serology[a] HCV serology Cryptococcosis antigen if CD4 cell count $\leq$100 cells/mm^3 [b] Screening for STIs Pregnancy test to assess if ART initiation should be prioritized to prevent HIV transmission to the child Assessment for major non-communicable chronic diseases and co-morbidities[c]
Follow-up before ART	CD4 cell count (every 6–12 months in circumstances where ART initiation is delayed)	
ART initiation		Haemoglobin test for starting AZT[d] Pregnancy test Blood pressure measurement Serum creatinine and estimated glomerular filtration rate (eGFR) before starting TDF[e] Alanine aminotransferase (ALT) NVP[f] Baseline CD4 cell count
Receiving ART	HIV viral load (at 6 months and 12 months after initiating ART and every 12 months thereafter) CD4 cell count every 6 months until patients are stable on ART	Serum creatinine and eGFR for TDF[c] Pregnancy test, especially for women of childbearing age not receiving family planning and on treatment with DTG or low-dose EFV
Suspected treatment failure	Serum creatinine and eGFR for TDF[c] Pregnancy test, especially for women of childbearing age not receiving family planning and on treatment with DTG or low-dose EFV	HBV (HBsAg) serology[a,g] (before switching ART regimen, if this testing was not done or if the result was negative at baseline and the patient was not vaccinated thereafter)

Notes

a If feasible, HBsAg testing should be performed at baseline to identify people with HIV and HBV coinfection and who should therefore initiate TDF-containing ART.

b Can be considered in settings with a high prevalence of cryptococcal antigenaemia (>3%).

c Consider assessing for the presence of chronic conditions that can influence ART management, such as hypertension and other cardiovascular diseases, diabetes and TB according to the WHO Package of Essential NCD interventions (PEN), mental health Gap Action Programme (mhGAP) or national standard protocols (see section 5.3 'Prevention, screening and management of other co-morbidities and chronic care for people living with HIV'). Monitoring may include a range of tests, including serum creatinine and estimated glomerular filtration rate (eGFR), serum phosphate and urine dipsticks for proteinuria and glycosuria. See formula for eGFR in **Chapter 17**, Renal disease.

d Among children and adults with a high risk of adverse events associated with AZT (low CD4 or low BMI).

e Among people with a high risk of adverse events associated with TDF: underlying renal disease, older age group, low body mass index (BMI), diabetes, hypertension and concomitant use of a boosted PI or potential nephrotoxic drugs.

f Among people with a high risk of adverse events associated with NVP, such as being ART-naïve, women with HIV with a CD4 count >250 cells/mm^3 and hepatitis C virus (HCV) coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity.

g For HIV/HBV coinfected individuals who are already using TDF-containing regimens and develop ART failure, this NRTI should be maintained regardless of the selected second line regimen.

ART antiretroviral therapy, AZT zidovudine, DTG dolutegravir, EFV efavirenz, eGFR estimated glomerular filtration rate, EID early infant diagnosis, HBV hepatitis B virus, HBsAg hepatitis B surface antigen, HCV hepatitis C virus, STI sexually transmitted infection, TDF tenofovir.

Source: *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection* (WHO, 2016, p. 128)

Comments

- **CD4 count:** It is important to know if the CD4 count is <200, as this will influence the decision to fast-track the management process, as per guidelines for 'the patient with advanced disease' (**Chapter 11**). If initiation of ART is delayed for some reason, it is important to continue to monitor the CD4 every 6 months, so that a significant drop in immunity can be acted on timeously.
- **Serum creatinine level and the calculation of creatinine clearance (CrCl):** See detail in **Chapter 17**. Renal impairment is a recognised complication of tenofovir (TDF) use, with prevalence noted to be approximately 1% in various studies. The use of TDF is not recommended if the CrCl is <50, so it is important to measure this at baseline, before starting TDF. However, if this test is not available, WHO states that this must not be a contra-indication to using tenofovir.

- **Nevirapine (NVP)** is known to be hepatotoxic in a proportion of people, so a baseline alanine aminotransferase (ALT) will help evaluate the degree of liver dysfunction prior to starting NVP. Similarly, WHO states that, if this test is not available, this must not be a reason not to use NVP, if no alternative is available.
- **Zidovudine (AZT)** is known to cause bone marrow suppression in a small proportion of patients, so a baseline haemoglobin will also be helpful in making a decision whether it is safe to use AZT or not. Again, if haemoglobin cannot be tested, this must not stand in the way of AZT being used, if it is the drug of choice.

It is recommended that creatinine, ALT and Hb are checked prior to starting TDF, NVP and AZT respectively, but if these tests are not available this must not be a contra-indication to doing so.

Step 5. Choose the correct three-drug regimen

Choosing the drugs to be used in the first line regimen

A standard ARV regimen consists of three drugs, made up of a combination of two NRTIs plus either an NNRTI, an INSTI or a PI. An easy way to think about it is to consider choosing one drug from each of three columns as illustrated in Figure 3.2 below.

In July 2018 WHO issued a new recommendation for the following preferred first line regimen: TDF + 3TC/FTC + DTG for all people over the age of 6 years, with caution in women who may conceive or be in their first trimester. See detailed guideline in Table 3.2 below.

Figure 3.2 Building a three-drug ART regimen

Column 1		Column 2		Column 3
NRTI	PLUS	**NRTI**	PLUS	**INSTI**
TDF or		3TC or		Dolutegravir
AZT or		FTC		or
ABC				**NNRTI**
				EFV or NVP

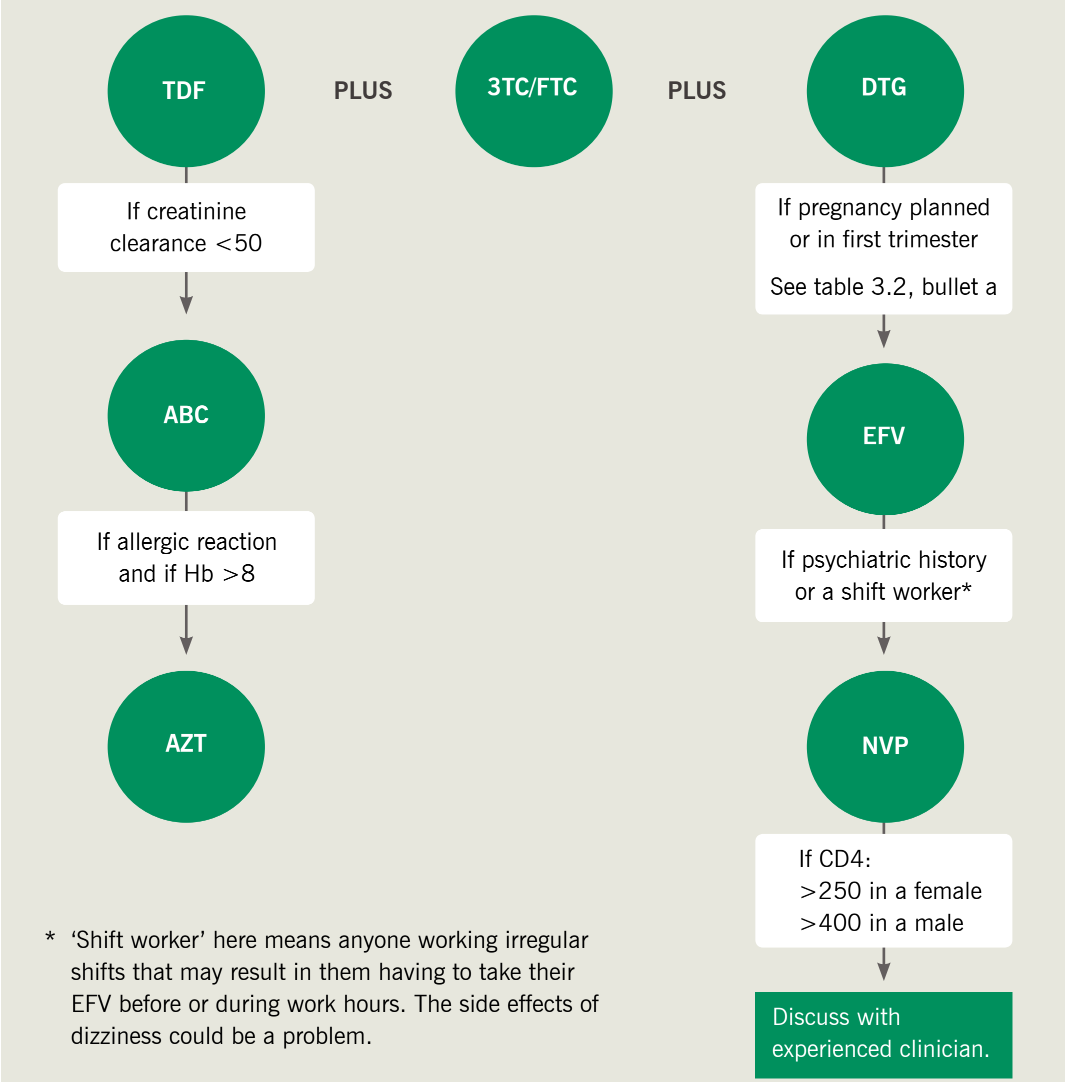
At times there may be contra-indications to one or more drugs in this regimen, in which case the decision process follows Algorithm 3.1 below.

A fixed-dose combination of TDF, 3TC and dolutegravir is now recommended by WHO as the first line ART regimen of choice. Precautions with women who may conceive while taking DTG are detailed later. See updates section on the **SAMU website** where updated information will be posted as it becomes available: https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Algorithm 3.1 Choosing a first line regimen

(See the Appendix 2.1 for dosages.)



* 'Shift worker' here means anyone working irregular shifts that may result in them having to take their EFV before or during work hours. The side effects of dizziness could be a problem.

Table 3.2 Summary of sequencing option for first-, second- and third-line regimens (WHO July 2018)

Population	First line regimens	Second line regimens	Third line regimens
Adults and adolescents (including women and adolescent girls who are of childbearing potential or pregnant)	Two NRTIs + DTG[a]	Two NRTIs[c] + ATV/r or LPV/r	DRV/r[d] + DTG[e] + 1-2 NRTIs (if possible consider optimization using genotypes)
	Two NRTIs + EFV[b]	Two NRTIs + DTG[a]	

a. Women and adolescent girls of childbearing potential with consistent and reliable contraception and who are fully informed of the benefits and risks can use DTG (please watch for WHO updates on this).

b. If population-level pretreatment resistance to EFV or NVP is >10% the choice of alternative options to EFV needs to be made weighing the drug availability and toxicity profile. DTG (as per note (a) or ATV/r are the drug options to be considered.

c. Following TDF or ABC failure AZT should be used to optimise the NRTI backbone and vice versa.

d. For PI-experienced people, the recommended DRV/r dose should be 600 mg/100 mg twice daily.

e. DTG-based third-line ART following the use of integrase inhibitors must be administered with DTG twice daily.

For guidelines for the use of DTG in those wishing to conceive and in pregnancy and breastfeeding, see page 136.

Step 6. Provide ART initiation counselling

Patient support is needed to enable a person to take ARVs faithfully every day. The person (or caregiver, in the case of a child) is educated on HIV and ART and is encouraged and empowered to take treatment for life.

After the patient understands what the treatment is about, why it is important to start ART and take it on a daily basis, and the specificities of lifelong treatment that requires good adherence, the ART counsellor explores whether or not the patient is ready to start treatment. Starting ART should be an informed choice made by the patient, but it is our duty as clinicians or lay providers to explain the benefits of starting treatment and potential risks if this is delayed.

Besides education and emotional support, ART initiation counselling includes a discussion on what might motivate the patient to take ART for life so they remain healthy, as well as about specific behavioural skills necessary to optimise adherence. This is achieved by working with the patient to develop a personalised ‘adherence plan’ that is adapted to their daily life.

Some questions to ask include:

- Who can support you to take medication?
- How will you return to the health facility for ART refills and medical check-ups?
- What is the most convenient time for you to take ARVs?
- How will you remember what time of day to take your medication?
- Where are you going to store medication?

The counsellor should also advise the patient on what to do in case of side effects, travelling, alcohol abuse, etc.

Whether ART initiation counselling is provided by a clinician or lay provider, it is important to show empathy and acknowledge that starting a lifelong treatment is never an easy task; however, a patient who feels this is respected and supported by the healthcare workers is more likely to feel motivated to take medication routinely and to return to the care facilities.

For further details on patient support, refer to **Chapter 25**.

Initial assessment and ART initiation: Key points

- There are many things to remember in the first consultation, all of which add up to optimum care for an HIV-positive patient presenting to your clinic. To help you record your notes, **download** the enrolment form from the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.
- Since 2016 **all** patients of all ages, regardless of WHO clinical stage or CD4 count are eligible to start ART immediately on diagnosis.
- Take a full history and perform a full clinical examination at the first visit to ensure that no conditions needing attention are missed.
- Though specific tests are recommended prior to starting certain ARVs, (creatinine, ALT and Hb) their unavailability should not prevent the clinician from starting ART.
- Patients should be initiated on a once-daily fixed dose combination (FDC) consisting of TDF 3TC/FTC and DTG or TDF 3TC/FTC and EFV, unless there are contraindications to one or more of the individual drugs.
- Ensure ongoing care of all HIV-related and HIV-unrelated (usually NCDs) conditions, ideally in an integrated consultation, where all conditions are managed in one visit.

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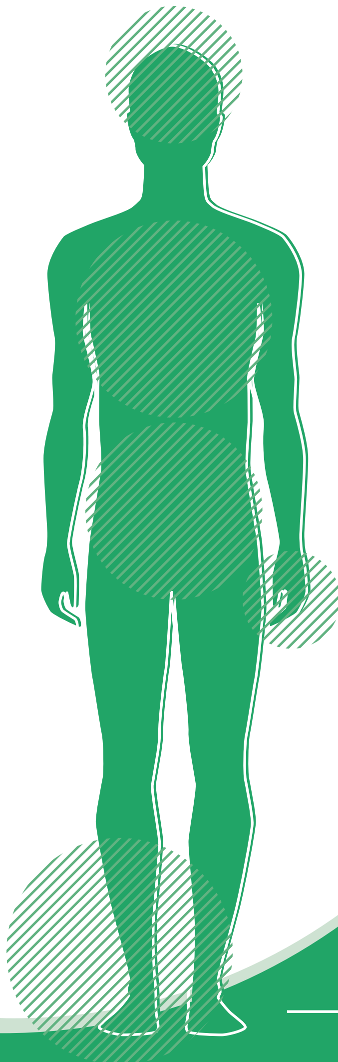
CHAPTER 4

ARV side effects

Side effects of individual drugs and guidelines for monitoring, prevention and management



Please note that this topic is covered more fully in the **SAMU HIV/TB E-Learning course**. See 'How to use this book' for more details.

The management of ARV side effects can be a complex process, for the following reasons:

1. However well we may know the detailed side effects of each ARV, the symptoms, signs or abnormal blood results that a patient may present with may also be caused by a co-existing illness or another drug.
2. Because of this, in the consulting room, we cannot often say with certainty that a particular symptom is due to a drug side effect. It is only by excluding other causes and reviewing the condition over a few weeks after stopping the suspected drug that we become more sure of the diagnosis.

The learning approach in this chapter on drug side effects therefore follows this sequence:

1. **Understand** the side effects of the individual drugs, in order to recognise them when they occur. The tables in this chapter include:
    - The side effects of the class to which a drug belongs, if relevant;
    - Guidelines for monitoring the drug, so that side effects are detected timeously;
    - Strategies to avoid or prevent side effects in the first place; and
    - Guidelines for managing the side effects.

↓

2. Develop a safe approach to the **diagnosis and management** of different abnormalities (symptoms, signs and laboratory tests) presenting at clinic visits, which may be due to ARVs.

Side effects of individual drugs and guidelines for monitoring, prevention and management

It is now clear that ARVs have a wide range of side effects that can present in a variety of ways – symptoms, examination findings or abnormal laboratory tests. However, such an abnormality could also be caused by a non-HIV drug, or as a result of a co-existing illness. Appendices 4.1–4.3 provide an approach to a symptom, sign or abnormal laboratory result that safely covers this complexity.

- Appendix 4.1 provides a table of ARVS (TDF, AZT, 3TC, ABC, NVP, EFV and the protease and integrase inhibitors) and their side effects.

- Appendix 4.2 gives a quick overview of some of the common side effects. However, as this table is not comprehensive, refer to Appendices 4.1, 4.3 and 4.4 for more detailed information.
- Appendix 4.3 gives a more comprehensive approach to possible side effects. Where the diagnostic approach involves investigations for other illnesses, references are made to other chapters in this book.
- Appendix 4.4 gives essential information for the diagnosis and management of side effects of stavudine (d4T) and didanosine (DDI). As these are now hardly being used at all worldwide, the signs and symptoms of their side effects have not been included in the approach given in Appendix 4.3. It is strongly recommended that, if any of your patients are on either d4T or DDI, they should be changed to another ARV.

Appendix 4.1 ARVs and their side-effects

Class: Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) – TDF, AZT, 3TC, ABC			
Tenofovir (TDF)			
Long half-life, so once daily dosing. Effective against hepatitis B (see **Chapter 6**, section 10 on managing the patient with hepatitis B)			**Elimination:** Kidneys
Side-effects	**Monitor**	**Manage**	**Prevent**
Nephrotoxicity Risk <1% Worse if underlying renal disease, older age, advanced HIV, other nephrotoxic drugs	Ideally regular monitoring of creatinine. Consult national guidelines. WHO – go ahead even if no ability to monitor.	If cr.cl drops <50, need to investigate causes. If TDF suspected, stop drug. See **Chapter 6**, section 9 on single drug switches for details on best replacement. (See national guideline for pregnant women)	Don't prescribe with other nephrotoxic drugs (e.g. kanamycin in DR TB). Caution in children – follow national guidelines.
Bone loss is known to occur	Nil specific		Caution in children. See **Chapter 10**.
Zidovudine (AZT)			
Must be taken twice a day.			**Elimination:** Kidneys
Side-effects	**Monitor**	**Manage**	**Prevent**
Common, not dangerous Fatigue, headache, nausea and diarrhoea, muscle pains, blue nail discolouration	NIL	Reassure and consider a drug switch only if ongoing and intolerable.	
Less common Can cause lipo-atrophy and high lactate – **Appendix 4.4**.	Clinical	NIL	If significant, change to TDF or ABC.
Myopathy with raised LDH or CPK	Clinical	Stop AZT and replace with TDF or ABC. Improves in 2-4 weeks.	
Potentially dangerous Bone marrow suppression Hb drops first, usually within 2–3 months, then WBC at up to 6 months Worse if low marrow reserve (e.g. disseminated TB)	Ideally monitor in first 6 months (consult national guidelines). WHO – go ahead even if no ability to monitor.	Stop AZT if Hb drops to <6.5 or to >25% of baseline.	Don't use AZT if Hb <8.

Lamivudine (3TC)	
Once daily dosing Important as the second drug for treating hepatitis B, so must stay on it if hep B positive. See **Chapter 6, section 10**. Almost identical to emtricitabine (FTC), so is used inter-changeably.	**Elimination:** Kidneys
Side-effects	Rarely causes side-effects, so no monitoring needed.

Abacavir (ABC)			
Once daily dosing or dose split and given twice a day.			**Elimination:** Liver
Side-effects	**Monitor**	**Manage**	**Prevent**
Hypersensitivity reaction. Very rare in African populations. • Usually a combination of fever, rash and either respiratory flu-like symptoms or GIT symptoms, such as diarrhoea, nausea, vomiting and abdominal pain. • Most happen in the first few weeks but can occur later. • Usually get worse soon after taking the drug. Higher risk of heart attack. Can cause DRESS (see **Chapter 20** on skin diseases).	No tests performed but important to ask about development of a rash as outlined in side-effects column.	Consider other drug causes – NVP, CTX, TB drugs. Consider OIs (e.g. TB IRIS causing respiratory symptoms). Stop drug immediately if suspected. If diagnosed, **never** re-challenge as deaths have been reported, sometimes within hours.	More caution in using it in non-African people and with high CD4. Give patient warning leaflet and explanation when prescribing ABC. The higher risk of a heart attack is not a contra-indication if cardiac risk factors present but, if possible, choose another NRTI.

Class: Non nucleoside reverse transcriptase inhibitors (NNRTIs)

Class side-effects:

- Rash and hepatitis
- Moderate enzyme inhibitors (see **Chapter 7** on drug interactions)

Nevirapine (NVP)

Must be given twice a day (for PMTCT, see paediatric section). Given as 200 mg once a day for the first 2 weeks, then 200 mg twice a day thereafter. Has 2 potentially serious side-effects – skin rash and hepatitis. Don't use for PrEP, as CD4 usually high and therefore higher risk of toxicity.	**Elimination:** Liver

Side-effects	Monitor	Manage	Prevent
Skin rash Wide spectrum, from mild, itchy measles-like rash to full-blown Stevens-Johnson syndrome. Can also cause DRESS. (see **Chapter 20** on skin diseases). Most occur in first 2–4 weeks. Occurs in women more frequently than men.	Clinical monitoring important and rapid response if a rash develops.	If mild rash, no fever, no oedema, no mucosal lesions, no blistering of skin – use antihistamines (no benefit in steroids). If any of the above, think DRESS or early SJS and refer immediately for more experienced help.	Always give NVP in stages, 200 mg daily for 2 weeks then 200 mg twice daily. Try not to start with CTX at the same time, as this can also cause a similar rash; if both needed, preferably start ART first. Do not prescribe to women with CD4 >250 and men with CD4 >400, as risk of adverse reaction is higher.
Hepatitis Occurs in up to 17% of people on NVP. Occurs in women more frequently than men. Happens at higher CD4; women >250, men >400. Greater risk if underlying liver disease or taking liver-toxic drugs. Occurs in first 6–12 weeks. Can be fatal. Can also be part of DRESS (see **Chapter 20**, Skin diseases).	CD4 essential before starting NVP. ALT ideally done before starting but WHO says not essential. Check ALT only if any symptoms of liver toxicity – nausea, vomiting, abdominal pain, jaundice.	If no symptoms of liver toxicity (nausea, vomiting, abdominal pain, jaundice) and ALT <200, watch closely for new symptoms and repeat ALT in 1–2 weeks. If any symptoms and ALT >120, need to stop drug and evaluate further. See Appendix 4.3. See **Chapter 16**, Liver disease, section on DILI.	Caution if other liver disease or if elevated ALT. Don't use in women if CD4 >250, men >400 as risk of adverse reaction is higher. Don't use for PrEP as CD4 usually high and therefore higher risk of liver toxicity.

Efavirenz (EFV)			
			Elimination: Liver
Side-effects	**Monitor**	**Manage**	**Prevent**
Neuro-psychiatric Symptoms often noted on day 1 and usually settle within 2–4 weeks. Dizziness, sleepiness; abnormal thinking and decreased concentration. Insomnia, agitation; odd dreams, nightmares. 2% can have psychiatric side-effects – depression, mania, psychosis, hallucinations – worse if pre-existing psychiatric illness or substance abuse. Prolonged EFV use can cause ataxia, encephalopathy and loss of weight; reversible on stopping EFV – do not re-challenge; switch to another drug.	Clinical – specifically ask at the first and follow-up consultations.	Encourage patient to persevere with symptoms for the first 2–4 weeks. May need to switch to DTG or possibly EFV 400 if ongoing or if more severe side-effects.	Warn patient before start. Take drug at night. Not with fatty meal, as this increases absorbtion and worsens side-effects. Avoid driving in the first few weeks. Avoid alcohol initially as effects can be worsened.
Rash Maculo-papular Less frequent and less severe (SJS & DRESS rare) Median time is 11 days. See **Chapter 20**, Skin disorders.	Clinical	Give anti-histamines as needed for itch. Rarely discontinue meds. If rash significant, switch to PI or INSTI not NVP.	
Hepatitis Generally less frequent than NVP; can develop more severe EFV toxicity 6–9 months after starting (see **Chapter 16**, section on DILI).	Clinical. Liver function tests only if symptoms develop – nausea, vomiting, abdominal pain, jaundice.	If any evidence of hepatitis, follow same guidelines as for NVP. If switch needed, change to PI or INSTI, not NVP. See also Appendix 4.3 and **Chapter 16**, Liver disease, section on DILI.	

Teratogenicity

Following more detailed data analysis, EFV is no longer considered to place the foetus at higher risk of abnormalities. It is therefore no longer contra-indicated in the first trimester of pregnancy.

Gynaecomastia

Efavirenz tends to cause development of actual breast tissue, as opposed to PIs and d4T, which tend to cause merely increased fat accumulation in the breast, similar to that seen in significantly overweight men.

If troubling the patient, a switch to another drug needs to be made, but not all gynaecomastia reverses.

Protease inhibitors (PI) – Lopinavir (LPV), Ritonavir (RTV), Atazanavir (ATV), Darunavir (DRV)

Class side-effects are:

Nausea, diarrhoea, hepatitis, lipid abnormalities and impaired glucose tolerance.

The LPV/RTV combination has more side effects than ATV- or DRV-based combinations.

ATV/r combination once daily (available as FDC). LPV/r – 2 tabs twice daily. DRV is taken once daily in combination with ritonavir. (No FDC available yet.)	**Elimination:** Liver

Side-effects	Monitor	Manage	Prevent
Ritonavir can cause tingling around the mouth, loss of appetite, taste changes.	Clinical	Little to be done as RTV is essential as a booster for all PIs.	Warn patient before starting drug.
Hepatitis	Clinical Liver function tests only if symptoms develop – nausea, vomiting, abdominal pain, jaundice.	See Appendix 4.2: hepatitis.	Caution if existing liver disease and monitor more closely for symptoms.
Lipid and glucose abnormalities	Ideally lab tests for total cholesterol, triglycerides and fasting glucose before starting ART, and then at 3 months.	Manage according to national NCD guidelines Switch to ATV/r if significant changes since commencing the PI.	
Nausea, vomiting and diarrhoea	Clinical monitoring. Ask about these symptoms in case absorbtion of ARVs is being affected.	Initially try metoclopramide and/ or loperamide and evaluate for other causes of diarrhoea (see **Chapter 15**). If significant and distressing, may need to switch LPV/r to ATV/r.	Warn patient before starting drug.

Atazanavir can cause an asymptomatic jaundice. Patient feels well with no symptoms – nausea, vomiting, abdominal pain.	Clinical If jaundice develops and patient is asymptomatic, check ALT and if possible, bilirubin (total and conjugated) as ATV causes an unconjugated hyperbilirubinaemia).	If asymptomatic and normal ALT, no need to stop ATV unless patient cannot tolerate it. If hepatitis, see management of hepatitis in **Chapter 16**.	Warn patient before starting drug.
Integrase inhibitors – Raltegravir (RAL), Dolutegravir (DTG). **Also referred to as integrase strand transfer inhibitors (INSTIs)**			
Class side-effects are: Nausea, diarrhoea, headache and insomnia. More serious but rare: - Hepatitis with increased risk if HBV or HCV infection - Hypersensitivity reaction.			
DTG once daily vs RAL twice a day			**Elimination:** Liver
Side-effects	**Monitor**	**Manage**	**Prevent**
Dolutegravir Headache and insomnia, also some nausea and diarrhoea	Clinical	Symptomatic relief If hypersensitivity reaction will need to substitute with drug from another class.	Caution in pre-exisiting liver disease Avoid in women and adolescents not on family planning who are not yet pregnant but intending to conceive.
Raltegravir Can cause rhabdomyolysis and renal impairment	Clinical	As for DTG above	Caution in pre-exisiting liver disease

Appendix 4.2 Early and late side effects of ARVs

Important! This is just a quick reference. Please see appendices 4.1, 4.3 and 4.4 for the important details.

Early side effects possible in the first 3 months

Symptom	Think of…	Important actions
Rash	Drug-related cause (NVP, ABC, cotrimoxazole, or TB drugs)	Grade the rash. Treat according to grade.
Nausea	AZT and LPV/RTV frequently cause this If abdominal pain, think of hepatitis	See row below.
Vomiting	Hepatitis PI side-effects	Correct any dehydration. Check ALT. See appendices 4.1 and 4.3 for more detail. Metoclopramide as required if severe.
Abdominal pain	Hepatitis	Check lipase. Check ALT. See appendices 4.1, 4.3 and 4.4 for more detail.
Weight loss	Not a side effect, but probably an undiagnosed OI (TB, chronic diarrhoea).	Investigate, especially for TB. Send stool sample for investigation.
Confusion/ psychosis	Rule out infection and other causes before blaming this on efavirenz.	Refer for lumbar puncture. Consider changing efavirenz to another ARV if no meningitis or other causes found.
Weakness	Anaemia (if on AZT)	Check haemoglobin (Hb).
Fever, constitutional symptoms, cough, sore throat, rash	Hypersensitivity reaction to abacavir (ABC) (See page 43).	If confirmed, stop ABC immediately and never try again. If doubtful, allow the patient to take one more dose and watch closely in the clinic.

Late side effects possible after 3–6 months on ARVs

With the world-wide phasing out of d4T, most of the later onset side-effects are no longer being seen. For those who have patients on d4T, all information on d4T is in Appendix 4.3.

Symptom	Think of…	Important actions
Abdominal pain	Hepatitis, especially due to EFV. Can be severe and usually occurs 6–9 months after starting it	Check ALT and see other appendices for details.
Weakness	Anaemia (if on AZT)	Check haemoglobin (Hb).
Creatinine clearance <50 ml/min	TDF toxicity	After ruling out other causes of acute renal insufficiency (dehydration, sepsis, other nephrotoxic drugs, etc.), change TDF to AZT.

Appendix 4.3 Grading and management of possible side effects to ARVs

Possible drug-related signs and symptoms

Symptoms and diagnoses to consider, plus likely ARVs responsible	Grading of symptoms
Abdominal pain with or without nausea	
NVP TB drugs Cotrimoxazole Consider non-HIV-related conditions	If pain is present due to hepatitis (nausea/vomiting/abdominal pain and tenderness/ jaundice/raised ALT) this needs urgent attention. See management of drug-induced liver injury (DILI) in **Chapter 16.**
Diarrhoea with or without nausea/vomiting	
PIs – LPV/r more than ATV/r	This is a fairly frequent symptom with PIs, especially LPV/r. If it is only once or twice a day with manageable nausea, stay on the same drug and watch. If, however, it is unmanageable by the patient or is causing more than 5–6 stools a day (affecting absorbtion of the drug or dehydration), LPV/r needs to be changed to ATV/r, once other causes of diarrhoea have been excluded (see **Chapter 15**).
Jaundice (patient's skin and eyes go yellow)	
NVP, EFV PIs, specifically ATV/r Also, RIF, INH, PZA Cotrimoxazole	Check ALT and bilirubin. If symptoms – nausea, vomiting, abdominal pain – see assessment and management of hepatitis (**Chapter 16**). If asymptomatic and normal ALT with just elevated bilirubin, may be a benign side-effect of rifampicin or ATV. Seek more experienced guidance.

Symptoms and diagnoses to consider, plus likely ARVs responsible	Grade 1	Grade 2	Grade 3	Grade 4
Nausea and vomiting	**Once per day and/or lasting <3 days**	**<4 episodes per day and not dehydrated**	**Vomits >3 times per day, and dehydrated**	**Dehydrated – too sick for primary care treatment**
NVP-related hepatitis (remember other drugs too – eg TB drugs and cotrimoxazole) AZT PIs, especially LPV/r Need to consider wider range of causes, such as GIT infections, malaria, CNS disease, etc. If patient vomits within 2 hours of taking pills, repeat the dose, as the medication will not have been adequately absorbed.	Check for other symptoms of hepatitis. If present, see management of DILI in **Chapter 16**. If not, reassure patient, but have patient return early if worsens. Consider metoclopramide 10 mg up to 3 times a day, as needed.	Give ORT. Encourage frequent small meals. Give metoclopramide 10 mg up to 3 times a day, as needed. Take blood for ALT and re-assess in 2–3 days.	Give ORT. Give metoclo-pramide 10 mg up to 3 times a day, as needed. Refer to doctor.	Refer to hospital.
Dizziness/ psychological/ psychiatric	**Dizziness only**	**Vivid dreams**	**Mood changes or persistent disturbing dreams**	**Acute psychosis, hallucinations, confused behaviour**
EFV Also consider TB drugs – INH, cycloserine/terizidone	Reassure patient; consider switching to another drug only if persisting beyond 4–6 weeks. Confirm EFV is being taken at night.	Reassure patient. Symptoms usually go away after few weeks. If symptoms persist after 6 weeks, refer or discuss with an experienced clinician.	Confirm EFV is being taken at night and not with fatty foods. Refer to doctor if not settling.	Refer to hospital. Needs fuller psychiatric and neurological evaluation. Only restart ARVs when symptoms have fully resolved (use NVP or DTG instead of EFV).

	Mild	Moderate	Severe
Skin rash	**Can be serious. See section on adverse drug reactions in skin, in Chapter 20.**		
Causes	Red, itchy. No fever and feels otherwise well.	Maculo-papular rash or dry scales. No fever and feels otherwise well.	Blisters or moist loss of skin. Rash involves mucous membranes or eyes, with or without sloughing of skin.
NVP more common than EFV ABC Also consider TB meds Cotrimoxazole	Reassure but have patient return early if worsens. Consider giving chlorpheniramine 4 mg every 8 hours prn or other antihistamine as available, if itch is significant. Check ALT as there may be liver involvement	Give aqueous cream with or without 0.1% betamethasone. Consider giving chlorpheniramine 4 mg every 8 hours prn. Check ALT, and reassess in 2–3 days. Patient to return early if rash worse, or abdominal pain. Consider switch to EFV.	URGENT: Refer to hospital same day. Give chlorpheniramine 4 mg every 8 hours prn or other antihistamine as available. When symptoms have resolved, restart ARVs, using a PI. Never use NVP, EFV ABC or Cotrimoxazole again. Regarding TB drugs see section on skin adverse drug reaction in **Chapter 20**.

Symptoms and diagnoses to consider, plus likely ARVs responsible	**Grading of symptoms**	
Painful or cold feet	**Discomfort ranging from mild to day-and-night symptoms**	**Functional impairment (difficulty walking, etc.)**
Commonly caused by HIV itself or INH. AZT more rarely. If on d4T or AZT, see **Appendix 4.4** for d4T related peripheral neuropathy.	In general, evaluate for possible causes and manage accordingly. Amitriptyline 12.5 – 25 mg nocte can give symptomatic relief. See detailed section in **Chapter 14** on neurological diseases.	URGENT: refer for fuller neurological assessment.

Possible drug-related laboratory abnormalities

Anaemia (low haemoglobin, in gm/dl)	**What is important in diagnosing AZT-related anaemia is if the Hb has dropped since starting it. The columns below refer to an Hb that has dropped since starting AZT. For more detail see Chapter 18 on haematology.**		
Causes	8–9.4	6.5–7.9	<6.5
AZT Cotrimoxazole	Take history and examine patient to rule out bleeding, or a new problem, especially TB. If no problem, continue ARVs. Recheck Hb in 2 weeks.	Take history and examine patient to rule out bleeding, or a new problem, especially TB. Consider referral for fuller assessment. Stop AZT. If less than 6 months on ART, can change to TDF without first checking viral load.	Refer to hospital for fuller assessment. Stop AZT. If less than 6 months on ART, change to TDF without first checking viral load.
Dropping creatinine clearance	**What is important in diagnosing TDF-related renal toxicity is if the creatinine clearance has dropped since starting TDF.**		
Causes	Creatinine clearance >50 ml/min	Creatinine clearance 30–50 ml/min	Creatinine clearance <30 ml/min
TDF	Continue TDF	Check for urine infection. Recheck creatinine after 1 week. If persistent, substitute TDF, preferably with ABC. Check hep B status (see next column). Evaluate the cause of the renal disease and adjust NRTI doses (see **Chapter 7**, renal disease).	Stop TDF. If hep B positive, as TDF is an essential drug in the management of hepatitis B, seek more experienced help in managing this.
Elevated ALT	**As ALT is not routinely measured, these abnormalities will rarely be noticed. This guide is for the occasions when an ALT has been sent off because of some concern about liver disease.**		
Causes	ALT 50–120	ALT 120–200	ALT >200
NVP more commonly than EFV. Also consider TB meds or cotrimoxazole. Also alcoholic liver disease, hep B & C.	Continue ARVs, but recheck ALT in 1 month. Check HepBsAg and consider other causes of liver disease (e.g. hep C, alcohol-related).	If nausea, vomiting, abdominal pain or jaundice, refer or seek more experienced help. If no symptoms, continue ARVs and check ALT again after 2 weeks.	Urgently refer or seek more experienced help.
High cholesterol, triglycerides & glucose	**In ideal circumstances a fasting lipogram and glucose should be done before starting a PI and then repeated at 3 months.**		
PIs	The PIs are known sometimes to cause disorders of lipid and glucose metabolism. If the levels rise to those considered unacceptable according to national NCD guidelines, the first step is to change LPV/r to ATV/r, as this has a lesser effect on lipid and glucose profiles. If it remains high, follow the routine (non-HIV) national guidelines. If on a PI, simvastatin is contraindicated and can be substituted with pravastatin or atorvastatin.		

Appendix 4.4 DDI and d4T

DDI is no longer used around the world and d4T is being rapidly phased out. The information about these drugs is, therefore, for reference purposes for those clinicians who may still be encountering patients on d4T. If anyone is still on d4T and/or DDI, every effort should be made to change patient to another NRTI.

General

Both drugs have a similar side-effect profile, featuring 2 key components.

- They have relatively few side-effects in the first 6 months of use. After 6 months to several years of use, significant side-effects start to appear.
- They arise from toxicity to the mitochondria, which results in a combination of specific side-effects.

Neurological

They are well known to cause a peripheral neuropathy, usually presenting with symptoms of numbness, tingling or of feeling cold in the feet. (See also section on peripheral neuropathy in **Chapter 14.**)

Liver

Hepatic steatosis is the most common manifestation, presenting with various elevations of liver enzymes.

Pancreatitis

DDI is the commonest cause, but d4T can also cause it.

It presents in the usual way with severe abdominal pain, nausea and vomiting. This can be life-threatening and needs urgent attention. These patients need admission to hospital for confirmatory tests (amylase or lipase) and for inpatient management.

Lipodystrophy

There are 2 main types.

1. Lipo-hypertrophy (fat accumulation in specific sites, usually abdomen, breasts and back of neck). This is more commonly associated with the PIs.
2. Lipo-atrophy:
    - Lipo-atrophy is a well recognised side-effect of d4T and DDI, usually starting after 6 months or more on it. It is one of the many manifestations of mitochondrial toxicity noted with DDI, d4T, and to a lesser extent, AZT.
    - There is a decrease in fat in the tissues of the face, buttocks and limbs.
    - It can be very disturbing and stigmatising for the patient, which can impact negatively on adherence.

- Management is essentially changing the offending drug to one that is far less likely to cause the same condition (TDF or ABC). As always, ensure that the patient is virally suppressed before changing just one drug. (See **Chapter 6**, section 9 on managing high viral loads.)

  Unfortunately, there is no guarantee that the atrophy will reverse on stopping the medication. It is, therefore, important to diagnose this condition early and make a drug switch as soon as possible.

Metabolic: Hyperlactataemia

This potentially dangerous, life-threatening side effect starts with an asymptomatic elevation of lactic acid, progressing to mild symptoms of weight loss, nausea and abdominal pain and progressing to lactic acidosis, which can be rapidly fatal.

Symptomatic hyperlactataemia and lactic acidosis

This side effect has become less common, with fewer patients starting ART with d4T and with the use of lower doses. However, clinicians should remain vigilant in patients receiving d4T and be aware that this side effect can occur with all other NRTIs, although very rare with ABC, TDF, 3TC and FTC. Mildly elevated lactate is not uncommon in patients treated with NRTIs, but is generally asymptomatic. Asymptomatic elevated lactate does not predict the development of lactic acidosis; it is therefore unnecessary to monitor levels in asymptomatic patients.

The potential of NRTIs to cause elevated lactate varies (from most likely to least likely):

stavudine/didanosine > zidovudine > tenofovir/emtricitabine/lamivudine/abacavir.

Lactic acidosis is a serious, rare, potentially fatal side effect of NRTIs, most commonly associated with d4T, particularly when combined with DDI. Symptomatic hyperlactataemia without acidosis is more common, but seldom seen with the safer NRTIs recommended. (See Algorithm 4.1 on next page.)

High lactic acid might also be caused by any situation of circulatory or respiratory failure (e.g. shock, severe infection, severe pneumonia). All these conditions have to be detected early and managed appropriately in order to prevent mortality.

Algorithm 4.1 Risk factors and treatment for hyperlactataemia

The combination of d4T and DDI is associated with a high risk of symptomatic hyperlactactaemia or lactic acidosis (particularly in pregnancy). This combination should therefore be avoided. Symptoms are non-specific and include nausea and vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

Risk factors and management for hyperlactataemia include:

- female gender
- obesity
- the use of NRTIs for >6 months
- the development of NRTI-induced peripheral neuropathy or fatty liver.

A raised lactate of >5 mmol/l together with metabolic acidosis confirms the diagnosis of lactic acidosis.

Low serum bicarbonate (<20 mmol/l) is the most sensitive marker of acidosis. Associated abnormalities include elevated ALT and AST, lactate dehydrogenase and creatinine kinase. Treatment is supportive. High-dose riboflavin (50 mg) and L-carnitine may be used (no evidence for either intervention). Management depends on the lactate and bicarbonate concentrations.

Lactate <5 mmol/l and bicarbonate >20 mmol/l and minor symptoms.

NRTIs should be switched to agents less associated with hyperlactataemia: TDF or ABC (if these are unavailable, then AZT could be used) plus FTC or 3TC. Symptoms and serial lactate should be monitored for several months (lactate levels decrease slowly over weeks).

Lactate >5 mmol/l and bicarbonate >15 mmol/l.

NRTIs should be discontinued and the patient should be admitted. If the patient is on an NNRTI regimen, a boosted PI should be added. If the patient has already failed an NNRTI and is on a boosted PI, RAL and/or etravirine (ETV) should be added, if available, or the patient should be continued on the boosted PI only. When lactate has normalised, the patient should be switched to TDF or ABC with 3TC or FTC, as above.

Lactate >5mmol/l and bicarbonate <15 mmol/l.

NRTIs should be discontinued and the patient should be admitted, preferably to an intensive care unit. If the patient is on an NNRTI regimen, a boosted PI should be added. If the patient has already failed an NNRTI regimen and is receiving a boosted PI, RAL and/or ETV should be added, if available, or the patient should be continued on a boosted PI only. Bicarbonate replacement is controversial, but most experts would use this strategy to partially correct severe acidosis. Broad-spectrum antibiotics are recommended, as sepsis can mimic NRTI-induced lactic acidosis (this can be discontinued if procalcitonin is normal). On recovery, all NRTIs should be avoided in future regimens (some experts would be prepared to use safer NRTIs, as above).*

* For further guidance: Southern African HIV Clinicians Society. 2006. 'Guidelines for the prevention, diagnosis and management of NRTI-associated symptomatic hyperlactataemia and lactic acidosis'. *Southern African Journal of HIV Medicine* 7: 8-15.

CHAPTER 5

Follow-up of the patient on ART and IRIS

Follow-up consultation

Immune Reconstitution Inflammatory Syndrome

Summary: follow-up of patients on ART

Please note that this topic is covered more fully in the **SAMU HIV/TB E-Learning course**. See ‘How to use this book’ for more details.

Follow-up consultation

Follow-up consultation needs to cover 6 key areas:

- Evaluating the status of the HIV infection (are the ARVs doing their job?)
- Monitoring for side effects of the ARVs
- Following up known illnesses
- Addressing the patient’s current concerns and checking for new illnesses
- Identifying the patient with advanced disease
- Evaluation of adherence

Evaluating the status of the HIV infection (are the ARVs doing their job?)

The foundation of the entire management of HIV is to ensure that the patient takes effective ARVs on a long-term basis in such a way that they stop the reproduction of the virus. Two tests are done to evaluate this, the CD4 count and the viral load (VL). All WHO and national guidelines have specific recommendations regarding when the tests need to be done and how to interpret them. In summary:

- The CD4 informs us regarding the level of immunity.
- The viral load tells us the degree to which viral replication is happening. A detectable level tells us that either the drugs are not being taken optimally or they are not working (resistance has developed).

This is covered in detail in **Chapter 6**.

Monitoring for side effects of the ARVs

WHO guidelines

Refer to your national guidelines

WHO recommends the following monitoring tests for patients receiving ART (as always, consult your **national guideline**, as this may differ in some areas from WHO):

Table 5.1 Monitoring tests for patients receiving ART

Test	Recommendation	Comments
Viral load (VL)	First test 6 months after starting, then at 12 months, then annually thereafter.	However, if the VL is >1 000, the recommendations for VL testing change[1].
CD4 cell count	Before starting ART, 6 months after starting, and then no longer necessary once the patient is stable on ART[2]. If VL is not available, the CD4 remains an essential monitoring tool and needs to be done 6 monthly.	CD4 count is far less sensitive for detecting poor adherence and treatment failure, so is used only when VL testing is unavailable.
Serum creatinine	No specific recommendation.	If creatinine testing is available, it is useful for detecting TDF toxicity. Ideally, it should be done at months 1, 4 and 12 and then annually thereafter.
Full blood count (FBC) or haemoglobin (Hb)	No specific recommendation.	If Hb or an FBC is available, it is useful for testing for AZT-induced bone marrow suppression. As this is usually an early effect, it should ideally be done at months 1, 2, 3 and 6, and no longer after that.
ALT	No specific recommendation.	Routine use of ALT for monitoring for nevirapine (NVP) toxicity is not necessary. ALT is tested only if there are signs of NVP toxicity (skin rash or hepatitis).
Pregnancy test	Only for females of child-bearing age, not receiving family planning and on treatment with dolutegravir or low dose (400 mg) efavirenz.	EFV 400 has not yet been proved safe in pregnancy.
Fasting cholesterol and triglycerides	No specific recommendations but the ideal would be to check these at month 3.	Lopinavir is known to increase both cholesterol and triglyceride levels.

Notes

1. See **Chapter 6** for a comprehensive approach to the management of the patient with possible treatment failure.
2. WHO defines people as being stable on ART according the following criteria: On ART for at least one year, no current illnesses or pregnancy, good understanding of lifelong adherence and evidence of treatment success (2 consecutive viral loads below 1 000).

As noted in earlier chapters, each ARV has the potential for specific side effects. Certain tests are recommended in the guidelines (see Table 5.1) to try and detect these side effects early. Others may only be identified when a patient complains of symptoms or a clinician asks about a specific symptom.

Chapter 4 is designed to help with an approach to these.

Following up known illnesses

Following up of known illnesses is self-explanatory, as it refers to the management of existing known illness that require ongoing attention. This may be HIV-related (e.g. anaemia, a specific side effect, TB, etc.) or not HIV-related (e.g. hypertension, diabetes. etc.).

Addressing the patient's current concerns and checking for new illnesses

As in any consultation, the patient's concerns need to be addressed. These may reveal a drug side effect or a new illness, related or unrelated to HIV. Look for new illnesses that may indicate worsening immunity: in particular, TB and any new stage four disease, as this points towards the development of treatment failure.

Chapter 6 deals with treatment failure in more detail.

Identifying the patient with advanced disease

While addressing the patient's current concerns and checking for new illnesses, the clinician may find specific features that identify a patient as having advanced disease. In 2017, WHO defined advanced disease in the adolescent or adult as anyone presenting with a CD4 count <200 or with a new stage 3 or 4 disease. Advanced disease is associated with a higher mortality, so patients in this category require a more specialised package of care. See **Chapter 11** for detailed guidelines.

Evaluation of adherence

While much of the counselling and adherence support is done by the counsellors, the clinician needs to play an oversight role in the ongoing assessment of the patient's adherence to treatment. This involves a brief, non-threatening question regarding adherence at each visit, and if any concerns are noted, engagement with both the patient and the counsellors.

See **Chapter 25** for more detail.

Prompted stationery or a checklist for follow-up of the patient on ART

As with the initial assessment of a patient, with the clinician having to remember many different things to do, it is recommended that a checklist or prompted stationery is used to ensure that all the areas for follow-up are covered.

One example of such a checklist is provided here as a template and to explain the key elements of a follow-up consultation. (Note: This document is ideally printed in landscape format on A3 paper but can be split into smaller units on A4 pages. It can be downloaded from the **SAMU website** from the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018) A consultation is represented by each of the 5 columns. For the purpose of explanation in this chapter, sections of the stationery are shown along with explanatory notes:

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Example checklist: Top part

Folder No:			Date	
			N/D (name of nurse or doctor)	
Weight/ Temp			Weight:	Temp:
PAST HISTORY	TB details	Past TB	Details:	
		Current TB	Dx	Start date
			Regimen	Phase IP CP
		IPT	Y N Date started	
		TB screen	Cough Night sweats Fever Nodes	
	HIV	Time on ART	Months on ART	Months on regimen
		Latest HIV bloods	Last CD4: / /	Last VL: / /
			Result	Result
	PROBLEM LIST - NEW AND ONGOING		1	
			2	
			3	
			4	
			5	
	Condoms FP		Condoms	FP

- **Weight** is an essential examination that must be done at every visit. Loss of weight, or failure to gain weight in a child, is an important marker of illness, especially TB. Having 5 consecutive weights across the page gives a good picture of the patient's overall condition.
- **Temperature**, especially between 37 and 38 degrees is often missed in the examination.

Past history

- **TB details**: This includes not only the past history but also provides space for a brief review of current TB being treated. As this information is often recorded on separate stationery, it is sometimes missed. If the patient does not have active TB, he/she should be on IPT (**Chapter 12**). This entry on the card provides an opportunity to attend to this. There is also a slot here to ensure that TB is screened for at every consultation.
- **HIV information**: Every consultation with an HIV-positive patient must include a review of the patient's current immune status and the effectiveness of the ART. This means actively looking for and noting the most recent CD4 count and viral load (VL) and ordering the next tests if they are due. In addition, as you note the ARV regimen, look at previous consultations for the routine blood tests that should be done.
- **Problem list**: This is an opportunity to note from previous consultations any ongoing illnesses or problems, such as: NCDs, active TB, recent cryptococcal meningitis and still on fluconazole, a side effect being monitored, anaemia, etc. Viewing this list ensures that nothing is overlooked.

Example checklist: Middle part

TODAY	Condoms FP	Condoms FP	C
	STI Pap	STI Pap	S
	HISTORY		
	EXAM		
	ASSESSMENT		
	PLAN including referral		

Today's consultation

Routine checks

- Do a routine check on condom use and family planning (and provision of it if needed).
- Do a routine screen (in every consultation) for STIs and a check that cervical screening is up to date according to national guidelines and that the result has been found and noted in the patient's records (see **Chapter 19**).

Example checklist: Bottom part

PLAN	CD4	Barcode		
	Viral load			
	ALT			
	Hb/WCC/Plt			
	Creatinine			
	Other			
TREATMENT	Counselling Psychosocial			ARV stop code
	ARV 1			
	ARV 2			
	ARV 3			
	TB/other			
	TB/other			
	TB/other			
	Other			
	Other			
	Cotrimoxazole			
	TB prophylaxis			
	Fluconazole			
	Date of next visit			
	Signed (Initialed)	Clinician	Data capturer	

Treatment plan

Next is a space for noting the present complaints, reviewing anything noted above in the notes made so far, and noting examination findings and the start of the management plan.

This list guides the rest of the management plan:

- Ordering specific tests as needed;
- Referral for counselling;
- Prescribing medications: ART, prophylaxis, other chronic medication and acute meds that may be required on the day; and
- Scheduling the follow-up visit.

Evaluation of adherence

Please note that any side effects not identified and addressed are likely to affect adherence. See Chapter 25 for additional counselling guidelines.

Example consultation sheet: Showing first two consultation columns

Folder No:			Date N/D (name of nurse or doctor)	Date N/D
Weight/ Temp			Weight: Temp:	Weight: Temp:
PAST HISTORY	TB details	Past TB	Details:	Details:
		Current TB	Dx Start date Regimen Phase IP CP	Dx Start date Regimen Phase IP CP
		IPT	Y N Date started	Y N Date started
		TB screen	Cough Night sweats Fever Nodes	Cough Night sweats Fever Nodes
	HIV	Time on ART	Months on ART | Months on regimen	Months on ART | Months on regimen
		Latest HIV bloods	Last CD4: / / | Last VL: / / Result | Result	Last CD4: / / | Last VL: / / Result | Result
	PROBLEM LIST - NEW AND ONGOING		1 2 3 4 5	1 2 3 4 5
TODAY	Condoms FP		Condoms FP	Condoms FP
	STI Pap		STI Pap	STI Pap
	HISTORY EXAM ASSESSMENT PLAN including referral			
PLAN	CD4		Barcode	Barcode
	Viral load			
	ALT			
	Hb/WCC/Plt			
	Creatinine			
	Other			
TREATMENT	Counselling Psychosocial		ARV stop code	ARV stop code
	ARV 1			
	ARV 2			
	ARV 3			
	TB/other			
	TB/other			
	TB/other			
	Other			
	Other			
	Cotrimoxazole			
	TB prophylaxis			
	Fluconazole			
	Date of next visit			
	Signed (Initialed)		Clinician | Data capturer	Clinician | Data capturer

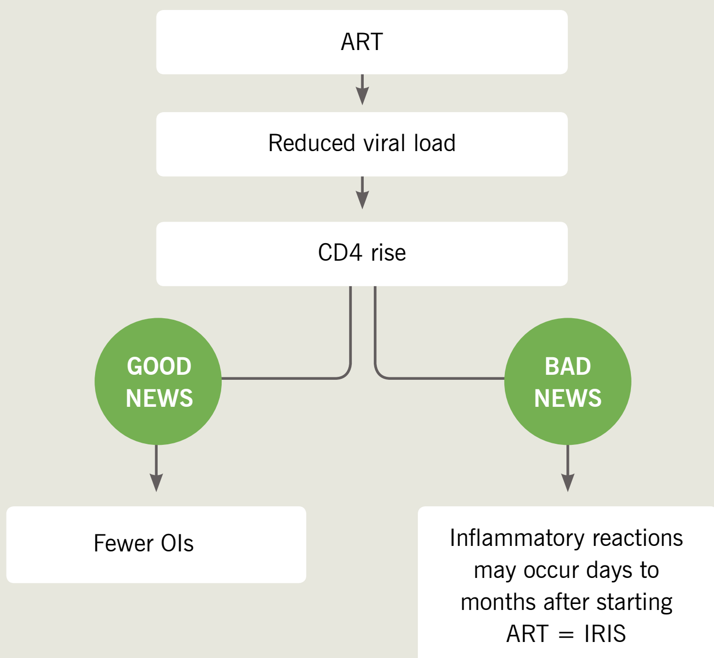
Immune Reconstitution Inflammatory Syndrome

What is Immune Reconstitution Inflammatory Syndrome (IRIS)?

IRIS is an ART-related condition, occurring within the first few days, weeks or months after starting ART. It therefore needs to be recognised when it presents in early follow-up consultations after starting ART or when changing to a new regimen after treatment failure.

On starting ART there is usually a rapid drop in viral load, along with an equally rapid initial rise in CD4 count. With the latter, there is an upward surge in immunity, which results in the body's dormant inflammatory responses suddenly waking up. This has both advantages and disadvantages. The immune restoration does what we want it to do – it decreases the chance of developing OIs. However, the disadvantage is that some patients show clinical deterioration after ART (see Figure 5.1).

Figure 5.1 Consequences of a rapid CD4 rise



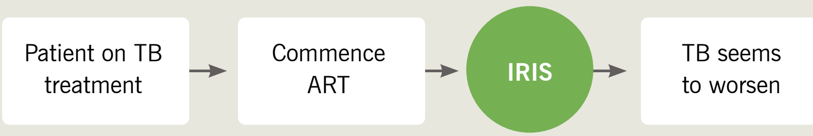
Two main types of IRIS

The two main types of IRIS are paradoxical and unmasking IRIS. Essentially, they are a manifestation of the same process, but are named differently because of the way they present.

Paradoxical TB IRIS

Where one would expect the patient's condition to improve after starting treatment, it paradoxically gets worse.

Figure 5.2 Paradoxical TB IRIS

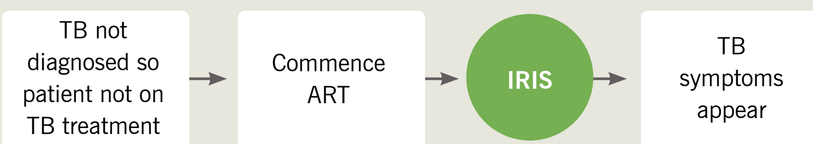


- On average, it occurs in 15–20% of TB cases.
- It usually appears within the first 3 months of starting ART, any time from the first 48 hours.
- It usually lasts 2–3 months, though some patients have prolonged IRIS, lasting many months (TB pus collections, including psoas abscesses, lymph nodes – peripheral and abdominal – and tuberculomas).
- Morbidity is common but mortality is rare. When death occurs due to IRIS, it is usually in neurological conditions, such as cryptococcal and TB meningitis (this is the reason for delaying ART for 4 weeks, to decrease the chance of developing a serious IRIS. See section on correct timing of commencement of ART, page 70.

Unmasking TB IRIS

The patient has not been diagnosed with TB because it has been missed; there were just very mild symptoms or there was subclinical disease. Due to the rapid immunological recovery after starting ART, the features of the quiescent TB are **unmasked**.

Figure 5.3 Unmasking TB IRIS



What are the signs and symptoms of IRIS?

IRIS typically presents with symptoms and signs reflecting the increased inflammatory response. It therefore often looks exactly like a deterioration of the existing condition, or the development of a new illness. For example, lymph nodes are often hot, red and tender, and misdiagnosed as TB abscesses. Fever and tachycardia are common, often prolonged, and may be the only features of IRIS.

Which conditions commonly cause IRIS?

- IRIS is commonly seen with TB and cryptococcal disease and can have serious consequences with neurological manifestations of these conditions, especially cryptococcal and TB meningitis.
- Though seen less frequently, IRIS is also seen with other conditions caused by mycobacteria, fungi and viruses. It is also recognised in common skin conditions (acne, folliculitis, molluscum contagiosum and warts) as well as in Kaposi's sarcoma.

What predisposes patients to IRIS?

There are three key factors:

1. A low CD4 count. A very low CD4 count usually results in a proportionately higher rise in immunity when a patient starts ARV treatment. For example, a CD4 rise from 10 to 100 represents a far more dramatic rise in immunity than one from 210 to 300.
2. A high organism load. As one would logically expect, the higher the volume of infecting organism, the more there is going to be an inflammatory response to it.
3. A short gap between starting treatment for the infection and commencing ART may cause paradoxical IRIS. This is a logical combination of the first 2 points. If ART is started within a few days of starting antimicrobial treatment, the volume of infecting organisms will still be high and the rapid rise in immunity is more likely to cause IRIS.

Since TB IRIS is the commonest manifestation of IRIS and where most of the research has been done, TB IRIS is the focus of this section of **Chapter 5**. Cryptococcal IRIS is covered in **Chapter 14** and for the many other conditions in which IRIS occurs, the principles of pathophysiology, diagnosis and treatment are very similar.

How does TB IRIS manifest?

It can be worsening of the original symptoms or new symptoms of the same disease.

- Worsening night sweats, fever and weight loss;

- Worsening examination findings clinically and on chest radiology – increased lung infiltrates and cavitation;
- Fever and tachycardia, systemic signs of inflammation, are common these may sometimes be the only manifestations of IRIS and are important to consider in a patient with fever recently starting ART (see **Chapter 23**);
- Intra-abdominal TB:
    - Enlarging lymph nodes seen on ultrasound or CT scan;
    - Abscess formation – e.g. psoas;
    - Worsening ascites;
    - Liver involvement – enlarged, tender liver and elevated enzymes (ALP and GGT often proportionately higher than the AST and ALT) (see detail re interpretation of liver enzymes in **Chapter 16**); and
- Neurological symptoms that worsen due to worsening of TB in the brain or spinal cord. This ranges across the spectrum of neurological manifestations of TB: meningitis, tuberculomas, cord pathology. In various studies this has been shown to have a mortality rate of up to 25%.

How do you diagnose TB IRIS?

(The following approach is presented for the diagnosis of paradoxical TB IRIS but the same principles apply to unmasking TB IRIS, as well as to IRIS related to other conditions.)

The starting point for a diagnosis is to think about IRIS in the first place.

> Have a high index of suspicion for IRIS in any patient developing new symptoms in the first few months of starting ART.

There is no diagnostic test for IRIS, so once IRIS is being considered, diagnosis is made by running through this checklist:

1. Was the diagnosis of TB confirmed when TB treatment was initiated?*
2. Was there initial improvement on TB treatment prior to starting ART?
3. Is the onset of new symptoms within 3 months of starting ART (typically within 1–3 weeks)?
4. Are there worsening signs and symptoms of TB?
5. Have I excluded other possible diagnoses?
    - DR TB*
    - Other OIs, including malignancy*.

* In different settings, especially those with limited resources, these list items cannot always be confirmed with certainty. A degree of clinical judgment and pragmatism therefore needs to be applied.

Differential diagnosis for different manifestations of TB IRIS

While not an exhaustive list, it will be helpful to consider and look for the following conditions before diagnosing TB IRIS (Table 5.2):

Table 5.2 Differential diagnosis for TB IRIS

Presentation	Differential diagnosis
pulmonary infiltrate	bacterial pneumonia PCP Kaposi's sarcoma
pleural effusion	bacterial empyema Kaposi's sarcoma
meningitis	bacterial cryptococcal
new neurological presentation	toxoplasmosis cryptococcoma CNS TB
fever with general deterioration	Bacterial sepsis non-tuberculous mycobacteria lymphoma or Kaposi's sarcoma
lymph node enlargement	lymphoma Kaposi's sarcoma Castleman's disease

How do we treat IRIS?

Treatment of TB IRIS

(Note: The management of cryptococcal IRIS is more complex and is covered in **Chapter 14.**)

Considering that ART has caused a rapid rise in immunity, leading to IRIS, it would be logical to think that a solution would be to stop ART. However, this is very rarely done. Patients need ART, so if they are stopped, a decision will need to be made to restart very soon and IRIS will occur again. Very occasionally, if there is severe neurological IRIS, ART is stopped but this decision is made only for very sick patients in hospital.

Once IRIS has been diagnosed, the question is essentially whether to add steroids or not. This decision is made by weighing up the merits in each situation, based on the following evidence:

- For life-threatening IRIS (neurological, cardiac tamponade, respiratory failure) the consensus is to give steroids (this decision will, however not be made in an outpatient setting).

- For moderate IRIS (non-life-threatening, but severe enough for the patient to need hospitalisation or frequent clinic appointments), steroids have been shown to decrease duration of hospitalisation and the number of outpatient procedures. They have, however, not been shown to decrease mortality from IRIS. (Mortality is rare in patients with moderate TB IRIS.) **In these patients, steroids essentially make the patient feel more comfortable by treating the symptoms.**

Potential risks of steroids:

- Strongly contra-indicated in Kaposi's sarcoma (KS), as steroids can significantly worsen the condition, sometimes fatally. Even if KS IRIS develops, don't give steroids.
- Herpes virus conditions can be re-activated or worsened.
- Undiagnosed DR TB can be worsened.
- Diabetes control can deteriorate.

If steroids are used, the recommendation is prednisone 1.5 mg/kg/day for 2 weeks, followed by 0.75 mg/kg/day for another 2 weeks.

Occasionally the symptoms flare up again after stopping the steroids or reducing the dose, in which case the merits of restarting them are weighed up as before. Prolonged IRIS is most commonly seen in lymph node IRIS, often with suppuration. The treatment is to aspirate peripheral lymph nodes to decrease pain or discomfort, sometimes repeatedly over several weeks or months. Psoas abscesses need to be drained in hospital. Prolonged steroids for up to 4 months may be necessary.

Treatment of unmasking IRIS

- Treat the opportunistic infection.
- Continue ART; do not stop it.
- Drain any collections.
- Steroids may be used for prolonged, severe or neurological manifestations. Decisions are made on a case-by-case basis, as there have been no randomised control trials for unmasking IRIS.

Prevention of IRIS

There are two evidence-based interventions:

1. Correct timing of the commencement of ART after starting treatment of specific infections

With cryptococcal meningitis and all manifestations of TB, the development of IRIS has been shown to be linked to a combination of the CD4 count and the timing of the commencement of ART after starting treatment for the infections. Evidence-based guidelines have been developed for this and are as follows:

TB:

- If CD4 <50, start ART within 2 weeks after starting TB treatment.
- If CD4 >50, the start of ART can be delayed up to 8 weeks after starting TB treatment; however, in practice ART is started within the first 2–4 weeks of starting TB treatment. The closer the CD4 to 50 the closer to 2 weeks ART is started.
- If TB meningitis, delay the start of ART by 4 weeks, as higher mortality has been shown if ART is started sooner.

Cryptococcal meningitis:

- Regardless of CD4 (which is usually low, anyway) the commencement of ART needs to be delayed by 4 weeks (in general) after the start of treatment. Following very severe disease, the commencement of ART can be delayed up to 6 weeks.

2. The role of steroids in preventing IRIS

Steroids may have a role in preventing IRIS. A recent study (PredART) has shown a reduced incidence of IRIS for ambulatory patients with TB and CD4 counts <100, when moderate dose prednisone was started at the same time as ART. In the coming years, with further studies, this is likely to develop into standard protocols for patients who are at higher risk of developing IRIS.

This has particular relevance in the timing of steroid use in patients with TB meningitis (TBM) who have not yet started ART. The standard management of TBM includes the addition of prednisone for the first 4 weeks of TB treatment. The end of steroid use is the exact time when ART is started, which, in turn, is the time when the risk of IRIS increases. It has been common practice, therefore, to extend the use of the steroid for another 2 weeks to decrease the likelihood of this occurring. This study now provides a stronger evidence base for using steroids prophylactically in this way.

Key points – IRIS

- IRIS usually presents as a worsening of an existing condition, a new manifestation of the same disease or a new infection presenting in the first few months after starting ART.
- As there is no diagnostic test for it, it is diagnosed firstly, by having a high index of suspicion in the above circumstances, followed by a careful check for other conditions that may be causing the symptoms.
- The outpatient management of IRIS is essentially symptomatic and close observation.
- Steroids have been shown to be of benefit for moderate IRIS. Because there can be adverse effects of high-dose steroids, ensure regular follow-up by an experienced clinician at primary care.
- To decrease the incidence of IRIS, it is important to adhere to the guidelines for the timing of the commencement of ART following cryptococcal meningitis and TB in all its forms.

Summary: Follow-up of patients on ART

There are several different areas that need focused attention in the follow-up consultations of an HIV-positive patient on ART:

- Evaluating the status of the HIV infection (are the ARVs doing their job?);
- Monitoring for side effects of the ARVs;
- Following up known illnesses;
- Addressing the patient's current concerns and checking for new illnesses, including IRIS;
- Identifying and appropriately managing the patient with advanced disease; and
- Evaluation of adherence.

As with the first visit, it is not easy to remember all these areas, so it is recommended that the clinician uses either a checklist or prompted stationery to ensure that no steps are omitted.

CHAPTER 6

Managing possible ART failure

1. How does an ART regimen fail?
2. What is the best way to monitor the effectiveness of ART?
3. How is treatment failure defined?
4. Do all clinical, immunological or virological abnormalities mean treatment failure?
5. How do I interpret and manage a high viral load result?
6. Why is it important to act on diagnosed treatment failure without any further delay?
7. Who is responsible for a patient presenting with a high viral load: the patient, clinician or health system?
8. How do I switch a patient to a second line regimen?
9. What are the principles of single drug switches?
10. What special care needs to be taken with ART in managing a patient with hepatitis B?
11. How do I manage a patient presenting with high viral loads on a PI-based regimen?
12. What are the principles of using genotypes?
13. How does one build a third line regimen?

Summary

Please note that this topic is covered more fully in the **SAMU HIV/TB E-Learning course**. See ‘How to use this book’ for more details.

The management of possible failure is one of the key challenges of the 2010–2020 decade. This chapter will cover enough detail for the outpatient clinician to do so effectively. For those who wish to further their training in this area, references are made to additional resources.

In this chapter we will answer the following key questions:

1. How does an ART regimen fail?
2. What is the best way to monitor the effectiveness of ART?
3. How is treatment failure defined?
4. Do all clinical, immunological or virological abnormalities mean treatment failure?
5. How do I interpret and manage a high viral load result?
6. Why is it important to act on diagnosed treatment failure without any further delay?
7. Who is responsible for a patient presenting with a high viral load: the patient, clinician or health system?
8. How do I switch a patient to a second line regimen?
9. What are the principles of single drug switches?
10. What special care needs to be taken with ART in the management of the patient with hepatitis B?
11. How do I manage the patient presenting with high viral loads on a PI-based regimen?
12. What are the principles of using genotypes?
13. How does one build a third line regimen?

High viral load management algorithm

At the end of the chapter is an algorithm that guides the clinician through the steps to be taken in the management of the high viral load.

1. How does an ART regimen fail?

The natural history of HIV in the body is (broadly speaking) as follows:

The virus invades the CD4 cell, turns it into a virus-making factory, which, in turn, causes the viral load to increase.

→

After a while the infected CD4 cells start to die, resulting in a drop in CD4 count.

→

With the progressive drop in CD4 count, the immunity drops, resulting in increasingly severe opportunistic infections.

Taking effective ART reverses this whole process, resulting in the viral load dropping, followed by the CD4 rising, and, with time, a progressive reduction in severity and frequency of OIs.

If the ARVs are stopped, the situation again reverses. The logical solution would be to take the ARVs again, ensuring that they are taken regularly, in the correct dose. This sometimes works, but unfortunately it is more complicated than this because anything that causes ARV blood levels periodically to drop below therapeutic blood levels can lead to the development of **resistance**. If resistance has developed, even if the ARVs are taken properly, they won't reverse the process.

Resistance develops by an accumulation of mutant viruses that are resistant to particular ARVs. Once a mutant virus has been allowed to grow into a sizeable population it remains in the body forever (it is '**archived**'), resulting in permanent resistance to that particular ARV.

If a cluster of mutant viruses has developed that are resistant to all three ARVs, that full regimen will no longer work, regardless of how well the patient takes them. We then refer to this as **treatment or regimen failure**, for which there is only one solution; to change to a new regimen of effective drugs.

These mutant viruses, often referred to by their mutations (e.g. M184V, K65R) can all be detected by a specific test called a genotype. It is, however, not necessary to know their names, or even understand how mutations work, in order to effectively manage treatment failure. How we detect and manage resistance is the subject of much of the rest of this chapter.

How good must adherence be to prevent resistance developing?

Unfortunately, there is very little room for error in the taking of ART. The adherence needs to be more than 95%, which effectively means no more than two mistakes a month.

What is a mistake?

- With the commonly used combination of TDF+ 3TC+ EFV or TDF+ 3TC+DTG, a mistake is a delay of over 12 hours.
- With AZT and the PIs a mistake is a delay of over 2 hours.

The dangerous situation for the development of resistant mutant viruses is when the virus is able to reproduce in the presence of a sub-therapeutic blood level of ARV. Therefore:

- If the ART is taken 50–90% of the time, the level of ART in the blood rarely rises to a level that completely suppresses all viral replication. In addition, ART is not stopped long enough for the drug to fully leave the blood stream. This combination, therefore, means that the existing viral population is almost constantly exposed to sub-therapeutic levels of ART. This is worst for developing resistance. In earlier years of ART management, clinicians were taught to 'cover the tail'. This is not a concern for patients on TDF, 3TC and EFV/NVP: see box on page 400 in skin ADR section.
- If the ART is taken only 10–20% of the time, while the level is unlikely ever to be therapeutic, it will, however, frequently drop so that there is no ART in the blood at all. For some of the time the virus replicates without any ART in the blood at all, thus lowering the likelihood of the development of mutant viruses. Though, of course, this scenario is not at all ideal, the chance of developing resistance with 10–20% adherence is actually lower than 50–90% adherence.
- Following this logic, stopping ARVs all at once and not restarting is unlikely to lead to the development of resistance. In earlier years of ART use clinicians were taught to 'cover the NNRTI tail'. See detail on page 400.

Taking an ART history is, therefore, always important when evaluating a high viral load, as it helps evaluate the likelihood of the development of resistance.

Resistance develops at different times for different ARVs

HIV becomes resistant to different ARVs at different speeds.

- Fairly quickly (within a few months) to specific NRTIs: (TDF, 3TC, ABC) and the two commonly used NRTIs (EFV and NVP) and RAL;
- More slowly to the thymidine analogue NRTIs, (drugs ending in 'T' – AZT and d4T) which take 6–12 months; and
- Far more slowly to the PIs, to which resistance rarely develops in less than 12 months, often taking longer.
- The development of resistance to DTG takes the longest of all.

There are many causes of decreased blood levels of ARVs

The commonest cause is poor adherence by the patient. Contrary to common belief, this is largely not the patient's fault, nor is the problem solved by being angry and judgmental. How to deal with the patient not adhering properly is addressed more comprehensively in **Chapter 25**.

Other causes that are entirely the responsibility of the clinician are:

- Not double-dosing LPV/r with rifampicin (see **Chapter 7**);
- Not increasing the dose as a child gains weight;
- Not switching the anti-epileptic to valproate if the patient is epileptic (see **Chapter 7**);
- Not detecting and advising the patient if there is significant diarrhoea and/or vomiting that will reduce absorption of the ARVs; and
- Not detecting mental illness or substance abuse which often considerably affect adherence.

2. What is the best way to monitor the effectiveness of ART?

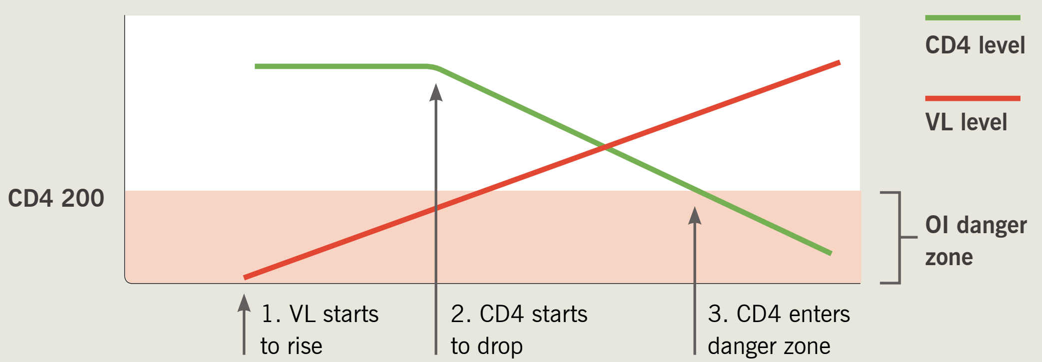
In light of the natural progression of the virus's behaviour on and off ART, monitoring the effectiveness of ART logically involves the three components mentioned:

- The amount of virus in the blood, using the viral load (VL);
- The patient's immunological status, using the CD4 count; and
- The patient's clinical status, based on the development of new infections.

The changes in these three components happen in a particular order, which, in turn, indicate the reliability of their use in the early detection of treatment failure.

Represented on a graph it looks like this:

Figure 6.1 Broad overview: CD4 and VL changes in untreated HIV



Notes

The earliest indicator of something going wrong is the rising viral load.

The next is the dropping CD4 count, which may follow the viral load by a month or two.

The last is the development of new infections, which do not necessarily occur, even with a very low CD4 count.

WHO guidelines

On the basis of significant supportive studies, WHO now recommends that **viral load is the preferred monitoring approach** to diagnose ARV treatment failure. Only if VL monitoring is not available should CD4 and clinical monitoring be used.

What do I do if I do not have routine viral load available for monitoring?

WHO recognises that not all countries have access to routine viral load monitoring and has given guidelines for diagnosing treatment failure; using CD4 and clinical status, not just viral load.

3. How is treatment failure defined?

WHO guidelines

Table 6.1 shows the WHO definitions of clinical, immunological and virological failure, to inform the decision to switch ART regimens. Please consult your **national guideline** as this may differ from the above WHO definitions.

Table 6.1 WHO definitions of clinical, immunological and virological failure in adults and adolescents

Failure	Definition	Comments
Clinical failure	New or recurrent clinical event indicting severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment	The condition must be differentiated from IRIS occurring after initiating ART.
Immunological failure	CD4 count at or below 250 cells following clinical failure Or Persistent CD4 levels below 100 cells	The condition must be without concomitant or recent infection to cause a transient decline in the CD4 cell count.
Virological failure	Viral load above 1 000 copies/ml, based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test	An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed.

4. Do all clinical, immunological or virological abnormalities mean treatment failure?

Table 6.1 represents the specific conditions that must be met for a diagnosis of treatment failure to be made. If treatment failure is diagnosed, the ARVs must be changed as they are no longer working. However, many situations suggest a problem is developing but do not yet qualify for a diagnosis of treatment failure and a switch of regimen. These are important to recognise, as their early detection and management may prevent resistance from developing and the drugs becoming ineffective.

- For those without access to viral load testing, any drop in CD4 or any new infection that does not fit into the above criteria for treatment failure are warning signs that something, usually adherence, needs to be attended to and that the patient needs to be followed up more closely. For detail on this, refer to your national guideline.
- For those with access to viral load testing, the next section deals with the interpretation of a raised viral load.

5. How do I interpret and manage a high viral load result?

A high viral load means that the body is not getting effective ART in sufficient doses to stop replication of the virus. There are two possible reasons for this:

1. The patient is not taking ART properly (poor adherence), or there is some other reason why the drugs are not getting into the body (e.g. under-dosing, diarrhoea, etc., as noted in section 1 of this chapter).
2. The virus has become resistant to the ARVs.

The difficulty lies in sorting out:

- when there is treatment failure;
- when the drugs are still working; and
- how best to manage things from there.

The different terms are often used interchangeably, often causing confusion. It is important that everyone knows what is being referred to.

Resistance: The term is used when a resistant mutation to a particular drug has developed. ‘Resistance’ is also used to refer to a whole regimen (i.e. none of the drugs work).

Treatment failure or regimen failure: The current drug treatment regimen is no longer working (i.e. the patient’s virus is now resistant to all the drugs in the regimen).

Virological failure: This refers to the specific type of failure (see Table 6.1).

For every patient presenting to the clinician with a high viral load, by the end of the consultation one of two possible diagnoses needs to be made, each with its own decision (Figure 6.2).

Figure 6.2 High viral load management overview

Patient presents with a high viral load

We **cannot diagnose** treatment failure yet.

Persevere with the existing ART regimen and address adherence issues and/or clinician errors.

There is **enough evidence** to diagnose treatment failure.

Switch to a new ART regimen and address adherence issues and/or clinician errors as well.

Every country has its own algorithm to guide the clinician through the management of the patient with a high viral load. All algorithms lead the clinician to one of these choices. This section explains the principles behind the algorithm flow, so that, with greater understanding, the clinician can make more informed decisions.

Consider the following scenario:

You are a shop assistant in a hardware store and a customer requests help with an ant infestation that he has at his home. You give him a 100 ml bottle of poison, a 10 ml syringe and 500 ml spray bottle and tell him to put 10 ml of poison into the bottle and top it up to 500 ml with water. You instruct him to spray this all round the house daily for a full week.

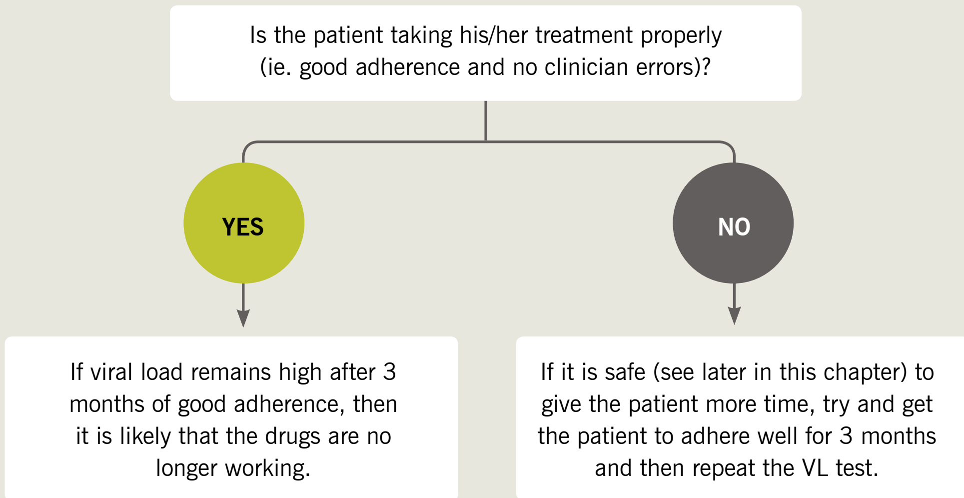
He returns a week later, and tells you that the poison isn't working. You ask how he used it and he informs you that, because it was expensive, he mixed only 5 ml poison into the water and also, as he came home late three nights of the week, he only sprayed around his house four times.

Is the poison useless or is it worth another try?

Clearly, the problem is that he hasn't been using it properly so we cannot make a decision about whether the poison is working. If he comes back again after another week, having used it exactly according to your instructions, it will be a valid claim that the poison isn't working and another one needs to be recommended.

With HIV treatment, we follow the same principle as in the ant analogy above:

Figure 6.3 Taking a decision based on high viral load



What is needed is a practical way of applying this. WHO has defined treatment failure as: Viral loads above 1 000 copies/ml based on 2 consecutive viral load measurements in 3 months, with adherence support following the first viral load test.

In practice, this can be remembered by using a simple '**123A rule**':

1. The viral loads must both be above **1** thousand (a value that can be measured in most settings and that suggests that the drugs are either not working or not being taken properly).
2. There must be **2** of them (we have to be able to have a baseline and then one later, after good adherence, so we can evaluate what happened to the viral load when the drugs were taken properly – consider the ant poison example).
3. They must be **3** months apart (most viral loads, even in the hundreds of thousands become undetectable after 2 months so 3 months is easily enough time if there is good adherence and the drugs are working).

A. There must be good **adherence** during those 3 months (if the patient is not taking the drugs adequately, then we cannot say if the drugs are working or not).

If you cannot tick 1, 2, 3 and A in a patient presenting with a high viral load, you cannot diagnose virological failure according to WHO criteria. Therefore, look for clinician errors and adherence challenges and address them.

Addressing adherence isses is one of our biggest challenges.

Non-judgmental, empathetic engagement with the patient is essential.

Example (*in an empathetic, friendly tone*): 'I can see from your results that the viral load is up and this suggests you are missing some of your doses. How often do you think that this is happening?' (*Stating in a non-judgmental way that the patient is missing doses avoids an argument about whether it's true or not and the friendly tone communicates that you are not angry with them and will support them when they talk about it.*)

For more detailed guidelines see **Chapter 25**.

Exceptions to the '123A rule'

a. **What if your local clinic is able to provide viral load values under 1 000, and a patient keeps getting levels between 100 and 1 000? Is this a problem?**

As long as there is a value, even if it is 120 copies, it means that the virus is reproducing and if this is happening in the presence of some blood level of ARV, there is the potential for the development of resistance. However, as the levels are low, this is not going to happen very quickly. The 2016 WHO guideline recommends that, as long as the viral load stays below 1 000 copies per ml, there is no need to change the regimen. Watch for updates to this ruling as this may change in the future. However, even though the regimen may not be changed, this is an early warning sign that adherence is not ideal, so is a good indication for an adherence intervention.

b. **What if there are two consecutive viral loads above 1 000 but they are more than 3 months apart?**

This doesn't fall strictly within the 123A rule (WHO guidelines for treatment failure), so the diagnosis of treatment failure will need interpretation. If, on more detailed questioning, it seems that the patient's adherence has been good during the time since the last viral load, especially in the 3 months before the second viral load was done, it would suggest that the drugs are not working. Treatment failure can therefore be diagnosed. Alternatively, if the adherence has been poor, especially in the 3 months prior to the second viral load, the existing drug regimen has not been adequately tested for resistance (see the ant analogy on page 80) so this may qualify for a postponement of a switch, provided there is no evidence of more advanced disease – see (c) below.

c. **What if the adherence is poor or we are not sure about it?**

There is increasing morbidity and mortality due to a delay in people being switched from first to second line. This delay often happens because a patient has not yet completed the required adherence sessions or it is believed that more time needs to be spent trying to optimise adherence. **It is therefore recommended rather to err on the side of switching too soon than leaving it too late.** This principle is strongly reflected in the suggested algorithm at the end of this chapter for the management of the patient with a high viral load.

The CD4 count or the patient's clinical condition will also help to make a decision. If the CD4 is low or there is a new, significant opportunistic infection, there is no time to waste trying for a bit longer to address adherence issues, as the patient may die soon from a serious OI. Even if the adherence is not ideal, on a new second line regimen the viral load is more likely to respond to drugs that are definitely effective than to ones where we are not sure.

If there is no new OI and the CD4 is high, it may be appropriate to delay the switch a bit longer while work is done on adherence. However, it is important to ensure that it is easy to keep in touch with the patient so that he/she does not get lost to follow-up.

d. There is a difference between patients on NNRTI-based and PI-based regimens.

As noted in section 1 in this chapter, resistance to ARVs develops at different speeds. It takes a lot longer for resistance to PIs to develop to than to an NNRTI-based regimen. If the two consecutive elevated viral loads are within the first year on a PI, further attempts must be made to look for adherence or clinician errors before diagnosing treatment failure (see **section 11** in this chapter).

6. Why is it important to act on diagnosed treatment failure without any further delay?

- If we have diagnosed treatment failure, it means that the drugs are no longer working. This is, therefore, the same as the patient not taking them at all. Continuing the same ARVs will result in a progressive drop in CD4, worsening immunity and eventual death from an OI.
- The longer a patient stays on a failing regimen, the more drugs the HIV becomes resistant to. For example, if a patient on TDF, 3TC and EFV is left on this regimen when it is no longer working, that patient's virus will, over a year or two, become resistant to AZT and, with time, other drugs as well. One of these drugs may be recommended in the second line regimen and now be ineffective.

For this reason, as soon as treatment failure has been diagnosed, the drugs must be changed. Such delays are an increasing cause of morbidity and mortality in HIV clinics.

7. Who is responsible for a patient presenting with a high viral load: the patient, clinician or health system?

Regrettably, the patient is often at the receiving end of harsh criticism from healthcare workers for having a high viral load. While the patient can at times be irresponsible, there are many situations in which it is really not the patient's fault.

Table 6.2 Responsibility for cause of high viral load in a patient

Responsible person or entity	Cause of high viral load
Clinician responsible	Not double-dosing LPV/r with rifampicin.
	Not increasing the dose as the weight increases (common error in children).
	Not switching to valproate if patient epileptic.
	Not detecting and advising patient if there is significant diarrhoea and/or vomiting.
	Not detecting mental illness or substance abuse or making efforts to help.
Health system responsible (a few examples)	Poor counselling strategies, resulting in inadequate advice to start with.
	Poor lost-to-follow-up tracing mechanisms.
	Little opportunity for patient to ask questions or raise concerns.
	Drug stock-outs.
	Clinic management of viral load results.
Patient-related	Treatment fatigue.
	Food insecurity.
	Stigma.
	Alcohol or substance abuse.

It is, therefore, strongly recommended that, before the blame is placed on the patient, the clinician runs through this checklist in Table 6.2 to first establish if any of these issues could be contributing.

Even if the patient is found to be irresponsible, being harsh is guaranteed to make the problem worse. An approach that seeks to understand and support is far more likely to achieve the required outcome. (See the example earlier in this chapter as well as **Chapter 25** for more detail on patient support and counselling.)

8. How do I switch a patient to a second line regimen?

The ideal second line regimen would be worked out by doing a test in which the resistance profile of each ARV drug is detailed. However, as this is expensive, drug combinations are worked out based on an assessment of the likely resistance patterns.

Choice of regimen

In the *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection* (WHO, 2016, p. 150) Table 4.8 recommends second line regimens. However, please also consult your national guidelines, as they may differ.

WHO guidelines

The following main principles apply:

Figure 6.4 Choice of second line drug

First line	TDF or ABC	AZT	3TC /FTC	NVP/EFV	DTG*
	↓	↓	↓	↓	↓
Second line	AZT	TDF	3TC /FTC	DTG*	ATV/r or LPV/r

If the choice of a second line drug is contra-indicated (e.g. AZT with severe anaemia, TDF with severe renal impairment) the other NRTIs can be used. If there are still complications, seek additional support.

* See Table 3.2 on page 36 for more detailed guidelines regarding DTG. As more data become available these guidelines may be further updated. Please check for updates on the **SAMU website**: https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Patient support during the change

Support of the patient (in understanding the reason for the change and the potential new side effects, and addressing all the fears and concerns) is an essential component of this switching process (see **Chapter 25**).

Patient support (see Chapter 25)

9. What are the principles of single drug switches?

When is it safe to make a single drug switch?

Single drug switches are made most commonly when unacceptable side effects develop to a particular drug. As a rule the ARV can simply be switched to another one that doesn't have the same side effect profile. However, if at the time of the switch there is resistance to the current regimen the likelihood is high that the newly introduced drug will also become resistant.

If the regimen has failed, this means that all three drugs are no longer working. If you then change one drug only (e.g. TDF for AZT in a failing regimen of TDF, 3TC and EFV), the patient will be on only one effective ARV. It will not take long for this new drug to become resistant as well, thus removing this new drug from effective use in a second line regimen.

When doing a single drug switch, it is important therefore first to evaluate whether it is possible that resistance has developed to the current regimen. If this possibility exists two actions need to follow:

1. The decision about the switch needs to be made. This varies according to whether the offending drug is an NRTI or an NNRTI; and
2. The usual process must be followed for the management of possible failure as detailed above.

NRTIs:

- It is acceptable to make a single drug switch in the first 6 months after starting ART as it is very unlikely that resistance will have developed to any of the drugs by that stage. Fortunately, most of the side effects requiring switches to be made occur during this time.
- If a single drug switch of an NRTI needs to be made for a patient on ARVs for >6 months, an assessment needs to be made regarding the likelihood of failure on the current regimen. If a viral load test has not been done for more than 3–4 months, it should ideally be done before making the switch, to ensure that the patient is not failing the regimen. If there is no time to wait for the result, clinical judgment will have to be used regarding whether to make a single drug switch or a change to second line. Experienced advice is recommended before doing this.
- If failure is unlikely, the following principles apply when switching NRTIs:
    - TDF ideally changes to ABC because it is better to keep AZT for a possible switch to second line in the future.
    - AZT ideally changes to TDF as ABC is not as effective in a second line regimen.
    - If, however, the ideal drug for the switch is not available or contra-indicated, any NRTI option can be used.

NNRTIs:

Switches between EFV and NVP can be done regardless of whether there is a possible failing regimen or not. Such a switch may be necessary, for example, if a patient is on NVP and needs to start TB treatment – where NVP is not ideal – or, if a patient on EFV gets significant neuropsychiatric side-effects. The resistance patterns of NVP and EFV are almost identical, so if resistance has developed to one it has developed to the other. By changing to one you cannot cause resistance to the other one to develop because it has already developed. Make the single-drug switch immediately. The issue of possible ARV resistance needs to be attended to in the usual way.

10. What special care needs to be taken with ART in managing a patient with hepatitis B?

Optimal treatment for hepatitis B is to use two drugs, 3TC and TDF, with TDF being the more potent of the two. If TDF is stopped, leaving 3TC as the only active anti-hepatitis B drug, over 90% of patients will become resistant to the 3TC within five years. Therefore, try to do everything possible to keep both drugs in the regimen. In order to do so, follow these guidelines:

- If a patient fails his/her first line regimen of TDF, 3TC and EFV and is hepatitis BsAg positive, the TDF needs to be kept in the regimen, even though it is not doing anything for the HIV. The first choice regimen would, therefore, have four drugs: AZT, 3TC, the PI, plus TDF.
- If a patient is failing this same regimen and the hepatitis B status is unknown, if resources allow it is important to test the HBsAg before deciding whether TDF needs to be kept in the second line regimen.
- If TDF is contra-indicated due to renal impairment, seek more experienced advice. This may involve continuing to use TDF but at a reduced dose and with close renal monitoring, or accessing entecavir, a more renally safe treatment of hepatitis B.

11. How do I manage a patient presenting with high viral loads on a PI-based regimen?

The management is founded on two principles that are different from the process with a patient on an NNRTI-based regimen:

1. As mentioned in section 1 of this chapter, it is very unlikely that the virus will have developed resistance to a PI in the first 18–24 months, even in the presence of intermittent, 50–90% adherence. It often takes even longer than that.
2. Part of the management is to do a genotype. They are expensive so should not be done unless there is a good chance that they will show resistant viruses.

Therefore, for a patient on a PI-based regimen presenting with all the WHO criteria for failure (123A rule), we defer the diagnosis of virological failure if the patient has been on the PI-based regimen for less than a year, often longer. Studies have shown that in the majority of situations the cause is poor adherence rather than a resistant virus. Review the approach that is recommended in **section 7** in this chapter.

Only when we have exhausted all these possibilities do we consider the diagnosis of treatment failure and start engaging in the process of requesting a genotype and assessment for third line drugs. Please consult your national guideline for the details.

As always, if the CD4 is very low, the patient is at high risk for developing fatal OIs and action must be taken sooner to start the process of requesting a genotype and assessing for a third line regimen.

12. What are the principles of using genotypes?

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

It is not within the scope of this book to deal comprehensively with genotypes and the choice of third line drugs. If more detailed study is needed, we recommend the following book, ‘*HIV & TB Drug Resistance and Clinical Management Casebook*’, which can be downloaded from the **SAMU website**, https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

A decision regarding the choice of a third line regimen should never be taken without first doing a genotype test to establish the exact resistance profile of the particular patient.

There are a few important principles in interpreting genotypes:

- The criteria for treatment failure on a PI-based regimen, as outlined in **section 11** in this chapter, must have been met. If not, time and money will be wasted doing an unnecessary test:
  - The patient must have been on the PI-based regimen for at least one year.
  - The 123A rule for diagnosing treatment failure must apply.
  - Substantial effort must have been made to address adherence issues.
- The patient must still be taking the failing regimen at the time of drawing the blood for the genotype. If not, they must restart the same meds again and be on them for at least 4 weeks before drawing the blood. If this is not done, the genotype cannot be correctly interpreted.
- The result of a genotype test can be correctly interpreted only with the detailed ARV history.

The above three points are standard requirements on the usual application form for consideration for a genotype and a third line regimen.

13. How does one build a third line regimen?

For details regarding the classes and the individual drugs used in a third line regimen, please see Appendix 4.1.

The third line regimen is built as follows:

OBR = optimum background regimen of NRTIs chosen by genotyping (usually 2 drugs)	**PLUS**	**A combination of two of:** DRV/r = Darunavir/ritonavir INSTI* = Raltegravir (RAL) / Dolutegravir (DTG) ETV = Etravirine

* INSTI = Integrase Strand Transfer Inhibitors

The commonly used regimens at the time of writing in 2018 are:

DRV/r **PLUS** DTG/RAL **PLUS** 2 x NRTIs based on genotype	**OR**	DRV/r **PLUS** new NNRTI (Etravirine) **PLUS** 2 x NRTIs based on genotype

Summary

The effective management of a patient presenting with possible ART failure is a key challenge in the management of HIV worldwide. The difficulties cross a wider spectrum than merely good clinical knowledge, incorporating many programmatic elements that require the full engagement of facility managers. This chapter has presented the essential information to support improved clinical skills in this key area.

High viral load management algorithm

For a guideline for rapid application of the above principles, see Algorithm 6.1.

Algorithm 6.1 VL testing for patients on first and second line regimens

Routine VL testing is done 6 and 12 months after starting ART and then, if less than 1 000, annually. The rest of this algorithm tracks the management of the viral load >1 000.

Routine VL testing. Day zero.

First, evaluate if patient:

- Has a known CD4 <200[1]
- Is non-ambulant
- Has a new stage 4 disease[3]

YES → May need to be switched rapidly to second line. Needs investigation first. **Take VL and follow guidelines for advanced disease in Chapter 11.**[2]

NO → Give brief information on VL, take blood for VL and provide ARV refill till routine return visit. Clinic to ensure the high VLs are flagged and patients brought back earlier.[4]

VL result visit

If VL <1 000[5]

↓

Routine care

If VL >1 000

↓

First, evaluate if patient:

- Has a known CD4 <200[1]
- Is non-ambulant
- Has a new stage 4 disease[3]

YES → May need to be switched rapidly to second line. Needs investigation first. **Follow guidelines for advanced disease in Chapter 11.**[2]

NO → **Enhanced Adherence Counselling (EAC)**

Ideally give patient a one-month refill and ask to return for follow-up EAC and drug refill. If not possible, ask patient to return in time for repeat VL (3 months after first VL blood).

Prioritise, where possible:

- Pregnant women
- Adolescents and children
- CD4 <350
- TB

↓

- Flag
- Ensure follow up
- Refer to most experienced clinician

EAC follow-up visit

Extra EAC follow-up session(s) must be scheduled according to need and ability of patient to attend in the 3 months following the high VL. ART refill given till repeat VL test visit.

Repeat VL visit

First, evaluate if patient:

- Has a known CD4 <200[1]
- Is non-ambulant
- Has a new stage 4 disease[3]

YES

May need to be switched rapidly to second line. Needs investigation first. **Take VL and follow guidelines for advanced disease in Chapter 11.**[2]

NO

Recap information on VL, take blood for VL and provide ARV refill (according to local practice and results turn-around time). Ask patient to return for result.

Ensure follow-up of result.

VL result visit

If VL <1 000[5]

Routine care

If patient on EFV/NVP:

This qualifies for a switch to second line. The switch must be done:

- within 2 weeks of receipt of second VL >1 000
- no later than 6 months after first VL >1 000

If experienced clinician immediately available, discuss first. If not, switch to second line.

If patient on a PI:

- It is highly likely that there are adherence issues as the development of resistance to a PI is very unlikely in less than one year, often longer.
- If on a PI for more than 12 months, discuss with experienced clinician and consider genotyping. See management detail in section 11 above.

If VL >1 000

First, evaluate if patient:

- Has a known CD4 <200[1]
- Is non-ambulant
- Has a new stage 4 disease[3]

NO

YES

Needs to be switched rapidly to second line and needs further investigation. **Take VL and follow guidelines for advanced disease in Chapter 11.**[1]

At the time of writing, experience with DTG resistance is limited. Ask for expert advice if a patient is failing a DTG-based regimen.

Notes

1. If CD4 is unknown, take blood to check it and follow up at next visit.
2. Patients are dying because they are not being switched when they should. The red boxes represent the important check to ensure that serious life-threatening illnesses are not missed. If the VL turn-around time is likely to be >3 months, the red box assessments are especially important.
3. A new stage 4 disease is a WHO clinical indicator for clinical treatment failure according to WHO criteria, so a switch to second line is indicated. It is important to follow the guidelines in the red box, too.
4. Early identification of patients with high viral load results and bringing the patients back to the clinic as soon as possible are essential programmatic elements in decreasing morbidity and mortality.
5. If a more accurate VL result <1 000 is available, encourage patients with VL between 400 and 1 000 to reach an undetectable VL, as low level viraemia can eventually lead to resistance.

Drug-drug interactions in HIV/TB

Different types of interaction

A brief review of how the body handles drugs (pharmacokinetics)

Summary: drug interactions in HIV/TB

Please note that this topic is covered more fully, including quizzes and case histories, in the **SAMU HIV/TB E-Learning course**. See 'How to use this book' for more detail.

With HIV/TB co-infection rates sometimes being as high as 75%, and now with HIV-positive patients living into middle age and longer, we commonly find our patients on three ARVs, four TB drugs, cotrimoxazole, a few other drugs for non-communicable diseases (NCDs) and quite often herbal and traditional medications as well. It is inevitable that there will be some problematic drug interactions, so the purpose of this chapter is to outline what we need to be aware of in our HIV/TB clinics.

The bulk of the chapter explains the mechanisms of the interactions and at the end you will find tables summarising the key interactions and how to manage them.

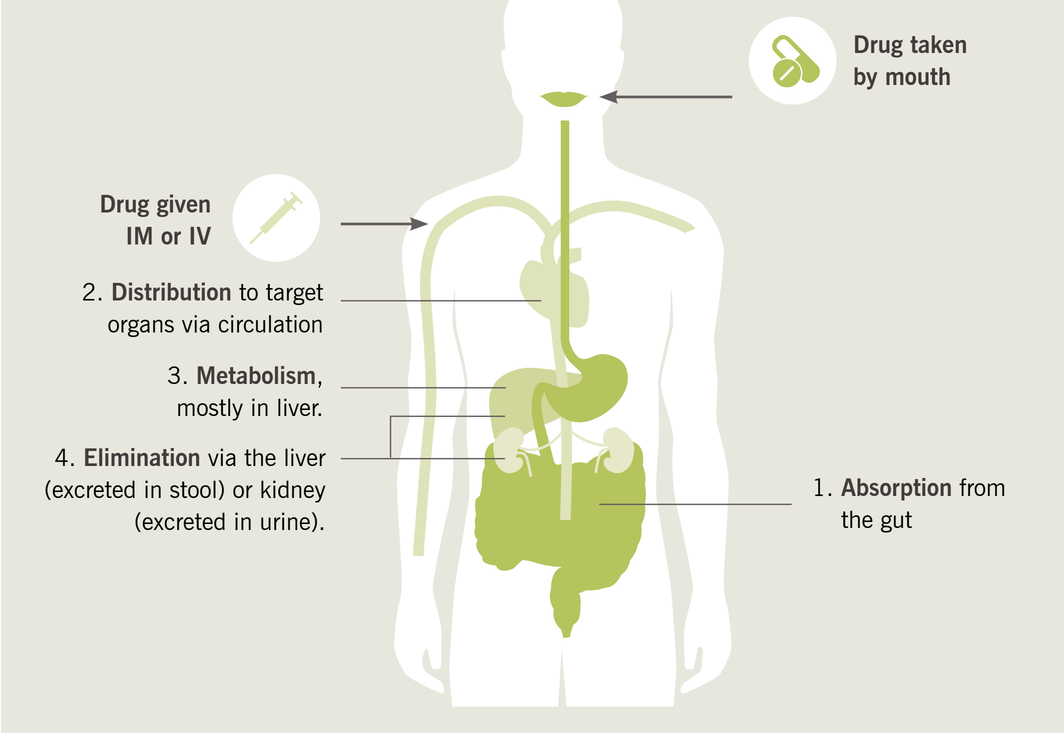
Different types of interaction

- Combinations of ARVs that must not be given together because they become either toxic or ineffective;
- Situations where absorption of the drug is affected;
- Using two drugs that can both be toxic to the kidney;
- Using two drugs that can be toxic to the liver; and
- Enzyme induction and inhibition.

A brief review of how the body handles drugs (pharmacokinetics)

Figure 7.1 describes pharmacokinetics. Refer also to Figure 7.3.

Figure 7.1 Pharmacokinetics



1. **Absorption**: The drug is absorbed from the gut into the blood stream or directly via IM or IV injection.
2. **Distribution**: It makes its way throughout the body, to sites of action and metabolism.
3. **Metabolism**: The drug is metabolised, mainly by the liver. Drugs may become activated or deactivated by metabolic processes, or may also pass unchanged.
4. **Elimination**: It is then excreted from the body, mainly via the liver, kidneys or both.

Combinations of ARVs that must not be given together

In Chapter 3, we looked at how, when choosing the ARVs to make up a regimen, we can think in terms of three columns. Almost without exception, no two drugs must be given from the same column (see Figure 7.2). For example, we don't give TDF along with ABC or AZT, except in the exceptional situation of the management of hepatitis B (**Chapter 6**, section 10).

We do not give 3TC with FTC, nor do we give EFV, NVP or DTG together.

Figure 7.2 Building a three-drug ART regimen

Column 1		Column 2		Column 3
NRTI TDF or AZT or ABC	PLUS	**NRTI** 3TC or FTC	PLUS	**INSTI** Dolutegravir or **NNRTI** EFV or NVP

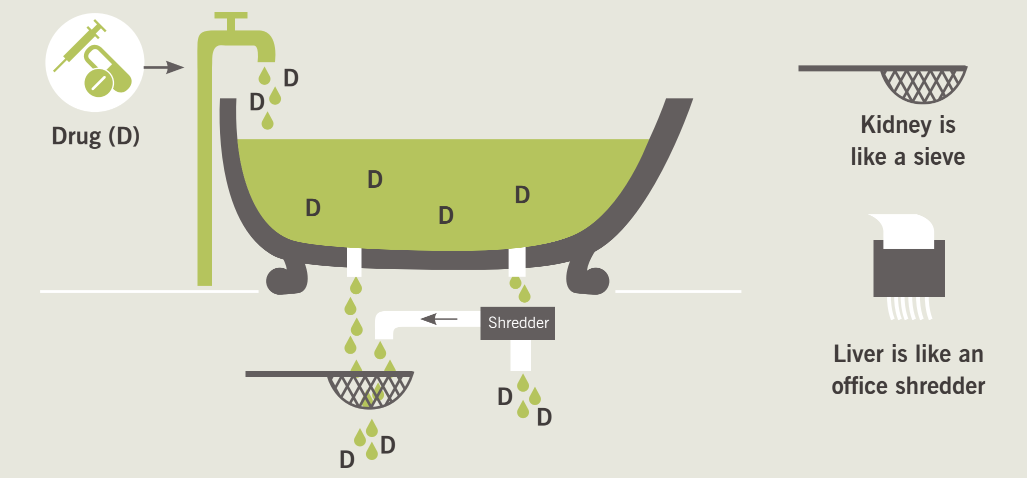
Situations where absorption of the drug is affected

In certain situations the absorption of drugs can be affected:

- If the patient has a lot of vomiting and diarrhoea, some drug is lost in the stool or vomitus. This can result in blood levels that are too low to be effective. As a general guideline, if a patient vomits within 2 hours of taking pills, they should repeat the dose, as the medication will not have been adequately absorbed.
- PIs are best absorbed in an acid medium. They are therefore best taken with food, when the stomach secretes more acid. Omeprazole decreases the stomach acid level so must not be given with atazanavir (ATV). The other PIs are not affected.
- If EFV is taken with a fatty meal it is too well absorbed and tends to give more side effects. Fatty food is therefore best avoided when taking EFV.

This simple diagram (Figure 7.3) explains absorption, distribution and elimination.

Figure 7.3 Absorption, distribution and elimination of drugs



Absorption: The drug (D) arrives in the body via mouth, IMI or IVI (represented by the tap).

Distribution: It enters the circulation and reaches a particular blood level (represented by the Ds in the bath water).

Metabolism and Elimination: The drug is then excreted mainly via the kidney or the liver, or sometimes broken down first in the liver and then excreted via the kidney (shown by the arrow).

- The kidney can be understood very simply as a sieve that filters out various chemicals.
- The liver can equally be understood simply as an office shredder. Drugs go in the one end and emerge out the other, changed or broken up into little bits. This metabolism process can turn a drug into its active form, or make it ready to be excreted.

In both instances, the dosage of the drug coming in at the tap is based on pharmacokinetic properties of the drug, so that it matches the speed at which it leaves the body **if the liver and kidneys are all working well** (e.g. 500 mg 3 times a day or 200 mg once a day).

This understanding is a necessary foundation for the next three categories.

Using two drugs that can both be toxic to the kidney

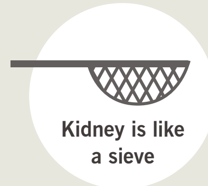
There are occasions when two drugs that are both potentially toxic to the kidney are needed for the different conditions that are being treated. If this situation occurs, it may be better to use different drugs to reduce the risk of nephrotoxicity as much as possible.

The same principle applies when drugs that are excreted via the kidney are needed, but the patient has kidney disease. (See **Chapter 17** on renal disease.)

Sometimes the situation can be managed by reducing the dose, based on kidney function, and monitoring as closely as possible.

In order to understand the decisions made, it is important to know which of the drugs commonly used in HIV/TB clinics are eliminated via the kidney (see Figure 7.4).

Figure 7.4 Drugs that are excreted renally



1. All the NRTIs **A**part from **A**BC.
2. None of the first line TB drugs **E**xcept for **E**thambutol.

Note, too, that some drugs are merely excreted via the kidney, while some are potentially toxic to the kidney as well.

NRTIs:

Tenofovir*
3TC
d4T
AZT

TB drugs:

Ethambutol
Streptomycin*
Kanamycin*
Capreomycin*

*** Also potentially toxic to kidney**

Clinical relevance

This situation is relevant clinically when a patient is on TDF and also requires an aminoglycoside (kanamycin or capreomycin), as happens frequently in the management of DR TB.

The solution is to change the TDF to ABC or AZT, until the aminoglycoside is no longer needed.

Using two drugs that can be toxic to the liver

All the NNRTIs and PIs are potentially toxic to the liver, and all the first line TB drugs, except for ethambutol, are, too. The main clinical relevance for this is when giving both TB treatment and ARVs. NVP is generally avoided with TB treatment and when patients are taking TB treatment with ARVs the likelihood of developing drug-induced liver impairment (DILI) is often higher (see **Chapter 16** on liver disease).

The following can all be toxic to the liver:

Liver is like an office shredder

TB drugs

- Rifampicin
- INH
- PZA
- Ethionamide
- Prothionamide
- PAS
- Bedaquilline

ARVs

- NVP/EFV
- PIs

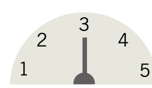
Other

- Cotrimoxazole
- Fluconazole

Enzyme induction and inhibition

Enzyme induction and inhibition refers to altered metabolism speeds of drugs that results in either toxicity or insufficient blood levels. To better understand this, let's return to the idea that the liver is like a paper shredder, changing or breaking the drug down into small bits in order to excrete it (Figure 7.3). In reality, the shredder is a complex network of enzymes, the main ones being the cytochrome P450 enzymes (CYP 450), with many different sub-units responsible for breaking down different drugs.

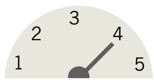
For our understanding, though, it is sufficient to use the shredder analogy. The shredder has the capacity to run at different speeds, ranging from 1 to 5, where 3 is the normal speed.



Enzyme inducers

Some drugs speed up the shredder to speed 4 or 5. The process of speeding up the shredder is fairly slow, taking on average 2–4 weeks. The enzymes are induced to work harder, so this is called **enzyme induction.** Practically, this means that drugs are metabolised faster, reducing the amount of drug available in the body.

Nevirapine and efavirenz



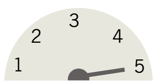
They both turn the speed up to 4.

This means that many drugs that pass through the liver are metabolised more quickly when the person is taking either NVP or EFV.

Clinical relevance

Oral contraceptives and the progesterone implants are metabolised by the liver, passing through the shredder. In the presence of NVP or EFV they are broken down more quickly, resulting in reduced blood levels that make them unsafe. They are therefore contra-indicated in patients on these ARVs. Use injectable contraceptives or IUCDs instead.

Rifampicin

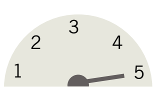


This is a potent enzyme inducer that turns the shredder speed up to 5, meaning that drugs passing through the liver will be even more rapidly broken down, with lower blood levels and high potential for not being effective.

Clinical relevance when taken with rifampicin

- Lopinavir/ritonavir (LPV/r) passes through the shredder and when it is running at speed 5 the LPV/r level drops to ineffective levels in the blood. We solve this problem by doubling the dose of LPV/r. Due to different metabolism processes in younger children, this is not effective in children under 5 years of age. The solution is different and is covered in the next section on enzyme inhibition.
- Atazanavir/ritonavir (ATV/r) passes through the same system, with the same drop in blood levels. However, as insufficient clinical trials have been done to know the correct dosage adjustment of the ATV/r, this must not be used with rifampicin. Instead patients are switched to LPV/r and the dose is doubled.
- NVP levels also drop, but not quite enough to cause this to be a contra-indication. However, because of the additional complication of NVP and rifampicin both being toxic to the liver, it is preferable to change the NVP to EFV.
- EFV levels also drop but not enough to affect the blood levels when the standard 600 mg dose is used. At the time of writing there is insufficient evidence to show that the 400 mg dose of EFV can be used safely with rifampicin.
- Dolutegravir metabolism is increased, resulting in a significant reduction in blood levels. The dose of DTG needs to be doubled to 50 mg twice a day.

Phenobarbitone, phenytoin and carbamazepine

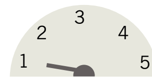


These are all potent enzyme inducers, pushing the shredder speed up to 5.

Clinical relevance

If EFV or NVP are given with any of these three drugs, blood levels drop too low to be effective. As there is no recommended dosage adjustment for the EFV or NVP, the standard practice is to change the anti-epileptic to sodium valproate. If this is not available, the best of the three drugs to use is carbamazepine but it is still not ideal. (See **Chapter 6**, section 7 which warns of the dangers of not switching standard epileptics to valproate when starting ART.)

Enzyme inhibition



Some drugs slow down the action of the enzymes, a process called **enzyme inhibition**. The shredder speed is slowed down, resulting in a build-up of the blood levels in the body. The process of slowing down the shredder happens much faster than induction, taking only a few hours to a few days from starting the inducing drug.

The main inhibitors in common use are the PIs, especially ritonavir (RTV)

Clinical relevance

The addition of RTV is often used therapeutically to slow down the metabolism of other protease inhibitors, in order to raise the blood level. This is seen in the following situations:

- RTV is added to all PIs for this very reason. This is a process called ‘boosting’. Failure to do so results in inadequate drug levels of the therapeutic PI, which will eventually lead to the development of resistance.
- Extra RTV is added to the regimen in all children who are on a PI and who need TB treatment. Remember, rifampicin reduces the level of LPV/r, which we compensate for by doubling the dose of LPV/r. As noted above in the section on enzyme induction, this doesn’t work in children under 5 years. Instead, we add more RTV to slow down the metabolism of the LPV and thus raise the blood level. This is a process called ‘super-boosting’. (See also TB treatment in children in **Chapter 10**.)

There are certain drugs that, when taken with RTV (e.g. a patient on second line ART), result in dangerously toxic levels because the patient’s metabolism has been considerably slowed down.

- Fluoxetine levels can rise significantly, causing toxicity. The solution is use another antidepressant, such as citalopram, or, if this is not available, to halve the dose of fluoxetine initially.
- Simvastatin levels can also reach toxic levels, resulting in kidney damage, so the recommendation is to change to atorvastatin or to halve the dose of simvastatin initially.
- Amlodipine levels, too, can rise significantly, causing hypotension. The solution is to use an alternative drug or halve the dose initially.

Summary: Drug interactions in HIV/TB

- All drugs are metabolised in the kidneys or liver so the presence of liver or kidney disease (both common in HIV/TB) can affect their metabolism.
- Many of the drugs used in HIV/TB are toxic to either kidneys or liver and can result in a variety of toxicities or drug interactions that the clinician needs to be aware of.
- Rifampicin, EFV, NVP and the commonly used anti-epileptic medications increase liver metabolism, resulting in insufficient blood levels of other important drugs that may be co-prescribed in HIV/TB management.
- The PIs often result in slowing down liver metabolism, at times resulting in toxic levels of some co-prescribed drugs. The clinician should check for drug interactions with any drugs prescribed with a PI.

An important principle to follow when any drug is added to a PI-based regimen is to check first for drug-drug interactions. The following tables summarise the drug-drug interactions commonly seen in HIV/TB clinics.

Table 7.1 Interactions between ART and commonly used drugs

Drug 1	ARV	Interaction	Management
Antibiotics			
Streptomycin, Kanamycin, Capreomycin	TDF	Both drugs toxic to kidney.	Change TDF to ABC or AZT.
TB drugs	See under separate section.		
Anti-fungals			
Itraconazole (Inhibitor)	Ritonavir (Inhibitor)	Both drugs cause the other's blood level to rise.	Halve the itraconazole dose and watch for RTV toxicity.
Itraconazole	EFV	Can lead to decreased itraconazole levels.	May need to increase the dose of itraconazole.
Direct anti-virals (DAAs) for treatment of hepatitis C			
Daclatasvir (DCV)	EFV/NVP	EFV/NVP lower the blood levels of DCV.	Increase the dose of DCV to 90 mg daily.
Daclatasvir (DCV)	ATV/r (Inhibitor)	ATV/r causes the blood level of DCV to rise.	Decrease the dose of DCV to 30 mg daily.

Drug 1	ARV	Interaction	Management
BP medications			
Amlodipine	EFV/NVP	EFV/NVP may drop the blood level of amlodipine.	Monitor blood pressure. May need to increase dose of amlodipine.
Amlodipine	Ritonavir (Inhibitor)	RTV causes the blood level of amlodipine to rise	Halve the dose of amlodipine and watch blood pressure.
Nifedipine	Ritonavir (Inhibitor)	RTV causes a modest rise in these drugs.	Monitor the drug effects clinically.
Verapamil	Ritonavir (Inhibitor)		
Propranolol	Ritonavir (Inhibitor)		
Atenolol	Ritonavir (Inhibitor)		
Carvedilol	Ritonavir (Inhibitor)		
Enalapril	All ARVs	No clinically significant interaction.	
Captopril	All ARVs	No clinically significant interaction.	
Anti-epileptics			
Phenobarbitone, phenytoin, carbamazepine (Inducer)	EFV, NVP	Phenobarbitone, phenytoin, carbamazepine drop the blood levels of EFV, NVP significantly.	Change anti-epileptic to valproate or lamotrigine.
Sodium valproate	AZT	May significantly increase AZT blood levels.	Watch for toxicity. May need to decrease AZT to 200 bd.
Psychiatric medications			
Fluoxetine	Ritonavir (Inhibitor)	RTV can cause significantly elevated blood levels of fluoxetine.	Decrease the fluoxetine dose or change to citalopram.
Amitryptilene	Ritonavir (Inhibitor)	Can increase the amitryptilene blood level.	Caution and watch for toxicity.
Haloperidol	NVP/EFV (Inducer)	May decrease the haloperidol blood level.	May need to increase the dose.
Haloperidol	Ritonavir (Inhibitor)	May increase the haloperidol level.	May need to decrease the dose.

Drug 1	ARV	Interaction	Management
Cholesterol-lowering medications			
Simvastatin	Ritonavir (Inhibitor)	RTV can cause significantly elevated blood levels of simvastatin.	Avoid. Change to pravastatin or atorvastatin. If no alternative statin, start with a quarter of half-dose of simvastatin.
Atorvastatin	EFV (Inducer)	EFV drops the blood level of atorvastatin by 30–40%.	May need to increase the atorvastatin dose.
Pravastatin	Darunavir (Inhibitor)	Okay with other PIs, but DRV may result in 80% increased levels.	Caution with this combination.
Drugs for ischaemic heart disease			
Nitrates (eg Isordil)	ARVs	No significant interactions.	
Aspirin	TDF	Mildly increased risk of nephrotoxicity.	Monitor creatinine.
Digoxin	Ritonavir (Inhibitor)	May increase the levels of digoxin.	Watch for toxicity.
Diabetic drugs			
Glibenclamide	NVP/EFV (Inducer)	Theoretically, may decrease glibenclamide levels.	Monitor glucose levels accordingly.
Gliclazide	EFV (Inducer)	Theoretically, may decrease gliclazide levels.	Monitor glucose levels accordingly.
Metformin	NRTIs	Possible risk of lactic acidosis.	Monitor, especially if using d4T or DDI.
Miscellaneous			
PPIs (eg omeprazole)	Atazanavir (ATV)	ATV works poorly in an alkaline medium.	Don't take PPIs with ATV.
Lansoprazole	ATV/r	May decrease the ATV/r levels considerably.	Co-administration not advised.
Steroids	Ritonavir (Inhibitor)	Can cause the steroid level to rise considerably so may result in Cushing's effects.	May need to decrease the steroid dose.
Garlic preparations	EFV, PIs	Garlic can decrease blood levels of both drugs.	Co-administration not advised.
Morphine	EFV	May increase morphine levels.	Monitor drug effect and adjust dose accordingly.
Morphine	PIs	May decrease morphine levels.	Monitor drug effect and adjust dose accordingly.
Warfarin	PIs and EFV/NVP	Warfarin levels may increase or decrease.	Monitor INR carefully.

Table 7.2 TB drugs with ART and other drugs

TB drug	Drug 2	Interaction	Management
Rifampicin (inducer)	LPV/RTV (adults)	Rifampicin significantly decreases the levels of LPV/RTV.	Double dose of LPV/RTV in adults.
	LPV/RTV (children)	Rifampicin significantly decreases the levels of LPV/RTV.	Add extra RTV in children as per paediatrics dosage charts.
	Atazanavir (ATV)	Rifampicin significantly decreases the levels of ATV.	Change rifampicin to rifabutin and decrease the rifabutin dose (see rifabutin interactions below) or change the ATV to LPV/RTV and double its dose.
	Itraconazole	Rifampicin significantly decreases the levels of itraconazole.	Do not co-prescribe as itraconazole levels are too low.
	Moxifloxacin	Decreased levels of moxifloxacin.	Switch to another quinolone e.g. levofloxacin.
	Raltegravir	Rifampicin decreases the levels of raltegravir.	Dosage adjustment not needed, however.
	Dolutegravir	Rifampicin significantly reduces the DTG blood levels.	Increase the DTG dose to 50 mg twice daily.
Rifampicin, INH or PZA	NVP	All toxic to liver.	Change to EFV, or, if not possible, watch closely for liver toxicity.
Rifabutin	LPV/RTV (Inhibitor)	RTV increases the blood levels of rifabutin.	Decrease dose of rifabutin from 300 mg daily to 150 mg daily or even every alternate day.
Rifabutin	Dolutegravir	No significant interaction.	No dosage adjustment needed.

Sources for Tables 7.1 and 7.2: http://hivclinic.ca/drug-information/drug-interaction-tables/

You can download the app of Liverpool HIV iChart. Look for the following icon:

CHAPTER 8

Prevention strategies in the HIV-positive patient

Introduction

There are numerous different strategies used for preventing not only the transmission and acquisition of HIV itself, but also that of other infections associated with HIV. These can be broadly categorised as follows:

The HIV-positive person can make themselves less infectious to others:

- By being on HIV medication and maintaining an undetectable level of HIV virus in the blood (U=U; undetectable = untransmittable).
- By remaining free of STIs, and, if these are developed, getting treatment as soon as possible. The presence of an STI increases the transmission of HIV.
- By pregnant and breastfeeding women optimising strategies to prevent transmission of HIV to their babies. This is known as Prevention of Mother-To-Child Transmission (PMTCT). See **Chapter 9**.

The HIV-negative person can take precautions to avoid becoming infected with HIV:

- By using barrier protection methods during sex with people infected with HIV or those with unknown HIV status.
- By using adequate lubricant during sex, especially in men who have sex with men (MSM). This will decrease the risk of developing small cuts or tears that increase access of HIV directly into the bloodstream.
- By remaining free of STIs, and, if these are developed, getting treatment as soon as possible. The presence of an STI increases the risk of acquiring HIV.
- By taking preventative medication prior to high risk exposure to HIV (pre-exposure prophylaxis – PrEP).
- By taking preventative medication after a high risk exposure (post-exposure prophylaxis – PEP)
- By males getting circumcised. The inside of the foreskin has a high concentration of CD4 receptors, so one would assume that removing it would reduce access of the virus to the body. Studies have confirmed this, showing a 60% decrease in acquiring HIV after circumcision.

Health system contributions to decreasing transmission of HIV include:

- A wide spectrum of activities offering ongoing counselling and support to all HIV-positive patients and their partners (includes HIV education, safe sex practices, nutrition, awareness of the symptoms of opportunistic infections and knowledge about what to do about them, effective taking of lifelong HIV medication).

- A wide range of public health strategies aimed at early testing and treating of people who may be at risk of becoming infected with HIV, as well as ensuring that they stay on their medication and continue with an undetectable viral load.
- Free HIV care, including consultations and medication.
- A range of activities to decrease stigma in communities.
- Needle exchange programmes for IV drug users.
- Screening of blood donors and testing of blood products.

Appropriate medications the HIV-positive person can take to decrease the risk of developing opportunistic and other infections:

- Cotrimoxazole: significantly decreases the risk of acquiring pneumocystis pneumonia, toxoplasmosis, common GIT protozoal infections, some bacterial infections and malaria (see Appendices 8.1 and 8.2 at the end of this chapter for details).
- INH monotherapy: a prevention strategy for tuberculosis in HIV-positive patients, both on and off HIV medication (see **Chapter 12** and consult national guidelines).
- Fluconazole: for cryptococcal disease (see details in **Chapter 11**, advanced disease and **Chapter 14**, neurology).
- Annual influenza vaccine and the pneumococcal vaccine: Decreases the risk of influenza and pneumococcal infections (consult national guidelines).

There is clear evidence that vaccination reduces morbidity and mortality in HIV-infected individuals. See full section later in this chapter.

This chapter focuses on three key interventions (PrEP, PEP and vaccinations), all with strong evidence bases supporting their effectiveness, so that clinicians are equipped with all the necessary information to apply them effectively in primary care settings.

Pre-exposure prophylaxis (PrEP)

PrEP is recommended in *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection* (WHO, 2016): 'Oral pre-exposure prophylaxis (PrEP) containing TDF should be offered as an additional prevention choice for key populations at substantial risk of HIV infection as part of combination HIV prevention approaches.'

Background

Over the previous few years, before the WHO recommendation was published, several studies were done to evaluate the effectiveness of a single ARV, or combinations thereof, in preventing acquisition of HIV by HIV-negative people at higher risk. Different ARVs were assessed, using a variety of delivery systems. The current recommendation is made for the use of oral TDF (alone or with 3TC/FTC).

Who are 'key populations' and what is 'substantial risk'?

WHO defines 'key populations' as groups of people that are at increased risk of acquiring HIV, due to specific higher risk behaviour, irrespective of the epidemic type or context. 'Substantial risk' is considered to exist when the risk of acquiring HIV is more than three per hundred years in person-time. Targeting of people according to these criteria has meant that the offer of PrEP can now be expanded to any high risk group in a particular community. This will be determined by local HIV demographics, rather than generically targeting specific key population groups.

The WHO PrEP Risk Screening Tool contains a set of questions recommended by WHO to help identify individuals who may benefit for PrEP.

WHO PrEP Risk Screening Tool

- PrEP should be provided to people who want to use PrEP if local criteria for its use are met.
- PrEP providers need to be sensitive, inclusive and non-judgmental and support people who want to benefit from PrEP, rather than develop a screening process to discourage it.
- Preferably, frame screening questions in terms of people's behaviour, rather than their sexual identity, and refer to a defined time period.

General screening questions:

- In the past 6 months:
    - Have you had sex with more than one person?
    - Have you had sex without a condom?
    - Have you had sex with anyone whose HIV status you do not know?
    - Have you injected drugs and shared injecting equipment?
    - Have you received a new diagnosis of a sexually acquired infection?
    - Have you used or wanted to use PrEP or PEP for sexual or drug-using exposure to HIV?
- Are any of your partners at risk of contracting HIV, through sexual or drug-using behaviour?
- Do you desire pregnancy?

For people who have a sex partner with HIV, the following questions will help to ascertain whether that person might benefit from PrEP:

- Is your partner taking ART for HIV?
- Has your partner been on ART for more than 6 months?
- At least once a month, do you discuss whether your partner is taking HIV medication daily?
- If you know, when was your partner's last HIV viral load test? What was the result?
- Do you desire pregnancy with your partner?
- Do you use condoms every time you have sex?

The following additional questions may indicate a situation that confers increased vulnerability to HIV and help to identify someone who may benefit from PrEP:

Are there aspects of your situation that may indicate higher risk of HIV? Have you:

- Started having sex with a new partner?
- Ended a long-term relationship and are you looking for a new partner?
- Received money, housing, food or gifts in exchange for sex?
- Been forced to have sex against your will?
- Been physically assaulted, including assault by a sexual partner?
- Injected drugs or hormones using shared equipment?
- Used recreational or psychoactive drugs?
- Been forced to leave your home, especially if due to your sexual orientation or violence?
- Moved to a new place, possibly having a higher prevalence of HIV exposure?
- Lost a source of income, such that you may need to exchange sex for shelter, food or income?
- Left school earlier than you planned?

The evidence base for PrEP

Twelve trials on the effectiveness of oral TDF-containing PrEP have been conducted on a range of people considered to be at higher risk of acquiring HIV, namely: sero-discordant couples; heterosexual men and women; men who have sex with men; people who inject drugs; and transgender women. Where adherence to the regimen was good, there was an overall risk reduction of 51%. Below is a summary of the key finding of the trials:

- The effectiveness correlated directly with the level of adherence.
- The effectiveness did not differ according to age, gender, whether TDF was used alone or in combination with 3TC/FTC, or mode of acquisition (rectal, vaginal or penile).
- The side effect profile showed no statistical difference from placebo.
- The impact on the effectiveness of oral contraceptives showed no statistical difference from placebo.
- There was no evidence that people used condoms less or exposed themselves to more high-risk sex because they felt safer on the PrEP.
- There was no evidence of the development of TDF resistance in the study groups. However, the impact of a wider rollout of PrEP is currently unknown.
- There is no evidence of adverse outcomes in pregnancy or in the infant.

How to use PrEP

Baseline evaluation before starting:

- HIV rapid diagnostic test (RDT): An HIV rapid test should be performed as a screening test at baseline and then every 3 months to look for seroconversion. This is important, as giving two-drug PrEP to an HIV-positive person will rapidly result in resistance to TDF and 3TC/FTC. The HIV-positive person needs to be changed to a full ART regimen.
- HBsAg RDT: Hepatitis B is endemic in many parts of the world where HIV is transmitted. As a combination of TDF and 3TC/FTC is the recommended treatment for the management of more advanced liver disease in hepatitis B/ HIV co-infected persons, knowledge of the HBsAg status is important. This will, firstly, ensure that the combination, rather than just TDF alone is used, and, secondly, promote its continued rather than intermittent use, as stopping it may result in a hepatitis B flare-up.

  HepB testing guidelines (WHO, 2017): https://tinyurl.com/WHO-HebBguidelines
- Creatinine: A creatinine level must be checked, to ensure that there is no prior renal impairment that may be worsened by the TDF.
- Comprehensive initial counselling must be provided to the recipient, to ensure maximum understanding and adherence to the programme.

tinyurl.com/WHO-HebBguidelines

Please note that protective levels of TDF/3TC in the vagina take longer to establish, compared with levels in the rectum, and vaginal levels drop off rapidly after stopping the PrEP. Therefore adherence, although important for both genders, is especially so for women.

Dosing

- TDF 600 plus 3TC/FTC 300 mg daily, ideally starting a week prior to intended high-risk sexual encounter, and continuing for one month after the last high risk encounter.
- Preventative tissue levels of the drugs are achieved within 4 days for rectal mucosa and 7 days for penile and vaginal epithelium. If a high risk encounter occurs before the tissue levels have been achieved, it is recommended that PEP, instead of PrEP, is taken for the next 28 days. (See PEP guidelines later in this chapter.)

Monitoring for side effects of PrEP

Tenofovir is well known for its potential renal toxicity. In addition, nausea, cramps and headache are known side effects. The latter are, however, mild and usually disappear after the first few weeks.

3TC and FTC have only very rare side effects, so there is no need to inform the patient of anything, nor monitor anything specific.

Recommendation for monitoring: Creatinine level should be checked at baseline, then every 3 months for the first year, then annually thereafter.

Table 8.1 PrEP monitoring summary

Timing	Test/intervention
Baseline	HIV rapid test
	Creatinine
	HBsAg RDT
	Counselling and linkage to other healthcare services
Months 3, 6, 9 and 12	HIV rapid test
	Creatinine
	Counselling and linkage to other healthcare services
Ongoing three monthly as long as PrEP is being used	HIV rapid test
	Counselling and linkage to other healthcare services
Annually	Creatinine

Implementation

The programmatic aspects of the provision of PrEP are outside the scope of this clinical handbook. However, it is worth noting the following and referencing the fuller detail in the WHO or local guidelines:

Patient support (see Chapter 25)

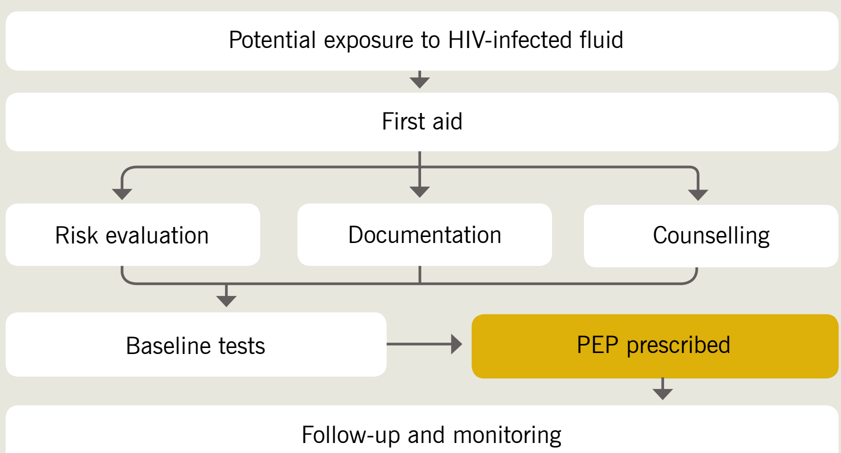
- There should be a comprehensive patient support programme to ensure clear understanding of all aspects of the programme as well as provision of all aspects of support needed. See also **Chapter 25**, Patient Support.
- PrEP should be given along with other preventative measures, such as harm reduction (e.g. needle exchange programmes for IV drug users), condom distribution and family planning.
- Community engagement in the rollout of PrEP plays an important role.
- The provision of PrEP should link recipients to other services, such as hepatitis B vaccination, SRH services (especially STI management), mental health, general primary care and legal services.
- It should be ensured that the providers of PrEP are adequately trained to deal not only with the specific population groups accessing PrEP, but also to promote the different elements of PrEP rollout noted above.

Post-exposure prophylaxis (PEP)

WHO guidelines

PEP is recommended in *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection* (WHO, 2016): 'Oral post-exposure prophylaxis (PEP) should be offered and initiated as early as possible in all individuals with an exposure that has the potential for HIV transmission, preferably within 72 hours.'

Figure 8.1 Steps in the use of post-exposure prophylaxis



There are 3 key components to deciding whether someone has had an exposure to HIV that could result in infection:

1. **The HIV status of the source**. If this cannot be obtained, other factors to be taken into consideration may include background prevalence and local epidemiological patterns. In high HIV-prevalence environments, the default is to consider the source as HIV positive.
2. **The fluid from the source:**
    - The following fluids may contain HIV: Blood or any blood-stained fluids, breast milk and sexual secretions.
    - The following may contain HIV but usually need access by a health care worker: amniotic, peritoneal, synovial, pericardial or pleural fluids and cerebrospinal fluid.
    - The following are considered to be non-infectious (if not contaminated with above fluids): Sweat, tears, saliva, sputum, urine and stool.
3. **The nature of the exposure to the source's fluid:**

    Exposures that may result in HIV transmission:

    - Mucous membrane contact (sexual exposure, splashes to eye, nose or oral cavity).
    - Directly into the bloodstream – e.g. needle stick injuries, via open cuts or wounds.

First aid

In the case of any immediate exposure, the following guidelines should be observed:

- If it is a needle-stick injury or contamination of an open wound, let the wound bleed (without squeezing), wash both the wound and surrounding skin with water and soap (without scrubbing) and then rinse.
- If it is an exposure involving the eyes or mucous membranes, rinse the exposed area immediately with an isotonic saline solution for 10 minutes. Antiseptic eye drops can also be used for eye exposure. If none of these solutions are available, use clean water.

Risk evaluation

The following are considered not to be at risk and are therefore not eligible for PEP:

- The exposed person is already HIV positive.
- The source is reliably negative.
- The exposure is to body fluids that do not pose a significant exposure risk (see point 2 above).

Table 8.2 Risk evaluation for PEP

Type of exposure	HIV status of source		
	Positive	Unknown	Negative
Percutaneous exposure to infectious fluids	Three drug prophylaxis	Three drug prophylaxis	No PEP
Mucous membrane exposure to infectious fluids	Three drug prophylaxis	Three drug prophylaxis	No PEP
Mucous membrane exposure to non-infectious fluids	No PEP	No PEP	No PEP
Intact skin exposure to any fluids	No PEP	No PEP	No PEP

Documentation

Ensure careful completion of all the necessary documentation according to local requirements. This will be important for both workmen's compensation, in the case of an occupational health exposure, and for medico-legal reasons, in the case of sexual assault.

Counselling

PEP studies report low completion rates in all populations, especially in adolescents and following sexual assault. Counselling should be individualised for each person and should incorporate the following components:

- Management of anxiety. This is always to be taken seriously and may need more than one counselling session.
- Explain that the risk, even with a significant exposure, is still very low if PEP is taken correctly and timeously.
- Explain the drugs, their side effects and the time-line for the process in the future.
- Encourage the patient to return if side effects are unmanageable, rather than stopping the medication.

Baseline tests

Testing of the source patient

If possible, this should be done in all instances of potential exposure and include the following:

- HIV rapid test
- Hepatitis B sAg
- Syphilis: TPHA or RPR
- Hepatitis C Ab (dependent on regional prevalence and the profile of the source)

Testing of the exposed person

If available, ideally all of these tests should be done:

- HIV rapid test.
- Hepatitis B sAb and sAg:
  - If both are negative, the patient needs to be vaccinated.
  - If HBsAg is positive the patient will need to continue with TDF and 3TC/FTC after the PEP to prevent a post-PEP hepatitis flare-up. The availability of the HBsAg test is however not a pre-condition for TDF- and 3TC/FTC-based PEP.
- Hepatitis C Ab (only if high risk contact – high prevalence area and/or source is an IV drug user).
- STIs should be screened for, and treated following established guidelines.
- Pregnancy testing should be offered to all women at baseline and emergency contraception offered as soon as possible within 5 days of sexual exposure.
- Tetanus immunisation should be offered if indicated, according to standard guidelines.

The following should be done as pre-PEP safety tests:

- Creatinine if TDF will be used
- Hb if AZT will be used.

PEP prescribed

For adults, adolescents and children older than 6 years or > 15 kg

- The regimen of choice is TDF + 3TC/FTC + DTG. RAL is recommended if DTG is not available.
- The first dose is given as soon as possible after exposure, ideally in the first 72 hours.
- If the ideal drugs are not immediately available, give whatever triple drug regimen is at hand and switch to the ideal drugs as soon as possible.
- The PEP regimen is given for 28 days.
- This needs to be supported by full adherence counselling.

Notes

- If TDF is contra-indicated, AZT is recommended as the alternative NRTI.
- All adolescent girls and women should be offered pregnancy testing at baseline and during follow-up.
- Emergency contraception should be offered to girls and women as soon as possible within 5 days of the sexual exposure and information provided on the risks (including neural tube defects) and benefits of DTG. For those who do not want to take emergency contraception or DTG, an alternative ARV to DTG (such as a boosted PI) should be provided.
- Alternative third drugs are darunavir/ritonavir (DRV/r), ATV/r, LPV/r or EFV.
- ATV/r and DRV/r have the least side effects of the commonly available NNRTIs and PIs, so are the best alternative if RAL is not available.
- LPV/r has significant gastro-intestinal tract (GIT) side effects so is best avoided.
- EFV, though a safe drug, is not ideal for PEP as its potential neuro-psychiatric side effects will be unhelpful in a patient already anxious about an HIV exposure.
- NVP should not be used for PEP in anyone over 2 years old because of the high risk of adverse event associated with a higher CD4.

For children younger than 6 years or <15 kg

- AZT, 3TC and LPV/r is the recommended regimen.
- The same principles noted above for adults (immediate first dose, given for 28 days, full adherence support) apply to children as well.

Notes

- ABC can be given as an alternative to AZT.
- If LPV/r is not available, an age-appropriate regimen can be identified among ATV/r, RAL, DRV/r, EFV and NVP.
- NVP must not be used in children >2 years of age.

Follow-up and monitoring

Table 8.3 Baseline and follow-up tests for PEP

Test	Source	Exposed person		
	Baseline	Baseline	Six weeks	Three months
HIV	HIV rapid test*	HIV rapid test		HIV rapid test
HBV	HB sAb	HB sAg and HB sAb		
HCV	HCV Ab	HCV Ab		
Syphilis	RPR/TP Abs	RPR/TPHA/FTA		RPR/TPHA/FTA
Tetanus		Tetanus Abs		
Pregnancy		Standard test		
Creatinine		If TDF in regimen		
Hb		If AZT in regimen		
Counselling		Yes	Yes	Yes

* **Notes**

- Ideally all HIV rapid tests are accompanied by a 4th generation ELISA HIV test.
- See ‘Testing of the exposed person’ under the heading ‘Baseline tests’, above.
- Counselling, as always, is ideally individualised and needs to include:
  - ongoing support and reassurance;
  - management of anxiety;
  - monitoring for ARV toxicities;
  - encouraging adherence for the full 28 days; and
  - follow-up HIV testing.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Vaccines in HIV-infected children and adults

The fuller text of this section, including all the references, can be read or downloaded from the **SAMU website**: https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

Objective of this section

There is clear evidence that vaccination reduces morbidity and mortality in HIV-infected individuals. While the availability of specific vaccines and HIV-specific schedules in a given project is usually in the hands of the programme managers and beyond the scope of activity of the consulting clinician, there are still important roles that the clinician can play:

- to be aware of the local vaccination schedules and to ensure that they are being implemented;
- to be aware of the need for specific additional vaccine interventions for HIV-positive people and to know what is available locally to meet these requirements; and
- to advocate with local programme managers for these specific additional interventions, if they are not available.

The **objectives** of this section are therefore to:

- outline the important principles underlying vaccinations in HIV-positive patients; and
- provide guidelines for recommended vaccines for HIV-positive people. (Although based on evidence coming mostly from **high income countries**, these are tailored to **low and middle income countries** (LMIC), the settings where MSF intervenes.)

Vaccination overview

Immunisation is one of the most successful and cost-effective public health interventions preventing 2 to 3 million deaths annually. The **Expanded Programme on Immunisation (EPI)** was launched in 1974 to decrease morbidity and mortality of **vaccine-preventable diseases (VPDs)** worldwide. As part of the programme, each country has developed a national EPI calendar that includes the list of vaccines provided and the specific age and interval at which each antigen should be received.

Despite improved survival of HIV-positive people in the last decades, patients are still dying from diseases that can easily be prevented, including VPDs. This situation is further worsened by poor living conditions and hygiene.

Because of the many public health benefits for proactive immunisation of all HIV-positive people, free vaccination for HIV-positive individuals must be considered a priority in all settings where MSF intervenes and should be included in the package of care offered to HIV-positive patients.

Additional vaccine interventions needed for HIV-positive people

The underlying principle of giving a vaccine is to expose the body to a dose of an infecting agent so that an immune response is mounted that gives long-term immunity to that particular infecting agent. Doses and schedules for each disease have been worked out following extensive studies, so must be followed carefully if the desired outcome of long-term immunity is to be achieved. The infecting agent given in the vaccine, however, must be either dead ('inactivated') or alive and significantly weakened ('live and attenuated') so that it doesn't actually cause the very infection the vaccine is trying to prevent.

There are two important consequences of this in the HIV-positive patient with severe immunosuppression (see box):

- The body may not have enough of an immune response to develop the antibodies needed for the desired protection.
- Where live attenuated vaccines are used, the possibility exists that there is enough infecting ability to actually cause an infection because the body's immune response is not sufficient to prevent this from happening.

Severe immunosuppression is defined as:

- individuals aged ≤5 years must have CD4 percentages <15% for ≥6 months
- individuals aged >5 years must have CD4 percentages <15% or CD4 cell counts ≥200 lymphocytes/mm^3 for ≥6 months).

Specific vaccination recommendations have, therefore, been made for HIV-positive patients, to allow for:

- More aggressive strategies for VPDs, to accommodate increased prevalence and virulence of VPDs;
- Potentially poor immune responses in patients with low CD4s; and
- The risk of patients with low CD4s being infected by live attenuated vaccines.

Table 8.4 Inactive and attenuated vaccines

Inactive vaccines	Live, attenuated vaccines
Pneumococcus	BCG
Diphtheria	Polio, oral
Polio, injected	Varicella
Tetanus	Herpes zoster
Hepatitis A and B	Yellow fever
Meningococcal vaccine	Rotavirus
Influenza	Measles, mumps, rubella
Haemophilus B	

General principles regarding vaccinations in HIV-positive individuals

- All inactivated vaccines can be administered safely to all HIV-positive individuals, regardless of CD4 count. They may, however, not be as effective if CD4 count is low (see third bullet below).
- Live-attenuated vaccines should ideally not be given to patients with severe immunosuppression. These patients are, however, at higher risk than those with better immunity for complications of varicella, herpes zoster, yellow fever and measles, diseases for which only live vaccines are available. The benefit of vaccination in these cases appears to outweigh the risks, so HIV status should not be considered an absolute contra-indication to vaccination with live vaccines.
- Vaccines vary in their ability to stimulate an immune response. This has been studied in relation to viral load and CD4 levels. Vaccination schedules have been developed with due consideration for these situations.
- As with HIV-negative individuals, if a schedule is interrupted, it can be resumed without repeating previous doses.
- Clinicians should ensure that the vaccination status of each HIV-infected individual is up to date and information about received or delayed vaccination should be included in the clinical file.
- There are no interactions between ART and vaccines.

Recommended vaccination schedules for HIV-positive patients

These are provided below, categorised according to different age groups. The motivation for giving vaccines has already been outlined above, but where additional data exists to provide further motivation, this is provided.

> Remember at all times to document the vaccinations given on the vaccination card. If the patient doesn't have a card, ensure that they get one.

HIV-exposed but uninfected (HEU) infants

Motivation

- In studies in low and middle income countries (LMIC), HIV-exposed but uninfected (HEU) infants have been shown to have higher early mortality (primarily because of bacterial pneumonia and sepsis) than those born to uninfected mothers.
- There is increasing evidence for insufficient maternally derived antibody levels in HEU infants that put those infants at increased risk of pneumococcal and other vaccine-preventable infections.

Ensuring that these HIV-exposed children receive timely vaccination should be a priority in all HIV projects.

HIV-positive children up to 5 years of age

Motivation

- In addition to ART, vaccination is one of the most important interventions to prevent viral and bacterial infections in HIV-infected children.

Vaccinations

- Vaccination status for all recommended vaccines should be reviewed at every clinical visit.
- Ensure that they are timeously vaccinated, according to the country's EPI schedule.
- Although there is concern about the magnitude, quality or duration of immunologic response from vaccines given pre-ART, there is no consensus about the need for routine re-vaccination once on effective ART (with the exception of measles-containing vaccines; see below).

Table 8.5 Vaccinations for HIV-positive children up to 5 years of age

Vaccine	Notes
Polio	Give OPV/injectable as per EPI schedule.
BCG	This is a live attenuated vaccine so has the potential to cause an active infection with mycobacterium bovis, the TB strain used in the vaccine. BCG vaccination should be given routinely as soon as possible to HIV-exposed babies; ideally at birth. The baby must be closely followed for early identification and treatment of any BCG-related complication such as lymphadenitis, osteomyelitis, or disseminated TB infection. Exceptions to this: At birth: If the mother has pulmonary TB BCG, vaccination should be delayed and INH prophylaxis therapy (IPT) given to the baby for 6 months. BCG is then given 2 weeks after completion of IPT, provided active TB in the child has been excluded. In the first 6 weeks, if the vaccine wasn't given at birth: • If the baby has symptoms of TB, TB treatment should be started. • A child who is known to be HIV-infected should not receive BCG.
Hepatitis B	One dose of Hep B monovalent vaccine provided as soon as possible after birth is >90% effective in preventing HBV-perinatal transmission. The Hep B series should be completed with either monovalent Hep B or a combination vaccine containing HepB. Infants who did not receive a birth dose should receive 3 doses of a Hep B-containing vaccine on an age-appropriate schedule.
Measles-containing vaccine (MCV)	The first dose of measles vaccine should be given to all HIV-infected or -exposed infants at 6 months (not the usual 9 months). In addition, they should get the usual 2 doses of MCV, the first one at 9 months. The second is usually given sometime in the second year, but, in unstable/conflict settings, where a future opportunity may be missed, the vaccine can be given at any time from 4 weeks after the 9-month dose. If there is any evidence of severe immunosuppression, delay till the CD4 has increased. Once children are on ART, current recommendations are for routine MCV re-vaccination after ART. All HIV-infected individuals, regardless of their immunological status, should be vaccinated against measles in case of outbreak.

Anti-pneumococcus pneumoniae	HIV-infected children have a markedly higher risk of pneumococcal infection than do HIV-uninfected children. Give the pneumococcus conjugate vaccine available in the EPI schedule. • Children below 12 months: 3 doses of PCV vaccine at minimum interval of 4 weeks • Children 12–23 months: 2 doses at minimum interval of 8 weeks • Children >23 months: 1 dose In children aged ≥2 years the administration of 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended at least 8 weeks after the last dose of PCV13. A single revaccination dose should be administered 5 years thereafter.
Haemophilus influenzae type b (Hib)	HIV-infected children are at increased risk of Haemophilus influenzae type b (Hib) infection. Three doses of Hib-containing vaccine should be administered at a minimum interval of 4 weeks to all children below one year of age. For children up to 5 years of age, combined vaccine against diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenza type b (DTP/HepB/Hib*) is used for routine vaccination.
Rotavirus	Rotavirus is a live vaccine but considerably attenuated (weakened). HIV-exposed or -infected infants should receive rotavirus vaccine according to the national EPI schedule for uninfected infants.
Meningococcal vaccine (MenACWY)	HIV infection is associated with an increased risk of meningococcal disease. The vaccine can be ordered from MSF projects, as it is available in the MSF catalogue. For all HIV-infected children aged ≥9 months, dose is 2 x MenACWY doses 2–3 months apart for children aged 9–23 months and at least 2 months apart for children aged 2–10 years.
Yellow fever	In endemic countries one dose of yellow fever vaccine is recommended for all HIV-infected individuals aged ≥9 months who do not have evidence of current severe immunosuppression (or suggestive clinical appearance). Current recommendation is that an antibody test is done every 10 years and if the level is too low, a booster dose is given. Alternatively, just give a booster dose every 10 years anyway. All HIV-infected individuals, regardless of immunological status, should be vaccinated against yellow fever in case of outbreak.

Note

* This vaccine is often called Pentavalent as 5 antigens are included in the formulation.

HIV-positive children aged 6–18 years

Table 8.6 Vaccinations in HIV-positive children aged 6–18 years

Vaccine	Notes
Polio	If there is no proof of vaccination, a series of 4 doses bOPV at a minimum interval of 4 weeks should be provided (IPV to be given with 1st dose of bOPV). If primary series of bOPV has been completed, one dose of IPV should be provided.
Diphtheria, tetanus, pertussis	Apart from the primary vaccine series, a single dose of a vaccine containing tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis (dTap) should be administered to all individuals aged 6 years and older who have not received dTap previously. Universal administration of tetanus toxoid and reduced diphtheria toxoid (Td) boosters every 10 years is also recommended because of waning immunity against tetanus and diphtheria over time*.
Hepatitis B	Same recommendation as for adults (see adult section below).
Measles-containing vaccine (MCV)	Two doses of MCV vaccine at a minimal interval of 4 weeks are recommended for all HIV-infected individuals who do not have evidence of measles immunity (no past measles vaccine and never actually had measles) and/or have no evidence of current immunosuppression. (See box at beginning of this section). All HIV-infected individuals, regardless of immunological status, should be vaccinated against measles in case of outbreak.
Pneumococcal vaccines	A single dose pneumococcal conjugate vaccine (PCV13 or PCV10, according to the country schedule) should be routinely administered to HIV-infected children aged 6 through 18 years who did not previously receive a dose of PCV13 before age 6 years. In children aged ≥2 years the administration of 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended at least 8 weeks after the last dose of PCV13. A single revaccination dose should be administered 5 years thereafter.
Human papillomavirus (HPV) vaccine	Although HPV vaccines are more effective when given before exposure to HPV through sexual contact, HPV vaccination is recommended in HIV-positive individuals because of the high burden of HPV-related diseases in this vulnerable group. The minimum age to received HPV vaccination is 9 years. For all HIV-infected adolescents up to age 26 years the vaccine should be administered according to a 3-dose schedule (0.5 ml at 0, 2, 6 months).
Meningococcal (MenACWY**)	As for healthy children, HIV-infected children should routinely receive meningococcal conjugate vaccine at age 11–12 years and again at age 16.
Yellow fever	In endemic countries one dose of yellow fever vaccine is recommended for all HIV-infected individuals aged ≥9 months who do not have evidence of current severe immunosuppression. Current recommendation is that an antibody test is done every 10 years and if the level is too low, a booster dose is given. Alternatively, just give a booster dose every 10 years. All HIV-infected individuals, regardless of immunological status should be vaccinated against yellow fever in case of outbreak.

Notes

* Tetanus-containing vaccines recommended for children older than 7 years and adults are those with reduced diphtheria toxoid. This is indicated by the letter 'd' in the formulation: dTap and Td.

** Quadrivalent-conjugate vaccines

Recommended vaccines for HIV-positive adults

Although HIV-infected adults are at increased risk of contracting vaccine-preventable diseases (VPDs), they don't have access to free vaccination as they are not part of EPI target.

Table 8.7 Recommended vaccines for HIV-positive adults

Vaccine	Notes
Polio	If there is no proof of vaccination, a series of 4 doses at a minimum interval of 4 weeks should be provided (IPV to be given with 1st dose of bOPV). If primary series of bOPV has been completed, one dose of IPV should be provided.
Diphtheria, tetanus, pertussis	Apart from the primary vaccine series, a single dose of a vaccine containing tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis (dTap) should be administered to all HIV-infected adults who have not received dTap previously. One dose of tetanus-containing vaccine should be administered to adults and adolescents who were not previously vaccinated or for which vaccination status is uncertain. All adults should receive one dose of tetanus and diphtheria toxoids (Td) booster every 10 years. One dose of dTap should be administered to women during each pregnancy, preferably during weeks 27–36 of the pregnancy. Before circumcision, two doses of tetanus-containing vaccine are given, one 6 weeks before and the second 2 weeks before the procedure.
Hepatitis B	All HIV-infected patients are at increased risk of hepatitis B virus (HBV) infection due to shared modes of transmission. Hepatitis B virus (HBV) co-infection is responsible for high morbidity and mortality among HIV-positive people, despite the advent of ART. Vaccination is the most effective way to prevent HBV infection and its consequences. All HIV-infected patients susceptible to HBV should receive hepatitis B vaccination. The vaccination series for HBV should be initiated at first visit, regardless of CD4 cell count. Different authorities have varying approaches to vaccination: 1. Administer the standard three-dose regimen at 0, l month and 6 months. 2. Start with a double dose of vaccine (e.g. Engerix-B vaccine at 40 rather than 20 mcg/mL), then 20 mcg/mL at months 1 and 6. 3. Give the same as option two but give an extra 20 mcg/mL dose at month two.

Measles-containing vaccine (MCV)	Two doses of MCV vaccine 4 weeks apart are recommended for all HIV-infected individuals who do not have evidence of measles immunity (no past measles vaccine and never actually had measles) and/or have no evidence of current severe immunosuppression. (See box at beginning of this section). All HIV-infected individuals, regardless of immunological status should be vaccinated against measles in case of outbreak.
Pneumococcal vaccines	Streptococcus pneumoniae is the leading bacterial opportunistic infection in HIV-infected individuals and the risk of invasive disease is still 20- to 40-fold greater than age-matched general population. In the setting of high TB prevalence, it is often difficult to differentiate between TB and pneumococcal infection, resulting in frequent misdiagnosis of TB and unnecessary TB treatment. Vaccinating HIV-positive people against pneumococcus helps narrow down the diagnostic options. In addition to pneumococcus conjugate vaccine, the administration of 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended at least 8 weeks after the last dose of PCV13. Revaccination is subsequently performed with PPSV23 at least 5 years after the initial PPSV23 dose.
Meningococcal (MenACWY)	The current recommendation is routine MenACWY vaccination of people with HIV infection. This group should receive a 2-dose primary series of MenACWY administered 2 months apart followed by booster doses every 5 years.
Yellow fever	In endemic countries one dose is recommended for all HIV-infected individuals aged ≥9 months who do not have evidence of current severe immunosuppression. If the latter, defer immunisation till CD4 has risen. Current recommendation is that an antibody test is done every 10 years and if the level is too low, a booster dose is given. Alternatively, just give a booster dose every 10 years. All HIV-infected individuals, regardless of immunological status should be vaccinated against yellow fever in case of outbreak.
Human papillomavirus (HPV) vaccine	Although HPV vaccines are more effective when given before exposure to HPV through sexual contact, HPV vaccination is recommended in HIV-positive individuals because of the high burden of HPV-related diseases in this vulnerable group. The minimum age to received HPV vaccination is 9 years. For all HIV-infected adolescents up to age 26 years the vaccine should be administered according to a 3-dose schedule (0.5 ml at 0, 2, 6 months).

Appendix 8.1 Cotrimoxazole prophylaxis

(also see Appendix 8.2 for desensitisation schedule)

Recommended dose/ Protection against	Indications to start	Indications to discontinue	If allergy or intolerance to cotrimoxazole
Recommended dose Adults: CTX 960 mg od. Infants and children: dosage according to body weight (see Table 10.2 on page 160). **If taken regularly, CTX protects against** • pneumonia, **especially PCP** • brain infections (toxoplasmosis) • certain types of diarrhoea • other bacterial infections, such as UTI • malaria. CTX is a combination of two antibiotics: trimethoprim (TMP) and sulfamethoxazole (SMX). There are several trade names for CTX: Bactrim®, Septrim®, etc.	**HIV-infected adults** CD4 <350 cells/µl or clinical stages 2, 3 or 4.	**HIV-infected adults** On ARVs and CD4 >200 cells/ µl on 2 consecutive occasions 3–6 months. In settings with **high prevalence of malaria and/ or severe bacterial infections** (most low and low middle income countries), **may be continued** in adults with HIV infection, **regardless** of CD4 cell count and WHO clinical stage.	**Non-severe side effects (grades 1 and 2):** • Desensitise adults (see Appendix 8.2). • Desensitisation should not be done in children. **Grade 3 toxicity to CTX or desensitisation not successful:** • Dapsone 100 mg daily (protects against PCP, but limited protection against toxoplasmosis). • Therefore, add pyrimethamine 50 mg + folinic acid** 25 mg weekly to protect against toxoplasmosis if available. In case of severe reactions to CTX (grade 4 skin, liver, kidney or bone marrow toxicity), dapsone should not be used, as there may be cross-reactivity. Dapsone is safe in pregnancy. Dapsone (2 mg/kg/day) can be given to infants and children unable to tolerate CTX. *** Note that folinic acid is not the same as folic acid.*
	All HIV-exposed infants Starting at 6 weeks of age.	**HIV-exposed infants** Negative PCR or rapid HIV test at least 6 weeks after complete breastfeeding cessation and absence of clinical signs of HIV infection.	
	HIV-infected children • All children <5 years. • If >5 years, follow same guideline as for adults; all those wtih stages 2, 3 and 4 or CD4 <350 cells/µl.	**HIV-infected children without previous PCP or toxoplasmosis*:** • Age 0–5: Do not stop cotrimoxazole. • Age >5: On ARVs and CD4 >200 cells/µl on 2 consecutive occasions 3–6 months apart. **HIV-infected children with previous PCP or toxoplasmosis*:** • <5 years: Do not stop. • >5 years: On ARVs and CD4 >200 cells/µl on 2 consecutive occasions 3–6 months apart. ** Children at risk of malaria should be maintained on CTX until that risk subsides.* In settings with **high prevalence of malaria and/ or severe bacterial infections** (most low and low middle income countries), **may be continued** in adults with HIV infection, **regardless** of CD4 cell count and WHO clinical stage.	
	In settings with **high prevalence of malaria and/or severe bacterial infections** (most low and low middle income countries), CTX prophylaxis should be **considered in all** adults and adolescents with HIV infection **regardless** of CD4 or WHO stage. Refer to your national guidelines.		

Appendix 8.2 Desensitisation to cotrimoxazole

Desensitisation can be offered rapidly or over a longer period of time.

Do not desensitise anyone who has had an anaphylactic reaction to cotrimoxazole or a severe skin rash such as Stevens-Johnson syndrome.

Do not attempt in children.

Desensitisation is usually about 60% effective. Rapid desensitisation ideally should be performed during the day in a setting where emergency resuscitation can be provided and adrenaline can be given. Observations during rapid desensitisation should take place every 30 minutes, before each dose is given, and should include temperature, pulse, and blood pressure.

If only mild rash or pruritus occurs, administer antihistamine (e.g. chlorpheniramine or promethazine) and continue. If more serious side effects occur, such as severe wheeze, severe or symptomatic hypotension, severe rash, and so on, discontinue desensitisation, manage appropriately, and do not try to restart desensitisation.

Once cotrimoxazole has been started, it can be continued indefinitely as long as no reactions are noted, but if the drug is stopped at any time, there may be a risk of reaction when it is restarted.

Using a 1 ml syringe, put 0.5 ml of paediatric cotrimoxazole 240 mg/5 ml syrup in 1 000 ml of 5% dextrose and mix well.

Give as follows:

Minutes	Quantity of above mixture given orally
0	1 ml (use 10 ml syringe)
30	10 ml (use 10 ml syringe)
60	100 ml (use 10 ml syringe)

Then switch to paediatric cotrimoxazole 240 mg/5 ml syrup in adults.

Minutes	Quantity
90	0.5 ml
120	5 ml
150	480 mg tablet
180	Start full prophylactic or therapeutic dose.

CHAPTER 9

Prevention of mother-to-child transmission of HIV

Please note that prevention of mother-to-child transmission of HIV (PMTCT) is covered in a more interactive learning environment in Module 4 of the 2018 edition of the **SAMU HIV/TB e-learning course**. See 'How to use this book' for details.

The pillars of PMTCT programming

Prevention of mother-to-child transmission of HIV (PMTCT) is not just about providing antiretroviral interventions for the HIV-positive mother and the exposed infant. PMTCT can be divided into 4 pillars (Figure 9.1)

Figure 9.1 The pillars of PMTCT programming

Primary prevention of HIV in women of child-bearing age	Family planning	HTS and ART PMTCT interventions	Ongoing care for the HIV-positive mother and father
• Behaviour change • Condom use • ART for positive partner • PrEP	• Preventing unwanted pregnancies • Providing pre-conception planning for HIV-positive women	• HIV testing in antenatal, maternity and postnatal settings • Provision of ART to HIV-positive women during pregnancy, at delivery and during breastfeeding • Management of the HIV-exposed infant (provision of ARV and cotrimoxazole prophylaxis and early infant diagnosis)	• Maintenance of lifelong ART

Primary prevention of HIV in women of child-bearing age

All HIV-negative women of child-bearing age should be provided with health education on how to remain HIV negative. The following elements of a comprehensive prevention package should be offered to all HIV-negative women, including in antenatal and postnatal care settings.

- HIV testing services (HTS) for the woman;
- HTS for all sexual and drug-injecting partners;
- Male partner referral for ART if HIV positive;

- Male partner referral for voluntary male medical circumcision (VMMC) if HIV negative (in VMMC priority countries). This decreases his chances of becoming infected and then infecting the woman;
- STI screening and treatment;
- Condom promotion;
- Risk reduction counselling; and
- Offer, start or continue PrEP, based on individual risk assessment. PrEP can also be included as part of the safer conception package if an HIV-positive male partner is not virologically suppressed. It is now considered that sexual transmission of HIV does not occur if the HIV-positive person is virally suppressed. There is however a risk of transmission if the viral load is elevated. Ideally unprotected sex should not be happening at this time but should there be any risk of this occurring, PrEP will offer significant protection. (**Chapter 8** details the use of PrEP).

Existing safety data supports the use of PrEP in pregnant and breastfeeding women who remain at continuing substantial risk of HIV infection. A risk assessment tool should be used to assess eligibility for PrEP. The WHO PrEP Risk Screening Tool is provided on page 110 of **Chapter 8**. For further information on the choice of antiretrovirals and monitoring requirements refer to **Chapter 8.**

Experience of using PrEP in antenatal and postnatal settings is limited and may have to be implemented within an operational research framework. Three scenarios in which PrEP should be considered in HIV-negative pregnant and breastfeeding women include:

- A woman taking PrEP who subsequently becomes pregnant and remains at substantial risk of HIV infection;
- A pregnant or breastfeeding HIV-negative woman living in a setting with high HIV incidence, who is at substantial risk of HIV acquisition;
- A pregnant or breastfeeding HIV-negative woman at substantial risk of HIV infection due to high risk exposures (e.g female sex worker, partner of unknown HIV status in high prevalence settings);
- A woman whose partner is HIV positive but is not virologically suppressed (see **Chapter 8**).

Family planning

For HIV-positive women who wish to conceive, advice should be given that they wait until their viral load has suppressed, usually after 6–12 months on ART. If presenting with advanced HIV disease (CD4 <200 cells/mm^3 and/or stage 3 or 4) it is advised to wait for all opportunistic infections to be treated and ideally for CD4 to increase to >350 cells/mm^3. For information on family planning for HIV-positive women see **Chapter 19**.

HTS and ART PMTCT interventions

Integration of PMTCT and sexual and reproductive health (SRH) services

Once an HIV-positive woman becomes pregnant, and until the baby is tested HIV negative 3 months after cessation of breastfeeding, there are several interventions that need to occur, as outlined in pillar 3 of Figure 9.1. PMTCT services should be integrated within antenatal care, delivery and postnatal services and postnatally, mother and baby should be seen together on the same day in a 'family approach'. The aim of an integrated service is to maximise the likelihood of retention in care by providing the woman with both the SRH and HIV services required on:

- the same day;
- in the same consultation room; and
- by the same healthcare worker.

Ongoing care for the HIV-positive mother and father

Once the pregnancy and breastfeeding episode is completed it is important that all HIV-positive members of the family are retained in long-term care. The child needs to be connected to an ART clinic, with consultations ideally scheduled on the same day as the mother. Both parents need to be linked to HIV care so that they remain virally suppressed, not only for their own health but also in the best interests of PMTCT in future pregnancies.

The PMTCT cascade

PMTCT interventions can be broken down into the steps shown in Figure 9.2. Gaps at each step may lead to HIV-positive women not being identified and increased risk of HIV transmission to the baby.

Antenatal care attendance

Women should be encouraged to test for pregnancy early, i.e. after missing a period. All clinics should have access to pregnancy tests to detect early pregnancy, and, where feasible, access to pregnancy tests in the community should be encouraged (e.g. through community health workers).

Women should also be encouraged to book into antenatal care early in their pregnancies, both for the benefits of antenatal care and to enable early initiation of ART for those testing positive. Ideally, any HIV-positive pregnant woman identified in pregnancy should receive at least 12 weeks of ART prior to delivery. For those women who receive less than 4 weeks of ART, their infant will be classified as high risk and require enhanced prophylaxis.

Figure 9.2 The PMTCT cascade

Antenatal care attendance	HIV testing and re-testing	ART for the HIV-positive mother	Exposed baby follow-up
• Early identification of pregnancy • Early attendance at antenatal clinic	• HIV testing at first antenatal clinic visit • Re-testing of negative clients in third trimester, at delivery and during breastfeeding • Re-testing of HIV-positive clients prior to initiation of ART	• During pregnancy • During delivery • During breastfeeding • Continuation of lifelong ART for the health of mother and to protect future pregnancies • Achievement of virological suppression throughout	• Provision of ARV prophylaxis • Provision of cotrimoxazole prophylaxis • Early infant diagnosis • Access to EPI • Growth monitoring

HIV testing and re-testing

All women who are pregnant, in labour or breastfeeding, who had an unknown or HIV-negative status more than 3 months previously, should be offered HIV testing at the first contact. Pre-test counselling may be performed as a group during first antenatal booking visits. HIV testing should be performed at the same time as the other antenatal blood tests. If the woman does opt out, she should be counselled at subsequent visits and encouraged to test.

If tested positive, all women should be re-tested for HIV according to the HIV testing algorithm for the setting prior to initiation of ART.

Guidance on re-testing of women with an initial HIV-negative test **will vary according to the prevalence of the context and local resources**.

MSF guidance for re-testing is:

- If tested negative in the first or second trimester, the woman should be re-tested in the third trimester (usually at 32 weeks – refer to **national guidelines**).
- Women with unknown status or a negative HIV test before the third trimester should be re-tested at delivery.
- In high prevalence settings, women should be re-tested during breastfeeding, ideally every 6 months. These women will not be attending for their own health but will attend EPI visits for their child. Therefore, linking re-testing to EPI visits is a programmatic strategy to enhance the uptake of re-testing, e.g. re-test at 6-week EPI visit if not tested at delivery; re-test at 9-months measles visit.

Refer to your national guidelines

All partners should be encouraged to test. Women should be asked to invite partners to the facility to be tested at future ANC visits or to attend voluntary counselling and testing (VCT) services at any time. The use of invitation letters has been shown to increase the uptake of partner testing. If not successful, with the consent of the woman, community-based partner testing should be offered. Use of HIV self-tests for women to offer to their partners is also a strategy to enhance partner testing.

ART for the HIV-positive mother

Where to initiate ART in PMTCT?

ART and SRH services should be integrated and provided at MCH clinics, antenatal wards, labour and delivery or postnatal clinics.

When to initiate ART in PMTCT?

In PMTCT, same-day initiation is the goal, but the client must be clinically and psychologically ready to start ART. If same-day initiation is not feasible, aim to initiate ART within 7 days.

Initiation should be offered during clinic hours in antenatal care and postnatal care, but be available 24 hours at the maternity setting.

Who initiates ART in PMTCT?

Any trained healthcare worker, including trained nurses and midwives, can initiate ART to a pregnant or breastfeeding mother.

Who should provide psychosocial support in PMTCT?

Psychosocial support may be provided by the clinician, nurse, midwife or lay counsellor. Where possible, linking a newly diagnosed pregnant mother with an HIV-positive woman who has already undergone PMTCT (e.g. mothers-to-mothers programme) has been shown to support adherence, encourage disclosure and decrease loss to follow-up.

What happens at initiation of ART in PMTCT

All women who test positive antenatally, during pregnancy and during breastfeeding should be initiated on ART as soon as possible. Compared to EFV, dolutegravir (DTG) has the advantages of more rapid rates of suppression, a lower side-effect profile and high levels in breast milk; preferred features for pregnancy and breastfeeding. However, due to preliminary data showing a higher incidence of neural tube defects in women who were taking DTG at the time of conception, the following are current WHO recommendations for PMTCT:

- Pre-conception and in first trimester: TDF + 3TC/FTC + EFV (please watch for WHO updates on this)
- During second and third trimester and breastfeeding: TDF + 3TC/FTC + DTG

In addition to the medical history and examination outlined in **Chapter 3**, a full obstetric history and examination should be performed. Baseline investigations should be performed as outlined in **Chapter 3**, including CD4, in order to determine whether the advanced disease package should be implemented. However, if there is no clinical indication to delay ART initiation, lack of access to baseline investigations or their results should not delay the offer of same-day initiation. If at a subsequent visit the baseline CrCl is shown to be <50ml/min, substitute TDF with AZT (if the HB is >8g/dl). Low CrCl in pregnant women is very rare (<1% in most settings).

The psychosocial assessment for ART initiation should follow the steps as outlined in **Chapter 3**. However, as same-day initiation is aimed for, emphasis should be on the adherence plan, explanation of side effects and supporting the plan for disclosure (see PMTCT section in **Chapter 25**)

Patient support
(see Chapter 25)

For full details of the counselling sessions in PMTCT please refer to the **MSF PMTCT Counselling Guidelines** and accompanying flip chart. (https://samumsf.org/en/resources/hiv/pmtct)

samumsf.org/en/
resources/hiv/pmtct

ART follow-up for pregnant and breastfeeding women

Integration of SRH with ART services is a key principle of differentiated ART delivery for pregnant and breastfeeding women. Throughout pregnancy and breastfeeding, SRH and HIV services should be provided as a one-stop service (same day, same room and same healthcare worker).

Women newly initiated on ART should be seen after 2 weeks on ART, if initiated on the same day as diagnosis; at month 1; and then monthly during antenatal care and until their exposed infant is 6 months old. After 6 months, the mother and exposed baby should be seen together every 3 months in a ‘family’ approach, until the child is tested HIV negative, 12 weeks after cessation of breastfeeding.

Women already on ART, who are stable and receiving their ART through a differentiated model of ART, such as clubs or community ART groups, may choose to continue to receive their ART through this model. However, they must attend the additional antenatal and postnatal visits, including the appropriate follow-up of the HIV-exposed infant.

Viral load testing in PMTCT

Monitoring for ART toxicities is the same as outlined in **Chapter 5**. Viral load monitoring is the strategy of choice to monitor the response to ART.

- For women newly initiated on ART, the first VL test should be performed after 6 months on ART.
- For women already on ART, a viral load test should be performed at the first antenatal visit, if the previous VL test was more than 6 months ago.
- For a woman more than 6 months on ART, if the first VL is >1 000 copies/ml, she should receive enhanced adherence counselling (see **Chapter 25**) and the VL should be repeated after 3 months. If the repeat VL remains >1 000 copies/ml, switch to second line immediately.

Patient support
(see Chapter 25)

- Where available, use point-of-care VL testing for pregnant and breastfeeding women on ART.
- Where resources allow, consider 6-monthly viral load monitoring during pregnancy and breastfeeding.

Special considerations during labour and delivery to reduce the risk of HIV transmission:

- limit the number of vaginal examinations;
- limit the time between rupture of membranes and delivery and avoid artificial rupture of membranes; and
- avoid invasive procedures during delivery where possible (vacuum extraction, forceps and episiotomy).

Identification of advanced HIV disease in pregnant and postpartum women

Most HIV-positive pregnant women are healthy, and have pregnancies uncomplicated by opportunistic infections and other HIV-related medical complications. However, HIV remains a major risk factor for maternal mortality. TB is the most common cause of mortality amongst HIV-positive pregnant and postpartum women; available data shows there are many gaps in care resulting in late diagnosis and treatment. Febrile illness, including TB, is a cause of miscarriage and preterm delivery. Pregnant women with undiagnosed TB and advanced HIV are at high risk of pregnancy complications: when admitted to a maternity ward, the focus is often on the pregnancy, and serious illness in the mother is not recognised or managed with urgency.

Differentiated service delivery is essential to identify and optimally manage pregnant and postpartum women with advanced HIV (CD4 <200 cells/mm^3 or new WHO stage 3 or 4 disease). They are categorised as 'unstable' in terms of the advanced HIV package of care, and this needs to be implemented jointly between HIV and maternity care services (see **Chapter 11**, Ambulatory patient with advanced disease).

At primary care:

- Ensure pregnant and postpartum women with advanced HIV are identified, and the 'unstable' package of care implemented.
- Work together with your local maternity services to train midwives, clinicians and counsellors in the advanced HIV protocols.
- Avoid gaps in care; ensure maternity staff are able to recognise women who are unwell and may have TB or other new opportunistic infections. Ensure there are referral and communication pathways in place when maternity staff need clinical support, particularly when faced with problems outside their experience.

Continued on page 140.

Algorithm 9.1 Summary of antenatal interventions for HIV-positive pregnant women

Pregnant women with **unknown HIV status** or a negative HIV test done more than 3 months ago:

First antenatal visit

↓

Offer HIV testing.

Women with **known HIV-positive status**, already on ART

↓

Take VL test if last VL more than 6 months ago. Manage as on page 133.

Women with **known HIV-positive status**, not on ART

HIV negative

Offer couple counselling to determine status of partner.

If partner HIV-positive, link to ART services.

If partner HIV-positive and VL not suppressed or status unknown in high prevalence settings, offer PrEP to pregnant women (see PrEP section in **Chapter 8**).

Re-test women in the third trimester (at 32 weeks); at delivery if not tested in the third trimester, and in high prevalence settings, six-monthly during breastfeeding.

HIV positive – first antenatal visit

Take full medical and obstetric history and examine to stage the patient.

Screen for TB and advanced HIV disease.

Screen for syphilis and STIs.

Take baseline CD4, and, where available, creatinine. Routine antenatal investigations should be done and other tests triggered according to clinical need.

Manage women with advanced HIV according to **Chapter 11**. (Important: Fluconazole should not be used during pregnancy, unless life-threatening situation.)

Give CTX according to guidelines in Appendix 8.1.

↓

Re-test all HIV-positive women with a second sample and ideally by a second HCW prior to initiation of ART. If second HCW is not available, the same HCW may test the client again after 2–3 hours.

↓

Offer **same-day initiation of ART** with TDF 3TC and DTG/EF*, based on the assessment of clinical and psychological readiness. If not ready, rebook for further counselling. Aim to initiate within 7 days.

↓

Review at weeks 2 and 4, month 2, and then monthly during antenatal care.

Take VL after 6 months on ART.

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* See important detail in Table 3.2 on page 36.

Continued from page 138.

- Ensure viral load monitoring is performed regularly, and that there is a system for fast-tracking results. Women failing first line ART need to be identified early, without lengthy delays in switching to second line ART.
- Have a 'welcome back' approach for pregnant women returning to care at both HIV and maternity clinics.
- Teach maternity healthcare workers the danger signs, so that women who are seriously ill are identified promptly. Ensure pregnant and postpartum women and their families know the danger signs.

Exposed baby follow-up

All exposed infants should be seen together with their mothers in a 'family approach'. In addition to the specific PMTCT interventions outlined below:

- All exposed infants should be examined and history taken for symptoms and signs of TB.
- Weight, height and ideally head circumference should be plotted on the standard centile charts at each visit.
- All exposed infants should be immunised according to the standard EPI schedule. Exposed infants with no available nucleic acid HIV test (NAT) result at the time of immunisation but with no symptoms or signs of presumptive HIV should receive all EPI vaccinations as per local protocols.

Antiretroviral prophylaxis for the exposed infant

Prophylaxis should be started as soon as possible post-delivery, but should also be started postnatally for exposed infants identified during the breastfeeding period. Antiretroviral prophylaxis for the exposed infant is either with dual or monotherapy, and is for 6 or 12 weeks, depending on whether the infant is defined as high or low risk. High-risk infants are born to women who:

- have been on ART for less than 4 weeks at the time of delivery;
- are identified as HIV positive in the postpartum period;
- have had a VL >1 000 copies/ml documented antenatally, if VL available; and
- acquire HIV infection during pregnancy or breastfeeding.

Algorithm 9.2 outlines the prophylaxis interventions for exposed infants. Note: If the second ARV prophylaxis medication is not available for high risk infants, give 12 weeks of monotherapy.

Algorithm 9.2 Antiretroviral prophylaxis for exposed infants

For any infant born to an HIV-positive mother, ask the following at delivery or during breatsfeeding:

1. Has mother been on ART for less than 4 weeks?
2. Was the mother diagnosed HIV-positive while breastfeeding?
3. Has the mother had a viral load >1 000 copies/ml during antenatal period?
4. Has the mother seroconverted to become HIV-positive during pregnancy or breastfeeding?

No for ALL scenarios:

Low risk exposed infant

- Breastfeeding infant: Give 6 weeks of NVP od* **OR** 6 weeks of AZT bd
- Formula fed infant: Give 6 weeks of NVP od* **OR** 6 weeks of AZT bd

Yes to ANY of the scenarios:

High risk exposed infant

- Breastfeeding infant:

  Give 12 weeks of NVP od **AND** AZT bd**

  If not feasible, options are:

  1. Give 6 weeks of NVP od **AND** AZT bd followed by 6 weeks of NVP od **OR** AZT bd
  2. Give 12 weeks of NVP od

- Formula fed infant:

  Give 6 weeks of NVP od **AND** AZT bd

* NVP is the preferred monotherapy prophylaxis.

** Where there is no access to separate AZT syrup and to support feasibility of implementation in some settings, fixed-dose combination (FDC) tablets of AZT/3TC or AZT/3TC/NVP may be used (Tables 9.1 and 9.2). Where no AZT formulation is available, use 12 weeks of NVP alone.

Exposed infants identified post-partum

In infants identified post-partum, where the mother has not been on ART, there is a high risk that the infant is HIV-positive. Such infants may benefit from presumptive treatment until proven HIV negative. The infant should be tested with an age-appropriate HIV test (NAT test if <18 months; rapid HIV testing algorithm if >18 months) and considered as a 'high risk infant'.

The mother should start ART without delay and with counselling support.

The infant:

- If the infant virological test is available, same day (POC):
  - Result is positive, *start ART treatment* without delay, according to weight, with ABC (or AZT)/3TC + LPV/r. Confirm NAT result with a second sample.
  - Result is negative, start enhanced prophylaxis, according to age/weight (see tables 9.1 and 9.2).
- If the infant virological test result is delayed (e.g. using a dry blood spot (DBS) test, *start presumptive treatment* with AZT (or ABC)/3TC + LPV/r while awaiting the result of DBS-PCR test.
  - If the DBS-PCR result is negative, presumptive treatment can be stopped and the infant continued on enhanced prophylaxis for a total of 12 weeks from when the mother started ART.
  - Perform another DBS-PCR or other rapid diagnostic test (RDT) first, according to age) at the end of the prophylaxis. Then follow the early infant diagnostic algorithm from the appropriate time point.

Tables 9.1 and 9.2 outline the options for formulations and dosing for infant ARV prophylaxis according to age or weight. FDC tablets have also been included, recognising possible challenges of availability and feasibility of administration of syrups. The addition of 3TC does not influence toxicity. The indication for dual or monotherapy and the duration of prophylaxis is as per Algorithm 9.2.

Cotrimoxazole prophylaxis for the exposed infant

Cotrimoxazole prophylaxis should be given from 6 weeks of age until the baby is confirmed HIV negative at 18 months or 12 weeks after cessation of breastfeeding, whichever occurs first. Table 9.3 gives the dosing guidance for cotrimoxazole prophylaxis.

Table 9.1 Dosing of NVP and AZT prophylaxis by age

	NVP syrup 10 mg/ml	NVP 50 mg dispersible tablet	AZT syrup 10 mg/ml	AZT 60 mg tablet	AZT 60/3TC 30	AZT 60/3TC 30/NVP 50
Birth to 6 weeks 2 000–2 499 g*	10 mg (1ml) od		10 mg (1ml) bd		Quarter tab bd	Quarter tab bd
Birth to 6 weeks ≥2 500 g	15 mg (1.5ml) od		15 mg (1.5ml) bd			
6–12 weeks	20 mg (2ml) od	Half tab od	60 mg (6ml) bd **	1 tab bd **	1 tab bd	
3–6 months	20 mg (2ml) od	Half tab od				
6–9 months	30 mg (3ml) od	Half tab od				
9 months to end of breastfeeding	40 mg (4ml) od	1 tab od				

Source: *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection* (WHO, 2016: 388)

* For infants weighing <2 000g and older than 35 weeks gestational age, the suggested doses are: NVP 2mg/kg once daily and AZT 4mg/kg twice daily.

** No dose established for prophylaxis, treatment dose 60mg bd to be used.

Table 9.2 Prophylaxis dosing in infants by weight*

Weight	AZT syrup 10 mg/ml	AZT60/3TC 30 dispersible tablet
3.0–5.9 kg	6ml bd	1 bd
6–9.9 kg	9ml bd	1.5 bd
10–13.9 kg	12ml bd	2 bd
14–19.9 kg	15ml bd	2.5 bd

* To be used primarily for exposed infants identified during breastfeeding

Table 9.3 Cotrimoxazole prophylaxis dosing table

Simplified cotrimoxazole prophylaxis			
Weight	**Oral suspension 200/40 mg per 5 ml OD**	**Dispersible tablets 100/20 mg OD**	**Scored tablets 400/80 mg OD**
3–5.9 kg	2.5 ml	1	-
6–9.9 kg	5 ml	2	½ (crushed)
10–13.9 kg	5 ml	2	½ (crushed)
14–19.9 kg	10 ml	4	1

Patient support (see Chapter 25)

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Infant feeding

Counselling on infant feeding should be started during the antenatal period and continued postnatally. For further details see the PMTCT section in **Chapter 25** and see the counselling guide available on the **SAMU website** at http://samumsf.org/sites/default/files/2017-06/4_english_Patient_education_and_counselling_guide_for_PMTCT.pdf

Unless formula feeding is 100% available, feasible, affordable, sustainable and safe (AFASS) for a minimum of 6 months, all HIV-exposed infants should be exclusively breast fed for the first 6 months. After 6 months, complementary foods should be introduced, while continuing to breastfeed for the first 12 months of life. Breastfeeding should then stop, once a nutritionally adequate and safe diet without breast milk can be provided. Where the mother is too sick to breastfeed or where the child is orphaned, formula feeding should be made available.

For breastfeeding mothers:

- Ensure correct latching occurs, ideally within an hour of delivery, to prevent cracked and sore nipples.
- Mother to check the baby's mouth for sores and thrush and to report this for treatment.
- Mothers to have their nutritional status assessed during the clinical review.
- No teats, bottles or pacifiers should be used.

Early infant diagnosis

Infants under the age of 18 months should be tested according to the early infant diagnostic algorithm (Algorithm 9.3). Any infant presenting with symptoms or signs of presumptive HIV (see **Chapter 10)** should be tested at any time. Below 18 months, any positive rapid test should be confirmed with NAT, due to maternal HIV antibodies still being present in the infant's blood.

WHO has given a conditional recommendation to introduce birth testing for exposed infants. Where birth testing is implemented, a repeat NAT test is still required at 6 weeks to identify infants with intrapartum infection. Implementation of birth testing will be context specific; influenced by HIV prevalence, coverage of the PMTCT programme and available resources. Where resources are limited and birth testing for all infants is not feasible, priority should be given to testing all infants at 6 weeks, and, if feasible, consideration of birth testing for high risk infants. Algorithm 9.3 below outlines the recommendations for early infant diagnosis.

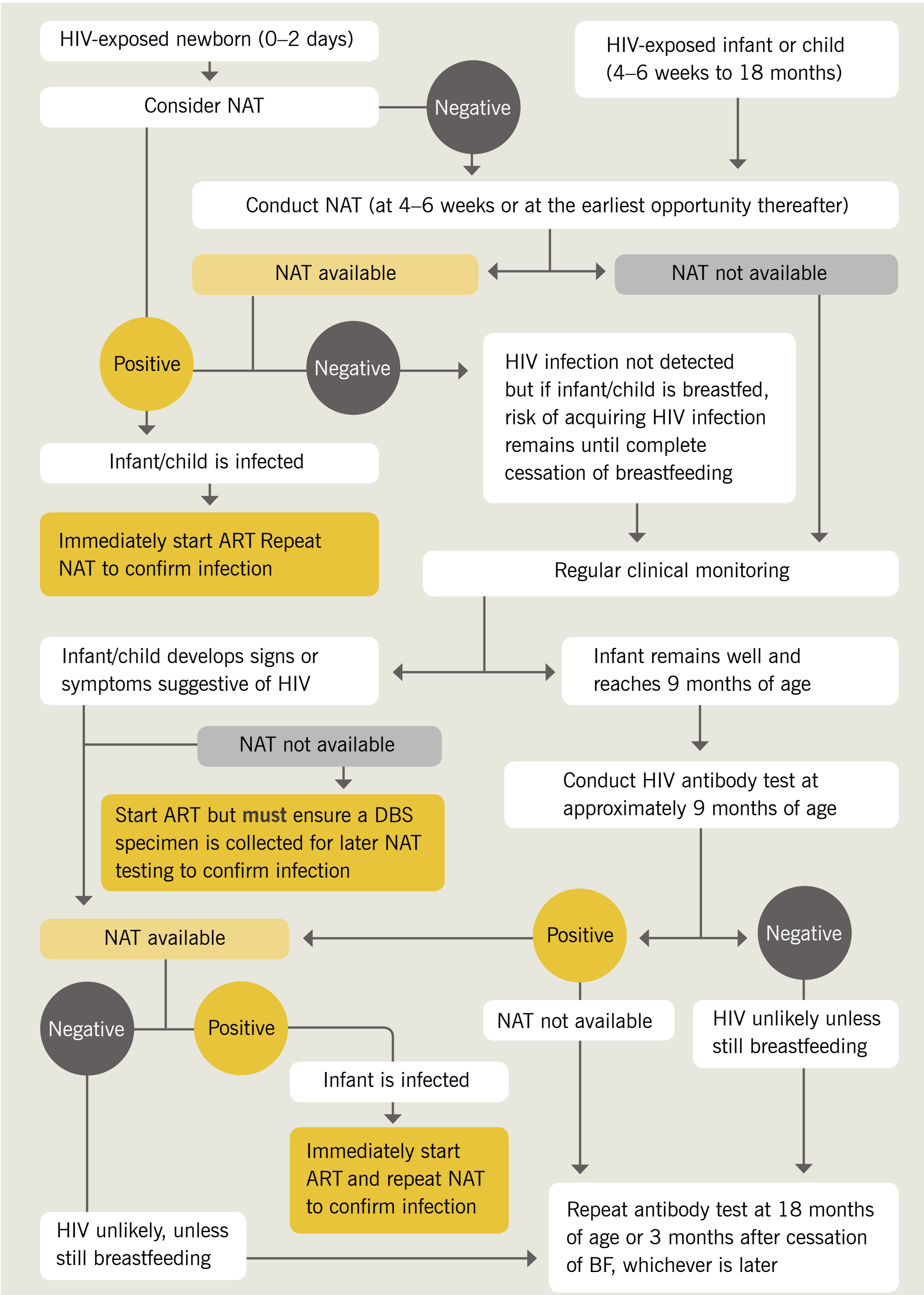
Consult local algorithm for early infant diagnosis.

Further information on PMTCT

For further information, implementation and training resources on PMTCT, please go to the PMTCT resource page on the **SAMU website** at https://samumsf.org/en/resources/hiv/pmtct .

samumsf.org/en/resources/hiv/pmtct

Algorithm 9.3 Early infant diagnostic algorithm



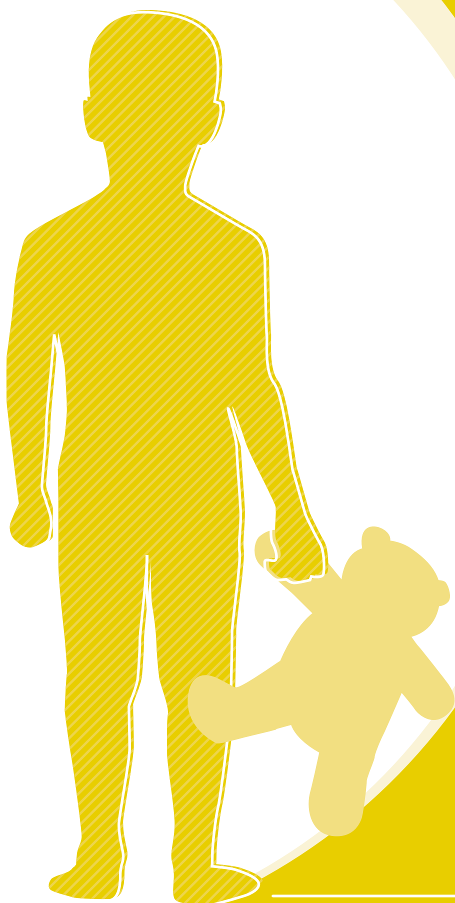
Source: *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection* (WHO, 2016: 380)

Food for thought: Operational research questions for PMTCT

- How can we identify HIV-positive pregnant women earlier in pregnancy? (Consider the role of community-based pregnancy testing.)
- How is conception advice being given in our programmes? What is the VL of women on ART in our programmes when they become pregnant?
- Is use of PrEP during pregnancy and breastfeeding feasible for HIV-negative women in discordant couples?
- Are women who are in cohorts that are supported by MSF accessing family planning?
- How should family planning be integrated into ART clinics, including within differentiated models of ART delivery?
- Is classification of infants as high or low risk and implementation of the enhanced prophylaxis protocol feasible in programmatic settings?
- What are the outcomes for infants classified as high risk, and was the correct prophylaxis provided?
- Where at birth early infant diagnosing (EID) is implemented, what is the yield (positivity rates) and what is the clinical profile of infants testing positive?
- What is the role for polyvalent PCR platforms that include EID in both high and low prevalence settings?

CHAPTER 10

HIV in children and adolescents



Many clinicians feel uncomfortable caring for children with HIV, as formal training in the field of paediatrics is often minimal. However, despite clear differences from adult management, with a little practice you will find that caring for children with HIV is not so difficult. Below are a few general points to keep in mind when caring for children:

1. As children grow, their emotional, intellectual and social needs change. For example, caring for a one-year-old is vastly different from caring for a five-year-old, which is different from treating a ten-year-old, etc. It is important to tailor your care to the age and developmental level of the child.
2. Doses of medications must be constantly adjusted to the child's weight.
3. Going to the doctor is often anxiety-provoking for both the child and caregiver. It is important to make the family feel as comfortable as possible during the office visit. Be friendly and communicate with children in the same way you would communicate with them in a casual setting. Making children feel at ease will make the interaction more productive, since a calm environment will allow you to gather the information necessary to make proper assessments. Even simple gestures are helpful, such as calling the child by his/her name, asking him/her about a favourite activity or best friend, or asking how the child is doing in school. Try to involve the child in the discussion.
4. There are many difficulties for teenagers to navigate, including school pressure, peer pressure, issues surrounding individuality and sexual awareness. In addition, adolescents often lack insight and have a sense of invincibility. All these things create a 'perfect storm' for poor adherence so special attention needs to be given to this age group.

Key rules of a paediatric and adolescent HIV clinic:

Confidentiality: The importance of confidentiality cannot be overstated. Caregivers and adolescents must feel that whatever they discuss with you is not shared with other people. Given the many issues surrounding HIV and stigma, confidentiality is particularly vital.

Honesty: Honesty needs to work both ways. It is imperative for clinicians to be honest with patients and to accurately and honestly explain the medical realities of their situation. Likewise, the patient must be honest with the clinician. For example, if a caregiver or adolescent is missing doses, they must inform the clinician. It becomes very hard for a clinician to make progress with a patient's care if the clinician is basing clinical decisions on misinformation.

Trust: Trust is essential for engaging with the child in all the different components of care. To gain a child's trust involves hard work on the part of the clinician, who must build on a foundation of confidentiality and honesty.

Non-judgement: Being non-judgmental is essential. It is important to realise that the caregiver is in a difficult position and that monitoring children and giving them their medicine is hard. If the caregiver feels judged and/or scorned, they will likely default from care. This rule applies to adolescents, as well.

Paediatric and adolescent HIV is a broad topic that could fill an entire book. This chapter will focus on the essential areas needed to meet core primary care needs. The following sections will be discussed:

1. HIV diagnosis
2. HIV disease progression
3. Assessment and follow-up of HIV-exposed and infected children
4. Growth and nutrition
5. Developmental assessment
6. Starting anti-retroviral therapy (ART)
7. ART side effects
8. Notes on adherence
9. Process of disclosure
10. Treatment failure
11. Specific paediatric conditions
12. Take-home messages
13. HIV care of the adolescent

1. HIV diagnosis

How do children acquire HIV?

More than 90% of HIV infection in children is acquired through mother-to-child transmission (MTCT) during pregnancy, labour and delivery, and later through breastfeeding. Importantly, the risk of HIV transmission through the whole process, from conception to the end of breastfeeding, can be reduced if the HIV-positive mother is on lifelong ART and has an undetectable viral load. Thus, it is important to implement effective strategies for PMTCT (see **Chapter 9**). Other ways children can become infected are through:

- transfusion with contaminated blood;
- sexual abuse; and
- injury from contaminated sharp objects, such as razors, needles or non-sterile circumcision instruments.

As children become adolescents, risk factors for HIV become the same as those found in adults.

Table 10.1 Transmission and prevention of HIV infection in childhood

Mode of transmission		Risk group	Preventative strategy
Mother-to-child This constitutes the vast majority of children in Africa (>95%) and is mostly preventable.	Pregnancy (in utero)	Foetus	ARV (prophylaxis or treatment)
	Birth (intra-partum)	Newborn	ARV Safe delivery practices
	Breastfeeding (Post-partum)	Infant	ARV, formula/exclusive breastfeeding
Sexual	Abuse	ALL	Always test mother and siblings if child is index case.
	Consensual	Adolescent	Target adolescents with prevention strategies, such as education on safe sex.
Infected blood or blood products		Blood transfusion Unsterile injection procedures	Screen donors; do not give unnecessary transfusions.
Other		Cultural rituals, such as scarification	Support safe practices; work with traditional healers.

Important definitions

HIV-exposed: This term is used for children born to HIV-infected mothers when the child's status is not yet confirmed. Further diagnostic tests are needed to determine the HIV status.

HIV-infected: This term implies that definitive testing has been done to confirm HIV infection.

- A positive HIV DNA PCR (which detects viral DNA) is diagnostic in infants and children under the age of 18 months. It is required that all first positive PCRs are confirmed by repeating HIV testing, either with another PCR test, or with an HIV viral load (consult your national guidelines).
- For children above 18 months of age, two positive rapid HIV tests (which detect antibodies) are adequate to confirm HIV infection.

HIV-uninfected: It is confirmed that the child does not have HIV in his/her blood and is therefore not infected with HIV. Note: for a child who has a history of breastfeeding to be considered HIV un-infected, the HIV test must be performed 12 weeks after the cessation of breastfeeding. Therefore, continued surveillance is needed and repeat testing is required for children who are still breastfeeding.

Which children should be tested for HIV and when should testing be performed?

There are two different types of testing:

- **Provider-initiated testing and counselling (PITC)**

  The healthcare provider offers HIV testing to the patient and initiates the discussion about testing.

  PITC has been shown to increase testing levels in children dramatically and should be offered to children and adolescents in all health facilities, in both in- and outpatient settings.

  PITC is the recommended approach to testing children and is advocated by the WHO.

- **Voluntary testing and counselling (VCT)**

  The caregiver/patient asks the healthcare provider for an HIV test

  The table below illustrates the major differences between VCT and PITC.

VCT	PITC
Voluntary	Voluntary
Individual pre-test counselling	Group pre-test informaton
Non-routine client initiated referral	Routine provider initiated referral
Individual post-test counselling	Individual post-test counselling
Risk assessment done pre-test	Risk assessment done post-test
Opt-in	Opt-out

Who should be offered testing?

The signs and symptoms of HIV infection in children and adolescents are often non-specific, and can mimic those of other illnesses. Therefore, it is important to have a high index of suspicion for HIV in order to make a timely diagnosis.

Initiate PITC for HIV for the following children:

- all children known to be HIV-exposed;
- any infants with uncertain HIV exposure;
- children diagnosed with TB or who have a history of TB;
- orphans or abandoned children;
- children with signs and symptoms suggesting HIV infection:
  - pneumonia;
  - persistent diarrhoea;
  - ear discharge (acute or chronic);

    - very low weight for age and/or diagnosed with severe acute malnutrition (SAM);
    - oral thrush;
    - parotid enlargement; and
    - generalised lymphadenopathy;
- children who are suspected of being victims of sexual assault;
- when there is a family or social indication: (parental request, father or sibling with HIV, death of the mother, father, or sibling, or when the mothers status is unknown); and
- When for any other reason, according to the clinician's judgment, it is in the best interest of the child.

Test healthy children as well

Since many children, particularly those infected during the breastfeeding period, may present outside of the newborn and infant periods, testing should also occur whenever an opportunity arises. This includes testing 'healthy' children coming for routine visits, such as for vaccinations. (Details appear in the next section on which tests to use, and how to interpret them.)

Refer to your national guidelines

Consult your **national guidelines** for additional information regarding your country's HIV testing procedures.

Which laboratory tests are available to test for HIV?

Testing for immune response to the HIV virus	Testing for the HIV virus directly
'Rapid tests'	PCR-DNA (qualitative) • detects the presence of the virus • use only for diagnosis
Laboratory ELISA	PCR-RNA (quantitative) • determines the quantity of viral copies/ml of blood (viral load) • use for monitoring treatment response • can be used to confirm diagnosis in infants
Western blot test	
Oraquick rapid test for saliva	

Which laboratory test should be used at different ages?

The mother's antibodies to HIV freely cross the placenta and remain in the baby after birth for up to 18 months of age (and in some cases even beyond 18 months). This, therefore, has implications for the diagnostic tests that are done before and after 18 months of age.

Less than 18 months of age:

- In light of the above, a positive antibody test could merely be reflecting the presence of HIV antibodies from the mother. Even though it cannot confirm infection of the baby it is however useful in confirming that the child is HIV-exposed.
- Based on this, the following guideline is followed in most settings:
    - In children <9 months, the first test is a PCR DNA. In children >9 months the first test is an antibody test. If it is negative, then the child is negative and no further tests are needed. If it is positive, it may reflect maternal or infant antibodies, so a confirmatory PCR DNA needs to be done.

Children older than 18 months (and >12 weeks after stopping breastfeeding):

By this stage, tests looking for HIV antibodies can be used to diagnose HIV infection, because any HIV antibodies found in the baby's blood are being produced as part of the baby's response to infection with HIV. As with adults, a positive antibody test must always be confirmed by another different antibody test.

A study has shown that up to 14% of HIV-exposed infants of mothers who have been adherent on their PMTCT regimens can remain positive for longer than 18 months. (See https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.) A negative PCR test or undetectable pre-ART viral load will identify these false-positive children.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

2. HIV disease progression

Children's organ systems, including the immune system, develop over time. As such, infants' and children's immature immune systems are less able to suppress HIV viral replication once infected, resulting in HIV disease often progressing much more rapidly than it does in adults. It is for this reason that untreated HIV in children has high early morbidity and mortality in children.

Figure 10.1 Mortality rate of untreated HIV by age

Age of child	Mortality rate
0–3 months	20–30%
<2 years	50%
<5 years	Approximately 75%

Immature immune system + Developing organs + High viral load

↓

Rapid disease progression with high morbidity and mortality

An organ that is particularly susceptible is the brain, where HIV infection can severely affect neurological development.

Given this rapid disease progression, the goal when caring for children suspected of having HIV is to diagnose them and start treatment as soon as possible.

3. Assessment and follow up of HIV-exposed and infected children

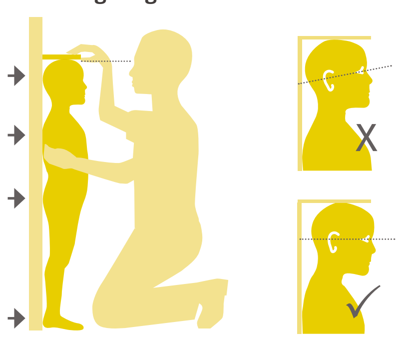
Effective treatment relies upon early testing for HIV and the commencement of anti-retroviral treatment when diagnosed with HIV.

Essentials steps for a clinic visit for an HIV-positive child

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

As noted in **chapters 3 and 5**, it is advised that some sort of checklist or consultation prompt is used to remind the clinician of all the different issues to be covered in a consultation. The tables below provide a detailed explanation of each step in the paediatric consultation. This is followed by a shorter checklist that can be referred to. In addition, **paediatric consultation stationery can be downloaded** from the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

Table 10.2 Paediatric consultation guideline

Consultation item	Notes
Introduce yourself	Greet caregiver and child cheerfully. Children are often frightened by coming to the clinic. Speak to the caregiver first and then the child. Having ‘child-friendly’ material (toys, coloring material) can be helpful in making the child feel more comfortable.
Weight/ height/head circumference	Plot and document weight, height and head circumference on the percentile charts and note any decline across the centiles. (See Figures 10.4–10.10 at the end of this chapter.) **A child should never stop growing so any decrease in weight or lack of growth needs to be evaluated.** Nutritional status should be assessed in all patients (see **Chapter 24**, Malnutrition and weight loss).
	Notes on measuring weight: Do: • Undress the child (or, at least minimally clothed). • Try to use the same scale at each visit. • Calibrate and service scales on a routine basis. • If <18 months old, use baby scale. If a baby scale is not available, weigh mother and child, then mother alone. Then subtract mother’s weight to obtain the child’s weight. • Document the weight in the patient’s file at every visit. • Plot the weight on the appropriate growth curve at every visit.
	Notes on measuring length/height: Do: • Use a standing height measure for children >2 years of age. • Perform supine measurements on a solid surface for children <2 years of age. • Ensure that the heel, buttocks, and shoulder blades are touching the wall or the apparatus behind the patient. See below: **Standing height measurement**  **Supine measurement** 

	• For children <1 year, measure height every month. • For children >1 year, measure and plot height every 3 months. • Do not perform a supine length/height measurement by yourself. Have the caregiver assist with holding the patient's head straight.
	Notes on measuring head circumference: Do:  • Measure head circumference midway between the eyebrows and hairline at the front of the head and the occipital prominence at the back of the head. • Measure and plot head circumference (HC) monthly for infants until 1 year of age, then every 3 months until age 3 years. Do not: • Assume the child's head circumference is normal if a past measurement is within the normal range.
Assess disclosure status of child	Knowing disclosure status of the child is important for two reasons: It determines the level of engagement you are able to have with the child. It guides the clinician regarding what can be discussed in front of him/her. If fully disclosed, acknowledge that, since the child is aware of his status, you will be conducting the visit with the child with support from the caregiver. Involve the child in the clinical visit – talk to both the caregiver and child about the child's HIV and how he/she is doing. If partially disclosed to or not disclosed, first spend time with the caregiver to discuss the child's status (for example viral load results). Discuss the disclosure process with the caregiver. Then consult with the child. See disclosure section (section 9 in this chapter) for further detail.
Current complaints	Ask if there are any concerns from the caregiver today. Ask about any symptoms: • Cough • Headache • Rash • Diarrhea • Sores in the mouth • Abdominal pain • Vomiting • Weight loss • Fatigue • Fever **Important**: Be specific when asking about complaints/symptoms. A caregiver may forget a particular problem until prompted by the clinician.

Past medical history	Ask specifically about: • TB • General past medical history. Ask specifically about any past illnesses, hospital stays, and treatments.	
	TB questions	
	1. Has the child had TB in the past?	If yes, what regimen was he/she on?
	2. Has the child been on TB prophylaxis in the past?	If yes, when was TB prophylaxis given and what medications were used?
	3. Does the child currently have any symptoms of TB?	Symptoms/signs of TB include cough, night sweats, fever, enlarged lymph nodes and lack of energy. Symptomatic children may require a CXR, sputum sample and/or referral for specialised care. (See **Chapter 12** and **section 11**, Specific paediatric conditions, in this chapter.)
	4. Has anyone in the household been diagnosed with drug sensitive or drug resistant TB in the past year?	If anyone in the house has been diagnosed with DR TB, do a TST test and chest x-ray and refer to doctor. Alternatively, follow local strategy for managing DR TB contacts.
	HIV questions	
	1. Is the child on ARVs?	All children, regardless of age, symptoms, or CD4 count, should start ARV treatment when diagnosed. If the child is not on ARVs, ask the reason why.
	2. What is the last CD4 count?	CD4 count is used to monitor response to ART. In children under age 5, use CD4% and in children >5, use absolute CD4 count. CD4 counts less than 200 or <15% put the child at greater risk for developing OIs. In addition, any drop in CD4 count is concerning.
	3. What was the last viral load?	Viral load is used to monitor response to ART. A viral load >1 000 copies is considered high and may indicate adherence problems or development of ARV drug resistance.
	General past medical history questions:	
	1. Has the child been sick since his/her last visit?	A new infection may indicate that the child is failing treatment.
	2. What other medical problems has the child had in the past?	List the child's past and current medical problems in a problem list, to ensure continuity of care, with the next clinician seeing the child.

Feeding history	**How is the child's appetite?** Poor appetite can be a sign of an illness or infection. For example, thrush can be painful and cause poor feeding. Other illnesses such as TB can cause poor appetite, and certain ARVs can cause nausea.	
	Severe acute malnutrition Children with severe acute malnutrition must be identified and managed correctly, including giving therapeutic feeding. (See **Chapter 24**.)	
	Stunting in children Stunting means that a child's height-for-age is <3rd centile. Beware, as a child may appear to be proportional (normal weight-for-height) but still be stunted. Chronic malnutrition in the HIV-infected child can be a cause.	
	Note: See Section 2 on development assessment, in this chapter, for further information.	
Development history	1. Has the child continued to learn new things?	Developmental delay can indicate progression of HIV and/or treatment failure.
	2. Is there anything the child could do before, but can no longer do now?	Regression in development is also concerning and can indicate progression of HIV and/or treatment failure.
	3. If the child is in school, how is he/she doing?	School failure may be an indication of treatment failure.
	4. Does the child keep up with his/her peers when playing?	Inability to keep up with classmates during activities may indicate HIV infection or treatment failure.
Immunisation history	Assess whether child's immunisations are up to date. Refer to your local immunisation schedule. All children should be immunised according to the national immunisation schedule and according to the WHO Expanded Programme on Immunisation (EPI). Note that there are specific recommendations for HIV-positive children, especially when using live vaccines. They have the potential to cause an actual infection of the very condition that the vaccine is trying to prevent. Checking for BCG vaccination is an important part of the routine HIV consultation in children. (See **Chapter 8, Table 8.5**.)	

Medication history	1. What medicine (other than ARVs) is the child taking?	Check side-effects of other medications and interactions with ARVs.
	2. Does the child get his/her ARVs everyday as prescribed?	Poor adherence is the main cause of treatment failure in children. **Note**: See Section 8 on adherence and Section 10 on HIV treatment failure for additional information.
	3. Who gives the child his/her medicine? Or does the child take the medicines him/herself?	It is important that a caregiver takes responsibility for giving the medicine. Often, when the child takes the medicine by him/herself, there is an increased risk of poor adherence and a high VL.
	4. Ask caregiver to demonstrate how they draw up the medication.	Gently correct any mistakes.
Psycho social and family situation	1. Who lives with the child?	See section below on adherence for additional information.
	2. Who is the primary caregiver?	
	3. Has the primary caregiver changed in the past year?	
Physical exam	Identify signs of disease progression	Clinically assess the child, including any existing problems.
Clinical assessment	General tips for the physical examination: • Create a 'child-friendly' environment in your exam room, using age-appropriate posters and toys. • Be creative and adaptable: use play when possible to calm the child and distract them during the physical examination. • A complete physical exam should be done at every visit. • The child should be undressed to his/her undershirt and underwear/nappy for the physical exam. Make sure any covered parts are still examined. • Try to perform the physical examination in the same order each time (often from head to toe). However, take advantage of a quiet child and perform the 'listening' parts of the exam (heart and lung exam) first, if the opportunity exists. • Perform potentially uncomfortable procedures last (such as mouth and ear examinations). • Ear, nose and throat (ENT) examination is essential. To look in the ears and mouth you will need an otoscope and a tongue depressor. • Look for physical changes indicating HIV progression such as thrush, organomegaly, lymphadenopathy, dermatitis, etc. • Poor growth can be an important indicator of HIV infection in exposed children and can indicate disease progression in HIV-positive children. Remember that children with HIV develop both common childhood illnesses and opportunistic infections, so be comprehensive in your assessment and address any clinical findings in a timely fashion.	

Prescribing medications

Prescribe ARVs

Refer to your national ARV dosing chart and ensure dose is calculated according to current weight.

Prescribe for opportunistic infections (OIs)

Common OIs include conditions such as oral thrush, PCP pneumonia, herpes (such as oral lesions) and TB. Draw on more experienced help if more severe OIs are suspected.

Prescribe prophylaxis medications:

Cotrimoxazole (CTX):

If taken regularly, CTX provides some protection against pneumonia, especially pneumocystis jirovecci (also referred to as PCP) but also bacterial pneumonia, TB, toxoplasmosis, malaria and diarrhoeal disease.

For HIV-exposed infants:

- Cotrimoxazole should be given to all HIV-exposed infants from 6 weeks of age.
- Cotrimoxazole can be stopped after a definitive HIV-negative test taken at least 12 weeks after cessation of breastfeeding).

For HIV-infected infants:

- Cotrimoxazole should be given to all HIV-positive infants aged <1 year until the age of 5 years.
- After 5 years of age, cotrimoxazole may be stopped, as per the adult guidelines (e.g. two consecutive CD4 >200 cells/μl after a minimum of 12 months on ART). Refer to Appendix 8.1 or your national guidelines.
- Cotrimoxazole should be given according to the weight of the child (see table below):
    - Suspension: 200 mg SMX/40 mg TMP per 5 ml
    - Dispersible (disp.) tab: 100 mg SMX/20 mg TMP
    - Single-strength (SS) tab: 400 mg SMX/40 mg TMP

3–4.9 kg	2.5 ml or 1 disp. tab OD
5–13.9 kg	5 ml OD
14–29.9 kg	10 ml OD or 1 SS tab OD
>30 kg	2 tabs OD

INH:

Give INH to all HIV-infected children with positive TST or household contact with DS TB. Give only after excluding active TB.

Dose: INH 10 mg/kg daily (max 300 mg daily) x 6 months

Note: Also repeat the 6-month dose with each new exposure, as well as immediately after TB treatment has been completed.

Multivitamin:

Under 10 kg give 2.5 ml daily, 10–30 kg give 5 ml daily, and >30 kg give 10 ml or 1 tab daily.

Vitamin A supplementation:

Non-breastfed infants 0–5 months old: 50 000 IU single dose at 6 weeks old

Infants 6–11 months old: 100 000 IU single dose between 6–11 months old

Children 1–5 years old: 200 000 IU single dose at 12 months, then every 6 months until 5 years old

Regular de-worming:

Albendazole single dose:

<2 years old, 200 mg

>2–5 years old, 400 mg

OR

Mebendazole:

12 to 24 months or <10 kg	100 mg BD for 3 days every 6 months
> 24 months or >10 kg	500 mg single dose every 6 months until 5 years

Note: See national guidelines for de-worming guidelines, as recommendations may change, based on prevalence of soil-transmitted helminth infections in the area.

Other 'prophylaxis':

Teach caregivers how to use oral rehydration fluid for gastroenteritis.

Teach caregivers how to treat fever using paracetamol or ibuprofen.

Dental caries (tooth decay) and periodontal disease are common in HIV-infected children of all ages. Advise and encourage good oral hygiene and refer to a dentist when indicated.

Laboratory investigations	Consult national guidelines
	Monitoring on ART
	CD4 count: CD4 count at baseline: Ideally CD4 for all, though not always possible. For all, next CD4 at 12 months. Then: If <5 years old, every 6 months until stable on ART* If >5 years and CD4 <200, repeat every 6 months until CD4 >200; if CD4>200, can stop monitoring routinely, provided child has remained virally suppressed.
	VL: VL at 6 months, 12 months, then every 12 months thereafter.
	FBC: FBC at baseline if starting AZT. If FBC not available, a POC Hb is sufficient. If neither is available, this is, however, not a contra-indication to starting it.
	Fasting cholesterol and triglycerides: At baseline, 12 months, then annually, if on a PI regimen.
	Creatinine + urine dipstick: At baseline for all children, starting TDF and then ideally at 1 and 4 months, then annually. See national guideline. If abnormal, this suggests renal disease and needs careful evaluation.
	ALT: ALT at baseline if known liver disease, jaundiced or on TB treatment.

* WHO defines people stable on ART according to the following criteria:

- on ART for at least one year;
- no adverse drug reactions requiring regular monitoring;
- no current illnesses or pregnancy;
- good understanding of lifelong adherence; and
- evidence of treatment success: two consecutive undetectable viral loads (or in the absence of viral load monitoring, rising CD4 counts or CD4 counts above 200 cells/mm^3).

Paediatric ART visit: Checklist

1. Date: ______________________________
2. Measure weight, height and head circumference: Weight:________ Height: ________ HC: ________
3. Assess disclosure: Fully ☐ Partially ☐ None ☐
4. Any complaints?______________________________
5. TB questions:
   - Any TB in the past? If so, when? Yes ☐ No ☐ ______________________________
   - Any TB prophylaxis in the past? If so, when? Yes ☐ No ☐______________________________
   - Any current symptoms? (cough, fevers, weight loss, decreased energy) Yes ☐ No ☐
   - Does anyone in the house have symptoms of TB? Yes ☐ No ☐
6. Most recent CD4 count? ______________________________
7. Most recent viral load? ______________________________
8. Any illnesses or hospitalisations since the last visit one year ago? Yes ☐ No ☐
   If yes, describe the illness and treatment ______________________________
9. How is the child eating? Good appetite?______________________________
10. How is the child doing in school? Has he/she continued learning new things? __________________
11. Are the child's immunisations up to date? (check immunisation card): __________________
12. Assess adherence/home life:
    - Does the child get his/her ARVs everyday as prescribed? If no, why not? __________________
    - Who is the primary caregiver? ______________________________
    - Any change in primary caregiver in the last year?______________________________
    - Who else lives at home? ______________________________
13. Perform physical exam.
14. Prescribe ARVs.
15. Prescribe if indicated:
    - Cotrimoxazole
    - INH
    - Multivitamin
    - Vitamin A supplementation
    - De-worming
16. Make any diagnoses as needed and amend problem list.
17. Prescribe medication for any OIs if needed.
18. Perform laboratory tests as needed (VL, CD4 count, etc.).

15\. Do they have any questions? ______________________________

Note: This is merely a summary checklist. If the answers to any of the above questions are concerning, ask additional questions to learn more about the issue. Don't be limited by the amount of space available to write onto. Seek more experienced help if needed.

4. Growth and nutrition

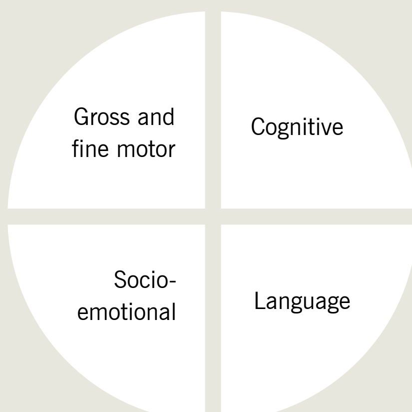
In the section above on the assessment and follow-up of HIV-exposed and infected children, the importance of the regular measurement of growth parameters (weight, height and head circumference) was made. Deviations in any of these parameters outside the normal ranges, or any changes across percentiles need to be investigated carefully. In addition, deviations can indicate malnutrition, a condition that has been identified as an independent risk factor for morbidity and mortality in HIV-infected children. The assessment and management of this is detailed in **Chapter 24**.

5. Developmental assessment

HIV crosses the blood–brain barrier and directly affects the brain. As such, HIV can have a detrimental effect on a child's neurodevelopment. Moreover, neurodevelopmental delays become more difficult to address as a child ages, so it is important to screen for and identify any delays as soon as possible. A common misconception is that few interventions exist for children with neurocognitive issues. Many interventions do in fact exist, and with early intervention significant progress and advancement of skills can be achieved.

It is important to ask screening questions related to each of the areas of neurodevelopment, as doing so will provide a more thorough picture of the child's overall neurocognitive status. Many different developmental screening tools exist, varying considerably in their scope and complexity. However, the main goal of any screening tool is the same: to identify delays in children of different ages, so that early intervention can be started.

Figure 10.2 Four areas of neurodevelopment



Below is an example of a developmental screening tool recommended for the particular benefits it offers.

- It is formulated as a series of questions to be asked at specific ages.
- It screens all four areas of neurodevelopment.
- It is quick and can be performed in just a few minutes.

Note that there is a broad age range of ‘normal’ for neurodevelopmental milestones. However, at a certain point, a delay is pathological and needs further evaluation and management. Key markers of delay in certain milestones form part of this table.

Table 10.3 Developmental checklist with normal milestones and warning signs

Age	Normal	Warning signs
1 month	Raises head, alert to sound, makes crawling movements.	
6 weeks		No eye contact, no smile, poor suck, floppy, excessive head lag.
2 months	Holds head at midline, lifts chest off the table, smiles.	
4 months	Rolls front to back, laughs.	
6 months	Sits supported, babbles.	Doesn’t reach for an object with both hands, no response to sound, poor social response to people.
9 months	Pulls to stand.	
10 months		Unable to sit unsupported, hand preference, fisting. Persistence of primitive reflexes.
12 months	Walks alone, uses single words.	Unable to bear weight on legs.
18 months	Can remove garment, scribble, run.	No walking. No single word with meaning.

Management recommendations on finding delays in development milestones vary significantly from country to country. We encourage all clinicians to investigate what is **available in your country** and set up appropriate referral pathways to use as needed.

Refer to your national guidelines

6. Starting ART

WHO guidelines

The 2016 **WHO guideline** recommends that anti-retroviral treatment should be started for any HIV-positive child or adolescent at the time of their diagnosis, regardless of age, CD4 count, or presence of symptoms. In addition, any symptomatic HIV-exposed infant should be presumptively diagnosed with HIV and initiated on ARVs, without waiting for laboratory confirmation.

General points:

- Choice of regimen should be made according to WHO recommendations or those of your national guidelines.
- A thorough assessment of the child's or adolescent's clinical status should be performed before commencing ART, including any recommended pre-ART laboratory tests.
- A thorough assessment of the child's or adolescent's psychosocial situation should be performed, ideally before commencing ART. This is particularly important as poor adherence is the major cause of treatment failure in children. (See section 10 in this chapter on treatment failure for more information.)

WHO guidelines

WHO guidelines for starting ART

At the time of writing this handbook, new guidelines are currently being developed for the use of ART in children. This has become necessary for a few reasons:

- With increasing HIV testing of babies at birth there is a growing need to initiate treatment in newborn babies. However, babies <4 weeks of age metabolise LPV/r very poorly so another treatment option needs to be found. The drug of choice at present is raltegravir.
- Dolutegravir, with its well-recognised benefits, is now validated for use in children >6 years of age or >15 kg.

As these guidelines may develop further over the next few years, please consult both national and WHO guidelines to keep abreast with the updates.

Starting ART in children 0–6 years old

Table 10.4 Summary of first line ART regimens for children younger than 6 years

Age group	Preferred/alternative regimens	Regimen
Birth to 4 weeks of age	Preferred regimen	AZT + 3TC/FTC + RAL[a]
	Alternative regimens	ABC[b] + 3TC/FTC + RAL
		ABC/AZT + 3TC/FTC + NVP[c]
4 weeks to 6 years[d]	Preferred regimen	ABC + 3TC/FTC + LPV/r
	Alternative regimens	AZT + 3TC/FTC + LPV/r
		ABC/AZT + 3TC/FTC + RAL

a. Due to poor metabolism of LPV/r by premature infants and neonates up to 4 weeks of age, it should be avoided in this age group. Restrictions also apply to LPV/r pellets where administration challenges extend to infants up to 3 months of age. Raltegravir is the drug of choice at present. See dosing details in Table 10.10.

b. Based on the general principle of using non-thymidine analogues in first line regimens and thymidine analogies in second line regimens, ABC should be considered as the preferred NRTI whenever possible. Availability and cost should be carefully considered.

c. Where RAL is not available, NVP should be used and then substituted with LPV/r at the earliest opportunity, preferably at 4 weeks.

d. LPV/r or RAL should be changed to DTG as soon as it is validated for this age group.

Starting ART in children 6 years to 35 kg

Table 10.5 Summary of first line ART regimens for children older than 6 years and <35 kg

Preferred regimen	ABC + 3TC/FTC + DTG
Alternative regimens	AZT + 3TC/FTC + DTG
	ABC/AZT + 3TC/FTC + LPV/r

The use of dolutegravir is validated for children >6 years, thus making it the new drug in the preferred first line regimen. As TDF may not currently be used in children weighing less than 35 kg, NRTI options are limited to ABC/AZT and 3TC/FTC.

Starting ART in adolescents

Table 10.6 Summary of sequencing option for first-, second- and third-line regimens (WHO July 2018)

Population	First line regimens	Second line regimens	Third line regimens
Adults and adolescents (including women and adolescent girls who are of childbearing potential or pregnant)	Two NRTIs + DTG[a]	Two NRTIs[c] + ATV/r or LPV/r	DRV/r[d] + DTG[e] + 1-2 NRTIs (if possible consider optimization using genotypes)
	Two NRTIs + EFV[b]	Two NRTIs + DTG[a]	

a. Women and adolescent girls of childbearing potential with consistent and reliable contraception and who are fully informed of the benefits and risks can use DTG.

b. If population-level pretreatment resistance to EFV or NVP is >10% the choice of alternative options to EFV needs to be made weighing the drug availability and toxicity profile. DTG (as per note (a) or ATV/r are the drug options to be considered.

c. Following TDF or ABC failure AZT should be used to optimise the NRTI backbone and vice versa.

d. For PI-experienced people, the recommended DRV/r dose should be 600 mg/100 mg twice daily.

e. DTG-based third-line ART following the use of integrase inhibitors must be administered with DTG twice daily.

For guidelines for the use of DTG in those wishing to conceive and in pregnancy and breastfeeding, see page 136.

Notes about administering medication to children

- Administering medication to children can be challenging. Unfortunately, fixed dose combinations are not readily available for children and hence the pill burden is significant, especially for children who have co-morbidities, such as TB. Also, many ARVs are unpalatable, often having an extremely bitter taste. Therefore, children may refuse to swallow the medication, or vomit the medication after taking it.
- Due to these issues, it is important to counsel caregivers extensively on the importance of giving the medications. Provide information regarding each medication (what to look out for, side effects, etc.) and give them tips to help them administer the medicine. For example, eating peanut butter or yoghurt at the same time as giving ARVs can be helpful towards achieving better adherence.

Notes on dosing and prescribing medications

- Dosing ARVs is usually based on weight, occasionally BSA (body surface area). Therefore, it is essential that the child is properly weighed at each visit and the medication doses adjusted accordingly.
- Giving the child **too little** medication for his/her weight will cause the HIV to develop resistance to the medication more quickly.
- Giving the child **too much** medication for her/his weight will increase the risk of drug-related side effects.
- **When prescribing ARVs, it is best to watch the caregiver practise giving the medication to the child at the clinic.** By doing this, you not only ensure the child will get the correct doses of medication, but you will also help the caregiver gain confidence when giving medication.
- **Pill boxes can be very helpful as a way of organising a child's ARVs. When first prescribing the ARVs, watch the caregiver practise filling the pillbox at the clinic and gently correct any mistakes. Re-check their ability to correctly do this at subsequent visits.**
- Switch from syrups to tablets/capsules as soon as possible. This is can often be done when the child is 5–6 years old. Practice pill swallowing using a small gummy sweet (see pill-swallowing video in the additional resources folder on **SAMU website**: https://samumsf.org/en/resources/hiv/paediatric-and-adolescent-hiv and look in implementation resources).

samumsf.org/en/resources/hiv/paediatric-and-adolescent-hiv

ART dosing charts

Table 10.7 Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing for infants and children 4 weeks of age and older [a]

Drug	Strength of tablets (mg)	Number of tablets by weight band morning and evening										Strength of adult tablet (mg)	Number of tablets by weight band	
		3.0–5.9 kg		6.0–9.9 kg		10.0–13.9 kg		14.0–19.9 kg		20.0–24.9 kg			25.0–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
AZT/3TC[a]	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg/150 mg	1	1
AZT/3TC/NVP[a]	Tablet (dispersible) 60 mg/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg/150 mg/200 mg	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600 mg/300 mg	0.5	0.5
ABC/3TC	Tablet (dispersible) 120/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600 mg/300 mg	0.5	0.5

a For infants younger than 4 weeks of age, see Table 10.10 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolize medication. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birthweight infants.

Table 10.8 Simplified dosing of child-friendly solid and oral liquid formulations for once-daily dosing for infants and children 4 weeks of age and older [a]

Drug	Strength of tablet (mg)	Number of tablets or capsules by weight band once daily					Strength of adult tablet (mg)	Number of tablets or capsules by weight band once daily
		3.0–5.9 kg	6.0–9.9 kg	10.0–13.9 kg	14.0–19.9 kg	20.0–24.9 kg		25.0–34.9 kg
EFV[b]	Tablet (scored) 200 mg	-	-	1	1.5	1.5	200 mg	2
ABC/3TC	Tablet (dispersible) 60/30 mg	2	3	4	5	6	600 mg/ 300 mg	1
ABC/3TC	Tablet (dispersible) 120/60 mg	1	1.5	2	2.5	3	600 mg/ 300 mg	1
ATV[c]	Capsules 100 mg	-	-	1	2	2	300 mg	2 (100 mg)[d] or 1 (300 mg)
TDF[e]	Oral powder scoops 40 mg/ scoop	-	-	3	-	-	300 mg	1 (200 mg)[d] or 1 (300 mg)
	Tablets 150 mg or 200 mg	-	-	-	1 (150 mg)	1 (200 mg)		
DTG	10 mg and 25 mg tablets available	-	-	-	15–20 kg	20–30 kg	50 mg tablet	>30 kg
		-	-	-	2 x 10 mg tabs	1 x 25 mg tab		50 mg daily

a For infants younger than 4 weeks of age, see Table 10.10 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolise medication. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birth weight infants.

b EFV is not recommended for children younger than 3 years and weighing less than 10 kg. The United States Food and Drug Administration approved EFV for use for children younger than 3 years weighing more than 3.5 kg during the finalisation of these guidelines (3.5–5.0 kg: two 50 mg capsules; 5.0–7.5 kg: three 50-mg capsules; 7.5–15.0 kg: one 200-mg capsule), but more data are urgently needed to inform recommendations for using EFV in this age group.

c ATV is only approved for use for children 3 months and older. ATV single-strength capsules should be administered with RTV 100 mg for all weight bands. The ATV powder formulation enables administration of ATV to infants and children as young as 3 months. Infants and children weighing 5–10 kg should be administered 200 mg of ATV powder (4 packets, 50 mg per packet) with 80 mg of RTV oral solution (5 ml). http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206352s003,021567s038lbl.pdf

d 200 mg should be used for weight 25.0–29.9 kg and 300 mg tablets for 30.0–34.9 kg.

e TDF is only approved for use for children 2 years and older. Target dose: 8 mg/kg or 200 mg/m^2 (maximum 300 mg). The Paediatric Antiretroviral Working Group developed this guidance to harmonise TDF dosing with WHO weight bands and to reduce the numbers of strengths to be made available. The WHO generic tool was used based on the target dose provided by the manufacturer's package insert. In accordance with the standard Paediatric Antiretroviral Working Group approach, dosing was developed ensuring that a child would not receive more than 25% above the maximum target dose or more than 5% below the minimum target dose.

Table 10.9 Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing for infants and children 4 weeks of age and older [a]

Drug	Strength of tablets (mg) or oral liquid (mg/ml)	Number of tablets or ml by weight-band morning (AM) and evening (PM)										Strength of adult tablet (mg)	Number of tablets by weight band	
		3.0–5.9 kg		6.0–9.9 kg		10.0–13.9 kg		14.0–19.9 kg		20.0–24.9 kg			25.0–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
Solid formulations														
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
NVP[b]	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200 mg	1	1
LPV/r[c]	Tablet[d] 100 mg/25 mg	-	-	-	-	2	1	2	2	2	2	100 mg/ 25 mg	3	3
	Pellets[e] 40 mg/10 mg	2	2	3	3	4	4	5	5	6	6	100 mg/ 25 mg	3	3
DRV[f]	Tablet 75 mg	-	-	-	-	3	3	5	5	5	5			
RAL	Chewable tablets 25 mg	-	-	-	-	3	3	4	4	6	6	400 mg	1	1
	Chewable tablets 100 mg	-	-	-	-	-	-	1	1	1.5	1.5	400 mg	1	1
	Granules[g] (100 mg/ sachet)	0.25	0.25	0.5	0.5	-	-	-	-	-	-		-	-
Liquid formulations														
AZT	10 mg/ml	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	-	-	-	-	-	-	-
ABC	20 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	-	-	-	-	-	-	-
3TC	10 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	-	-	-	-	-	-	-
NVP[b]	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	-	-	-	-	-	-	-
LPV/r[c]	80/20 mg/ml	1 ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml	-	-	-
DRV[f]	100 mg/ml	-	-	-	-	2.5 ml	2.5 ml	3.5 ml	3.5 ml	-	-			

a For infants younger than 4 weeks of age, see Table 10.10 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolise medication. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exists on the dosing of ARV drugs for preterm and low-birth-weight infants.

b NVP dose escalation with half dose for 2 weeks when initiating ART is still recommended to avoid toxicity from high initial NVP levels. However, secondary analysis from the CHAPAS-1 trial recently suggested that younger children have a lower risk of toxicity, and consideration can be given to starting with a full dose (Fillekes Q et al. *Is nevirapine dose escalation appropriate in young African HIV+ children?* 20th Annual Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, USA, 3–6 March 2013 (http://retroconference.org/2013b/Abstracts/46904.htm, accessed 15 May 2015). More definitive evidence is expected from an ongoing trial.

c LPV/r liquid requires a cold chain during transport and storage. The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed.

d The adult 200/50 ml tablet could be used for children 14.0–24.9 kg (1 tablet in the morning and 1 tablet in the evening) and for children 25.0–34.9 kg (2 tablets in the morning and 1 tablet in the evening).

e The LPV/r pellets formulation should not be used for infants younger than 3 months. More details on the administration of LPV/r pellets is available at http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30-September-2015.pdf.

f DRV must be administered with 0.5 ml of RTV 80 mg/mL oral suspension if the child weighs less than 15 kg and with RTV 50 mg solid formulation for children weighing 15–30 kg.

g RAL granules are approved for use for children as young as 4 weeks, but the feasibility and acceptability of such formulations has not been widely investigated, and concerns have been raised regarding administration in resource-limited settings. The bioequivalence of RAL chewable tablets dispersed in liquid is currently being explored, and more guidance will be provided as soon as additional evidence becomes available.

f DRV must be administered with 0.5 ml of RTV 80 mg/mL oral suspension if the child weighs less than 15 kg and with RTV 50 mg solid formulation for children weighing 15–30 kg.

g RAL granules are approved for use for children as young as 4 weeks, but the feasibility and acceptability of such formulations has not been widely investigated, and concerns have been raised regarding administration in resource-limited settings. The bioequivalence of RAL chewable tablets dispersed in liquid is currently being explored, and more guidance will be provided as soon as additional evidence becomes available.

Table 10.10 Drug dosing of liquid formulation for twice-daily dosing for infants < 4 weeks of age

<table>
<tr><th>Drug</th><th>Strength of oral liquid (mg/ml)</th><th colspan="2">2–3 kg</th><th colspan="2">3–4 kg</th><th colspan="2">4–5 kg</th></tr>
<tr><td>AZT</td><td>10 mg/ml</td><td colspan="2">1 ml</td><td colspan="2">1.5 ml</td><td colspan="2">2 ml</td></tr>
<tr><td>NVP</td><td>10 mg/ml</td><td colspan="2">1.5 ml</td><td colspan="2">2 ml</td><td colspan="2">3 ml</td></tr>
<tr><td>3TC</td><td>10 mg/ml</td><td colspan="2">0.5 ml</td><td colspan="2">0.8 ml</td><td colspan="2">1 ml</td></tr>
<tr><td>LPV/r</td><td>80/20 mg/ml</td><td colspan="2">0.6 ml</td><td colspan="2">0.8 ml</td><td colspan="2">1 ml</td></tr>
<tr><td rowspan="3">RAL</td><td rowspan="3">10 mg/ml suspension</td><th colspan="3">Birth to 1 week: daily dosing</th><th colspan="3">1–4 weeks: bd dosing</th></tr>
<tr><th>2–3 kg</th><th>3–4 kg</th><th>4–5 kg</th><th>2–3 kg</th><th>3–4 kg</th><th>4–5 kg</th></tr>
<tr><td>0.4 ml daily</td><td>0.5 ml daily</td><td>0.7 ml daily</td><td>0.8 ml bd</td><td>1 ml bd</td><td>1.5 ml bd</td></tr>
</table>

For detail regarding the ARV dosing in this age and weight category please see additional detail in the 2016 consolidated ART guidelines, table 4, page 394.

Please also refer to the dosing charts in your **national guidelines**. An additional useful dosing chart is available for download via the **SAMU website**, https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018/ additional resources.

7. ART side effects

(See also **Chapter 4**.)

Abacavir (ABC)

In general, abacavir is well-tolerated in children. However, although rare in African people, a potentially life threatening hypersensitivity reaction can occur. Caregivers must be warned about a potential severe progressive reaction, which may include fever, rash, respiratory and GI problems. If the hypersensitivity reaction occurs, it is usually during the first 6 weeks of therapy, and symptoms tend to worsen in the hours immediately after the dose and worsen with each subsequent dose. Of note, once a hyersensitivity reaction has occurred, the child or adolescent should never be given abacavir again as the repeated reaction can be fatal.

Tenofovir (TDF)

According to the WHO, tenofovir is part of the preferred ART regimen for children aged 10 years or older, or >35 kg. It is also included as an acceptable choice for children aged 3–10 years of age. Two significant side effects may develop: decline in renal function and a loss in bone mineralisation. As such, it is usually safest to monitor both renal function and bone mineralisation on a regular basis. However, as this is not routinely available, please consult your national guidelines for details.

Zidovudine (AZT)

The major side effect of AZT is anaemia. As such, all children and adolescents starting AZT should have their haemoglobin checked before starting the drug. Haemoglobin should be monitored routinely (see your national guidelines). There are no food restrictions and oral solution may be stored at room temperature. Capsules may be opened and powder contents dispersed in water or mixed with a small amount of food (e.g. yoghurt) and immediately ingested. Currently, available tablets are not scored. Use with caution in children with anaemia, ideally not with an Hb <8g/dl, due to potential for bone marrow suppression.

Stavudine (d4T)

Due to its toxic side-effect profile d4T is rapidly being phased out worldwide. If patients are still on it, they should be changed to a more suitable ARV, according to your national guidelines. If, however, for some reason the patient is still taking it, see **Chapter 4**, Appendix 4.4 for details of side effects and their management.

Lopinavir/ritonavir (LPV/r)

This has a relatively good side effect profile. Aside from nausea and gastro-intestinal disturbance that can occur especially in the first 3 weeks of starting the drug, few side effects are experienced. The major issue with lopinavir/ritonavir syrup and pellets is its extremely bitter taste and the adherence problems that accompany this. Some techniques to increase tolerance and palatability include coating the mouth with peanut butter, dulling the taste buds with ice and following the dose immediately with sweet foods. The solution should be taken with food, as this increases absorption. The syrup is ideally refrigerated but can be stored at room temperature for up to 6 weeks. Tablets must not be chewed or crushed but swallowed whole, with or without food. There are many drug interactions with ritonavir (see **Chapter 7**).

Efavirenz (EFV)

Efavirenz is not approved for children under age 3 years and/or 10 kg. CNS side effects can develop, including vivid dreams. Long-term side effects include gynaecomastia. Tablets must not be chewed or crushed but swallowed whole with or without food. Capsules may be opened and powder contents dispersed in water or mixed with a small amount of food (e.g. yoghurt) to disguise the peppery taste, and immediately ingested. Food, especially high fat meals, increase absorption. Best given at bedtime to reduce CNS side effects, especially during first two weeks. Be aware of potential drug interactions (see **Chapter 7**).

Nevirapine (NVP)

Once daily dosing during the first 2 weeks of treatment reduces the frequency of rash. If a mild rash occurs during the induction period, continue once daily dosing and only escalate the dose to twice daily once the rash has subsided and the dose is well tolerated.

Dolutegravir (DTG) and raltegravir (RAL)

See adult section on side effects of dolutegravir and raltegravir in **chapters 2 and 4**.

8. Notes on adherence

General points:

- The ideal adherence needed to achieve successful treatment with ART is 95% or more. This means missing only one or two doses a month and represents a substantial challenge to the HIV-positive person taking meds for life. Most of us struggle to complete a 5-day course of antibiotics without missing a dose. The ability of children and adolescents to take their ARVs effectively is dependent on many psychosocial factors outside their direct control. The ability of their primary caregivers to take responsibility for their healthcare is particularly important. **Performing a thorough psychosocial history is therefore imperative when prescribing ART to children and adolescents.**

A psychosocial history attempts to obtain as much information as possible from caregivers and/or adolescents about their lives, particularly looking for trouble areas and barriers to treatment.

- Such a history should include the following questions:
    - Who lives with the child or adolescent?
    - Who will be the main person responsible for giving the medication, that is, the primary caregiver of the patient?
    - Is there a 'treatment supporter' available? A treatment supporter is another family member, friend or neighbour who helps the primary caregiver give the medication when the primary caregiver is not available. They also help remind the primary caregiver to give the medication.
    - Does everyone living with the child know the child has HIV? Do not assume that everyone living with the child knows that the child is HIV-positive. Lack of disclosure within the family can cause poor adherence to treatment.
    - Understand the daily routines in the home:
        - Who will be giving the medication in the morning and in the evening? Address any scheduling barriers that may exist.
        - Although there is substantial flexibility in terms of the time when ARVs need to be given, establishing times can help the caregiver to remember to give the medication. Assisting caregivers with setting cell phone alerts, and providing tools, such as pill boxes and pill calendars, can also be helpful to support adherence.

Understanding the daily routine of the child or adolescent will help identify and address the barriers to adherence.

9. Process of disclosure

Disclosure is the process by which a child learns about his/her HIV status. It can happen at any stage, from the moment the child is first diagnosed up to when the child has been on treatment for some time. This section is designed to equip the clinician to be able to:

- communicate appropriately with the HIV-positive child or adolescent and his/her carer;
- refer appropriately to a counsellor when the next step in the disclosure process needs to occur; and
- support the disclosure process him/herself if there is no counsellor available.

This topic is covered more comprehensively in the MSF's *Patient Support, Education & Counselling Guideline for Children and Adolescents Living with HIV*, which can be found in the additional resources folder on the **SAMU website** at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018/ .

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Why disclose the child's HIV status?

There are many important reasons why a child should be disclosed to:

- An honest, trusting relationship between the child and caregiver is important not only in the management of the HIV but also for the child's overall psychological and emotional development:
    - Children often know the truth before we think they do. Avoiding talking about it breeds distrust and may be associated with increased behavioural problems.
    - Children should know why they go to the hospital and have blood taken regularly.
    - Caregivers often fear how the child will cope but children often do better with the truth than we anticipate.
    - Knowing their status gives the child permission to talk openly about HIV with caregivers.
    - Disclosure can provide the child with a sense of control over their lives.
- Similarly honest, trusting relationships between the healthcare worker, child and caregiver are also important, so open communication is important here, too.
- How much the child knows about this can be a major factor in how he/she adheres to treatment and to what extent the child is able to protect others from infection.
- It's their right to know.

Who does the disclosure?

Ideally, this is done by the most trusted person in the child's life, with support from a healthcare provider (counsellor or clinician). Sometimes, the caregiver is reluctant to do this, for a variety of possible reasons. Some of the common reasons are:

- Belief that the child is too young to know.
- Fear that the child cannot maintain a secret.
- The caregiver may feel ashamed to talk to the child about the transmission of the disease.
- The mother/father may feel guilty about having passed on HIV to their child.
- Importantly, many people fear that disclosing to a child may jeopardise the caregiver–child relationship and decrease the chance that the child or adolescent adheres to his/her treatment. Studies have shown this is not true. Disclosing to a child has actually been shown to INCREASE the chance that the child/adolescent adheres to his/her treatment.

Time will need to be taken: hearing and addressing the concerns, explaining the process and encouraging the caregiver regarding all the benefits of disclosure.

If the caregiver refuses to be involved in the disclosure process, it needs to be handled very carefully by the counsellor or healthcare worker. (See Patient Support, Education and Counselling in the additional **resources folder** at: https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018/.)

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

When to disclose the status

Informing children about their HIV status needs to be done in a way that matches their ability to understand it. Disclosure is therefore a staged process that starts with the child having no knowledge of his/her HIV status, progresses to the first specific stage called **partial disclosure** and is followed by **full disclosure**. What is discussed is directly related to the stage that they are in and is detailed below. These stages are loosely linked to different ages but should also be guided by the developmental stage and health status of the child.

Disclosure can be integrated into a consultation, or, if done by the patient support team, done during the same visit to the clinic.

In general, the first recognised stage of the disclosure process, partial disclosure, only starts at about 5 years of age. **The first 5 years or so are therefore a time when most children have no understanding of their HIV status.** This time needs to be acknowledged for two reasons.

Firstly, the entire healthcare team needs to be aware of it, so that the chance of accidental disclosure is minimised. The documentation process noted below will help with this. In addition, action can be taken to initiate the disclosure process if the child has reached an appropriate age and stage to start.

Secondly, there are basic guidelines on communication principles during this time:

- The counsellor/clinician can educate the caregiver on the need for disclosure in the future and thus start to prepare for this at an early stage.
    - The counsellor/clinician gives no explanation of clinic visits or medication but rather focuses on building trusting relationships between child, caregiver and the healthcare team.
- This models the principles of honesty and open communication for the caregiver and contributes to laying a good foundation for when the disclosure process starts.
    - Communication with the child is more about their day, their friends, favourite games, etc. than on medical issues.
    - Clinical communication is limited to general hygiene and germ awareness (e.g. hand washing) and the fact that pills keep them strong.

There are 2 key steps in the active disclosure process, partial disclosure and full disclosure, also roughly corresponding to different age groups.

1. **Partial disclosure:**

   This usually occurs in the 5–7 year age group, though it can vary a bit, depending on the levels of perception and communication of the child. It can be started when the child starts to ask questions regarding regular visits to the clinic or why meds are taken daily.

Because the child will initially need to be protected from some of the information, early consultations in this process will need to be split between having the healthcare worker alone with the clinician/counsellor, and then later including the child.

In this stage, the caregiver and healthcare worker talk about what is happening in his/her body **without naming the virus** and the disease. Explanations must be simple but comprehensive. Examples of communication in this stage are to explain, using simple ideas, for example:

- 'You have a sleeping germ.'
- 'The pills you take keep the germ asleep so it won't make you sick.'
- 'The nurse takes your blood to check if the germ is sleeping.'

If counsellors are available in the clinic, the clinician needs to refer the child to them at the right time to manage this process. If not, it is critical that clinicians take responsibility for this themselves.

2. **Full disclosure:**

This is usually in the 8–10 year age group, but, as above, can be dealt with sooner, or delayed. It should ideally be completed by the age of 10 and no later than 12, as leaving the HIV status un-discussed by the onset of adolescence creates significantly more challenges. (See adolescent section at the end of this chapter.)

Full disclosure can be started when the child starts to ask questions regarding the name of the infection or the details of the treatment. The early consultations in the process may also need to have the child initially excluded from the consultation and then join later.

In this stage, the child gets to know that he/she is infected with HIV and is given all the information needed to understand HIV more fully. For example:

- Name the sleeping germ as HIV.
- Provide guidance to the child on disclosure to others.
- Explain how HIV is transmitted.
- Include the child when talking about his/her health/blood results, explaining that the sleeping germ is called HIV and giving details regarding HIV transmission and non-transmission. The healthcare worker also starts to include the child in discussions about health.

As above, clinicians need to take responsibility for managing the disclosure process, either by appropriate and timeous referral to a counsellor, or taking responsibility themselves, if a counsellor is not available.

3. **After full disclosure:**

Once full disclosure has been completed the child is included in decisions and discussions about health, relationships and safe sex. Attempts are made to address internal stigma and answer other questions, which inevitably change as the child gets older.

For every HIV-positive child under their care, clinicians should know how much the child knows about his/her illness and a plan should be in place to ensure that the appropriate disclosure stage is reached.

Documenting the disclosure status

The disclosure status of a child/adolescent should be indicated on the front of the file, using a code that the entire health team is aware of, e.g. empty circle for non-disclosed (ND); half circle for partially disclosed (PD); or a full moon circle for fully disclosed (FD); or simply the initials, ND, PD or FD to alert the team of the disclosure stage. This will increase the chance that all the relevant health team members are aware of this and will therefore speak to the child/adolescent in such a way that accidental disclosure is avoided.

Unacknowledged disclosure

This refers to when a child has unfortunately come to know of his/her HIV status through an unplanned or unsupported disclosure. This can occur in different circumstances and vary in the psychological impact on the child. Examples of this are:

- Involuntary disclosure: a child discovers about his/her status from reading posters, seeing his medications, hearing adults talk about HIV and working out that he/she is infected.
- Disclosure is made in a moment of crisis, for example, by a frustrated parent trying to get a child to take his/her medication.

The implications of an unacknowledged disclosure are that the child has not only skipped a carefully planned disclosure process but may also be traumatised as the result of how it was done. The counsellor or clinician needs to be alert for those who give signals that they know something about their status, but that all the key information is not yet fully out in the open, especially between the child/adolescent and caregiver. The management of this type of disclosure requires careful and sensitive handling, best guided by the more detailed PSEC guideline referred to earlier.

In order to avoid an unacknowledged disclosure and its potential consequences, the planned and structured disclosure process referred to in this section should not be delayed. The clinician plays a critical role in identifying the disclosure status of each child or adolescent under his/her care and referring timeously for appropriate management.

10. Treatment failure

The management of possible ART failure is covered comprehensively in **Chapter 6**. Most of the concepts in that chapter apply equally to children, so will not be repeated here. The focus of this chapter is on those aspects of treatment failure that need special attention in children and adolescents.

Treatment failure rate for children and adolescents with HIV is much higher than in adults.

Great strides have been made in the field of paediatric HIV over the last 15 years. Improvements in ART have enabled many children to reach adulthood and achieve their goals. However, many problems with paediatric HIV treatment remain, and often place children and adolescents at risk for failing their treatment. These problems include:

- The small number of available ARVs for children;
- The unpleasant taste of existing ARVS;
- A lack of research and development for paediatric ARVs;
- Dosing complications with paediatric ARVs; and
- The many psychosocial issues surrounding the administration of chronic lifelong medication and maintaining long term adherence.

Because of all these problems, it is not surprising that the treatment failure rate for children and adolescents with HIV is much higher than in adults. Whereas the failure rate for adults ranges from 10 to 15%, depending on location, reports on the failure rate for children range from 19% (after only 3 years of treatment) to as high as 57%.

What is paediatric HIV treatment failure?

Treatment failure in children with HIV is categorised in the same way as adults: virological, immunological, clinical failure or some combination of the three. The definition of HIV treatment failure will vary, depending on the HIV guidelines of the country where you are working and the resources that are available to you. In particular, the definition will differ, depending on the availability of viral load testing:

Without viral load testing:

In some locations, viral load testing is not available, so treatment failure is defined using immunological or clinical criteria. Of note in children, pay attention to the neuro-development indicators as well, since poor neurological development can be an early sign of clinical failure.

With viral load testing:

When viral load testing is available, the principles are the same as in adults.

What are the causes of paediatric HIV treatment failure?

The principles of how failure develops are detailed in **Chapter 6**, section 1 and are the same for children. Of note, failure due to resistance strains of HIV that have been passed from the mother to the child is uncommon. For the vast majority, the cause is secondary ARV failure, due to **poor adherence**.

There are numerous causes for poor adherence, falling into the same three categories seen in adults. Below is the same table used in **Chapter 6** (Table 6.2) but note changes specific to children.

Table 10.11 Responsibility for cause of high viral load in a child

Responsible person or entity	Cause of high viral load
Clinician responsible	Not double-dosing LPV/r with rifampicin
	Not increasing the dose as a child gains weight
	Not switching to valproate if patient epileptic
	Not detecting and advising patient if there is significant diarrhoea and/or vomiting
	Clinician not detecting mental illness or substance abuse and making efforts to help
Health system responsible (a few examples)	Poor counselling strategies resulting in inadequate advice to start with
	Poor mechanisms for lost-to-follow-up tracing
	Little opportunity for patient to ask questions or raise concerns
	Drug stock-outs
	Clinic management of viral load results
	Complicated treatment regimes
	Unpleasant taste of drugs
Patient-related	Treatment fatigue
	Food insecurity
	Stigma
	Alcohol or substance abuse
	No treatment supporter
	Unwell/irresponsible caregiver
	Disclosure issues
	Unstable home life

Why is having a high viral load detrimental for a child or adolescent with HIV?

There are two key impacts of a prolonged high viral load:

- All the organs in the body have the potential to be damaged by the virus. Of particular importance in a child is that fact that HIV affects the developing brain and neurological system of children and adolescents, potentially affecting neurodevelopment. The longer a child or adolescent remains with a high viral load, the greater the effects of HIV to the developing brain and body.
- As with adults, having a high viral load, particularly while still taking ARVs, places the child at risk of developing **resistance** to ARVs. This, too, is detailed in **Chapter 6**, section 1.

One of the complications of the development of resistance that has particular relevance to children is when resistance develops to the commonly used NNRTIs, NVP and EFV. If resistance develops to one, it automatically develops to the other and so-called 'cross-resistance' occurs. The impact of this in a patient who has failed PMTCT is illustrated in the following diagram.

Figure 10.3 How cross-resistance develops

The infant receives nevirapine during the PMTCT intervention.

→

Unfortunately, some infants still become infected. However as nevirapine is continued as part of the PMTCT regimen, resistance develops to it.

→

The PMTCT-exposed infant is likely to be resistant to all NNRTIs (including efavirenz).

A PI-containing regimen is now required.

Another complication specific to children is related to the relative unavailability of paediatric drugs. As a result of this, resistance and cross-resistance can potentially lead to a situation where **no effective ARV options** are left for the child. Such an extreme situation places the child at high risk of morbidity and mortality.

For these reasons, a high viral load in a child or adolescent should be considered an **emergency** and be addressed in a timely fashion before any new OIs, neurodevelopmental delay or resistance develops.

When to switch to second or third line ART

When treatment failure has been diagnosed according to the criteria noted above and detailed in **Chapter 6**, this means that the drugs are no longer working. For effective suppression of the viral load, a switch to a second line regimen containing effective, non-resistant drugs is therefore needed. Because of the psychosocial situations so often complicating the development of failure in childhood and adolescence, the decision to switch to second line ART should ideally be made by a multidisciplinary team that includes both a clinician and a counsellor. However, as noted in **Chapter 6**, section 5, the difficulties of arranging this combined consultation must not allow a potentially life-threatening delay in switching to a new regimen.

If the child's failing regimen (whether first or second line) is PI-based, the switch will need to be made to a second or third line regimen containing newer drugs, such as dolutegravir, and newer PIs, such as darunavir. This decision will involve a genotype, so more experienced help will be required.

Choice of second line ART regimen:

The second line ART regimen will depend on the age of the child and which first line ART combination has been used. The WHO table below shows the preferred second line regimens for patients of different ages. Please note that these regimens may be different depending on the availability of ARVs in your setting.

Table 10.12 Preferred second line ART regimens for children

Population	First line	Second line	Third line
Children <6 years	2 x NRTIs + EFV	2 x NRTIs[a] + LPV/r[b]	DRV/r + RAL + 1-2 NRTIs, ideally chosen using genotyping
	2 x NRTIs + LPV/r	2 x NRTIs + RAL[c]	
Children >6 years (or >15 kg)	2 x NRTIs + EFV	2 x NRTIs + DTG	DRV/r + DTG[d] + 1-2 NRTIs, ideally chosen using genotyping
	2 x NRTIs + LPV/r	2 x NRTIs + DTG	
	2 x NRTIs + DTG	2 x NRTIs + ATV/r	

a. Optimised NRTI backbone should be used: AZT replaces TDF or ABC failure and vice versa.

b. ATV/r can be used as an alternative PI for children older than 3 months of age.

c. RAL remains the preferred second line for those children for whom approved DTG dosing is not available.

d. DTG-based third line following use of an INSTI must be administered with DTG taken twice daily.

Important programmatic elements when addressing treatment failure

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It is beyond the scope of this clinical guide to detail all the programmatic elements needed to more effectively manage treatment failure in children and adolescents. The core components are, however, noted here and more detailed documentation of this can be found on the **SAMU website** in the additional resources section under https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

Components included in your intervention will depend on the resources available to you. Ideally, the intervention should be integrated within the existing services of the clinic:

- Flagging system for high viral loads;
- Good adherence counselling – the most important intervention that takes place in a paediatric treatment failure intervention. See PSEC guideline at https://samumsf.org/en/resources/hiv/paediatric-and-adolescent-hiv;
- A dedicated consulting space for managing those failing their treatment – whilst it can be beneficial to have a separate space for the intervention, it is not necessary;
- Paediatric 'Champions' – the selection of one particular clinician, with a particular interest in paediatrics, who makes a point of promoting the specific needs of paediatric care. Care must be taken, however, to ensure that this person doesn't end up being the only clinician seeing children. He/she will also promote the development of a passionate paediatric healthcare team;
- Support Groups; and
- Adolescent-focused services.

11. Specific paediatric conditions

Many of these conditions are covered comprehensively in other chapters in this book. Information specific to children is covered here, while reference is made to specific chapters detailing the fuller picture of the individual illnesses in adults.

HIV/TB co-infection

(See **Chapter 12**.)

Tuberculosis (TB) is a bacterial infection caused by *mycobacterium tuberculosis*. While it often affects the lungs, the disease can affect every organ system of the body. TB and HIV often go together. In fact, having HIV significantly increases the chance of TB disease. Moreover, patients with HIV have worse outcomes with TB than HIV-negative patients. Given this situation, it is not surprising that TB is the most common cause of death in paediatric patients with HIV.

Clinical presentation

The symptoms of TB in children are often not 'typical', and a wide range of symptoms can occur. Furthermore, symptoms are often non-specific and overlap with many other illnesses. Thus, a high index of suspicion is needed to diagnose TB in children. More frequent symptoms include a cough, lack of energy or 'just not playing the way he/she used to', weight loss, and fever. Night sweats are not as significant a feature as they are in adults. Organ-specific symptoms will depend on the organ affected.

Diagnosis

Confirming a diagnosis of TB in a child is far more difficult for a variety of reasons detailed below.

1. It is difficult for children to produce sputum. Thus, alternative methods of specimen collection are required such as induced sputum, nasopharyngeal aspirate and gastric aspiration. While feasible in many settings, these methods require equipment and proper training to perform well.
2. Unlike adult sputum, a child's sputum is often 'pauci-bacilliary, meaning few organisms in the sputum. Therefore, most samples from children are 'smear-negative'.
3. Obtaining a contact history for a child can be difficult. As healthcare workers, we rely on the caregivers to provide us with an accurate account of any exposures. The situation can become complicated when multiple caregivers are involved, when migration occurs, or when other factors make a caregiver's history unreliable.

Often in children, because of the difficulty in establishing bacteriological proof of TB, there needs to be a greater preparedness to start empirical treatment.

> Multiple modalities should therefore be used when attempting to diagnose TB, since, aside from a positive sample (which is difficult to obtain), there is no 'one test' that reliably diagnoses TB.

An overall clinical assessment can be made using the following modalities:

1. **History taking**
    a. History of TB contact: Be specific when asking questions about contacts! Ask if any family members or friends have visited recently, if a neighbour who spends time in the house has been coughing, if the child spends time travelling in mini-buses, etc.
    b. Symptoms consistent with TB: Early disease may be asymptomatic. Symptoms of later disease include persistent cough for more than 2 weeks, documented weight loss, reduced playfulness, and persistent fever. Ask about any organ specific symptoms.
2. **Physical examination**

    Include a growth assessment! Check vital signs and perform a full examination, not only of the chest, but also any other part of the body that could be affected (especially heart, abdomen, bones and joints, including the spine).

3. **Bacteriologic confirmation whenever possible**

    a. A bacteriologic confirmation should always be sought; however, lack of it should not delay treatment if clinically indicated.

    b. Bacteriologic confirmation is especially important for children with one or more of the following:

    - Suspected drug resistance;
    - Complicated or severe disease.

4. Investigations relevant for suspected pulmonary and extra-pulmonary TB:

    a. TB LAM: Recommendations in children are the same as in adults; in all severely ill patients in need of admission, regardless of CD4; and in ambulatory patients with a CD4 <100, with signs/symptoms of TB.

    b. CXR: Although there are no specific TB signs on CXR, common findings include:

    - Increased density in the hilar and/or para-tracheal region;
    - Compression of the airways from diseased lymph nodes;
    - Lung parenchymal disease; and
    - Unilateral pulmonary effusion.

    For a comprehensive guide to reading paediatric chest x-rays, see https://samumsf.org/en/resources/tb/paediatric-tb and then look under 'implementation resources' for a series of **training videos**.

samumsf.org/en/resources/tb/paediatric-tb

    c. FNA: There can be a low yield if an inadequate sample is obtained.

    d. Gastric washing:

    - Up to 50% yield if performed in standardised manner
    - Best results if performed first thing in the morning after 8 hours of fasting and before the child gets up from bed, so this is not an ideal outpatient procedure.

    e. Induced sputum:

    - Inhalation of 3–5% hypertonic saline in a nebuliser.
    - Proper training needed and must be performed in a well-ventilated place.
    - The yield from one induced sputum equals the yield from 3 gastric washings.

    f. Nasopharyngeal aspirate is another useful means of accessing mycobacterial proof of TB. (For more detail, see additional resources folder on the **SAMU website** at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.)

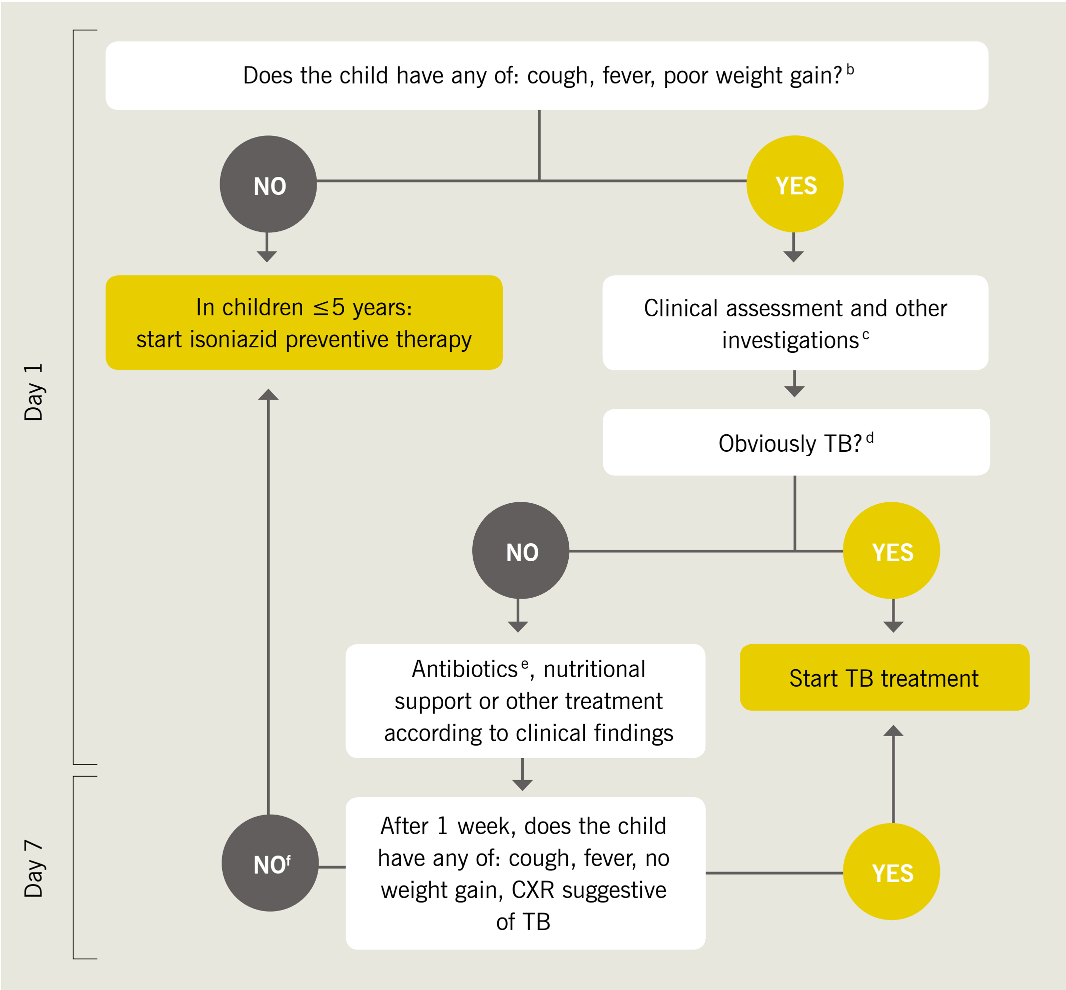
samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

5. HIV testing:

    a. Repeat HIV testing if there is any uncertainty about the positive diagnosis.

    b. Obtain a CD4 count and viral load if possible.

Algorithm 10.1 Paediatric diagnostic algorithm for a TB contact [a]



a. Contact: child living in the same household or in close and regular contact with any known or suspected TB case in the last 12 months.

b. Malnutrition or growth curve flattening.

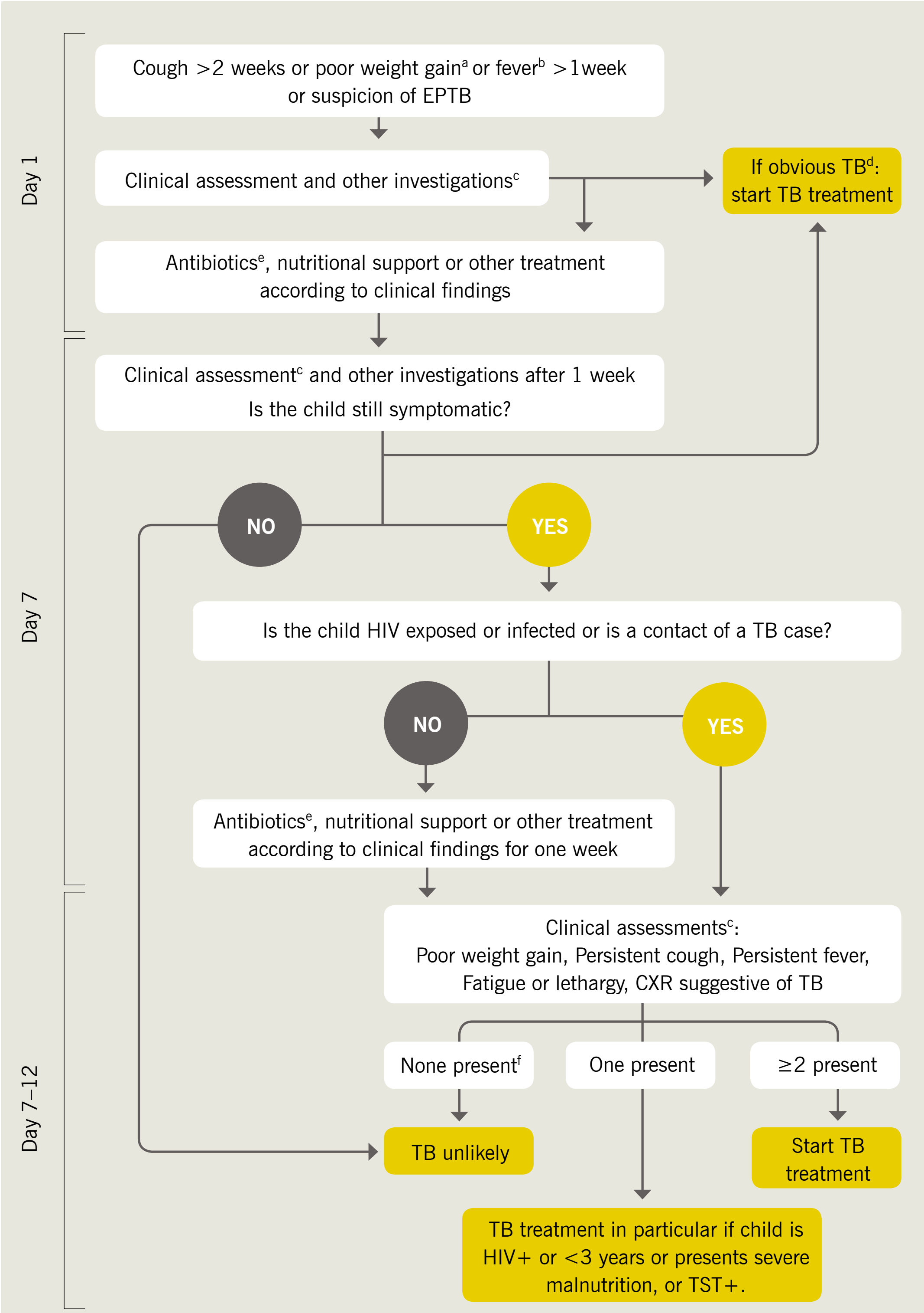
c. Clinical assessment (including growth assessment), bacteriological tests, HIV testing (in high HIV prevalence areas), and when relevant and available: X-ray (CXR), investigations for EPTB, TST. TB LAM is recommended for use in all severely ill patients in need of admission, regardless of CD4, and in ambulatory patients with a CD4 <100 with signs/symptoms of TB.

d. Examples of 'obvious TB' may include cases of Pott's disease, TB meningitis, lymph node TB with fistula formation, smear or Xpert MTB/RIF positive or highly suggestive chest X-ray (e.g. hilar lymphadenopathy, upper lobe infiltrates, miliary picture).

e. Broad spectrum ATB:
- If no danger signs: amoxicillin PO for 7 days;
- If danger signs: parenteral ATB (e.g. ceftriaxone).

f. Clinical response to a broad-spectrum antibiotic does not rule out TB. Carer should be informed to consult if symptoms re-occur.

Algorithm 10.2 Paediatric diagnostic algorithm for a child with TB symptoms



a. Malnutrition or growth curve flattening.

b. Temperature >38°C.

c. Clinical assessment (including growth assessment), bacteriological tests, HIV testing (in high HIV prevalence areas), and when relevant and available: X-ray (CXR), investigations for EPTB, TST. TB LAM is recommended for use in all severely ill patients in need of admission, regardless of CD4, and in ambulatory patients with a CD4 <100 with signs/symptoms of TB.

d. Smear microscopy positive or Xpert MTB/RIF positive, CXR showing suggestive lesions (e.g. hilar lymphadenopathy, upper lobe infiltrates, miliary picture), gibbus.

e. Broad spectrum antibiotics:

- If no signs of severity:
    - first line: amoxicillin PO for 7 days (NO fluoroquinolones). Advise carer to return with the child if no improvement after 48 hours of antibiotics;
    - if a second course of antibiotic if needed: azithromycin PO for 5 days.
- If signs of severity: parenteral antibiotics (ceftriaxone ± cloxacillin if *S. aureus* is suspected). In addition: PCP treatment should be given presumptively to all HIV-exposed or HIV-infected children <1 year of age, and any older child with severe immune suppression and not on CTX prophylaxis. For all other HIV-exposed or HIV-infected children, it should be considered if there is poor response to broad spectrum antibiotics after 48 hours.

f. Clinical response to a broad-spectrum antibiotic does not rule out TB. Carer should be informed to consult if symptoms re-occur.

Treatment

- See paediatric TB dosage guidelines at the end of this chapter.
- For additional information regarding TB treatment see **Chapter 12** as well as the **additional resources** folder for **Chapter 10** at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

General comments about treatment of HIV/TB co-infection in children:

1. Children should be treated with 2 months of RHZE and 4 months of RH, except for TB meningitis and osteoarticular TB, where the treatment is 2 months RHZE and 10 months RH.
2. Ethambutol is considered safe, regardless of the child's age, in particular regarding ocular toxicity, provided it is correctly dosed at 20 mg/kg/day. It is routinely used to treat drug-susceptible TB in children.
3. Streptomycin should be avoided in children because irreversible auditory nerve damage may occur and the injections are painful.
4. TB treatment must always be started before anti-retroviral treatment (ART).
5. Use pyridoxine supplementation for HIV-positive patients and those who are malnourished.
6. All HIV-positive children on TB treatment should also be prescribed cotrimoxazole.

7. Be aware of drug–drug interactions and adjust ART regimen as needed.
    a. Rifampicin–nevirapine: change to efavirenz.
    b. Rifampicin–lopinavir/ritonavir:
        i. If >5 years old, double the dose of lopinavir/ritonavir.
        ii. If <5 years, the double-dose LPV/r is not effective. Either add additional ritonavir at 3/4 of the volume of LPV/r (e.g. if giving 2 ml LPV/r, add extra 1.5 ml ritonavir). If ritonavir not available, use a triple NRTI regimen of AZT/3TC/ABC.
8. Correct timing of the commencement of ART after starting treatment of specific infections: With cryptococcal meningitis and all manifestations of TB, the development of IRIS has been shown to be linked to a combination of the CD4 count and the timing of the commencement of ART after starting treatment for the infections. Evidence-based guidelines have been developed for this and are as follows:

    TB:

    - If CD4 <50, start ART within 2 weeks after starting TB treatment.
    - If CD4 >50, the start of ART can be delayed up to 8 weeks after starting TB treatment, but in practice ART is started within the first 2–4 weeks of starting TB treatment. The closer the CD4 to 50, the closer to 2 weeks the ART is started.
    - If TB meningitis, delay the start of ART by 4 weeks, as higher mortality has been shown if starting ART sooner.

    Cryptococcal meningitis:

    - Regardless of CD4 (which is usually low anyway) the commencement of ART needs to be delayed by 4 weeks after the start of treatment.

Respiratory: Bacterial pneumonia

Bacterial pneumonia is very common in young children and is, in fact, the single largest infectious cause of death in children worldwide, according to the WHO (2016). As such, having a high index of suspicion and starting treatment early is important. Pneumonia is diagnosed if the child has either fast breathing (tachypnoea) or lower chest wall in-drawing (retractions) (WHO 2016).

Clinical presentation

Simple pneumonia: The child has cough and/or tachypnoea, with or without fever and chills.

Severe pneumonia: The child has severe tachypnoea, in-drawing at rest, or other concerning symptoms, such as convulsions, altered consciousness, or hypothermia.

Remember: The definition of tachypnoea changes depending on the age of the child:

- 60 breaths/minute or more in children aged <2 months;
- 50 breaths/minute or more in children aged 2–11 months;
- 40 breaths/minute or more in children aged 12 months to 5 years.

Management

Most children with **simple pneumonia** can be treated successfully as outpatients with oral antibiotics. Children with **severe pneumonia** require inpatient management. Good clinical judgement is paramount to achieve a successful outcome.

- Simple pneumonia is commonly treated with amoxicillin 30 mg/kg/dose 3 times daily for 7 days or 50mg/kg/dose twice a day for 7 days.
- Reassess within 2 days of starting antibiotics.

Severe pneumonia requires admission to the hospital.

- Prior to hospital referral, administer oxygen by mask.
- Give the child a first dose of ceftriaxone IV or IM at a dose of 50–75 mg/kg:
    - 3–5 kg: 250 mg (1 ml)
    - 6–9 kg: 500 mg (2 ml)
    - 10–14 kg: 750 mg (3 ml)
    - 15–25 kg: 1 g (2 ml in each thigh).
- Check for hypoglycaemia with a point-of-care glucometer, if possible.
- For HIV-exposed or HIV-infected children, especially those <1 year of age, it is important to initiate therapy with high-dose cotrimoxazole (CTX) in addition to the treatment described above, since pneumocystis pneumonia (PCP) cannot be excluded and is rapidly fatal if untreated. See section on PCP below for further information.
- Severely immunocompromised children over 1 year of age who have not been on CTX prophylaxis should be treated for both PCP and bacterial pneumonia.
- Total treatment duration (IV and oral) for severe bacterial pneumonia is typically 10–14 days. Continue cotrimoxazole for 21 days for treatment of PCP pneumonia.

Respiritory: Pneumocystis pneumonia (PCP)

PCP (or PJP, as it is often now called) is an opportunistic infection of the lungs caused by the organism pneumocystis jiroveci. PCP is common in HIV-infected children less than 1 year in age. In older children, it is seen mainly in severely immune-compromised children not on cotrimoxazole preventive therapy (CPT).

Clinical presentation

- PCP in children typically presents with:
  - Tachypnoea (see Appendix 10.1 for normal vital parameters in children);
  - Dyspnoea (severe difficulty in breathing);
  - Cyanosis; and
  - Sudden onset of fever, although a fever may not always be present.
- Chest auscultation is less specific. The amount of respiratory distress is a more important sign.
- The chest x-ray may show a diffuse interstitial infiltrate.

PCP is frequently seen in children who are not taking cotrimoxazole prophylaxis. However, it is important to note that being on cotrimoxazole does not exclude the diagnosis, especially in an infant or a child with a low CD4 count.

Management

- Children with PCP initially require inpatient management.
- Oxygen should be started promptly upon admission.
- Cotrimoxazole 100 + 20 mg/kg/day given in divided doses (i.e. 3 or 4 times a day) for 21 days. See weight-based dosages in Table 10.13 below.
- The first dose of CTX should be given prior to hospitalisation. In hospital, the CTX should be administered intravenously 4 times a day.
- Once the child begins to improve and can be managed as an outpatient, CTX can be administered orally 3 times daily.
- Treatment with cotrimoxazole can be given in addition to the usual treatment for pneumonia (e.g. amoxicillin).
- In severe cases, add prednisolone 1 mg/kg/dose twice daily for 5 days, then 1 mg/kg/dose once daily for 5 days, then 0.5 mg/kg/dose once daily for 5 days. IV steroids, such as dexamethasone, may also be used.
- After completion of treatment, secondary prophylaxis with cotrimoxazole is important.
- If the child is allergic to cotrimoxazole, dapsone 2 mg/kg/day can be given as an alternative for prophylaxis.

Table 10.13 High-dose cotrimoxazole for treatment of PCP in children

Dose given 4 times a day*			Dose given 3 times a day	
Weight (kg)	**Syrup/disp tab***	**SS tab***	**Syrup***	**SS tab***
<5	2.5 ml		4 ml	
5–9.9	5 ml		7 ml	
10–14.9	7.5 ml		10 ml	1 tab
15–21.9	10 ml	1 tab	15 ml	1½ tab
>22	15 ml	1½ tab		2 tabs

* Syrup: 200 mg SMX/40mg TMP per 5 ml
Dispersible (disp.) tab: 100 mg SMX/20 mg TMP (1 disp. tab = 5 ml syrup)
Single-strength (SS) tab: 400 mg SMX/40mg TMP

Neurology: Peripheral neuropathy (PN)

(See also **Chapter 14**.)

Clinical presentation

- Peripheral neuropathy is a disorder of the peripheral nerves.
- Although peripheral neuropathy is less common in children than in adults, it is an important diagnosis to make in children, as it can cause significant morbidity.
- When it occurs in children, it is often a side effect of isoniazid (INH) treatment.
- Symptoms include weakness, paresthesia and extremity pain.

Management

- Management should be tailored depending on the underlying cause. Consult with a more experienced clinician to review management options.

Prophylaxis of peripheral neuropathy in a child on INH

Pyridoxine:

- <5 years: 5–10 mg OD
- >5 years: 10 mg OD

Treatment of peripheral neuropathy in a child on INH

If vitamin B6 deficiency is suspected, treat with higher doses of pyridoxine:

- <5 years, give 25 mg/day.
- >5 years, give 50 mg/day.

In severe cases, consult with a paediatrician or experienced clinician and consider amitriptyline in older children.

- 6–12 years: 10 mg at bedtime;
- >12 years: 25 mg, plus paracetamol 15 mg/kg as needed, three to four times/day.

Neurology: Bacterial meningitis

Clinical presentation

- As symptoms early in the course of bacterial meningitis can be non-specific (such as fever or vomiting), it is important to have a high index of suspicion for meningitis during your evaluation.
- Symptoms can include: fever, headache, lethargy/coma, irritability, abnormal cry, poor feeding, vomiting, stiffness of the neck, and convulsions. In infants, the fontanelle may be bulging (although this is not always present).

Management

Refer to hospital

These patients must be referred for management in hospital.

While preparing for referral, do not delay in giving the first doses of antibiotics, since meningitis can cause devastating permanent brain damage very quickly.

a. Check your hospital protocol for preferred medications and dosages in your setting.

b. In the absence of a hospital protocol, the following can be used as an initial guide:

    - Children <3 months: ampicillin and ceftriaxone.
        - IV ampicillin (check local protocol for dose) and ceftriaxone 100 mg/kg loading dose, then 100 mg/kg daily divided 1–2 times a day.
        - Note that ampicillin, unlike ceftriaxone, is also active against listeria monocytogenes.
        - Ceftriaxone is contra-indicated in premature neonates who have hyperbilirubinaemia.Instead, use cefotaxime: Dosage varies according to age:
            - if preterm, 50 mg/kg twice daily
            - in first week of life, 8 hrly
            - in first 2-4 weeks of life, 6 hrly

- Children ≥3 months:
  - Ceftriaxone is at 100mg/kg/day given in a single dose or 2 divided doses. (Maximum 2g per dose). If giving twice a day, can give IV or IM but if a daily dose, it must be given by IV infusion only. Be careful when giving the dose IV, not to use the solvent that comes with the IM dose.
  - As these doses may sometimes vary it is important to check your local protocol for dosage guidance.

If IV access is difficult to establish, rather give the first dose of ceftriaxone IM than miss a potentially life-saving dose of medication.

Neurology: Cryptococcal meningitis

Clinical presentation

Similar to bacterial meningitis, early signs and symptoms of cryptococcal meningitis can be non-specific and subtle, with headache, fever, and vomiting being common. Thus, being aware of the possibility of cryptococcosis infection is paramount to making a timely diagnosis. Cryptococcal meningitis is most frequently seen in severely immune-compromised children who have CD4 counts below 100.

Management

Refer to hospital

- **These patients must be referred for management in hospital.**
- The updated 2018 WHO guideline for adults, adolescents and children recommends:
  - A one-week induction regimen with amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day);
  - Followed by a consolidation phase of fluconazole 12 mg/kg/day (up to 800 mg/day) for another 8 weeks;
  - Followed by a maintenance phase of fluconazole 6 mg/kg/day (up to 200 mg/day) as secondary prophylaxis.
- In children aged 2–5 years, secondary prophylaxis with fluconazole can be discontinued, if the child is stable on ART and anti-fungal maintenance treatment for at least one year, and has a CD4 count >25% (preferably on 2 measurements taken 6 months apart).
- It is not currently recommended to discontinue secondary prophylaxis in children aged <2 years.

Neurology: Toxoplasmosis

Clinical presentation

- Toxoplasmosis usually occurs in severely immune-compromised patients (those with CD4 counts <100).
- Symptoms include headache, fever, focal neurological symptoms, such as weakness, ataxia, or paralysis, and encephalitis-like symptoms, including altered mental status and decreased levels of consciousness.
- Fundoscopic examination may reveal focal lesions in the choroid/retina and/or papilledema (indicating increased intracranial pressure).

Management

Refer to hospital

- **These patients must be referred for management in hospital.**
- High dose cotrimoxazole (sulfamethoxazole + trimethoprim). Check your national guidelines for dosing.

> Toxo lesions generally resolve within 3 weeks of starting treatment. If an HIV-positive patient with focal neurological signs (and a low CD4 count) does not respond to empirical anti-toxoplasmosis treatment, the cause is probably not toxoplasmosis and the patient should undergo further assessment.

If resources are limited in your setting, consider empiric TB treatment (a full course), since a cerebral tuberculoma is another treatable cause of such symptoms.

CNS lymphoma can only be diagnosed definitively with a brain biopsy and is untreatable.

Other causes of a focal neurological deficit, usually without an encephalitis picture or fever, include ischaemia, haemorrhage, neurosyphilis, TB meningitis and HIV vasculopathy.

Neurology: HIV encephalopathy

Encephalopathy may be the first indication that a child has HIV infection. It is important to recognise this condition, because early diagnosis and ARV treatment can significantly diminish the long-term sequelae of encephalopathy.

Clinical presentation:

Suspect HIV encephalopathy if:

- A child's head circumference (HC) has not increased or has fallen off the growth curve.

- A child's developmental milestones are delayed or have regressed (for example, a child who was able to sit by himself/herself now is unable to do so).

The risk of encephalopathy is an important reason to measure and plot the head circumference of every child until 3 years of age, and to assess developmental milestones of all children. Always ask the caretaker how the child is developing.

Management:

- **Important:** HIV encephalopathy is a diagnosis of exclusion. Therefore, before diagnosing it, first investigate fully for other causes.
- If HIV encephalopathy is suspected, ensure that ARVs are initiated.
- For the child with HIV encephalopathy, a multidisciplinary approach works best, including clinical management, psychosocial support and physiotherapy where feasible.

Malaria

Where malaria is common, it occurs more frequently and more severely in HIV-infected patients. Clinicians need to ensure that in areas of higher malaria prevalence children are tested and promptly treated and that the child sleeps under a bed-net.

Gastrointestinal disorders

Chapter 15 details the many conditions seen in the gastro-intestinal tract in adult patients living with HIV. Most of the conditions in children are the same as they are in adults. Where there are differences, these are noted in the text wherever there is a paediatric icon. Dehydration in children is detailed in Appendix 15.1.

Skin diseases in HIV-positive children

Skin conditions in HIV-positive children present and are managed very similarly to skin conditions in adults. Therefore, paediatric skin conditions are dealt with in **Chapter 20**.

Fever of unknown origin

After pneumococcal infection, the most frequent cause of bacteremia in an HIV-infected child is non-typhi *salmonella bacteremia*. A fever of unknown origin in these children should, therefore, be taken seriously and the child referred to hospital for urgent attention. For a guide to both persisting fever and appropriate antibiotic use in adults, much of which is relevant to children, see **Chapter 23**.

12. Take-home messages

- Children are NOT small adults! Caring for them requires an understanding of their unique characteristics and the differences between adult HIV and paediatric HIV.
- Be a 'detective' when performing histories and physical examinations on children and adolescents with HIV! Be specific when questioning caregivers and enquire further if the initial responses raise concern.
- Since even small mistakes in management can result in poor outcomes, attention to detail is essential. Be thorough when taking histories and performing physical exams.
- Know the side effect profiles and dosing specifics of every ARV you prescribe to children and adolescents! If you are not clear and accurate in the information you give to the caregivers, the child will not be given them properly.
- Nobody can remember the detailed dosing for every possible weight band so weigh the child at every visit and always use an ARV dosing chart when prescribing medicines for children and adolescents.
- Think TB, think TB, think TB! Since HIV/TB co-infection is common, be aware of the possibility of TB in any child or adolescent with respiratory or other characteristic symptoms.
- Assess every child's nutritional status and plan appropriate nutritional support.
- Be aware of the importance of routine immunisation and the need for specific additional vaccine interventions in HIV-positive children.
- Treatment failure is common in children and adolescents! Follow the viral load results of your patients, investigate psychosocial barriers to adherence and do not delay making a regimen switch when treatment failure is diagnosed. If unsure, ask for more experienced help, provided it doesn't further delay the management.
- Adherence is the biggest cause of HIV treatment failure in children and adolescents. As such, learning how to perform a thorough psychosocial history to find treatment barriers is essential.
- Ask for assistance from superiors and specialists when questions about clinical management remain.
- Advocate for children and adolescents! Children have rights and deserve quality care. As clinicians, we have the responsibility to be advocates for children's rights. Additionally, if a child's or adolescent's psychosocial situation appears unsafe, or neglect seems to be present, safeguard the child and alert the proper authorities/social services, so an evaluation can be made.

HIV care of the adolescent

There are many challenges in this increasingly important age group, related largely to the many psychosocial factors at play, as these young people go through the necessary developmental process of the transition from a dependent child to an independent adult. The presence of these challenges, manifesting in overall poorer outcomes has led to adolescents being classified by WHO as a key population needing special attention (see **Chapter 26**.)

This section of the chapter is aimed primarily at supporting the clinician in maximising care in the consulting room and give a brief overview of the following:

- Who exactly make up this group;
- Some global epidemiology data to frame the challenges;
- The unique challenges in adolescent HIV care; and
- Key recommendations to address the challenges.

It is not within the scope of this book to provide the comprehensive information, both clinical and programmatic, needed to adequately care for this challenging population. However, additional references for **further reading** are provided in the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Who makes up the group 'adolescents'?

Adolescents are defined by WHO as the age group from 10 to 19 years and 'young adults' is the term used for those 20–24 years of age. In addition, it is also clinically important to identify whether the adolescent was **perinatally infected** (also referred to as **vertically infected**) or acquired HIV by transmission other than during pregnancy or breastfeeding (also referred to as **horizontally or behaviourally infected**) There are some differences between the two groups, mainly the greater prevalence of chronic systemic disease in the vertically infected group and the fact that they sometimes have different support needs.

Global epidemiology of HIV-infected adolescents

- Adolescents are currently the fastest growing HIV-positive population, with sub-Saharan Africa home to 6.2 million (63%) of the world's 15–24 year olds living with HIV.
- Regarding outcomes, adolescents are doing particularly poorly, with a 50% increase in AIDs-related mortality between 2005 and 2012. HIV is the second biggest cause of death worldwide in this age group and the biggest cause of death in Africa.
- In addition, adolescents are a particularly difficult group to treat, with much evidence of low access to HIV testing and counselling, poor adherence and poor retention in care. Viral suppression rates, though variable, are low in most studies.
- Studies show high lost-to-follow-up (LTFU) rates with the risk higher in those perinatally infected.

- High LTFU rates are linked to poor adherence and poor mental health.
- In a UNICEF report from 2016 it was shown that 32% of new HIV infections among adolescents from 15–19 years occurred outside sub-Saharan Africa. Therefore, HIV remains a global issue when it comes to prevention among adolescents.

The unique challenges in adolescent HIV care

Adolescence is a time of rapid physical, biological, intellectual, behavioural and emotional growth. Each component has the potential to worsen outcomes in the HIV-infected individual. The individual is no longer a child and no longer wishes to be treated as such, but, at the same time, is not ready to embrace the rigors of adulthood and the different components of HIV care that accompany it. There are many challenges to be addressed if this transition process is to be managed effectively, with as little impact on outcomes as possible. Key challenges have been identified as follows:

Poor knowledge of HIV

HIV knowledge amongst adolescents is low, with just 26% of girls having comprehensive HIV knowledge (*For Every Child, End AIDS: Seventh Stocktaking Report,* 2016, UNICEF).

This low level of HIV literacy amongst adolescents makes prevention measures especially challenging to implement. For example, only 32% of girls with multiple sexual partners reported having protected sex.

Impact on 90:90:90

In its 90:90:90 plan for 2020, WHO set the goal of 90% of all people with diagnosed HIV infection knowing their status, 90% of those patients being on antiretroviral therapy and 90% of those on this therapy achieving viral suppression. However:

- Adolescents are less likely to present for testing. Globally, in 2015 only 13% of adolescent girls were tested for HIV and had received their results in the previous 12 months.
- Adolescents are less likely to link to a health centre to initiate ART.
- Once on ART, adolescents face many challenges staying on it long term:
    - Their socialising hours often clash with the times that they need to take ARVs.
    - Their resilience in the face of side effects is lower.
    - Intermittent and often permanent stopping of ART is common.

Psychosocial support

- Adolescents' need for support is not only greater, but also the type of support needed is different from adults. There is a preference for peer support and engagement with healthcare workers who have a specific understanding of their unique needs.

- The more detailed nature of this support also varies, with important distinctions needing to be made between the 10–14 and 15–19 year age groups.
- The impact of stigma on the adolescent in this very sensitive, peer-aware stage of life is great and there is generally a lower level of acceptance of a positive HIV status in an adolescent in the community.
- Receiving support from parents can frequently be fraught with conflict; for the vertically infected adolescent it is complicated by the realities that the mother passed the virus on to the child, and for the horizontally infected, it can be an identifier of unacceptable sexual activity.

HIV services

In terms of HIV services, there are many challenges related to this specific age group, where the adolescent is not yet ready to be an adult, yet no longer wants to be a child. Adolescents often have:

- An intolerance for sitting in long queues in routine HIV clinics;
- Resistance to sitting with large numbers of adults;
- Experience of clinicians as being harsh and judgmental;
- Aversion to the limited privacy, so essential for the adolescent; and
- Difficulty accessing the clinics, due to inconvenient hours (clashing with school activities or socialising) or clinics being a significant distance from home.

Specific health services

- Sexual and reproductive health: Again, and for a variety of reasons, adolescents are reluctant to join adults in their clinics.
- Mental health: There has been little measuring of the impact of adolescent mental health issues on HIV care, limited evaluation of adolescent mental health interventions and poor development of systems to promote adolescent mental healthcare.

Key recommendations to address the challenges

In attempts to address these multiple challenges, the following have been recognised as key to improving adolescent HIV outcomes:

Confidentiality

Confidentiality is important to all adolescents, especially those living with HIV, as they fear rejection, family and peer abuse. Studies have shown that youth often do not receive the care they need, due to their fears of confidentiality not being maintained. Surveys have shown that, in general, adolescents tend to trust doctors to maintain confidentiality but tend to be more concerned about whether other clinic staff will do so.

Confidentiality needs to be respected as much as possible. There are, however, times when decisions have to be made, such as HIV testing, contraception and

Refer to your national guidelines

consent for procedures. If the adolescent is under the legal age for being able to make independent decisions, an adult will need to authorise these, thus interfering with the confidentiality that the adolescent is hoping to maintain. Before engaging the authorising adult however, this must always be communicated first to the adolescent. As the legal age status of an adolescent varies between different countries, please consult **national guidelines**.

Recommendations:

- Train ALL STAFF on the importance of confidentiality (including technicians, pharmacists, counter staff).
- Have individual counselling alone with the patient, without the caregivers.
- Close the clinic room door when seeing a patient!

Respectful treatment

Adolescents are very sensitive to rude, judgmental behaviour and attitudes from staff. This can lead to poor retention rates and poor adherence to care. Studies have shown fear of embarrassment to be a major deterrent to clinic attendance and that judgmental attitudes create negative barriers to open, honest communication.

Recommendations:

- Train ALL STAFF on the importance of treating youth with respect.
- Train clinicians how to raise sensitive issues, such as sexual health.
- Explain reasons for tests, etc.

CLINIC RULES

Confidentiality   Honesty   No judgment

Comprehensive, integrated service

Attending an integrated clinic is more beneficial than having to attend many different clinics for varied health needs. Providing this can also help decrease stigma, because 'nobody knows why' the adolescent is at the clinic.

Recommendation

Create a 'one-stop-shop' providing primary care, reproductive health services, STI/HIV and substance abuse treatment and mental health care in the same venue.

Competent, friendly staff

Adolescents want staff trained in 'youth friendly' services that are sensitive to cultural differences.

Stereotyping creates a barrier to effective care.

Recommendations:

- Establish continuous, ongoing training regarding adolescent and youth priorities, cultural diversity and norms.
- Establish clear, unambiguous policies against discrimination of any kind – and advertise this well.
- Pay attention to language diversity.

Easy access to care

This is critical to adolescents and youth. Barriers include transportation difficulties, difficult appointment times (school and socialising conflicts), not knowing where to go while at the medical facility and difficulty scheduling and keeping follow-up appointments (e.g. returning for test results).

Recommendations:

- Introduce flexible hours of operation (after hours, Saturdays).
- Improve the location of services (decentralised spaces outside of the main clinic).
- Establish a 'Help Line' for adolescents to use to inquire about services.
- Make correspondence easy for them (texting appointment dates, etc.).
- Though controversial, providing incentives may be helpful (e.g. transportation vouchers, free internet at clinic, vouchers for good attendance).

Family planning/reproductive health services

Adolescents want and need these services as teenage pregnancy and STI rates are high.

Recommendations:

- Train staff in reproductive health.
- Integrate these services into general adolescent services.
- Have adequate space for care/counselling.
- Use standardised forms for eliciting sexual history.
- Offer many forms of contraception (and explain them well).
- Screen for STIs.

A youth-friendly environment

Adolescents like having an environment geared towards them. There is some evidence that patients failing treatment can benefit from this type of environment.

Recommendations

With an eye on simple things, like paint colour, age appropriate posters and furnishings, try and create a space that gives the adolescent some sense of uniqueness, ownership and belonging.

Peer support

There are many benefits to peer support. It is a source of psychological support, helps to build confidence and reduce anxiety and promote a sense of belonging. It is also a source of practical information and tends to increase motivation to continue with long-term adherence.

Recommendation:

Incorporate peer support interventions into your programmes.

General recommendations

Promote communication between parents and adolescents, as better adolescent/caregiver communication has been shown to positively affect adolescent behaviour. Programmes to strengthen parenting and communication skills will add value.

'One size does not fit all': adolescents are a varied group, so what works for one adolescent may not work for another. It is therefore best to have multiple interventions and give them a choice of services. Clinic populations may differ, so it is important to take into account specific needs of the population.

Choice of ART

There are a few important principles in the choice of the ART regimen that will support improved adherence:

- Choose a regimen that is potent but with minimal toxicity.
- Wherever possible, start on or change to a regimen that can be taken once a day.
- Try and choose ABC or TDF, along with 3TC/FTC as the NRTIs, so that AZT can be preserved for second line.
- Dolutegravir, with its high barrier to resistance and lower side effect profile, is a preferred option to EFV as the third drug in the regimen. Be guided by national guidelines and WHO guidelines from 2018 onwards.
- Try and choose a regimen that is likely to be continued in adulthood.

The vertically infected adolescent

In more resource-limited settings, unfortunately, many vertically infected children do not survive into adolescence. If they do, however, they are faced not only with the challenges noted above, but also a variety of potential clinical conditions. These not only require clinical vigilance to detect them, but also care in long-term management. These include:

- growth failure;
- cardiac disease;

- chronic lung disease;
- neurocognitive disease;
- skin disease;
- renal and bone disease;
- infections; and
- malignancy.

For a selection of references for further reading on both programmatic and clinical topics please see the additional resources folder on the **SAMU website**: https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

HIV care in the adolescent – key points

- There is a high HIV-positive burden among adolescents, with millions of adolescents infected.
- Unlike all other age groups, the mortality rate for adolescents has increased over the last decade.
- Healthcare workers should be upskilled in the provision of 'youth-friendly' approaches to care, being especially careful to show respect, provide confidentiality, be honest, and show no judgment towards the adolescents.
- 'One size does not fit all'; an individualised approach is needed to care for adolescents with HIV.
- Care for adolescents should be made accessible and offer multiple services at the same centre.
- Peer support is a powerful tool to help provide education and support for adolescents with HIV.

Appendix 10.1 Normal values for children

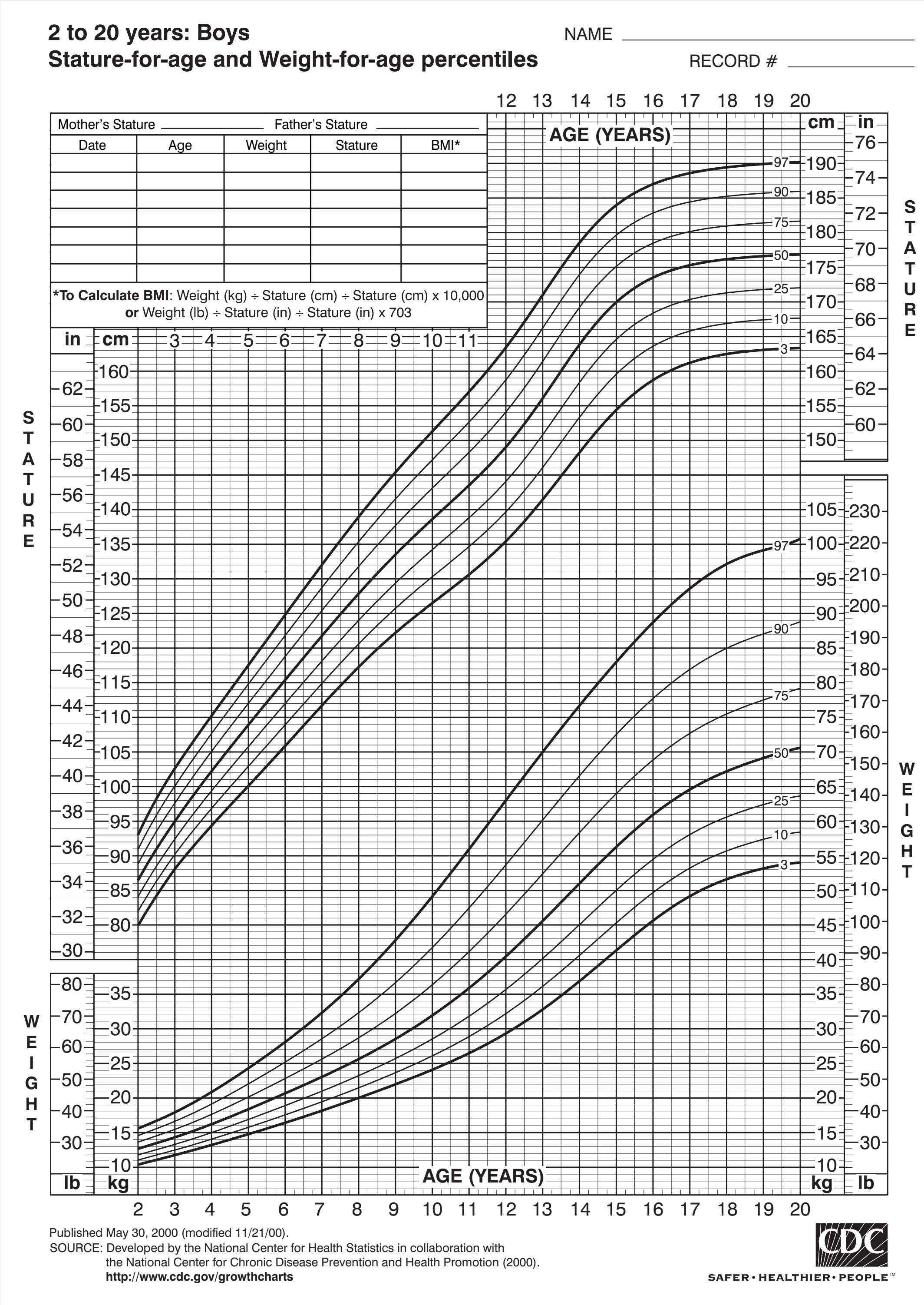
Normal ranges heart rate:

Age	Heart rate
Premature:	120–170
0–3 months:	100–150
3–6 months:	90–120
6–12 months:	80–120
1–3 years:	70–110
3–6 years:	65–110
6–12 years:	60–95
>12 years:	55–85

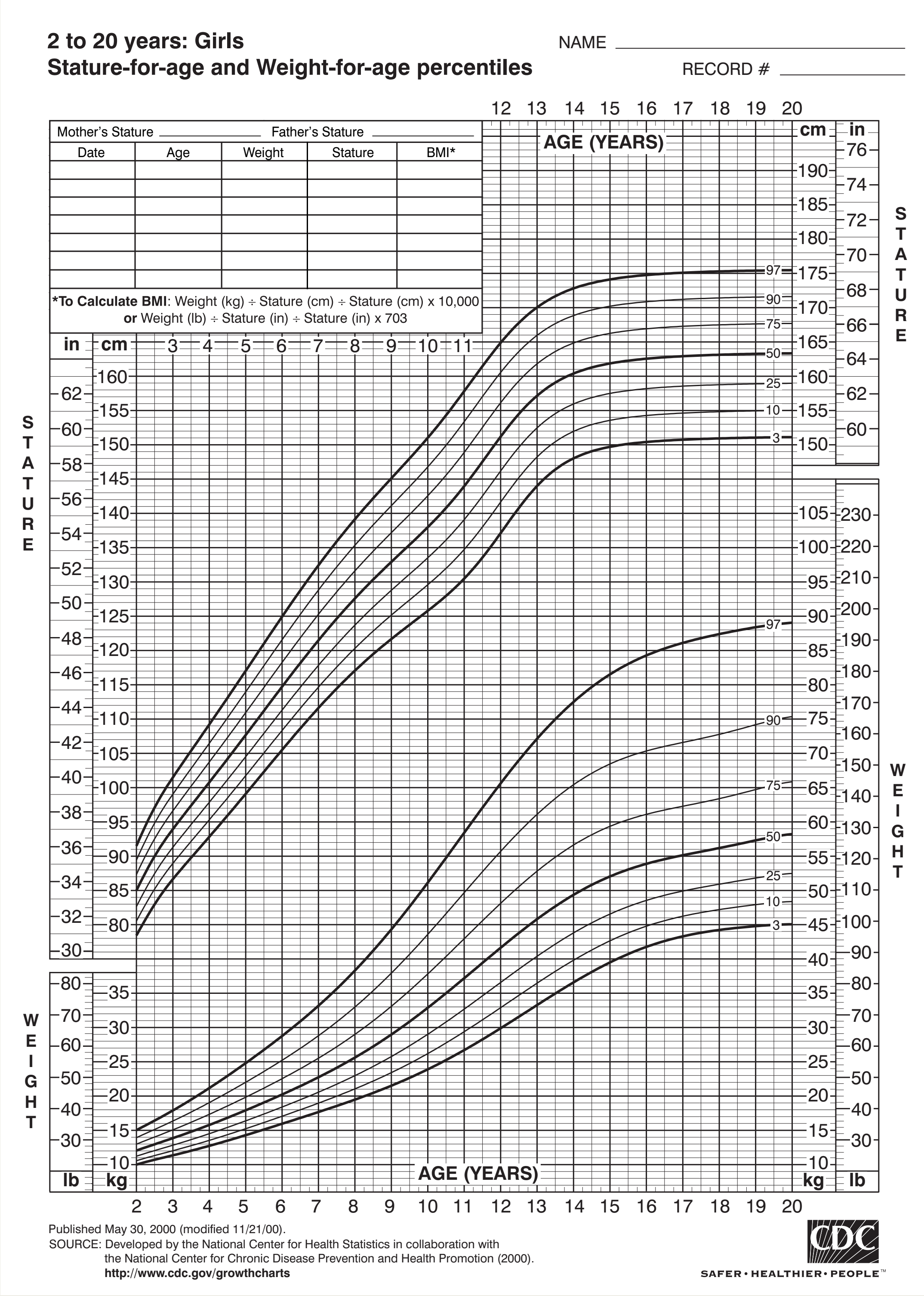
Normal ranges respiratory rates:

Age	Normal range
Premature	40–70
0–3 months	35–55
3–6 months	30–45
6–12 months	25–40
1–3 years	20–30
3–6 years	20–25
6–12 years	14–22
>12 years	12–18

Height and weight chart: Boys 2–20 years

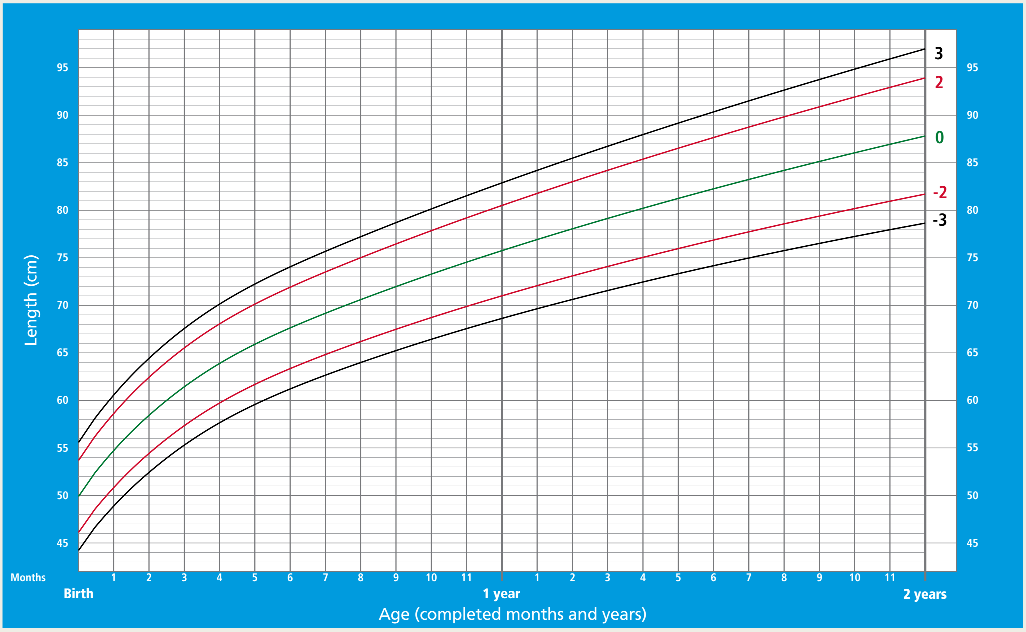


Height and weight chart: Girls 2–20 years



Length-for-age: Boys

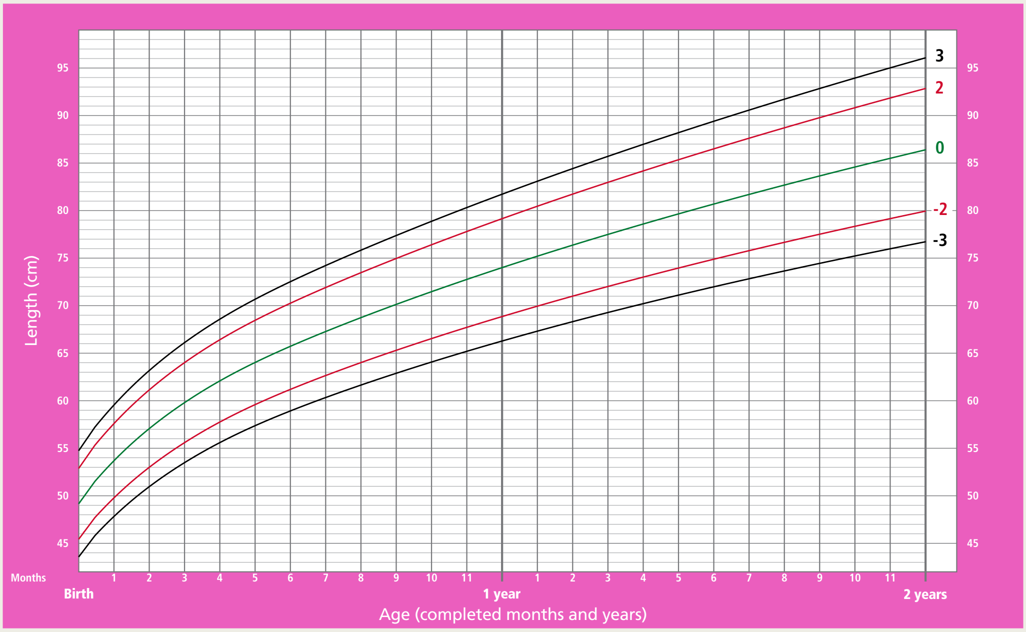
Birth to 2 years (z-scores)



WHO Child Growth Standards

Length-for-age: Girls

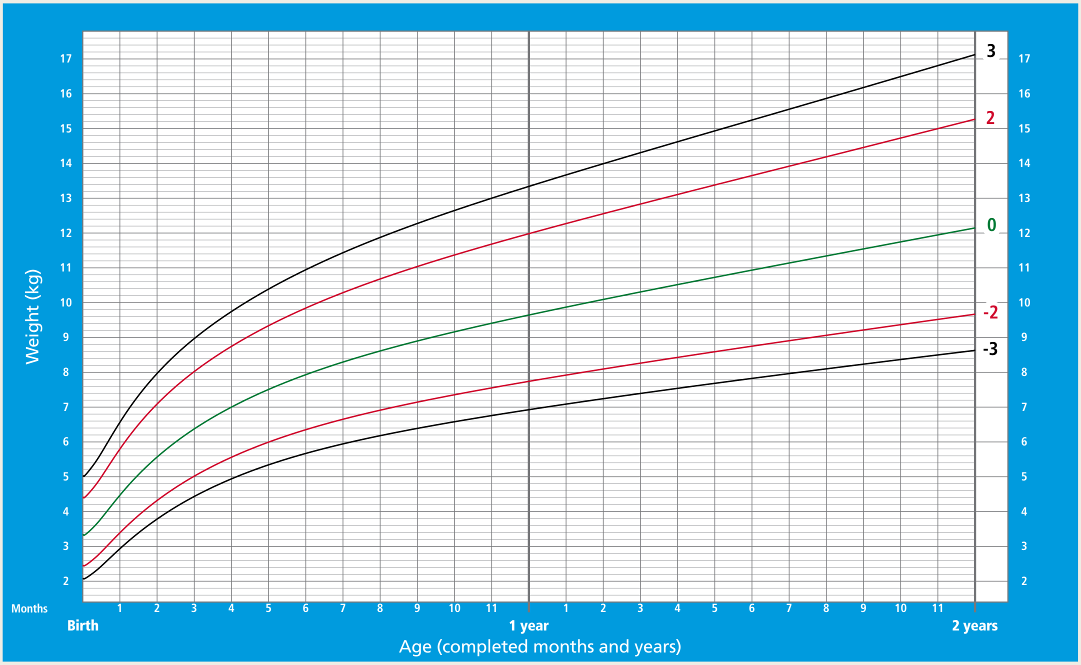
Birth to 2 years (z-scores)



WHO Child Growth Standards

Weight-for-age: Boys

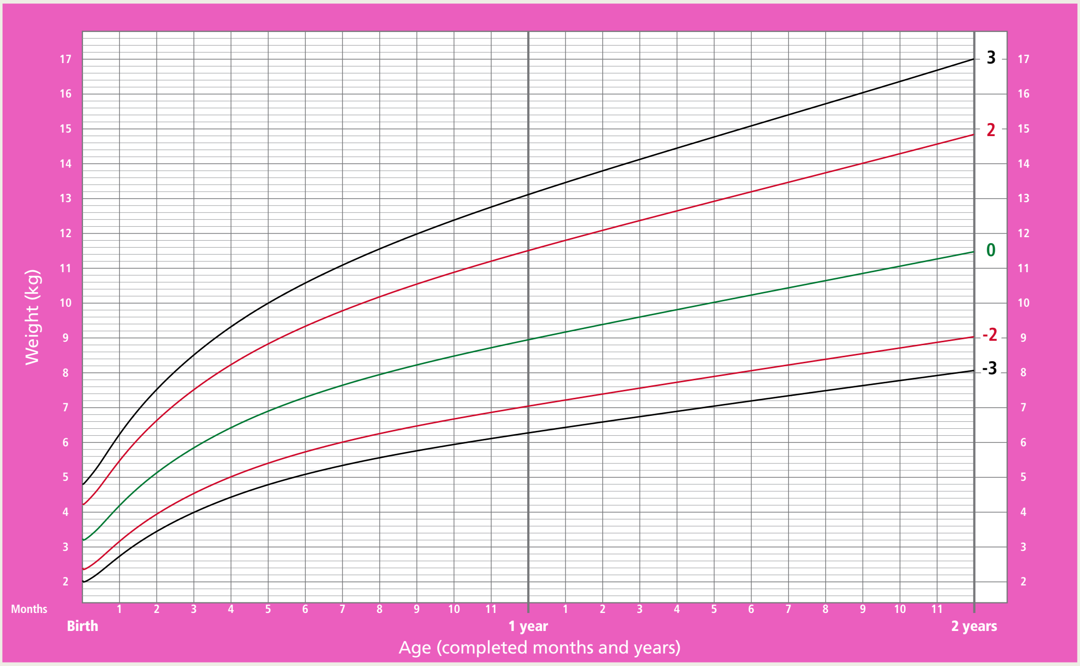
Birth to 2 years (z-scores)



WHO Child Growth Standards

Weight-for-age: Girls

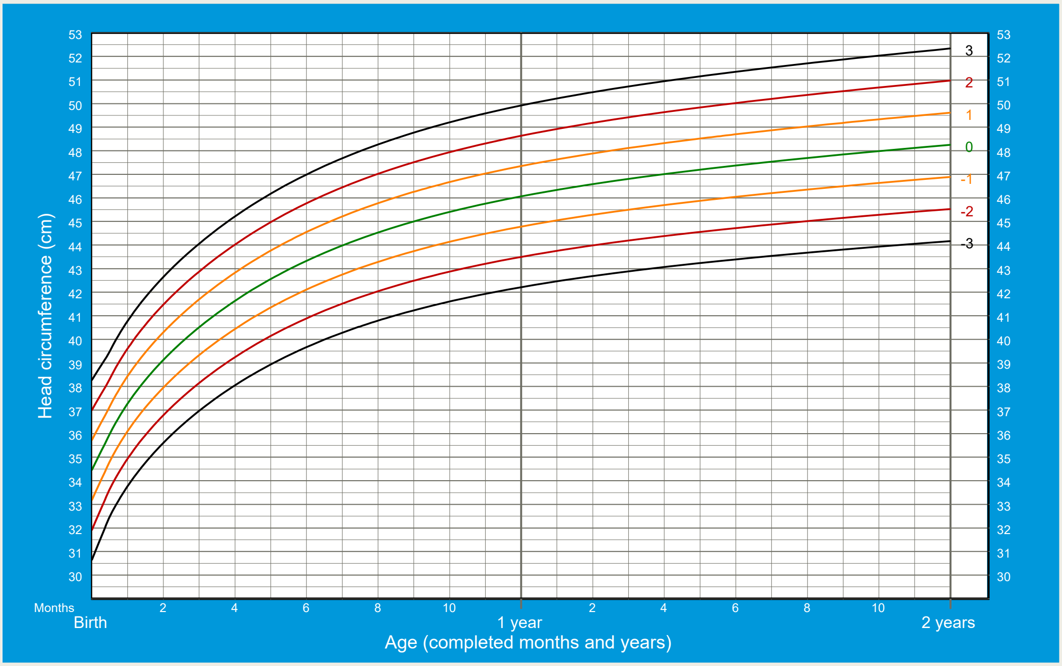
Birth to 2 years (z-scores)



WHO Child Growth Standards

Head circumference-for-age: Boys

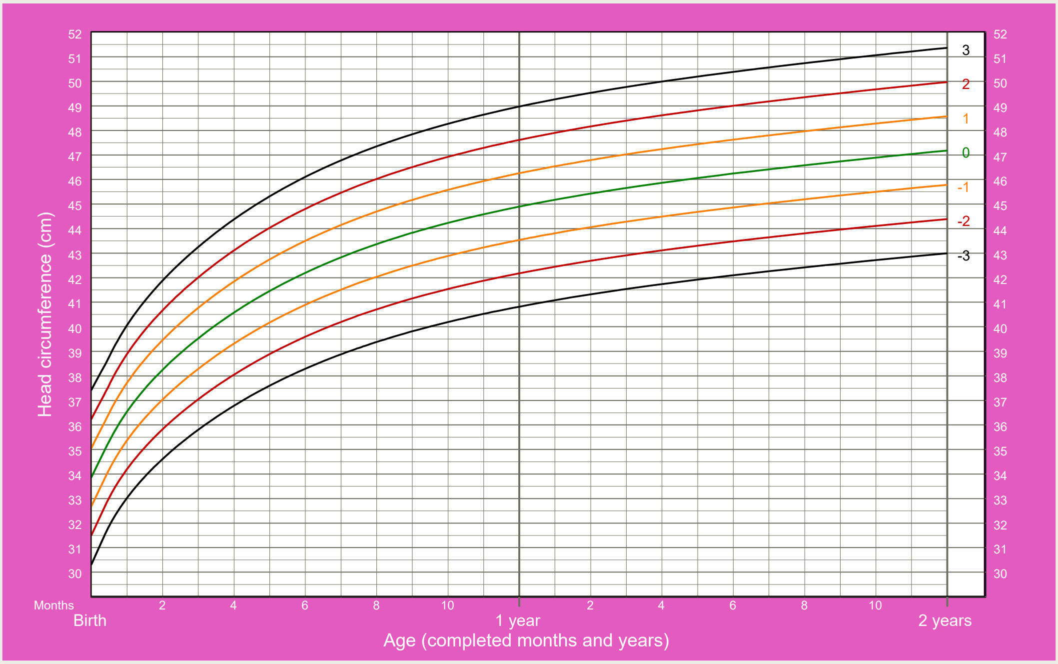
Birth to 2 years (z-scores)



WHO Child Growth Standards

Head circumference-for-age: Girls

Birth to 2 years (z-scores)



WHO Child Growth Standards

Appendix 10.2 Guidelines for TB treatment in young children using FDCs

(Taken from the 2014 WHO guidance document for national TB programmes on the management of TB in children)

To allow the currently available fixed-dose combinations (FDCs) to be used to achieve the desirable doses of anti-TB drugs for children, WHO has compiled the dosing charts in this annex as an interim measure, based on the following:

- Quality-assured dispersible tablets should be used wherever possible, especially for children who cannot swallow solid tablets.
- Regimens are based on FDCs, but in some cases may also require administration of single-component products.
- These doses are for once-a-day dosing regimens, and, wherever possible, avoid the need for splitting tablets.
- The recommended doses are generally below the upper limit of the dose ranges to minimise risk of toxicity.

These guidelines replace the interim recommendations published by WHO in 2009: *Dosing instructions for the use of currently available fixed-dose combination TB medicines for children.*

Once children achieve a body weight of 25 kg, adult dosage recommendations can be followed and adult preparations used.

Weight band	Number of tablets		
	Intensive phase		Continuation phase
	RHZ (60/30/150)	E (100)	RH (60/30)
4–6 kg	1	1	1
7–10 kg	2	2	2
11–14 kg	3	2	3
15–19 kg	4	3	4
20–24 kg	5	4	5

Treatment of TB in young children (less than 25 kg) using currently available FDCs (RHZ 60/30/150), and dosages achieved per weight

Body weight (kg)	Number of tablets	Actual dosage (mg/kg) received when using number of tablets containing dosages listed for that weight band		
		Rifampicin 60 mg	Isoniazid 30 mg	Pyrazinamide 150 mg
4	1	15.0	7.5	37.5
5	1	12.0	6.0	30.0
6	1	10.0	5.0	25.0
7	2	17.1	8.6	42.9
8	2	15.0	7.5	37.5
9	2	13.3	6.7	33.3
10	2	12.0	6.0	30.0
11	3	16.4	8.2	40.9
12	3	15.0	7.5	37.5
13	3	13.9	6.9	34.6
14	3	12.9	6.4	32.1
15	4	16.0	8.0	40.0
16	4	15.0	7.5	37.5
17	4	14.1	7.1	35.3
18	4	13.3	6.7	33.3
19	4	12.6	6.3	31.6
20	5	15.0	7.5	37.5
21	5	14.3	7.1	35.7
22	5	13.6	6.8	34.1
23	5	13.0	6.5	32.6
24	5	12.5	6.3	31.3

Advanced disease – ambulatory patient

The package of care for a primary care clinic

1. ART status
2. How stable they are clinically

In its 90:90:90 plan for 2020, WHO set the goal of 90% of all people with diagnosed HIV infection knowing their status, 90% of those patients being on antiretroviral therapy and 90% of those on this therapy achieving viral suppression. With the 90:90:90 goals, the global focus in HIV care is to reduce HIV infections and ensure that all PLHIV are on ART and are virally suppressed. However, people are still dying from advanced disease.

The focus here in addressing the care of the patient in primary care with advanced disease is to reduce mortality. With the rapid scale-up of ART globally from the early 2000s, the mortality rate from HIV dropped over the next 10 years by over 40%, but after this, the rate of this decline began to slow down. Studies have shown two new trends.

- A constant proportion of patients are still presenting with advanced immune suppression with CD4s <200 and many <100, despite the scale-up of ART.
- An increasing proportion of these people have previously been on ART, with one or more episodes of treatment interruption, or are currently on ART and failing their regimen.

This has given rise to a change in terminology, so that the previous term, 'the late presenter' has now been replaced by the term, 'patients presenting with advanced HIV disease'.

WHO guidelines

The 2017 **WHO definition** of the adolescent and adult presenting with advanced disease includes those with a CD4 count <200 or a new stage 3 or 4 disease.

Further evaluation of studies in many sub-Saharan countries showed that, in patients who presented to hospital with advanced disease, the mortality rate ranges from 25% to 50%, a third of which is in the first 48 hours of admission. A further 20% die after transfer back to primary care, and, on average, 30% are re-admitted to hospital within a short time of discharge.

The major causes of death are TB – the majority of which is disseminated – cryptococcal meningitis, pneumocystis pneumonia and severe bacterial infections. Other important contributors to mortality are toxoplasmosis, Kaposi's sarcoma, chronic diarrhoea and renal impairment.

A four-pronged approach is needed

All of this adds up to a serious problem that needs urgent attention, with the result that there is a large drive internationally to define and implement strategies to address the patient presenting with advanced disease. This challenge needs to be approached at four different levels:

1. **At community level**, especially targeting enhanced treatment literacy and educating people on the danger signs. The strategising around this falls outside the scope of this clinical guide.
2. **In primary health clinics**, through early identification of danger signs, focused screening and prophylaxis, early ART management, effective early treatment of OIs and timeous referral. This is detailed in the rest of this chapter.
3. **In hospital**, by ensuring rapid investigation and management (e.g. by creating an HIV-focused rapid assessment unit within a hospital's emergency unit.

Refer to the MSF HIV/TB Guide: Hospital Level

For a comprehensive guide for clinicians to manage patients in a hospital setting, see the **MSF HIV/TB Guide: Hospital Level**.

4. **Post-discharge re-linkage to primary care** within a public health strategy:
   - Patients with advanced disease need to be seen for ongoing care by designated, experienced healthcare workers, as part of differentiated service delivery. Ensure your clinic has a plan for these patients. Stable patients can be followed up by an experienced nurse but unstable patients should be followed up by an experienced clinical officer or doctor.
   - Patients with advanced HIV who have been discharged from hospital are at high risk of mortality. Together with your referral centre, develop a good system of two-way communication between the primary care site and the referral centre, to ensure optimal communication regarding diagnoses, management and clinic appointment dates.

The package of care for a primary care clinic

The evaluation of the patient with advanced disease involves two important new clinical concepts:

1. ART status

With the ART public health programme growing older, an increasing proportion of patients are stopping or interrupting their treatment regimens, resulting in the development of ART resistance.

Unnecessary delay in switching to an effective regimen is resulting in steady worsening of immune status, the development of serious opportunistic infections and death. To address this, these guidelines therefore recommend strengthened VL monitoring and provide specific criteria for a rapid switch to a second line regimen on the assumption that treatment failure is highly likely. **The diagnosis of treatment failure in patients with advanced disease therefore does not always follow the standard criteria of 2 consecutive VL >1 000 cp/ml, 3–6 months apart in the presence of good adherence.**

In order to make this important decision regarding a regimen switch, the ART status needs to be carefully evaluated, based on 4 key components:

- Is the patient ART-naïve or non-naïve?
- Have there been any treatment interruptions?
- Allowing for interruptions, has the total time on ART been > or < 6 months?
- What is the CD4 count?

ART-naïve refers to the patient who has never taken ART before. It is important to take a good history to clarify this, as patients have often been on ART many years previously and do not admit to this unless specifically asked. Any patient who has ever taken ART, however long ago, is considered to be **ART non-naïve**.

2. How stable they are clinically

Patients defined as clinically unstable are at higher risk of rapid deterioration and death, so warrant specific focused attention by a more experienced clinician.

The first step is the identification of the patient with danger signs and the commencement of emergency care and referral. Those without danger signs but who are clinically unstable require focused history, examination and rapid tests looking for specific illnesses identified as contributing to high morbidity and mortality in advanced disease (**especially pulmonary and disseminated TB, neurological and respiratory disease**).

By using the 2 key criteria of ART status and clinical stability to evaluate patients with advanced HIV disease, we are able to implement further diagnostic and management packages according to the patient's category. They are summarised in Figure 11.1, referencing the use of the 5 figures that follow.

The commonly held belief that all adherence problems must be sorted out before switching is not true! It is better to switch to an effective regimen, even if taking it inadequately, than to keep pushing for improved adherence in a patient who dies from an overwhelming opportunistic infection.

Refer to your national guidelines

Figures 11.1–6 will need to be used in the context of any **local guidelines** and constraints. We would encourage MSF to work with the Ministery of Health in their implementation. Due to the unnecessary delays caused by second line committees, these committees should ideally be abolished and replaced by more efficient means of decision-making.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Figures 11.1–6 can be downloaded from the additional resources folder on the **SAMU website** https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018 (under resources/HIV/advanced disease) and printed in black and white or colour in whatever size and format they are needed for easy reference in clinicians' workplaces.

Figure 11.1 Overview of approach to the patient with advanced disease

Patients enter this algorithm if identified with new stage 3 or 4 disease or with a CD4 <200. Many patients with a CD4 <200 may be otherwise well but a triage system in a busy outpatient waiting room will identify the sicker patients with stage 3 or 4 disease and enable fast-tracking into the process outlined below.

First step for all patients with advanced disease is to check for danger signs.

If no danger signs, take fuller history, examination and do rapid diagnostic tests (Figure 11.2)

Patient is placed into one of 4 categories based on **clinical stability** and **ART status** (Figure 11.3)

ART-naïve or ART <6 months	**STABLE** and ART-naïve or on ART for <6 months	**UNSTABLE** and ART-naïve or on ART for <6 months
Total ART >6 months (ongoing or interrupted)	**STABLE** and on ART for >6 months; ongoing or interrupted	**UNSTABLE** and on ART for >6 months; ongoing or interrupted

Packages of care defined by above 4 categories and detailed in figures 11.3, 11.4 and 11.5.

If danger signs present, (see Figure 11.2) provide urgent supportive management; eg, oxygen, IV fluids, and refer.

If transfer to referral site delayed provide whatever additional emergency management is possible (Figure 11.6)

Refer to hospital

Figure 11.2 Clinical approach to patients with advanced disease

Advanced HIV: CD4 <200 or new WHO stage 3 or 4

Clinical approach to patients: all patients

If there are any danger signs, refer to hospital immediately:

- Respiratory rate >30
- Heart rate >120
- Systolic BP <90
- Temperature >39°C
- Moderate/severe dehydration
- Unable to walk unaided
- Saturation <90%
- Altered mental state: confusion, strange behaviour, reduced level of consciousness
- Any other neurological problem: new onset severe headache, seizures, paralysis, difficulty talking, cranial nerve problems, rapid deterioration in vision

While organising referral:

- Point of care investigations
- Urgent management, (e.g. IV fluids, oxygen)
- Start urgent treatment: (e.g. pneumocystis treatment, antibiotics, TB treatment). If delay in referral, see Figure 11.6.

If NO danger signs: History and examination looking for ART status, OIs and co-morbidities:

TB assessment

Patients with advanced HIV are at high risk for TB.

Disseminated TB frequently does not present with respiratory symptoms.

Past history: Any previous TB?

Currently history: On treatment now? Not improving on treatment?

Symptom screening today: Loss of weight, fever, night sweats, cough?

Examination: Pleural effusion, nodes, tender or distended abdomen, ascites, hepatomegaly?

History and examination

ART history:

Which regimens and when? Previous CD4 and VLs: Is treatment failure suspected?

Co-morbidities: Diabetes, hypertension, epilepsy, kidney or liver disease.

Hospitalised recently: Within past 3 months? Include reason.

Neurological conditions: All are danger signs – refer.

Respiratory conditions: If danger signs – refer.

Kaposi's sarcoma: Palate, skin.

CMV retinopathy in high risk areas.

Chronic diarrhoea.

Assess for **dehydration**.

Investigations for ALL patients

CD4:

- <200: do serum CrAg.
- <100: do TB LAM.
- 100–200: do TB LAM if TB symptoms.
- Collect sputum if productive cough.

Haemoglobin.

Urine dipstick: If proteinuria, do serum creatinine.

Routine viral load if not done within past 6 months.

Targeted viral load if not done within past 3 months, or if stage 4 condition, or last VL >1 000.

Malaria rapid test if endemic.

Hepatitis B if available and not yet done.

Management is now based on two key criteria:

1. Is the patient clinically STABLE or UNSTABLE?
2. Is the patient ART-naïve (or on ART for <6 months) or on ART >6 months?

Communication with hospital:

- Patients, apart from those with danger signs, may need referral – if appropriate investigation or management is not available at primary care, or if rapid decision-making for regimen switch for treatment failure is necessary at referral level.
- Establish a 'hotline' with hospital clinicians for clinical advice, case discussion, referral and back-referral – particularly when transfer is difficult.

Figure 11.3 Management plans based on clinical stability and ART status

Definition of an UNSTABLE patient:

- One or more danger signs
- Clinical suspicion of any new stage 4 disease or any TB (including PTB)
- IRIS; commonest is TB or cryptococcosis
- Serum CrAg positive
- Adverse drug reaction, requiring ongoing management
- Discharged from hospital within past 3 months
- Pregnant
- Mental health or substance abuse problems
- Co-morbid conditions requiring frequent follow-up (for example: diabetes, unstable hypertension, epilepsy, renal or liver impairment)

Definition of a STABLE patient: CD4 <200 but otherwise well

	STABLE	UNSTABLE

ART-naïve or ART <6 months	**STABLE and ART-naïve or ART <6 months**
	Package of care:
	• ART management:
	  • If no prior ART start immediately (see point 7 on page 225).
	  • If defaulted, start first line ART.
	  • Check VL after 6 months of continuous ART.
	Follow-up:
	• After 2 weeks, then monthly.
	• Care to be provided by experienced nurse.
		UNSTABLE and ART-naïve or ART <6 months
		Package of care:
		• Care package for unstable patient. See Figure 11.5.
		• ART management:
		  • If no prior ART start immediately (see point 7 on page 225).
		  • If defaulted, start first line ART.
		  • Check VL after 6 months' continuous ART.
		Follow-up:
		• After 1–2 weeks then 2–4 weekly.
		• Care to be provided by experienced clinical officer/doctor.

ART >6 months (ongoing or interrupted)	**STABLE and total ART >6 months** Package of care: • ART management: see Figure 11.4. Follow-up: • After 2 weeks, then monthly. • Care to be provided by experienced nurse. • VL and ART management according to Figure 11.4.	**UNSTABLE and total ART >6 months** Package of care: • Care package for unstable patient. See Figure 11.5. • ART management: see Figure 11.4. Follow-up: • After 1–2 weeks, then 2–4 weekly. • Care by experienced clinical officer/doctor. • VL and ART management according to Figure 11.4.

All patients need the following prophylaxis and patient and community support packages:

Prophylaxis package

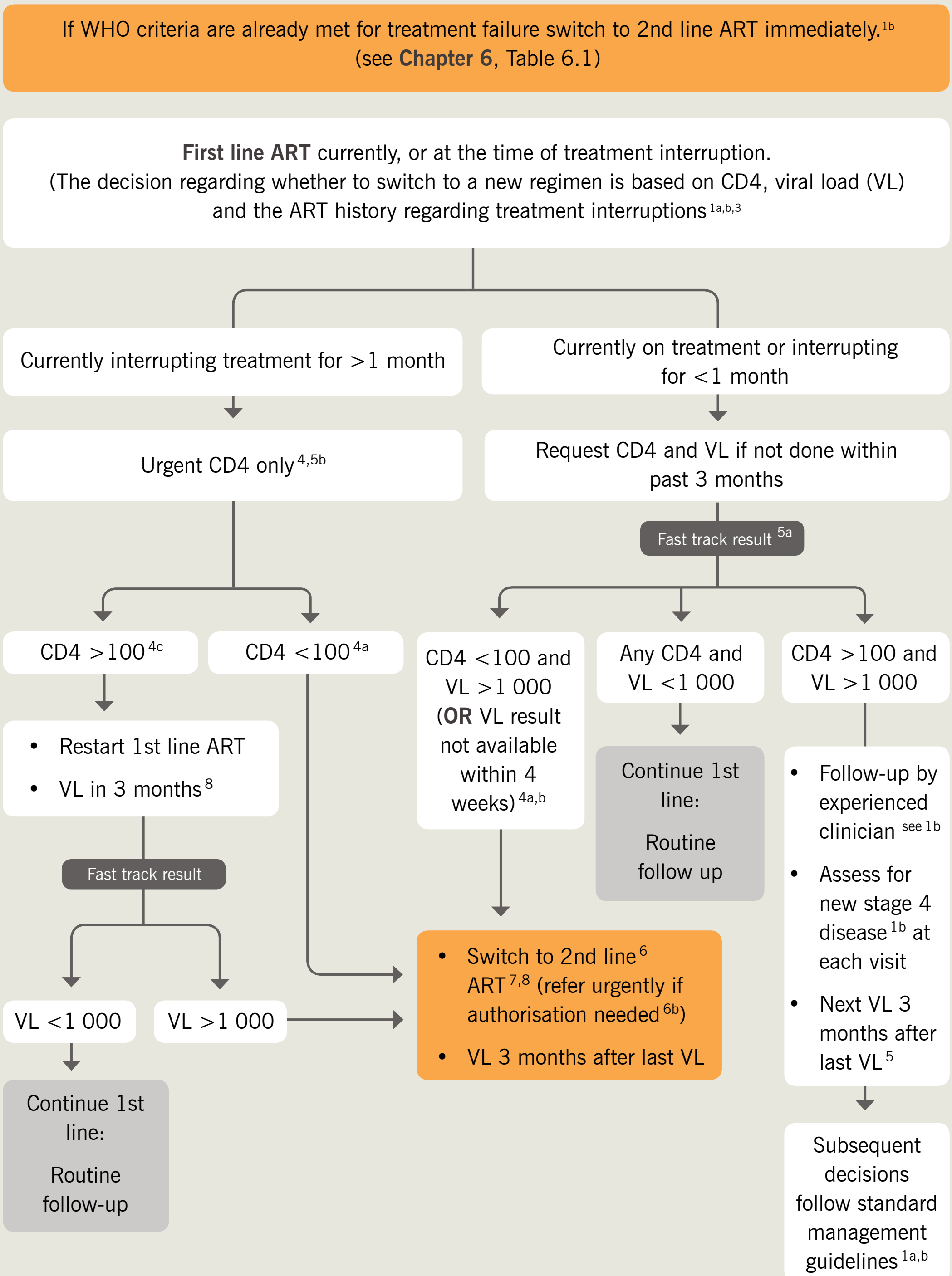
- Cotrimoxazole.
- Isoniazid/B6, if not on TB treatment; if on TB treatment, start after completion. Duration, 36 months or longer (WHO).
- Fluconazole, if serum CrAg positive, CrAg unavailable; and secondary prophylaxis for patients with cryptococcal meningitis.

Patient and community support package

- Adherence support.
- Community worker tracing if appointments defaulted.
- Teach danger signs to patients and family, and when/how to access health care, if concerns.

Figure 11.4 Advanced HIV ART management diagram

Management of patients with advanced HIV[1], total ART >6 months[2], NO new stage 4 illness



Notes for Figure 11.4

1. **Patients presenting with advanced disease are at high risk of mortality and morbidity.**
   a. A decision may need to be made to switch to second line ART outside standard guidelines. This will be guided by:
      - Whether the patient is currently on ART or has interrupted (see also note 3);
      - CD4 <100 indicates high risk of developing a fatal OI; requires an urgent decision;
      - The timeous availability of VL for confirming treatment failure.

   b. If there is already a clear basis for diagnosing treatment failure (**Chapter 6**, sections 3–5) according to WHO criteria (virological, clinical or immunological) the ART regimen must be switched immediately. Note that a new stage 4 disease qualifies for clinical failure.
2. The total time on ART. The longer one is on an NNRTI-based regimen, the greater the opportunity for errors leading to the development of resistance. Conversely, it is very unlikely that resistance will develop in less than 6 months of total ART exposure.
3. ART-naïve or prior ART. As it is being increasingly noted that patients presenting with advanced disease have been on ART previously, it is important to take a careful ART history, going back many years, to establish the criteria noted in point 2 above.
4. The urgency with which the decision to switch needs to be taken is affected by the CD4.
   a. CD4 is <100: the risk of developing a fatal OI in the next few months is high. Delaying for 3 months for adherence sessions and follow-up viral load may prove fatal. A rapid empirical switch may be indicated.
   b. If CD4 <100 and there is a delay of >4 weeks in getting VL result (including not having VL at all), a fatal OI may develop while waiting. Therefore switch empirically.
   c. CD4 >100: More time is available for a re-trial of first line medication to determine if there is resistance. If minimal change at follow-up VL at 3 months, switch to a new regimen. If significant change, defer switch for one month and repeat VL. (If the laboratory gives a log value, consider a log drop >2 to be significant.)
5. Sequential viral load results are important in the decision regarding a switch to a new regimen.
   a. Viral load tests should therefore be prioritised and the results fast-tracked.
   b. If the patient has currently interrupted treatment for >1 month the viral load will already be elevated, so it is not useful to do it.
6. A rapid switch outside standard guidelines may save lives:
   a. In the hands of more experienced clinicians, this is merely a guide for management decisions in patients presenting with advanced disease so clinical judgment must be applied.
   b. If there is insufficient experience or authority to make this decision, more experienced help must be sought the same day.
7. When to start ART or switch to 2nd line:
   - If TB and cryptococcal disease are excluded, offer same day initiation.
   - If serum CrAg positive + patient asymptomatic + LP not possible **or** LP has been done and CSF CrAg is negative, start ART the same day.
   - If non-CNS TB, once TB treatment has been initiated, start ART as soon as possible within 1–2 weeks.
   - If neurological TB or cryptococcal meningitis, delay ART till 4 weeks after OI treatment started.
8. PS (patient support) intervention recommended: both for suspected treatment failure and if starting a new regimen.

Figure 11.5 Care package for the unstable patient

TB is common major cause of death. Treat empirically if there is high suspicion.

TB LAM:

- TB LAM positive: Start TB treatment.
- TB LAM negative: **TB is not excluded!** Start empiric treatment if high suspicion of TB.

Xpert MTB/RIF:

Sputum or non-sputum samples: Pleural fluid, centrifuged CSF, centrifuged urine, pus. Bring patient back for result within 1 week:

- GeneXpert positive: start TB treatment.
- GeneXpert negative: **TB is not excluded!** Start empiric treatment if high suspicion of TB – do not wait for result if long turnaround time.

IPT: If no clinical evidence of TB, start isoniazid preventative therapy.

CrAg positive (finger-prick or serum):

- Symptoms of meningitis: Fluconazole 1 200 mg immediately and refer for lumbar puncture and ongoing treatment. If amphotericin B is available, start it while arranging transfer. See also Figure 11.6.
- Asymptomatic: Refer for lumbar puncture. If not possible, start fluconazole 800 mg daily for 2 weeks, 400 mg daily x 2 months, then 200 mg daily for at least one year or until CD4 >200.

Co-morbidities:

- Co-morbidities needing active follow-up mean the patient is categorised as ‘unstable’.
- Common co-morbidities:
  - Diabetes, hypertension.
  - Cardiac failure, chronic kidney disease: Often caused by the above, look for other reversible causes.
  - Chronic liver disease: Check for hepatitis B and C, and alcohol excess.

Chronic diarrhoea:

This is often overlooked until patients need admission to hospital with severe dehydration, kidney failure and electrolyte wasting. Parasite opportunistic infections are a common cause, particularly *Isospora belli*, and *cryptosporidium*. See **Chapter 15** for details.

CMV retinopathy:

In higher prevalence settings, ask about recent visual deterioration, and, if present, check visual acuity and refer for more comprehensive assessment.

Follow-up:

- Arrange follow-up appointment to ensure continuity of care.
- Ensure ongoing care is done by clinician with appropriate level of experience.
- Educate patient regarding danger signs and other reasons to return sooner.

Avoid overuse of antibiotics – use only if bacterial infection is likely:
(See *Chapter 23*)

- If antibiotics are used, document the reason.
- If a patient has had a course of antibiotics and has not improved, do not give another course without a clear reason. Look for other causes of symptoms, especially TB.

Figure 11.6 Management if transfer to hospital is delayed

Definition of 'seriously ill':
One or more danger signs

DANGER SIGNS

- Respiratory rate >30/min
- Temperature >39°C
- Heart rate >120/min
- Systolic BP <90mm Hg
- Saturation <90%
- Moderate/severe dehydration
- Unable to walk unaided
- Altered mental state: confusion, strange behaviour, reduced level of consciousness
- Any other neurological problem: new onset severe headache, seizures, paralysis, difficulty talking, cranial nerve problems, rapid deterioration in vision

Mortality is high:
Do not delay investigations and management

Common causes of mortality: see box
Often there is more than one cause

- Take a good history
- Examine the patient
- Focus on respiratory & neurological systems and ART history

Disseminated TB is the most common cause of mortality

1. ART failure
2. Neurological disease (Big 3):
   - TB
   - Cryptococcal meningitis
   - Toxoplasmosis
3. Respiratory disease (Big 3):
   - Pneumocystis pneumonia
   - Pulmonary TB
   - Bacterial pneumonia
4. Severe diarrhoea
5. Other bacterial infections
   - Bacterial meningitis
   - Blood stream infections
   - Urinary tract infection
6. Other non-infectious causes
   - Hypoglycaemia
   - Renal failure
   - Abnormal sodium, potassium
   - Liver disease
   - Drug side effects

Investigations: DO IMMEDIATELY
Basic package of point-of-care tests

- HIV testing
- CD4
- Serum CrAg
- TB LAM
- Rapid malaria test
- Glucose
- Haemoglobin
- Urine dipstick

Additional investigations: Do what is available

Basic TB investigations:

- GeneXpert (sputum)

For TB LAM or GeneXpert: treat if positive, but a negative result does not exclude TB.

Other TB investigations::

- Sputum microscopy
- GeneXpert on non-sputum. Samples: urine, CSF, pus
- CXR
- Abdominal ultrasound

Lumbar puncture:

- Necessary if there is any abnormal neurology
- Request: CrAg, cell count and differential, protein, glucose, gram stain, geneXpert
- If LP not possible or inevitable delay: do serum CrAg and give empiric treatment as indicated (see pages 228, 292).

Blood tests:

- Creatinine, sodium, potassium
- Full blood count
- VDRL
- Jaundice or hepatomegaly: bilirubin, ALT
- Bacterial infection possible: blood/ urine cultures

Continues on next page

Management: Initiate without delay

Start empiric treatment for diseases where clinical suspicion is high, but where there is no diagnostic test available or where diagnostic tests cannot exclude the disease.

Emergency management

Hypoglycaemia: 50 mls of 50% dextrose

Dehydration, renal impairment (see Chapter 17):

- IV fluids, electrolytes
- Chronic watery diarrhoea: empiric treatment for *Isospora belli* (cotrimoxazole)
- Beware nephrotoxic drugs

Liver failure: Beware hepatotoxic drugs (see **Chapter 16**)

Severe anaemia (Hb <5g/dL): Transfuse, oxygen (see Figure 18.1 in **Chapter 18**)

Bloodstream infection: If fever and other danger signs or other evidence suggesting bacterial infection, give empiric antibiotics

Neurological disease

Treat for cryptococcal meningitis if:

- CSF CrAg positive
- Abnormal neurology, serum CrAg positive and LP not possible (or CSF CrAg unavailable)

Give fluconazole prevention regimen if:

Serum CrAg positive and CSF CrAg negative

Treat for CNS TB if:

Neurology signs AND:

- Proven TB (LAM/GXP) or strongly suspected clinically
- CSF CrAg negative

Treat for toxoplasmosis if:
CD4 <200; new focal neurology; or other abnormal neurology and no other diagnosis

Respiratory disease

Respiratory danger signs: RR >30 or saturation <90%

- Give oxygen
- Empiric treatment for pneumocystis and bacterial pneumonia
- Empiric treatment for TB if indicated

No danger signs:

- CXR – treat accordingly
- CXR not available, consider empiric treatment: pneumocystis, bacterial pneumonia, TB

Clinical indications for immediate empiric TB treatment:

Do available investigations while starting treatment.

- CNS TB likely
- Miliary TB or other CXR evidence of TB
- Clinical presentation strongly suggests TB; investigations not available or unable to exclude TB
- Clinical condition life-threatening, patient deteriorating, or not improving after 3 days of hospitalisation

CHAPTER 12

Drug-sensitive and drug-resistant tuberculosis in PLHIV

Please note that TB is covered in a more interactive learning environment in the 2015 edition of the **SAMU HIV e-learning** course. See *How to use this book* for details.

Tuberculosis (TB)

Tuberculosis is the most common cause of morbidity and mortality in people living with HIV. It is caused by the organism *mycobacterium tuberculosis* (MTB), which is transmitted through the air via infectious respiratory droplets that originate from a person with active pulmonary disease, most commonly as a result of coughing.

It is important to distinguish between infection with MTB and active disease due to MTB. Upon inhalation of MTB, a person with a healthy immune system will control it such that, in most cases, the MTB infection remains latent with only a 10% lifetime risk that it will ever develop into active TB disease. However, those with weakened immune systems, such as young children and people living with HIV (PLHIV), are less able to control the MTB, and in any given year, have an approximate 10% risk that the *mycobacterium* will begin to replicate uncontrollably, leading to active TB disease and the development of signs and symptoms.

- When TB disease involves the lungs (pulmonary TB or PTB) a person will have a cough and frequently other constitutional symptoms, e.g. loss of appetite, loss of weight, fever and night sweats.
- TB disease can also spread and cause active disease outside the lungs in almost any organ in the body (extra-pulmonary TB or EPTB). Patients frequently present with the above constitutional symptoms as well as focal signs, depending on exactly which organ is involved (e.g. headache if TB meningitis, effusion if joint involvement, etc.)

Types of active TB disease

It is helpful to think of active TB disease according to the following:

- smear-positive PTB, the most infectious form;
- smear-negative PTB, which is more difficult to diagnose, often leading to a dangerous delay in initiation of treatment; and
- EPTB, which is also difficult to diagnose, and requires thorough clinical assessment.

Each of the above 3 types of TB disease can be caused by either drug-sensitive or drug-resistant (DR TB) strains. DR TB requires a longer duration of treatment and will be described in a separate section of this chapter.

Clinical presentation of pulmonary TB in PLHIV

TB and HIV together = double trouble.

The clinical presentation and diagnostic approach are different when someone with active TB is co-infected with HIV. This is because active TB disease presents differently in the presence of a weakened immune system.

The presentation of active pulmonary TB disease generally varies according to the level of the persons immune deficiency. HIV-positive people with high CD4 counts usually present similarly to those who are HIV-negative, and HIV-positive people with lower CD4 counts tend to present with different clusters of symptoms. There are two key reasons for this:

- The signs and symptoms of TB are produced largely by the body's immune response. For example, a strong immune response results in more marked fever and more cavitation in the lungs. Cavitation refers to the process whereby cavities develop, as the initial solid focus of infection in the lung tissue is hollowed out as the infection progresses. These cavities are filled with TB bacilli and make the detection of TB in the sputum easier.
- A lower immunity not only results in less local lung cavitation but also usually in a lesser ability to contain the infection to a focal area, often resulting in more widespread disease in the body.

These different expressions of TB in the body, in turn, affect the ability to find a diagnostic means of confirming the diagnosis. This is discussed in more detail later in the chapter.

Because there is less cavitation, there are fewer organisms in the sputum, resulting in greater difficulty in diagnosing pulmonary TB using smear microscopy.

Symptoms of PTB in those with higher CD4 counts (similar to HIV-negative patients):

- chronic cough (≥2 weeks);
- loss of appetite and recent unintentional weight loss;
- night sweats;
- any fever;
- general weakness and tiredness;
- chest pain – the position of which (left or right) could indicate the presence of a pneumonia or pleural effusion; and
- sometimes haemoptysis (blood in the sputum when coughing).

With more advanced immunodeficiency (i.e. lower CD4 counts), an HIV-positive person with PTB is likely to present with different symptoms:

- general malaise and weakness (deterioration has been severe if the patient is having difficulty with activities of daily living i.e. washing themselves, making food);
- looks really sick;
- significant weight loss (>10% of previous body weight);
- less coughing, which tends to be dry (i.e. no cough);
- shortness of breath; and
- anaemia.

Clinical presentation of extra-pulmonary TB (EPTB)

Since PLHIV are at risk of rapid clinical deterioration due to active TB, **clinicians need to avoid excessive delays in diagnosis and treatment initiation!**

The clinical presentation of EPTB will depend on the organ system in which the active TB disease is present. Don't forget that in HIV-positive people there is a higher risk of developing EPTB forms compared to HIV-negative people. Children, with their more fragile immune state, are also particularly at risk of EPTB.

The main sites and signs/symptoms of EPTB:

- TB meningitis: Headache/confusion and fever, vomiting, stiff neck, sometimes loss of consciousness.
- Lymph node (LN) TB: One or more enlarged LN (e.g. >2 cm), often but not always painless nodes in the neck, axillae, or inguinal areas.
- TB pericarditis: Chest pain and symptoms related to heart failure (shortness of breath, peripheral oedema, and sometimes abdominal swelling).
- TB pleurisy: Chest pain (usually unilateral) and shortness of breath.
- Abdominal TB: Non-specific symptoms (e.g. alteration in bowel habit) that can include pain and distension due to ascitic fluid.
- Genito-urinary TB: Dysuria, nocturia, abdominal pain, haematuria.
- TB spine (known as Pott's disease): Localised pain, followed by deformation.
- TB arthritis: Mainly mono-articular, insidious onset, mild pain with progressive destruction of the joint.
- Miliary TB (see box below).

Miliary TB, a severe form of TB, also known as disseminated TB, results from the spread of TB through the bloodstream to a variety of organs, where it settles diffusely, like small seeds, throughout the particular organ. It is clinically characterised by systemic and often non-specific symptoms, such as high fever, headache, and progressive general deterioration with or without cough and dyspnoea. Diagnosis (see also Table 12.1) is usually made by CXR, which shows characteristic small disseminated nodular opacities in both lungs.

Since pulmonary TB can occur simultaneously with EPTB, sputum specimens should be sent for TB investigations if possible (if dry cough, sputum induction can be considered) together with extra-pulmonary samples. Please refer to Table 12.1 for assessment and diagnostic management of a patient with presumed EPTB.

Diagnostic investigations

Laboratory investigations for TB

(For more details on these tests, refer to MSF TB Guidelines, 2014.)

- **Smear microscopy** is a useful investigation for identification of patients with PTB, but only if the concentration of *mycobacteria* in the sputum sample is high enough (>5 000 bacilli/ml of sputum). It's benefits are that its cheap and easy to perform, even in very peripheral health facilities. It's less sensitive, though, than other tests (i.e. Xpert and culture) and cannot distinguish between MTB and other mycobacteria, other than MTB (also called NTM or MOTTs). Unfortunately HIV-positive patients, especially those with low CD4 counts, have low bacterial concentrations in their sputum, most of the time resulting in negative smear microscopy results
- **Xpert MTB/RIF,** also called GeneXpert, is a molecular (genotypic) test that can identify the DNA of MTB in sputum and in some extra-pulmonary samples. It is also able to detect the presence of resistance to rifampicin. It has a high sensitivity and specificity in sputum when compared to culture, as well as in smear negative samples.

  Xpert is the recommended first test for diagnosis of TB in PLHIV.

  It has a number of advantages compared to smear microscopy:

  - The test itself is able to give results in about 2 hours but access to the result may be longer, depending on access to the GeneXpert machine and the administration of results.
  - This 2-hour process also includes the detection of rifampicin resistance, a much faster process than culture and drug sensitivity testing (DST), which can take more than 8 weeks.
  - GeneXpert is fully automated and does not require a high-level laboratory.

Xpert in EPTB samples is currently recommended for: CSF, lymph node aspirates and some other tissues (e.g. biopsies). Other non-respiratory samples, such as urine, stool, blood, can also be tested with Xpert, although evidence on sensitivity and specificity is still limited.

- **Xpert MTB/RIF Ultra** is a new cartridge, which has improved sensitivity for detection of TB and rifampicin resistance. This will be of particular use in PLHIV, including those with smear negative PTB and EPTB. This is probably going to be the standard test in the future, particularly for TB diagnosis in HIV patients and children.
- **TB LAM** is a lateral flow-assay test, which can detect antigens of MTB in **urine.** Its added value is that it is a rapid point-of-care test, does not require a sputum specimen, is cheap, fast and easy to perform and can be done by lay workers.
    - Its the only test which has shown to reduce mortality in PLHIV admitted in hospital.
    - See algorithms later in this section for use of TB LAM in diagnosis of TB.

TB LAM is currently recommended only for PLHIV with advanced disease; i.e. patients with severe immunosuppression (CD4 <100) or any seriously ill patient, independent of CD4 count.

- **Culture** is considered the gold standard for diagnosis of TB. It is more sensitive than any other test and allows for identification of MTB (and MOTT), early identification of failures and monitoring of response to drug-resistant TB treatment, among others. Challenges include the need of a higher-level and quality-assured laboratory and longer turn-around time for results (up to 8 weeks, depending on the method used).
- **Drug Susceptibility Testing (DST)** detects resistance to anti-TB drugs. DST can be phenotypic (done on positive cultures) or genotypic (molecular tests, which include Line Probe Assays and also Xpert). More details are provided later in the DR TB section and in the 2014 MSF TB Guidelines.

Radiology

- **Chest radiology** can be useful as an additional diagnostic test, but it's not specific for TB. Typical findings include cavitation and upper lobe infiltrates, but in PLHIV the radiological findings might be different, and include:
    - miliary or diffuse micronodular opacities (see disseminated TB in 'Clinical presentation of extra-pulmonary TB' above);
    - large heart (especially if symmetrical and rounded, suggesting pericardial effusion);
    - pleural effusion; and
    - enlarged lymph nodes inside the chest.

- Radiology of other organs can be useful for EPTB diagnoses, e.g. bony changes in TB of the spine or joints (see 'Clinical presentation of extra-pulmonary TB', above).

Evaluating for active TB disease in PLHIV

A TB diagnostic algorithm specific to your setting should already exist (if not, make one with the help of your coordination and TB/HIV adviser).

Such algorithms help to standardise the diagnosis of TB using clinical examination and locally available investigations and are especially helpful in diagnosing smear-negative PTB without unnecessary delay. We include here two examples of TB diagnostic algorithms for PLHIV. See algorithms 12.1 (for PLHIV with no danger signs) and 12.2 (for PLHIV with danger signs) and a table for the evaluation of patients with suspected EPTB.

For diagnostic algorithms in children, see **Chapter 10**.

With all patients, first look for danger signs. If any are present refer immediately to the nearest inpatient facility.

Refer to hospital

Figure 12.1 Clinical danger signs

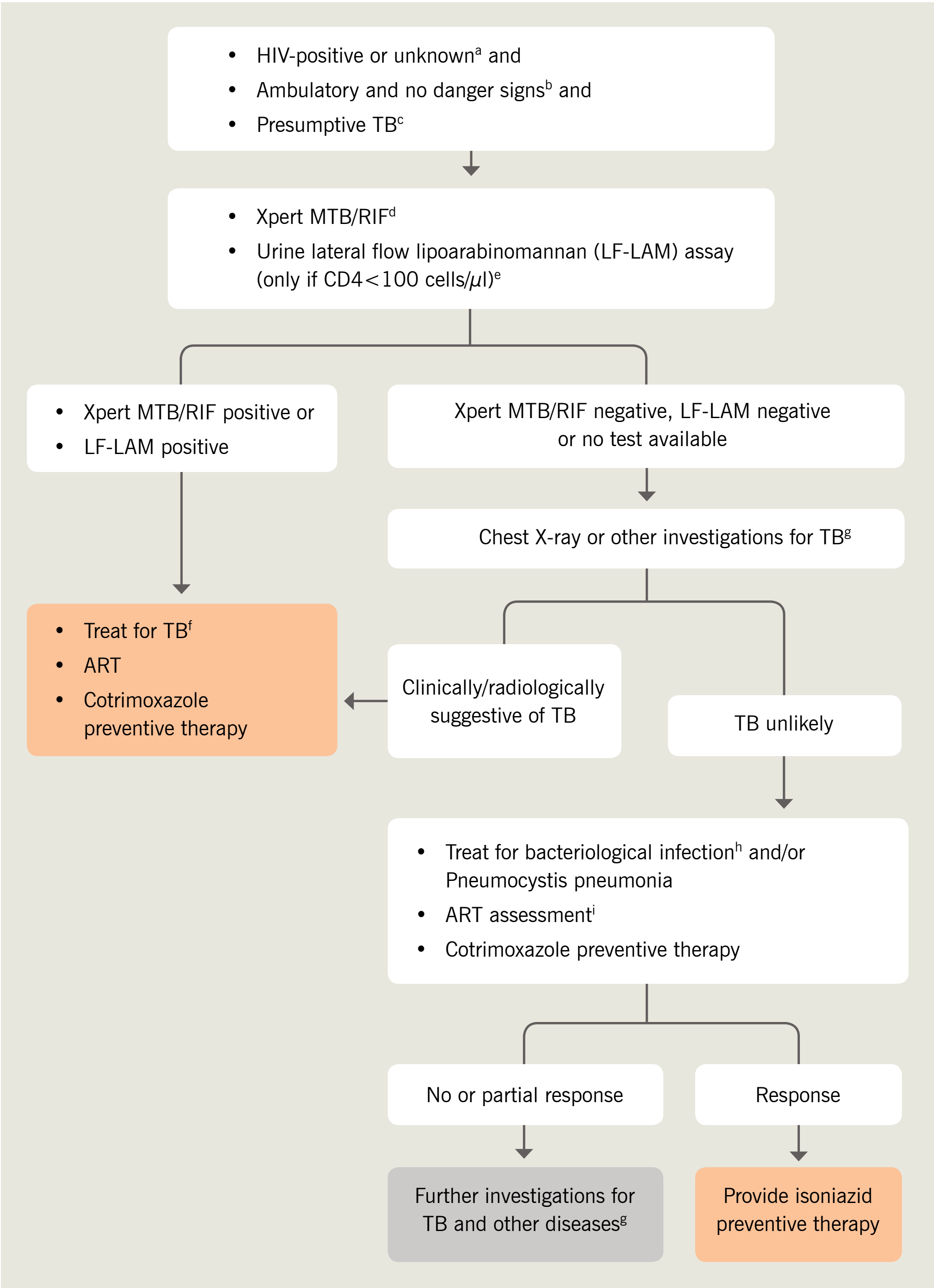
Respiratory rate >30 Temperature >39 Heart rate >120/min Systolic BP <90 mm Jaundice	Moderate to severe dehydration – reduced skin elasticity, collapsed veins, sunken eyes. Unable to walk unaided. Altered states of consciousness, confusion, strange behaviour, reduced level of consciousness.	Any neurological problem – headache, seizures, paralysis, difficulty talking, cranial nerve palsies, rapid vision deterioration.

Some general tips when evaluating a patient:

1. Always perform a good physical examination in an adult or child whom you suspect has active TB, looking especially for signs of extra-pulmonary TB.
2. Send two sputum samples for testing with GeneXpert (preferred) and/or smear microscopy. Make sure the patient provides sputum from the lungs, and not saliva from the mouth. Although early morning sputum has traditionally been requested, there is now sufficient evidence that a same-day diagnostic approach (i.e. spot–spot) is equivalent in terms of diagnostic accuracy. Thus, efforts should be made, whenever possible, to diagnose TB on the same day of presentation.

3. TB-LAM is recommended as a diagnostic tool for TB in patients with advanced HIV. This includes patients with a CD4 <100 and those who are seriously ill, regardless of the CD4 count. This applies to both adults and children. The test can be performed immediately, even at the bedside, resulting in rapid initiation of treatment if positive. If concomitant bacterial infection is suspected, prescribe an antibiotic while waiting for the sputum test results (amoxicillin in a typical adult dosage of 1 g 3 times daily, or, if allergic to penicillin, erythromycin 500 mg 4 times daily).
4. If GeneXpert or TB LAM detects MTB or if acid-fast bacilli (AFB) are seen on smear microscopy, start TB treatment immediately.
5. It is important to note that if GeneXpert or TB LAM does not detect MTB and if AFBs are not seen under a microscope, **the person may still have active TB. No test can exclude TB.** If TB symptoms persist, and there remains a suspicion of TB, start empiric treatment. If the patient has danger signs start TB treatment immediately!
6. If GeneXpert is not available in your setting and DR TB is suspected, TB culture and DST must be performed. Note, however, that in some settings a culture/DST result can take two months or longer.
7. All TB patients must be started on cotrimoxazole prophylaxis plus pyridoxine (vitamin B6) to reduce the risk of peripheral neuropathy caused by INH.
8. Effective ART (initiated, re-initiated or switched to second line) is essential in order to prevent other opportunistic infections (OIs). Follow the guidelines for when to do this in relation to commencement of the TB treatment (see IRIS section in **Chapter 5**).

Algorithm 12.1 Managing people living with HIV and suspected of having TB (without danger signs)



Notes for Algorithm 12.1

a For all people with unknown HIV status, HIV testing should be performed according to national guidelines.

b Danger signs include any one of the following: respiratory rate >30 per minute, temperature >39°C, heart rate >120 beats per minute and unable to walk unaided.

c Presumptive TB is defined by the presence of any one of the following symptoms.

- For adults and adolescents living with HIV: current cough, fever, weight loss or night sweats.
- For children living with HIV: poor weight gain, fever, current cough or history of contact with a TB case.

d For people suspected of having extra-pulmonary TB, extra-pulmonary specimens should be obtained for Xpert MTB/RIF (cerebrospinal fluid, lymph nodes and other tissues: Xpert MTB/RIF has low sensitivity for pleural fluid and data are limited for stool, urine or blood). If Xpert MTB/RIF is not available, conduct AFB microscopy. AFB-positive is defined as at least one positive smear and AFB-negative as two or more negative smears. Refer the specimen for TB culture where feasible.

e The LF-LAM assay may be used to assist in diagnosing active TB in peripheral settings among outpatients with CD4 <100. LF-LAM should be considered as the initial diagnostic test for patients unable to produce sputum.

f If Xpert MTB/RIF shows rifampicin resistance, treatment for multidrug-resistant TB should be initiated. If the person is considered at low risk for rifampicin resistance, a second Xpert MTB/RIF test should be performed on a fresh specimen. Collect and refer a sample for culture and additional drug sensitivity testing.

g Further investigations for TB include chest X-ray, clinical assessment, a repeat Xpert MTB/RIF using a fresh specimen and referral of sample for culture where feasible. If EPTB is suspected, extra-pulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed.

h Antibiotics with broad-spectrum antibacterial activity (except fluoroquinolones) should be used.

i ART should be recommended for all adults, regardless of CD4 cell count or clinical stage. In ART-naïve patients, ART should be started as soon as possible following start of TB treatment. Patients already on ART should be assessed for ART failure through VL.

Table 12.1 Evaluating and diagnosing EPTB

Site	Symptoms	Investigations	Other
Meninges (covering the brain and spinal cord)	Headache/confusion and fever, leading to vomiting, stiff neck and loss of consciousness.	Lumbar puncture and investigation of CSF (protein, glucose, cell count, AFB, TB culture, GeneXpert – plus India ink, CrAg/CLAT, VDRL).	TB meningitis is common in children, in whom symptoms tend to be non-specific (e.g. drowsiness, irritability).
Lymph nodes (see Appendix 12.1)	One or more enlarged (e.g. >2 cm), painless nodes in the neck, axillae, or inguinal areas.	Needle aspiration if node is fluctuant (easy) Fine needle aspirate cytology if not fluctuant (not so easy) Smear, Xpert, culture See Appendix 4 in 2014 MSF TB Guidelines.	TB-related lymphadenopathy can also occur inside the chest or abdominal cavities.
Pericardium (i.e. TB pericarditis)	Chest pain and symptoms related to heart failure (shortness of breath, peripheral oedema, and sometimes abdominal swelling).	Chest x-ray Echocardiogram.	
Pleural effusion (often one-sided)	Chest pain (often unilateral) and shortness of breath.	Chest x-ray. Pleural tap for: straw-coloured fluid suggests TB vs pus, which suggests empyema GeneXpert, smear, culture.	AFB often not found in pleural fluid in TB-related pleural effusion. In a high-TB burden setting, a clinical diagnosis of TB can be made upon finding of a one-sided pleural effusion in a PLHIV and having TB symptoms.
Abdominal	Non-specific symptoms (e.g. alteration in bowel habit) that can include pain and distension due to ascitic fluid.	Abdominal ultrasound Ascitic tap for GeneXpert, smear, culture.	A doughy abdomen on palpation, sometimes tender, is sometimes described as being suggestive of abdominal TB.
Spine (also known as Pott's disease)	Localised pain, often with deformity.	X-Ray can show erosive disease and the deformity.	Destruction of the spine may lead to neurological symptoms and signs.

Site	Symptoms	Investigations	Other
Joint	Swelling, but not so much pain, usually involving a hip, knee or elbow.	X-Ray can show erosive disease.	
Note that active TB disease can involve almost any organ in the body: kidneys, adrenal glands, thyroid, breast, genitals, skin, etc.			
Miliary TB (also known as disseminated TB)	Constitutional symptoms (fever, weight loss), which can lead to serious morbidity if it goes undiagnosed.	Urine TB LAM of urine if CD4 <100 Miliary pattern on chest x-ray.	Also known as disseminated TB, caused by haematological spread of bacilli throughout the body.

Clinical staging of TB patients co-infected with HIV (see also Appendix 1.1 at the end of **Chapter 1**)

Stage 3: PTB in adults or children and lymph node TB

Stage 4: EPTB in adults or children, apart from lymph node TB

- Note that patients with a pleural effusion are classified stage 4, as a pleural effusion, although inside the chest cavity, is outside of the lungs. Using the same logic, those people with TB pericarditis or intrathoracic TB lymphadenopathy noted on chest radiology are also stage 4.
- Children and adults with a miliary pattern on chest radiology are considered stage 4, as this is disseminated disease, a type of EPTB.

TB treatment and management

TB treatment regimens

Drug-sensitive TB can be cured relatively inexpensively, using a combination of anti-TB drugs for 6 months, called first line drugs.

Treatment is divided in two phases:

1. An intensive phase, which consists of 4 anti-TB drugs (RHZE): Rifampicin (R) Isoniazid (H), and Pyrazinamide (Z), Ethambutol (E), taken for 2 months.
2. A continuation phase, which consists of two anti-TB drugs: R and H (RH), taken for 4 months.

Dosages for all anti-TB drugs mentioned above are based on weight.

Table 12.2 Anti-TB drug dosages

Drug	*Average daily dose	Weight class			
		<33 kg	33–50 kg	51–70 kg	>70 kg
Isoniazid (H) (100, 300 mg)	4–6 mg/kg daily	By weight	300 mg	300 mg	300 mg
Rifampicin (R) (150, 300 mg)	10–20 mg/kg daily	By weight	450–600 mg	600 mg	600 mg
Ethambutol (E) (400 mg)	25 mg/kg daily	By weight	800–1200 mg	1200–1600 mg	1600–2000 mg
Pyrazinamide (Z) (500 mg)	30–40 mg/kg daily	By weight	1000–1750 mg	1750–2000 mg	2000–2500 mg

Fixed-dose combinations (FDCs) are commonly available in 4-in-1, 3-in-1, and 2-in-1 combinations; these reduce pill burden and can improve adherence. If not available in your national TB guidelines, tables showing the daily dose of anti-TB drugs using FDCs can be found in Appendix 8 of the 2014 MSF TB Guidelines.

New paediatric first line formulations are now available. They are dissolvable, have a good taste, and, most importantly, contain the correct dosage of TB drugs per band weight. See **Chapter 10**.

Notes on treatment of drug-sensitive TB

Different treatment regimens

Based on treatment history, TB cases are defined as:

- **New cases:** These are patients who have never been treated for TB before (or have taken anti-TB drugs for <1 month).
- **Retreatment cases:** These are patients who have received one month or more of anti-TB drugs in the past, and include:
  - patients who completed previous TB treatment and present with a new episode (relapses);
  - patients who failed previous treatments (failures); and
  - patients who did not complete previous treatments (lost to follow-up).

  Please note:

  - Retreatment categories, and especially failures of previous TB treatment, are at higher risk of harbouring DR TB strains. (Before the roll-out of Xpert, these categories were often prescribed the eight-month category 2 treatment, including streptomycin. **Category 2 is no longer recommended**, as evidence has shown that it not only offers no benefits but is actually harmful.

- If drug-sensitive TB treatment is given to someone with DR TB, treatment will not be effective and it is likely to make the drug resistance worse (resistance amplification).
- There are therefore now two treatment options: either 6 months with first line drugs for drug-sensitive TB, or longer with second line drugs for drug-resistant TB.

All efforts should, therefore, be focusing on excluding drug-resistant TB through systematic access to DST (i.e. Xpert) for these patients and providing the appropriate treatment:

Rifampicin drug interactions

- Rifampicin interacts with a number of other medications, something that is covered in more detail in **Chapter 7**. Be particularly careful if the patient is taking:
    - warfarin
    - contraceptives
    - fluconazole
    - nevirapine and the PIs.

INH and peripheral neuropathy

All patients receiving isoniazid (abbreviated as INH or just H) should receive pyridoxine (vitamin B6). INH can cause decreased levels of pyridoxine which can cause a peripheral neuropathy:

- adults and children >5 years: 10 and 25 mg daily are both acceptable doses.
- children <5 years: 5–10 mg OD.

Monitoring the response to TB therapy

All those on TB treatment need to be monitored for a response to therapy. There are key elements to be looked for on history, examination and laboratory investigations:

- **History:** Ask specifically for improvement of the following:
    - coughing
    - night sweats
    - appetite
    - general ability to perform activities of daily living.
- **Examination:** There should be:
    - weight gain (another important reason to check the weight at every visit)
    - less fever
    - fewer of the original clinical findings (fewer chest signs, smaller effusions, etc.).

- **Laboratory:**
  - Follow-up sputum specimens are collected routinely the end of month 2 and month 5, in order to check for the presence of AFB using smear microscopy.
  - Those diagnosed with active TB using GeneXpert still need to monitor the response to therapy using smear microscopy (and culture in case of DR TB).
  - As a GeneXpert result can be positive even in the presence of dead bacilli, it is not recommended for monitoring response to treatment. Gene Xpert should be considered during monitoring if a patient with DSTB is failing treatment, with the aim to detect rifampicin resistance in a patient started on DSTB therapy.

For more details on monitoring response to TB therapy with sputum testing, including management according to smear results, see your **national TB programme guidelines** or the 2014 MSF TB Guidelines.

Refer to your national guidelines

The patient not responding to TB treatment

This is a fairly common occurrence, for which there are many possible causes. To evaluate this, the clinician will need to take a bit more time to review the notes and take a more detailed history and re-examine the patient.

Algorithm 12.2 details a comprehensive approach to the patient not responding to TB treatment.

Algorithm 12.2 Patients deteriorating or not improving on TB treatment

- This is a common problem.
- Patients with TB on treatment should be improving.
- It is important to find the reason patients are not doing well, and correct the cause.
- Many of these patients have disseminated TB and non-specific symptoms. It always important to review the initial diagnosis, as per algorithm.

1. Essential background information

1. Evolution of illness:

- Pattern of improvement/deterioration.

- Initial improvement on TB treatment?
- No improvement at all?
- Improved with TB treatment, deteriorated when ART started?

2. Was TB proven?

- How? When? Drug sensitive?

If not proven or no sensitivity testing:

- Send all possible samples.
- GeneXpert very helpful: sputum, urine or refer if other tests, not available in the clinic are required. when ART started?

3. TB medication history:

- When started? Regimen?
- Detailed adherence history: from folder, patient, family.

Poor adherence is a common cause:

- Poor adherence – why?

4. ART history:

- On HAART?
- When started? Regimen?
- Detailed adherence history: from folder, patient, family.
- CD4 and VL history.

Timeline always important: When started? When stopped? When restarted?

- Poor adherence: Virological failure?
- Recently started ART: IRIS?
- No longer taking ART but not documented?
- If poor adherence, why?

2. Consider specific causes

Drug-sensitive TB proven, therapeutic level of drugs too low:

- Dose too low.
- Malabsorption:
- Chronic diarrhoea, vomiting.
- Rifampicin levels sub therapeutic.

Not drug-sensitive TB:

- DR TB
- MAC.

Adverse drug effects:

- TB meds
- ART
- Cotrimoxazole
- Efavirenz
- Others.

Additional diagnosis:

- Original TB diagnosis correct, but now something extra.

Alternative diagnosis:

- Original diagnosis of TB not correct.

→

- New OI: For example, pneumocystis, cryptococcal disease.
- Other HIV related problem.
- HIV-unrelated problem.

If cause cannot be found:

- Retake history… anything missed?
- Re-examine patient – again and again.

↓

- **Infection**: Viral, bacterial, parasite, fungal. Infections may be acute or chronic.
- **Malignancy**: For example, KS, lymphoma, lung cancer.
- **Organ failure**: Cardiac, renal, liver, blood, chronic lung disease…and look for the cause.
- **Other chronic disease**: For example, diabetes.
- Drugs, alcohol, smoking, traditional medication.

Possible adverse events due to first line TB drugs

First line anti-TB drugs are usually well tolerated. Each of the drugs, though, may lead to adverse events (i.e. side effects). Whether they are minor side effects (e.g. nausea) or major ones (e.g. hepatitis), all side effects need to be diagnosed and managed early.

The international standard for those on drug-sensitive TB treatment is merely to monitor for such side effects clinically, without any routine laboratory testing. However, in those at high risk for specific adverse events, it is prudent to monitor with suitable laboratory investigations (e.g. ALT in a person with a pre-existing liver problem).

Some of the more common possible side effects due to first line anti-TB drugs and their general management are outlined in Table 12.3. Note that sometimes it will not be possible to know for certain which drug is responsible for a specific side effect. Also, make sure to rule out other causes for the symptoms, instead of automatically blaming it on a TB drug.

Table 12.3 Possible side effects due to first line anti-TB drugs and their general management

Side effect	Likely responsible drugs	Suggested management (see 2014 MSF TB Guidelines for details)	Comment
Nausea and vomiting	All	Ensure hydration. Give anti-emetic 30 minutes prior to TB treatment.	Nausea and vomiting generally subside over time. Always rule out other causes.
Peripheral neuropathy (PN)	H E	Pyridoxine 25–50 mg daily.	Pyridoxine should be given routinely to all those being initiated on TB treatment, in an effort to **prevent PN**.
Orange urine	R	None.	It is important to warn the person at the time of treatment initiation to expect this side effect.
Rash	S, E, Z, R, H	**Stop TB therapy** if any concern of a generalised hypersensitivity reaction (e.g. mucous membrane involvement). See **Chapter 20**, Skin diseases.	Monitor closely for additional signs (fever, headache, vomiting, etc.), suggesting worsening, as there is a significant associated mortality, especially if the culprit drug is not discontinued.
Renal toxicity	S	Replace/discontinue likely offending drug.	The diagnosis and management of drug-induced renal dysfunction is detailed in **Chapter 17**.
Optic neuritis	E	Discontinue ethambutol.	Early diagnosis depends on screening with the Ishihara test at each visit (see Appendix 12.1 at end of this chapter).
Hepatitis	Z but also H, R, E	This is a potentially dangerous condition that requires caution with the initial diagnosis, followed by a careful step-wise approach to the management. For detailed diagnosis and management guidance, see **chapters 4 and 16**.	

* H = isoniazid, E = ethambutol, R = ritanovir, S = streptomycin, Z = pyrazinamide

TB treatment and ARVs

All TB patients co-infected with HIV are eligible for ART.

1. If TB disease is diagnosed before the person has been initiated on ART, the following notes apply:
    - All HIV-infected adults and children with active TB disease are eligible for ART.
    - Start TB treatment first, followed by ART initiation as soon as possible and within the first 2–8 weeks of TB treatment, as explained in Table 12.4 below. (In practice, the closer the CD4 to 50, the sooner we start ART.)
    - Those at high risk of mortality, especially patients with low CD4 (<50), should be initiated on ART within 2 weeks.
    - If the person is clinically stable and has a higher CD4 count, some clinicians prefer to delay ART to reduce the pill burden, the risk of additive drug side effects and the risk of IRIS (see **Chapter 5**), unless other serious HIV-related conditions are present (e.g. KS). In any case, ART must be started within the first 8 weeks of TB treatment.
    - The preferred choice of ARV regimen is the FDC of TDF + 3TC/FTC + DTG with caution regarding women who may conceive or be in the first trimester. (See Algorithm 3.1 on page 35 and Table 3.2 on page 36.) If on rifampicin the DTG dose needs to be doubled to 50mg bd.
2. If an adult or child already on ARVs is diagnosed with TB, the ARV regimen may need to be modified due to drug interactions (see Table 12.5 below and **Chapter 7**).

Table 12.4 Timing of ART initiation in an adult already on treatment for TB

Clinical situation	Timing of ART initiation
All TB cases with CD4 count <50	Within 2 weeks
All TB cases with CD4 count >50	Within the first 2–8 weeks
Young children (especially <1 year)	Within 2 weeks if possible
All DR TB cases	Within 2 weeks if DR TB treatment tolerated

Table 12.5 Changes to ARV regimen if TB treatment needed

Regimen includes	Patient group	Change drug to
NVP	All adults and children >3 years*	EFV
	Children <3 years or <10 kg	Two options: 1. Triple NRTI regimen (ABC + 3TC + AZT), returning to the other regimen once TB treatment has been completed*** 2. NVP up to dose of 200 mg/m^2
LPV/r	Adults	Double dose of LPV/r or double-boosted RTV**
	Children < 3 years	Two options: 1. Triple NRTI regimen (ABC + 3TC + AZT), returning to the other regimen once TB treatment has been completed*** 2. Continue LPV/r, adding RTV (super-boosting) to achieve the full therapeutic dose in a ratio 1:1.
Atazanavir/ritonavir (ATV/r)****	All, since ATV/r cannot be used with rifampicin	Temporarily change to LPV/r (as above)
Dolutegravir (DTG)	Adults	Double the dose of DTG (to be given twice daily instead of once a day)

Notes:

* Children >3 years on an NVP-based regimen can also be given the option of a triple NRTI regimen.

** Continue double-dose LPV/r (or double-boosted ritonavir) for 2 weeks after stopping the rifampicin-containing TB regimen.

*** Triple NRTI regimen is only recommended for the duration of TB treatment. PI- or NNRTI-based regimen should be restarted once TB treatment ends.

****Since it causes less enzyme induction compared to rifampicin, rifabutin can be used together with protease inhibitors, such as LPV/r and ATV/r. If available, change rifampicin to rifabutin. (For more information on the use of rifabutin, see **Chapter 7** and Appendix 9 in the 2014 MSF TB Guidelines.)

Five 'I's to reduce the burden of TB in PLHIV

A number of different strategies can be employed to reduce the burden of TB in PLHIV in your setting. The ones below are the key ones:

1. Intensified case-finding (ICF) through TB symptom screening at each visit of a PLHIV to a health facility, plus screening strategies within the community;
2. Isoniazid preventive therapy (IPT) to prevent development of active TB disease;
3. TB infection control measures to reduce the risk of transmission to others;
4. Integration of TB and HIV services in high-burden settings to improve outcomes; and
5. Early initiation of ART to help prevent development of active TB disease.

The 2nd, 3rd, and 5th 'I's directly prevent the occurrence of new cases of active TB, while the 1st and 4th ones indirectly do so.

1. Screening for TB in PLHIV

Intensified case finding (ICF) for TB can help increase the chances of early detection in PLHIV.

TB symptom screening should be performed routinely in PLHIV, in health facilities and within the community, at each contact with a healthcare worker.

The standard WHO clinical symptom screening includes 4 questions:

- For adults and adolescents: current cough (of any duration), fever, weight loss, and night sweats;
- For younger children, caregivers should be asked about: current cough, fever, poor weight gain, and contact history with a TB case.

All children and adults found to have one or more TB symptoms during the screening process need to be evaluated for TB, using a setting-specific TB diagnostic algorithm (Algorithm 12.1) for adults and **Chapter 10** for children).

Those infected with HIV but not reporting one or more symptoms are unlikely to have active TB disease and should be offered isoniazid preventive therapy (IPT) or another preventive treatment.

Beside the WHO symptoms-based screening, growing attention is being paid to screening strategies for active case finding of TB, which include CXR. You can find more information on this and other approaches on the **SAMU website**: https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

2. Isoniazid preventive therapy (IPT)

IPT involves prescribing a single TB medication, Isoniazid (INH), on daily basis, in order to prevent development of active TB disease. IPT has shown to reduce incidence of TB and mortality in PLHIV.

IPT has shown to reduce mortality in PLHIV so it is essential that **all HIV-positive patients** are screened for active TB disease and given IPT if screened negative.

The latest recommendations for PLHIV are to provide at least 36 months of IPT (as a proxy for lifelong IPT) to PLHIV who are TST positive or unknown. Some national guidelines recommend only 6 months to be provided every 3 years. Both options are acceptable, although providing IPT for 36 months has shown to have a longer effect in preventing the development of active disease.

Before using INH, one must be certain that the person does not have active TB, as giving INH monotherapy to a person with active TB would promote resistance of the TB organism against INH.

As an alternative to IPT, the combination of rifapentin and isoniazid (3HP), given once a week for 12 weeks has also proven to be effective in preventing TB in both HIV co-infected and HIV-negative patients. WHO now recommends 3HP as alternative to IPT in PLHIV.

www.who.int/tb/publications/2015_ipt_update/en/

WHO recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB and HIV-prevalence settings: 2015 update: http://www.who.int/tb/publications/2015_ipt_update/en/ (See also **SAMU website** for key scientific evidence for IPT: https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018)

3. TB infection control

TB infection control refers to a set of measures/controls that can reduce the transmission of TB.

1. Administrative controls. These are the most important and include:
    - Prompt identification of infectious TB cases (e.g. cough triage and fast track for coughing patients).
    - Physical separation of patients known or suspected of having TB (e.g. a person with pulmonary TB should sleep in a separate room while infectious).
    - Coughing patients to wear surgical masks.
    - Patients to be instructed about cough hygiene.

- Infection control policy and functioning infection control committee to be in place.
- Infection control risk assessment to be undertaken in all healthcare facilities.

2. Environmental controls:
   - Maximise natural ventilation.
   - Avoid being downwind from an infectious patient.
   - Maximise the amount of natural light in a room.
   - NB: In resource-limited settings, mechanical ventilation and UV lamps are not the priority.
3. Personal respiratory protection:
   - At-risk staff to wear N95 respirator masks.

The most effective way to prevent TB transmission is through early diagnosis and treatment of active TB disease! TB patients quickly become non-infectious once started on an effective treatment regimen.

4. Integration of TB and HIV services

TB and HIV services should be integrated, especially in settings where both diseases are common.

Approximately 10% of people living with HIV develop active TB every year, while up to 70% of those receiving treatment for TB are HIV-positive in high-HIV burden settings (whether they know it or not).

Integration of HIV and TB services helps to reduce overall morbidity and mortality, both by reducing diagnostic delay of TB in HIV patients and by encouraging TB patients to know their HIV status, which, in turn, allows for earlier care and treatment of other HIV-related conditions. In addition, integration allows for more efficient use of human resources for health, as it prevents some duplication of work that currently exists in parallel TB and HIV programmes.

Some of the objectives of TB/HIV integration include:

- Screening for TB symptoms in all children and adults living with HIV at every visit to a health facility (including at HIV testing sites, antenatal clinics, outpatient department, etc.), followed by rapid evaluation for active TB disease in all those who are coughing or who have at least one other TB symptom.
- All people receiving TB treatment know their HIV status (HIV testing should be offered to all patients prior to TB treatment initiation).
- All HIV-positive people with pulmonary or extra-pulmonary TB (drug-sensitive or drug-resistant TB) being initiated on ART.

5. Early initiation of ART

www.who.int/tb/publications/2015_ipt_update/en/

Early initiation of ART in TB patients co-infected with HIV is a key life-saving intervention. Risk of mortality is much higher in patients for whom ART is delayed or not started on time. What treatment to start, and when, is described above in this chapter. See also the **SAMU website** for the most important studies on this subject: http://www.who.int/tb/publications/2015_ipt_update/en/

Drug-resistant tuberculosis (DR TB)

The purpose of this section on DR TB

The management of DR TB requires a combination of specific, detailed clinical and programmatic knowledge relevant to the country or region that the clinician is working in. This management includes:

- Comprehensive initial assessment of the DR TB patient with history, examination and a battery of special investigations;
- Contact tracing of all those at risk, especially children <5 years;
- Careful planning of a treatment regimen best suited to the specific resistance profile;
- Close clinical monitoring of the patient throughout the duration of the treatment;
- Intensive patient support throughout the treatment duration;
- Early identification of those interrupting treatment;
- Numerous programmatic elements; and
- The different components of monitoring and evaluation with all its administrative requirements.

For these reasons, there are comprehensive national and international guidelines readily available to those clinicians who are required to play a part in the care of DR TB patients.

References to DR TB guidelines and resources

Online resources

- Training: http://endtb.org/resources/elearning-modules
- *endTB Clinical Guidelines*, Version 4. See the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018
- WHO resources:
    - http://www.who.int/tb/publications/pmdt_companionhandbook/en/
    - http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/

This DR TB section, therefore, does not aim to provide comprehensive management guidelines.

It does, however, aim to support clinicians working in HIV/TB clinics, so that they are able to make the necessary clinical decisions should they encounter a patient with suspected or diagnosed DR TB in the course of their routine work. The aims of this section are, therefore, for the clinician:

- To have a broad overview understanding of DR TB;
- To know when to consider that a patient may have DR TB;
- To know how to diagnose it;
- To have a broad understanding of the different drugs and regimens that are used;
- To be aware of the different side effects so that they are recognised when they present; and
- To be aware of the essential components of patient support.

Epidemiology overview

Drug-resistant TB (DR TB) is an increasingly recognised threat. According to the 2016 WHO TB report, 3.9% of new cases worldwide and 21% of previously treated cases are estimated to be due to TB strains that are multidrug-resistant. In addition, just fewer than 10% of patients with MDR TB have XDR TB. However, it is important to note that the rate of DR TB varies considerably by region, and that the vast majority of DR TB cases currently go undiagnosed (and therefore untreated).

Data on incidence of DR TB is poor in many countries, but unfortunately it is highly likely that it is increasing worldwide.

Transmitted more than acquired

It is well known that resistance to HIV treatment develops in individuals largely as a result of poor adherence. In TB however, though poor adherence always needs to be addressed and does at times contribute to the development of resistant strains of TB, **the vast majority of DR TB is transmitted** from one patient to another. This, therefore, requires DR TB management programmes to pay significant attention to issues of infection control, first of all including early diagnosis and start of DR TB treatment to reduce primary transmission.

Classification of DR TB

DR TB (drug-resistant TB) is a broad term covering all the different combinations of drugs that the TB bacillus could be resistant to. For treatment purposes, the most important is to know resistance to rifampicin and to second line drugs, fluoroquinolones and second line injectable drugs (SLIDs). For classification purposes, it is important to know resistance to first line drugs and the same second line drugs – FQ and SLIDS.

There are two rapid molecular diagnostic techniques that are able to give resistance results within a few days.

- Xpert MTB/RIF, which detects resistance to rifampicin only; and
- Hain test, which detects resistance to rifampicin and isoniazid and to fluoroquinolones and aminoglycosides.

WHO guidelines

As a result, we rarely know if a patient is resistant to any of the other drugs. The focus of this section is therefore on the following **WHO definitions** that refer to resistance combinations that qualify for an MDR regimen, the subject of the rest of this section.

Rifampicin resistance (RR): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.

If RR is present, one of the second line TB drug regimens referred to in this section is required for adequate treatment.

The following categories all have RR as the common feature and thus qualify for a DRTB regimen with second line drugs:

- **Multidrug resistance (MDR):** Resistance to both isoniazid and rifampicin.
- **Pre-XDR:** Resistance to both rifampicin and INH, as well as either a fluoroquinolone or an aminoglycoside (a sort of half-way mark between MDR and XDR). Pre-XDR TB, though an important definition clinically, is not an official definition.
- **Extensive drug resistance (XDR):** Resistance to any fluoroquinolone (ofloxacin/levofloxacin/moxifloxacin/gatifloxacin) and at least one of three second line injectable drugs (capreomycin, kanamycin and amikacin) **in addition to MDR as defined above**.

Other resistance pattern definitions are:

- **Mono-resistance:** A term that refers to resistance to one first line anti-TB drug only (rifampicin, INH, pyrazinamide or ethambutol). Rifampicin mono-resistance is important because it requires a second line TB drug regimen. Mono-resistance to drugs other than rifampicin is rarely detected, as it is rarely tested for. If present, there are specific regimens that are used but do not require an MDR regimen.
- **Poly-resistance (PDR):** Resistance to more than one first line anti-TB drug, other than both isoniazid and rifampicin. Again, apart from rifampicin, these resistance patterns are rarely detected, as they are rarely tested for. If present, there are specific regimens that are used but do not require an MDR (second line) regimen.

The focus of this section is on only those drugs and regimens used to treat patients with a resistance pattern that includes resistance to rifampicin. All patients with this profile require a DRTB regimen with second line drugs.

Table 12.6 Differences between DS TB and DR TB

	DS TB	DR TB
Symptoms and signs	No difference detectable	
CXR, ultrasound	No difference detectable	
Smear	No difference detectable	
Xpert MTB/RIF	Rifampicin-susceptible	Rifampicin-resistant
Culture and sensitivity	Susceptible to all first line drugs	Rifampicin-resistant, isoniazid resistant, resistance to other TB drugs is possible.
Rx duration	6 months	9–24 months, depending on resistance profile
Number of drugs	4	5 or more
Drug-drug interactions	Yes	Yes
Side effects	Sometimes	Mostly
Fixed drug combinations	Yes	No

Diagnosing DR TB

It will be noted from the first three rows of Table 12.6, which shows the differences between DS TB and DR TB, that they both present in the same way. DR TB cannot, therefore, be differentiated from DS TB on the basis of history, examination, radiological tests and microscopy. Though DR TB may be suspected in various situations, it can only be confirmed with specific laboratory tests.

When to consider that a patient may have DR TB

The following people are at risk for DR TB:

- A person who has been in close contact with someone with DR TB (especially if living in the same household);
- Those with a history of TB drug use: relapse after treatment, return after default, treatment failure (greatest risk), history of using poor or unknown quality of drugs, history of illness or other medications that interfere with TB drug absorption;
- Healthcare workers, including laboratory workers and auxiliary staff (e.g. hospital cleaners);
- Those in congregate settings: miners, prisoners and prison guards; and
- A person on TB treatment, adherent to their treatment but not improving.

Under these circumstances, one or more specimens is sent for smear microscopy, molecular testing and/or culture and drug sensitivity testing (DST) (see Table 12.7).

Table 12.7 Tests for DR TB

Test	Role	Time to result	Other
Xpert MTB/RIF (i.e. GeneXpert) (Genotypic test)	Can detect rifampicin (RIF) resistant strains of MTB.	<2 hours	Rifampicin resistance detected by GeneXpert needs to be confirmed by DST (especially true for low prevalence settings) since GeneXpert can sometimes give a false positive result, or confirmed by second GeneXpert test.
Line Probe Assay (LPA), also known as Hain test (Genotypic test)	Used to detect H and R resistant strains (also on smear negative) and resistance to SLID and fluoroquinolone agents.	<2 hours	Validated from May 2016 for second line drugs (injectable and FQ). Specific mutations detected by LPA first line can confer resistance to Eto/Pto (INH A mutation) and high-dose INH (KAT G mutation).
Culture/DST	Can be used to detect resistance to first line drugs (H, R, Z, E, S).	2–3 weeks if liquid culture (e.g. MGIT). >1 month if solid culture (L–J).	DST results to H, R, FQs and injectables tend to be reliable and reproducible. DST of other drugs is much less reliable. There is cross-resistance between the injectables amikacin (Am) and kanamycin (Km), and also capreomycin (Cm), but less so. The phenotypic DST also able to give resistance to other drugs (Z, Cs, PAS, Eto/Pto) but they are less reliable and their clinical significance is unknown.
	Can be used to detect resistance to second line drugs (injectables, FQs, etc.).	Even longer, since second line DST is usually performed sequential to first line DST.	
Smear microscopy	Determines level of infectiousness in those with PTB: Smear-positive PTB patients are more infectious. Smear-negative PTB patients are less infectious.		Note that patients with only EPTB are not infectious (unless they have co-existing PTB). Note that patient on treatment could be smear-positive but not infectious (dead bacilli).

Management of the patient with DR TB

Once the diagnosis of DR TB is made, the patient needs to start treatment as soon as possible. Urgent referral is needed for enrolment in the local DR TB management programme, involving:

- A full history including contact history, especially for children <5 years;
- A full examination;
- Several initial tests in preparation for a prolonged course of treatment with potentially toxic drugs (in preparation for the first visit at the referral site the following tests could be done in your clinic if available: Hb and full blood count, liver function tests, creatinine, electrolytes, TSH, audiometry); and
- Several patient support counselling sessions, including information regarding DR TB, infection control and a psychosocial evaluation.

As noted at the beginning of this section, this information can be found in both national and international guidelines, such as those from WHO.

HIV and DR TB: The risk of mortality is higher in a DR TB patient co-infected with HIV. It is, thus, important to make the diagnosis and start DR TB treatment as early as possible. All HIV-positive DR TB patients are eligible for ART, regardless of CD4 count and should be started on ART within 2 weeks of starting the DR TB treatment.

The different drugs and regimens that are used

With the emergence of newer drugs to treat DR TB combined with the outcomes of trials using various shorter drug regimens incorporating them, the management of DR TB has changed considerably over the last few years. In August 2018 WHO issued a rapid communication document to outline the key changes. This will be followed by a more comprehensive document before the end of the year. (see the '**updates**' folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018)

It is beyond the scope of this manual for primary care to detail the comprehensive management of a patient with DR TB. For this it is recommended that the endTB and WHO documents are consulted along with your national guidelines. An overview of the drugs and the general principles of how to use them are presented in the following short section.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Bedaquilline (BDQ) and delamanid (DLM)

Two new drugs have emerged over the last 4–5 years that have significantly changed the way we are able to treat DR TB. The drugs are very active against MTB and are now playing a significant role in the management of these patients. Unfortunately, in many settings access to these drugs remains challenging.

Their side effects are detailed in the tables below but please note the following regarding their use with ARVs. BDQ can be administered with NVP, but not EFV. BDQ can be administered with LPV/r, but there needs to be closer monitoring due to a higher risk of adverse events.

Regarding the full range of drugs available for the management of DR TB, table 12.8 shows them in the categories recently revised by WHO. In addition, this table gives a guideline for the overall approach to designing a regimen.

Table 12.9 lists the different side effects of the drugs and guides the clinician in an approach to monitoring and managing them.

Table 12.10 lists many of the overlapping toxicities that need to be considered especially in patients also taking ART.

Table 12.8 Second line TB drugs

This table details the different second line TB drugs used, how WHO has classified them along with an overall approach to designing a DR TB regimen.

Group A. **Include all three medicines (unless they cannot be used)**	Levofloxacin **OR** Moxifloxacin Bedaquilline Linezolid	Lfx Mfx Bdq Lzd
Group B **Add both medicines (unless they cannot be used)**	Clofazamine Cycloserine **OR** Terizidone	Cfz Cs Trd
Group C. **Add to complement the regimen and when medicines from Groups A and B cannot be used**	Ethambutol Delaminid Pyrazinamide Imipenem-cilastatin **OR** Meropenem Amikacin **OR** Streptomycin Ethionamide **OR** Prothionamide Para-amino-salicylic acid	Emb Dlm PZA Ipm-Cln Mpm Am (S) Eto Pto PAS

Treatment regimens

Standardised regimens of 18–20 months, and increasingly, shorter ones of 9–12 months, are recommended for the management of any drug-resistant TB that includes resistance to rifampicin. Recent studies of the shorter regimens have shown an overall comparable likelihood of treatment success with longer regimens, with a lower risk of treatment interruption. However, shorter regimens were also associated with higher risk of treatment failure and relapse compared to longer regimens. Guidelines are emerging to support the clinician in the decision regarding which regimen to use.

The shorter regimens

These shorter regimens were recommended in 2016 by WHO for selected categories of patients. The following situations exclude people from use of this regimen:

- Resistance to FQ or injectable agents;
- Previous exposure to second line TB drugs included in the regimen;
- EPTB; and
- Pregnancy.

WHO's recommended standard shorter regimen consists of:

- Intensive phase: 4–6 months of Am + Mfx + Cfz + Z + H^h* + E
- Continuation phase: 5 months of Mfx + Cfz + Z + E

* H^h is high dose INH, usually 1 000 mg, once daily.

However, evidence for the effectiveness of these shorter regimens is still lacking. Researchers are therefore encouraged to do pilot studies under operational research conditions using shorter regimens, especially replacing the injectables with suitable alternative drugs.

Side effects

If a patient with DR TB is co-infected with HIV, then tenofovir (TDF) is best avoided during the intensive phase of treatment, due to the additional risk of nephrotoxicity from both TDF and the second line injectable drug (i.e. amikacin/kanamycin, capreomycin).

Table 12.9 shows the side effects of the different drugs, the monitoring tests or procedures performed and the routine prophylaxis given. For more detailed information please consult the two references referred to in bullet 1 immediately above Table 12.9.

Table 12.10 shows potential overlapping and additive toxicities of ART and anti-tuberculosis therapy.

Table 12.9 DR TB meds, side effects and monitoring

(Notes:

- For more detailed reference see 2014 WHO *DR TB Companion Handbook* (2018 version due by end 2018) and endTB Clinical Guidelines, Version 4.0. https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018
- 40% of DR TB patients have gastro-intestinal tract side effects; psychiatric side effects are often not reported.)

Drug	Side effect	Monitoring	Prevention	Management
Isoniazid (INH)	Peripheral neuropathy; Psychiatric disturbance, especially in higher doses; Liver toxicity.	Symptomatically	Pyridoxine 25 mg daily to prevent the peripheral neuropathy.	See WHO and endTB reference books/guidelines.
Pyrazinamide	Liver toxicity; Arthralgia; Elevated uric acid.	As treatment is prolonged for more than 2 months in DR TB, monitor ALT monthly throughout the treatment.		See WHO and endTB reference books/guidelines.
Ethambutol	Optic neuritis presenting with decreasing visual acuity or colour blindness.	Ask about vision on each occasion.		Stop the drug. See WHO and endTB reference books/guidelines.
Ethionamide/ Prothionamide	Common gastro-intestinal side effects (nausea, anorexia); Hypothyroidism; Neurotoxic.	Monitor TSH and T4 at 6 months and then as needed.	Pyridoxine 150 mg daily.	Take with food at bedtime; Can halve the dose and take bd; If TSH >10, check T4 and add thyroxine 0.05-0.1 mg daily. See WHO and endTB reference books/guidelines.
Levofloxacin	Nausea and diarrhoea; Headache and dizziness.	Nil.		
Moxifloxacin	Nausea and diarrhoea; Headache and dizziness; Can cause QTc prolongation.	Symptomatic.		
Cycloserine	Psychiatric/Neurological: Anxiety, depression, confusion, psychosis, vertigo, drowsiness, speech changes, parasthesia, convulsions; Peripheral neuropathy.	History check each time.	Pyridoxine 150 mg daily.	See WHO and endTB reference books/guidelines.

Drug	Side effect	Monitoring	Prevention	Management
Kanamycin/ Amikacin/ Capreomycin	Nephrotoxic; Ototoxic; Can cause electrolyte depletion with low, K, Mg and Ca but Kanamycin and Amikacin less so than Capreomycin.	Monthly creatinine; Monthly audiometry or hearing assessment; Monthly K and if low potassium, check Ca and Mg.		See WHO and endTB reference books/guidelines.
PAS	GIT side effects: nausea, vomiting, diarrhoea; Reversible hypothyroidism.	TSH and T4 at 6 months and then as needed.		See WHO and endTB reference books/guidelines.
Clofazamine	Skin darkening; GIT intolerance; Prolonged QTc interval on ECG.			Symptomatic management; Take with food. If QTc prolongation, see *endTB Clinical Guidelines*, Version 4.0.
Linezolid	Myelosuppression; Nausea, diarrhoea; Optic neuropathy; Peripheral neuropathy (PN); DDIs with SSRIs – can lead to a serotonin syndrome.	Monthly FBC; Regular monitoring of visual acuity.	Pyridoxine 150 mg daily.	If QTc prolongation, see *endTB Clinical Guidelines*, Version 4.0.
Bedaquilline	Nausea, headache, arthralgia; Prolonged QTc interval on ECG; CYP 3A4 metabolism causes drug interactions – ARV use: no EFV, can use NVP and LPV/r with caution; Caution with other drugs causing prolonged QTc interval – cfx or mfx.	Baseline ECG, then at 2 weeks, then monthly; Check K Ca Mg at baseline and follow up if prolonged QTc; Monitor ALT and bili.		Stop BDQ if QTc >500 msec; If QTc prolongation, see *endTB Clinical Guidelines*, Version 4.0. Stop if bili >2x upper limit of normal or ALT >8 x upper limit of normal.
Delamanid	Nausea, headache, dizziness; Prolonged QTc interval.	Baseline ECG, electrolytes at baseline then regular monitoring; Baseline albumin – must be more than 28 g/l.		Please refer to *endTB Clinical Guidelines,* Version 4.0 for important detail.

Table 12.10 Potential overlapping and additive toxicities of ART and anti-tuberculosis therapy

(Note: Drugs that are more strongly associated with the side effects appear in bold.)

Abbreviations used in this table:

BDQ – bedaquilline, Cm – capreomycin, Cs – cycloserine, E – ethambutol, Eto – ethionamide, Gfx – gatifloxacin, H – INH, Km – kanamycin, LZD – linezolid, PAS – para-amino salicylic acid, Pto – prothionamide, Rfb – rifabutin, RTV – ritonavir, Z – PZA

Toxicity	Antiretroviral agent	Antituberculosis agent	Comments
Central nervous system (CNS) toxicity	**EFV**	**Cs**, H, Eto/Pto, Fluoroquinolones	At present, there are limited data on the use of EFV with Cs; concurrent use is accepted practice with frequent monitoring for CNS toxicity. Frank psychosis is rare with EFV alone.
Depression	**EFV**	**Cs**, Fluoroquinolones, H, Eto/Pto	Severe depression can be seen in patients both on EFV and Cs. Consider substituting these drugs if severe depression develops. The severe socio-economic circumstances of many patients with chronic disease can also contribute to depression.
Headache	**AZT, EFV**	**Cs** BDQ	Rule out more serious causes of headache such as bacterial meningitis, cryptococcal meningitis, CNS toxoplasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration may help. Headache secondary to AZT, EFV and Cs is usually self-limited. Headache has been reported as one of the most frequent adverse effects (>10%) in controlled clinical trials with BDQ.
Nausea and vomiting	**RTV, d4T**, NVP, and most others	**Eto/Pto, PAS, H, E, Z** and others **BDQ**	Nausea and vomiting are common adverse effects and can be managed with modalities described in Chapter 11 of the 2014 WHO *DR TB Companion Handbook*. Persistent vomiting and abdominal pain may be a result of hepatitis secondary to medications (see **Chapter 16**).
Abdominal pain	**All ART treatment has been associated with abdominal pain**	**Eto/Pto, PAS**	Abdominal pain is a common adverse effect and often benign; however, abdominal pain may be an early symptom of a drug-induced hepatitis (see **Chapter 16**).
Diarrhoea	**All protease inhibitors, DDI (buffered formula)**	**Eto/Pto, PAS**, Fluoroquinolones	Diarrhoea is a common adverse effect. Also consider opportunistic infections as a cause of diarrhoea, or clostridium difficile.

Toxicity	Antiretroviral agent	Antituberculosis agent	Comments
Hepatotoxicity	**NVP, EFV, all protease inhibitors** (RTV >other protease inhibitors), **all NRTIs**	**H, R, E, Z,** PAS, Eto/ Pto, Fluoroquinolones **BDQ**	Follow hepatotoxicity treatment recommendations (see **Chapter 16**), remembering that cotrimoxazole can also be a cause. BDQ plus other drugs used to treat TB can result in liver toxicity. If aminotransferase elevations are accompanied by total bilirubin elevation >2 x ULN, or aminotransferase elevations are >8 x ULN, or aminotransferase elevations persist beyond 2 weeks, BDQ is to be discontinued.
Skin rash	**ABC, NVP, EFV, d4T** and others	**H,R, Z, PAS,** Fluoroquinolones, and others	Do not re-challenge with ABC (can result in life threatening anaphylaxis). Do not re-challenge with an agent that caused Stevens-Johnson syndrome. Also consider cotrimoxazole as a cause of skin rash if the patient is receiving this medication.
Renal toxicity	TDF (rare)	**Aminoglycosides, Cm**	TDF may cause renal injury in approximately 1% of users. As there is a risk of toxicity with the aminoglycosides as well, TDF is usually substituted with AZT or ABC when an aminoglycoside is used. Remember to adjust the relevant anti-tuberculosis medications for renal insufficiency (see Table 17.1 in **Chapter 17**).
Bone marrow suppression	AZT	**Lzd**, R, Rfb, H	Monitor blood counts regularly. Replace AZT if bone marrow suppression develops. Consider suspension of Lzd. Also consider cotrimoxazole as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if receiving cotrimoxazole.
Optic neuritis	DDI	**E**, Eto/Pto (rare)	Permanently suspend agent responsible for optic neuritis and replace with an agent that does not cause it.
Dysglycaemia (disturbed blood sugar regulation)	**Protease inhibitors**	**Gfx**, Eto/Pto	Protease inhibitors tend to cause insulin resistance and hyperglycaemia. Eto/ Pto tend to make insulin control in diabetics more difficult, and can result in hypoglycaemia and poor glucose regulation. Gatifloxacin is no longer recommended use in treatment of TB due to this side effect.

Patient support

Support of DR TB patients is of paramount importance and should be offered throughout treatment.

A DR TB patient can have difficulty adhering to the prolonged treatment regimen for a number of reasons, including:

- psychological distress;
- social problems;
- knowledge and beliefs regarding the purpose of treatment;
- separation from family/friends;
- adverse events (due to medication or other reasons);
- inconsistent immediate effect; and
- lack of trust in the provider.

Strategies to support patients with these numerous difficulties are many, but a basic package of support should include:

- DR TB patients should receive sufficient information and education about their disease and its treatment to enable them to take some responsibility for their own outcome. It is very important that patients understand that if they do not adhere to their treatment, they risk amplifying the resistance of their strain of DR TB, such that it may become less treatable, and the strain can be passed on to their families.
- Psychological support – individually and/or in groups.
- Intense medical support to treat side effects of drugs, addictions, other medical conditions, psychiatric disease and other pre-existing conditions or results of treatment.
- Social support, including enablers such as social grants, food, accommodation, and transport, plus other needs of the patients and their families. It is important that these resources are accessible in the community.
- Some flexibility in treatment delivery to enable patients to stay adherent.

Key points

- Drug-resistant TB is a growing problem globally with potential huge impact on patients and health systems.
- Unlike HIV resistance, which mostly develops due to poor adherence, the vast majority of DR TB is transmitted from one person to another.
- In the HIV-positive patient it is especially important to recognise and diagnose it early and commence treatment as soon as possible.
- There are numerous potential side effects to the drugs used, as well as some important overlapping toxicities between ARVs and DR TB drugs.
- The risk of default is high, so close monitoring throughout the treatment is important, along with early recognition and management of side effects.

Appendix 12.1 Approach to lymphadenopathy, including fine needle aspiration (FNA)

Lymphadenopathy (enlarged lymph nodes) is often a result of infection but can also be caused by cancer (e.g. lymphoma or Kaposi's sarcoma). The lymphadenopathy can be generalised or localised. Do not confuse enlarged lymph nodes with swollen parotid glands (in the cheeks) or other swollen salivary glands (diffuse infiltrative lymphocytosis syndrome or DILS).

Causes of lymphadenopathy

Causes of generalised lymphadenopathy

- HIV itself (but often <2 cm in size) most commonly during acute seroconversion
- secondary syphilis.

Causes of localised lymphadenopathy:

- tuberculosis
- bacterial infection
- STIs (groin)
- Kaposi's sarcoma (KS)
- lymphoma
- cervical carcinoma (groin).

Symptom management

REMEMBER: Think of TB when a person presents with any enlarged lymph node that is chronic.

Clinical presentation

- swollen lymph nodes
- sometimes tender
- located in neck, axillae or groin.

Clinical examination

- Take body temperature.
- Assess for weight loss.
- Measure and note size of lymph nodes (fine needle biopsy indicated if >2 cm).
- Check all other lymph node areas (neck, axillae, groin).
- Check for liver or spleen enlargement.

Management

- Correct management depends on the specific diagnosis, so it is important to make an accurate diagnosis.

- A trial of antibiotic therapy is reasonable for localised, enlarged lymph nodes, especially while waiting for needle biopsy results: cloxacillin 250–500 mg four times daily x 5 days (depending on weight of adult).
- If the node is >2 cm in adults, needle aspiration should be performed by a trained clinician as follows:
    - If the node is fluctuant, aspiration is easy and can be performed by the nurse or doctor; liquid aspirate should be sent in a sputum jar for TB testing (AFB +/– culture).
    - If the node is not fluctuant, a **fine needle aspiration biopsy (FNAB)** should be performed by a trained clinician and the material sent on slides for AFB examination and cytology to rule out other possible causes (lymphoma, KS, etc.).
- Needle biopsy material should be sent for:
    - TB smear (AFB)
    - Cytology (to identify any lymphoma).

Fine needle aspiration biopsy (FNAB)

An FNAB allows cellular material from lymph nodes to be examined for microscopic evidence of TB or other pathology (fungal infections, lymphoma, etc.).

Equipment needed:

- gloves
- povidone-iodine solution (or alcohol swab)
- sterile gauze
- sterile needle (23 gauge is best)
- 10 ml syringe
- sterile water
- 2 microscope slides (frosted at one end)
- spray fixative
- pencil.

Fine needle aspiration technique:

- Label both microscope slides with patient identification and the date.
- Disinfect the skin overlying the lymph node with the povidone-iodine solution (or alcohol swab).
- With the needle attached to the syringe, draw some sterile water into the syringe.
- Immediately expel the water from the syringe (so that there is now a small ‘coating’ of water inside the needle and syringe).
- Immobilising the lymph node with one hand, insert the needle deep into the lymph node and pull back on the syringe plunger in order to create a vacuum (of about 2 ml).
- Without exiting the lymph node, withdraw and insert the needle several times at different angles in a ‘back-and-forth’ motion, all the while maintaining constant suction, in order to allow cells from the lymph node to enter the bore of the needle.

- Once material (or blood) appears in the needle hub, the aspiration should be stopped; the more cellular material aspirated, the better, since it improves the specificity and sensitivity of this diagnostic intervention.
- Release the negative pressure before removing the needle from the lymph node. If not, the aspirated material will enter the barrel of syringe and be less available for introduction onto the microscope slides.
- With the gauze, ask the patient to apply gentle pressure over the entry site.

Slide preparation

It is important to prepare the microscope slides **immediately** after aspiration as follows:

- Detach the needle from the syringe.
- Gently fill the syringe with air (while the needle is still detached).
- Reattach the needle to the syringe and quickly expel all of the ‘air’ while the needle tip is touching close to the frosted end of one of the slides. By doing so, moist cellular material will be released onto the slide.
- Gently place the second ‘clean’ slide face down over the slide with the aspirate on it.
- With the two slides now touching each other, move them in opposite directions in order to spread the cellular material across both slides simultaneously. Avoid pressing the slides together forcefully so as to avoid crushing the cells from the lymph node.
- Allow one slide to air dry.
- Spray the other slide with fixative.

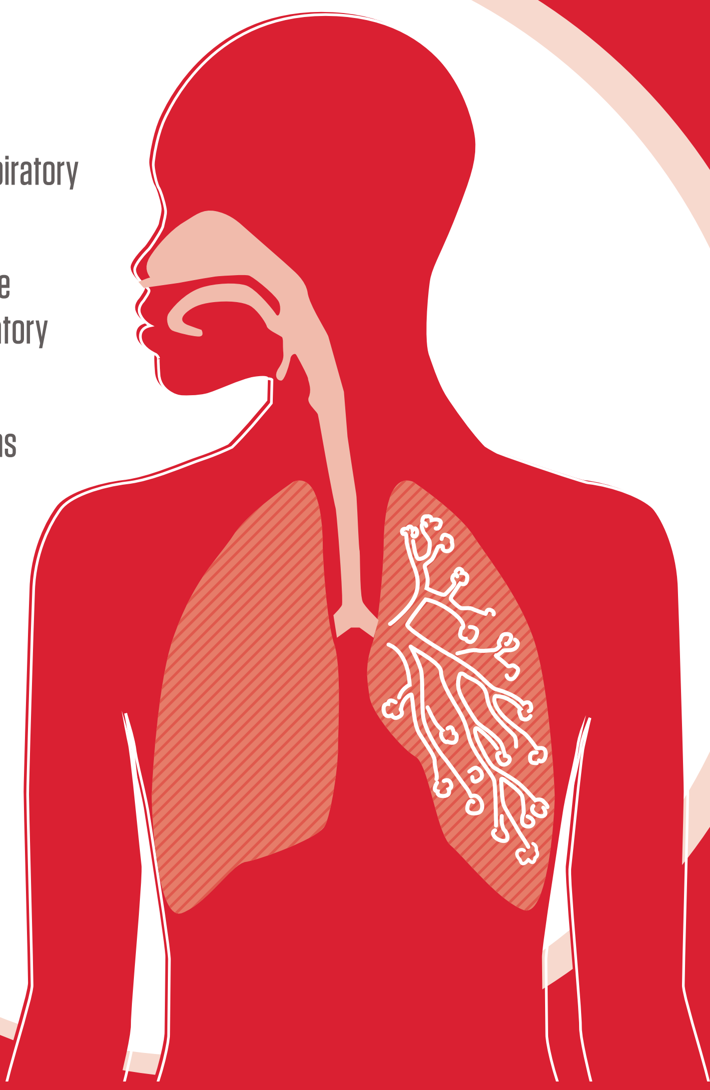
Slide transport

The microscope slides must be well protected during transport to the laboratory.

CHAPTER 13

Respiratory disease

- Overview of respiratory conditions
- Key points of the more commonly seen respiratory conditions
- The 'don't forget' conditions
- An approach to respiratory symptoms presenting in primary care clinics



Respiratory disease is very common in the HIV-positive patient and unfortunately remains a significant cause of mortality. The commonest errors made in the primary care health centres are:

- Failure to identify, refer or adequately manage patients with danger signs;
- Routinely giving antibiotics to all patients with respiratory symptoms (many patients have viral upper respiratory infections or TB); and
- Failing to diagnose TB.

This chapter provides an overview of the key features of the commonly seen respiratory conditions, and an algorithm guiding an approach to the patient in primary care clinics who presents with respiratory symptoms.

Overview of respiratory conditions

The 'big 3'

- TB
- Pneumonia
- Pneumocystis pneumonia

Don't forget group (urgent and often missed)

- Pleural effusion (including empyema)
- Pneumothorax
- Pulmonary embolism

Other causes that are sometimes misdiagnosed as active TB

- Heart failure
- Lung cancer
- Lung metastases from other cancers
- Chronic lung disease: post TB bronchiectasis, silicosis (miners)

Table 13.2 provides a list of different respiratory conditions in relation to CD4 count.

Key points of the more commonly seen respiratory conditions

The 'big 3'

1. TB

Chapter 12 is devoted entirely to the diagnosis and management of TB. In summary, however, the following points are noteworthy when making a diagnosis of TB:

- TB is extremely common, frequently missed and remains the most common cause of mortality in HIV-positive patients.
- It can present with the classic cluster of symptoms – cough, fever, weight loss and drenching night sweats – but can also present with minimal signs and symptoms (more often with lower CD4 counts).
- The presentation is usually subacute, developing over a week or two, but can progress very rapidly in patients with low CD4 counts.
- The examination findings may range from absolutely nothing to multisystem diseases affecting lungs, heart, brain, abdomen, bones and joints. A full examination looking for all of these is therefore important.

2. Bronchitis and pneumonia

These two conditions are commonly seen in outpatient settings. Both conditions usually present with acute onset of cough, shortness of breath and fever. The table below summarises the key features.

The history and physical examination of the chest really does make a difference. Without an examination of the chest, a pneumonia and/or pleural effusion will often be missed.

Table 13.1 Key features of bronchitis and pneumonia

	Bronchitis	Pneumonia
Cause	>90% viral.	Mostly bacterial: strep pneumonia, haemophilus influenza, moraxella, mycoplasma.
Pathology	Inflammation of the airways with mucous production but no consolidation.	Inflammation of the lung tissue, in which there is consolidation, due to filling of the airways with fluid.
History	Can have diffuse chest pain. Often blocked nose and sore throat as well. Productive cough does not always mean bacterial infection or TB.	If chest pain present, often localised to one side.
Examination	Fever not always present but may occur. Wheeze but no bronchial breathing (focal area of louder breath sounds) or obvious decreased breath sounds in a particular area.	Fever and increased respiratory rate common. Often bronchial breathing or obvious decreased breath sounds in a particular area.
Chest x-ray	Normal.	Focal or scattered areas of consolidation.
Treatment	Rarely needs inpatient management. Bronchitis is commonly associated with a runny nose and clear, yellow or even green sputum. It is a viral infection and does not need antibiotics.	**May require inpatient management (see danger signs below).** Antibiotics are chosen empirically to cover the likely bacteria. In outpatients, usually amoxicillin 1g 3 x a day for 5 days.

3. Pneumocystis pneumonia

This is an opportunistic infection of the lungs caused by the organism *Pneumocystis jiroveci*. It used to be called *Pneumocystis carini*, hence the term PC pneumonia (PCP) still in common use.

Always think of *Pneumocystis* pneumonia if there is significant, frequently progressive shortness of breath, often associated with a dry cough. People with a CD4 ≤200 are at risk, especially those who have not been taking cotrimoxazole preventive therapy (CPT).

Clinical presentation

- Dyspnoea (shortness of breath) caused by clogging of the alveoli is the main symptom. **This is the key presenting feature of PCP**.
  - Initially this occurs only on exertion, but later, also at rest.
  - The patient can progress to severe dyspnoea quite quickly.

- Low blood oxygen levels (hypoxaemia) can be confirmed with the use of a pulse oximeter device, but remember that a rapid respiratory rate can often compensate for hypoxaemia, resulting in reasonable oxygen saturation.

- A dry cough (non-productive) is often also present.
- Tachypnoea (fast breathing), often with flaring of the nostrils. Respiratory rate is often more than 30, which is a danger sign and requires rapid referral to hospital. Apart from this, the rest of the chest examination is often normal.
- Temperature may be normal or high, and may be over 40 degrees.
- Chest x-ray characteristically shows a ground glass (hazy) appearance that is more pronounced in the lower lung zones. Intrathoracic lymph nodes are not a radiological feature of pneumocystis pneumonia.

Management

Most patients with PCP have danger signs, and, therefore, meet the criteria for admission to hospital. PCP is a clinical diagnosis. If suspected and danger signs present, start oxygen, cotrimoxazole and prednisone and transfer as soon as possible. (See doses below.)

For more details, consult the **referral level HIV/TB guide**.

Refer to the MSF HIV/TB Guide: Hospital Level

Is there ever a place for management as an outpatient?

This is rare. However, if the patient's history and examination are suggestive of PCP, the dyspnoea is not severe enough to be a danger sign, and there is good home support, consider outpatient treatment as follows:

- High-dose cotrimoxazole (CTX):
  - 21 days of single-strength cotrimoxazole tablets; one tablet for every 4 kg body weight per day in three divided doses (e.g. a 48 kg person gets 4 tablets 3 x a day).
  - Prednisone is indicated for moderate-to-severe disease. If it is needed, the patient should be admitted to a hospital and not be managed as an outpatient.
  - Give folic acid, 5 mg daily, whenever a person is taking high-dose cotrimoxazole, since CTX depletes the body of folic acid.
  - Monitor for CTX-associated rash, as this is common.
  - The patient should have easy access to the clinic and be well informed of all the danger signs and action to be taken if any develop.
- In adults with an allergy to CTX:
  - Get more detail on the nature of the allergy and whether it is life threatening.
  - Refer to hospital, where clindamycin 600 mg qds + primaquine 15–30 mg daily for 14 days may be used.

Follow-up

- If the symptoms of PCP have resolved after 3 weeks of treatment with high-dose cotrimoxazole, don't forget to continue giving a maintenance (preventive) dose of cotrimoxazole (2 x 480 mg tabs once daily), or the PCP can recur.

Pneumocystis pneumonia is a stage 4 disease, so the patient needs effective ART as soon as possible. In other words, if ART-naïve, ART needs to be started as soon as possible and if on ART or defaulted from it, a decision needs to be made whether to continue with the current ARV regimen or switch to a new one.

The 'don't forget' conditions

Pulmonary Kaposi's sarcoma (KS)

This is a serious diagnosis with a poor prognosis, even in patients on ART. (See also **Chapter 20**, Skin diseases.)

Clinical presentation

- Suspect pulmonary KS whenever a patient with cutaneous or oral KS lesions is having respiratory symptoms. **Important: Always look in the patient's mouth.** Pulmonary KS can, however, occur when cutaneous lesions are absent.
- Pulmonary KS may have a similar presentation to pulmonary TB (PTB) or PCP.
- Pleural effusion is common (and often blood-stained).
- Chest x-ray may show linear infiltrates radiating from the hilar, along with some nodules. These are, however, not very specific for KS and can look like many other HIV-related lung conditions, such as pneumonias, TB and fungal infections.

Diagnosis

- In patients with cutaneous or oral KS lesions, who have pulmonary symptoms, it is still necessary to rule out active PTB.
- Arrange for sputum samples to be sent for TB testing (Xpert MTB/RIF, smear microscopy). However, if TB is suspected as well, start empiric treatment, as a delay in starting treatment must be minimised in these patients.
- Examine the chest, listening especially for decreased breath sounds at the bases and for dullness on percussion, both of which suggest a pleural effusion. Any pleural effusion should be tapped and the appearance of the pleural fluid noted. The presence of blood suggests pulmonary KS.
- Send the fluid for TB testing, protein analysis, culture and sensitivity, and, if available, cytology.

- Perform a CXR if possible.
- Any suspected pulmonary KS is an HIV emergency with very high mortality and should be referred the same day for urgent chemotherapy. The most efficacious is IV pegylated liposomal doxorubicin (PLD). In some countries, this is making its way into national management protocols. There is no role for primary care management. Bronchoscopy and biopsy are not necessary, even in well-resourced settings as these delay treatment.

Pulmonary embolism

Pulmonary embolism can present in a variety of ways. It can be gradually progressive dyspnoea, sometimes with pleuritic chest pain, shortness of breath, and hypoxia. It can also present with sudden catastrophic hemodynamic collapse. Pulmonary embolism should be suspected in patients with respiratory symptoms unexplained by an alternative diagnosis. Always look for deep vein thrombosis (DVT). Most of these patients present with danger signs, so qualify for oxygen and immediate referral.

Pneumothorax

This is a fairly common complication of pneumocystis pneumonia. It usually presents with acute onset shortness of breath and chest pain. Examination usually shows a patient in respiratory distress, with tachypnoea and tachycardia, and, on examination of the chest, there are absent breath sounds on one side. This patient will have danger signs and qualifies for oxygen and immediate referral.

Empyema

This is a collection of pus in the pleural space, the commonest cause of which – in the HIV-related setting – is as a complication of pneumonia. It commonly presents with fever, cough, respiratory distress and pleuritic chest pain, and on examination, the features are the same as those of a pleural effusion: decreased breath sounds and dullness to percussion.

The diagnosis is confirmed with pus seen in a pleural tap; plus a laboratory can confirm with the cell count showing neutrophils. A gram stain is also helpful in identifying the organism. Ideally, this needs hospital treatment with an intercostal drain, or if not possible, repeated pleural taps until dry, and a long course of IV antibiotics.

Chronic lung disease

This is a diagnosis covering several different diagnoses. The focus here is on:

- bronchiectasis following recurrent TB
- COPD due to smoking (covered in more detail in **Chapter 21**).

These can occur at all CD4 counts and usually present with chronic dyspnoea, chronic cough and chronic hypoxia.

Post-TB bronchiectasis

There is usually a past history of one or more episodes of pulmonary TB or occupational exposure (e.g. mining). These episodes damage the lungs, causing a degree of bronchiectasis that often results in chronic dyspnoea and recurrent episodes of bacterial bronchitis or pneumonia.

If chest radiology is available, it often shows features of post-TB destructive lung disease – fibrosis and cystic changes. A comparison with previous CXRs shows a similar picture.

Treatment

Episodes of bacterial infection need to be treated with ampicillin/amoxicillin or coamoxyclav, according to local guidelines.

TB treatment is often given unnecessarily, so avoid empiric TB treatment on the basis of just the above symptoms or CXR findings, unless there are clear signs of active TB (non-dense infiltrates, intrathoracic lymph nodes and pleural effusions). Look for a positive sputum Xpert, microscopy or culture.

An approach to respiratory symptoms presenting in primary care clinics

Key points

- Respiratory conditions are common presentations in primary care HIV clinics.
- Always look for respiratory danger signs, and, if present, refer as soon as possible.
- Always consider the big three: TB, pneumocystis pneumonia and bacterial pneumonia.
- TB is frequently missed, contributing to an ongoing significant mortality in our HIV-positive populations.

The following three pages provide an algorithmic approach to the patient presenting with respiratory symptoms in a primary care clinic.

Notes to Algorithm 13.1

Always assess first for danger signs, and if any are present, act urgently as guided by the algorithm

If no danger signs present:

History and examination will help detect a pleural effusion, which points more towards pneumonia, TB, Kaposi's sarcoma or empyema. The absence of respiratory findings on examination could mean a viral bronchitis, but, because in the HIV-positive patient there is always the strong likelihood of TB, the recommended approach is:

- Perform available investigations for TB (microscopy, GXP, and if CD4 <100, urinary LAM).
- Review the patient a few days later to view the TB results and to assess for clinical improvement.
- Manage further, based on the findings of this consultation. (Kaposi's and empyema will need referral.) If TB tests are negative, review diagnosis and consider a course of azithromycin to treat atypical pneumonias.
- In addition:
    - Do not give antibiotics without a clear indication for doing so.
    - Consider other causes of respiratory illness.
    - Maintain a high index of suspicion for TB, even if all TB investigations are negative. Consider empiric treatment, especially if more advanced disease (see **Chapter 11**, The ambulatory patient presenting with advanced HIV disease, and **Chapter 12**, Drug-sensitive and drug-resistant tuberculosis in people living with HIV).
    - Establish immune status by getting CD4 result as soon as possible.

Table 13.2 Association of common pulmonary infections with different CD4 levels

The conditions in this table associated with higher CD4 counts can occur at any CD4 level, while those tabled here with lower CD4 counts generally do not occur at higher CD4 counts.

Most pulmonary infections occur with increasing frequency at lower CD4 counts.

<table>
<tr><th>CD4 cell counts when infection first occurs</th><th>Pulmonary infections</th><th>Non-infectious pulmonary conditions (any CD4)</th></tr>
<tr><td rowspan="3">>500 cells/ μl</td><td>Acute pharyngitis, bronchitis, sinusitis</td><td rowspan="8">Chronic lung disease
Pulmonary embulism
Lung cancer
Kaposi's sarcoma (KS) is often but not always associated with CD4 <100. (See also Chapter 20, skin diseases.)
Spontaneous pneumothorax – often associated with PCP and KS</td></tr>
<tr><td>Pneumonia</td></tr>
<tr><td>Pulmonary TB (occurs at all CD4 count levels but with increasingly atypical presentations as the CD4 decreases)</td></tr>
<tr><td rowspan="2">200–500 cells/uL</td><td>Recurrent bacterial pneumonia</td></tr>
<tr><td>Pulmonary TB and disseminated TB</td></tr>
<tr><td rowspan="3"><200 cells/uL</td><td>PCP</td></tr>
<tr><td>Disseminated TB</td></tr>
<tr><td>Fungal pneumonias – cryptococcosis, histoplasmosis</td></tr>
</table>

Algorithm 13.1 Approach to respiratory problems in primary care

Clinical presentation

- Dyspnoea
- Cough: productive or dry?
- Fever.

Check immediately for **respiratory danger signs:**

- Respiratory rate >30
- Hypoxia: oxygen saturation <90%
- Haemoptysis (coughing up blood)
- Confusion
- Blood pressure <90/60.

If no danger signs, initial assessment:

History:

- Duration of onset, additional symptoms

Examination: look for

- lymph nodes
- pleural effusion
- wasting
- skin lesions.

Investigations:

All patients are TB suspects, therefore investigate for TB with whatever tests you have available:

- If pleural effusion, diagnostic tap
- (therapeutic tap if large and causing respiratory distress)
- CXR for all patients, if possible.

Emergency management if danger signs present:

- Oxygen if RR >30 or hypoxia
- Initiate antibiotics immediately if bacterial pneumonia suspected
- Empiric PCP treatment if suspected
- **Refer** and consult HIV/TB guide – referral level if delay in transfer.

All patients are TB suspects

There may be more than one respiratory condition. Look for alternative/additional causes

***Tuberculosis: investigations**

Pulmonary TB; any CD4 count

- Sputum for GeneXpert (microscopy if not available)
- TB LAM if CD4 known or considered <100
- Other investigations, as indicated: e.g .pleural tap, lymph node aspiration biopsy.

Infection control:

- surgical mask for patients not needing oxygen; move to TB isolation area
- Open windows!

Chronic lung disease

- All CD4 counts
- Chronic dyspnoea, chronic cough, chronic hypoxia
- CXR: post TB destructive lung disease – fibrosis, cavities, bronchiectasis on CXR
- Comparison with previous CXRs shows this is chronic: treat TB if proven, avoid empiric treatment on the basis of CXR alone.

Acute onset: days

***Bacterial pneumonia**

- Occurs with any CD4 count
- Auscultation: Bronchial breathing and crepitations
- Send off sputum for available TB tests (GXP or microscopy)
- CXR: Pulmonary infiltrate or consolidation. Empyema may occur (purulent pleural effusion, mostly neutrophils); needs referral to hospital.

Treatment:

- Amoxycillin 1g 3 x a day
- Follow up closely for improvement or development of danger signs
- Duration of antibiotics: 5–7 days.

Look for Kaposi's sarcoma

- CD4 often <200; can be higher
- Look for KS lesions on skin, palate.

Treatment:

- Fast track for ART and referral for chemotherapy.

Subacute onset: up to 2 weeks

Bronchitis

- Occurs with any CD4 count
- Auscultation: No bronchial breathing or significant crepitations noted
- Send off sputum for available TB tests (GXP or microscopy)
- CXR unlikely to show any abnormalities
- This is a viral infection and does not need antibiotics, even if associated with yellow or green mucous.

Treatment:

- Bring patient back in about 3 days for follow-up and for TB results.

Do not give repeated courses of antibiotics if the patient has not responded. If suspicion of TB and investigations for TB are negative, start empiric TB treatment. Seek advice if uncertain.

***Pneumocystis pneumonia**

- CD4 count generally <200
- Usually not using CTX prophylaxis
- Progressive dyspnoea: often dry cough
- Very high respiratory rate (>40) and hypoxia are common
- Sudden deterioration due to a pneumothorax is common and life-threatening
- Auscultation: crepitations or may be normal.

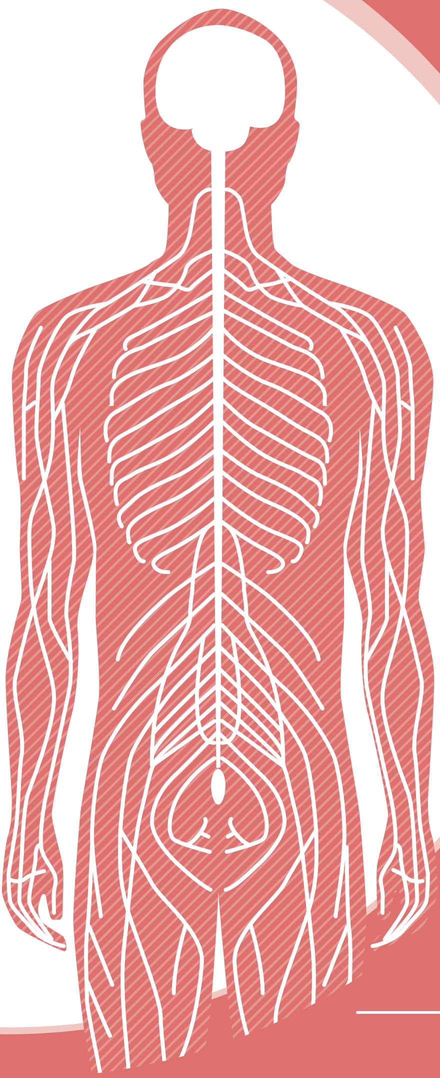
Treatment:

- Cotrimoxazole 480mg 1 tablet for each 4 kg of body weight, in 3–4 divided doses (if 48 kg, 4 tablets 3 x day)
- Prednisone is indicated for more severe disease, so this patient will need referral.

*** The 'big 3' diseases may co-exist, so always look for all 3.**

CHAPTER 14

Neurological disease



- Chapter overview
- Continued patient care on return to primary care after discharge from hospital
- The approach to the patient with a positive serum CrAg
- Peripheral neuropathy (PN)
- Summary

Patients with neurological conditions can present to primary care clinics in a variety of ways; symptoms of meningitis, acute severe headache, altered levels of consciousness, confusion or strange behavior, focal neurological symptoms and seizures.

- **Any abnormal neurology (apart from most peripheral neuropathy) is a danger sign;**
- **Neurological disease has a high mortality;**
- **Most patients with neurological problems have advanced HIV;**
- **Emergency management and initiation of treatment for likely opportunistic infections may need to be given at primary care, particularly if transfer is delayed.**

Refer to hospital

These patients need **urgent referral** for investigation and management in hospital: the hospital clinicians cannot refuse to accept the patient.

If you have the ability to do more in your clinic than is suggested in this chapter, please refer to the **MSF HIV/TB Guide: Hospital Level** booklet that accompanies this primary care guide.

Refer to the MSF HIV/TB Guide: Hospital Level

Outpatient neurology: Two other presentations, rarely requiring immediate referral and that the primary care clinician needs to know how to manage are peripheral neuropathy and the asymptomatic patient with a positive serum CrAg.

Chapter overview

This chapter will take the reader through:

- An overview of the different neurological presentations and their possible causes
- Core information regarding the common neurological conditions, especially ‘the big 3’
- The immediate emergency management and initial assessment of the patient with a neurological presentation
- The immediate management of common neurological conditions while waiting for transfer to the referral site
- Guidance for continued care after discharge back to primary care
- The approach to the patient with a positive serum CrAg
- The diagnosis and management of peripheral neuropathy

Neurological conditions and their causes

Algorithm 14.1 presents the different ways in which neurological conditions present in primary care along with the disease commonly associated with them.

Notes to Algorithm 14.1

Algorithm 14.1 (presentation of neurological disease) is divided into three sections:

Section 1: Symptoms

There are 4 types of neurological presentation – they may occur alone or in combination:

1. Symptoms of meningitis
2. Global: mostly an altered mental state but also includes headache
3. Focal neurology
4. Seizures

Section 2: Pathology

With any of the above presentations there is some pathology going on in the brain. This is detailed in Section 2.

Section 3: Diseases

Section 3 covers the common diseases that cause the different presentations. Via the colour-coded circles, the presenting features in the first section (meningism, global, focal, seizures) are linked to possible diseases causing them.

Seizures in an HIV-positive patient are always serious: the cause must be investigated, and the patient started on anti-convulsant treatment.

Beware of calling a hemiplegia a stroke, and not investigating the patient further. Classical stroke is of sudden onset, and occurs generally in older patients with diabetes or hypertension. Even if the patient has some of these risk factors, HIV-positive patients need investigating for OIs, and must be referred.

- Toxoplasmosis and cryptococcal meningitis occur in patients with CD4 counts <200, most often <100.
- CNS TB is more common at low CD4 counts but can occur with higher CD4s.

Algorithm 14.1 How does neurological disease present in primary care?

Symptoms

Meningism
Any of the following:
- Neck stiffness
- Photophobia
- Headache.

Global
- Reduced level of consciousness
- Strange behaviour
- Confusion
- Headache.

Focal
- Hemiplegia
- Cranial nerve abnormalities
- Cerebellar problems.

Seizures
- Focal
- Generalised.

Diseases

***Prolonged EFV use** can cause ataxia, encephalopathy and loss of weight; reversible on stopping EFV. Do not re-challenge. Switch to another drug.

'Big 3' neurological diseases:
- Tuberculosis
- Cryptococcal disease
- Toxoplasmosis.

Blood vessel involvement:
- Blocked: Diabetes, hypertension
- Inflamed: Tuberculosis, syphilis.

Other common infections:
- Malaria
- Syphilis
- Bact meningitis.

Other HIV related:
- HIV encephalopathy
- PML
- CMV encephalitis.

Metabolic conditions:
Hypoglycaemia, hypoxia, sepsis, low or high sodium, renal disease, liver disease

Drugs:
EFV, INH, cycloserine/terizidone

Algorithm 14.2 Common neurological conditions

'Big 3' CNS opportunistic infections: Look for all of these in all patients.

Cryptococcal meningitis

- Headache, meningitis symptoms, or altered level of consciousness;
- Focal neurology: ophthalmoplegia and visual disturbance are common.

Investigations:

- CD4 low (usually <100)
- CSF CrAg positive

Treatment:

- Amphotericin B and fluconazole;
- Measurement of opening pressure and therapeutic LPs are essential;
- Full protocol: see 'Cryptococcal meningitis', page 289.

Toxoplasmosis

- Reactivation of latent disease, causing space occupying lesions;
- Any abnormal neurology: focal symptoms, any type of altered mental state.

Investigations:

- Toxoplasmosis IgG positive (if available);
- This shows previous exposure; cannot confirm that there is reactivation.

Treatment:

- Treat if CD4 <200 and any neurological symptoms;
- Cotrimoxazole 400 mg/80 mg 1 tablet for each 8 kg body weight, given in 2 divided doses for 1 month;
- Half the dose for 3 months, then continue normal prophylaxis dose.

There should be a rapid response to treatment; there should be a clear clinical response within 14 days.

Tuberculosis

- Meningitis;
- Tuberculomas: space-occupying lesions – causing encephalitis symptoms and focal neurology.

Investigations:

- LP – Lymphocyte predominance, high protein, low glucose (however, LP may be normal);
- GeneXpert may be positive on centrifuged CSF;
- Look for evidence of TB elsewhere: TB LAM, sputum microscopy, CXR, abdominal ultrasound.

Treatment:

- Treat for CNS TB if any abnormal neurology and evidence of TB elsewhere, or CD4 <200.
- CNS TB and toxoplasmosis cannot be distinguished on clinical grounds; treat for both if CD4 <200.
- Treatment: TB treatment plus steroids: prednisone 1.5 mg/kg/day for 6–12 weeks, depending on clinical response.

Other common infectious causes

Malaria

- Rapid malaria test positive;
- Blood film positive if rapid test not available;
- Malaria may not be the only cause of an altered mental state in a patient with a low CD4 count.

Neurosyphilis

- Positive CSF VDRL;
- Rapid test positive on blood, with suggestive clinical presentation.

Note rapid test is not validated for CSF.

Bacterial meningitis

- Raised WCC on CSF with >80% neutrophils;
- Organisms may be seen on microscopy;
- If LP is done after antibiotics, organisms rarely seen and cell count may be reduced.

Remember trypanosomiasis in endemic areas: Do CSF microscopy for parasites.

Other HIV-related causes

HIV-associated dementia (HAD):

- Usually CD4 <200
- A slowly progressive dementia from chronic HIV infection of the brain, typically presenting as a triad of:
  1. Impaired short-term memory, concentration and mental slowing;
  2. Behavioural changes – apathy, withdrawal, irritability and depression;
  3. Motor changes of tremor, leg weakness, ataxia and Parkinson's-type symptoms.

It is a diagnosis of exclusion of other conditions noted in this algorithm. A positive **IHDS test** (Table 14.1) can support the diagnosis. Treatment is ART, though the condition is not always reversible.

Other rarer causes include CMV encephalopathy, progressive multifocal leuco encephalopathy (PML) and primary CNS lymphoma.

Non-infectious causes

- Cerebro-vascular accident (stroke):

  Usually presents as focal neurology but a large CVA can present with reduced level of consciousness. Common causes are hypertension and diabetes.
- Metabolic conditions – see Algorithm 14.1.

Table 14.1 International HIV dementia scale (IHDS)

Test	What to do	How to score
Memory-registration:	Give four words to recall (*dog, hat, bean, red*) – 1 second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.	
1. Motor speed	Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.	4 = 15 in 5 seconds 3 = 11–14 in 5 seconds 2 = 7–10 in 5 seconds 1 = 3–6 in 5 seconds 0 = 0–2 in 5 seconds
2. Psychomotor speed	Have the patient perform the following movements with the non-dominant hand as quickly as possible: • Clench hand in fist on flat surface. • Put hand flat on surface with palm down. • Put hand perpendicular to flat surface on the side of the fifth digit. • Demonstrate and have patient perform twice for practice.	4 = 4 sequences in 10 seconds 3 = 3 sequences in 10 seconds 2 = 2 sequences in 10 seconds 1 = 1 sequence in 10 seconds 0 = unable to perform
3. Memory-recall	Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (*dog*); piece of clothing (*hat*); vegetable (*bean*); color (*red*).	Give 1 point for each word spontaneously recalled. Give 0.5 points for each correct answer after prompting. Maximum – 4 points.
Total IHDS score: This is the sum of the scores on items 1–3. The maximum possible score is 12 points. A patient with a score of ≤10 should be evaluated further for possible dementia.		

Algorithm 14.3 Neurological presentations: Emergency management and assessment

Emergency management – attend to first:

If global signs or seizures:

- Immediate finger prick glucose: if hypoglycaemia (<4 or <80, depending on units) treat with 50 mls of 50% dextrose IV immediately, or the highest strength dextrose available, and continue to monitor point-of-care glucose (hourly until the patient is transferred).
- Immediate rapid malaria test (endemic areas; possibility of travel to endemic areas, particularly people who have returned to visit their home countries and are unaware they may no longer be immune).

Malaria may not be the only cause of an altered mental state in a patient with a low CD4 count.

- If there are seizures on admission:
  - Diazepam 10 mg IV or rectally to stop the seizure;
  - Place in recovery position to protect airway;
  - Face mask oxygen if available.

If bacterial meningitis is possible and LP cannot immediately be done, see guideline on page 290.

History

- If the patient is unconscious or unable to talk, a relative or friend accompanying the patient can give useful information.
- When did problem start? Suddenly or gradually? Has there been progressive deterioration?

Answer the 2 key questions:

- Is the patient taking ART? If so, is it likely the patient is failing?
- Is the patient taking TB treatment? If so, did the patient improve initially on treatment? Has adherence been good?

(For both of these questions, if your clinic provides ART or TB care for the patient, it will be a great help to the hospital if you can provide information about ART and TB treatment, CD4 counts and VL results, and if on TB treatment, whether the diagnosis was confirmed.)

Examination basics

- Is the patient alert, confused or is there an altered level of consciousness?
- Basic cranial nerve examination: Are eye movements abnormal? Do the pupils react to light? Can the patient see? Visual loss is common in cryptococcal meningitis, but many patients do not realise they should report this.
- Is the patient moving all limbs spontaneously? If the patient is conscious, ask the patient to raise both arms above their head and hold them there. Any weakness can be detected. Ask the patient to raise each leg separately, and hold it while you press the leg down.
- Can the patient sit unaided and walk unaided? If the patient can walk, is this normal, or is one leg stiff or is the patient about to fall to one side?

Investigations

In addition to the immediate emergency investigations, do as many of the following point-of-care tests as you can:

- CD4 count;
- TB LAM – indicated for all patients who are 'seriously ill', irrespective of CD4 count, which includes all patients with abnormal neurology;
- Serum CrAg;
- Rapid syphilis test;
- Haemoglobin;
- Urine dipstick;
- Pregnancy test for women of reproductive age if pregnancy cannot be excluded. (Eclampsia can cause seizures or reduced level of consciousness.)

Patient care while awaiting transfer

In primary care settings, patients with neurological signs qualify for referral for fuller investigation and inpatient management. However, for a variety of reasons, there may be a delay, often prolonged, in transferring a patient. The following are basic management principles in patient care to be attended to while awaiting transfer to the referral site:

- Ensure observations are done regularly, and that accompanying friends or relatives know to report if there is any deterioration.
- If the patient was hypoglycaemic, after emergency treatment with 50% dextrose, continue a dextrose infusion and check the point-of-care glucose hourly. If the patient is conscious, give sugar in water to drink.
- Write a comprehensive referral letter, including:
    - ART history;
    - Any CD4s of VLs that you may have on record;
    - Any tests you may have done (at times MSF has access to tests in clinics that the MoH does not have in the referral hospital); and
    - Medications given and the dose and time.
- The full treatment regimens for the various conditions are noted below to enable clinicians, in the event of a delay, to give first doses, possibly more, of appropriate medications and to do whatever there is capacity for in their primary care clinic.

Malaria

Start treatment: Give first dose of IV/IM artesunate if available: 2.4 mg/kg slowly IV over 2–3 minutes. This is followed by the same dose at 12 hours, then at 24 hours, then once daily. As soon as the patient can swallow, change to oral doses.

Cryptococcal meningitis

Induction

One week of amphotericin B (0.7–1 mg/kg/day in a once daily dose IV) + flucytosine (100 mg/kg/day orally in 4 divided doses) is the preferred option for treatment of cryptoccocal meningitis in PLHIV.

Alternative induction regimens are:

- Two weeks of fluconazole 1 200 mg/day + flucytosine (above dosage);
- Two weeks of amphotericin B (above dosage) + fluconazole 1 200 mg/day.

Consolidation

Fluconazole 800 mg daily for adults for 8 weeks following the induction phase.

Maintenance (or secondary prophylaxis)

Fluconazole (200 mg daily) is recommended following the consolidation phase.

Bacterial meningitis

If the patient has meningitis symptoms or signs, bacterial meningitis is possible. A short history (unwell for a few days) and fever support this diagnosis. If bacterial meningitis is possible and LP cannot be done immediately, give antibiotics according to your local guideline (generally ceftriaxone 2g IVI twice daily). Give the first dose immediately. Steroids are not recommended for bacterial meningitis.

Toxoplasmosis

Cotrimoxazole 480 mg tabs:

- Daily dose of one tablet per 8 kg body weight in 2 divided doses for 4 weeks;
- Then step down to 2 tablets twice daily for 12 weeks;
- Then maintenance dose of 2 tablets once daily until CD4 is >200;
- Add folate 5 mg daily until the start of the maintenance dose.

Suspected bacterial infections

Fever has many causes including TB, other opportunistic infections, malaria and bacterial infections (see **Chapter 23**). If there is an identified source of bacterial infection (eg; respiratory symptoms, ear infection, pyelonephritis symptoms, severe PID or suspicion of puerperal sepsis) give appropriate antibiotics according to your guidelines. Bacterial infections may also be bloodstream infections, without an identifiable source. If the patient is critically ill (hypotension, tachycardia) give antibiotics unless there is another more likely cause. The usual antibiotic used in these circumstances is ceftriaxone 1–2 g IM or IV.

Tuberculosis

TB is a common cause of neurological problems and the most common cause of death in HIV patients. If TB LAM is positive, start TB treatment. If TB LAM is negative or cannot be done, start TB treatment, unless there is a good alternative diagnosis (for example, serum CrAg is positive, rapid malaria test is positive or clinical presentation strongly suggests bacterial meningitis – both of the latter in patients who are otherwise well, with an acute history, without wasting, respiratory signs or symptoms, or other evidence suggesting TB (e.g. lymphadenopathy).

Seizures

If the patient had seizures at home or on admission, start anti-convulsive medication to prevent further seizures.

To stop a seizure: If the seizure continues for longer than 3 minutes, give diazepam 10 mg, diluted in 8 ml 5% glucose or 0.9% sodium chloride, slowly IV.

To prevent future seizures:

Ideally valproate; starting at 300 mg twice a day.

If valproate not available:

- Carbamazepine, starting at 200 mg daily orally; OR
- Phenobarbitone, 2 mg/kg/day taken at night (don't exceed 100 mg at start); OR
- Phenytoin, starting at 3–4 mg/kg once a day.

Continued patient care on return to primary care after discharge from hospital

- **Letter from the hospital.** Ensure you have a letter with the diagnosis and treatment. If not, contact the hospital for this information.
- **Is there treatment to be continued?** For example:
    - TB treatment;
    - High dose cotrimoxazole for toxoplasmosis;
    - Fluconazole for cryptococcal meningitis: Stock outs and interruptions to fluconazole prescription are a major cause of relapse. Fluconazole prophylaxis, 200 mg daily, should be taken for at least 12 months and must only be stopped after two consecutive CD4s >200.
- **Effective ART is critical**. Effective ART means using non-resistant ARVs taken regularly in the correct dose. Does the patient need to start ART, re-start or change regimens? If so, when? The hospital clinicians should have made a decision and either started it already or given guidelines as to when to do so. If not, **the primary care clinician needs to take responsibility for effective ART**. Consider the following in the decision-making process:
    - Patients referred to hospital for neurological disease almost always have stage 4 disease. A new stage 4 opportunistic infection in a patient who has been on ART for more than 6 months represents clinical failure (WHO definition) so qualifies for a switch to a new regimen.
    - In many countries, the majority of patients with advanced HIV have already been on ART at some stage (ART-non-naïve). They may, therefore, have failed their first line regimen and need to be switched to a second line regimen.

  When to commence effective ART (see IRIS section, **Chapter 5**):

    - **After cryptococcal meningitis or CNS TB**, it should be delayed till 4 weeks after treatment was started for these opportunistic infections, as neurological IRIS is often fatal.
    - **After toxoplasmosis**, it should be delayed just 2 weeks after starting cotrimoxazole (provided there is no TB treatment as well). Toxoplasmosis responds rapidly to treatment, so, after 10–14 days of treatment, brain lesions are considerably reduced in size and the risk of IRIS is low.

- **Contraception** with women of reproductive age needs to be discussed. Should she hope to become pregnant in the near future advise that, for a healthy mother and baby, she (and her partner) should be well, with opportunistic infections treated, and virologically suppressed on ART.

The approach to the patient with a positive serum CrAg

Cryptococcal meningitis remains a leading cause of death in advanced HIV disease. Many of these deaths can be prevented by early identification of the disease in its pre-clinical stage and the commencement of fluconazole prophylaxis to prevent progression to full-blown disease.

The cryptococcal agglutination (CrAg) is a simple point-of-care test, performed on finger-prick blood and can be done by trained lay healthcare workers in primary care clinics. If positive, *Cryptococcus* is present in the blood, and without treatment there is a high risk of crypococcal meningitis developing within the next few weeks.

Routine screening using the CrAg is recommended for all patients with a CD4 <200 (in some settings it is <100) and should form part of the routine management of patients presenting with advanced disease. (For management of results, see full detail in **Chapter 11**, especially pages 226, 228.)

Peripheral neuropathy (PN)

Peripheral neuropathy (PN) is a condition that frequently affects HIV-positive individuals, occurring in one-third of patients with CD4 <200 cells/μl. There are many different causes, but in the context of our primary care HIV clinics there are only a few common ones.

Clinical presentation

- Decreased sensation in a glove and/or stocking distribution (hands and/or feet), although symptoms related to the lower legs and feet are most common (especially the soles).
- Patients complain of different symptoms: pins and needles, a burning sensation, cold legs and feet, leg cramps.
- If prolonged, this may progress to motor signs with significant disability, some of which may be irreversible. It is important, therefore, to look for motor signs at presentation.

Causes of PN

Common:

- HIV infection itself;
- TB drugs (INH, terizidone/cycloserine, linezolid).

Less common:

- Alcohol excess;
- Other drug-related causes (vincristine for KS, patients still on d4T or DDI); AZT can also be a cause, but it is not commonly seen;
- Diabetes.

Key points on some of these conditions

HIV infection itself

HIV is what is called a neurotropic virus as it readily invades neural tissue, be it peripheral nerves and/or the brain. It is not surprising, therefore, that peripheral nerves are commonly involved; the more advanced the disease the more it is likely to be present. This usually starts with sensory changes and, with time, progresses to more severe symptoms, including progressive loss of motor function.

Treatment

- The primary treatment is, of course, to start ART.
- In addition, if pain is a significant feature, follow the guidelines on pain management below (page 295).
- Please note that pyridoxine is not a treatment for peripheral neuropathy. It is merely the replacement of vitamin B6, where a lack of it is thought to be the cause of the neuropathy.

Drug-related neuropathies

- Usually present after the first month of treatment.
- With INH and cycloserine/terizidone (Cs/Trd) the usual pathology is depletion of vitamin B6 caused by the drugs, so ensure that the recommended preventative doses are being given (25 mg daily for INH and 150 mg daily for Cs/Trd).

Treatment is to first address the potential deficiency by treating for 1 month:

- INH-induced B12 deficiency is 100 mg daily;
- Trd/Cs deficiency is 150 mg daily.

If there is no change or deterioration at 1 month and the symptoms are significant, the drug may need to be changed. Seek more experienced help, as the choice of drugs for DR TB needs careful consideration.

Alcohol excess

Here, the cause is most often due to vitamin deficiencies (B1 – thiamine, B6 – pyridoxine and B12) related to the generally poor nutrition of the alcohol abuser.

Treatment, naturally, is to try and address the alcohol issues and to supplement with B vitamins.

Diabetes

Peripheral nerves are damaged via microvascular damage to the nerves, due to poor glucose control. There is often, therefore, other target organ damage (eyes, heart, kidneys, brain). A feature of diabetic PN is frequently a significant stabbing pain in the legs.

Treatment is, again, to treat the underlying condition, but, at the same time, offer symptomatic relief with amitriptyline as dosed below (page 295).

An approach to the patient presenting with PN symptoms

If you have ever sat for a while in a position that resulted in an uncomfortable tingling or burning pain in an arm or leg, you will know that this is not a pleasant sensation. In addition, impairment will progressively worsen and may be permanent if not treated promptly. Aim therefore to treat it aggressively by removing or treating the underlying cause and providing symptom relief.

Ask the patient:

- What is the distribution of the neuropathy?
    - Symmetrical and merely sensory: glove and/or stocking distribution point to the common causes above.
    - Unilateral and/or with motor symptoms could be related to the brain or spinal cord, so need further investigation.
- Look for the different causes noted above: drugs, diabetes and alcohol excess.

Examination

There is not a lot to look for but it is important to do a quick check for:

- Symmetry – is the sensory loss the same on both sides?
- Is there any weakness, and, if so, is it the same on both sides?

Tests

The one quick test that can be done is a finger-prick glucose to check for diabetes.

If the presenting symptoms are atypical (not symmetrical, not typically glove and stocking distribution, have more motor signs and symptoms or are particularly severe), refer or seek more experienced help. The cause may not be a simple peripheral neuropathy.

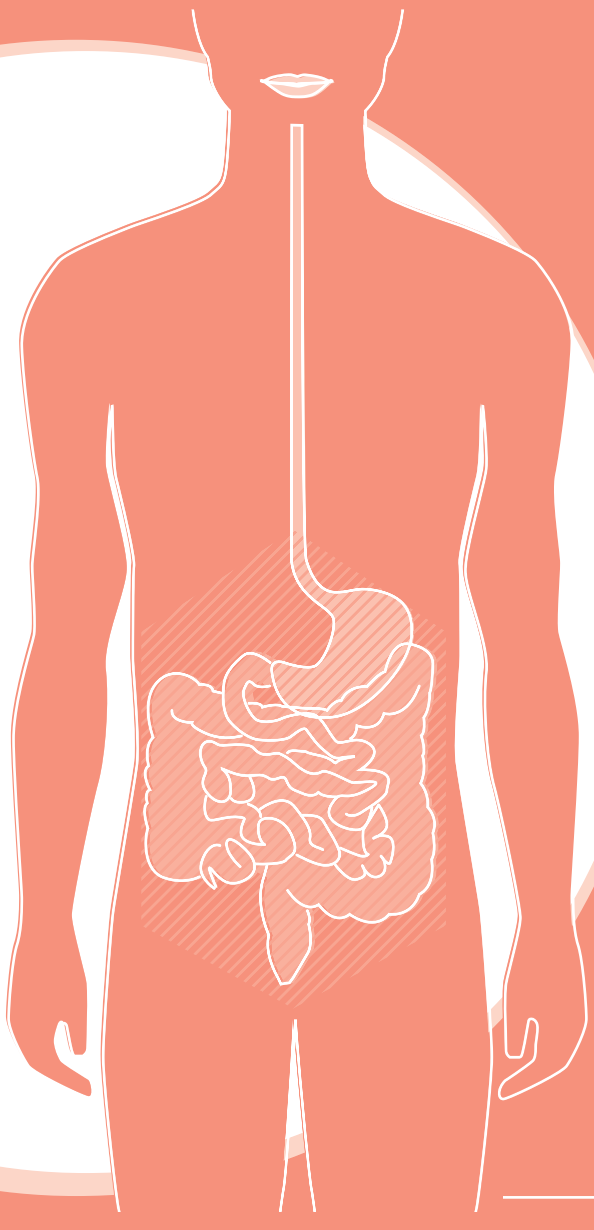
Treatment

- Treat underlying cause(s) as per diagnosis, as outlined above.
- Provide symptomatic pain relief, treating the PN according to its severity:
  - Start by prescribing basic analgesics; paracetamol 500–1 000 mg 4 x daily as required.
  - If no improvement, upscale to paracetamol + codeine 1–2 tablets 3–4 x daily as required (only if PN is severe). Caution the patient about constipation and provide a laxative (lactulose works well) as this is highly likely in higher doses.
  - In HIV medicine, especially those with more advanced disease, it is better to avoid ibuprofen and other NSAIDs, as there is often some form of renal impairment, which will be worsened by the NSAID.
  - Amitriptyline may be helpful as an adjuvant therapy (i.e. used together with analgesics.) Remember that amitriptyline is very sedative, so start low at 12.5 mg nocte and build up slowly (every 1–2 weeks) to a maximum of 50 mg if necessary.
  - If no improvement, review the diagnosis.
  - Standard anti-convulsants are often helpful, but unfortunately all three of the commonly used ones (carbamazepine, phenytoin and phenobarbitone) interact significantly with ART, so are contra-indicated (see **Chapter 7**). The newer anti-convulsants, gabapentin and lamotrigine, though unlikely to be available, are other options that have been shown to provide pain relief in HIV-related sensory neuropathy conditions.

Summary

- Neurological presentations are common in primary care settings, especially in patients with lower CD4 counts.
- Apart from peripheral neuropathy, all neurological presentations have a high mortality and are emergencies requiring urgent action and referral for further investigations and management.
- Always be on the alert for the ‘big 3’ neurological conditions, TB meningitis, cryptococcal meningitis and toxoplasmosis.
- Ensure good continuity of care after transfer back to primary care after hospital admission.

Gastro-intestinal conditions



Oral pathology

Diarrhoea and common intestinal parasites

Anal lesions

A variety of different conditions are found in the HIV-positive patient throughout the full length of the gastro-intestinal tract.

- While rarely life-threatening, conditions in the **oral cavity** cause significant discomfort that can often be significantly eased by correct diagnosis and management.
- **Diarrhoea** is a common and under-recognised cause of morbidity and mortality in the patient presenting with a low CD4 count.
- **Anal lesions** are a common cause of significant discomfort, and as with lesions in the mouth, can be easily managed, with a fairly simple approach and low-cost medication.

Oral pathology

Part of the routine examination of a patient presenting to an HIV clinic should always include a brief look inside the mouth. Quite often, patients will not report the presence of oral lesions, some of which could place a person in stage 3 or 4 disease category or perhaps point to more severe disease, such as visceral Kaposi's sarcoma. In this section we will cover the following conditions:

- Candidiasis (thrush): oral and oesophageal
- Angular stomatitis
- Oral ulcers
- Kaposi's sarcoma
- Necrotising gingivitis.

Oral candidiasis (oral thrush)

Oral candidiasis is caused by a yeast called candida albicans. It occurs fairly commonly in HIV-negative people, such as in infants, the elderly and diabetics. In HIV-positive people it is a pointer towards more advanced immunodeficiency, with persisting oral thrush qualifying as stage 3 disease.

Thrush on palate

Thrush on tongue

Clinical presentation

It is commonly seen as white patches (which can be removed with a tongue depressor) surrounded by a reddish border. These involve mostly the oral mucosa, the pharynx and inside the lips.

Patients often complain of having no taste.

Swallowing is frequently painful, but just in the back of the throat, not lower down behind the sternum. See oesophageal thrush below.

Management

Nystatin oral suspension 1 ml swished around the mouth for a few minutes and then swallowed; 4 times a day for 5 days usually cures it. If the thrush persists or recurs, fluconazole 200 mg once daily for one week is very effective.

Oesophageal candidiasis (thrush)

Since the oesophagus cannot be visualised on physical examination, a diagnosis of oesophageal thrush is more difficult.

Clinical points

- As oral thrush can cause pain in the back of the throat on swallowing, the important question to ask when diagnosing oesophageal thrush is if the patient has pain behind the sternum on swallowing.
- It is more commonly associated with lower CD4 counts, especially if oral thrush is present. Oesophageal thrush qualifies as stage 4 disease.
- Because of the extreme discomfort experienced, it is often associated with patients not eating and consequent weight loss. If the patient is not able to eat or take oral fluids, refer to hospital for IV fluids and further investigation (see point below).
- Other possible causes of painful and difficult swallowing include:
    - Gastro-oesophageal reflux disease (GORD);
    - An oesophageal ulcer, which can be either idiopathic (i.e. aphthous ulcer) or related to HSV;
    - Ulceration of the oesophagus with cytomegalovirus (CMV) (consider this if CD4 <50);
    - Kaposi's sarcoma (KS) (see later in this chapter).

Oesophageal candida often co-exists with other stage 4 diseases, particularly disseminated TB. Do not attribute loss of weight, lethargy or any danger signs to oesophageal candida alone. Investigate fully and have a low threshold for empiric TB treatment.

Management

- Prescribe fluconazole 200 mg daily for 10–14 days and check the response to treatment after 7 days. If there is a good response, continue the fluconazole for 10 days to 2 weeks.
- If fluconazole is not effective after one week, consider the other causes listed above:
  - If not responding to fluconazole treat for HSV with acyclovir 400 mg, 3 x daily for 10 days.
  - The majority of those with CMV-related oesophagitis will develop CMV retinopathy as well. Even though vision may deteriorate late in the disease, still ask about it and assess the fundi if possible. The treatment is ganciclovir or valganciclovir, so **refer to hospital**.
- Ensure effective ART is being taken after screening for TB.

Refer to hospital

If ART-naïve, start ART immediately if there is no evidence supporting TB. If on ART >6 months, new stage 4 diseases should not occur so there may be treatment failure. Request an urgent viral load; if failing first line ART, switch to second line treatment.

Angular stomatitis

Angular stomatitis presents as inflamed, painful cracks at the corners of the mouth and is usually caused by candida; can also be caused by iron deficiency, and occasionally bacteria.


Angular stomatitis

Management

It usually responds well to 10 days of a simple antifungal cream, such as clotrimazole or even nystatin drops rubbed into the cracks.

Children: Fluconazole loading dose – 6 mg/kg/dose once on day 1; maintenance – 3–6 mg/kg/dose once daily for 4 to 21 days (maximum: 400 mg/day).

Oral ulcers

Oral ulcers may be due to:

Aphthous ulcers (canker sores)

One or more ulcers on the mucosa of the mouth, the inner lips, and sometimes the tongue.

- Cause unknown, presumed to be viral;
- Often persistent and very painful, especially in patients with lower CD4 counts;

Aphthous ulcers on palate

Treatment is effective ART. If already on ART, ensure that the patient is virally suppressed.

Herpes simplex virus (HSV)

- May present as shallow ulcers and/or blisters that are painful, extensive and/or recurrent;
- Often on lips as well.

Herpes simplex in mouth

Treatment:

- Avoid acidic foods;
- Pain relief: paracetamol with codeine or tramadol;
- Give acyclovir 400 mg three times daily for 5–10 days.

Children: The dose of acyclovir (15 mg/kg/dose 5 x per day for 7–10 days; max 200 mg per dose) may decrease the duration of illness if started within 72 hours at the onset of symptoms. Topical acyclovir is ineffective.

Syphilis

- The ulcer of a primary syphilis chancre looks very similar, but the key difference is that they are almost always painless. Do rapid syphilis test. Treatment is benzathine penicillin 2.4 MU IMI weekly for 3 weeks. This is covered in more detail in **Chapter 19**, Sexual and reproductive health.

Kaposi's sarcoma (KS)

The possibility of a Kaposi's sarcoma lesion on the palate is a key reason why it is essential to look in the mouth as part of a routine examination of an HIV-positive patient.

This topic is covered in more detail in **Chapter 20,** Skin diseases in HIV.

KS on palate

KS on palate

Clinical presentation

- Purplish fleshy swelling on the roof of the mouth or gums;
- May often bleed.

If KS is present on the palate or oral cavity, it may indicate pulmonary or gastro-intestinal tract (GIT) involvement as well. Investigate with a chest x-ray, especially if any respiratory symptoms and check the Hb as GIT KS can result in anaemia from hidden (occult) GIT bleeding.

Diagnosis

A diagnosis is usually made just on history, appearance of the lesion and the distribution. (See **Chapter 20**.)

Management

- This is a stage 4 disease: the patient needs to be on effective ART. If ART-naïve, start ART immediately. If on ART >6 months, new stage 4 diseases should not occur so there may be treatment failure. Request an urgent viral load; if failing first line ART, switch to second line treatment.
- In addition, refer the patient urgently for chemotherapy.

Necrotising gingivitis

Clinical presentation

- This is an inflammation of the gingiva (gums).
- It may lead to tooth loss, severe pain and foul-smelling breath.


Necrotising gingivitis

Management

- Oral hygiene;
- Antiseptic mouthwashes;
- Antibiotics: metronidazole 400 mg tds for 7 days;
- Pain management – paracetamol or paracetamol/codeine.
- As this is a stage 3 condition, ensure the patient is on effective ART. See first bullet under 'Management' in section on Kaposi's sarcoma.

Diarrhoea and common intestinal parasites

Diarrhoea in the HIV-positive patient (additional notes for children)

Diarrhoea is common in HIV-positive patients, particularly in the context of advanced HIV. Chronic diarrhoea in advanced HIV is often under-recognised, poorly managed, and the serious complications under-appreciated, resulting in significant morbidity and mortality.

Most diarrhoea does not need antibiotics. However, due to limited availability of stool microscopy and difficulty identifying the cause of the diarrhoea on clinical grounds, there is an over-reliance on antibiotics as treatment for diarrhoea. In addition, renal failure and severe electrolyte abnormalities are common and cause mortality if undiagnosed and untreated.

The aim of this part of the chapter is to aid identification of the cause of diarrhoea in HIV patients, based on the clinical clues available and to provide a rational basis for empiric antibiotic treatment when it is necessary. In addition, it guides the clinician in the early identification of danger signs requiring referral.

Definition

Diarrhoea is three or more stools a day, with decreased consistency (taking the shape of the container). There may be associated symptoms – particularly nausea, vomiting, fever and abdominal pain.

Definition of diarrhoea for children: An increase in stool frequency to twice the usual number per day in infants or three or more loose or watery stools per day in older children.

Diarrhoea can be categorised as inflammatory or non-inflammatory.

- Inflammatory diarrhoea occurs when pathogens invade the wall of the large bowel, causing an immune response and mucosal bleeding.
- Non-inflammatory diarrhoea is a consequence of pathogens that superficially invade the epithelial layer of the small bowel, and cause increased secretion of water and electrolytes into the lumen.

Complications:

- Dehydration often progressing to an acute kidney insult;
- Electrolyte abnormalities;
- Malnutrition;
- Systemic sepsis resulting from bacterial causes.

All cause significant morbidity and mortality.

Causes of diarrhoea

Diarrhoea has many causes across the full spectrum of infecting organisms: viruses, bacteria, fungi, parasites and mycobacteria. In addition, remember that drugs, especially lopinavir/ritonavir can cause diarrhoea. There are several factors that point the clinician in the direction of a possible cause: whether it is acute or chronic, the CD4 count and whether it is inflammatory or non-inflammatory. These factors are all included below in the approach to the HIV-positive patient presenting with diarrhoea.

An approach to the patient presenting with diarrhoea

Refer to hospital

First, look for any danger signs or signs of severe diarrhoea. If present, refer to hospital.

If referral is not possible treat as below with daily visits for IV and oral rehydration.

Standard danger signs that may occur with severe diarrhoea

- Moderate or severe dehydration; decreased skin elasticity, sunken eyes;
- HR >120;
- Systolic BP <90;
- Fever >39 (with diarrhoea, a fever >38 is considered a danger sign);
- Respiratory rate >30 (with severe diarrhoea this could be due to acidosis in severe renal failure);
- Being unable to walk unaided; and
- Confusion, seizures, generalised weakness (sepsis, severe renal impairment, electrolyte abnormalities).

Additional danger signs in severe diarrhoea:

- Bloody diarrhoea;
- Abdominal guarding; this may indicate bowel perforation, and peritonitis. This is a medical and surgical emergency. *Salmonella* is a common cause.
- New or worsening renal impairment (high creatinine).

Danger signs that may occur in children with severe diarrhoea

- A heart rate (HR) and/or respiratory rate (RR) that is outside of the normal range for age (see Appendix 10.1: Normal values for children);
- Signs of moderate or severe dehydration, including decreased skin turgor, sunken eyes, sunken anterior fontanelle, decreased energy level or drowsiness, lethargy, irritability, no tears when crying, dry or cold skin, confusion, seizures, decreased urine output. The assessment and management of dehydration in children differs somewhat from adults. See Appendix 15.1 at the end of this chapter for details;
- Bloody diarrhoea;
- Abdominal pain and/or guarding.

Where are you working?

- Before you even start with taking a history, it is important to know what organisms cause diarrhoea where you work. What are common regional or local pathogens? For example, both *giardia lamblia* and *strongyloides stercoralis* are common in tropical and sub-tropical regions.
- If your laboratory can perform stool microscopy, collecting data on the pathogens that are identified will help decide on appropriate empiric treatment.
- Be alert to cholera outbreaks if your area is at risk.

Take a history

There are **3 key questions** that help define the likely cause of diarrhoea, and therefore guide treatment.

1. **Is the CD4 count <200 or >200?**
    - For patients with advanced HIV (CD4 <200), chronic parasite diarrhoea is common (most often *cryptosporidium* or *Isospora belli*), and causes considerable morbidity and mortality. These particular types of diarrhoea are WHO stage 4 conditions and are usually associated with low CD4 counts. Occasionally, however, they can occur at CD4 counts >200.
    - A low CD4 is often due to treatment failure, so a full ART history is important, along with an assessment for treatment failure.
    - Dont forget that **lopinavir/ritonavir is a common cause of diarrhoea**, often including nausea and vomiting.
2. **What is the timeline?**
    - Acute diarrhoea (<14 days) or chronic diarrhoea (>14 days)?
3. **Is the diarrhoea non-inflammatory or inflammatory diarrhoea?**
    - **Non-inflammatory diarrhoea** (small bowel): Large volume of watery stool, without blood or mucous. Unless there is severe diarrhoea of rapid onset, bacteria are rarely the cause. Antibiotics are therefore rarely needed.
    - **Inflammatory diarrhoea** (large bowel): Abdominal cramps, fever, blood and mucous in the stool are common.

Investigations for patients with severe or chronic diarrhoea. Do whatever is possible in your setting (refer if acute severe diarrhoea or chronic diarrhoea and you are unable to request creatinine and electrolytes at your clinic, or if results are regularly delayed):

- Creatinine, sodium and potassium;
- Haemoglobin if there is bloody diarrhoea;
- White cell count if available and infective diarrhoea is suspected to be bacterial in origin;
- CD4 count, viral load;

- Stool microscopy: many low-resource settings do not have access to this – if available, it should be requested for all patients with severe or chronic diarrhoea and hospitalised patients.

If ongoing and empiric treatment has not resolved the diarrhoea, refer for further investigations.

General management:

- Rehydration with fluid and electrolytes is central to preventing mortality:
    - Oral rehydration solution if mild or moderate dehydration and patient is able to drink;
    - If referral is not possible or delayed and electrolyte testing is unavailable, rehydrate intravenously using safe IV fluids, such as sodium chloride or Ringer's lactate or other electrolyte solution you have available.
- Use anti-motility agents (e.g. loperamide) only if bacterial diarrhoea can be confidently excluded. For example, it is appropriate to use for chronic parasite diarrhoea in patients with advanced HIV.
- Nutrition is also important. Ensure the patient continues to eat and give food supplements if available.
- The use of antibiotics is detailed below in the systematic approach to diagnosing and managing diarrhoea. A few general principles:
    - They are not to be used unless the history and examination point strongly in the direction of a specific cause that requires an antibiotic.
    - When they are needed, base your choice of antibiotics on the likely bacteria. Ensure the correct dose and duration of treatment.
    - As a rule, acute non-inflammatory diarrhoeas need antibiotics only if there are danger signs or signs of severe diarrhoea, whereas acute inflammatory diarrhoeas are caused mainly by bacteria and need prompt antibiotic treatment, or are caused by parasites and need specific treatment.

The mainstay of **therapy for children** with diarrhoea is supportive care and keeping up with the fluid loss which occurs from frequent stooling. Loperamide or other agents are rarely used to stop the diarrhoea in children.

The tables below use the information gathered in the above history and examination to categorise diarrhoea into acute or chronic and inflammatory or non-inflammatory. Additional information directs the clinician towards a likely causative organism and the recommended treatment. A box under each table provides extra information about key conditions.

Acute diarrhoea

- Acute diarrhoea is best considered as either non-inflammatory (small bowel) or inflammatory (large bowel).
- Table 15.1 (acute non-inflammatory diarrhoea) and Table 15.2 (acute inflammatory diarrhoea) outline the causes and specific management.
- A quick guide to antibiotic use is that acute non-inflammatory diarrhoea only requires antibiotics for acute severe diarrhoea or if danger signs are present, whereas acute inflammatory diarrhoea is caused mainly by bacteria or parasites, and requires prompt, specific antibiotic treatment.

Table 15.1 Acute non-inflammatory diarrhoea

Diagnostic pointers	Probable organism	Treatment
Affected household contacts	Viruses • Rotavirus • Enteroviruses • Norovirus Toxin secreting bacteria • some *E. coli*, food poisoning bacteria	Viruses are the most common cause. Diarrhoea due to viruses and toxigenic bacteria cannot be distinguished clinically; however both are usually self-limiting and need oral rehydration and nutrition only. **Adults:** Antibiotics are only necessary if danger signs present: ciprofloxacin 500 mg bd for 5 days. **Children**: Treatment of toxin secreting organisms for children (such as *E.coli*) – antibiotic use is controversial. Some reports have shown an increased risk of haemolytic uremic syndrome. However, children with systemic symptoms require inpatient management with IV antibiotics.
Cramps and/or nausea	*Giardia lamblia*	**Adults:** Metronidazole 2g daily for 3 days, or tinidazole 2g single dose. **Children**: Metronidazole (not approved by FDA – however, very effective) 15 mg/kg/24h divided tid PO for 5–10 days. Also can use tinidazole for children ≥3 years old: 50 mg/kg, max 2 g; single oral dose.
Severe diarrhoea with rice water stools; household or community contact	Consider cholera	Infection control and outbreak response measures need initiating immediately: see **MSF cholera guidelines** in additional resources in https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Table 15.2 Acute inflammatory diarrhoea[1,2] (small volume frequent watery stools)

Diagnostic pointers	Probable organism	Treatment
Blood and/or mucous and/or cramps	*Shigella*[3] (more common) *Salmonella* *Campylobacter* Some *E. coli*	**Adults:** Ciprofloxacin 500 mg 2x a day for five days. In SE Asia particularly, *Salmonella* is increasingly resistant to ciprofloxacin – usually remains sensitive to ceftriaxone (1g daily x 3–5 days) **Children:** Similar to adults – 500 mg twice a day for 5–7 days.
Bloody diarrhoea with or without cramps	*Amoebiasis*	**Adults:** Metronidazole 400 mg 3 x day for 5 days. **Children:** Metronidazole 35–50 mg/kg/day in divided doses every 8 hours for 7 to 10 days. Maximum dose: 750 mg/dose.
Recent antibiotics	*Clostridium difficile*[4]	**Adults:** Metronidazole 400 mg 3 x day for 10 days (must be oral). **Children:** Metronidazole 30 mg/kg/day divided every 6 hours for ≥10 days (maximum: 2 000 mg/day)

1. Managing acute inflammatory diarrhoea in general: If no danger signs, treat with ciprofloxacin first and if no response, add metronidazole to cover amoebiasis. If danger signs, treat empirically with both.
2. Complications of inflammatory diarrhoea are more common in HIV patients. These include septicaemia and infections at distant sites (such as bone), bowel perforation and toxic megacolon.
3. *Shigella* is highly infectious, ingestion of 10 organisms is enough to cause severe diarrhoea!
4. *Clostridium difficile* diarrhoea may occur during a course of antibiotics, or 5–10 days afterwards; however symptoms may begin up to 10 weeks after antibiotics.

Chronic diarrhoea

Chronic diarrhoea is common, particularly in advanced HIV. **A history of chronic diarrhoea should be an immediate alert to WHO stage 4 parasite infections, and possible treatment failure in patients on first line ART.**

- Table 15.3 lists the causes of chronic diarrhoea and specific management. Chronic diarrhoea can also result from other systemic opportunistic infections, or non-infectious causes.
- Dont forget that lopinavir/ritonavir is a common cause of chronic diarrhoea!

Table 15.3 Chronic non-inflammatory diarrhoea (large volume, watery stools)

Diagnostic pointers	Probable organism	Treatment
No blood, mucous or cramps	Coccidian parasites: • *Isospora* • *Cryptosporidium* • *Microspora* • *Cyclosporidium*	• Significant weight loss, renal impairment and severe electrolyte deficiencies are common. • As special stool microscopy stains are rarely available, start empiric treatment with cotrimoxazole for *Isospora belli* (see below). • For the other causes, there is no specific treatment available apart from ART. (In some regions *microsporidium* responds to albendazole: 400 mg bd for 2–4 weeks) • All of these infections generally occur in advanced HIV. Effective ART is, therefore, central to management. Start ART in patients who are ART-naïve and switch to second line in patients failing first line ART. • Loperamide can safely be given to adults. (Note: For children do not give loperamide.)
	Giardia lamblia	Metronidazole 2 g daily for 3 days, or tinidazole 2 g single dose. **Children**: Metronidazole (not approved by FDA; however, very effective) 15 mg/kg/24 h divided tid PO for 5–10 days. Also can use tinidazole for children ≥3 years old older: 50 mg/kg, max 2 g; single oral dose.
Endemic regions: sub-Saharan Africa, SE Asia; Larvae disseminate widely, autoinfection occurs, so increasing the parasite burden; May be asymptomatic or cause epigastric pain, small bowel obstruction, chronic diarrhoea, recurrent urticaria and larva currens (rapidly elongating skin eruption).	*Strongyloides stercoralis*	• If untreated it can lead to hyperinfection syndrome in patients with advanced HIV – causing meningitis and multiorgan failure. • Treatment of choice is ivermectin, 200 μg/kg orally as a single dose for 1–2 days. If ivermectin is unavailable, treat with albendazole 400 mg bd x 7 days. Ivermectin has a higher rate of parasite eradication. • If suspected, or found incidentally – always treat.

Chronic diarrhoea in children

Clinical presentation

Chronic diarrhoea is usually defined as diarrhoea that lasts longer than 4 weeks. Many causes exist and include:

- Infections (including parasitic and protozoal infections);
- Inflammatory bowel disease;
- Malabsorption syndromes; and
- Food allergies and food intolerances (such as lactose intolerance).

Management

Manage dehydration as described above.

Obtain a stool sample if possible and treat according to any pathogen found. If no pathogen is identified, give empiric treatment as follows:

- CTX 40 + 8 mg/kg per dose three times daily + metronidazole 10 mg/kg/dose three times daily for 5–7 days.

Always assess children with acute or chronic diarrhoea for other infections. Illnesses such as urinary tract infections (UTIs), ear and throat infections or pneumonia can all be associated with diarrhoea.

Isospora belli

Features:

- CD4 almost always <200;
- Entry to body is via ingestion in food/water;
- Associated vomiting is common;
- There is usually significant loss of weight;
- Causes chronic, severe non-inflammatory diarrhoea with dehydration, electrolyte loss; and
- There may also be chronic renal impairment and electrolyte deficit caused by pre-renal failure and electrolyte loss. These can be fatal if not diagnosed and treated.

Treatment:

- Cotrimoxazole 4 x 480 mg tablets bd for 2 weeks;
- Then 2 tablets bd for 3 weeks;
- Then normal prophylaxis dose 2 tablets daily;
- If hypersensitivity to cotrimoxazole, desensitisation is usually possible (see Appendix 8.2).
- If desensitisation is not safe (life-threatening hypersensitivity) treat with ciprofloxacin 500 mg bd for two weeks.

Recurrent Isospora belli

Despite ART with CD4 well over 200 (even up to 1 000) and a suppressed VL, some patients have recurrent episodes of isospora. The reason is unknown, possibly defective gut immunity that is not restored by ART.

These patients need to be managed in hospital with high-dose cotrimoxazole (intravenous if available for 2 weeks), with or without ciprofloxacin. Thereafter, they require higher doses of maintenance cotrimoxazole at 2 x 480 mg tablets twice daily long term, rather than 2 tabs daily.

For children: TMP-SMX, 5 mg/kg per dose of the trimethoprim component, given twice daily, for 10 days. If symptoms worsen or persist, the TMP-SMX dose may be increased to 5 mg/kg/dose of the trimethoprim component, 3–4 x daily, for 10 days or the duration of treatment lengthened (up to 3–4 weeks).

Table 15.4 Other causes of diarrhoea in HIV-positive patients

- Affects either small or large bowel, causing watery or bloody diarrhoea;
- Associated GIT symptoms and signs are common, for example, abdominal pain, rectal bleeding.

Cause	Diagnosis and management tips
Mycobacteria: • *M tuberculosis* and Mycobacterium Avium Complex (MAC). These cannot be distinguished on clinical grounds.	• Affects small or large bowel; terminal ileum is often affected. • Abdominal pain, distention or rectal bleeding may occur. • Clinical findings may include hepatomegaly, abdominal tenderness and ascites. Abdominal ultrasound may show lymph nodes and splenic micro-abscesses. • May be evidence of disseminated TB.
Viral: • CMV (CD4 <100)	• Causes ulceration of both small and large bowel. • Diagnosis is usually made when a patient with diarrhoea or rectal bleeding is found to have CMV retinopathy on fundoscopy, or in centres able to perform sigmoidoscopy and biopsy. • **Treatment**: valganciclovir.
Kaposi's sarcoma	• Affects small or large bowel. • Around 80% of patients with Kaposi's sarcoma have gastro-intestinal system involvement; undiagnosed KS is commonly seen at post-mortem. • Often there are no specific symptoms of GIT involvement. Anaemia is common and in a patient with KS GIT involvement is likely. • **Treatment**: Urgent chemotherapy and effective ART.
Lopinavir/ritonavir	• GIT symptoms are common, particularly watery diarrhoea and abdominal pain. • If other causes are excluded, loperamide can be given. • Switch to atazanavir/ritonavir if available; if also on TB treatment, atazanavir/ritonavir must be taken with rifabutin and not rifampicin (see **Chapter 7**).

Diarrhoea in HIV: Key points

- It is common and associated with significant morbidity and mortality due to its often unrecognised complications.
- Always check first for danger signs, and, if present, refer for inpatient management.
- Avoid routine use of broad-spectrum antibiotics. Rather, use a systematic approach incorporating the CD4 count, the duration, and the type of diarrhoea, in order to make an informed decision regarding empiric diagnosis and treatment.

Common intestinal parasites (worms)

These are common in resource limited settings, and prevalence is higher in HIV patients.

- Hookworm and Ascaris are the most common. They do not cause diarrhoea.
- *Strongyloides* is discussed in the chronic diarrhoea section above.

Hookworm

Hookworm is a common cause of anaemia: treat all patients with anaemia with albendazole 400 mg as a single dose.

Ascaris

- Often asymptomatic and diagnosed when worms are excreted or vomited.
- Can cause serious complications: can cause bowel obstruction, obstructive jaundice if there is invasion of bile ducts, and pulmonary symptoms when larvae invade lungs.
- Treatment: albendazole 400 mg single dose.

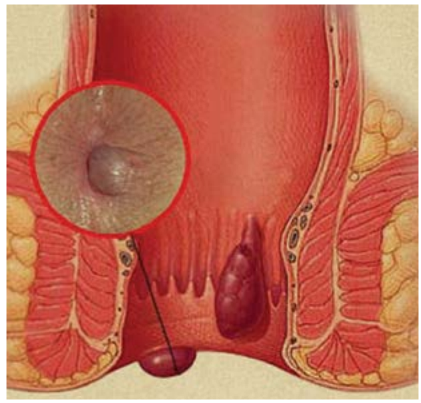
Anal lesions

Lesions of the anus are a common cause of discomfort and pain in HIV-positive patients and are not restricted just to men who have sex with men (MSM). Patients will often complain of pain, a lump, a discharge or just say they have piles.

This section gives an overview of the different anal lesions we are likely to encounter along, with brief details regarding diagnosis and management. Not all of them are specifically HIV-related but all can cause significant discomfort. They are divided into infective and non-infective causes.

Non-infective causes – six main lesions

1. Peri-anal haematoma



History: Patient usually complains of piles or a painful lump, worsened when passing stools. Patient is quite often constipated.

Examination: Shows a painful purplish bump clearly visible in the anal skin, due to the rupture of a blood vessel under the surface of the anal skin. It is usually a bit painful due to the stretching of the skin.

Treatment: Leave it to absorb on its own and ideally soften the stool. Local anaesthetic such as Emla gel applied regularly will help ease the pain from stretched skin.Commercial preparations for piles (Anusol®, Procotosedyl®, Scheriproct®) make no difference at all.

2. Anal fissure

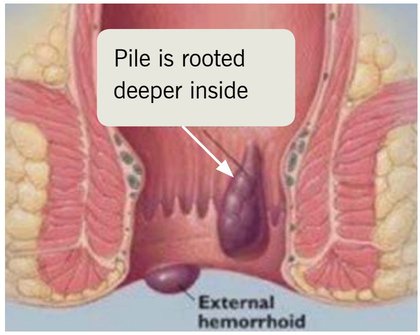
History: Patient often just complains of piles, a lump and anal pain, worsened when passing a stool.

Examination: Looks very similar to a peri-anal haematoma but on closer examination, using both gloved hands and good light (you may need some help), there is a clear split in the deeper anal lining, that may bleed while examining.

Fissure visible only with deeper examination

Treatment: Get the pharmacist to grind up 8 x 10 mg TNT pills (Isordil or similar angina meds) in 50 g of soft paraffin. Patient applies this 2 X day for 10 days. This is usually highly effective, but if no success, surgery is needed. Commercial preparations for piles make no difference at all.

3. Haemmorhoids (piles)



History: They are not painful and present only with fresh red bleeding noted in the toilet with passing a stool or on the toilet paper.

Examination: Piles are deeper inside the anal canal so they are not visible from the outside and can be seen only with a proctoscope.

Treatment: Commercial preparations for piles can help a bit but the definitive treatment is surgery when the bleeding persists.

4. Thrombosed pile

History: Acute onset painful, swollen lump in the anus, often with bleeding.

Examination: Red, tender, fleshy swelling emerging from the anus (not connected to the outside skin).

Treatment: This is a surgical emergency and needs immediate **referral**.

Refer to hospital

5. Peri-anal abscess

This is like any other abscess, tender, hot and often looks as if there is pus inside.

Treament is incision and drainage.

6. Peri-anal fistula

History: Presents mostly with a painless anal discharge and itch.

Examination: On full opening of the anus the distal end of the fistula is often seen as a small site actively discharging pus.

Treatment: Chronic discharging peri-anal sinuses in HIV patients are very likely to be TB. Start TB treatment and ensure effective ART. Surgery has no role if cause is TB, and can cause severe complications.

Table 15.5 A guide to peri-anal lesions

		Haemmor-hoids	Peri-anal haematoma	Anal fissure	Peri-anal abscess	Thrombosed internal piles	Fistula-in-ano
History	**Pain**	No	Yes	Yes	Yes ++	Yes ++	No
History	**Bleeding**	Yes	Sometimes	Mostly yes	No	Sometimes	Mostly discharge, may be bloodstained
History	**Lump**	No	Yes	Yes	Yes	Yes	No
Exam	**Can see with direct vision**	No	Yes	Yes – deep exam	Yes	Yes	Yes
Exam	**Proctoscope needed**	Yes	No	No	No	No	No
Treatment		Surgical	Local anaesthetic	Tnt paste	Surgical	Surgical	Surgical

Infective causes – five main lesions

1. Herpes simplex

This presents the same way as herpes lesions elsewhere with a painful cluster of vesicles or shallow ulcers.

The treatment is the same, acyclovir 400 mg tds for 5–7 days.

2. HPV (Human papilloma virus) lesions

There are two different ways in which this can present:

a. As warts, condylomata acuminata, with their typical cauliflower appearance. Treat according to locally available preparations, usually podophyllin.

b. As an anal ulcer or sore. This is a pre-malignant condition and needs to be referred for further management.

Anal wart

3. Proctitis (gonorrhoea or chlamydia)

This presents with anal discharge/itch/pain in the rectum, ranging from mild to severe.

Treatment is according to standard local protocols for these STIs.

4. Syphilis

This can present with a primary chancre, the classic painless ulcer with raised edges, or as a wart, looking similar to HPV warts but just less raised.

Treatment is according to standard local protocols.

5. TB

See detail re peri-anal fistula above.

Appendix 15.1 Classification of dehydration in children

Signs	Classify as	Identify treatment (Urgent pre-referral treatments are in bold print)
Two of the following signs: • Lethargic or unconscious; • Sunken eyes; • Not able to drink or drinking poorly; • Skin pinch goes back very slowly.	Severe dehydration	**If child has no other severe classification:** give fluid for severe dehydration Or **If child also has another severe classification:** • **Refer URGENTLY to hospital with mother giving frequent sips ORS on the way.** • **Advise the mother to continue breastfeeding.** • **If child is two years or older and there is cholera in your area, give antibiotic for cholera.**
Two of the following signs: • Restless, irritable; • Sunken eyes; • Drinks eagerly, thirsty; • Skin pinch goes back slowly.	Some dehydration	Give fluid and food for some dehydration. If child also has a severe classification: • **Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way.** • **Advise the mother to continue breastfeeding.** • Advise mother when she should return immediately. • Follow up in 5 days if not improving.
Not enough signs to classify as some or severe dehydration.	No dehydration	Give fluid and food to treat diarrhoea at home. Advise mother when she should return immediately. Follow up in 5 days if not if improving.

Management notes

The following signs and symptoms are concerning and require immediate attention:

- looks unwell or deteriorating
- altered responsiveness (e.g. irritable, lethargic)
- sunken eyes
- tachycardia (fast heart rate)
- tachypnoea (breathing fast)
- poor fluid intake
- decrease in skin turgor.

Mild/moderate dehydration:

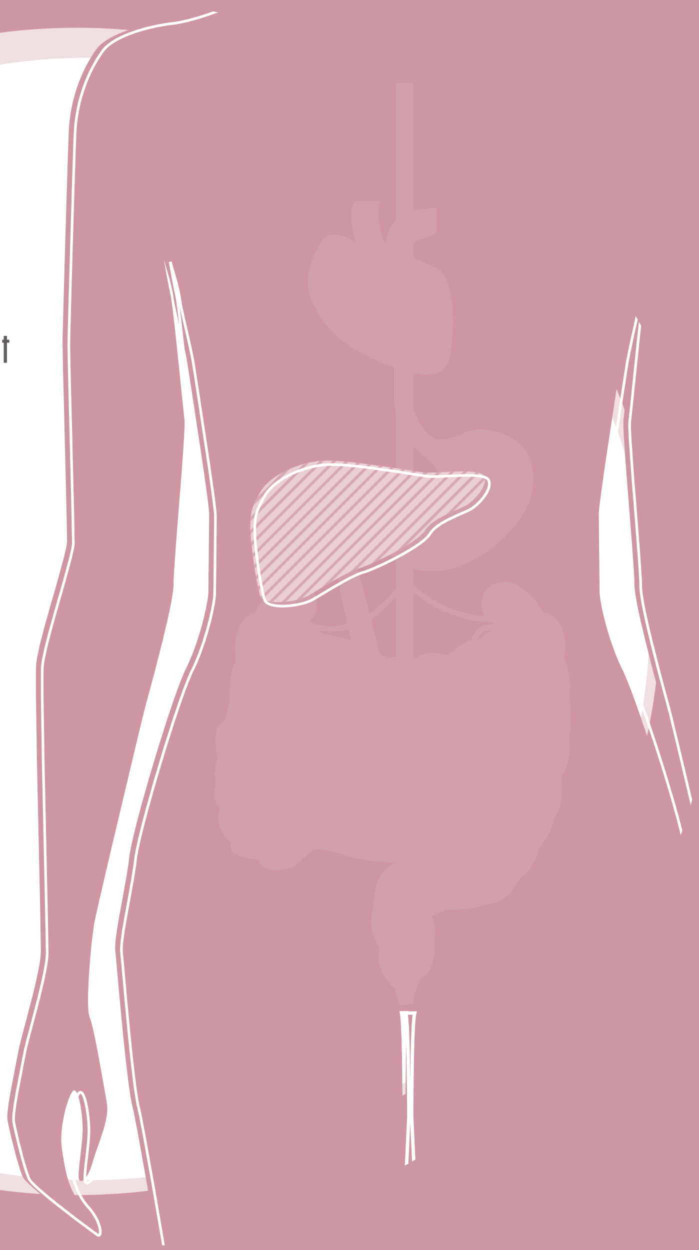
- If not vomiting and able to tolerate oral feeds, give oral rehydration solution (ORS) 40 ml/kg over 4 hours. Increase the amount if the child wants more, and encourage the mother to continue breastfeeding where applicable.
- Give 10 ml/kg of fluids after each loose stool:
    - <2 years: 50–100 ml
    - >2 years: 100–200 ml
    - Zinc supplements may lessen the duration of diarrhoea and stool frequency:
        - Age <6 months: 10 mg daily for 14 days
        - Age 6 months to 5 years: 20 mg daily for 14 days

Severe dehydration:

- Give an intravenous bolus of 20 ml/kg of Ringer's lactate or normal saline rapidly. Refer urgently to hospital.
- If blood in stool: ciprofloxacin 15 mg/kg/dose twice daily for 3 days.
- If not on exclusive breast milk, offer viscous fluids (e.g. soft porridge, yoghurt), sugar salt solution or ORS.
- Be cautious with rehydration in severely malnourished children and seek expert opinion if uncertain of management.

CHAPTER 16

Liver disease



A. How does liver disease present to us in our HIV/TB clinics?

B. What tests are done to evaluate liver disease?

C. An overview of the common conditions seen in our clinics

D. An approach to the patient presenting in primary care with possible liver disease

It is important that clinicians consulting in HIV/TB clinics have an understanding of the liver diseases that may be encountered. Not only are they a cause of morbidity and at times mortality in their own right, but also the presence of liver disease often complicates treatment of both HIV and TB.

In this chapter we will look at the following:

A. How does it usually present in our clinics?

B. What tests are used to evaluate it?

C. An overview of the common conditions seen in our clinics

D. An approach to the patient presenting in primary care with possible liver disease

A. How does liver disease present to us in our HIV/TB clinics?

- An incidental discovery of an elevated ALT
- A patient presenting with any of the following symptoms: nausea, vomiting, abdominal pain, jaundice, dark urine and pale stools
- Signs of chronic liver disease noted during a routine examination

The following may be noted on examination in chronic liver disease:

- Jaundice
- Palmar erythema (redness)
- Spider naevi on the skin
- Ascites
- Hepatomegaly, though not necessarily tender
- Gynaecomastia.

B. What tests are done to evaluate liver disease?

Table 16.1 shows the different tests that are done to evaluate liver disease. Frequently many of them are not available but they are included for completeness.

Table 16.1 Tests used to evaluate liver function

Test	What the test evaluates
Transaminases (markers of inflammation)	
ALT (alanine transaminase) Also known as SGPT	Both of these evaluate inflammation of the liver, which is commonly elevated in hepatitis and DILI (drug-induced liver impairment). AST can be elevated in other conditions so ALT is a more specific test for the liver.
AST (aspartate transaminase) Also known as SGOT	
Canalicular enzymes (markers of obstruction)	
GGT (gamma glutamyl transferase)	These tests give an indication of obstruction or blockage in the biliary drainage system. ALP can be elevated in other conditions, especially bone disorders. GGT is more sensitive in liver disease but is also elevated in other conditions.
ALP (alkaline phosphatase)	
An independent marker of obstruction and/or sepsis and/or haemolysis	
Bilirubin	Elevated with blockage in biliary drainage system. Often elevated with sepsis and is generally a marker of a poorer prognosis. (Can be elevated in haemolysis.)
Markers of synthetic function i.e. the ability of the liver to make (synthesise) the things it is supposed to	
INR	The liver makes many different molecules, including clotting factors, albumin and glucose. If the liver is sick, it struggles to make them. Decreased ability to make clotting factors causes the INR to be elevated. Decreased synthesis of glucose and albumin can result in low albumin and glucose levels.
Albumin	
Glucose	
Serological tests for specific diseases	
Hepatitis A antibody	These are the standard tests performed when screening for these different types of hepatitis. Other more detailed serological tests, though helpful, especially with hepatitis B, are so rarely available in poorly resourced settings they are not mentioned here. In some settings, where a rapid diagnostic test is available for hepatitis E, this can also be performed.
Hepatitis B surface antigen	
Hepatitis C antibody	
Hepatitis E antibody	

C. An overview of the common conditions seen in our clinics

We will look at the following conditions in a bit more detail.

- drug-induced liver impairment
- viral hepatitis
- alcoholic liver disease

Drug-induced liver impairment (DILI)

DILI is a toxic liver reaction to one or more drugs, characterised by elevations in specific liver-related lab tests, often combined with signs and symptoms of acute liver injury.

You will remember from **chapters 4, 7 and 12** that several ARVs and TB drugs are potentially toxic to the liver, as well as other drugs frequently used in the HIV/TB setting, such as cotrimoxazole. It is not surprising, therefore, that at times patients will present to the clinic or hospital with drug-induced liver impairment. When diagnosed according to standard criteria, this is a condition with a significant mortality so it is important that clinicians are familiar with how to diagnose and manage it.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

A comprehensive article from the *HIV Clinicians Society Journal* can be downloaded from the additional resources section on the **SAMU website** (https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018).

As a brief refresher before continuing, review the diagrams in **Chapter 7**, pages 97–99 that illustrate the metabolism and excretion sites of the different ARVs and TB drugs. This will be necessary to identify the possible culprit drugs when we encounter liver impairment in the HIV/TB setting.

Diagnosis of DILI

Most DILI events occur within 10–30 days of starting the drug but it can take up to 3 months to occur. DILI is diagnosed when one of more of the following criteria is met:

- ALT level >120 IU/l, **and** symptomatic (nausea, vomiting, abdominal pain, jaundice)
- ALT level >200 IU/l, **and** asymptomatic
- Total serum bilirubin concentration >40 μmol/l
    - jaundice is usually visible at around 40 μmol/l
    - 40 μmol/l = 2.3 mg/dl

For many years, efavirenz was thought to have only mild liver side effects within 6 weeks of starting treatment. Recently, cases have been reported of more severe DILI reactions occurring 6–9 months after starting and are more frequently associated with women with higher CD4 counts. EFV must be switched to a PI or dolutegravir, as continuing it can lead to liver failure (see **additional resources** section at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018).

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Important to differentiate DILI from hepatic adaptation

Hepatic adaptation is a **mild, transient, asymptomatic elevation of ALT or AST (<200)** and is common with the introduction of many drugs, especially those used for TB. This is known as hepatic adaptation, and, as it is a physiological process as the name suggests, it is not a reason for interrupting the treatment.

In most instances, it is unlikely even to be noted because we are no longer doing routine ALT measurements in the monitoring of ARVs. However, on occasion an ALT is requested and noted to fall into this category. In these instances it is important to differentiate it from DILI as drugs may be unnecessarily stopped or even replaced with more toxic ones.

Check for other causes of liver impairment

- Check for hepatitis A, B and C if possible, and in high-prevalence settings, hepatitis E. Hepatitis is not only a potential cause of the symptoms, but chronic hepatitis could be an aggravating factor in the DILI response. Patients can have a viral hepatitis B and a DILI.
- Consider a hepatitis IRIS, especially if symptoms have started in the first few months after starting ART (**Chapter 5**).
- Sepsis, though not necessarily causing liver impairment, can result in an elevated bilirubin.

(Atazanavir can cause significant jaundice by interfering with the bilirubin transport mechanism. Even though this condition is benign and is not due to a hepatitis, it may need to be changed because it is cosmetically unacceptable to the patient.)

DILI outcomes

DILI has a significant mortality rate. In one study in a large district hospital in Cape Town, it was noted to be approximately 30%. The majority died from liver failure or the co-morbidities of sepsis or disseminated TB.

People with malnutrition, other liver disease such as hepatitis B or C, or alcoholic liver disease generally have poorer outcomes.

Patients presenting with an **elevated ALT and symptoms** (nausea/vomiting/abdominal pain) or with an **elevated ALT and jaundice** have been noted to have a poorer prognosis.

Management of DILI

Please note that these management recommendations refer to DS TB. If DILI occurs while on DR TB treatment, seek expert advice, as extreme care needs to be taken with alternative drug regimens.

Given that this diagnosis is associated with a high mortality rate, urgent action needs to be taken:

- All potentially causative drugs must be stopped immediately. Regarding stopping ARVs abruptly there is no longer a need to 'cover the tail'. (See box on page 400 in skin ADR section).
- The patient should be **referred immediately** to the nearest hospital for close observation and monitoring and to follow the required protocol for management of this condition.

Refer to hospital

On occasions, the patient with milder disease may be managed as an outpatient. To qualify, however, the following criteria **must** be met:

- The clinician must be comfortable/competent to manage this condition.
- The patient must be able to return to the clinic twice a week.
- The clinic must have access to the necessary blood tests, with a rapid turnaround time for the result (3 days maximum).
- The patient is generally well (symptomatic patients do much more poorly with the drug re-challenge).
- The glucose level must be normal (low levels suggest poor liver function with worse outcomes).

When DILI is definitively diagnosed according to the above criteria, the management is as follows:

1. Stop all potential causative drugs. This includes all three ARVs (even though the NRTIs are not the cause),TB drugs, cotrimoxazole and any other known liver-toxic drugs such as fluconazole.
2. Review the basis for TB diagnosis. If there really is limited indication for the diagnosis, it may be possible to stop the TB treatment altogether.
3. Decide whether to give alternative TB medication (often referred to as the 'backbone regimen'). This decision is based on how sick the patient is with the TB. If the patient is generally well, he/she can afford to stay off TB Rx for a few weeks while the liver settles down. If, however, the patient is ill (e.g. disseminated TB or TB meningitis) it is too risky to interrupt the TB treatment, even for a few weeks. An alternative 3-drug TB treatment regimen, less toxic to the liver, needs to be prescribed while the liver injury recovers. This usually consists of an aminoglycoside (e.g. kanamycin), a quinolone (e.g. levofloxacin) and ethambutol.
4. If there are significant renal problems that contra-indicate the use of an aminoglycoside, ethionamide can be used, instead.

5. The presenting symptoms need to be monitored and the liver function tests (ideally those that were noted to be abnormal when the diagnosis of DILI was made) need to be checked twice a week until stabilised.
6. Once stabilised, the re-challenge regimen can be started (see below).

The re-challenge

The patient has TB and is HIV positive, so needs to end up back on drugs to treat both these conditions. Cotrimoxazole, despite its important role in prophylaxis in patients with lower CD4 counts, should not be re-challenged, nor should it be substituted with dapsone.

The TB drug re-challenge is done first, followed by re-introduction of ART.

i) TB drugs

An attempt to get the patient back onto the original TB drugs, especially rifampicin, is the next step in the management of DILI and the chance of success is, fortunately, quite high.

The re-challenge protocol is started when the liver has settled down sufficiently to do so. The following cut-off values are used as a guideline:

- ALT <100
- Bilirubin <30 (or the jaundice is no longer clinically visible).

A re-challenge is not done when there is significant mortality risk should the patient react again. This is when the patient has had fulminant hepatitis (encephalopathy or coagulopathy). However, this decision is very unlikely to be made in a clinic as the sicker patient would have been referred to hospital earlier.

The re-challenge protocol

The TB drugs are re-introduced, in full dose as calculated for body weight, in the following sequence (the exact day is not critical but an attempt should be made to check the ALT twice a week):

Day 1: Rifampicin (and if on the backbone regimen, drop the aminoglycoside now).

Day 3: Check ALT.

Day 4: If ALT is unchanged, add INH (and if on the backbone regimen, drop the quinolone now).

Day 7: Check ALT.

Day 8: If ALT is unchanged, consider PZA re-challenge in patients who cannot risk a sub-optimal TB regimen, i.e. those with severe TB (miliary, TBM) or DR TB.

If your facility doesn't have the individual TB drugs, you can use the different combinations that are more likely to be available. Start with INH first then change this to the rifampicin/INH combination then, if there are no contra-indications to trying PZA (noted above), the full 4-drug pill.

If at any of these steps the ALT goes up, the most recently introduced drug is the likely cause and needs to be stopped and the liver allowed to settle again.

Most of the time, patients tolerate all four TB drugs, but what do you do if it is clear that one of them is the cause and must no longer be used? The individual drugs have different modes of action with varying potency, so removal of them from the regimen for the rest of the treatment needs to be accommodated. The table below outlines the different regimens.

Table 16.2 Alternative TB regimens when one drug is removed

Drug omitted	Total duration	Intensive phase	Continuation phase
Rifampicin	18 months	INH, moxifloxacin, ethambutol, kanamycin x 2 months	INH, moxifloxacin, ethambutol x 16 months
INH	12 months	Rifampicin, moxifloxacin, ethambutol, x 2 months. Ideally kanamycin x 2 months	Rifampicin, moxifloxacin, ethambutol, x 10 months
PZA	9 months	Rifampicin, INH, ethambutol, x 9 months	

ii) ART

- Once the patient is safely back on a TB regimen, the ART is re-introduced. If the DILI happened within 3 months of starting ART, then the NNRTI or PI is a possible culprit drug and the ALT needs to be checked again at 3–4 days. If, however, it was started before this, then it is unlikely that it was the cause of the DILI and special precautions do not need to be taken.
- Do not re-challenge nevirapine. Efavirenz re-challenge can be considered, unless DILI was severe (coagulation abnormalities or hepatic encephalopathy).
- If DILI occurred on double dose lopinavir/ritonavir with rifampicin, replace the rifampicin with rifabutin and standard dose LPV/r if possible; otherwise give half-dose lopinavir/ritonavir with gradual dose escalation to full dose over a few weeks.

Subsequent follow-up

In different studies, the median time for recurrences to show was 2 weeks. It is therefore necessary to keep checking the ALT weekly for the next month after a successful re-challenge. It is also noteworthy that, because of this delay to recurrence, though the protocol suggests it, an elevated ALT during a re-challenge is not always caused by the most recently re-introduced drug.

Viral hepatitis

Hepatitis A usually presents as an acute illness and has a relatively short self-limiting course. Hepatitis B and C however, while they may present initially as an acute illness, often progress to a chronic illness with significant morbidity and long-term mortality, especially in the HIV-positive patient. Hepatitis E, though not as prevalent as B and C, can also cause chronic liver disease.

Hepatitis A

It is caused by the hepatitis A virus and is spread by what is known as the faecal-oral route, i.e. passed from hand to mouth via poor hygiene, often from unwashed vegetables and fruit.

Presentation

Usually presents with a fairly acute onset of fever (often >39° C), along with nausea, loss of appetite, vomiting, abdominal pain, dark urine, pale stools.

There can be a history of others in the family being infected.

Examination findings

Some or all of the following: jaundice; fever; tender, enlarged liver; and, on examination of the urine, it is noted to be dark and contains bilirubin on dipstick.

Lab findings include the following:

- Elevated WBC
- ALT and AST usually well over 5 times the upper limit of normal; can be as high as 4 000. Hepatitis A IgM Ab (antibody) test positive. The more commonly available IgG indicates both past and present infection, so does not confirm acute infection.

Natural history

It usually runs a course of about 6 weeks of illness, the first 2–3 weeks leaving the patient quite ill, followed by a slow recovery over the next 2–3 weeks. The vast majority of people recover fully.

As it is caused by a virus, treatment is symptomatic with bedrest. As paracetamol is metabolised in the liver, it is safer to avoid it in the acute phase. Diet is usually best regulated by the patient, who, in most cases, will naturally avoid fatty foods and alcohol.

Hepatitis B and C

These are two distinct illnesses caused by different viruses, but their clinical course is similar. Essentially they follow a course that starts with an acute infection, the severity of which can vary considerably. This then either resolves, leaving the patient with long-term immunity, or progresses to a chronic illness with progressive fibrosis, with some patients progressing further to cirrhosis or hepatocellular carcinoma.

These two illnesses are having a significant impact on public health, especially in sub-Saharan Africa, and drastic steps need to be taken to manage the growing epidemics.

Table 16.3 shows a comparative summary of their epidemiology, modes of transmission, treatment options and prevention measures.

Figures 16.1 and 16.2 show the natural history of the two illnesses followed by notes on each condition.

Table 16.3 Hepatitis B and C – epidemiology, transmission, treatment and prevention

	Hepatitis B	**Hepatitis C**
Epidemiology (2016 data)	240 million carriers worldwide.	185 million carriers worldwide.
	650 000 deaths per year.	350 000 deaths per year.
	Prevalence is >5% in sub-Saharan Africa – highest in world.	Prevalence in sub-Saharan Africa is 5.3%.
	4 million HIV/HBV co-infected.	4–5 million HIV/HCV co-infected.
Transmission	In sub-Saharan Africa most is by MTCT and in early childhood, between children while playing.	Biggest route is PWID.
	Sexual secretions and saliva	Other blood transmission: body piercing, blood products
	PWID	Risk of sexual transmission is much less than in HBV but is higher in HIV-positive people, especially HIV-positive MSM.
	Relative risk of transmission: HIV HCV HBV 0.3 3 30	
Treatment	Not curable but containable.	Now a curable disease.
	All HIV-positive patients to be given TDF and 3TC. Avoid 3TC monotherapy.	Needs specific evaluation to choose ideal treatment regimen. Currently moving towards a universal combination of two directly acting antivirals.
	All HIV-negative patients ideally to go onto TDF.	
Prevention	Screen wherever and whenever possible for HBsAg. Should ideally be in the same circumstances as HIV screening.	Screen wherever and whenever possible for HC Abs. Confirm with virological tests.
	Vaccinate all babies in routine EPI programme. Also vaccinate all HBsAg negative. (See **Chapter 8**.)	Screening ideally in all high risk groups: PWID, tattoos, dental, and blood giving in circumstances with poor hygiene. Also screening in key populations.
		MTCT risk higher in HIV-positive mothers.

Figure 16.1 Hepatitis B natural history

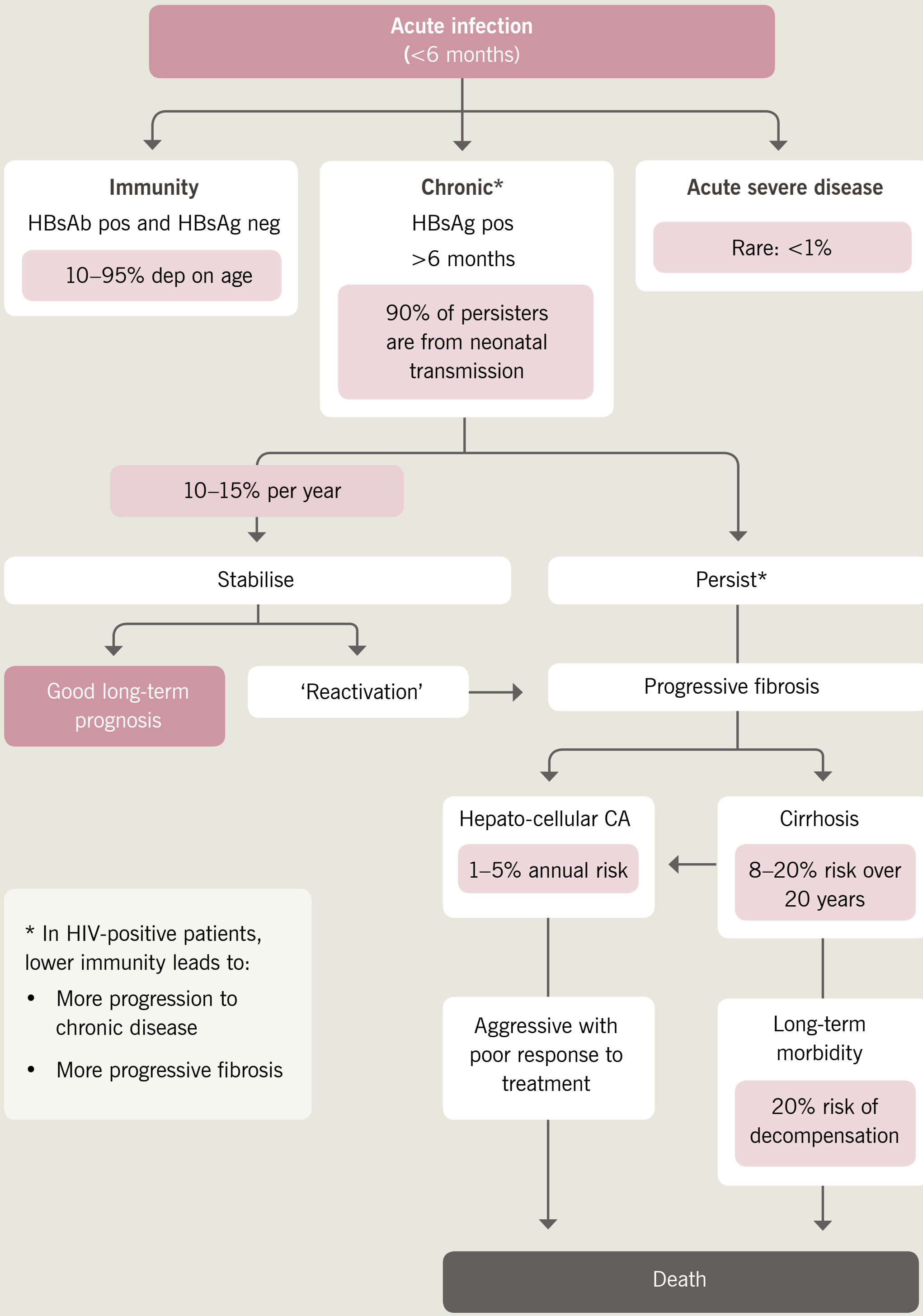
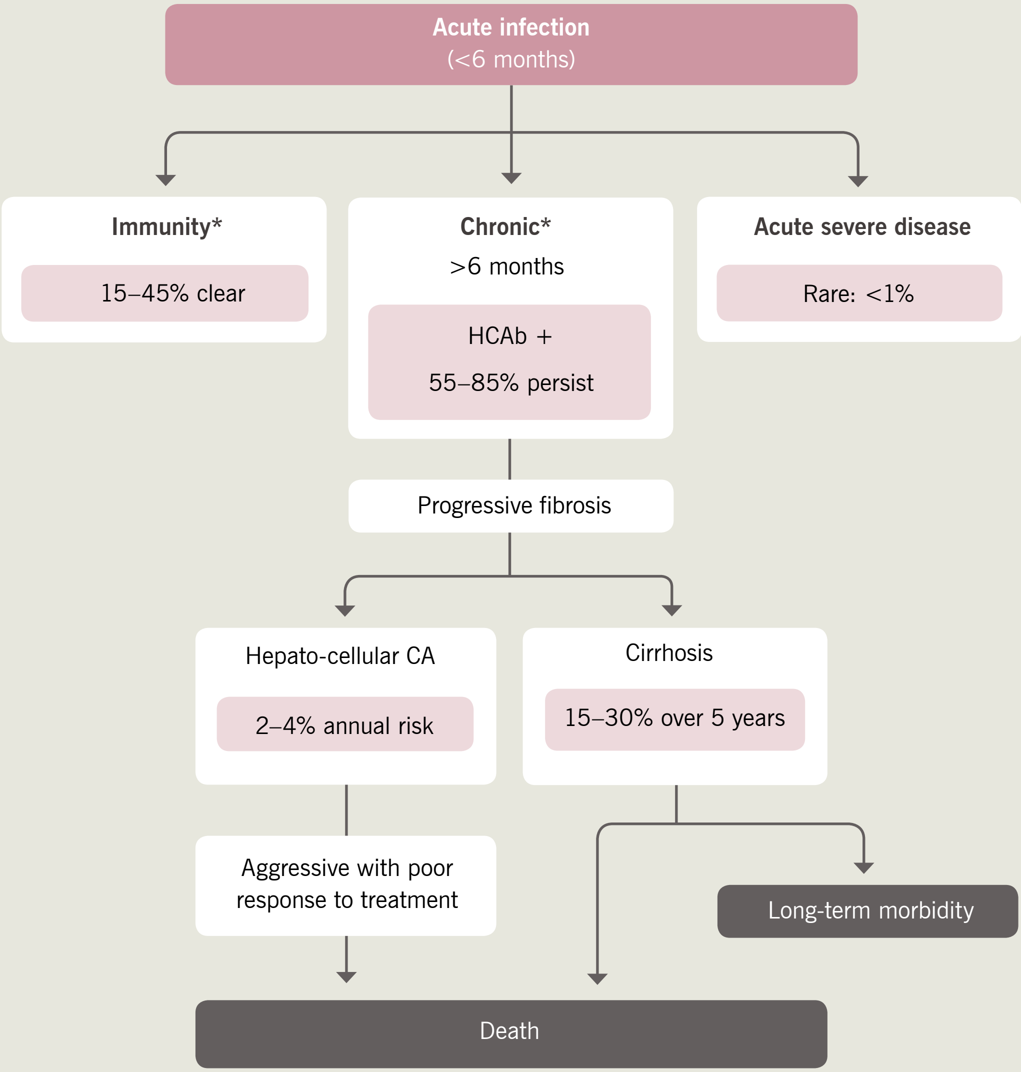


Figure 16.2 Hepatitis C natural history



* HIV (the lower the CD4)

- Less immunity
- More progression to chronic
- More progressive fibrosis

i) Hepatitis B

Co-infection with hepatitis B

The main focus of this book is the patient with HIV and/or TB, so other co-infections with hepatitis B will not be covered in this chapter.

- Hepatitis B co-infection with **HIV**

  The following are known associations:

  - As shown in the natural history diagram, fewer people develop spontaneous immunity and more people progress to the more severe complications of cirrhosis and hepatocellular carcinoma.
  - There is a higher mortality rate.
  - There is a poorer response to treatment.
  - There is a higher incidence of liver-related drug injury.

- Hepatitis B co-infection with **TB**

  The following are known associations:

  - Those who are infected with hepatitis B are at higher risk of developing TB for the simple reason that both conditions tend to have high incidence in the same geographical areas.
  - People on TB meds carry a 3–6 times higher risk of developing drug-induced liver injury (DILI) than those who are mono-infected.

Important conclusion from the above data: clinicians and the healthcare system must optimise screening and preventative strategies to minimise the co-infections in the first place, If co-infections do occur, they must provide appropriate counselling and monitoring.

Diagnosis

Several diagnostic tests can be done for hepatitis B, most of which are not available in resource-limited settings, due to cost. The standard diagnostic tests that are more readily available are the hepatitis B surface antigen (HBsAg) and the hepatitis B surface antibody (HBsAb).

As shown in the hepatitis B natural history diagram, one of two things happens in the first 6 months after the initial infection:

- The patient develops immunity: the HBsAg becomes negative and the HBsAb becomes positive.
- The patient progresses to chronic hepatitis B: the HBsAg remains positive and the HBsAb becomes negative.

Interpretation of the tests

If the HBsAg is positive, technically one should test again 6 months later as well as do the HBsAb.

- If the HBsAg remains positive and the HBsAb is negative, the patient has chronic hepatitis B.
- If the HBsAg is negative and the HBsAb is positive the patient is immune.

In practice, however, due to limits on resources, a positive HBsAg is considered to indicate chronic hepatitis B, even though the occasional person may be in the first 6 months after infection and may still develop immunity.

Screening

All the following should be screened:

- Household and sexual contacts of HBV-positive persons;
- HIV-positive people;
- People who inject drugs (PWID);
- Men who have sex with men (MSM) and transgender persons;
- Commercial sex workers;
- Prisoners; and
- Pregnant women.

Prevention

- Counselling

  In HBsAg-positive people, the following precautions should be taken:

  - Provide standard advice about condom use and regarding sharing of anything that could transmit the virus in blood or saliva (toothbrushes, razors, etc.).
  - All household and sexual contacts should be tested for HBsAg, and, if negative, should be vaccinated.
  - Counselling regarding alcohol use should be given, as it worsens the disease progression.
- PMTCT
  - In HIV-negative mothers, there is no recommendation for giving antivirals for PMTCT.
  - All HIV-positive mothers should routinely be given an ARV combination that includes TDF and 3TC.
- Vaccination should be offered to the following (see also **Chapter 8**):
  - Babies of HBsAg-positive mothers should be given their first vaccine dose at birth, especially if mother is eAg positive. (This is an additional HB antigen that, when present, implies a higher level of infectivity. It is, however, rarely available in resource-limited settings.)
  - All babies should be given routine HBV vaccination as per the EPI guidelines, starting at 6 weeks.
  - All HIV-positive persons.
  - All healthcare workers if they test negative for HBsAg. Ideally, the HBsAb should be done first. A value of >10 IU/ml suggests immunity, and, therefore, the vaccination is not required. However, if this test is not available, it is safer to vaccinate anyway.

Management of hepatitis B

- In **HIV-positive** patients:

  All HIV-positive patients now qualify for ART, regardless of CD4 count and HIV stage. This, therefore, includes all co-infected HIV/HBV patients. What is important for these patients is that they are on an ART regimen that contains **both 3TC and TDF**. These must therefore be included in the first line regimen and if a switch to second line is required the TDF needs to remain in the regimen as a third NRTI (see **Chapter 6**, section 10 on managing a patient with hepatitis B). This is important to avoid 3TC monotherapy, as 90% of HIV will become resistant to 3TC within 5 years.

  If there is renal impairment, the decision needs to be made – at times with more experienced support – about which is the more dangerous condition at the time:

  - If the renal impairment is mild, the dose of TDF can be adjusted according to the creatinine clearance and the renal function monitored.
  - If the renal impairment is severe, there is little sense in completely destroying the kidney with TDF but keeping the hepatitis B under control. In this case, the TDF will need to be replaced with AZT or ABC and the reality faced of hepatitis B becoming resistant to 3TC at some stage in the future.
  - In some places, entecavir can be used as an alternative to TDF, but another ARV must be given, as entecavir has no activity against HIV.

- In **HIV-negative** patients:

  The decision to treat HIV-negative people who are HBsAg positive is based on the degree to which there is likelihood of developing the long-term complications of fibrosis, cirrhosis or hepatocellular CA. It is beyond the scope of this book to go into the detailed management, as it is currently beyond the capacity of primary care clinics to provide it at this stage.

ii) Hepatitis C (HCV)

Hepatitis C can now be cured using a combination of two drugs from a class called directly acting antivirals (DAAs).

As hepatitis C is a condition with substantial global morbidity and mortality, even if effective treatment cannot at this stage be given due to cost constraints, the onus is on clinicians in primary care settings to screen actively for hepatitis C in those at higher risk. This will provide the data necessary to advocate for more comprehensive treatment strategies to be implemented.

Co-infection with hepatitis C

The main focus of this course is the patient with HIV and/or TB, so other co-infections with hepatitis C will not be covered at this stage.

- Co-infection with **HIV**

  The following are known associations:

  - As shown in the natural history diagram, as with hepatitis B, fewer people develop spontaneous immunity and more people progress to the more severe complications of cirrhosis and hepatocellular carcinoma.

    - There are known drug-drug interactions between the DAAs and some ARVs. Please consult more detailed guidelines when treating these two conditions (see also Table 7.1 in **Chapter 7**).

- Co-infection with **TB**

  The following are known associations:

    - Groups at risk of HCV are also at risk of developing TB.
    - People who inject drugs (PWID) are more at risk of developing TB, regardless of their HIV status.
    - Prisoners at risk of HCV are also at higher risk of acquiring TB.

Diagnosis

Diagnosis is made using a serological test to detect the presence of antibodies to hepatitis C. If it is positive, a further test for HCV RNA is recommended to confirm the diagnosis of chronic disease.

Screening

This should be done in areas of high prevalence, especially in specific groups at risk, namely;

- PWID;
- Men who have sex with men (MSM);
- Prisoners;
- People exposed to tattoos and piercings; and
- Pregnant women (in especially high prevalence areas).

If you are unable to treat the hepatitis C itself, it is important to look for and appropriately manage the known co-morbidities, namely hepatitis B, HIV, TB and substance abuse.

Prevention

- Counselling

  In hepatitis C Ab-positive people, the following precautions should be taken:

    - Provide standard advice about condom use, especially among MSM, and regarding sharing of anything that could transmit the virus in blood (e.g. razors, tattoo instruments).
    - Moderate to high alcohol intake has been shown to substantially increase the progression of cirrhosis. An alcohol intake assessment is therefore recommended, along with counselling and an alcohol reduction intervention for persons with moderate to high alcohol intake.

- Vaccination

  There is currently no vaccination for hepatitis C.

Treatment of hepatitis C

It is beyond the scope of this book to provide detailed guidelines for the management of hepatitis C. Please consult national or MSF guidelines, should you be involved in treatment. The following notes provide an overview of key principles used in treatment:

- **All HIV-positive patients need ART.** Even though the drugs used to treat HIV have no effect on hepatitis C, the effect of a rising immunity will progressively decrease the worsening effect of HIV on the progression of HCV.
- **Directly acting antivirals (DAAs)**

  This is a group of drugs specifically targeting HCV, that have revolutionised the management of hepatitis C over the last few years. DAAs now enable the disease to be cured rather than just contained. The principles of treatment involve an initial assessment of the degree of liver damage, including blood tests and specific tests to assess the level of fibrosis. Specific DAAs are then chosen, based on these results. The choice of DAAs – now limited almost entirely to one drug combination – and the subsequent monitoring is fortunately becoming progressively easier. As a result, treatment for this chronic disease will hopefully become more readily available in primary care settings and will be accompanied by local protocols and guidelines.

Alcoholic liver disease

Alcoholic liver disease or just alcohol abuse often goes unnoticed in the primary care environment because it is rare that a patient volunteers that he/she has an alcohol problem. When detected, it is usually secondary to investigation for other conditions. Liver disease secondary to alcohol has an aggravating effect on several conditions encountered in primary care clinics, so it is important that we not only look for it actively under certain circumstances but also that we manage it effectively when we find it.

Alcoholic liver disease increases both the likelihood of developing DILI and the morbidity that arises from it. It is also clearly identified as an aggravating factor in the natural history of both hepatitis B and C. In addition, alcohol abuse, let alone established liver disease resulting from it, is well recognised as a significant contributing factor to poor adherence to both ART and TB medication.

Who is at risk of alcoholic liver disease?

One unit of alcohol is 340 ml of beer, 150 ml of wine and 25 ml of spirits. The consumption of 21 units of alcohol per week for a man and 14 units per week for a woman places him/her at risk of progression to liver disease.

The presence of malnutrition and other liver disease (e.g. chronic viral hepatitis), and the taking of other toxins (e.g. traditional medicines) makes the condition worse.

Liver pathology

There are three recognised pathological conditions associated with alcohol.

- Acute fatty liver: 90% of binge drinkers develop this.
- Alcoholic hepatitis: This is a known precursor to cirrhosis.
- Cirrhosis: This is an established state of chronic irreversible liver disease associated with diffuse fibrosis and diminished liver function.

How does it present in primary care?

History

As patients very rarely present to the clinician, saying that they have an alcohol problem, it tends to be identified indirectly with careful, non-judgmental history-taking, triggered by a high index of suspicion. Situations that should trigger concern are:

- The patient presenting with a high viral load: Commonly, when investigating the adherence issues in a patient presenting with an elevated viral load, we find that poor adherence is due to alcohol abuse.
- A patient may present with a DILI, and on evaluation of the possible causes, it is discovered that alcohol abuse is a contributing factor.
- A patient may present with signs and symptoms of chronic liver disease as outlined above.
- It may just be the incidental finding of an elevated ALT and AST.

In all these situations, it will be the work of a competent clinician taking a careful, non-judgmental history, that will establish not only the diagnosis but also connection with the patient to enable his/her engagement with the support necessary to manage this patient effectively.

On **examination**, systematically look for all the signs of chronic liver disease noted above. Blood tests may show the following:

- Normal or elevated ALT and AST. Often, though not always, the AST is higher than the ALT. The levels are usually not more than 5 times the upper limit of normal.
- Elevated bilirubin may occur in an acute-on-chronic flare-up.
- The obstructive liver enzymes, GGT and ALP may also be elevated. Similar to the ALT and AST, these enzymes are also rarely more than 5 times the upper limit of normal.
- There may be anaemia secondary to poor nutrition, resulting in vitamin B12 or folate deficiency.
- In more advanced disease, the INR may be raised.

Management

Counselling is the cornerstone for a number of reasons:

- The patient needs to be aware of the long-term risk to his/her health, especially in the presence of other liver co-morbidities, such as chronic hepatitis.
- The alcohol abuse problem needs to be addressed, as it impacts on other issues wider than just liver disease, especially adherence to ART.
- See **Chapter 22**, Mental health disorders, for more detail on the management.

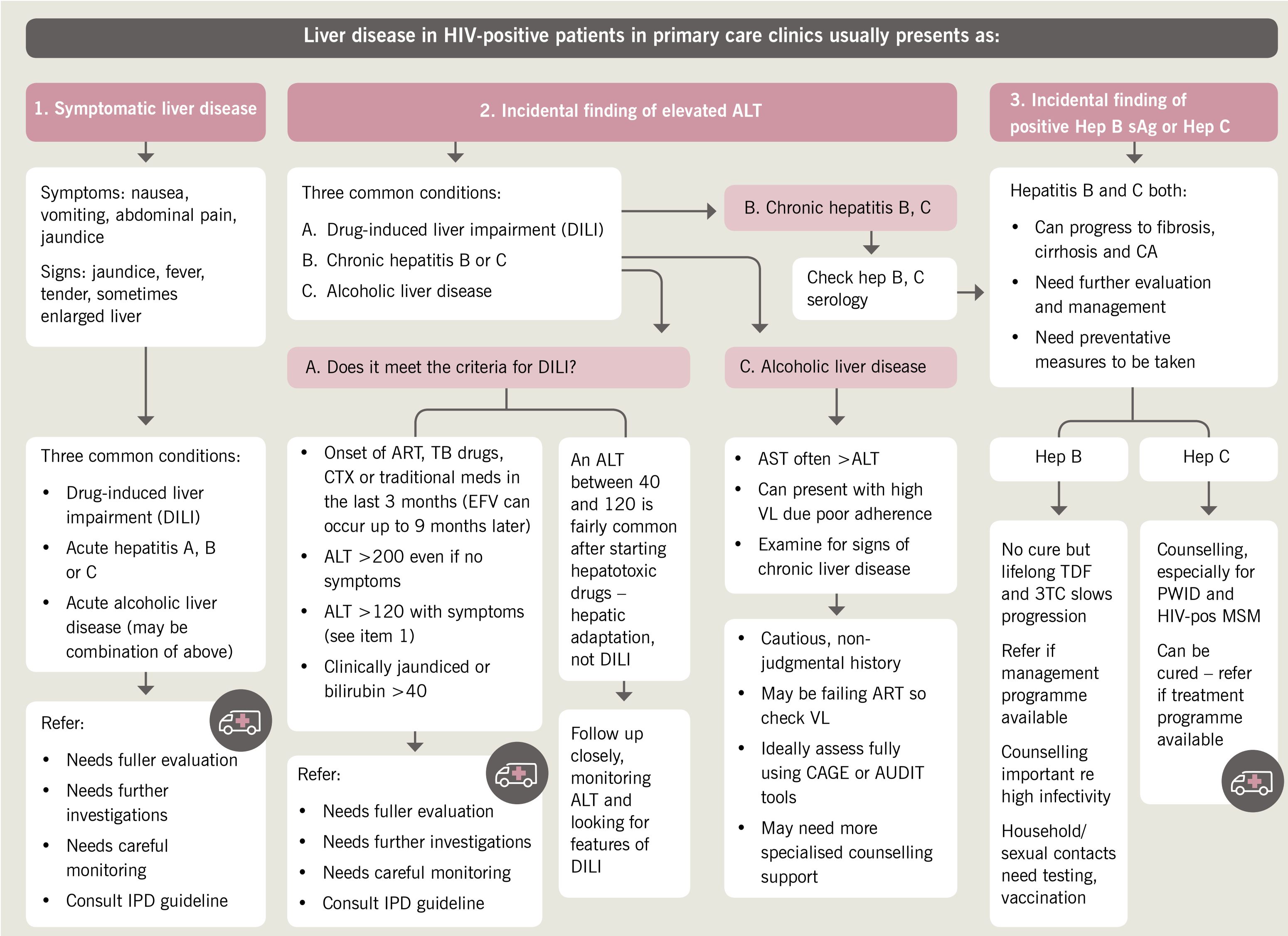
D. An approach to the patient presenting in primary care with possible liver disease

We have presented the key elements of all the common conditions that present to primary care clinics. Algorithm 16.1 on the next page provides an algorithmic approach to assist the clinician with the diagnosis and management of the patient presenting with possible liver disease.

Liver disease in primary care: Key points

- DILI, hepatitis B and C and alcoholic liver disease are not uncommon conditions seen in our primary care clinics. They cause significant morbidity and mortality, so early recognition and appropriate management are essential components for primary care.
- DILI is a fairly common side effect of ART, TB drugs and cotrimoxazole, and has a mortality of 25–30%. Rapid diagnosis and early referral to hospital are an important role for the primary care clinician.
- Hepatitis B and C are growing public health problems. Early detection and the adoption of prevention strategies are urgently required, along with rollout of treatment protocols for both conditions.
- Alcohol abuse and the liver disease associated with it are rarely the presenting problem. Awareness of who are at higher risk and how it affects them, along with careful identification and management of the patient will make a significant impact on many different aspects of HIV care.

Algorithm 16.1 Liver disease in HIV-positive patients



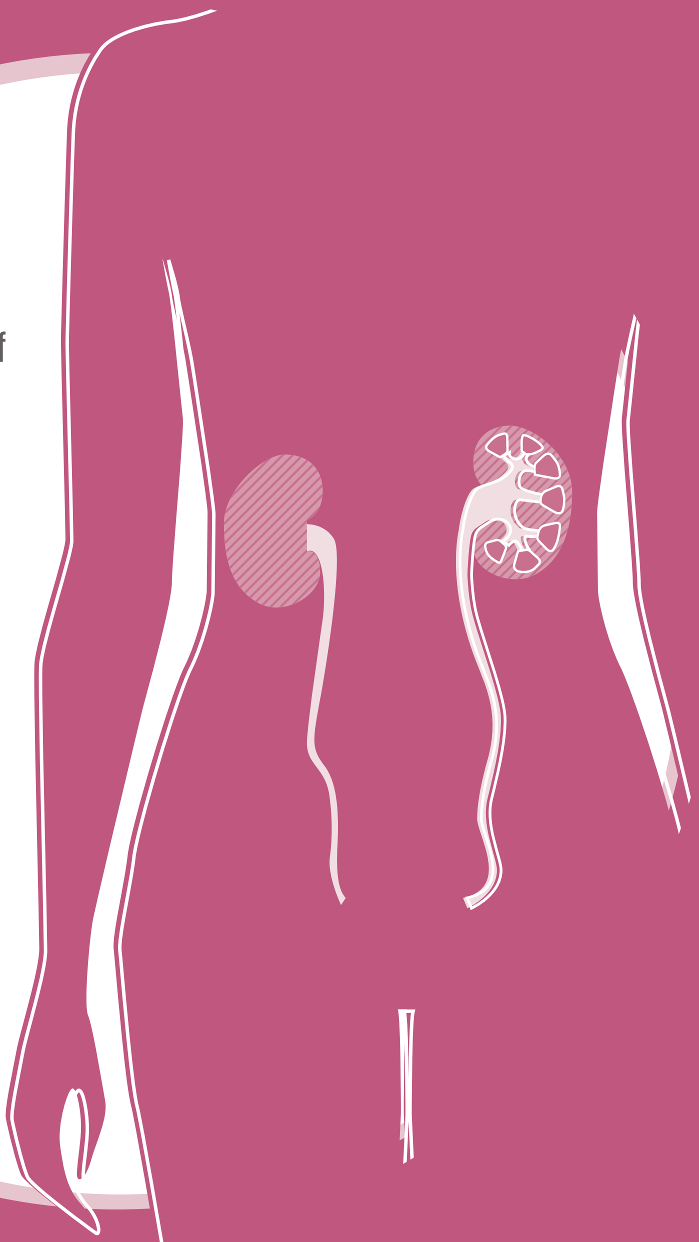
Renal disease

The signs and symptoms of renal disease

What is abnormal?

A. Overview of renal disease commonly seen in the HIV clinics

B. A practical approach towards a diagnosis for the patient with possible renal disease



Renal disease remains one of those feared subjects that continue to mystify clinicians. Firstly, it does not present with obvious symptoms or signs and secondly, when it has been identified, clinicians are often not sure what to do next. This chapter, therefore, hopes to make it not only easier to detect renal disease but also to help clinicians to completely manage the common renal conditions that present in the primary care setting.

The signs and symptoms of renal disease

- The symptoms of renal disease, if any, are fatigue and nausea, but, as these are so common in our HIV-positive patients, we are unlikely to diagnose renal disease based on them alone.
- By the time oedema is present the renal disease is already almost end-stage, so we will miss most renal disease if we are expecting it to present with oedema.
- Chronic kidney disease can present with anaemia, but again, this is a sign of more advanced renal disease.

How then **does** renal disease present in our clinics?

The commonest presentation is **the incidental discovery of an elevated creatinine** when done routinely before starting tenofovir or during TDF treatment.

The other way in which it may be detected is by noting **proteinuria on dipstick testing**.

What is abnormal?

1. **Elevated serum creatinine**

   Creatinine is a chemical that the body constantly produces from the breakdown of muscle. If the filtration mechanism of the kidney starts to fail, it will not be excreted as fast, resulting in a rise in the serum creatinine. The elevated serum creatinine points strongly towards the presence of renal disease, but the more accurate indicator is the creatinine clearance as it is a calculation that includes gender, weight and age, factors that affect the serum creatinine.

   Creatinine clearance

   There are various methods we can use to calculate creatinine clearance, in our attempts to find a value that most accurately reflects renal function across the range of heights, weights and ages of our patients. Many of the calculation methods have deficiencies, resulting in an inaccurate reflection of renal function in certain situations, especially when a patient has a low body mass. The eGFR value often provided by the laboratory with the laboratory creatinine result, the MDRD, or the value derived from applying the Cockcroft-Gault formula all have some limitations. Currently, consensus on the best formula is to use the CKD-EPI creatinine equation. (See app below.)

There is a **free app** that can be downloaded from the usual app stores, which calculates creatinine clearance for you off-line. Type in CKD-EPI and choose the app with the orange kidney icon. On opening the app, select the top option, CKD-EPI Creatinine 2009 Equation.

Search in app stores: CKD-EPI

You can save yourself time calculating the clearance by following this tip:

If patient's weight is >50 kg, age <50 years, serum creatinine <100 μmol/L and if the patient is not pregnant, there is no need to calculate the clearance, as it will be within normal range.

Practical tip

Creatinine clearance values

- Normal is a creatinine clearance >90 ml/minute.
- We need to monitor the creatinine clearance more closely if the creatinine clearance is <60 ml/min.
- We pursue the diagnosis of renal disease if the creatinine clearance is <50 ml/min.

At the end of this chapter are tables that remain useful for finding the creatinine clearance, especially for those unable to use the phone app (see Appendices 17.1–17.4). Please note that these have been drawn up using the Cockgroft-Gault equation, and therefore are not always reliable.

2. **Proteinuria**

Proteinuria is a common finding on routine urine dipstick testing:

- An acutely ill patient often has 1–3+ proteinuria, not necessarily caused by renal disease.
- Vaginal discharge contaminating a urine specimen can show proteinuria.
- A urinary tract infection often shows protein, along with the other abnormal findings of nitrites, leucocytes and cloudy appearance (see management Algorithm 23.2 at the end of **Chapter 23**.

It is, therefore, **important to re-test the urine** after treating any of the above. If the proteinuria is still present (2+ or more on dipstick) the patient needs to be investigated for renal disease.

What to do with an abnormal creatinine clearance or proteinuria

There are four actions that need to be taken:

- Avoid tenofovir until the renal problem has resolved. (If patient has hepatitis B, see **Chapter 6**, section 10.
- Adjust the doses of renally excreted drugs (see Table 17.1 at the end of this chapter).

- Always check both the serum creatinine **and** the urine dipstick. The initial renal evaluation is incomplete without both.
- Do the necessary thinking and tests, using what is available, to make a diagnosis of the renal problem.

The rest of this chapter deals with bullet **4: making a renal diagnosis.** We will do this in two stages by providing:

A. An overview of the commonly seen renal conditions in HIV clinics

B. A practical approach to the patient with possible renal disease, gathering the necessary information and processing it towards a diagnosis.

A. Overview of renal disease commonly seen in the HIV clinics

The good news is that there are only three main categories of renal disease that account for over 90% of the common conditions seen.

1. Acute kidney insult (AKI)
2. HIV-associated nephropathy (HIVAN)
3. Chronic kidney disease (CKD)

1. Acute kidney insult (AKI)

Overview

Acute kidney insult is the commonest presentation of renal disease in both primary care and hospital level settings. Much of it, however is missed, as the elevated creatinine result is seen only weeks after the blood has been drawn. If diagnosed and treated early, it can be reversed. If delayed, it can progress to acute tubular necrosis, a form of renal damage that is less reversible.

The commonest causes of AKI are dehydration, sepsis and drugs, so the wise clinician will actively consider renal impairment in these settings and either test the creatinine and urine early or refer for further investigations.

Dehydration and sepsis affect the kidney by dropping the pressure of the blood supply to it. This then decreases the ability of the kidney to do its job of filtering the blood. The solution is to get the pressure up again with rapid rehydration and management of the sepsis. These patients are best managed as inpatients, but if the capacity exists in a clinic to manage these, follow these guidelines:

- Stop all potentially nephrotoxic drugs such as tenofovir, cotrimoxazole and rifampicin. (Rifampicin, known to be toxic to the liver, can also affect the kidney by a sort of allergic reaction called acute interstitial nephritis).
- Rehydrate rapidly – 500 ml bolus over 1 hour, followed by 3 litres normal saline IV in 24 hours as well as pushing oral fluids.
- Treat any diarrhoea.
- Treat the sepsis.

2. HIV-associated nephropathy (HIVAN)

Characteristic findings

Direct damage to the kidney by HIV causes characteristic findings on examination and laboratory tests:

- **The characteristic finding is significant proteinuria, without which HIVAN cannot be diagnosed.** There is usually 2–4+ protein on dipstick, and, if the urine protein/creatinine ratio is available, a level of more than 0.1 is suggestive but it is often much higher.
- The creatinine is usually elevated but **HIVAN can present with proteinuria alone and a normal creatinine**.
- HIVAN is often a slowly progressive disease, but can also cause a rapidly rising creatinine, progressing to end-stage renal disease (ESRD) in a few months.
- It can occur at any CD4 count, but is always a stage 4 disease requiring fast-tracking for ARVs.
- It is a salt-losing renal condition, so there is rarely hypertension or oedema.
- If available, an ultrasound shows enlarged or normal-sized echogenic kidneys.

Diagnosis

- Prevention and early detection is important. Serum creatinine is done almost routinely pre-TDF but routine urine dipstick screening is rarely done in primary care. It would help considerably if all new patients to an HIV clinic had a once-off batch of routine observations done (pulse, blood pressure, respiratory rate, temperature and urine dipstick) before seeing the clinician. A lot of HIVAN is missed because urine dipsticks are not routinely performed in HIV clinics.
- Because biopsy (the only way to be 100% sure of the diagnosis) is rarely available, a presumptive diagnosis can be made if there is:
  - proteinuria ($\geq$2+ and/or a pr/cr ratio >0.1)
  - no hypertension and oedema.

Treatment

- Start ARVs as soon as possible, as there is clear evidence of the benefit. In one study, ART reduced mortality from HIVAN by 57%.
- Avoid TDF, preferably replacing it with ABC. (See **Chapter 6**, section 10 for details if patient has hepatitis B.)
- Protein damages the kidney so treat proteinuria with an ACE inhibitor, such as enalapril. Start with 2.5 mg bd and watch the blood pressure (it can drop) and potassium (it can rise, so check at one month).
- Continue to monitor the proteinuria and serum creatinine.

3. Chronic kidney disease (CKD)

CKD is at least three times more frequent in Africa than in developed countries. Common presentations seen in HIV clinics are chronic hypertensive and diabetic nephropathy. Less frequent but also seen are chronic HIVAN that was missed earlier in the disease and other chronic renal disease. Note that HIVAN that was missed a few years back can present as CKD, usually accompanied with significant proteinuria on dipstick.

By the time the hypertension or diabetes has resulted in an elevated creatinine or proteinuria, there is already significant irreversible renal disease. **However, careful management from this point onwards can slow the progression to end-stage renal disease (ESRD).**

Diagnosis

- Usually elevated creatinine with proteinuria and/or haematuria.
- If there are records in the patient's notes showing previous similarly elevated creatinine levels, this suggests that the problem has been around for a while, so is not an acute problem.
- The patient is often a known diabetic or hypertensive with poor control.
- An FBC often shows a normochromic, normocytic anaemia.
- An ultrasound, if obtainable, usually shows small kidneys (<9 cm).

Management

Even though some of the renal disease is irreversible, many actions can still help the patient.

1. The following have been shown to slow the progression to ESRD:
    - Get patient to stop smoking.
    - Optimise blood pressure management.
    - Optimise diabetes management.
    - Avoid NSAIDs as they further damage the kidney.
    - Start ART, avoiding TDF and ideally replacing with ABC or, if not possible, AZT.
2. Adjust renally excreted drug doses as needed (see dosing charts, Figure 17.1).
3. Monitor creatinine and urine 6-monthly.
4. Consider drawing on additional more experienced support when creatinine rises above 250 or creatinine clearance drops to below 30ml/minute.

B. A practical approach towards a diagnosis for the patient with possible renal disease

To recap, you will have arrived at suspecting renal disease by one of two routes:

- You will have incidentally noted that a patient has an elevated creatinine or protein and/or blood on urine diptstick.
- You will have deliberately considered the presence of renal disease in a patient presenting with significant diarrhoea, dehydration or sepsis.

Having referred early because of concern for an acute kidney insult, or because you have a patient with an elevated creatinine or abnormal urine dipstick findings, your task now is to evaluate this further. By asking specific questions, looking for particular things on examination, and using the limited range of diagnostic tests available in primary care settings, you can focus your diagnosis into one of three separate categories noted below – or a combination of these categories (point 4).

1. Could this be an acute kidney insult?

Assess for this first as it requires urgent treatment and can be reversed if managed early in the process. Actively look for the common causes:

A. **Could this be due to low blood pressure to the kidney?** Usually associated with hypovolaemia and low blood pressure. Look for dehydration, diarrhoea or sepsis. If suspected, the patient will need admission, IV fluids, investigation and management of the sepsis and inpatient monitoring.

B. **Could this be due to a nephrotoxic drug?**

   Tenofovir can damage the kidney either directly or via the mitochondria.

   - Can occur in weeks to months after starting it.
   - Can present as rising creatinine, glycosuria or even oedema.

   Cotrimoxazole and **rifampicin** can both damage the kidney via an allergic type of reaction called acute interstitial nephritis. Has either of these been commenced in the last few weeks? This can present with extra-renal manifestations of hypersensitivity, such as rash, fever and joint pain.

   - Can look like pyelonephritis with fever and flank pain.
   - Recurs on re-exposure to the drug.
   - Treatment is to stop offending drug and sometimes give steroids.

2. Could this be HIVAN?

- Proteinuria – usually ≥2+ on dipstick, urine pr/cr ratio >0.1 and no haematuria.
- Usually normal blood pressure, no oedema and no rash.
- CD4 not necessarily low. Can be >500.
- Usually normal to enlarged kidneys on ultrasound.

No definitive diagnosis without biopsy but a presumptive diagnosis can be made if bullets 1 and 2 are present and other conditions are excluded by the acute kidney insult screening process in section 1 above. If so:

- Start ARVs as soon as possible (stage 4 condition).
- Start enalapril, initially 2.5 mg bd, and watch the bp and potassium.
- Keep monitoring the creatinine and proteinuria.

3. Does this look like chronic kidney disease (CKD)?

- Commonly poorly controlled diabetes and/or hypertension;
- Other known CKD, e.g. chronic glomerulonephritis (GN);
- Some evidence of chronicity (a few similarly elevated creatinines a few months apart).

If so, ensure improved management of the chronic condition.

Commence CKD management principles to prevent further damage.

- Get patient to stop smoking.
- Treat bp.
- Treat diabetes (remember that serum glucose can drop with worsening CKD).
- Avoid TDF, preferably replacing it with ABC.
- Avoid NSAIDs.
- Adjust drugs as guided by Table 17.1.
- Highlight condition in patient's file to notify other clinicians.

Seek specialised help or refer when the CrCl/eGFR drops below 30.

4. Could this be a combination of CKD and HIVAN or AKI?

- Are there features of an acute kidney insult but also features to suggest chronicity?
  - Does the patient have evidence of chronic kidney disease, such as poorly controlled diabetes or hypertension, or perhaps other known CKD? On top of this, is there an acute problem of dehydration, sepsis or drug toxicity?
  - Are there features of chronic kidney disease but also high level proteinuria? This could be HIVAN that was missed earlier in the patient's HIV illness and is now chronic.
- If any of the above combinations, manage the acute problem as above and at the same time take appropriate care with CKD management as outlined above.

The approach to a patient with possible renal disease is also presented in Algorithm 17.1 below.

In addition, a more **comprehensive booklet** detailing the diagnosis and management of renal disease in primary care can be downloaded from the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Algorithm 17.1 Renal disease in the HIV-positive patient

Renal disease in HIV-positive patients

Acute kidney injury:
- ***Dehydration***
- ***Sepsis***
- **Nephrotoxic drugs:** particularly tenofovir, rifampicin, cotrimoxazole

HIVAN (HIV-associated nephropathy):
- If detected early, HIVAN is reversible.
- However, it may progress to chronic kidney disease.

Chronic kidney disease:
- ***Hypertension and diabetes*** are major risk factors for chronic kidney disease.
- Chronic kidney disease means patients are more vulnerable to acute kidney injury: i.e. ***acute-on-chronic-kidney injury***.

Clinical presentation
- The commonest presentation of kidney disease is an **incidental finding of elevated serum creatinine**.
- Kidney disease is often missed, as it is mostly asymptomatic or presents just with tiredness or nausea.
- Oedema is a very late sign and is also not seen with HIVAN. Its absence, therefore, does not exclude significant renal disease.
- Strongly suspect and look for renal disease in all patients with the risk factors ***in bold italics listed above***.
- Chronic renal disease may present with anaemia, due to reduced production of erythropoietin.

Investigations

Creatinine
- All patients needing hospital admission should have creatinine checked.
- The definition of normal varies considerably according to age, weight and gender. Creatinine clearance is more accurate **but is time-consuming to calculate**. A useful tip:

  If creatinine <100, weight >50kg, and age <50 years and the patient is not pregnant, the creatinine will be within normal range, so there is no need to calculate it.

If the calculation is needed, there is a free app that can be downloaded from the usual app stores that calculates the CKD-EPI value. Type in and choose the one with the orange kidney icon. On opening the app, select the top option, 'CKD-EPI Creatinine 2009 Equation'.

Sodium Potassium
- Look for associated electrolyte changes: abnormal sodium and potassium are common in acute kidney injury and may be life threatening.
- Potassium and sodium can be very low in severe acute or chronic diarrhoea.
- Potassium may be very high in chronic kidney disease.

Urine microscopy

WBC +/- bacteria – show urinary tract infection.

Urine dipsticks
- Protein and blood can indicate renal disease. This can be associated with a urinary tract infection (UTI) but findings usually include cloudy urine with white blood cells and/or nitrites.
- Kidney disease is frequently missed because abnormal dipstick findings are often assumed to be due to a UTI. **Always** do a follow-up dipstick after treatment to ensure resolution.

Renal ultrasound

Shows general anatomy, can suggest underlying HIVAN (large or normal echogenic kidneys), or end-stage kidney disease (small kidneys), but cannot give further information about the underlying cause.

An approach to the patient with probable renal disease

- Start by looking for acute kidney injury, as it can be reversed if treated promptly.
- Look for the underlying causes (marked **AKI**) – commonest are dehydration, sepsis and drugs.
- Start by looking for **pre-renal disease:** the most common, and reversible if treated early.
- The next most common cause is **acute tubular necrosis (ATN)**, also reversible if treated early.
- Always consider **HIVAN** and **Chronic Kidney Disease** then consider the other causes.

General management:

- Correct dehydration rapidly – 500 ml bolus over 1 hour, followed by 3 litres normal saline IV in 24 hours, as well as pushing oral fluids.
- Correct electrolyte abnormalities rapidly, and correct underlying cause.
- Look for sepsis: treat infections promptly.
- Stop all nephrotoxic drugs: for example, change tenofovir to another NRTI.
- Treat other co-morbidities causing renal disease: e.g. diabetes, hypertension.

Pre-renal AKI

Causes:
Hypo-perfusion - reduced blood flow to kidney:
- Hypovolaemia
- Hypotension
- Sepsis
- Cardiac failure

REVERSIBLE IF CORRECTED EARLY

Correct the underlying cause:
- Severe diarrhoea is a common cause: correct with fluids, correct electrolytes.

If not corrected rapidly acute tubular necrosis (ATN) develops.

Renal: damage is within kidney itself

Acute tubular necrosis (ATN) AKI

Causes:
Ischaemia
- pre-renal failure not corrected.

Toxins:
- Tenofovir
- Rifampicin
- Amphotericin B
- Aminoglycosides
- NSAIDS

REVERSIBLE IF CORRECTED EARLY

- Correct the underlying cause.
- Fluid and electrolyte replacement if hypovolaemia.
- Stop all nephrotoxic drugs.

Acute interstitial nephritis (AIN) AKI

Causes:
- Drug hypersensitivity

Most common:
- Rifampicin
- Cotrimoxazole

Others:
- Antibiotics: cephalosporins
- NSAIDS
- Traditional medicines

Management:
Usually reversible, if drugs are stopped early:
- Stop all implicated drugs – and do not re-challenge.
- The only exception is rifampicin if there is absolutely no alternative, and there is no doubt about TB diagnosis. Re-challenge; regular creatinine monitoring.

Chronic kidney disease

- Usually poorly controlled diabetes or hypertension;
- A few elevated creatinines in the past suggesting chronicity;
- Often proteinuria.

Treatment
- Treat underlying condition.
- Avoid NSAIDs.
- Stop smoking.
- Start ART.

Other

Many causes, including hepatitis B, syphilis, diabetes.
- Can be acute AKI or chronic.
- Presents with any of: proteinuria, RBC in urine, oedema, hypertension.

Pyelonephritis AKI
- Fever, flank pain
- Leucocytes & proteinuria on dipstick
- Start antibiotics immediately and intravenous fluids.

Post-renal (rarer)

Due to obstruction to urine outflow and back-pressure into the kidney
Most common causes:
- Prostatic hypertrophy in older men – urethral obstruction (do a rectal examination);
- Cervical carcinoma in women – ureteric obstruction (do a vaginal examination).

HIVAN

- Proteinuria must be present for diagnosis; urine dipstick essential.
- No hypertension; but may occur in patients with existing hypertension.
- It is a salt-losing condition, therefore oedema does not occur.
- Often low CD4 counts but may occur at any CD4 count.

Treatment:
- ART;
- ACE inhibitor to reduce proteinuria;
- Avoid nephrotoxic drugs.

Table 17.1 Drug dosing adjustments in renal impairment

Drug	Adjusted doses according to creatinine clearance or eGFR		
	Clearance >50	Clearance 10–50	Clearance <10
ARVs			
lamivudine	150 bd or 300 daily	150 mg daily	50 mg daily
d4T	30 mg bd	15 mg bd	15 mg daily
zidovudine	300 mg bd	No adjustment needed	300 mg daily
tenofovir	300 mg nocte	AVOID	AVOID
abacavir	No adjustment needed		
nevirapine, efavirenz	No adjustment needed		
Protease inhibitors (PIs)	No adjustment needed		
Anti-hypertensives			
enalapril	2.5–10 mg bd	75–100%	50%
atenolol	25–50 mg daily	50%	25%
HCTZ	12.5–25mg daily	100%	avoid
amlodipine	5–10 mg daily	No adjustment needed	No adjustment needed
doxazosin	2–4 mg daily	No adjustment needed	No adjustment needed
Diabetic meds			
gliclazide	40–80 mg bd	AVOID	AVOID
glibenclamide	2.5–5 mg bd	AVOID	AVOID
metformin	500–1 000 mg bd	AVOID	AVOID
Anti-fungals			
fluconazole	200–400 daily	50%	50%
itraconazole	100–200 bd	100%	50%. AVOID IV
Antivirals			
acyclovir	200–800mg 4–12 hourly	100%	200 mg bd
Antibiotics			
amoxycillin	250–1 000 mg tds	Every 8-12 hours	Every 24 hours
clarithromycin	250–500 mg bd	50%–100%	50%
ciprofloxacin	250–750 mg bd	50%–75%	50%
cotrimoxazole treatment	2 bd – 4 qid	50%	Seek advice
cotrimoxazole prophylaxis	2 tabs daily	No adjustment needed	No adjustment needed
penicillin G	0.5–4 MU 4–6 hourly	75%	25%
azithromycin	No adjustment needed.		
ceftriaxone			
clindamycin			
erythromycin			

Miscellaneous			
Drug	**Clearance >50**	**Clearance 10–50**	**Clearance <10**
NSAIDs	AVOID	AVOID	AVOID
metoclopramide	10 mg tds	75%	50%
omeprazole	20–40 mg daily	No adjustment	No adjustment
ranitidine	150-300 mg nocte	50%	25%

TB drugs		
Drug	**Adjusted doses according to creatinine clearance or eGFR**	
	Clearance >30	**Clearance <30**
Rifampicin	600 mg daily	No change necessary
Isoniazid	300 mg daily	No change necessary
Pyrazinamide	30–40 mg/kg daily	25–35 mg/kg/dose 3 x a week
Ethambutol	25 mg/kg daily	15–25 mg/kg/dose 3 x a week
Streptomycin	15–20 mg/kg daily	12–15 mg/kg/dose 2 or 3 x a week
Kanamycin	15–20 mg/kg daily	12–15 mg/kg/dose 2 or 3 x a week
Capreomycin	15–20 mg/kg daily	12–15 mg/kg/dose 2 or 3 x a week
Moxifloxacin	400 mg daily	No change necessary
Ofloxacin	15–20 mg/kg daily	600–800 mg per dose 3 x per week
P-aminosalicylic acid	150 mg/kg daily	4 g per dose. Max dose is twice daily.
Ethionamide/ prothionamide	15–20 mg/kg daily	No change necessary.
Terizidone/Cycloserine	15–20 mg/kg daily	250 mg daily or 500 mg 3 x a week
Linezolid	600 mg daily	No change necessary
Delamanid	100 mg bd for 24 weeks	No change in mild to moderate disease. Dosage not available for severe renal impairment.
Bedaquilline	400 mg daily for 2 weeks, then 200 mg 3 x a week for 22 weeks	No change in mild to moderate disease. Dosage not available for severe renal impairment.

Appendix 17.1 Creatinine clearance estimation table (in ml/min) – Female, age 15–40 years

N.B Creatinine must be measured in μmol/l to use these tables. These tables are provided to assist with manual calculation. Ideally this calculation should be done automatically from the laboratory.

Cr in μmol/litre	30-35 kg	36-40 kg	41-45 kg	46-50 kg	51-55 kg	56-60 kg	61-65 kg	66-70 kg
60	52-76	62-87	71-98	80-108	88-119	97-130	106-141	114-152
70	45-65	53-74	61-84	68-93	76-102	83-111	91-121	98-130
80	39-57	47-65	53-73	60-81	66-89	73-98	79-106	86-114
90	35-51	42-58	48-65	53-72	59-79	65-87	70-94	76-101
100	31-46	37-52	43-59	48-65	53-72	58-78	63-85	69-91
110	28-41	34-47	39-53	43-59	48-65	53-71	58-77	62-83
120	26-38	31-43	36-49	40-54	44-60	49-65	53-70	57-76
130	24-35	29-40	33-45	37-50	41-55	45-60	49-65	53-70
140	22-33	27-37	31-42	34-46	38-51	42-56	45-60	49-65
290	11-16	11-18	15-20	16-22	18-25	20-27	22-29	24-31
300	10-15	16-17	14-20	16-22	18-24	19-26	21-28	23-30
350	9-13	13-15	12-17	14-19	15-20	17-22	18-24	20-26
400	8-11	12-13	11-15	12-16	13-18	15-20	16-21	17-23
450	7-10	10-12	10-13	11-14	12-16	13-17	14-19	15-20
500	6-9	9-10	9-12	10-13	11-14	12-16	13-17	14-18
550	6-8	9-9	8-11	9-12	10-13	11-14	12-15	12-17
600	5-8	8-9	7-10	8-11	9-12	10-13	11-14	11-15
650	5-7	7-8	7-9	7-10	8-11	9-12	10-13	11-14
700	7-12	10-14	9-8	7-9	8-10	8-11	9-12	10-13

Appendix 17.2 Creatinine clearance estimation table (in ml/min) – Female, age 41–65 years

Cr in µmol/litre	30-35 kg	36-40 kg	41-45 kg	46-50 kg	51-55 kg	56-60 kg	61-65 kg	66-70 kg
40	59-90	70-103	80-116	90-129	99-142	109-154	119-167	129-180
50	47-72	56-82	64-93	72-103	80-113	87-124	95-134	103-144
60	39-60	47-69	53-77	60-86	66-94	73-103	79-112	86-120
70	33-51	40-59	46-66	51-74	57-81	62-88	68-96	83-103
80	29-45	35-51	40-58	45-64	50-71	55-77	59-84	73-90
90	26-40	31-46	36-51	40-57	44-63	49-69	53-74	65-80
100	23-36	28-41	32-46	36-51	40-57	44-62	48-67	58-72
110	21-33	26-37	29-42	33-47	36-51	40-56	43-61	53-66
120	20-30	23-34	27-39	30-43	33-47	36-51	40-56	49-60
220	11-16	13-19	15-21	16-23	18-26	20-28	22-30	27-33
230	10-16	12-18	14-20	16-22	17-25	19-27	21-29	25-31
300	8-12	9-14	11-15	12-17	13-19	15-21	16-22	19-24
350	7-10	8-12	9-13	10-15	11-16	12-18	14-19	17-21
400	6-9	7-10	8-12	9-13	10-14	11-15	12-17	15-18
450	5-8	6-9	7-10	8-11	9-13	10-14	11-15	13-16
500	5-7	6-8	6-9	7-10	8-11	9-12	10-13	12-14
550	4-7	5-7	6-8	7-9	7-10	8-11	9-12	11-13
600	4-6	5-7	5-8	6-9	7-9	7-10	8-11	10-12

Appendix 17.3 Creatinine clearance estimation table (in ml/min) – Male, age 15–40 years

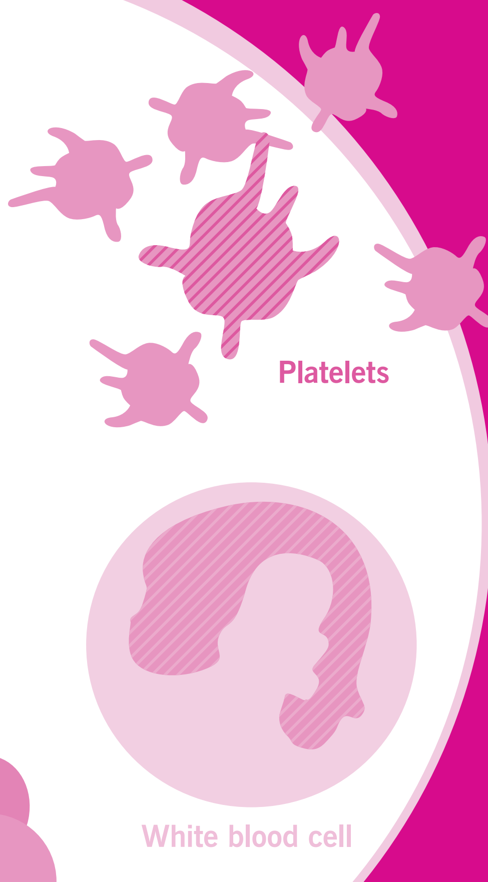
Cr in µmol/litre	30-35 kg	36-40 kg	41-45 kg	46-50 kg	51-55 kg	56-60 kg	61-65 kg	66-70 kg
70	53-77	63-88	72-99	81-110	90-121	98-132	107-143	116-154
80	46-67	55-77	63-86	71-96	78-106	86-115	94-125	101-135
90	41-60	49-68	56-77	63-85	70-94	77-103	83-111	90-120
100	37-54	44-62	50-69	57-77	63-85	69-92	75-100	81-108
110	34-49	40-56	46-63	51-70	57-77	63-84	68-91	74-98
120	31-45	37-51	42-58	47-64	52-70	57-77	63-83	68-90
130	28-41	34-47	39-53	44-59	48-65	53-71	58-77	62-83
140	26-38	32-44	36-49	40-55	45-60	49-66	54-71	58-77
150	25-36	30-41	34-46	38-51	42-56	46-62	50-67	54-72
160	23-34	28-38	32-43	35-48	39-53	43-58	47-62	51-67
170	22-32	26-36	30-41	33-45	37-50	41-54	44-59	48-63
350	11-15	13-18	14-20	16-22	18-24	20-26	21-29	23-31
400	9-13	11-15	13-17	14-19	16-21	17-23	19-25	20-27
450	8-12	10-14	11-15	13-17	14-19	15-21	17-22	18-24
500	7-11	9-12	10-14	11-15	13-17	14-18	15-20	16-22
550	7-10	8-11	9-13	10-14	11-15	13-17	14-18	15-20
600	6-9	7-10	8-12	9-13	10-14	11-15	13-17	14-18
650	6-8	7-9	8-11	9-12	10-13	11-14	12-15	12-17
700	5-8	6-9	7-10	8-11	9-12	10-13	11-14	12-15
750	5-7	6-8	7-9	8-10	8-11	9-12	10-13	11-14
800	5-7	6-8	6-9	7-10	8-11	9-12	9-12	10-13

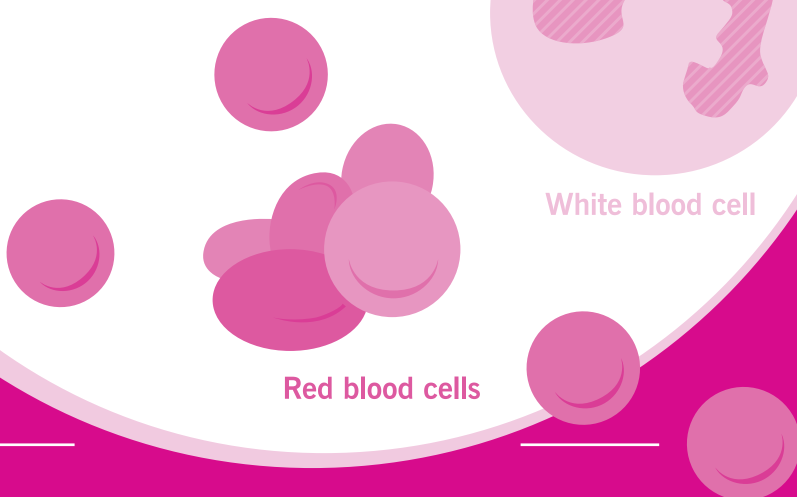
Appendix 17.4 Creatinine clearance estimation table (in ml/min) – Male, age 41–65 years

Cr in µmol/litre	30-35 kg	36-40 kg	41-45 kg	46-50 kg	51-55 kg	56-60 kg	61-65 kg	66-70 kg
50	55-85	66-97	76-110	85-122	94-134	103-146	113-158	122-170
60	46-71	55-81	63-91	71-101	78-112	86-122	94-132	101-142
70	40-61	47-70	54-78	61-87	67-96	74-104	80-113	87-122
80	35-53	42-61	47-68	53-76	59-84	65-91	70-99	76-107
90	31-47	37-54	42-61	47-68	52-74	57-81	63-88	68-95
100	28-43	33-49	38-55	42-61	47-67	52-73	56-79	61-85
110	25-39	30-44	34-50	39-55	43-61	47-66	51-72	55-77
120	23-36	28-41	32-46	35-51	39-56	43-61	47-66	51-71
130	21-33	26-37	29-42	33-47	36-52	40-56	43-61	47-66
260	11-16	13-19	15-21	16-23	18-26	20-28	22-30	23-33
300	9-14	11-16	13-18	14-20	16-22	17-24	19-26	20-28
350	8-12	9-14	11-16	12-17	13-19	15-21	16-23	17-24
400	7-11	8-12	9-14	11-15	12-17	13-18	14-20	15-21
450	6-9	7-11	8-12	9-14	10-15	11-16	13-18	14-19
500	6-9	7-10	8-11	8-12	9-13	10-15	11-16	12-17
550	5-8	6-9	7-10	8-11	9-12	9-13	10-14	11-15
600	5-7	6-8	6-9	7-10	8-11	9-12	9-13	10-14

CHAPTER 18

Haematological conditions





Anaemia is common in our HIV-positive patients; sometimes we see low platelets and occasionally a low white cell (WBC or leucocyte) count. Fortunately, the range of likely causes is not extensive, so, if a simple diagnostic algorithm is followed, these conditions can be managed with confidence and efficiency.

Answering two key questions when faced with these haematological abnormalities will immediately help towards making the correct diagnosis:

1. Which cell lines (RBC/WBC/platelets) are involved? Is just one line, two lines (bicytopaenia) or all three (pancytopaenia)?
2. Is there associated systemic disease? (For example, anaemia is common in both disseminated TB and Kaposi's sarcoma.)

Anaemia

A recommended approach to anaemia is to consider the different components in the life cycle of red cells. **Building materials (iron, vitamin B12, folate)** are required for the **factory (the bone marrow)** to make red blood cells to send out into the circulation. At the end of their life cycle, the cells are broken down and the components again contribute to the building blocks for the next cycle. In the circulation, however, the cells can be lost via two different routes; either by being **damaged (haemolysis)** or by simply **leaking out (blood loss)**. We will consider how these different components can be affected using Figure 18.1.

Approach to anaemia in primary care

Notes accompanying Figure 18.1

The numbers below and on page 362–363 match the numbered references in Figure 18.1.

Bottom half of the figure

The bottom half of the figure shows the causes of decreased red cell production.

The **bottom right** shows the different conditions that contribute to a lack of the essential building blocks of the red cell.

1. It is reasonable to give iron and folate supplements to all patients with anaemia; however this is rarely the main cause. **Continue to look for other causes!**

> Don't just prescribe iron and folate for patients with anaemia – look for other causes, especially TB.

Figure 18.1 Approach to anaemia in primary care

Anaemia

Loss of red cells

Blood loss

Blood loss may be clinically silent[5] – always think of the following:

Kaposi's sarcoma:

- GIT bleeding is common and is often chronic and not seen by the patient or medical staff.
- Always look at the palate, and **all** of the skin (undress the patient).

Hookworm:

- Endemic in many countries: albendazole 400mg single dose.

Obstetric and gynaeocological causes[6]:

- Ectopic pregnancy, miscarriage.
- Cervical cancer.

INVESTIGATE

- History of bleeding
- Look for KS
- Pregnancy test
- Vaginal examination for cervical cancer

Red cell destruction

Most common causes:

- Malaria[7].
- Rifampicin[8]: consider if severe anaemia occurred after starting TB treatment. Anaemia responds rapidly to stopping rifampicin. If it does not improve on stopping it, rifampicin is not the cause. As alternatives to rifampicin are rarely available, restart rifampicin with close monitoring. If anaemia recurs do not ever use rifampicin again.
- Cotrimoxazole[9] is the more likely cause if the patient is taking both drugs.
- Less common: sickle cell disease[10] in some African countries.

INVESTIGATE

- Malaria rapid test

Decreased red cell production

Bone marrow not working

- **Anaemia of chronic disease[2]:** both HIV and TB cause bone marrow suppression; anaemia responds to treatment with ART and TB treatment. This is the most common cause of anaemia in HIV-positive patients.

Drugs[3]: AZT, cotrimoxazole (see also common causes of anaemia)

- Switch AZT if other NRTIs are available; if possible, check patient is virologically suppressed before changing one drug in a regimen.
- If severe anaemia (Hb <5) stop prophylactic cotrimoxazole, but if being used for treatment on an OI look for alternative medication. (See notes below).

INVESTIGATE

- Look for TB

Lack of raw materials

Lack of erythropoietin:

- Occurs in severe, chronic renal failure[4] (routine pre-ART creatinine will identify this).
- Acute kidney injury does not cause anaemia.

INVESTIGATE

- Renal function – creatinine.

Nutritional deficiency[1]:

- Malabsorption (e.g. chronic diarrhoea) or poor diet causing:
  - Iron deficiency
  - Folate deficiency
- Note this is rarely the most important cause in HIV patients; always look for other causes.

Numbered references correspond to the numbered list under the heading 'Notes accompanying Figure 18.1'

The **bottom left** shows the conditions that cause the factory (the bone marrow) to decrease production of red cells:

HIV and TB, via their effect on the bone marrow, are the most common causes of anaemia in HIV-positive patients.

2. Anaemia of chronic disorders (perhaps better called anaemia of chronic inflammation) is caused by chronic immune activation, infection or malignancy. TB and HIV are common causes. Iron gets trapped in macrophages so it cannot be used, resulting in anaemia. In addition, the marrow, weakened by the chronic inflammation responds inadequately.
3. Drugs:
   - AZT is a fairly common cause, often causing a bicytopaenia (low Hb and WBC) but not low platelets (thrombocytopaenia).
   - CTX can affect all cell lines via interference with folate metabolism. CTX alternatives: for PCP, primaquine and clindamycin; and for toxoplasmosis, pyrimethamine and folinic acid.

   Rare causes of marrow suppression. The following, often causing an Hb of 3–5, can be considered if the anaemia persists and all other causes of anaemia have been treated or excluded:
   - Parvovirus B19; mostly associated with a low CD4 count and usually responds to effective ART. It is a diagnosis of exclusion, and may be the cause in patients with refractory anaemia when TB and HIV have been treated. Patients may need repeated transfusions over several months. Antibody test is not helpful as many patients are positive.
   - 3TC can cause a severe suppression of just the red cell line. This is very rare, and a diagnosis of exclusion. If all other causes have been investigated and treated, stop 3TC and give 2 NRTIs instead (e.g. tenofovir and AZT) together with an NNRTI or PI. Do a viral load before adding a new NRTI. If the patient is failing the regimen, it needs to be changed.
4. Don’t forget that severe, end-stage renal failure causes anaemia, because of lack of erythropoietin, which is made in the kidney. Hb levels can be as low as 4 or 5. A normal serum creatinine will exclude this.

Top half of the figure

The top half of Figure 18.1 shows the causes of red cell loss.

The **top left** shows the different areas where leaks (blood loss) need to be considered.

Take a quick history checking for blood loss where it is not obvious (haemoptysis/ haematemesis).

5. From the bowel, especially occult (hidden) blood loss e.g. Kaposi’s sarcoma or hookworm. In hookworm endemic areas, treat all patients with anaemia for hookworm (albendazole 400 mg single dose); but do not assume this is the major cause. Keep looking for other more likely causes.

6. Gynaecologically, look for:

   - Pregnancy – particularly first trimester complications, miscarriage, ectopic pregnancy;
   - Cervical cancer if there is any history of irregular bleeding or postmenopausal bleeding.

The **top right** shows the common causes of red cell destruction:

7. The malaria parasite destroys red cells.
8. Note the approach to the diagnosis of rifampicin-induced haemolysis.
9. Note, too, that cotrimoxazole can cause anaemia via haemolysis, as well as folate deficiency (see bottom right of diagram).
10. Remember sickle cell disease in those countries where it is more commonly seen.

Treatment of anaemia

Most of the treatment is self-explanatory as it is a matter of treating the cause that has been diagnosed. 'Symptomatic anaemia' is a commonly but incorrectly used term. The symptoms are often due to the underlying cause, rather than anaemia itself (e.g. TB in advanced HIV patients).

A few key points are worth mentioning:

- Look actively for TB, especially if clinical suspicion is high; treat immediately if diagnosed.
- Start the patient on effective ART as soon as possible by starting or re-starting a first line or switching to a second line regimen.
- If the cause of the anaemia is thought to be an AZT, ensure that the patient is virally suppressed before making a single-drug switch.

The role of blood transfusion

Transfusing someone with anaemia without working out the cause is like giving oxygen to someone with pneumonia but not giving an antibiotic. The **cause** must be identified and treated.

When to transfuse?

- There is no specific guideline but it is usually needed when the Hb is <5.5.
- If there are severe respiratory symptoms or haemoptysis, be prepared to transfuse at higher levels; Hb of 8–10, depending on availability of blood.

How much blood do we give? This is often limited by the amount of blood available. Under ideal circumstances:

- Aim to get the Hb to more than about 6.5.
- If there are severe respiratory symptoms or haemoptysis, aim for a higher Hb, ideally 10, but 8 is adequate if it is very difficult to source blood.

Thrombocytopaenia

A low platelet level is more commonly seen as part of a pancytopaenia. The causes are outlined in the algorithm in the bottom left section showing the causes of the marrow not working. The common causes are infections invading the marrow, especially TB, and drugs, especially cotrimoxazole. Note that AZT does not cause thrombocytopaenia, so is not contra-indicated when this is present.

From time to time isolated low platelets are noted on a full blood count. Diagnosis and management are important for two reasons:

1. There is always an underlying condition that needs to be treated.
2. Mild/moderate thrombocytopaenia does not have clinical consequences unless the patient needs surgery (e.g. caesarian section). See section 2 below.

Causes:

There are only a few common causes to be aware of in the HIV setting.

- **Sepsis** and **malaria** can cause destruction of platelets.
- **Drugs**:
    - Cotrimoxazole can cause low platelets via bone marrow suppression. It is, therefore, more commonly associated with a pancytopaenia involving all three cell lines, rather than just the platelets.
    - Rifampicin can cause low platelets via an autoimmune process that may also cause a haemolytic anaemia.
- **Idiopathic Thrombocytopaenic Purpura (ITP) i**s an antibody-mediated destruction of platelets.

    History: Usually occurs early in HIV infection. If the patient has advanced HIV and is unwell, it is not simply ITP.

    Examination: No splenomegaly.

    Investigation: Low platelets but Hb and WBC are normal. A blood smear shows large platelets (young platelets).

    Treatment: Give effective ART and steroids. They can both be started on the same day. Prednisone 60 mg daily for 2 weeks then 40 mg daily for 2 weeks.
- **Thrombotic Thrombocytopaenia Purpura (TTP)** is a serious condition that requires inpatient management. It can be asymptomatic initially, so awareness of the condition is important. It is diagnosed by the presence of red cell fragments in the blood smear. This is a key test available in most facilities, even with basic equipment, so should ideally be done in all cases of isolated thrombocytopaenia. It does, however, need a lab tech who knows what to look for. If thrombocytopaenia is present, **refer urgently to hospital**.

Refer to hospital

What level of thrombocytopaenia matters?

- The lower limit of normal depends on the individual laboratory; often around 140 x 10^9.
- The level at which thrombocytopaenia is a clinical concern is much lower:
    - 30–50; alert signal but, at this level, bleeding risk is low (see notes on lumbar puncture below).
    - <30 the risk of spontaneous bleeding is higher.
    - <10 the risk is significantly higher; can result in spontaneous bleeding, including intracranial bleeding).

Lumbar puncture and thrombocytopaenia

Doing an LP in the presence of a low platelet count runs the risk of epidural bleed. A serum CrAg in this instance will help with the diagnosis of cryptococcal disease.

Guidelines:

- If you cannot do platelet count – this is not a contra-indication to LP.
- If you have done a platelet count, the level at which LP is contra-indicated is controversial. A platelet level of 50 is considered safe; at <50 the actual risk is unknown, but is assumed to be higher. The decision is made on an evaluation of the risks vs benefits – i.e. how much useful information the LP is likely to give vs the risk of a bleed.

Treatment of thrombocytopaenia

- If the level drops acutely to <15 or is persistently <30 and does not respond to other measures (e.g. treating sepsis, stopping cotrimoxazole or rifampicin), steroids can be given to prevent a further drop in platelet count and spontaneous intracranial bleeding. Remember that they are contra-indicated in Kaposi's sarcoma. The standard dose is 1 mg/kg/day for two weeks and then 0.5 mg/kg/day for another two weeks. The dose needs to be increased by 50% if the patient is on rifampicin.
- Avoid NSAIDs as they tend to worsen the thrombocytopaenia.

Neutropaenia

Neutropaenia is defined as an absolute neutrophil count (<1.5 x 10^9/L) but the risk of infection usually increases only if the neutrophil count is <0.5 x 10^9.

A mild neutropaenia is common in HIV-infected patients:

- 10% of patients with early disease;
- 50–75% of patients with late stage disease.

Causes

Low white cell counts are not often encountered in isolation but more usually seen in association with a decrease in the other cell lines.

Bone marrow suppression with a greater focus on WBCs is caused by:

- Viral infections: HIV itself, viral hepatitis;
- Some acute bacterial infections (e.g. *salmonella*).

Other conditions that can lead to a leucopaenia:

- In the presence of vitamin B12 and folate deficiency, the Hb is usually affected first, followed by platelets and then white cells.
- Cotrimoxazole affects the blood via folate deficiency (see earlier in the chapter).
- AZT tends to cause a bicytopaenia with decreased WBC and Hb (platelets not affected).
- Infiltration by OIs and malignancies tends to affect all cell lines.

Management

- Remember that sepsis may cause neutropaenia, rather than the other way round. Therefore look for sepsis and treat it.
- Look for the causes noted above and treat accordingly.
- If advanced HIV, give effective ART by starting it, re-starting it or switching to a new regimen.
- Should you give prophylactic antibiotics?
    - HIV patients aren't at risk of neutropenic sepsis in the same way that bone marrow transplant patients are.
    - Antibiotic prophylaxis is not routinely given.

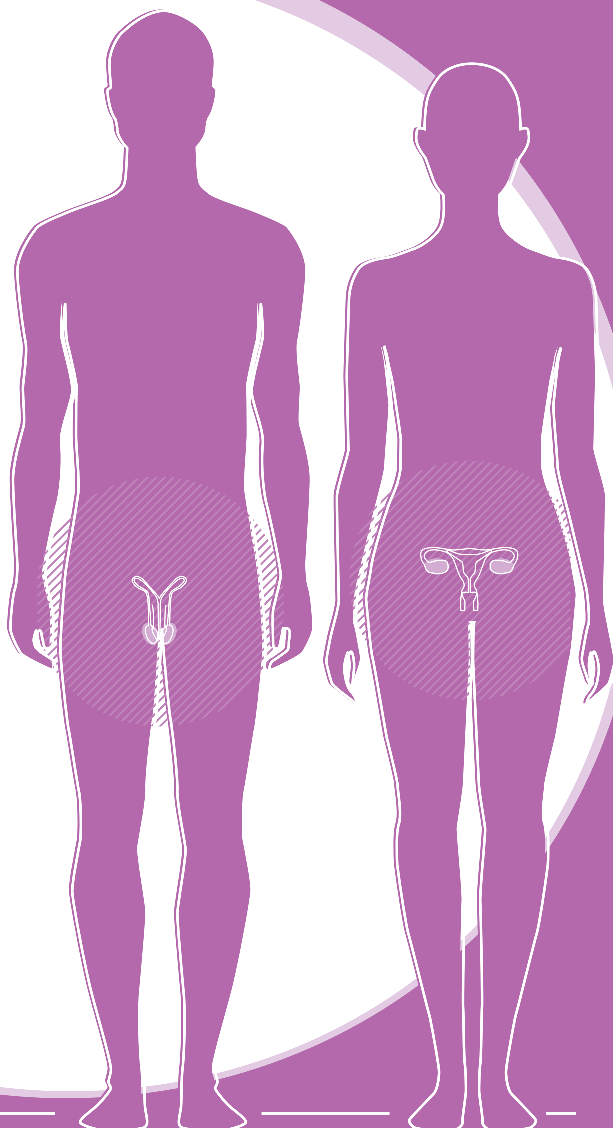
Haematological abnormalities in the HIV-positive patient: Key points

- In the management of anaemia, always look for the cause. Don't just treat with iron and folate or a blood transfusion.
- TB and HIV itself are the commonest causes of anaemia.
- Thrombocytopaenia has only a few common causes in HIV. Remember to look for fragments on the blood smear.
- Neutropaenia is more commonly caused by infection (HIV or sepsis) than the other way round.

CHAPTER 19

Sexual and reproductive health

1. Management of sexually transmitted infections (STIs)
2. Contraception and family planning for women living with HIV
3. Management of unplanned pregnancies
4. Management of sexual violence
5. Cervical screening and carcinoma of the cervix
6. Brief programmatic guidelines for SRH services



This chapter provides information on the provision of sexual healthcare for **people living with or at high risk of HIV** of all ages and gender. The topics covered are:

1. Management of sexually transmitted infections (STIs)
2. Contraception and family planning for PLHIV
3. Management of unplanned pregnancies
4. Management of sexual violence
5. Cervical screening and carcinoma of the cervix
6. Brief programmatic guidelines for SRH services

Communication is the cornerstone of all areas of sexual health practice, and healthcare workers should be adequately trained to address these topics with clients in a sensitive and holistic manner. Discussing options regarding SRH interventions should be done in a non-judgmental manner and women should be empowered to make choices regarding their sexual and reproductive health through provision of adequate information across all options.

The following should be present for an SRH consultation:

- A safe and confidential environment
- Establishment of good rapport and counselling skills
- Good knowledge of prevention and treatment of STIs
- Complete and accurate record keeping.

1. Management of sexually transmitted infections (STIs)

General principles

STIs are the most familiar adverse outcomes of sexual activity and are among the most common causes of ill health in the world. Timely diagnosis and treatment of STIs are a major strategy to prevent the transmission of HIV, as inflamed genital and oral linings increase both spread and receptivity of HIV.

Diagnosing an STI can be difficult as clinical features can vary, an infection may be asymptomatic and laboratory tests may not be reliable or available. The diagnosis is further complicated by the fact that infections are commonly caused by more than one organism (mixed infections).

Because of this, without using diagnostic tests, treatment is usually given based on clusters of presenting symptoms and signs (syndromes), using the standard WHO case management flowcharts.

Syndromic management is cost-effective and allows for rapid treatment of STIs. Since mixed infections are common, syndromic management covers the most likely organisms that may cause a specific symptom. (These are detailed below.)

Sexual risk assessment

Assessing for risk factors for an STI is important, as it not only raises the index of suspicion for an STI to start with, but also prompts the clinician to look for other sites or types of infection.

The following are increased risk factors for an STI:

- Patient aged below 24 (sexually active and single);
- Sexual partner has discharge or STI;
- New partner or more than one partner in the last 3 months;
- Patient has experienced sexual violence; and
- Patient is from one (or more) key population group (see **Chapter 26**).

Five categories of key populations are recognised by WHO:

- Commercial sex workers (CSWs);
- Men who have sex with men (MSM);
- People in prisons and other closed settings;
- People who inject drugs; and
- Transgender people.

All patients at high risk of STIs also need to be considered for PEP and/or PrEP. (See **Chapter 8**, Prevention strategies.)

The six Cs when dealing with STIs:

Practical tip

***Completion** of prescribed medication and **Contact** tracing (of partner) to achieve **Cure**. **Counselling** to **Change** behaviour and encourage **Condom** use.*

A quick check for STIs should be part of every consultation, as treating an STI not only decreases further spread of the infection but also decreases the spread of HIV.

Syndromic management of STIs

The 4 steps of syndromic management include:

A. History taking and examination

B. Syndromic diagnosis and treatment, using flow charts

C. Education and counselling on HIV testing and safer sex, including condom promotion and provision

D. Contact tracing and management of sexual partners

A. History taking and examination

Questions that will influence management and partner follow-up

- Last sexual intercourse (LSI)?
- Condom use? (likelihood of STI)
- Gender of partner and site of exposure? (vagina, anus, mouth)
- Previous partner (LSI) details?
- Last menstrual period? (screen for pregnancy if indicated)

Questions to address other issues at the same time

- Reason to be concerned about any related abuse or sexual exploitation? (sexual violence, transactional sex, child abuse)
- Contraception needs? (for both women and men)
- ART status? (pre-ART, on ART, interrupting and current CD4 and VL)

Practical tip

Tips for tricky questions

- Ask open-ended questions: e.g. Do you have sex with men, women or both?
- Use understandable language: e.g. What are you doing to protect yourself from HIV?
- Use ordinary language: e.g. Does your partner put his penis in your vagina/ anus?
- Respond to difficult queries with, for example, 'That's a good question. I'm not sure of the answer and I'd like to check it out and get back to you.'

A physical examination (genital area observation, bi-manual palpation, milking urethra and visualising cervix with speculum) can be carried out to confirm the symptoms, if the consultation environment allows.

Though it is better for several reasons to examine the patient, syndromic management can be done without it.

In women:

- Inspect for ulcers: Are they single or multiple, painful or painless?
- Confirm abnormal discharge performing a clinical examination: Inspection of vulva and if speculum available, visualise vagina and cervix (look for discharge and cervical abnormalities).
- Carry out abdominal and bimanual pelvic examinations to check for lower abdominal or cervical motion tenderness (PID), pelvic masses (abscesses and tumours).
- If ulcerated lesions or a palpable mass on the cervix, **refer immediately**.

Refer to hospital

In men:

- Inspect for ulcers: Are they single or multiple, painful or painless?
- Confirm urethral discharge by getting patient to milk urethra.
- If a painful or swollen testis is detected, refer to exclude testicular torsion.

B. Syndromic diagnosis and treatment, using flow charts

Based on the above history and examination, the syndrome can be identified using the table below and following the appropriate treatment algorithm. Treatment should be provided at the same visit and an appointment for reassessment in one to two weeks should be set.

Though not always possible, patient's response to STI treatment is important to assess within one week. If symptoms persist consider possible re-infection, poor adherence to treatment or a resistant strain of STI.

Table 19.1 Syndromic presentations of sexually transmitted infections

See page	Syndrome	Symptoms	Signs	Most common causes
372	Urethral discharge	Urethral discharge; Dysuria; Frequent urination.	Urethral discharge (if necessary ask patient to milk urethra).	Gonorrhoea; chlamydia.
374	Vaginal discharge	Unusual vaginal discharge; Vaginal itching; Dysuria (pain on urination); Dyspareunia (pain during sexual intercourse).	Abnormal vaginal discharge.	**Vaginitis:** – Trichomoniasis – Candidiasis **Cervicitis:** – Gonorrhoea – Chlamydia
376	Genital ulcer	Genital sore; Scrotal pain and swelling; Painful enlarged inguinal lymph nodes.	Genital ulcer; Enlarged inguinal lymph nodes; Fluctuation; Abscesses or fistulae.	Syphilis chancroid; Genital herpes; LGV chancroid.
378	Lower abdominal pain in women	Lower abdominal pain; Dyspareunia.	Vaginal discharge; Lower abdominal tenderness on palpation; Temperature >38°.	Gonorrhoea; Chlamydia; Mixed anaerobes.

Urethral discharge

Gonorrhoea and chlamydia are the most common cause of urethral discharge. Men may also complain of dysuria (painful urination) or testicular pain. If a painful or swollen testis is detected, refer to exclude testicular torsion.

Gonococcus and chlamydia can also present as an anal discharge. The treatment is the same.

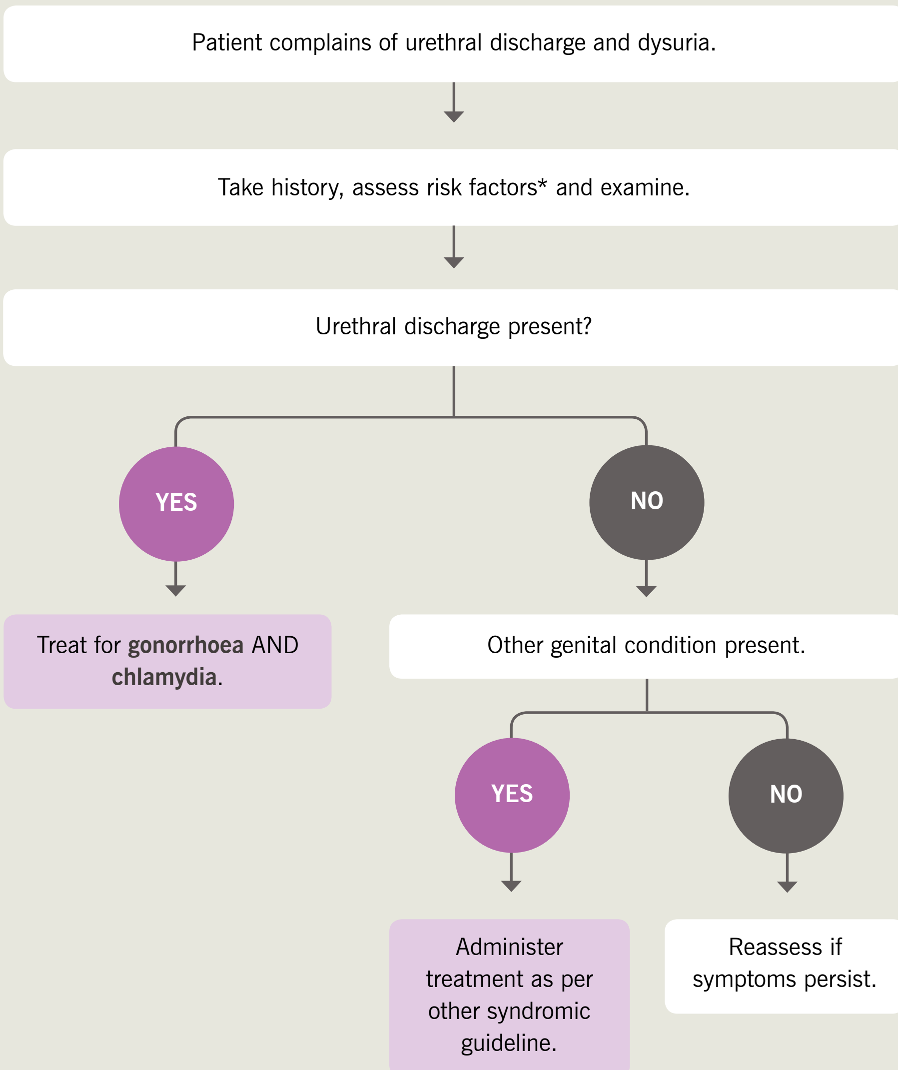
Sexual partners should receive the same treatment, regardless of symptoms.

Table 19.2 Drugs and doses for urethral discharge

Urethral discharge: Treat for chlamydia AND gonorrhoea	
Chlamydia	**Gonorrhoea**
Azithromycin 1 g PO single dose Or Doxycycline 200 mg PO 7 days	Ceftriaxone 250 mg IM single dose Or Cefixime 400 mg PO single dose

If symptoms persist or re-appear, this may be due to trichomoniasis or gonococcal resistance, for which there is increasing prevalence. Please check your local guidelines and seek expert advice.

Figure 19.1 Management of urethral discharge



* Risk factors: see page 369.

Vaginal discharge

A discharge can be normal or caused by a vaginal infection (vaginitis) or infection of the cervix (cervicitis).

- Some clear or white non-odorous vaginal discharge is normal.
- Vaginitis or cervicitis usually presents with a discharge of a different colour, consistency and odour, and/or pain, when having intercourse (dyspareunia).
- Vaginitis can also present with burning or itching of the vulva (pruritus).

Causative organisms:

- *Gardnerella*, trichomonas and candida are the likely causes of vaginitis.
- Gonorrhoea and chlamydia are the likely causes of cervicitis.

Cervicitis may be difficult to diagnose. When in doubt, administer treatment for cervicitis to women with abnormal vaginal discharge and any of the following risk factors:

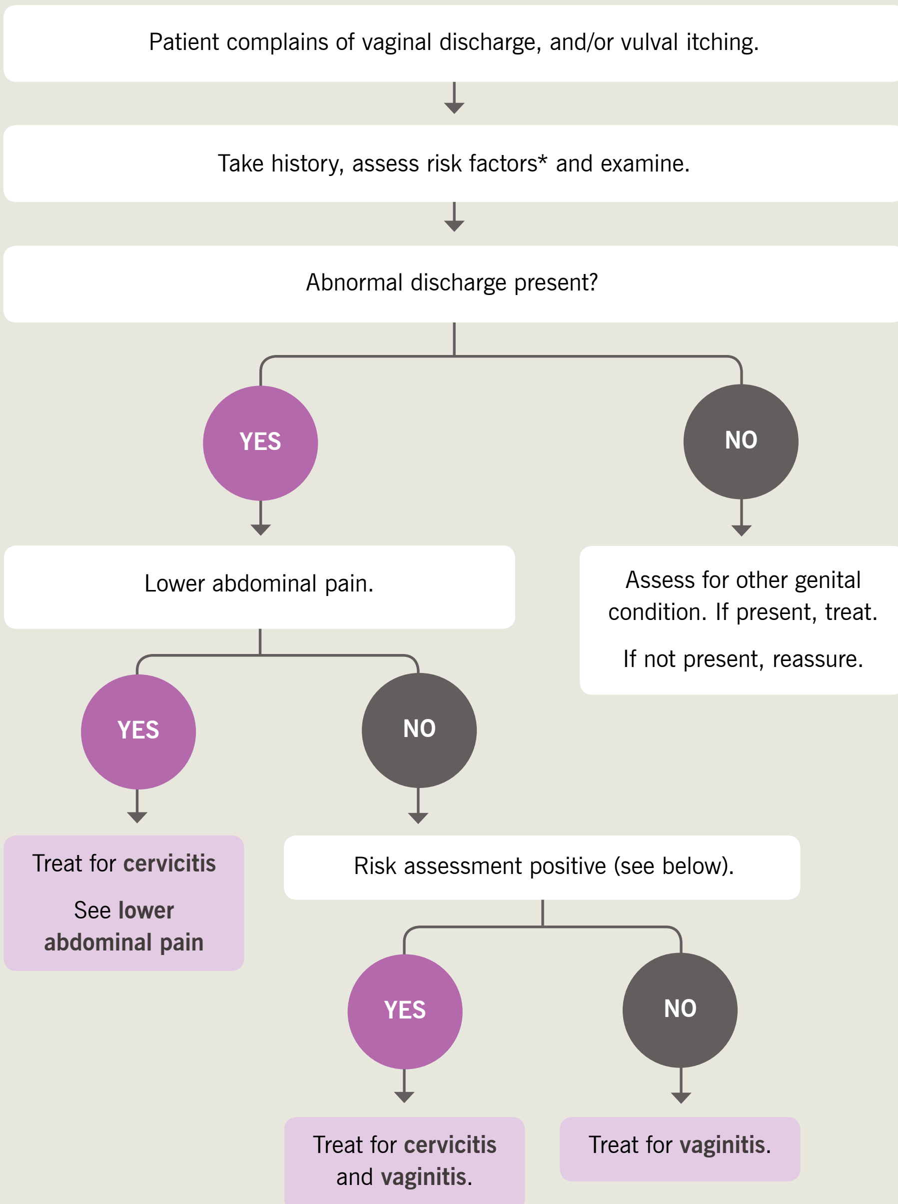
- Urethral discharge in the partner;
- Context of sexual violence or sex work;
- New partner or more than one partner in the preceding 3 months.

Practical tip

Vaginal hygiene tips for the patient

- Never use household cleaning products or washing powders to wash the vulva or vagina.
- Don’t insert traditional products to wash or dry the vagina.
- To cleanse after sex, squat and squeeze semen out of vagina, and rinse vulva with water.
- The vagina has a natural self-cleansing system too.
- Don’t leave period plugs like tampons or cotton inside the vagina for longer than 8 hours.

Figure 19.2 Management of vaginal discharge



* Risk factors: see page 369.

Sexual partners should receive the same treatment regardless of symptoms.

Table 19.3 Drugs and doses for vaginal discharge

If no risk of STI treat for vaginitis only	
***Gardnerella* and trichomonas**	**Candida (thrush)**
Tinidazole 2 g PO single dose Or Metronidazole 2 g PO single dose	Clotrimoxazole 500 mg vaginal pessary single dose (deep into vagina at bedtime) And Clotrimoxazole cream may complement but not replace (use cream on genitalia for 7 days)
If positive STI risk and vaginitis treat for cervicitis	
Chlamydia	**Gonorrhoea**
Azithromycin 1 g PO single dose Or Doxycicline 200 mg PO 7 days If pregnant: Azithromycin 1 g PO single dose or Erythromycin 2 g a day for 7 days	Ceftriaxone 250 mg IM single dose Or Cefixime 400 mg PO single dose

Pregnant women must be reviewed in one week. If there is no improvement, refer to the doctor.

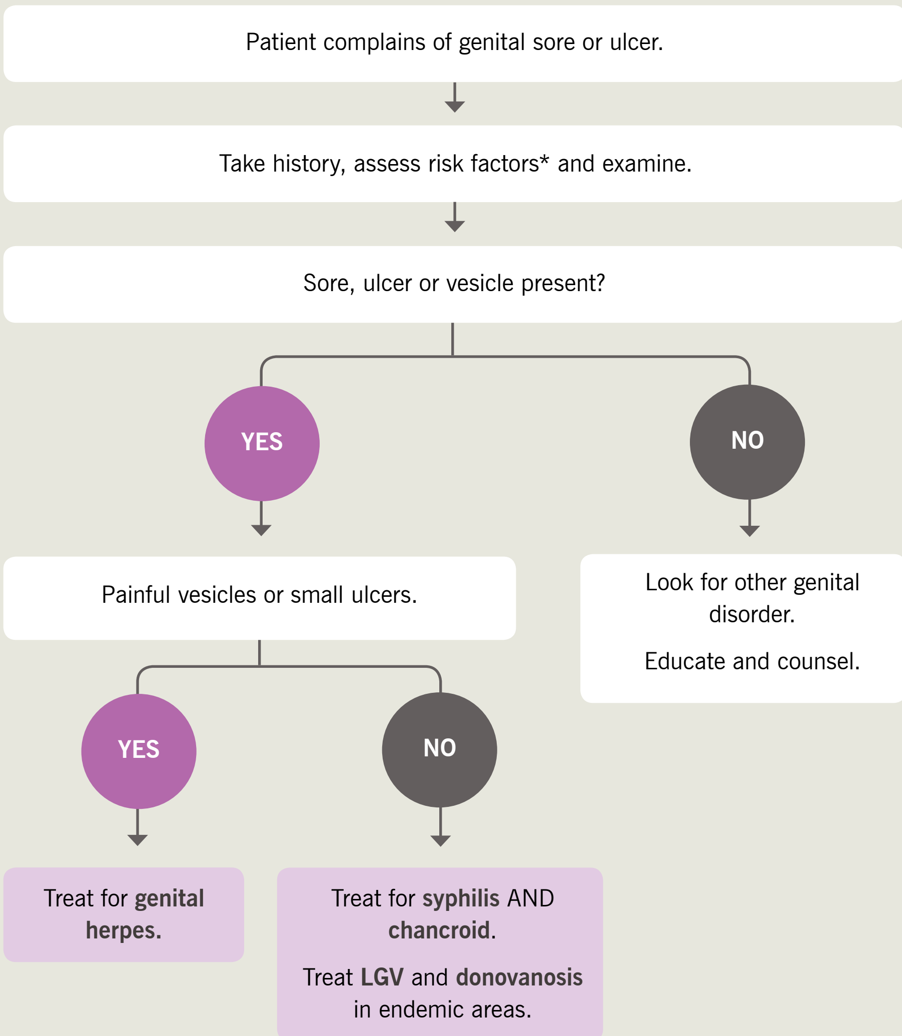
Genital ulcers

Genital ulcers may present as single or multiple ulcers, vesicles or erosions, with or without pain and with or without inguinal lymphadenopathy. They are most commonly caused by:

- Herpes simplex (note in HIV-positive patients, if present for more than 1 month, this is a stage 4 diagnosis);
- Syphilis;
- Chancroid; or
- Lymphogranuloma venereum and donovanosis (lymphogranuloma venereum, caused by chlamydia, and donovanosis are rare but endemic in parts of Africa, Asia and South America).

Sexual partners should receive the same treatment regardless of symptoms. Give pain relief as required and keep area clean and dry.

Figure 19.3 Management of genital ulcers



* Risk factors: see page 369.

If fluctuant lymph nodes are present, they may be aspirated and fluid sent for microscopy and testing for TB.

Lower abdominal pain (women)

Lower abdominal pain in women has many causes, including complications of pregnancy, upper genital tract infections and pelvic inflammatory disease. A thorough history and physical examination, as well as urine and pregnancy testing, are necessary to determine the cause.

Assessment

- If within 2 to 10 days after delivery or abortion, consider infection and treat with antibiotics as soon as possible.
- Take history, assess STI risk (see page 369), pregnancy and check temperature.
- Perform abdominal and bimanual pelvic examinations to check for:
    - rebound tenderness;
    - cervical motion tenderness;
    - tender pelvic mass; or
    - urethral and vaginal discharge.

Management

Refer to hospital

Danger signs requiring **referral to hospital**:

- dehydrated or in shock;
- patient cannot walk upright;
- temperature >38.5 °C;
- severe abdominal tenderness or pelvic mass;
- abnormal vaginal bleeding;
- pregnant (or missed or overdue period and pregnancy test not available);
- recent miscarriage, delivery or abortion; or
- abdominal mass.

Immediate management, while waiting for transfer to hospital:

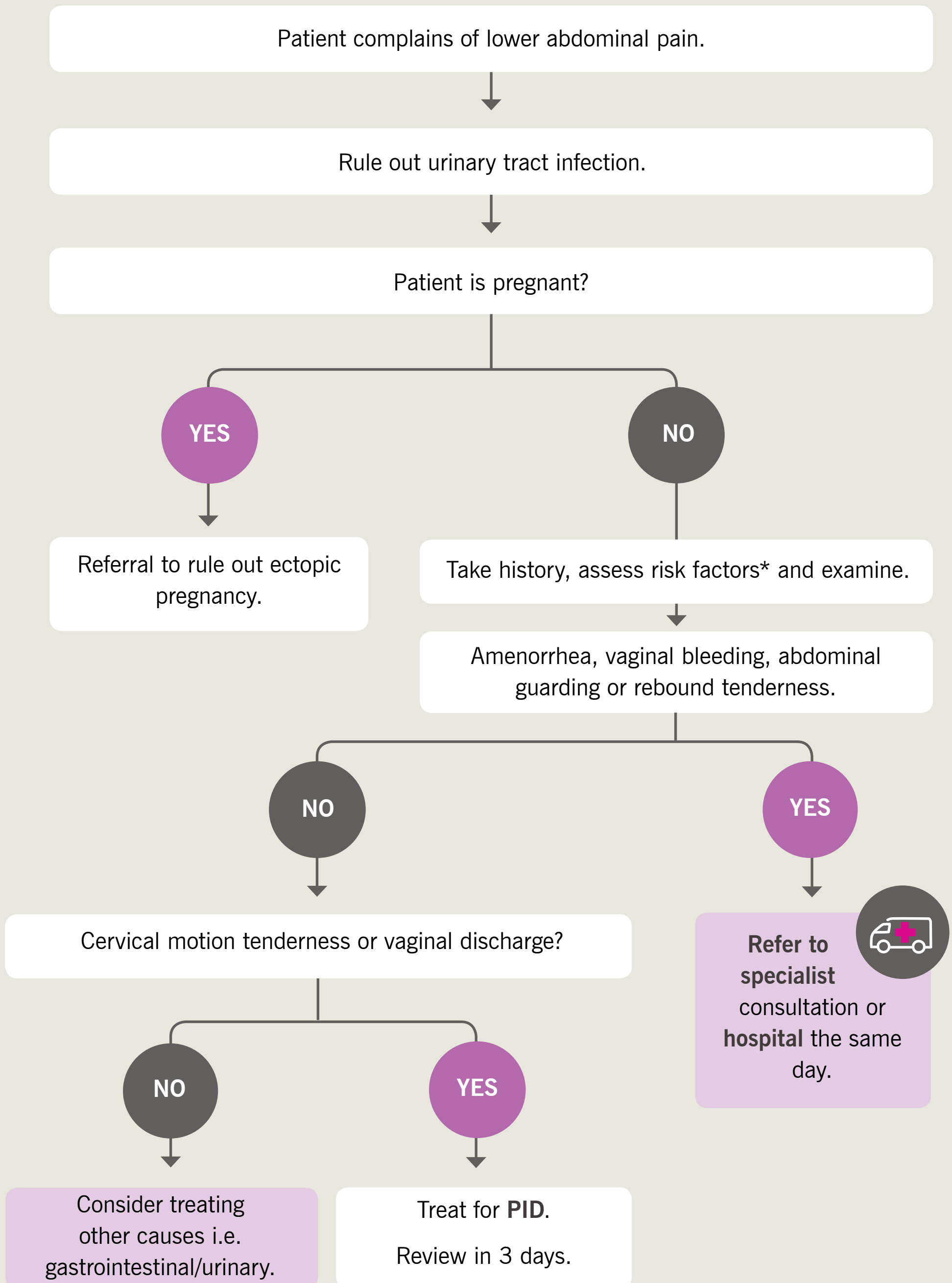
- Give antibiotics as soon as possible: ceftriaxone 1 g IM or IV stat metronidazole 400 mg orally stat.
- If dehydrated or in shock, give IV fluids (sodium chloride, Ringer's lactate or other christalloid solution stat).

If UTI has been excluded, treat as for moderate pelvic inflammatory disease (PID) as follows:

- Ceftriaxone 250 mg IM injection stat or cefixime 500 mg PO stat, and
- Doxycycline 200 mg PO 12 hourly for 7 days (if pregnant or breastfeeding give amoxicillin 500 mg 8 hourly for 7 days), and
- Metronidazole 1 g 12 hourly for 7 days (avoid alcohol).

Reassess in 3 days and refer to hospital if not improving.

Figure 19.4 Management of lower abdominal pain in women



* Risk factors: see page 369.

Periodic presumptive treatment

Clients from key population groups may be offered **presumptive periodic treatment (PPT)** (see also **Chapter 26**, Key populations). PPT is the periodic treatment of curable STIs, regardless of the presence or absence of signs or symptoms, based on the high risk and prevalence of infection in particular key populations. It is an effective short-term measure that can reduce the prevalence of STIs amongst high-risk populations, such as sex workers.

The usual treatment consists of one or two tablets with the aim of treating gonococcus, chlamydia and ulcerative STIs.

PPT is ideally implemented together with peer intervention and measures to increase condom and lubricant use. Consult local MSF or MoH guidelines for implementation details.

Prevention strategies for HIV

Strategies for preventing HIV transmission and acquiring HIV are more comprehensively addressed in the PrEP and PEP sections in **Chapter 8**, pages 108–9.

Detail for specific infections

Syphilis

Syphilis, caused by a spirochaete, *Treponema pallidum*, is a complicated disease, having different stages, signs and symptoms. It is, however, beyond the scope of this book to cover all of this detail. The focus is on general diagnosis and management in primary care HIV clinics, focusing on testing and the standard management of primary syphilis. Syphilis can also be transmitted from mother to child, so guidelines are also included for diagnosis and management in pregnancy.

For more detail, please consult your **national guidelines**.

Refer to your national guidelines

Clinical presentation

Commonly syphilis presents as a positive rapid test that has been done routinely as part of standard screening protocols. It can also present with a variety of different clinical features.

Large syphilitic ulcer (chancre)

Early stage: Primary or secondary signs:

Primary: Painless chancre (ulceration) occurring during initial infection; this often goes unnoticed because it is painless. It can resolve spontaneously in 6 weeks.

Secondary: Rashes appearing several months after primary infection, typically including the palms and soles, snail track ulcers in the mouth, condylomata lata, constitutional symptoms and arthralgia. Any organ may be affected (e.g. meningitis, hepatitis, nephritis). But also sometimes it is asymptomatic!

Latent stage: Asymptomatic or absence of primary or secondary signs.

Tertiary stage: Late stage of infection, causing skin, heart and neurological problems.

Testing for syphilis

Testing for syphilis is recommended for pregnant women and annually for all people at risk

There are two types of test:

- The RPR, which is positive in active disease and becomes negative after treatment. It can, however, be positive in other disease, such as rheumatoid arthritis, so another, more specific test is needed to confirm the diagnosis.
- Various specific antibody tests that confirm syphilis, but, once positive, they remain so for life. They are, therefore, not a marker of active disease.

Frequently, a combination of both is used, so that the diagnosis is confirmed using the antibody test, and the activity is indicated by the TPHA.

Management

If syphilis is suggested from a positive VDRL result, treat as described in Table 19.4.

Table 19.4 Treatment regimens for syphilis

Primary and secondary	Benzathine penicillin (2.4 MU IM as a single dose) is first choice OR Can also use doxycycline (100 mg 12 hourly) for 14 days if penicillin allergy.
If allergic to penicillin	Ceftriaxone 1 g daily for 14 days. OR Erythromycin (500 mg 6 hourly) for 14 days (only for pregnant women, who must be given a course of doxycycline after delivery as erythromycin does not reliably treat syphilis) OR Azithromycin 2 g stat as a single dose.
Latent syphilis	Benzathine penicillin (2.4 MU IM) at weekly intervals for 3 weeks OR Erythromycin (500 mg 6 hourly) for 28 days (only for pregnant women, who must be given a course of doxycycline after delivery, as erythromycin does not reliably treat syphilis) OR Ceftriaxone 1 g daily for 14 days OR Doxycycline (100 mg 12 hourly) for 28 days.
Pregnancy	Benzathine penicillin 2.4 MU IM weekly for 3 weeks. As only penicillin reliably treats the baby, consider desensitisation in penicillin-allergic patients.

Hepatitis B & C

Hepatitis B is readily transmitted sexually and is far more infectious than HIV. Hepatitis C is also transmitted sexually, but is much less infectious. Higher risk of sexual transmission of hepatitis C is generally associated with HIV-positive MSM. These conditions are covered more comprehensively in **Chapter 16**, Liver disease. Vaccinations are covered in **Chapter 8**, Prevention strategies.

Candida (Thrush)

Vulvo-vaginal candidiasis (also known as vaginal thrush or yeast vaginitis) is caused by a type of fungus (called candida). It can occur in all women, but is more common in those who are diabetic, pregnant, HIV positive or on steroids. It is not an STI.

Vaginal thrush is more common in HIV-positive women for two reasons:

- HIV-positive women may have weaker immune systems and are more likely to suffer from infections in general.
- HIV-positive women are more often given antibiotics, which disturb the normal balance of organisms in a woman's body, and this allows the candida yeast to overgrow.

Clinical presentation

- Burning or itching sensation in the vagina;
- White thick discharge; and
- Inflamed and itchy vulva.

Management

Topical therapies may be used, depending on what is available in your clinic (see Table 19.5).

Table 19.5 Management of vaginal thrush

Vaginal thrush (Candidiasis)	Clotrimazole vaginal tablet 500 mg stat, inserted high inside the vagina at bedtime. AND Clotrimazole vaginal cream applied twice daily on vulva for 7 days.
Recurrent >3 episodes	Oral treatment with fluconazole 150 mg stat dose (should be effective) OR Fluconazole 50 mg daily for 7–10 days (also effective but patients are less likely to adhere) OR Repeat clotrimazole treatment (as above).

Practical tip

Tips for managing vaginal thrush

- Avoid washing vulva and vagina with soap.
- Advise patient to return in 7 days if symptoms persist.
- Test for diabetes and pregnancy.
- If ongoing discharge but no vaginal thrush on examination, consider treatment for vaginitis (page 374).

Genital warts

Human papilloma virus (HPV) is a sexually transmitted virus. HPV types 6 and 11 can cause **genital warts** in men or women.

Clinical presentation

- HPV can present externally as genital warts (also known as condylomata acuminata): They start as small papules, which are often not noticed by the patient.
- Warts grow on moist surfaces and areas traumatised during sexual intercourse. They can be:
  - external: penile, vulva, perineum, peri-anal
  - internal: vagina, cervix.
- Genital warts can grow to become cauliflower-like lumps.

Management

Check for syphilis and other STIs (think co-infection). Refer to Table 19.6 for treatment.

Table 19.6 Management of genital warts

Small genital warts: (check for size criteria)	Large genital warts
Protect surrounding skin with petroleum jelly. Apply 20% tincture of podophyllin or podophyllotoxin topical solution (5 mg/ml) twice daily for 3 consecutive days (can repeat at weekly intervals if necessary for a total of five 3-day treatment courses). Do not apply podophyllin solution internally.	Cryotherapy is the preferred treatment, if available. Laser therapy is an alternative treatment. If big and/or not responding, patient can be referred for surgical treatment.

Do not use podophyllin and podophyllotoxin during pregnancy as it can cause foetal abnormalities.

C. Education and counselling

Patient education and counselling, with special emphasis on relationship counselling and an ability to undertake open discussion on sexuality and sexual behaviour can further assist patients in reducing sexual risk behaviours.

Advice on condom use is essential, including education and demonstration of correct use, if necessary.

D. Contact tracing and management of sexual partners

For all STI syndromes, contact tracing and treatment of all partners to avoid re-infection is an essential element in epidemiological management. This begins with a conversation with the index patient, advising them to inform their partners and providing referral options, including in person, phone, SMS, email or letter, depending on the ability or choice of the patient.

Clinician's approach to the partner with an STI:

- Advise patients diagnosed with an STI to encourage partners to attend for full screening and treatment, even if asymptomatic.
- Offer the patient the same treatment to give to partner, as, in reality, many partners do not attend clinics.

2. Contraception and family planning for women living with HIV

General principles

- Contraception and family planning aim to give people the freedom to choose whether and when to have children.
- This includes birth control, planning for a baby, spacing births and infertility advice and treatment. It also encompasses emotional wellbeing and affects the individual's enjoyment of his or her own sexuality. Male involvement is important, but often very difficult.
- Side effects of contraceptive methods will affect some women more than others. Tolerability of some side effects should be weighed up against the risk of an unplanned pregnancy.
- There are many barriers to effective contraception, including lack of knowledge, laws and policies, social norms, religious beliefs, myths and taboos. See Table 19.7.

Table 19.7 Contraception myths and misconceptions

Myths and misconceptions	Fact
Condoms block sperm and make you ill.	They neither block sperm nor cause illness. Condoms prevent STIs and pregnancies.
Depo-Provera can make you infertile.	Fertility returns on stopping Depo-Provera, but can take up to 18 months to do so.
Contraceptive pills cause cancer.	Contraceptive pills protect against cancer. Cervical cancer is related to other factors, such as STIs.
IUCDs are painful for the man during intercourse.	A well-fitted IUCD should not be felt by either the man or the woman during intercourse.

Living with HIV should not be a barrier to a healthy sexual and reproductive life.

Women and couples at high risk of HIV infection are eligible to use all forms of contraception and an informed decision is a key principle.

It is important to provide patients with information that addresses their particular needs. Active listening, paraphrasing and clarifying encourage patients to choose their preferred contraceptive method.

Counselling and informed consent:

- Facilitates the process of informed and free choice;
- Facilitates the participation of the beneficiary in their health-seeking behaviour;
- Helps with satisfaction in choice of contraception method;
- Helps towards correct use of a method of contraception; and
- Improves satisfaction with health services.

Methods of contraception

Table 19.8 outlines the methods of contraception available and specific considerations for women living with HIV. For comprehensive information, including the assessment of medical eligibility, see the 2018 **WHO family planning handbook**, https://www.fphandbook.org/sites/default/files/global-handbook-2018-full-web.pdf

Women should have the options explained to them and be empowered to make a choice regarding their contraception method.

www.fphandbook.org/sites/default/files/global-handbook-2018-full-web.pdf

Table 19.8 Contraception for PLHIV and those at risk of acquiring HIV

Method	Mechanism	Efficacy	Advice	HIV-positive women on ART
Natural methods				
Breastfeeding calendar method; Withdawal method	All follow fertility cycle.	Negligible	**Not recommended.**	**Reinforce VL suppression messages and offer FP choice.**
Barrier methods				
Male condoms; Female condoms	Prevents contact with genital fluids (infection and fertilisation).	99% if consistent use; Use lubricants to prevent condom break.	**Don't rely solely on condoms for contraception; use an additional method.**	**Highly recommended.**
IUCD (copper T)	Prevents fertilisation.	Almost 100%; Lasts up to 10 years.	**Recommended use with condoms.**	**Highly recommended LLM; ensure double protection.**
Hormonal progestogen and/or levonorgestrel				
Oral contraceptives	Stops development and release of ovum; Thickening of cervical mucous; and Thinning lining of uterus.	>90% if adherent to method.	Recommended but needs strict adherence	**Not advised with EFV or NVP (see Chapter 7).**
Injectables		>99% if regularly adherent to method (2 to 3 months).	Depo-Provera may increase risk of acquiring HIV*. **Use condoms for HIV protection***	**Recommended; Ensure regularity of injections.**
Implants		>99% (3 to 5 years)	Women taking ART with EFV may have lower efficacy. Advise alternative options.	**Recommended LLM.**

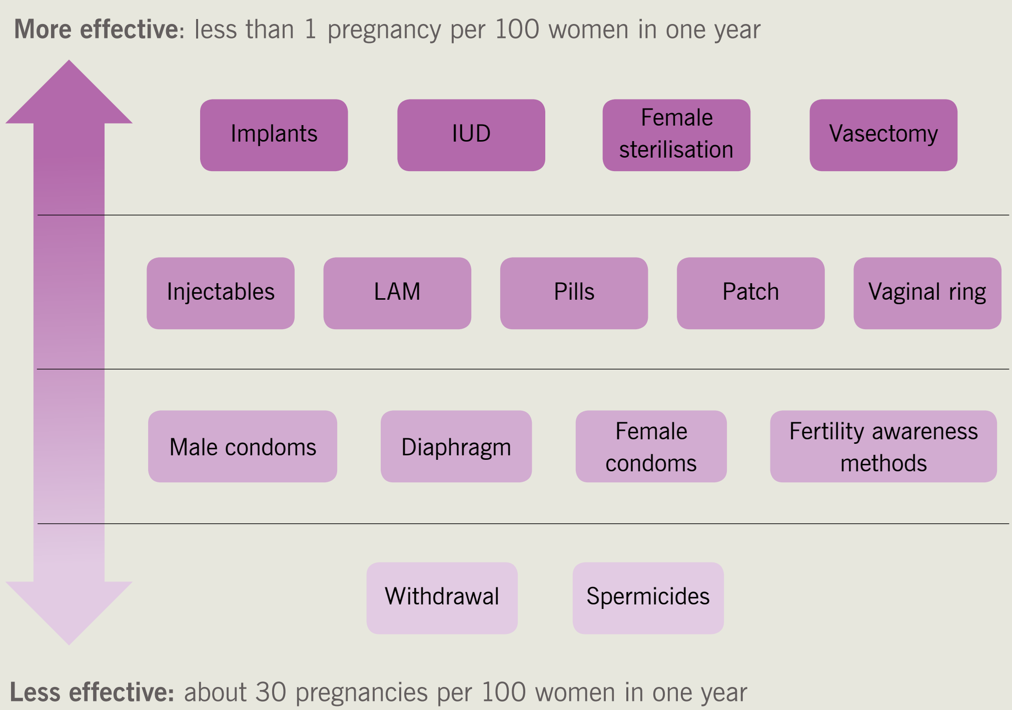
*Watch WHO guidelines for updates as it may be recommended that HIV-negative women at high risk of HIV infection use other contraceptive options first.

Emergency contraception

If UPSI or contraceptive method fails:

1. Do pregnancy test (PT). If positive, assess and offer choice of termination of pregnancy (CToP) or referral for antenatal care (see page 388).
2. If PT is negative, emergency contraceptive must be given within the first 5 days, according to following guidelines:
    - Standard emergency contraception: Levonorgestrel 1.5 mg stat PO, ideally within 72 hours, but may be given up to 120 hours.
    - If patient on rifampicin, EFV, NVP, phenytoin, phenobarbitone or carbamazepine, double the dose of levonorgestrel to 3 mg stat, to allow for the induction effect on the metabolism of the levornorgestrel (see **Chapter 7**, Drug-drug interactions).
    - An IUCD can also be given as emergency contraception within 5 days of unprotected sexual intercourse (ensure STI prophylaxis).
3. General advice
    - Use the opportunity to counsel on contraception choice and STI prevention.
    - Advise patient to return for a pregnancy test, if her period is delayed.

Figure 19.5 Effectiveness of family planning methods



Safe conception

All HIV-positive couples (discordant and where both partners are HIV positive) should be provided with safe conception advice as part of routine counselling.

Planning a family when the woman is HIV positive:

- Ideally the woman should be at least 6 months on ART with a suppressed viral load and no concurrent OIs.
- If not, use contraception for 6 to 12 months till viral load undetectable.

Planning a family when woman is HIV negative and man is HIV positive:

- Ensure man on ART is virologically suppressed.
- Offer PrEP to woman (see **Chapter 8**, Prevention strategies).

3. Management of unplanned pregnancies

It is not within the scope of this guide to describe the full assessment and management of abortions. For further information please refer to MSF SRH Guidelines.

- Post abortion care (PAC) refers to when a woman has started the process of abortion (naturally or induced).
- Safe abortion care (SAC) refers to when a woman has access to a safe abortion process on request.

Safe abortion care needs:

- A safe and confidential environment;
- Correct drugs or equipment; and
- A trained and certified practitioner.

Contraception (family planning) can start the same day as the abortion procedure.

Assessment

- Take history, assess STI risk, test for pregnancy and check temperature.
- Assess gestational age (LMP, fundal height, ultrasound if available).
- If process of abortion has started (naturally or induced) consider antibiotics as soon as possible.
- Perform abdominal and bimanual pelvic examinations to check for lower abdominal pain or cervical motion tenderness (PID) and tender pelvic mass (abscess). Check for urethral and vaginal discharge.

Management

Contraception/family planning method can often be started on same day of procedure. Provide:

- Counselling, informed decision, and consent;
- Pain management with combination analgesics; and
- Follow up in 10 to 14 days for post-abortion review.

Table 19.9 Safe abortion methods

Method	Procedure*	Timing/gestation**	Remarks
Medical abortion	Mifepristone and Misoprostol sublingual, oral or/and vaginal (WHO Gold Standard).	<12 to 14 weeks LMP	Can receive medication at home. Return for follow-up required.
Surgical abortion	Misoprostol sublingual or vaginal, manual vacuum aspiration (MVA).	<12 to 14 weeks LMP	Pain management and clinical environment. Antibiotic prophylaxis required.
	Instrumental D&C must not be used.	>14 weeks LMP	Absolute contra-indication: refer!

* Refer to *MSF Medical Guidelines, Obstetric and Newborn Care,* Chapter 12 https://medicalguidelines.msf.org/viewport/MG/en/guidelines-16681097.html

** MSF guidelines offer ToP up to 20 weeks. See local MSF and MOH guidelines

Key risks for abortion procedures:

- Patient's gestational age over the agreed limit and provider does not have right skills;
- Patient could have an unwanted abortion (hasty decisions);
- Patient could have an ectopic pregnancy.

4. Management of sexual violence

Sexual violence (SV) has physical, psychological, social and legal consequences. The medical response should not be limited to treatment of immediate medical injuries or infections but should incorporate psychological support for the client.

Sexual violence and rape are often under-reported. An open and non-judgmental attitude by the healthcare worker is essential. Patients may not bring up a history of sexual violence unless they feel at ease in the consultation, so be aware of more subtle signs, such as avoiding eye contact when talking. SV screening tools can be used to assess the patient's risks. The ASIST-GBV Screening Tool for Women is available in the **additional resources** section of the *MSF HIV/TB Guide for Primary Care*, https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

The consequences of sexual violence can be reduced through the provision of appropriate medical and mental healthcare.

Management guidelines

Management of sexual assault includes taking and documenting a thorough history and a physical examination followed by 5 key steps (for full guidance on the management of sexual assault please refer to the medical protocol for sexual violence care (revised 2014) in the **additional resources** section of the *MSF HIV/TB Guide for Primary Care*, https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

1. **HIV prevention**

- Give post-exposure prophylaxis (PEP) if the patient presents within the first 72 hours after the event and is HIV negative.

  MSF recommends three-drug PEP, using dolutegravir for all cases of rape.

  (See **Chapter 8**, PEP section, page 118 and consult local guidelines for national protocols.)

  - TDF + 3TC (or FTC) + dolutegravir 50 mg once daily for 28 days.
  - An alternative to TDF is AZT. Alternatives to dolutegravir are atazavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r).

2. **Pregnancy prevention**

   - Test for pregnancy and provide emergency contraception.
   - Give levonorgestrel 1.5 mg stat PO within 72 hours and up to 120 hours.
   - If patient on any enzyme-inducing drug (e.g. rifampicin, NNRTIs, protease inhibitors, carbamazepine, phenytoin or phenobarbitone) double the dose of levonorgestrel to 3 mg stat.
   - If pregnancy test positive, assess and offer choice of termination of pregnancy (CToP) provison and/or referral.

3. **STI treatment and prevention**

   Hepatitis B vaccination if source unknown: give first dose immediately, preferably within the first 24 hours, but can be up to 2 weeks after possible exposure.

   - If previously unvaccinated, give first dose immediately and then complete the course as per age-related schedules.
   - If in process of being vaccinated, ensure completion of the course as recommended.

Table 19.10 STI prophylaxis for sexual violence

Non-pregnant adults and children >12 years)	Pregnant adults or adolescents >12 years
Ceftriaxone 250mg IM stat (or cefixime 400 mg stat dose) AND Azithromycin 2 g PO stat dose (or doxycycline 100 mg twice a day for 7 days). AND Metronidazole 2 g PO stat dose	Ceftriaxone 250 mg IM stat dose AND Azithromycin 1 g stat (or erythromycin 500 mg 4 times a day for 7 days) AND Metronidazole 400 mg tds for 7 days

4. **Tetanus vaccination**
   - Provide tetanus toxoid.
5. **Mental health**
   - Provide psychological first aid by giving patient immediate attention.
   - Trauma counselling (post-traumatic stress, anxiety, depression, etc.).

Children

- Be aware of legal age of consent for HIV testing and HIV PEP in children in the national context.
- For children/adolescents >12 years, manage as above.
- Children <12 years should preferably be managed at a specialised site, where there is expertise in dealing with traumatised children and ART in children.
- For ARV prophylaxis (PEP) in children >40 kg and >6 years of age, the adult regimens may be given. For drug dosages according to weight, refer to Tables 10.8 to 10.10. For children <40 kg and/or <6 years of age give: AZT or ABC + 3TC + lopinavir/ritonavir (LPV/r).
- STI prophylaxis (see Tables 19.11 and 19.12 for dosages).

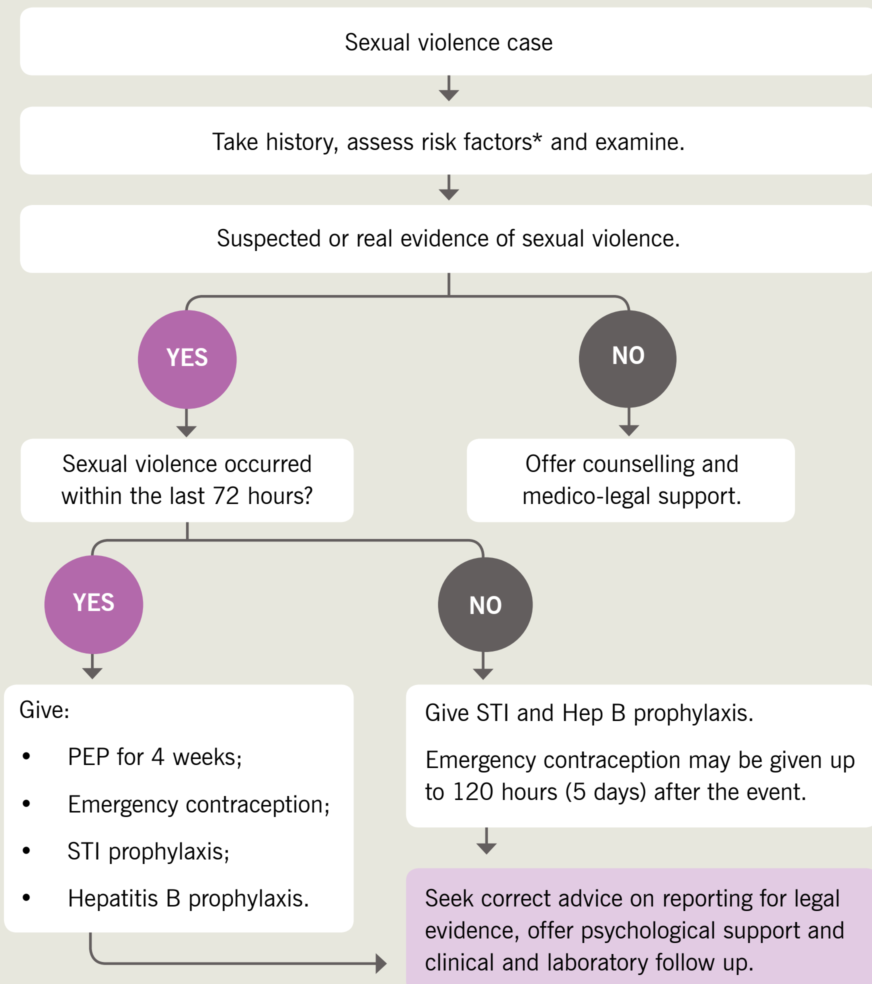
Table 19.11 Children's prophylactic medications against gonorrhoea and chlamydia

Medication	Children 5–14 kg	Children 12–25 kg	Children 25–45 kg
Cefixime stat	(100 mg/5 ml) 8 mg/kg powder/ suspension	(200 mg) 200 mg tablet/capsule	(200 mg) 400 mg tablet/capsule
Azithromycin stat	(200 mg/5ml) 20 mg/kg	(250 mg) 500 mg	(250 mg) 2 g

Table 19.12 Children's prophylactic medications against trichomonas

Medication	Children 5–14 kg	Children 12–25 kg	Children 25–45 kg
Tinidazole STAT	x	x	(500 mg) 50 mg/kg max 2 g tablet or powder for suspension
Metronidazole X 7 days	x	x	125 mg/ml, 250 mg/ml, 500 mg/ml 30 mg/kg/day tds tablet or powder for suspension

Figure 19.6 Summary algorithm for management of a patient following sexual violence



* See risk factors on page 369.

5. Cervical screening and carcinoma of the cervix

For further information, refer to the 2018 Cervical cancer guidance document in the **additional resources** section of the *MSF HIV/TB Guide for Primary Care*, https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Cervical cancer is one of the most common cancers in women in resource-poor settings. It is now known that cervical cancer is caused by a virus, human papilloma virus (HPV). There are about 100 different serotypes of HPV, of which types 16 and 18 most commonly cause carcinoma. HPV is sexually transmitted and can eventually result in carcinoma of the cervix.

Cervical cancer can be prevented through a combination of vaccination against HPV and cervical screening.

Vaccination

For all HIV-positive women and girls >15 years, a 3-dose schedule is recommended. For girls <15 years, 2 doses are given. Refer to your local Expanded Programme on Immunisation (EPI) guidelines for further information on the provision of vaccination against HPV.

Screening

After sexual transmission of the HPV, it infects the cells of the cervix, causing a progression of changes that can eventually progress to carcinoma. These changes are called cervical intraepithelial neoplasia (CIN) and are graded from mild CIN 1 through to more severe CIN 3 and ultimately invasive carcinoma of the cervix. In immunocompromised persons, the progression through these stages is often quicker, making it more important to do screening.

There are several methods of screening designed to detect precursors to carcinoma.

- A VIA (visual inspection assessment) of the cervix, using acetic acid that shows up the abnormal cervical cells;
- A PAP smear, which samples cervical cells, which are then graded by the CIN classification (this should be done every 12–36 months in HIV-infected women);
- Testing for HPV, using cervical swabs, is increasingly being integrated into cervical screening programmes.

If cervical abnormalities are found early, they can be treated before they develop into cancer. This can be done using cryotherapy, or, for more advanced lesions, an excision procedure called LLETZ or LEEP, using a hot wire loop. Where possible, cryotherapy should be performed on the same day that a lesion is identified (screen and treat). Consult the national guidelines for cervical screening and treatment in your country for further guidance.

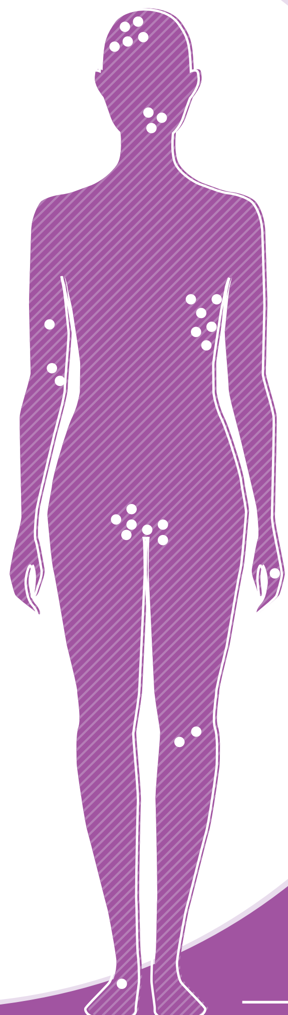
For HIV-positive women attending ART services, cervical cancer screening should be integrated into the clinical review appointment. If not feasible as a one-stop service, referral should be made and follow-up performed to ensure screening has been performed.

6. Brief programmatic guidelines for SRH services

Integration of SRH and HIV/ART services should be a key principle in all HIV programmes. Integration does not just refer to the provision of SRH services, but should include:

- Diagnosis, testing and treatment of STIs within the ART clinic;
- Integration of HIV testing into family planning services and clinics;
- Integration of contraception into ART clinics, including community outreach services and differentiated models or care;
- Provision of safe conception advice during HIV/ART counselling sessions, when starting ART and during the first months on ART; and
- Integration of screening and treatment for cervical cancer services into ART follow-up.

Skin diseases



- Approach to an HIV-positive person with a skin complaint
- History: Key information
- Examination: Key information
- Mapping of clusters of skin conditions
- A few principles of treatment in dermatology
- Dermatology in the primary care HIV clinic: Key points

Skin conditions are very common in people living with HIV, yet remain an ongoing challenge to the HIV clinician due to limited diagnostic tests and medications.

A diagnosis of a skin condition rests on a few important questions in the history, along with good visual inspection of the skin. This chapter is therefore designed to guide the clinician through the history and examination and then to match the findings to a diagnosis, using a large selection of pictures.

In the world of specialist dermatology, the diagnosis of a dermatological condition often involves skin scrapings, microscopy, biopsy and advanced blood tests. These are rarely available in primary care clinics, so are not included in the diagnostic approach here.

Treatment options are extremely limited in most of our primary care settings, so recommendations are limited only to those medications that are readily available or skin preparations that are relatively easy to prepare. With a bit of advocacy support, it may be possible to increase the range of dermatological products in a particular setting.

The chapter is organised as follows:

- The general approach to an HIV-positive person with a skin complaint
- The key questions needed in the history
- Key features to look for on examination
- Mapping of clusters of skin conditions according to these specifics of history and examination
- Detail of the important conditions and their management
- Principles of treatment in dermatology

Approach to an HIV-positive person with a skin complaint

When a patient presents with a skin condition, if we don’t instantly recognise it, there can be a tendency to give up on pursuing a diagnosis. However, if – as with the investigation for example of the cardiovascular system where we systematically check a standard sequence of things (pulse, blood pressure, JVP, etc.) – we also follow a standard checklist on history and examination, we will find that the diagnosis often surfaces with the gathering of this information.

Clinicians are taught in medical school to always take a history first, before starting an examination. Dermatology is the one exception to this important guideline. **You can start immediately with the examination and take the history while examining.** Do not, however, let this reversed sequence allow you to ignore the importance of the information the history can give you.

History: Key information

- **The CD4 count.** Just knowing this value can already narrow down the diagnostic options, as different CD4 levels are associated with specific conditions. Many common skin conditions fall into WHO clinical staging categories, especially stages 2 and 3 (see Table 20.2 at the end of this chapter).
- **Medication.** Have any new medications been started in the last few weeks to months? ARVs, TB meds, cotrimoxazole and anti-epileptics are common causes of adverse drug reactions.
- Knowing if the skin condition is **painful or itchy** helps further narrow down the diagnostic options.
- The basic story of the development of the skin condition will also help: when it started, how it developed, other illnesses associated with it, etc.

Examination: Key information

The more information that is gathered, the more you will be able to narrow down the diagnostic options. There are three details that will help with this:

- The shape (morphology) of the lesion (Figure 20.1);
- The arrangement of the lesions (Figure 20.2); and
- The distribution of the lesions (Figure 20.3).

Mapping of clusters of skin conditions

Armed with:

- A description of the skin: morphology, arrangement and distribution;
- Its key symptoms: itch, pain or asymptomatic; and
- The story of its development: possibly related to a recently started drug, how long present and how it developed ...

... find your way to a diagnosis using a combination of the algorithms and the more detailed text later in the chapter for each of following four groupings of signs and symptoms:

- Group 1: Adverse drug reactions, including Algorithm 20.1
- Group 2: Rash with pain or discomfort, including Algorithm 20.2
- Group 3: Rash and no or minimal itch, including Algorithm 20.3
- Group 4: Rash and itch, including Algorithm 20.4.

Figure 20.1 Common morphologies (shapes)

Macule (flat – cannot feel it)

Papule (raised, small)

Nodules (raised, large)

Plaques

Vesicles

Umbilicated lesion

Pustules

Crusts

Figure 20.2 Common arrangements of skin lesions

a. Annular (ring-shaped)

b. Grouped – e.g. herpes lesions in a cluster

Figure 20.3 Some common distribution patterns

a. Sun-exposed

b. Dermatomal

c. Body area e.g. torso, hands/feet, etc.

Group 1: Adverse drug reaction (ADR)

Refer to hospital

There are two main skin adverse drug reactions that can be life-threatening in HIV medicine. As soon as the diagnosis is suspected, the potentially offending drugs need to be stopped and the patient **referred to hospital**.

(See text below for detail and Algorithm 20.1 for an approach to a suspected ADR.)

There has been concern in the past regarding stopping ART abruptly and not covering the NNRTI tail. This is based on the fact that EFV and NVP both have a half-life of about a week where AZT and 3TC last only about a day. The result of stopping all three ART drugs at the same time would be that NVP or EFV levels would be sustained for nearly a week with very low levels of AZT and 3TC. This could result in the development of resistance due to the short period of monotherapy. The 'tail' used to be covered by continuing with the AZT and 3TC for an extra week. However, as TDF has a similarly long half-life the patient will have sustained levels of two drugs so the chance of developing resistance is much lower. Covering the tail when a patient is on TDF, 3TC and EFV/NVP is therefore no longer a concern but remains important if using AZT or ABC instead of TDF.

1. Stevens-Johnson (SJS)/Toxic epidermal necrolysis syndrome (TENS)

SJS/TENS

- A condition that usually starts with a morbilliform (measles-like) rash on trunk and limbs and over a few days involves specific mucosal surfaces and then progresses to diffuse blistering of the skin.
- The term SJS is used when the involved body surface area is <10% and TENS if >30% and SJS/TENS for 10–30%.
- The commonest causes are nevirapine and cotrimoxazole, but TB drugs and several other medications are also implicated (see Algorithm 20.1).
- In South African studies, HIV-positive females showed the highest incidence and the mortality rate was approximately 25%.
- Diagnosis is made on history and the appearance of the skin, rather than any specific blood tests. See Algorithm 20.1 for diagnostic process and management.
- As soon as mucocutaneous involvement or blistering of skin is noted **immediate referral** is needed.

Refer to hospital

- Hospital management is care of the skin and mucosal surfaces, and prevention of complications (essentially the same as for burn management).
- Note the drug re-introduction process later for TB drugs.

2. Drug reaction with eosinophilia and systemic symptoms (DRESS)

A condition that starts with a similar morbilliform rash, often with associated oedema and a fever. Rather than progressing to loss of skin, it tends to result in inflammation of different organs: lungs, kidney, liver, meninges.

Diagnosis is also on history and appearance of the rash, especially if oedema present. Elevation of LFTs and/or creatinine and often pancytopaenia and eosinophilia can support the diagnosis.

Hospital management is screening to see which organs are involved and supportive management (sometimes steroids) while the inflammatory/allergic process resolves.


Refer to hospital

Efavirenz: adverse drug reactions

Efavirenz rarely causes severe drug reactions like SJS/TENS or DRESS, and most of the time it is not necessary to stop the drug. In one significant study the commonest reactions to EFV were:

- palmar erythema;
- morbilliform rash;
- indurated erythema;
- facial oedema;
- annular erythema in a sun-exposed distribution.

Most reactions were mild, with the only a few more severe reactions noted. The worse ones were associated with a fever and hepatitis. The presence of a fever should, therefore, prompt the clinician to check the ALT for liver involvement. The presence of actual liver signs and symptoms would also be a reason for concern. EFV would then need to be stopped and guidance followed for drug-induced liver impairment (see **Chapter 16**).

Annular reaction on hand. It can also manifest as a lichenoid skin reaction - itchy purple macules and patches with an annular component and some vesicles.

Algorithms 20.2 to 20.4 on pages 403 to 405 are followed by more detailed text regarding the diagnoses.

Algorithm 20.1 Group 1: Approach to a possible adverse drug reaction (ADR) in the skin

Possible drug-related rash

History and examination

- Usually symmetrical, often involving palms and soles.
- Often morbilliform (measles-like).
- Temporal relationship to a new drug 'PATIENC(E)' ('E' in brackets as EFV rarely causes SJS/DRESS).
- Drugs commonly causing ADRs: **P**enicillins, **A**bacavir, **T**B drugs, **I**buprofen (NSAIDS in general), **E**pilepsy drugs*, **N**VP, **C**otrimoxazole. (Remember the drugs: **PATIENC(E)** with the 'E' in brackets as **E**FV rarely causes SJS/DRESS.)

***Epilepsy drugs:**
Phenobarbitone
Phenytoin
Carbamazepine
Valproate
Lamotrigine

Does not fit this profile

Other causes:

- Infection – fungal, bacterial;
- Viral;
- Neoplasm;
- Inflammatory;
- IRIS;
- etc.

Fits this profile

Look for '**MANS**'

M – mucocutaneous – lips, eyes, genitals
A – abnormal blood tests – ALT FBC and eosinophils
N – necrosis/blistering of skin
S – systemic symptoms

Not present

Continue drugs, add an antihistamine and watch for worsening or new signs/symptoms.

Present

Could be SJS/DRESS

Stop possible drugs – usually TB drugs, ART and CTX. Urgently refer and admit.

Much later, when settled: drug re-introduction.

Bactrim – never again, even for prophylaxis.

Nevirapine – do not use NVP, EFV or any other NNRTIs ever again. (Use a PI instead.)

TB drugs:

- Before ART, because of high TB mortality rate.
- RHEZ or HRZE instead. New drug every 3–5 days.
- Look for fever, itch or features of hepatitis.
- ART last – NRTIs and PIs not usually a problem.

Algorithm 20.2 Group 2: Rash with pain or discomfort

Rash with pain/ discomfort
+/- pain
+/- fever

- Grouped vesicles; red base. → Herpes simplex virus (HSV) 1&2

- Vesicles in dermatomal distribution. → Herpes zoster (shingles)

- Disseminated pustules, vesicles on face, torso and limbs, mouth; often fever. → Varicella zoster (chicken pox)

- If any blistering of the skin and/or mucosa. → Consider adverse drug reaction – SJS/TENS.

- Typically crusting lesions; honey-coloured. → Impetigo

- Small pustules in region of hair follicles. → Folliculitis

- Diffuse redness with swelling. → Cellulitis

Algorithm 20.3 Group 3: Rash and no or minimal itch

Rash and no or minimal itch

- **Scalp:** scaly patches, black dots, hair loss
  Trunk and limbs: Usually annular (in a ring). Often raised, flaky edge with the centre already healing. Usually clearly defined edge.
  - Tinea corporis; body

  - Tinea pedis; feet

- Purplish macules, papules and nodules.
  - Kaposi's sarcoma

  - Bacillary angiomatosis

- Papules, often hands, limbs. Cauliflour-like papules.
  - Warts

- Dimpled/ umbilicated

Cryptococcal disease

Molluscum contagiosum

- Papulo-squamous rash. Often scattered over whole body and involves palms and soles.
  - Secondary syphilis

Algorithm 20.4 Group 4: Rash and itch

- Rash and itch
  - Generalised skin changes
    - Eczema – can be dry/weeping, localised or widely distributed 
    - Psoriasis 
    - Xerosis
    - Scabies
  - Head and neck
    - Red oedematous papules
      - Eosinophilic follicullitis 
    - Scaly plaques
      -  Psoriasis, or
      -  seborrhoeic dermatitis
  - Extremeties
    - Papules
      - Papular pruritic eruption 
      - Scabies
    - Nodules
      - Nodular prurigo
    - Plaques
      -  Psoriasis, or
      -  Eczema
  - Folds
    - Seborrhoeic dermatitis 
    - Candida (often under breasts or in stomach folds)

More detailed text regarding above diagnoses follows below.

Group 2: Rash with pain or discomfort

(See Algorithm 20.2.)

Herpes simplex virus (HSV 1 & 2)

- Forms part of the human herpes virus family, which includes: VZV, EBV, CMV and HHV-8.
- HSV 1 & 2 are transmitted via close physical contact with an infected individual, through a break in the mucocutaneous surface.
  - HSV 1 – orolabial lesions
  - HSV 2 – genital lesions.

Key features

- Grouped vesicles on an erythematous base may evolve to painful erosions and ulcers; ± secondary crusting.
- May appear pustular; ± scalloped borders.
- Affected areas include lips, nose, tongue, oropharynx, buccal, gingival and ano-genital areas.

Oral herpes simplex

- May have a prodrome of burning and tingling.
- Usually recurs at same site, due to reactivation of latent virus migrating back via nerves to primary site of infection.

Diagnosis

- Clinical features. Always check for genital lesions – common in HIV.

Management

- Prevention:
  - Avoid skin-to-skin contact during flare.
  - Advise use of condoms in genital herpes.
- Lesions can be treated symptomatically, e.g. zinc sulphate in aqueous solution topically and sulphadiazine cream to prevent secondary infection. Topical acyclovir is of limited value.
- Oral antiviral agents
  - Are indicated for ocular lesions (NB: Refer to ophthalmologist) and genital lesions with frequent recurrences.
  - Are ideally started within 72 hours of start of lesions.
  - Adjust dose of acyclovir if creatinine clearance is <50 ml/min. (See dosage table in **Chapter 17**, page 352.)

Herpes zoster (shingles)

- After an initial infection with chicken pox (varicella zoster virus – VZV), the virus stores itself in spinal or cranial nerve roots. Then, often even decades later, during periods of a weakened immune system (e.g. stress-related, old age, HIV infection) the virus resurfaces. Typically it appears as localised clusters of chicken pox-type vesicles, but limited to the skin area that the nerve roots supply sensory fibres to (known as a dermatome).
- Because of the intense, burning pain it causes, it is often described in extreme terms, such as the belt of roses from hell.

Key features

- ± Prodrome of intense pain, tingling, tenderness, hyperesthesia in more than 90% of patients.
- Sometimes, though rarely, dermatomal pain can occur without the rash.
- Commonly forms grouped vesicles on an erythematous base, is unilateral, follows a dermatome and is usually on trunk, but can affect face and other areas.
- May heal with scarring and post-herpetic neuralgia (PHN).

Herpes zoster

Zoster involving the face

Zoster can involve any nerve roots and is fairly commonly seen involving the trigeminal nerve (V). Of particular concern is if it affects the ocular branch, as this has the potential to damage the eye. The feature of this that must always be looked for is Hutchinson's sign: one or more blisters on the tip of the nose. This means that the eye itself and not just the overlying skin is going to be affected, even if it is not obvious initially. Ideally refer to ophthalmologist but if not possible the following are all needed:

Herpes zoster

Management of eye zoster

- Acyclovir 800 mg PO 5 x day for 10 days;
- Chloromycetin ointment 4 x daily;
- Analgesia: paracetamol and codeine phosphate; and
- Amitryptiline 12.5–25 mg nocte x 3 months (titrate dose upwards if needed).

Diagnosis

- Clinical features.

Management of herpes zoster

- Pain control – (paracetamol ± codeine, add amitriptyline if not adequate).
- Acute vesicles – calamine lotion.
- Eroded areas – sulphadiazine cream or povidone-iodine cream.
- Treat secondary bacterial infection if present.
- Oral acyclovir 800 mg 5 x a day for 10–14 days is prescribed, ideally started within the first 72 hours of the onset of the rash. In practice, however, we usually extend this to about a week. The main reason for doing this is to decrease the chance of the patient developing post-herpetic neuralgia, an ongoing burning pain in the distribution of the rash, even well after the lesions have cleared up.

Varicella zoster virus (VZV)/chicken pox

- Varicella zoster or chicken pox is the original infection with VZV that may later reappear as shingles as described above. It is most common in children and is contagious.
- It is spread via direct contact with lesions or respiratory secretions.

Key features

- Mild prodromal symptoms with rash appearing 2–3 days later. Fever is common.
- Initial lesions usually appear on the face and scalp, then spread to trunk and limbs; can involve mucosa.
- Pruritic papulo-vesicular lesions (can be pustular) evolve over days to become scabs and crusts, with or without scars.
- Lesions usually form successive crops in various stages of evolution.
- Patients with lower CD4 counts are at higher risk of developing complications, such as pneumonitis, hepatitis and encephalitis. NB: Monitor closely for signs.
- The patient is infectious for approximately 4 days before the rash appears, and then until 4 days after crusting of all lesions.

Diagnosis

- Clinical features;
- Clue – lesions in scalp.

Management

- Isolate child or adult if possible, until all lesions have crusted over.
- Patients with normal immunity can be treated symptomatically with paracetamol, antihistamines, calamine lotion and tepid baths.

- If started within 72 hours of cutaneous eruption, acyclovir has been shown to decrease duration and severity of infection.
- Treat secondary bacterial infection.

NB: Refer to hospital if:

- Disseminated infection suspected (pneumonia, jaundice, neurological findings, etc.), as will need IV medication;
- Dehydrated, ill patient.

Refer to hospital

Impetigo

Common, contagious, superficial infection of the skin; more often seen in children. It is caused by both B-haemolytic streptococci and staphylococci. This is more commonly seen in areas of high humidity and poor living conditions and may develop after insect bites, sites of minor trauma or complicating condition, such as eczema and scabies.

Key features

Non-bullous impetigo:

- Due to streptococcus and staphylococcus.
- Yellow- to honey-coloured crusts, overlying an erosion.

Bullous impetigo:

- Blisters, flaccid or with cloudy content ± erythema.
- Caused by staphylococci that produce exfoliative toxins.

Management

- Soak off crusts with lukewarm water.
- For localised lesions, use antiseptic creams, such as povidone iodine
- For more extensive lesions, consider oral antibiotics, e.g. flucloxacillin.
- Advise patients on infectivity to others.

Folliculitis

As the name implies, this is an infection of the hair follicle, usually caused by a staphylococcus species. It is commonly in the beard area, but can be in any hair-bearing area.

Treatment

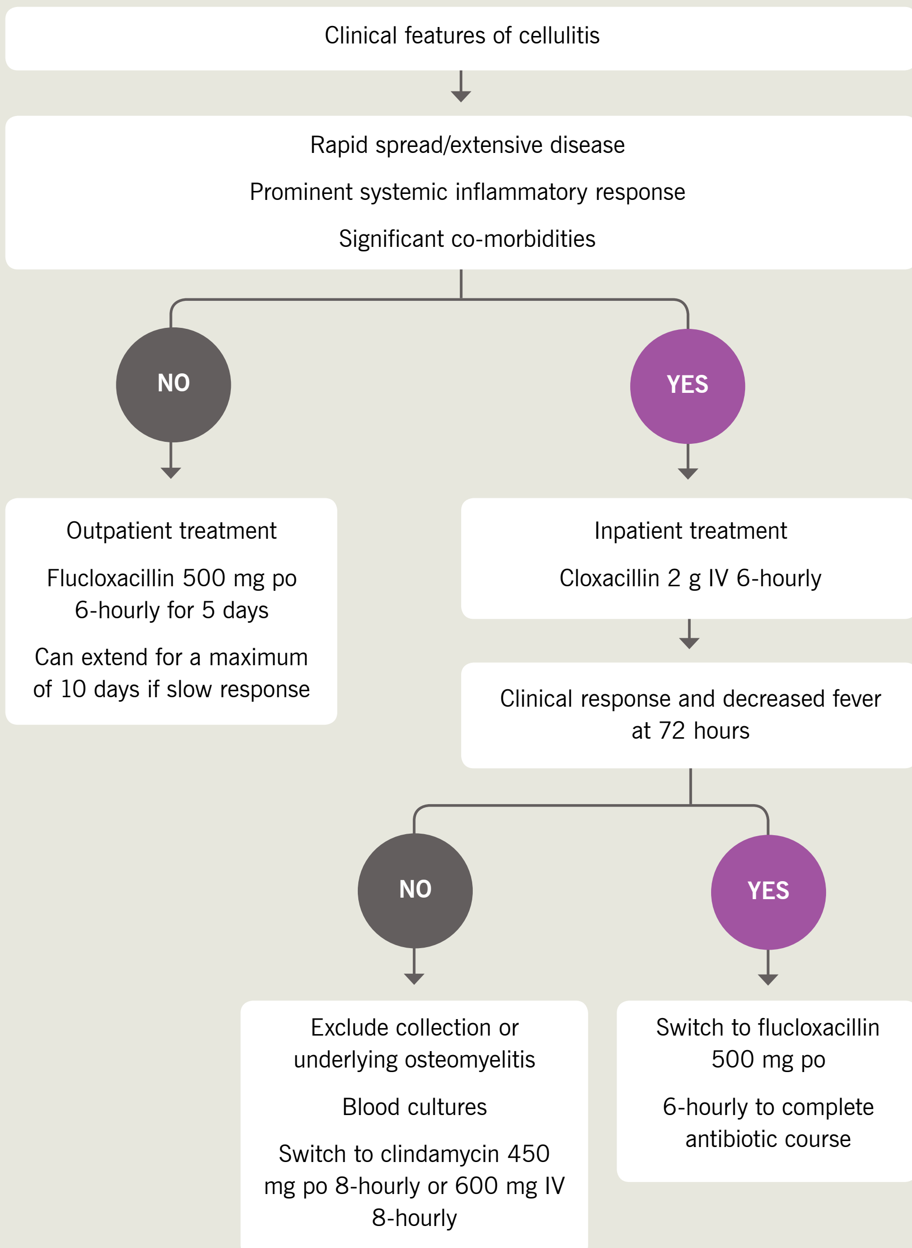
The first step is to use topical iodine preparations, if available, but for more severe conditions an oral antibiotic will be needed, such as flucloxacillin.

Folliculitis

Cellulitis

The key findings in this condition are erythema, pain, swelling and warmth. The condition is commonly caused by streptococci, sometimes staphylococci. Management can be as an outpatient, provided the condition is not severe.

Figure 20.4 Clinical features of cellulitis



If flucloxacillin is not available, or if poor response, change to clindamycin because this will cover many MRSA. Another alternative is coamoxyclav, 1 g 12-hourly for five days.

A DVT can look very similar to a cellulitis, so if there is any doubt the patient must be referred for admission, further investigations and anti-coagulation treatment. This readily predisposes to pulmonary emboli, an often fatal condition.

Deep vein thrombosis (DVT) and pulmonary embulism (PE)

Both HIV and TB are recognised independent risk factors for the development of DVT, and one of its potential sequelae, PE. Add to this the higher incidence of hospitalisation and immobility with these conditions and there exists a substantially higher risk of the development of DVT and PE.

Recommendations

- Clinicians should therefore have a higher index of suspicion for DVT, rather than just a cellulitis, in a patient presenting with a swollen leg.
- Pulmonary embulism should be higher than usual on the list of causes of acute shortness of breath. (See also **Chapter 13**, Respiratory disease.)

Group 3: Rash with no or minimal itch

(See Algorithm 20.3.)

Tinea

This is a common fungal infection seen in the scalp, the groin, the feet and most other places in the body. It is spread by infected humans, animals and soil.

Main features

- Trunk, face and limb will have annular lesions with a raised, red or vesicular, scaly edge (so-called active edge) with central healing (see photo).
- Scalp: Round scaly patches with partial hair loss; ± black dots or broken hairs.


Tinea corporis

Diagnosis

- Clinical appearance, looking for the above characteristics.

Management

Localised cutaneous lesions can be treated with topical Whitfield's ointment or clotrimazole cream. If in toe web spaces, keep area dry.

More extensive disease, groin, scalp and nail disease needs oral medication, e.g. griseofulvin 10 mg/kg/day or fluconazole. Clotrimazole cream is not effective.

Kaposi's sarcoma (KS)

- Vascular tumour due to infection of vascular endothelium by human herpes virus-8 (HHV-8) in the setting of HIV.
- KS can occur at any CD4 level but it is a stage 4 disease.

Key features

- Violaceous to purple, macules, patches, papules, nodules and plaques.
- Single or multiple with a smooth or scaly, ulcerated or haemorrhagic surface.
- Can be anywhere on the skin surface often trunk, limbs, tip of nose and genitals. Important always to look on the palate as this can be a pointer to organ disease (e.g. lung, bowel).
- With more extensive lesions there is frequently lymphoedema of the associated limb.

Kaposi's sarcoma

Patients with KS should be started on ART immediately, regardless of CD4 count and referred for fuller evaluation for chemotherapy.

Bacillary angiomatosis (BA)

Key features

- Gram negative bacillary disease, caused by bartonella species. It can involve skin as well as lymph nodes, liver, spleen and bone.
- Cutaneous and subcutaneous lesions can be solitary or multiple violaceous papules and nodules.
- The vascular-looking lesions may mimic KS.

Bacilliary angiomatosis (wrist)

Management

The mainstay of treatment is erythromycin or doxycycline.

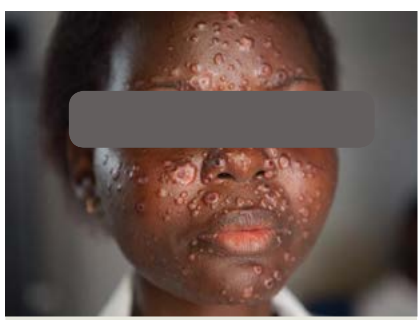
Molluscum contagiosum

- This is a viral infection, giving characteristic lesions in the skin.
- Common, especially in children, and is often an early sign of infection with HIV.
- Transmitted through skin-to-skin contact and can be spread sexually.

Key features

- Umbilicated (with central dimple) skin coloured papules, that can occur anywhere on the skin surface. Frequently seen on face (see photo), in axillae and around perineum in children, and is not necessarily evidence of sexual molestation (spread by scratching).
- May be extensive, coalesce, persist and be resistant to treatment.
- Must be differentiated from lesions of disseminated cryptococcal (see photo) or other deep fungal disease (histoplasmosis, penicilliosis) because missing these diagnoses could be fatal.
- May present as part of IRIS, post initiation of ART.

Molluscum on face



Cryptococcal disease

Diagnosis

- Clinical features, especially if dimpled lesions seen.

Management

- Reassure patient (usually resolves with ARVs in HIV setting but may get worse before getting better).
- Individual lesions may improve spontaneously but can be treated with wart paint, cryotherapy, trichloroacetic acid.

Warts

Caused by direct skin-to-skin contact or inoculation with the human papilloma virus (HPV), with different subtypes responsible for different variants of genital and non-genital warts.

Plane warts on face

Genital warts

Key features

- Single or multiple skin-coloured papules that may coalesce to form a plaque.
- Flat or raised and smoothed or roughened surfaces.
- Localised or extensive.
- Common on hands, face, feet, genitalia.
- On genitalia known as condylomata acuminata and may assume a cauliflower-like appearance.
- May last months to years and regress spontaneously if immunity normal.
- If low CD4, warts tend to be more florid and recur post-treatment.
- May present as a manifestation of IRIS, especially post-initiation of ART.

Diagnosis

- Clinical appearance.
- Clues to diagnosis: black dots on surface of wart, which are actually thrombosed blood vessels.

Management

- Non-genital warts: Reassure as they generally resolve spontaneously or with improved immune status. For children and flat warts, this may take time. Various methods for treatment of individuals for non-genital warts include:
    - wart paint (1 part salicylic acid, 1 part lactic acid, 3 parts collodion);
    - cryotherapy;
    - trichloroacetic acid.
- Genital warts
    - All of the above can be used.
    - Podophyllin 25% in tincture of benzoic compound (TBCO); apply every 1–2 weeks. Ensure protection of surrounding non-involved skin with Vaseline. Fix with talcum powder; advise patient to wash off after 4 hours.
    - More complicated cases may need referral.

Syphilis

Syphilis is known as the great imitator as it presents in so many varied ways. It is beyond the scope of this book to cover the disease comprehensively. It is however important always to remember that the rash of secondary syphilis can present in our primary care clinics.

A rapid syphilis test is easy to do and the treatment is 2.4 MU benzathine penicillin IMI once a week for three weeks.

Syphilitic wart

Secondary syphilis

Group 4: Rash and itch

Eczema

A common allergic condition of the skin, it starts in childhood and about a third progress into adulthood. It is commonly associated with respiratory allergy such as allergic rhinitis and asthma.

Characteristic features

It is typically itchy and can range in appearance from very dry thickened skin to red and weepy. The rash can be seen almost anywhere on the body but one of the common sites is the flexural creases (the fronts of the elbows and the backs of the knees)

It differs from fungal infections by the lack of a clearly demarcated edge. In addition, the eczematous lesions tend to be more diffusely dry and flaky or red and weeping as opposed to the healing centre characteristic of tinea.

Forearm crease

Treatment

As this is a primarily allergic condition it responds well to topical cortisone preparations. If you have the luxury of a choice of an ointment (Vaseline-type) or a cream, use the ointment for dry skin and the cream if it is red and weepy (see section on dermatological preparations, page 424).

If the clinic has different strengths of cortisone, use a 1% hydrocortisone for children and on the adult face. For any other parts of the adult body use betamethasone.

Xerosis

Abnormally dry skin. ('Xero' is a Greek word that means dry.)

May result from a variety of different factors, including dry climate, frequent washing, detergents, malnutrition and thyroid disease.

Key features

- Dull, dry, rough, scaly skin, which may have associated itch.
- In severe cases, it may have a fish-scale or crazy paving pattern of cracked, dry skin.
- May have an associated eczema.
- It is common in HIV infection.

Management

- May need to decrease exposure to excess water or detergents.
- Moisturising creams are needed but the range available is very limited. Try aqueous cream or Vaseline.
- If there is underlying eczema, may need topical cortisone.
- Check the TSH for thyroid disease if possible.

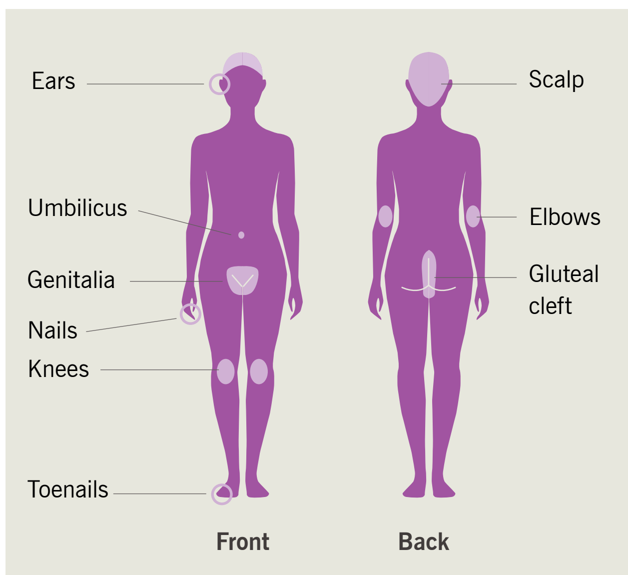
Psoriasis

- Papulosquamous condition of the skin that may involve skin, scalp, nails and joints.
- Overall incidence not increased in HIV, but the clinical presentation may be more dramatic and the patients may be more recalcitrant to treatment.
- Patients have a genetic predisposition set off by various triggers, e.g. infections (stress), drugs (B-blockers, lithium), stress, etc.

Key features

- Red to purple papules and plaques with a silvery scale.
- Usually little or no pruritis but this varies.
- More extensor surfaces on arms and legs, but also abdomen, back, scalp, palms and soles.
- Can involve skin folds as well.
- May develop an arthritis with the skin lesions, for which referral may be needed.

Psoriasis on back



Diagnosis

Clues to diagnosis:

- Nails may show pitting.
- Skin scratch test. Scrape a lesion with an orange stick, a key or a throat spatula split in half to create a sharp edge. If it is psoriasis, fine, silvery scales will fall off. If an actual plaque is removed and bleeding points are noted underneath, this also supports the diagnosis.
- Scalp: Thick, stuck-on scales.
- Koebner phenomenon: Psoriasis developing at sites of physical trauma (e.g. along the line of a scratch or a scar).

Management

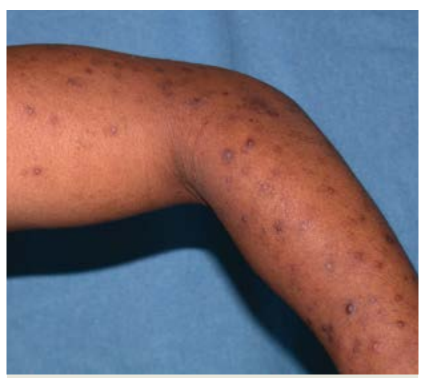
- All patients should be on effective ART (either starting or re-starting ART or, if failing, switching to an effective regime.
- A variety of topical preparations can be used but unfortunately few, if any, are available in our primary care clinics. The table below is included in case it is possible to get hold of any of them.
- Severe cases will need to be referred.

Table 20.1 Topical treatments

Examples of topical treatments applied to:	
Skin on trunk and limbs	5% LPC (liquor picis carbonis) 5–10% crude coal tar 5–10% salicylic acid in white soft Vaseline, modified Adamson's ointment
Body folds	Diluted cortisone, e.g. 10% betamethasone cream
Scalp	Selenium sulphide or tar shampoos, salicylic acid preparations, cortisone cream

Scabies

The scabies mite is a human parasite spread via close skin-to-skin contact, e.g. handshakes, sexual contact, infected clothing and bedding/fomites and can stay alive for more than 48 hours off human skin.



Scabies on arm

Key features

- Itch is a key feature, especially at night. It can take up to one month to manifest on first exposure but within 24 hours on re-infestation.

- The rash ranges from burrows, papules and nodules to pustules, involving hands, feet, web-spaces, axillae, abdomen, genitalia, trunk or limbs.
- Face usually spared.
- In infants, rash can be seen on palms and soles, ± pustules on scalp and face.

Diagnosis
Clinical features on history and examination.

Management
- Treatment should include patient and all close physical contacts, regardless of whether they are itching or not.
- Topical benzoyl benzoate lotion from shoulder down – wash off after 24 hours and repeat treatment in 7–10 days.
- In children (6 months–5 years) a 50% dilution of this may be used (diluted 1:1 with equal amounts of water).
- For infants less than 6 months, 5% sulphur ointment used nightly for 3 days.
- Persistent and severe case will require oral ivermectin.
- Treat itch with oral antihistamines, ± dilute topical steroids, as often it is accompanied by an eczematous rash.
- Wash clothing, bed sheets in hot water (approximately the hottest one can manage to immerse a hand in). When not possible, leave items sealed in a bag for 10 days.
- Post-treatment itching may persist for a further 2–4 weeks.

Norwegian scabies

- Massive infestation of mites proliferate to produce a thick greyish crust. This seems to be in response to an inadequate immune response.
- Scratching may be absent as itching is variable.
- Seen more commonly in immunosuppressed patients and those living together in small living spaces.


Norwegian scabies

Treatment
Topical preparations like benzoyl benzoate can help but this type of more severe infestation usually requires oral ivermectin.

Eosinophilic folliculitis

One of the more characteristic and common itchy skin conditions associated with HIV infection.

Eosinophilic folliculitis on face

Key features

- Oedematous, red, skin-coloured papules and pustules (looks a bit like acne).
- Itchy.
- Can involve face, scalp, neck and trunk.
- May fluctuate but usually improves with initiation of ART.

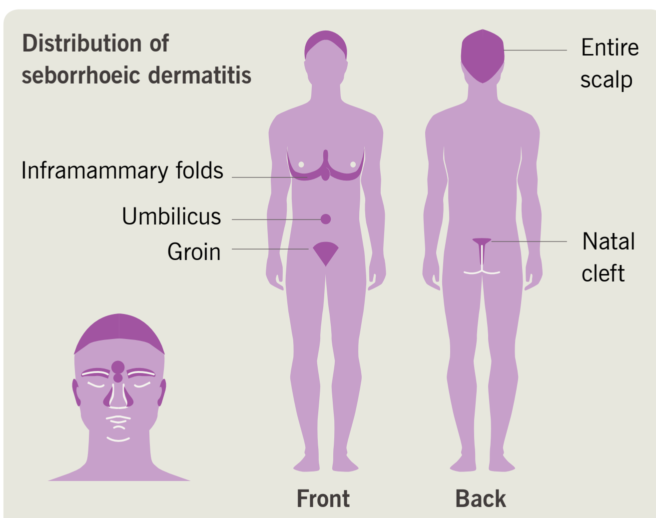
Seborrhoeic dermatitis

This is a common scaling, sometimes weeping rash, that typically involves inflammation in areas rich in sebaceous oil secreting glands common in HIV infection.

Key features

- Most common on face, ears, scalp, chest and body folds.
- Can be quite extensive with more advanced immunosuppression
- Infantile and adult forms exist.
- Sharply demarcated, pink or red patches.
- Yellow to brown flaky greasy scales, sometimes forming vesicles or crusts.
- Usually has a mild course and little discomfort.

Seborrhoeic dermatitis on face



Management
This inflammation of the skin is thought possibly to have a fungal component to it. The mainstay of treatment is, therefore, topical antifungals and cortisone.

Scalp

- Keep hair short; easier to manage.
- Cortisone and clotrimazole creams together.

Skin

- Face: 1% hydrocortisone cream.
- Flexures and rest of body: 10% betamethasone cream if available.
- Add an antifungal cream, such as clotrimazole.
- Treat bacterial secondary infections with antibiotics.

Infants

- Skin: 1% hydrocortisone cream.

Papular pruritic eruption (PPE)

Often reported as one of the most common rashes seen in HIV infection. This is a diagnosis of exclusion, as it is often lumped together in a mixed bag of conditions with insect bite reactions and eosinophilic folliculitis.

Key features
- Chronically itchy and usually symmetrically distributed.
- More on extensor surface of limbs, but also trunk and face; sparing palms and soles and mucous membranes.
- Initially non-descript red papules that often develop a purplish pigmentation and a thicker scaly appearance.
- Often the presenting sign of HIV and is more common when the CD4 count is <200 cells/μl.
- Can co-exist with fungal infections or scabies


PPE back of legs

Management
- Exclude other causes e.g. scabies.
- Oral antihistamines.
- Very resistant to treatment.

Nodular prurigo

Nodular prurigo is a skin condition characterised by very itchy firm lumps. It can occur at all ages but mainly in adults aged 20–60 years. Both sexes are equally affected.

The individual prurigo nodule is a firm lump, 1–3 cm in diameter, often with a raised, warty surface. The early lesion may start as a smaller red itchy bump. Crusting and scaling may cover recently scratched lesions. Older lesions may be darker or paler than surrounding skin. The skin in between the nodules is often dry. The itch is often very intense, often for hours on end, leading to vigorous scratching and sometimes secondary infection.

Nodular prurigo

Nodular prurigo lesions are usually grouped and numerous but may vary in number from 2–200. Nodular prurigo tends to be symmetrically distributed. They usually start on the lower arms and legs, and are worse on the outer aspects. The trunk, face and even palms can also be affected. Sometimes the prurigo nodules are most obvious on the cape area (neck, shoulders and upper arms).

New nodules appear from time to time, but existing nodules may regress spontaneously to leave scars. Nodular prurigo often runs a long course and can lead to significant stress and depression.

The **cause** of nodular prurigo is unknown. It is uncertain whether scratching leads to the lumps, or if the lumps appear before they are scratched. Up to 80% of patients have a personal or family history of skin or respiratory allergy.

Treatment is not easy. It is mainly reassurance that it is not a more serious condition, along with symptomatic relief in the form or oral antihistamines.

Candida intertrigo

Intertrigo is a skin inflammation of the body folds and is commonly seen under the breasts and in any areas where large folds of skin rub against each other (abdominal skin folds in overweight people, the axillae). The combination of moisture and irritation creates a type of eczema that is frequently secondarily infected by fungi. This can be by tinea or candida.

Treatment

Candida typically results in a frequently painful, bright red, well-demarcated rash. As tinea and candida both respond to clotrimazole, this is the ideal treatment. In addition, as the underlying problems are moisture and friction, combine with constant efforts to keep the area dry, along with a zinc cream or talcum powder.

Candida in the mouth

See **Chapter 15**, Gastro-intestinal conditions (oral lesions).

A few principles of treatment in dermatology

Primary care HIV clinics have a limited range of preparations for treatment of skin conditions. There are, however, a few principles that will give some help, even with the few preparations that are available.

Topical preparations are made up of a base and an active ingredient (see Figure 20.5).

Figure 20.5 Core composition of topical preparations

Base	+	Active ingredient
Ointment (like Vaseline)		Anti-fungal (e.g. Whitfield's or clotrimazole)
Cream (like aqueous cream)		Antiseptic (e.g. povidone iodine or silver sulphadiazine)
		Cortisone/steroid, e.g. 1% hydrocortisone, betamethasone, beclomethasone

Base

There is not often the luxury of a choice of an ointment or a cream when choosing an antifungal or a cortisone topical preparation. However, if it is possible to choose, use an ointment for dry, flaky skin and a cream for normal or moist skin.

Active ingredients

Antifungal ingredients

- Whitfield's is usually only in ointment form and is a weak antifungal treatment that works only on tinea infections. It has no effect on candida.
- Clotrimazole is widely available and is a good broad-spectrum anti-fungal agent with activity against both tinea species and candida.

Antiseptics

- Povidone iodine (Betadine®) is a widely available antiseptic used for a variety of antiseptic purposes, from surgical skin preparation to antiseptic dressings. It is usually available as an ointment, which makes it easier to remove dressings from moist wounds.

- Silver sulphadiazine is another antiseptic, commonly used in burn dressings, and causes far less burning than iodine preparations. It is known to be effective in decreasing the burn of active herpes zoster (shingles).

Cortisones (steroids)

- A 1% hydrocortisone preparation is usually available in the clinics, mostly in a cream rather than an ointment. This very mild preparation is usually reserved for adult faces and any part of the skin of a child. If used on any other part of an adult's skin, it will take many weeks to work (if it works at all).
- For adult skin other than the face, betamethasone or beclomethasone, which are about a hundred times more potent than 1% hydrocortisone, are far more effective. However, if used for a week or so on an adult face or anywhere on a child the steroids are likely to cause side effects of thinning and/or depigmentation of the skin. This is often irreversible.
- If the clinic has steroid preparations in both ointments and creams, remember to use the guideline noted above in the choice of the base.
- If using betamethasone or beclomethasone, as soon as the condition has settled down, the skin preparation can be progressively diluted over several weeks (in the same way that one weans oral steroids) to the weakest concentration that keeps the condition under control. Use Vaseline to dilute an ointment and aqueous cream to dilute a cream.

Oral medications

- There is virtually no place for oral steroids for skin conditions in the outpatient setting.
- Griseofulvin is an effective treatment for severe tinea infections of the skin and is the drug of choice for the groin, scalp, hair and nails.
- Fluconazole is also highly effective and has the benefit of having activity against tinea and candida, although it might not always be available for this indication. It is extremely effective against the most commonly seen fungal infections at a dose of 150–200 mg weekly for 2–3 weeks.

Dermatology in the primary care HIV clinic: Key points

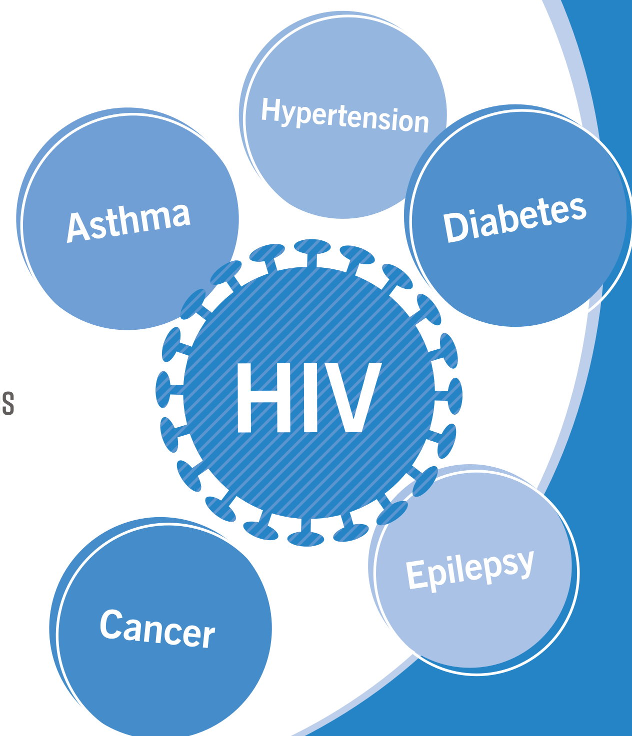
- Develop a systematic approach to skin problems and the diagnoses will be easier to make.
- First gather the information on history and then categorise (itch/pain/no discomfort), then use the pictures to try and build up a personal database of recognisable skin conditions.
- Find out what skin preparations are available in your local clinic and familiarise yourself with exactly how to use them.

Table 20.2 Skin disorders grouped by CD4 count

CD4 range (per μl)	Skin diseases
>500	Acute retroviral syndrome Oral hairy leukoplakia Vaginal candidiasis Seborrhoeic dermatitis Psoriasis Kaposi's sarcoma
200–500	Oral thrush Herpes zoster Herpes simplex Refractory psoriasis Hypersensitivity to nevirapine Condylomata acuminata Tinea infection Verruca vulgaris (common warts)
100–200	Disseminated herpes simplex Refractory seborrhoeic dermatitis Eosinophilic folliculitis Papular pruritic eruption Molluscum contagiosum Extensive Kaposi's sarcoma
<100	Cutaneous penicilliosis Bacillary angiomatosis Herpes simplex: large and unhealing Cutaneous cryptococcosis Disseminated cytomegalovirus

Source: http://www.info.gov.hk/aids/pdf/g190htm/21.htm

Non-communicable diseases and HIV



The term non-communicable diseases (NCDs) refers to a recognised cluster of common non-infectious conditions. The most common NCDs include:

1. Vascular diseases
   - ischaemic heart disease – angina and heart attacks
   - cerebrovascular diseases – strokes
2. Cancers
3. Chronic respiratory diseases – asthma and chronic obstructive airways disease (COAD)
4. Diabetes
5. Epilepsy
6. Depression

NCDs are becoming increasingly important in the comprehensive management of HIV-positive patients, for the following reasons:

- The successful rollout of ART to large numbers of patients is resulting in many more patients surviving until an older age, when NCDs are more prevalent.

  Comparison of data from 2010 with projections for 2030 has shown that:
  - Percentage of HIV-positive people who will be >50 years will increase from 28% to 73% in 2030.
  - The median age of HIV-positive patients will increase from 43.9 to 65.6 years.
- HIV itself, and many of the medications used to treat it, have been shown to increase the incidence of NCDs.

Clinicians therefore need to be aware of the clinical issues related to the diagnosis and management of NCDs in HIV-positive patients. Equally importantly, programme managers need to integrate care of NCDs into their HIV programme management strategies. As this is primarily a clinical guide, the focus of this chapter is equipping the clinician with current clinical information on the associations between HIV and NCDs.

For further information on the management of non-communicable diseases, refer to your respective MSF sections or national NCD guidelines.

Associations between HIV and NCDs

By 2030 it is predicted that:

- 84% of HIV-positive patients will have more than one NCD.
- 28% will have more than three NCDs.
- 54% will be taking chronic medications other than ART.

The effective management of NCDs will increasingly be part of the management of the HIV-positive patient over the next 10–15 years.

1. Vascular disease (heart and brain)

HIV infection is characterised by chronic inflammation (contributing to a vasculopathy, pathology of the blood vessels), immune activation and increased incidence of co-infections. Large cohort studies have shown that the risk of myocardial infarction and cerebrovascular disease is 40–70% higher among HIV-positive people.

The following are some of the more detailed associations between the HIV-positive patient and most of the traditional ischaemic heart disease (IHD) risk factors of hypertension, smoking, high cholesterol and diabetes.

Hypertension

Poorly controlled HIV-positive hypertensives have a poorer IHD risk and have a greater risk of progression to end-stage renal disease.

Caution needs to be taken with the use of amlodipine in patients on EFV, NVP and a PI, as the amlodipine blood level can be significantly elevated, due to a drug-drug interaction (see **Chapter 7**).

Smoking

There are many negative associations between smoking and HIV, especially in the realm of co-morbid respiratory diseases, like TB and pneumocystis (see later).

Regarding HIV and smoking, data shows:

- Overall mortality rate comparisons:
    - HIV-negative never-smokers: 1.76
    - HIV-positive never-smokers: 2.45
    - **HIV-positive smokers: 5.45**
- Smokers have a poorer response to ART.
- Smokers have more ART side effects.

Lipids

- Chronic HIV infection is known to cause elevated total and LDL cholesterol, raised triglycerides and lowered HDL, all identified risk factors for ischaemic heart disease.
- The PIs and NNRTIs are known to contribute to higher levels of lipids.
- Simvastatin should be used with a PI only with extreme caution, as a drug interaction between them can result in dangerously toxic levels of simvastatin (see **Chapter 7**). Atorvastatin in doses of 10–20 mg is much safer and is becoming increasingly available in MSF sites.

Diabetes

This is an independent NCD, in addition to being a significant risk factor for vascular disease. See more detail in section 4 below.

ART and vascular disease

- The D:A:D study (Data collection on Adverse events of anti-HIV Drugs) showed an increased incidence of myocardial infarcts (MI) with accumulated increase in exposure to combination ART.
- Several studies have shown increased incidence of MIs in patients taking ABC. While this needs to be considered in deciding on the choice of ART, this does not mean that ABC is contra-indicated in patients at higher risk of cardiovascular disease. The benefits of ABC may outweigh the small increased risk of an MI.
- However, despite these seemingly negative associations between ART and cardiovascular morbidity and mortality, the overall beneficial role of ART has been demonstrated to outweigh potential CVD risks in people with HIV.

Management recommendations

WHO guidelines

WHO recommendation

Assessment and management of cardiovascular risk should be provided for all individuals living with HIV, according to standard protocols recommended for the general population:

- People >40 years;
- Smokers;
- People with known hypertension or diabetes mellitus (DM);
- Waist >90 cm in women, >110 in men;
- Those with a family history of diabetes or premature cardiovascular disease; and
- Those with an elevated cholesterol.

WHO good practice statement

Strategies for the prevention and risk reduction of cardiovascular disease by addressing modifiable factors, such as high blood pressure, smoking, obesity, unhealthy diet and lack of physical activity should be applied to all people living with HIV.

2. Cancers

It is beyond the scope of this short chapter to detail the associations between HIV and cancers. In summary, the following observations can be made:

There are **three AIDS-defining** cancers (ADCs), Kaposi's sarcoma (KS), non-Hodgkin lymphoma and invasive cervical carcinoma. With increasing access to ART the incidence of ADCs has significantly reduced.

Non-AIDS-defining cancers (NADCs) are made up of all the other cancers affecting the general population. Skin cancers and anal cancer are more common in the HIV-positive population.

Regarding lung cancer, the following associations with people with HIV have been identified:

- There is increased susceptibility to developing it.
- It presents at a younger age.
- It is more advanced when it presents.
- Outcomes are generally worse.

Management recommendations

The clinical and programmatic significance of the above is that greater vigilance is required for detecting malignancies in the HIV-positive patient:

- Cervical screening should be regularly performed (see **Chapter 19**).
- Persisting anal sores, especially in men who have sex with men (MSM), should raise the suspicion of anal carcinoma and prompt further investigation.
- Kaposi's sarcoma should be looked for in every new patient presenting to an HIV clinic, as well as being on the differential diagnosis list for HIV-positive patients presenting with a new illness. This is especially relevant in the respiratory and gastro-intestinal systems in patients presenting with advanced disease.
- Non-Hodgkin lymphoma must always be a consideration in the patient presenting with enlarged lymph nodes peripherally or on chest radiology.
- All malignancies (ADCs and NADCs) should remain part of differential diagnoses in the same way they are in HIV-negative patients, perhaps more so, as not only does the incidence appear to be higher, but also the likelihood of the patient presenting later in the disease and having a worse outcome is probably greater.

3. Asthma and chronic obstructive pulmonary disease (COPD)

Asthma

As asthma is a disease related to the immune system, it is not surprising that there is a higher incidence of asthma in HIV-positive patients.

Regarding treatment, both inhaled fluticasone and budesonide are known to interact with the PIs. This is particularly important in children on a PI where significant amounts of these inhaled steroids can be swallowed. Their subsequent metabolism, slowed by the inhibitory effect of the PI, can result in levels high enough to cause cushinoid features.

Chronic obstructive pulmonary disease

As smoking is the largest contributing factor to the development of COPD, it is instructive to note the impact of smoking on the HIV-positive patient (mentioned above) and the respiratory conditions associated with it. The following associations have been made between COPD and HIV-positive patients:

- The frequency and severity of **bacterial pneumonias** is increased.
- There is a greater predisposition to developing **TB**, the response to treatment is poorer, there is a longer duration of infectivity, a higher likelihood of recurrence and a higher mortality, even with effective treatment.
- In addition, TB, via its destructive effects on the lung, is a significant contributing factor towards the development of COPD.
- The risk of developing pneumocystis pneumonia is higher, and worsens with a higher cigarette load.

HIV has been shown to be an independent risk factor for COPD, with HIV-positive people 50–60% more likely to have COPD than HIV-negative people.

Management recommendations

- Asthma diagnosis and treatment is the same as for HIV-negative persons. Use fluticasone with caution in children, as absorbtion of it after swallowing can result in a Cushing's-type syndrome. A safer alternative is beclomethasone, accompanied with close monitoring for the development of cushinoid features.
- Motivating patients to stop smoking is a greater priority for HIV-positive persons.
- Greater vigilance needs to be exercised in both the diagnosis and management of HIV-related respiratory disease, especially with the 'big three' diseases (TB, pneumocystis, pneumonia: see **Chapter 13**).

4. Diabetes

The mutually aggravating associations between HIV and TB are well known. In addition, diabetes has direct aggravating associations with both TB and HIV and vice versa.

Diabetes and TB

- Diabetics have a three times increased risk of developing TB than non-diabetics. The addition of this to the already increased risk of the HIV-positive person developing TB results in the HIV-positive diabetic having a substantial cumulative risk for the development of TB.
- Diabetes has also been shown to adversely affect the outcomes of TB treatment, with evidence of delayed culture conversion and increased TB-related mortality.

WHO recommendation

All patients diagnosed with TB should be screened for diabetes at the start of their treatment. All diabetic patients (in high-burden TB settings) should be regularly screened for TB.

WHO guidelines

Diabetes and HIV

Development of diabetes

- The HIV-positive patient is twice as likely to develop diabetes as the HIV-negative patient.
- The D:A:D study referred to under 'ART and vascular diseases' (page 430) has shown that the incidence of diabetes increases with cumulative exposure to combination ART.

Diabetes disease progression

In the HIV-positive diabetic, the following associations have been noted:

- Diabetic control is more difficult to achieve.
- There is an increased risk of developing metabolic syndrome.
- Renal complications are more prevalent, with both conditions predisposing to proteinuria, chronic kidney disease and renal failure.
- Similarly, both conditions predispose to neuropathy, resulting in more frequent development of this complication.
- Diagnostic complexity; the overlapping of specific symptoms can complicate some diagnoses:
    - Night sweats can be caused by TB and hypoglycaemia.
    - Visual disturbance can be caused by diabetes, hypoglycaemia and CMV retinopathy.
    - Weight loss can be due to poor diabetic control or opportunistic infections, especially TB.

Management complications

- Metformin:
  - The incidence of GIT side effects, especially diarrhoea, is increased.
  - Caution must be exercised when metformin is used with tenofovir, as there is a greater risk of renal impairment in both conditions. It is safer to start metformin at lower doses, 250 mg bd, and gradually increase the dose.
- Sulphonylureas are less effective in the presence of insulin resistance (higher in HIV-positive patients, as noted above).
- The PIs (less so with atazanavir) are known to increase insulin resistance and decrease insulin secretion.
- The additional pill burden and responsibility of self-management of another chronic co-morbidity may worsen adherence.

Management recommendations

In light of the above data, all HIV-positive patients should ideally be screened annually for diabetes, with a fasting glucose and a urine dipstick. Failing this, the following should be targeted for diabetic screening:

- People >40 years;
- Smokers;
- Waist circumference >90 cm in women, >110 in men;
- Those with a family history of diabetes or premature cardiovascular disease; and
- Patients on a PI.

5. Epilepsy

Seizures are a common presenting feature of neurological disease in the HIV-positive patient. New onset of seizures must always be investigated. (See **Chapter 14**.)

The drugs commonly used to treat epilepsy (phenobarbitone, carbamazepine and phenytoin) should ideally not be used at all with first line ART, as they substantially drop the blood levels of efavirenz and nevirapine, due to their powerful induction effect (see **Chapter 7**).

Epilepsy drugs of choice include sodium valproate, leverecitam and lamotrigine.

Management recommendations


Refer to hospital

- All HIV-positive patients presenting with seizures should be **referred** for further investigation before the diagnosis of idiopathic epilepsy is made.

- Avoid standard epilepsy medications in patients on ART; rather choose sodium valproate, leverecitam or lamotrigine. Exercise caution with using valproate for women of child-bearing age, as it can cause foetal abnormalities.

6. Depression

WHO recommendation

Assessment and management of depression should be included in the package of HIV care services for all PLHIV.

WHO guidelines

See more detail on the screening, diagnosis and management of depression in **Chapter 22**.

Programmatic considerations for clients with HIV and other chronic co-morbidities

- Routine health education messages during routine consultations and counselling sessions should include messages to prevent NCDs: stopping smoking; a healthy diet, including the reduction of salt; and taking regular and adequate exercise.
- Ideally, HIV-positive patients with one or more NCDs should receive care for all the diseases in an integrated approach (same day, same healthcare worker, and same consultation room).
- Clients with stable co-morbidities should be offered their medication refills thorough the same differentiated model of care as their ART, receiving the same duration of medication for the NCD as their ART, where available.

Conclusions

Due to the effective rollout of ART to substantially increased numbers of people worldwide, patients are now living long enough to develop one or more NCDs. This factor, combined with the negative associations between HIV and NCDs, means that NCD care is increasingly entering the scope of practice of the HIV clinician.

Clinicians need to be increasingly aware of the clinical implications of this and incorporate new knowledge into their consulting practices. Programme managers, too, will need to adapt their healthcare service models to incorporate NCD care into the overall care of the HIV-positive patient.

CHAPTER 22

Mental health disorders

How do mental health problems present?

Depression

Generalised anxiety disorder (GAD)

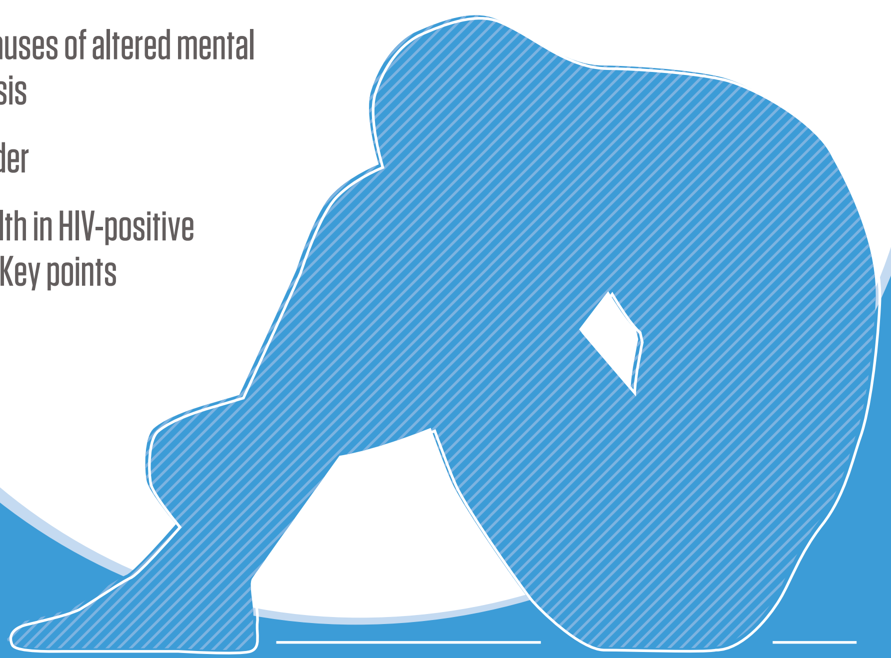
Substance use disorders

Psychoses and delirium

Psychiatric causes of altered mental state; psychosis

Bipolar disorder

Mental health in HIV-positive patients: Key points



NOTE: This chapter has been adapted from mhGAP Intervention Guide 2.0 version (WHO, 2016).

PLHIV have to cope throughout their lives with the consequences of a chronic disease, not only on their physical but also their mental health (MH). Mental health disorders, especially depression, anxiety and substance abuse are common in PLHIV, often with different contributing factors. Often the mental disorders/ difficulties are present to start with, resulting from having to cope with the many different aspects of having HIV or sometimes as a side effect of the treatment. Of importance is that MH disorders not only cause additional suffering and disability for patients and their families but they can also be a significant contributor to poor adherence to treatment, higher-risk behaviours and mortality. Unfortunately, despite this, little attention is paid to MH issues, leaving them undiagnosed and untreated. The good news, however, is that, even in primary care clinics without specialised MH care, it is possible to offer a range of treatment options for PLHIV.

This aim of this chapter is to assist the primary care clinician in the diagnosis and management of the common MH disorders seen in primary care, notably **depression, anxiety, substance abuse** and **psychosis**, including **bipolar disorder**. It guides the clinician through the clinical presentation, diagnosis, management and follow-up of these MH disorders. Note that sometimes there is overlap between some of these conditions, especially in a depressed patient, who can also experience anxiety symptoms.

www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/

refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf

For further information about management of MH disorders:

See mhGAP Intervention Guide 2.0 (WHO, 2016) http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/

MSF Clinical Guide 2016, Chapter 11 (MH disorders in adults) http://refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf

How do mental health problems present?

Usually, people do not come to a clinician complaining about a MH problem, so a diagnosis is made more often when the clinician makes a point of looking for it:

- As a minimum, at each visit patients should be asked about their mood and use of alcohol.
- Beyond this it is recommended that specific groups of people should be screened deliberately (see list below).
- There are certain situations where specific symptoms should prompt a high index of suspicion for a MH problem (see list below).

Deliberate screening is recommended for the following:

- Patients at start of their DR TB treatment;
- Patients with a high viral load test result;
- Patients from key populations (see **Chapter 26**);
- People living in conflict zones; and
- Patients in whom the clinician suspects a mental health disorder or if there is any past history of it.

Symptoms prompting a higher index of suspicion:

- Lack of sleep;
- Persisting, unexplained medical symptoms, such as abdominal pain, headache and nausea; and
- Persisting tiredness, despite normal history, examination and investigations.

Note that there are special groups of people: **children, adolescents, pregnant and breastfeeding women** and the **elderly**, who require special attention in their management, including the use of medications, as this is not necessarily the same as the standard recommendations described here.

Remember that HIV itself, opportunistic infections associated with it, medications and other non-HIV-related conditions can all cause MH problems, so these need to be looked for before confirming the diagnosis.

Depression

Depression is common and is under-diagnosed in PLHIV. Of particular importance is that it can contribute to **poor adherence**, **loss to follow-up** and otherwise **unexplained weight loss**.

Common clinical presentations are:

- Low energy, fatigue;
- Sleep problems;
- Persistent sadness or depressed mood;
- Loss of interest or pleasure in activities that are normally pleasurable; and
- Depression sometimes presents with anxiety symptoms.

(Depression presents in other ways, too: see PHQ9 below.)

Diagnosis of depression

Two basic but important screening questions should be asked:

- During the last 2 weeks, have you felt like you were losing interest or pleasure in doing things?
- Have you felt down, depressed or helpless?

If the patient answers yes to either of these questions, investigate further with a screening tool. See Table 22.1 Patient Health Questionnaire (PHQ9) below.

Table 22.1 Patient Health Questionnaire (PHQ9)

Name: ______________________________________ Date: ____________

Over the last 2 weeks, How often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
If one of the above symptoms are present more than half of the time, go on with the following questions:				
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating (on things linked with patient's usual activities)	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Throughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Add columns :				
TOTAL:				

10: If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all: ____

Somewhat difficult: ____

Very difficult: ____

Extremely difficult: ____

If you faced any difficulty, did it occur for two years or more? ________________

A patient is considered as having signs of depression if:

PHQ9 score	Provisional diagnosis	Recommendation
5–9	Minimal symptoms	Support and educate to contact clinic if worse
10–14	Mild depression *or* **chronic depression** (symptoms lasting for two years)	Support and watchful waiting Reassess in one/two weeks Consider starting treatment
15–19	Moderate depression	Refer to clinical officer/psychologist for assessment and treatment
>20	Severe depression	Major impairment and need for immediate medical treatment and counselling

- **If question #9 is answered with a score of 1 or more, then the patient requires referral and further assessment by the clinical officer/psychologist or other appropriate available clinician.**
- **For moderate, severe and chronic depression, treatment and follow-up consists of:**
  1. **Regular, supportive counselling**
     a. Reassure patient about his (her) symptoms, build a trustful and confidential relationship.
     b. Evaluate depression (when it started, precipitant, support systems, etc.)
     c. Assess functional impairment: ask question #10, be sure symptoms have been present for 2 or more weeks.
     d. Provide regular counselling sessions as complementary to medical treatment.
     e. Reassess evolution on a monthly basis with the PHQ9.
  2. **If score >15, refer to clinical officer/medical doctor for assessment for medical treatment.**

Don't forget to:

- Do available tests to check for possible underlying medical causes for the depression:
  - low thyroid;
  - significant anaemia;
  - HIV-associated dementia.
- Explore emotional and social issues that may be significant contributors to depression (e.g. bereavement due to loss of a close family member).
- Check for psychotic features (e.g. hallucinations) and bipolar disorder.
- Check for medications that may be causing it, especially cycloserine/terizidone and EFV.

Evaluation of suicide risk

Depressed patients should always have their suicide risk assessed, and, if high, be referred immediately to the most experienced person available. Asking about suicide, though difficult to do, does not increase the chance of the patients actually doing it. To talk about it is an important step to help patients. Possible ways of asking include:

- Has it ever become so (painful, frustrating, difficult, frightening) that you have thought about giving up? Have you thought about not want to live anymore? Have you thought about ending your life? Would you ever consider doing so? Under what circumstances have you considered this?
- Do you currently have any thoughts or plans to hurt yourself?

Management of depression

Education and counselling:

- Educate the person and their caregivers/relatives (when suitable) about depression.
- Assess for and try to reduce stressors.
- Promote functioning in daily activities and community life.
- Always establish a treatment plan, together with your team.
- If available, refer for psychosocial interventions with a counsellor, support group, social worker and/or a more experienced mental health professional, if necessary.

Medication

- If the depression is moderate (PHQ9 score 15 to 19) or severe (PHQ9 score >20), antidepressants may be needed. If severe, refer or start antidepressant medication in the same week.
- Amitriptyline has fewer interactions compared to other antidepressant medication, but has more side effects.
- Selective serotonin reuptake inhibitors (SSRIs) may also be considered (fluoxetine, sertraline, paroxetine). Fluoxetine should not be taken with a PI-based regimen (see **Chapter 7**) as the fluoxetine level can be significantly elevated.
- Educate the patient about the fact that medication takes 2–3 weeks to take effect.

Table 22.2 Guide to antidepressant use

Medication	Dosage	Common side effects	Contra-indications/Cautions
Amitriptyline (a tricyclic antidepressant (TCA)	Start 25 mg at bedtime. Increase by 25–50 mg per week to 100–150 mg daily (maximum 300 mg). Note: Minimum effective dose in adults is 75 mg. Sedation may be seen at lower doses. **Elderly/medically ill:** Start 25 mg at bedtime to 50–75 mg daily (maximum 100 mg). **Children/adolescents:** Do not use.	**Common:** Sedation, orthostatic hypotension with increased risk of falling, blurred vision, difficulty urinating, nausea, weight gain, sexual dysfunction. **Uncommon but serious:** ECG changes (e.g. QTc prolongation), cardiac arrhythmia, increased risk of seizure.	Avoid in persons with cardiac disease, history of seizure, hyperthyroidism, urinary retention, or narrow angle-closure glaucoma, and bipolar disorder (can trigger mania in people with untreated bipolar disorder). Overdose can lead to seizures, cardiac arrhythmias, hypotension, coma, or death. Levels of amitriptyline may be increased by anti-malarials including quinine.
Fluoxetine (a selective serotonin reuptake inhibitor (SSRI)	Start 10 mg daily for one week then 20 mg daily. If no response in 6 weeks, increase to 40 mg (maximum 80 mg). **Elderly/medically ill:** Fluoxetine is preferred choice. Start 10 mg daily, then increase to 20 mg (maximum 40 mg). **Adolescents:** Start 10 mg daily. Increase to 20 mg daily if no response in 6 weeks (maximum 40 mg).	**Common:** Sedation, insomnia, headache, dizziness, gastrointestinal disturbances, changes in appetite, and sexual dysfunction. **Serious:** Bleeding abnormalities in those who use aspirin or other non-steroidal anti-inflammatory drugs, low sodium levels.	Caution in persons with history of seizure. Drug-drug interactions: Avoid combination with warfarin (may increase bleeding risk). May increase levels of TCAs, antipsychotics, and beta-blockers. Caution in combination with tamoxifen, codeine, and tramadol (reduces the effect of these drugs). Fluoxetine taken with LPV/r: Start at 5 or 10 mg daily and don't give >20 mg as the combination can result in elevated fluoxetine levels, causing serotonin syndrome (typically rapid onset with hyperreflexia, tremors, myoclonus, diaphoresis, confusion, agitation, or shivering, muscular rigidity not invariably present).

Adults with thoughts or plans of suicide: SSRIs are the first choice:

- Overdose of TCAs such as amitriptyline may be fatal, and therefore should be avoided in this group.
- If there is an imminent risk of self-harm or suicide, give a limited supply of antidepressants (e.g. one week's supply at a time).
- Ask the person's carers to keep and monitor medications. Clinician to follow-up frequently, to prevent medication overdose.
- Avoid leaving the person alone.

Special groups

Adolescents 15 years of age or older

- If symptoms persist or worsen despite psychosocial interventions, fluoxetine may be used, but not other SSRIs or tricyclic antidepressants (TCA). If fluoxetine is prescribed, ask the adolescent to return weekly for the first 4 weeks, to monitor thoughts or plans of suicide.

Women who are pregnant or breastfeeding

- Avoid antidepressants, if possible.
- Consider antidepressants at the lowest effective dose if there is no response to psychosocial interventions.
- If the woman is breastfeeding, avoid long-acting antidepressant medication, such as fluoxetine.
- If the woman is pregnant, use sertraline or fluoxetine if really necessary.

Follow-up

- For patients not on antidepressants, re-assess symptom severity on a monthly basis with the PHQ9. Resume follow-up visits at same time as ARV refills.
- If on antidepressants, see monthly for the first 3 months, checking for side effects and monitoring adherence. Once symptoms have improved, medication can be combined with the ARV refill every 2–3 months.
- Patient should be encouraged to continue with the chosen medication until they are symptom-free for 9–12 months and not to stop it as soon as they are feeling better.
- When a decision is made to stop medication, the dose is usually halved every 2 weeks with close monitoring of symptoms. One is satisfied that the weaning has been successful when the person remains symptom-free after 4 weeks on no medication.

Generalised anxiety disorder (GAD)

Anxiety responses can commonly occur around the time of testing and HIV diagnosis, as well as with advancing disease. They are often accompanied by symptoms of depression and can also be a consequence of substance use disorder.

The key feature is excessive worry about a number of different things associated with heightened tension.

Clinical presentation

- Restlessness or feeling keyed up or on edge;
- Easily fatigued;
- Difficulty concentrating or mind going blank;
- Irritability;
- Muscle tension; and
- Sleep disturbance.

Diagnosis

First exclude any medical causes, especially hyperthyroidism and substance abuse.

The key starting question to ask is:
Over the last 2 weeks, how often have you been bothered by the following problems?

- Feeling nervous, anxious or on edge?
- Not being able to stop or control worrying?

If patient responds yes to any of these questions, proceed with the GAD-7 (Table 22.3).

If the total score is 10 or more, and the condition has been continuing for 6 months or more, the diagnosis can be made of generalised anxiety disorder.

Management

Counselling and lifestyle advice

- Provide psychosocial support when available.
- Recommend physical activities/activities that reduce stress.
- Refer for counselling and involvement in a support group.

Table 22.3 GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? (Use ✓ to indicate your answer.)	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
(For office coding: Total score T______ = ______ + _______+ _______)				

Medication

- If anxiety is severe or persists, medication will be needed.
- The mainstay of treatment is SSRIs, with initial combination with a benzodiazepine.
  - **SSRIs:** Fluoxetine tends to increase anxiety, so paroxetine or sertraline are preferred. Start at 10 mg paroxetine or 25 mg sertraline and increase 2 weeks later to reach 20 mg of paroxetine or 50 mg of sertraline. If needed, higher doses can be used: 40–60 mg of paroxetine or 100–200 mg of sertraline. (See Table 22.2 as side-effect profile is similar to fluoxetine.)
  - **Benzodiazepines:** All of this group have the potential to cause dependence, so should ideally be used only for a week or two, while the SSRI is taking effect. Use diazepam 5–10 mg daily.
  - **Antihistaminics:** Hydroxyzine is used for anxiety and insomnia, as well as for pruritus. It is a better alternative for anxiety than benzodiazepines, as it is non-addictive. Use 100–200 mg/day in 4 divided doses.

Follow-up

- For patients on medication, close follow-up is needed for the first 3 months.
- See monthly for the first 3 months, checking for side effects and monitoring adherence. Once symptoms improve, the medications can be combined with the regular ARV refill.
- Patient should be encouraged to continue with the chosen medication until they are symptom-free for 9–12 months, not to stop it as soon as they are feeling better.

Special groups

Adolescents 15 years of age or older

- If symptoms persist or worsen despite psychosocial interventions, consider fluoxetine, paroxetine or sertraline.
- If fluoxetine is prescribed, ask the adolescent to return weekly for the first 4 weeks, to monitor thoughts or plans of suicide.
- Hydroxyzine may be used to decrease anxiety. Use 50–100 mg/day in 4 divided doses.

Women who are pregnant or breastfeeding

- Avoid antidepressants, if possible.
- Consider antidepressants at the lowest effective dose if there is no response to psychosocial interventions.
- If the woman is breastfeeding, avoid long-acting antidepressant medication, such as fluoxetine.
- Consult a specialist if available.

Substance use disorders

- Use of alcohol or other drugs (e.g. cannabis) is a common reason for poor adherence to ARVs.
- Due to stigma and fear of discrimination, people usually do not volunteer that they have problems controlling their substance use. It should therefore be actively looked for in all patients presenting with a high viral load or with evidence of treatment failure.
- It is important to be direct, and, at the same time, respectful, while accessing substance use disorder. Judgmental attitudes can push a person into denial and prevent a patient from seeking healthcare.

Clinical presentation

- Smell of alcohol, slurred speech, sedation, erratic behaviour;
- Injuries due to falls;
- Deterioration of social functions (e.g. difficulties at work, getting into fights or trouble with the law; difficulty with relationships);
- Requests for sleeping tablets or painkillers;
- Signs of chronic liver disease;
- Withdrawal symptoms, such as tremor, sweating, confusion and seizures (fits), and
- Symptoms of depression.

Diagnosis

Use the following CAGE-AID questionnaire to screen for alcoholism or drug use:

C Have you ever felt you needed to **cut** down on your drinking or drug use?

A Have people **annoyed** you by criticising your drinking or drug use?

G Have you ever felt bad or **guilty** about your drinking or drug use?

E Have you ever had to have a drink or use a drug first thing in the morning **(eye-opener)** to steady your nerves or get rid of a hangover?

If substance abuse is suspected, screen for depression as well, as the two conditions often co-exist.

Management and follow-up

- It can be helpful to explore how the person started using substances, when they started using them and if they have tried to reduce their use.
- Assess patient for stressors and stigma and any motivation to stop.
- Assess for any depression or anxiety and manage accordingly, avoiding dependence-producing medication like benzodiazepines.
- Provide support. If patient is willing to stop, facilitate the process by referral to existing local services that manage alcohol or substance use. Follow-up to ensure that the patient has linked to care.
- If patient is not yet motivated to stop the substance abuse, provide information and education for the patient and his/her carer. Keep the door open for the future when the patient may wish to be referred.
- Follow up any signs of further deterioration in general health conditions, and re-evaluate regularly for self-harm and suicide risk.

NOTE: if the person is substance dependent, suddenly stopping the substance may provoke symptoms of withdrawal.

Special groups

Women who are of child-bearing age, pregnant, or breastfeeding

Discuss the harmful effects of substance use on foetal development and ensure that the woman has access to effective contraception when suitable. Advise women who are breastfeeding to avoid alcohol completely and stop using any illicit drugs.

Psychoses and delirium

Psychoses are characterised by the following symptoms:

- Marked behavioural changes, neglecting usual responsibilities related to work, school, domestic or social activities;
- Agitated, aggressive behaviour, decreased or increased activity;
- Fixed false beliefs not shared by others in the person's culture;
- Hearing voices or seeing things that are not there; and
- Lack of realisation that one is having mental health problems.

Delirium is defined as fluctuating global cognitive impairment associated with behavioural abnormalities. It is usually caused by a medical illness and features often include:

- Altered level of consciousness;
- Inappropriate agitation or aggression;
- Change in cognition or a perceptual disturbance;
- Onset is over hours to days (though this can be longer) with a tendency to fluctuate; and
- Loss of the normal circadian rhythm.

All patients with psychoses or delirium need **urgent referral** for further investigation and management (See page 285 for all medical causes of altered mental state – green dots – that need to be considered):

- Psychoses need to be contained initially in a primary care clinic but the patient needs to be referred for further management.
- Delirium is a fairly frequent presentation in HIV-positive patients, especially with a lower CD4 count, and carries a high mortality risk. It is, therefore, a danger sign prompting referral for investigation for the underlying cause.

Refer to hospital

Table 22.4 Pointers to delirium vs psychoses

	Delirium	Psychoses as psychiatric illness
Onset	Acute (over hours to days)	More chronic but can be acute
Symptoms and signs	Tremor, agitation; fluctuating mental status; hallucinations (usually visual); disruption of sleep-wake cycle	Impaired reality testing; delusions; hallucinations (usually **auditory** but sometimes visual)
Memory	Short-term memory loss	Memory loss less of a problem
History of previous mental illness	Absent	Often present

Refer to hospital

Patients with delirium ideally need **same-day referral** to an admission facility for investigation and further management. For more detail on patients presenting with altered mental state, see **Chapter 14**, Algorithm 14.1 (all conditions marked with a green dot).

Psychiatric causes of altered mental state; psychoses

Psychoses may be diagnosed in these conditions:

- Schizophrenia (psychosis)
- Manic phase of bipolar disorder (see below)

See also:

- *mhGAP Intervention Guide 2.0* (WHO, 2016) http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/
- *MSF Clinical Guide 2016*, Chapter 11; mental health disorders http://refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf

www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/

refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf

Management of psychoses

Psychoses are defined as thought disorders in which there is loss of contact with reality, often associated with hallucinations or delusions.

- Hallucinations are sensory perception in the absence of external stimuli, most often auditory or visual (hearing voices or seeing things).
- A delusion is a false personal belief that is not subject to reason or contradictory evidence and is not explained by a person's usual cultural and religious concepts.

If psychoses are suspected, start treatment at a low dose:

- Risperidone PO (2 mg in 2 divided doses on day 1, then 4 mg/day in 2 divided doses as of day 2. If insufficient, increase to 6 mg/day (8 mg/day maximum); or
- Haloperidol PO (5 mg/day in 2 divided doses; if insufficient, 10 mg/day in 2 divided doses; not to exceed 20 mg/day).

If available, haloperidol decanoate IM (long-acting form) can be used in the long-term treatment of psychoses in patients stabilised on oral therapy (100 mg every 4 weeks).

Extra-pyramidal effects, which are more common with haloperidol than with risperidone, can be counteracted by adding biperiden PO: 2 to 4 mg/day in 2 divided doses.

The goal of the treatment is to reduce psychological suffering and disabling symptoms, particularly on the relational level. It offers real benefits, even if chronic symptoms persist (tendency toward social isolation, possible relapses and periods of increased behavioural problems, etc.).

The treatment should last at least one year, with a gradual dose reduction. Low dose may be maintained for longer periods, if necessary.

Uncertainty about the possibility of follow-up at one year or beyond is no reason not to treat. However, it is better not to start pharmacological treatment for patients who have no family/social support (e.g. homeless), provided they do not have severe behavioural disorders.

Bipolar disorder

Clinical presentation

Bipolar disorder is characterised by periods of excessively elevated or irritable mood known as mania, followed by episodes of prolonged severe depression. The episodes of mania may be either **manic** or **hypomanic**.

Manic episodes are characterised by at least one week of:

- Abnormally elevated self-esteem;
- Delusions of grandeur;
- Extreme talkativeness with pressured speech;
- Racing thoughts, being easily distracted;
- A reduced need for sleep;
- Elevation of mood and/or irritability;
- Impulsive or reckless behaviours, such as expensive spending, making important decisions without planning and sexual indiscretion;
- Loss of normal social inhibitions, resulting in inappropriate behaviours; and
- Disorganised thoughts and possibly auditory hallucinations (psychotic features).

Hypomanic episodes are characterised by elevated, expansive, or irritable mood of at least 4 consecutive days' duration. The key difference is that the symptoms are not severe enough to cause significant impairment in functioning at work or at home. There is also the absence of significantly disordered thinking that may require hospitalisation.

If considering a diagnosis of bipolar disorder, a useful screening question is, have you had periods of feeling so happy or energetic that other people told you that you were talking too fast or were hyper?

Management

If bipolar disorder is suspected, patients should be referred for more experienced psychiatric help to confirm the diagnosis. It is beyond the scope of this book to deal with the comprehensive management of bipolar disorder here.

www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/

refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf

See also:

- *mhGAP Intervention Guide 2.0* (WHO, 2016) http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/
- *MSF Clinical Guide 2016,* chapter 11; mental health disorders http://refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf

However, as these patients may still be under the care of clinicians in HIV clinics, they need to be managed, but preferably with more experienced oversight.

Of note:

- Bipolar disorder can cause serious psychosocial and interpersonal impairment, so specific support needs to be arranged in the patient's community.
- If bipolar mood disorder is suspected, even if the patient is in the depressed phase, antidepressants should NEVER be prescribed without a mood stabilizer, such as carbamazepine or valproate, as this could lead to a manic episode.
- If symptoms of mania do develop, the patient and the carers should stop the antidepressant immediately and return for help.
- Maintenance treatment needs to be continued for at least 2 years after the last bipolar episode.

Mental health in HIV-positive patients: Key points

- Mental health disorders and/or psychological problems are common and contribute significantly to morbidity, not only from the mental illness, but also from the challenges the mental illness poses to the ongoing management of the HIV.
- Depression and anxiety disorders can often be diagnosed and treated effectively in primary care settings, without needing referral.
- Altered states of consciousness are frequently caused by medical, rather than psychiatric illness.
- All patients presenting with altered level of consciousness need urgent referral to hospital for investigation and management, as many of the medical conditions can be life-threatening.
- The management of the psychiatric causes also requires referral, as this is beyond the scope of the primary care clinic.

Fever and rational antibiotic prescribing

Fever in HIV-positive patients

There are many causes of fever in HIV-positive patients in primary care: infections due to bacteria, viruses, parasites (including malaria) and fungi. However, fever is caused not only by infections but also inflammatory conditions and other medical problems. Clinical presentation varies widely: patients may present critically ill with other danger signs, or have only minor symptoms and be otherwise well.

Algorithm 23.1 provides a clinical approach to fever in patients presenting to primary care and gives an overview of common causes. The notes below refer to this document.

Algorithm 23.1 Fever in HIV-positive patients

3 questions:

1. **Is this a medical emergency?**
   - Fever together with any other danger signs
   - Usually acute onset (days)
2. **Where is the site of infection?**

   Meningitis, respiratory, urinary tract, gynaecological, wound infection. There may be no localising signs, e.g. bloodstream bacterial infections, disseminated TB.
3. **Is the infection caused by bacteria and therefore requires antibiotics?**

Danger signs other than fever*:

- Respiratory rate >30
- Heart rate >120
- Systolic BP <90
- Severe dehydration
- Unable to walk unaided
- Confusion, altered mental state
- Paralysis, weakness, seizures, new onset severe headache, cranial nerve problems, any other new neurological problems

*Hypothermia (<36°C) can occur in bacterial sepsis.

Fever and no other danger signs: Look for cause, as not all patients need antibiotics!

Fever <u>together with</u> any other danger signs is an emergency:

Common causes:

- Malaria
- Bacterial infection
- Note: TB can present acutely in HIV patients.

Investigations and management – while arranging transfer:

- Emergency management: IV fluids, oxygen
- Start IV artesunate if malaria test positive: alternative is IV quinine
- Point of care investigations
- Start other urgent treatment before transfer, e.g. pneumocystis treatment if respiratory danger signs
- Start TB treatment if LAM-positive, neurological symptoms/signs or other high suspicion of TB
- **Start antibiotics immediately, unless there is another identified cause;** treat according to site of infection (Table 23.1).

POC tests:

- Malaria
- Glucose*
- Haemoglobin
- Serum CrAg
- TB LAM

*Bacterial sepsis is a common cause of hypoglycaemia

Not all patients with fever need antibiotics!

The decision to prescribe antibiotics in primary care is based on the likelihood of there being a bacterial infection. This is influenced by the answers to three questions:

1. Are there danger signs?
2. What is the site of the infection?
3. Is the cause likely to be a bacterial infection?

Malaria:

- Oral treatment: Co-artem

Viral respiratory tract infections:

- A common cause of fever in primary care.
- They are self-limiting and antibiotics are not indicated.
- Do not prescribe antibiotics for influenza symptoms.

Common bacterial infections in primary care (Table 23.1):

- Urinary tract infections
- Mild community-acquired pneumonia
- Diarrhoea
- Skin infections

TB:

- Investigate for TB: Remember investigations cannot rule out TB.
- Strong clinical suspicion of TB: Start empiric treatment.
- Fever may last up to 14 days after initiation of TB treatment

TB not improving or deteriorating on treatment: See Algorithm 12.3.

TB IRIS

- Fever and tachycardia are common; these may be the only signs. See **Chapter 5**.

Other opportunistic infections:

Most stage 4 infections causing fever result in danger signs (neurological, respiratory). When no danger signs, look for the following:

Fungal infections:

- Cryptococcal disease may present only with fever: serum CrAg positive.

Parasites:

- *Isospora belli* and other parasite diarrhoeas.

Herpes viruses:

- HSV: Primary infection can cause fever; look for oral and genital lesions.
- Herpes zoster

Non-infectious causes:

Malignancies such as Kaposi's sarcoma, lymphoma and others.

Deep vein thrombosis, pulmonary embolism:

- These are common in sick patients with HIV/TB.
- Be alert for these in patients recently discharged from hospital or patients bedbound at home.
- Red, hot, swollen and tender calf – think of DVT, not just cellulitis.
- Refer to hospital.

Drugs:

- Drug hypersensitivity.
- Drugs can cause fever without a hypersensitivity reaction: If you cannot find the cause, consider stopping all medication for a few days.
- Rifampicin, particularly, can cause fever.

1. Are there danger signs?

Danger signs commonly seen with fever include hypotension (septic shock, hypovolaemic shock), tachycardia, tachypnoea (e.g. bacterial or pneumocystis pneumonia) and reduced level of consciousness (e.g. meningitis, hypoglycaemia due to sepsis). If danger signs are present, the patient needs initial stabilisation and emergency management (e.g. fluids and oxygen), while transfer is being arranged.

Common causes of fever and danger signs:

- Bacterial infections are generally difficult to exclude on initial assessment, and are more likely in patients with danger signs. Unless bacterial infection is considered unlikely, start antibiotic treatment for patients with fever and other danger signs. Giving antibiotics as soon as possible under these circumstances saves lives. They can be stopped at the referral hospital, should an alternative diagnosis be found.
- If the malaria rapid test is positive, treatment should be started immediately, and not be delayed until the patient arrives at the referral centre. Bacterial sepsis is common in severe malaria: start broad spectrum antibiotics (e.g. ceftriaxone 1–2 g) while organising referral.
- If respiratory danger signs are present, treatment for pneumocystis pneumonia should be started in the clinic immediately, while awaiting transfer to hospital.
- TB can also present acutely in HIV-positive patients.

If the patient does not have danger signs, **look for the cause, as not all patients with fever need antibiotics!**

This process will be helped by answering the next two questions:

2. What is the site of the infection?

A careful history and examination checking all systems may help localise the site; for example neurological, respiratory, genitourinary, cellulitis, diarrhoea.

This information is essential in order to decide on the choice of antibiotics and the dose to give. National or local guidelines should be consulted, as there is a wide variation between countries, depending on antibiotic availability and whether there is information available on antibiotic resistance.

Table 23.1 shows widely used antibiotics for bacterial infections. Ensure the first dose of antibiotics is given immediately!

Antibiotic choice, route, dose and duration:

- Use local or national **antibiotic guidelines**, if available. If there are none, use MSF, 2016, *Clinical Guidelines*, available at http://refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf
- Document the indication for antibiotics in the patient's folder.

refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf

3. Is the cause likely to be a bacterial infection?

If an infection is caused by bacteria, it requires antibiotics, and, if caused by non-bacterial organisms, antibiotics are not indicated. Algorithm 23.1 shows many non-bacterial causes of fever for which antibiotics are of no benefit. They may even cause harm (hypersensitivity reactions, adverse effects, increasing antibiotic resistance – see antimicrobial resistance later in this chapter).

History and examination then help determine whether fever is likely bacterial in origin, or has another cause.

- **Bacterial infections are usually acute (days).**
- Symptoms and signs give clues:
    - If the cough started in the context of a cold and sore throat, it is likely to be a common viral infection.
    - A productive cough with acute onset shortness of breath is likely to be bacterial pneumonia.
    - A cough with weight loss and night sweats is likely to be TB.

Investigations that can confirm bacterial infection:

- Most are not available in primary care but if a white cell count or a CXR can be obtained it can sometimes be helpful.
- If there is an abscess or other pus collection, aspirate as much fluid as possible, for both diagnosis and treatment. Remember, not all pus collections are bacterial. TB and TB IRIS commonly cause enlarged lymph nodes, which may be large, red and tender with pus found on aspiration. Pus draining from sinuses may also be TB. If possible, send pus for cell count, gram stain and Xpert MTB/RIF at your referral centre.

If you are uncertain and the patient is stable, other relevant investigations (TB investigations, chest x-ray) and reviewing the patient after a few days are alternatives to giving antibiotics 'just in case'.

Figure 23.1 shows a general framework for decision-making, based on this approach. Remember that it is fine to acknowledge uncertainty; the severity of the patient determines whether uncertainty pushes you to starting antibiotics immediately or whether it is better to wait and look for other causes.

Table 23.1 Common bacterial infections in primary care

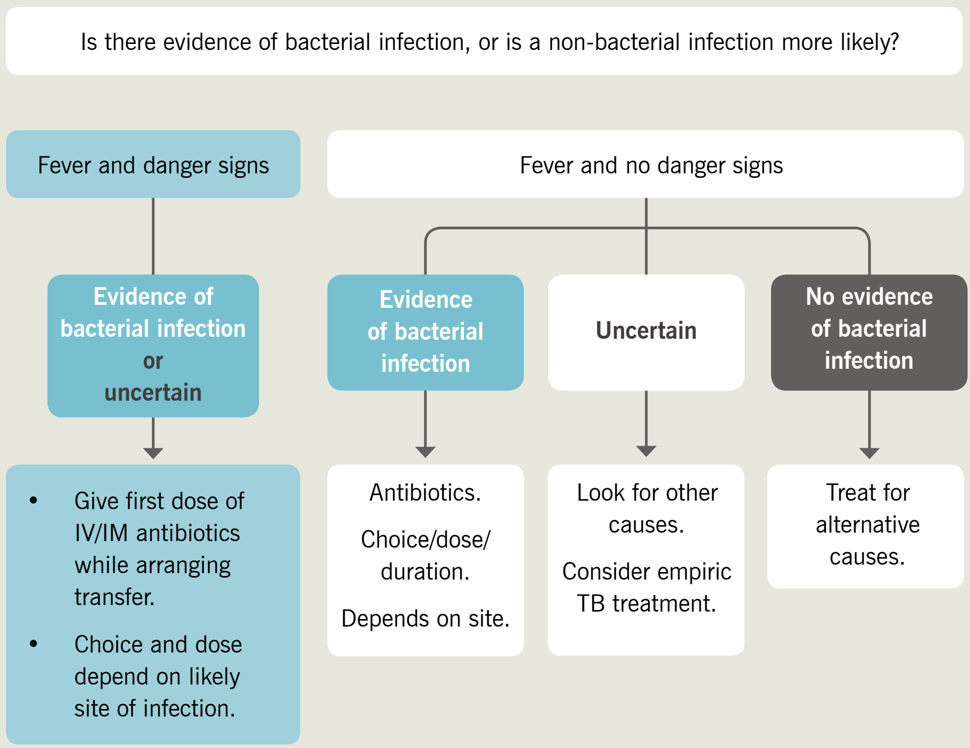
Infection	Notes	Antibiotics
Community acquired pneumonia	Fever with no other danger signs; Dyspnoea; +/- cough; Examination shows bronchial breathing, reduced air entry. Differential diagnosis: • Pneumocystis pneumonia; • Pulmonary TB; • Bacterial pneumonia. Don't prescribe antibiotics for viral upper respiratory tract infections.	Ambulatory patients: Amoxicillin 1 g orally 3 times a day for 5 days. Severe pneumonia: give first dose of IV/IM antibiotics according to local protocols while referring to hospital. Commonly used antibiotics are IV/IM penicillin, ampicillin and ceftriaxone. Ciprofloxacin should be avoided for respiratory infections, to conserve quinolone use for DRTB. See **Chapter 13**: Respiratory disease
Meningitis; Fever; Neck stiffness; Photophobia.	Differential diagnosis: • Cryptococcal meningitis; • TB meninigitis: • Bacterial meningitis. Serum CrAg and TB LAM can be done in primary care while arranging referral.	Give first dose of antibiotics while referring to hospital. Use local protocols; most widely used is Ceftriaxone IV 1–2 g x 12 hourly, for 10–14 days. See **Chapter 14**; Neurological disease
Fever and danger signs: no localising signs or symptoms.	This may be a bloodstream infection, which has high mortality.	Give first dose of antibiotics while referring to hospital. Use local/national protocols: 1–2 g Ceftriaxone IV daily is commonly used, for 5–7 days.
Urinary tract infection: Suprapubic pain; Dysuria; Frequency. (See Algorithm 23.2 at end of chapter for guidelines for UTIs in women.)	If patient presents with fever, chills, and flank pain as well, this is likely to be pyelonephritis.	Ceftriaxone 1 g IM/IV and refer to hospital.
	Complicated UTI: pregnant women.	Ciprofloxacin 500 mg bd for 5 days.
	Complicated UTI: men – who do not get typical cystitis. Look for STIs and prostatitis.	Prostatitis: Ciprofloxacin 500 mg bd for 14 days.
	Uncomplicated UTI: female, non-pregnant and no concerns about pyelonephritis. Do not treat for a UTI if abnormalities such as nitrites and/or leucocytes are found on dipstick but there are no symptoms.	Ciprofloxacin 500 mg bd for 3 days; Fosfomycin 3 g single dose.
Diarrhoea	Most acute non-inflammatory diarrhoea is viral, and does not need antibiotics.	See **Chapter 15**: Gastro-intestinal conditions
Skin infections	E.g. cellulitis	See **Chapter 20**: Skin conditions
Sexually transmitted infections	Gonorrhoea is increasingly becoming resistant to antibiotics: ciprofloxacin is no longer recommended, and there is increasing resistance to cephalosporins. Use your local guidelines; if unavailable use **WHO guidelines**: www.who.int/reproductivehealth/publications/rtis/gonorrhoea-treatment-guidelines/en/	See **Chapter 19**: Sexual and reproductive health

Antimicrobial resistance is a global crisis

The first part of this chapter has focused on causes of fever, and made the point that not all patients with fever need antibiotics. The second part of this chapter will explain why the inappropriate and excessive use of antibiotics is a problem.

The term antimicrobial resistance includes antibiotic resistance (ABR), drug resistant TB, resistance of HIV to antiretroviral drugs, antifungal resistance and anti-parasite resistance (particularly malaria). **This section concerns only antibiotic resistance (ABR)**, and focuses on how clinicians in outpatient departments can contribute to reducing the inappropriate use of antibiotics.

Figure 23.1 Does my patient need antibiotics?



Before antibiotics were available, common infections, such as pneumonia, puerperal sepsis and wound infections were fatal. Due to progressively increasing antibiotic resistance, we are heading back into a similar era, unless something is done to stop it. Antibiotics save lives, so using them when they are needed is essential. However, over-use is resulting in increasing resistance and needs urgent action. If antibiotics are used only when clinically necessary, overall use of antibiotics will reduce, leading to slower evolution of resistance.

This is an important issue for MSF, because we care for sick patients, and therefore frequently use antibiotics in both general and HIV projects.

Impact of ABR on low-resource settings

The antibiotic resistance agenda is largely driven by well-resourced countries, where the focus is on highly resistant organisms and the development of new antibiotics to treat them.

In resource-limited settings the antibiotic resistance crisis is less visible, but as with every crisis, the impact is greater:

- The burden of bacterial disease is higher.
- Infectious diseases remain a common cause of death.
- Limited availability of microbiological laboratories means there is little or no information on resistance to guide antibiotic prescribing.

Another side of the global crisis is the lack of access to basic medical care and antibiotics:

- Adults and children still die because there is limited access to antibiotics.
- Resistance to common, low cost antibiotics will have a severe impact on medical care.

'Instead of being the default treatment for a host of mild ailments, particularly coughs, colds and uncomplicated diarrhoea, antibiotics must be considered life-saving medicines to be used when needed.' *The State of the World's Antibiotics,* 2015: Center for Disease Dynamics, Economics and Policy (CDDEP)

At least 50% of antibiotic prescriptions are unnecessary

Antibiotics are commonly prescribed when there is no indication to do so, both in outpatient and inpatient settings. Common errors in outpatient settings include prescribing antibiotics under the following circumstances:

- The majority of **upper respiratory tract infections** are caused by viruses and not bacteria. Colds and flu do not need antibiotics!
- Most **acute diarrhoea** is viral, and does not need antibiotics (see **Chapter 15**).
- A patient with positive nitrites or leucocytes on routine urine dipsticks, but with **no symptoms to suggest urinary tract infection** does not need antibiotics (see Algorithm 23.2).
- HIV-positive patients with typical TB symptoms and no danger signs need TB treatment, not antibiotics.

What can we do to avoid unnecessary antibiotic use? The role of 'antibiotic stewardship'

Antibiotic stewardship aims to change behaviour regarding antibiotic prescribing by training healthcare workers (clinicians, nurses and pharmacists) and ensuring reducing over-use of antibiotics is a priority for policy-makers (including clinic and district management). Empowering patients and communities is also important, to address misconceptions about the role of antibiotics.

At outpatient clinics, who is responsible?

The answer is – everyone is responsible! As this is a clinical handbook, the programmatic issues are outside the scope of this chapter. Useful resources are listed at the end, and all clinics should ensure that addressing the over-use of antibiotics is on the priority agenda.

However every clinician can begin to address this problem in their own patient consultations, by looking at their own prescribing, and following good practice guidelines.

Rational antibiotic prescribing

- **Use antibiotics only when there is evidence your patient has a bacterial infection.**

  As an outpatient clinician, every time you prescribe antibiotics you should do so only when there is evidence your patient has a bacterial infection. However, in outpatient clinics with short consultation times and few available investigations, decision-making can be difficult. A differentiated service delivery approach allowing triage of patients who are unwell on arrival, immediate point-of-care tests, and review by clinicians allocated more time to assess patients will aid correct clinical diagnosis.

- **Always identify the indication for antibiotics and document it in the patient's folder.**

  Table 23.1 is a general guide to prescribing antibiotics, and ensuring they are not the 'default option' for all patients who are unwell.

- **If no improvement, avoid automatic repeating of a course of antibiotics.**

  If a patient has already had a course of antibiotics and returns for a follow-up appointment with no improvement, review the diagnosis, rather than just prescribing another course of antibiotics.

  - In particular, consider disseminated TB and other opportunistic infections in all patients with advanced HIV who are unwell (see **Chapter 11**). If TB cannot be excluded and investigations are negative, start empiric TB treatment.
  - Consider all non-bacterial causes of fever in HIV-positive patients (see Algorithm 23.1).
  - Clinics should put in place a policy that all patients who remain unwell after a course of antibiotics are reviewed by the senior clinician in the clinic, or referred if there is no experienced clinician available.

- **Prescribe antibiotics correctly.**
  - Correct antibiotic;
  - Correct dose and frequency;
  - Correct duration – most common infections treated in outpatient clinics need 3–5 days of antibiotics, not more; and
  - Correct route – only use intravenous antibiotics when necessary.

Use local or national guidelines for antibiotic prescribing. If there are none, use the 2016 *MSF Clinical Guidelines* (http://refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf) or it can be downloaded from the **SAMU website** from the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Have the guidelines to hand in your clinic or, better still, have a poster in all your consulting rooms with the antibiotic protocol for common infections. Table 23.1 is a guide to common prescriptions for common infections.

- **Manage patient expectations appropriately.**

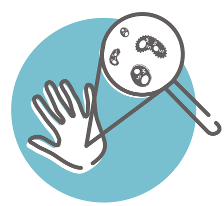
  Misconceptions in communities about the role of antibiotics are common. If a patient requests antibiotics when there is no clinical indication, don't allow yourself to be pressurised into prescribing antibiotics. Counsel the patient on why antibiotics are unnecessary, and about potential side effects. This is a first step towards community level antibiotic stewardship.

Hand hygiene

Reducing bacterial infections will reduce the need for antibiotics. Infection prevention and control is important for primary care – not just for hospitals.

Ensure good hand hygiene:

- Use alcohol gel before and after examining each patient.
- Ensure it is available in all consultation rooms and clinical areas.
- Ensure there are adequate facilities for patient and staff to wash their hands after using the toilet (particularly for patients with diarrhoea): soap, water and hand towels must be available.



Hospital-acquired infections

- A hospital-acquired infection (HAI) is defined as a new infection occurring 48 hours after hospital admission, or within 3 months of discharge (or, on a more pragmatic level, within 1 month of discharge). The majority are bacterial infections needing further investigation.
- If you suspect bacterial infection in a patient who has recently been discharged from hospital, the patient will need referral. HAIs are usually caused by resistant bacteria and cannot be treated in primary care.
- Up to 30% of hospitalisations in sub-Saharan Africa result in HAIs, so this is a major problem. Common types of infection include pneumonia, urinary tract infections and diarrhoea (see below).

Antibiotic-related diarrhoea: *Clostridium difficile*

- Patients who have received antibiotics are at risk of this highly infectious diarrhoea.
- It is more common in patients who have been hospitalised, but around one third of cases occur in the community in patients who have taken antibiotics.
- Onset may be during antibiotic treatment, or commonly 5–10 days afterwards. However, symptoms may begin up to 10 weeks later.
- Treatment is with oral metronidazole 400 mg tds x 10 days: stop any other antibiotics, unless life-saving.
- Good infection control is essential. Most patients will need hospital admission: if being treated as an outpatient, counsel the patient and their family on handwashing and sanitation (soap and water: do not use alcohol gel if *C. difficile* is suspected).

Useful resources

General:

ReAct – Action on Antimicrobial Resistance (www.reactgroup.org). The website has a comprehensive toolbox with extensive resources for healthcare professionals and civil society.

www.reactgroup.org

Clinical:

Stanford University: *To prescribe or not to prescribe? Antibiotics and outpatient infections.* Online CME course (free). https://med.stanford.edu/cme/courses/online/improving-antibiotics-pcs.html

WHO 2016. *Guidelines for the Treatment of Neisseria Gonorrhoeae.* http://www.who.int/reproductivehealth/publications/rtis/gonorrhoea-treatment-guidelines/en/

MSF 2016. *Clinical Guidelines: Diagnosis and Treatment Manual.* Available from: http://refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf

Public Health England 2017. *Diagnosis of Urinary Tract Infections (UTIs): Quick Reference Guide for Primary Care: For consultation and local adaptation.* https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/619772/Urinary_tract_infection_UTI_guidance.pdf

Programmatic:

MSF OCB Antibiotic Stewardship Toolkit Map. A programmatic guide to antibiotic stewardship is currently being developed. Check the ‘updates’ folder on the SAMU website https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018 for new information that may be posted.

WHO 2015. Global Action Plan on Antimicrobial Resistance. http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/

All countries must develop National Action Plans; some are completed, others in progress. Find out from your MSF co-ordination office or Ministry of Health what is happening in your country.

Fever in the HIV-positive patient: Key points

Fever is common in HIV-positive patients and has both infectious and non-infectious causes.

Many infectious causes are not bacterial, so will not respond to antibiotics: TB is a common cause.

The first step in the approach to these patients is to look for danger signs, provide urgent treatment and refer to hospital.

Antibiotic resistance is a global crisis requiring all players in the health system to play a role in antibiotic stewardship, including the outpatient clinician.

Rational antibiotic prescribing involves several important principles, foremost of which is using antibiotics only if there is a high likelihood of a bacterial infection.

Algorithm 23.2 Management algorithm for urinary symptoms in adult women <65 years

Notes

- Nitrites are produced by bacteria so a positive test implies the presence of bacteria. Nitrites can, however be present due to a discharge that has bacteria in it.
- Leucocytes are the body's response to infection, so are often present in bacterial infection. Leucocytes can be present in renal TB (called 'sterile pyuria' as no standard bacteria are seen or grown on culture).
- A UTI is extremely unlikely if there are no symptoms, so do not treat a urine abnormality if the patient is asymptomatic. Consider other causes, especially renal disease.
- Algorithm 23.2 guides the antibiotic decision based on a combination of symptoms and the presence of cloudiness, leucocytes and nitrites in the urine.

Severe or >3 symptoms of UTI

Dysuria
Frequency
Urgency
Polyuria
Haematuria
Suprapubic tenderness

→ **and** NO vaginal discharge → Give empirical antibiotic

Mild symptoms or <2 symptoms of UTI (as above) → Get urine specimen

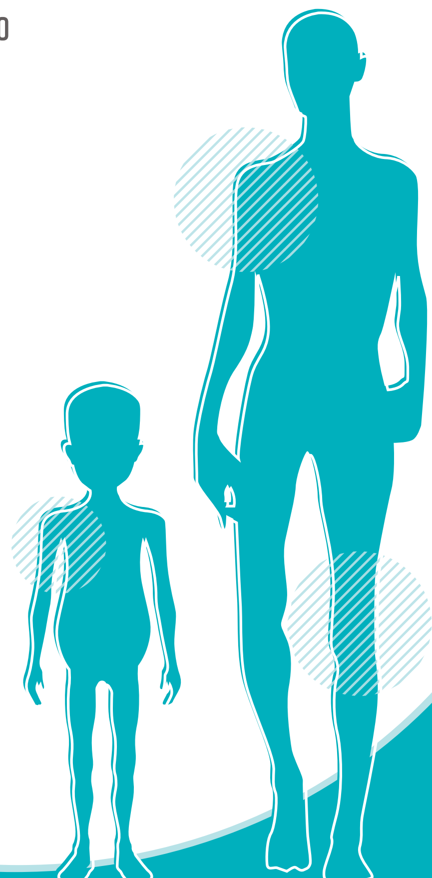
Urine cloudy: Do urine dipstick and wait recommended time before reading

- Positive nitrite and leucocytes and blood, or positive nitrite alone → Probable UTI → Treat with first line agents on local drug lists
- Negative nitirite, positive leucocyte → UTI or other diagnosis equally likely → Treat for UTI only if severe symptoms
- Negative nitrite, leucocytes and blood → UTI unlikely → Consider other diagnosis

Urine not cloudy → Consider other diagnosis

CHAPTER 24

Malnutrition and weight loss



This chapter covers two similar, but distinctly different conditions:

A. Malnutrition in HIV

B. The patient presenting with persisting weight loss

A. Malnutrition in HIV

A body mass index (BMI) less than 18.5 kg/m^2 is a recognised independent risk factor for morbidity and mortality in HIV-positive adolescents and adults, as is a Weight-for-height Z-score (WHZ) of <-3 in children. Indeed, many HIV-positive patients of all ages (but especially children) may be discovered to have HIV through investigations linked to their acute malnutrition. An initial nutritional status assessment and targeted further care is, therefore, an essential component of comprehensive care of the HIV-positive patient. This attention to the nutritional care of patients can also improve adherence to ART and retention in care as well as supporting their continuation, or return to, a productive life.

Evidence is continually changing in the world of nutrition and HIV (e.g. micronutrient recommendations), so any updates on the guidance below will be shared as they becomes available via the SAMU website/clinical resources. Obesity, the other end of the spectrum of malnutrition, will not be covered in this edition.

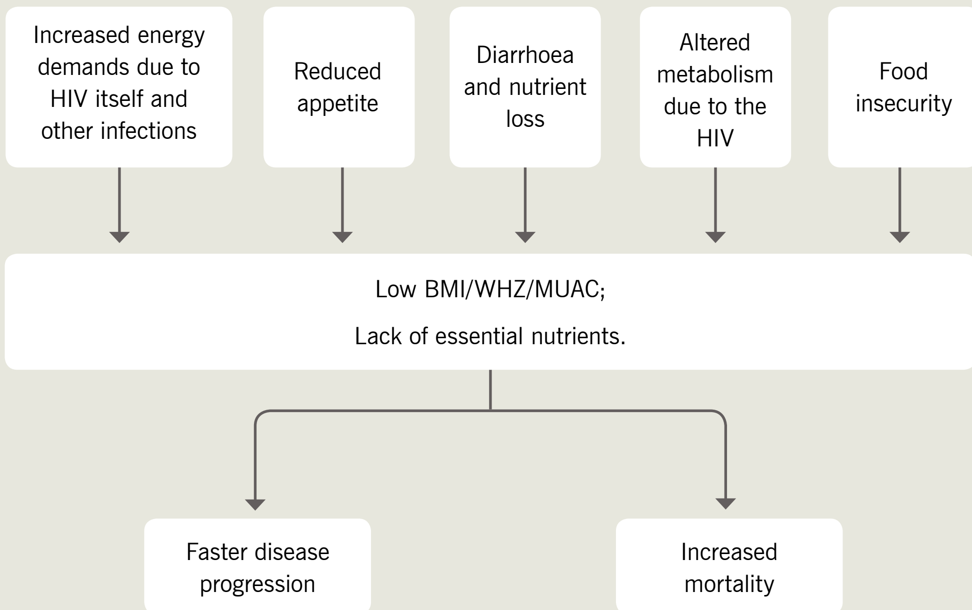
Anthropometric measurements are used to assess the size, shape and composition of the human body, e.g. body mass index (BMI), WHZ and MUAC.

- Weight-for-height Z-score (WHZ) is a nutrition index, which is a calculation of 2 measures – weight and height – into a single value. It is one of the values used in the assessment of malnutrition.
- MUAC, mid-upper arm circumference, is a simple measurement that identifies children and adults at risk.

HIV infection can substantially change the nutritional status

There are many contributing factors that can lead to a change in an HIV-positive patient's nutritional status and subsequent morbidity and mortality (see Figure 24.1).

Figure 24.1 Relationship between HIV and malnutrition



Malnutrition assessment and management overview

In light of the above, the assessment of the nutritional status of the HIV-positive patient needs to be part of the comprehensive care package offered. This involves specific key steps, whether done by the consulting clinician or someone else providing more specialised support in this area (e.g. nutrition advisor or specifically designated healthcare worker). These steps are summarised in Figure 24.2 and are followed by a more detailed explanation.

Figure 24.2 The three steps in malnutrition assessment and management

1. Nutritional status assessment:

- Anthropometric measurements
- Assessment for oedema
- Dietary history

↓

2. Classification of nutritional status

↓

Normal	At risk of acute malnutrition	Moderate acute malnutrition (MAM)	Severe acute malnutrition (SAM)

↓

3. Specific management plan according to nutritional category and age group

a. Nutritional counselling + b. Calculation of daily energy needs and nutritional management plan

The nutritional status assessment varies according to the age group, and the specific management plan varies according to both age group and the classification of the nutritional status. After the initial overview, the assessment, classification and management plans are detailed in three separate sections to cater for adults, children (1 month to 10 years old) and adolescents (10 to 19 years old).

1. Nutritional status assessment

This assessment is essential to knowing if the patient is well nourished or suffering from some degree of acute malnutrition, as well as planning the appropriate nutritional support.

This assessment is made up of:

1.1 anthropometric measurements;

1.2 assessment for oedema; and

1.3 dietary/food security history.

1.1 Anthropometric measurements (BMI/MUAC/WHZ)

No anthropometric measurement gives a diagnosis of acute malnutrition in adults or children. We use indices that have been shown in many studies and different contexts to be most associated with the syndrome we call acute malnutrition and the associated risk of mortality. Although anthropometrics are a vital part of a nutritional status assessment, they must not be used in isolation and we always clinically assess the patient, not the numbers. The anthropometric measurements used vary according the different age groups being assessed. This is detailed later in the age-specific sections.

1.2 Assessment for oedema

Presence and degree of oedema is an important index of malnutrition (always indicates SAM) and contributes in different ways according to the age of the patient. Oedema is not a reliable marker in pregnancy.

1.3 Dietary/food security history

Dietary/food security history

Many HIV-positive people live in parts of the world that suffer from food insecurity, whether permanent or seasonal. It is, therefore, of no value to give nutritional advice that someone cannot follow because they simply don't have enough access to food. This can be a sensitive topic and may need the development of trust before a patient divulges their true situation at home. This assessment can be done as part of taking a social history, or wherever it is most appropriate. There are a few key questions to ask:

- In the past month, did you worry that your household would not have enough food?
- In the past month, did you or anyone in your household have to eat fewer meals in a day because there was not enough food?
- In the past month, did you or anyone in your household have to go to bed hungry because there was not enough food?
- Do these things happen most months of the year? Is it worse at certain times of the year?

If the patient answers yes to one or more of these questions, then they are very likely to be experiencing food insecurity at home. This is when food supplementation is key, whether for an individual or a whole family, by referring the patient to a national/community programme for food supplementation.

It is also vital to ask about people's dietary preferences and beliefs; asking about what meals and snacks people eat in a normal day can reveal a lot in a small amount of time.

The key time to offer food supplementation or support for accessing food is at the beginning of ART, when the patient may still be recovering from opportunistic infections and regaining the ability to earn an income and get back to/start a healthier life.

There should always be an appropriate referral mechanism available for more comprehensive nutritional care, if this cannot be provided where the patient receives regular HIV follow-up.

2. Classification of nutritional status

The above nutritional status evaluation is used to place the patient in one of four categories (this evaluation applies to all three age groups):

1. Normal;
2. At risk of acute malnutrition (this includes patients who have normal anthropometric measurements, but are at the lower end of normal, and/or patients who are assessed as experiencing significant food-insecurity);
3. Moderate acute malnutrition (MAM); or
4. Severe acute malnutrition (SAM).

3. Specific management plan according to nutritional category and age group

A detailed management plan needs to be drawn up for each of the four categories of nutritional status. In addition, this plan varies according to the three different age groups. This is detailed in the rest of this section. The following are the two core components:

a. Nutritional counselling

Each patient requires nutritional counselling as outlined in the following box.

Nutrition counselling:

There are a number of tools available for full **nutrition counselling**. The list below covers the essential topics:

- Importance of nutrition in aiding recovery (see Figure 24.1 above);
- Identification of locally available food sources, and more importantly, what can the patient actually access? (money, transport, time, etc.);
- Identification of specific OIs impacting on nutrition (e.g. painful mouth from ulcers, painful swallowing from oesophageal candidiasis);
- Nutritional needs according to co-morbidities (e.g. hypertension, diabetes, renal disease, etc.);
- Meal planning (guided by daily energy needs);
- Hygiene in food preparation; and
- Linkage to community support and opportunities for economic strengthening.

Food and nutrition in the context of HIV and TB: https://www.wfp.org/content/nutrition-assessment-counselling-and-support-adolescents-and-adults-living-hiv

www.wfp.org

b. Calculation of daily energy needs and nutritional management plan

This calculation varies according to the age group and is detailed later under the three different age groups.

Broad management principles for all age groups:

1. Management of the patient with normal nutritional status

The detail provided later for normal nutritional status in each of the three age groups is the baseline management plan for all normal, at risk, MAM and SAM nutritional statuses.

2. Management of the patient at risk of acute malnutrition

Additional action will depend on a case-by-case evaluation of the patient's nutritional status and social situation. It may be the patient who is close to a BMI/MUAC or WHZ cut-off for acute malnutrition or one who seems to have severe food insecurity at home.

An important first step may simply be more frequent follow-up, if it is feasible for the patient to come more often. If you have resources for a community health worker to do a home visit, this could also assist in a closer follow-up of the patient.

A key moment of vulnerability for many patients is when they initiate ART. If a patient seems at risk of acute malnutrition at that time, it could be beneficial to provide some sort of food supplementation and review the situation 4–8 weeks after they have been on the ART for signs of improvement in their nutritional status and overall condition.

3. Management of the patient with moderate acute malnutrition (MAM)

There is no direct evidence to show that all untreated MAM leads to severe acute malnutrition (SAM), but practically we can see the logic of treating this group to prevent such progression, with its much higher associated mortality.

4. Management of the patient with severe acute malnutrition (SAM)

Patients with SAM have a significant risk of mortality. More detailed information is provided below as it varies according to the different age groups.

All HIV-positive patients need to be started on ART as soon as possible, as it is the combination of medical treatment and improved nutrition that has greatest impact for an individual.

The rest of this malnutrition section details the assessment and management of malnutrition in each of the three age groups: adults, children and adolescents.

Nutrition status assessment and management guidelines specific to the three age groups

Malnutrition in HIV-positive adults

1. Nutritional status assessment

Anthropometric measurements

As noted above, there are no specific measurements that can make a diagnosis of malnutrition in adults. However, in association with the clinical evaluation, the following are used:

Body mass index (BMI)

BMI = weight (kg)/height^2 (m)

Table 24.1: BMI value and interpretation for adults

Nutritional classification	BMI value for adults (kg/m^2)
Obese	>30
Overweight	≥25 and <30
Normal	≥18.5 and <25
Risk of acute malnutrition	≥17 and <18.5
Moderate acute malnutrition	≥16 and <17
Severe acute malnutrition	<16

Mid-upper arm circumference (MUAC)

The mid-upper arm circumference (MUAC) measurement is also used to estimate the adult patient's nutritional status. MUAC can sometimes be quicker and easier to measure than BMI, especially if a patient is bed-bound. Although there are no internationally agreed MUAC cut-offs in adults, there is enough evidence for us to have confidence in the values below:

Table 24.2 MUAC values and interpretation for adults

Nutritional classification	Adults >18 years	Pregnant or lactating women
Normal	≥210 mm	≥230 mm
Moderate acute malnutrition (MAM)	≥185 and <210 mm	≥190 and <230 mm
Severe acute malnutrition (SAM)	<185 mm	<190 mm

There is always the possibility of tailoring these cut-offs to the specific context and therapeutic approach (see below). This should be discussed with the clinical team and a nutrition advisor.

Assesment for oedema

Bilateral oedema is a sign of severe malnutrition. However, oedema in adults can be caused by other pathologies (renal, cardiac, hepatic, etc.) so these must be checked for, before deciding that the oedema is being caused by malnutrition. If the oedema is evaluated as definitely being nutritional in origin, then regardless of the BMI or MUAC, the patient should be assessed as having SAM.

Table 24.3 Grades of oedema for adults based on the Beattie classification

Grade	Extent of oedema
0	Absent
1	Minimal oedema on feet or ankles
2	Obvious oedema on feet or ankles
3	Oedema demonstrable up to knees (tibias)
4	Oedema demonstrable up to groin (inguinal area)
5	Oedema on the whole body (anasarca)

Dietary/food security history

See Dietary/food security history box on page 473.

2. Classification of nutritional status

NB remember to look for OIs and not just assume that a low BMI is due to lack of food.

Classify into one of the four categories:

- Normal;
- At risk of acute malnutrition (this includes patients who have normal anthropometric measurements, but are at the lower end of normal and/or patients who are assessed as experiencing significant food-insecurity);
- Moderate acute malnutrition (MAM); or
- Severe acute malnutrition (SAM).

3. Specific management plans

Follow the management guidance below, tailored to the classification of nutritional status.

3.1 Management of the adult with normal nutritional status

a. Nutritional counselling

See nutrition counselling box on page 474.

www.wfp.org

Food and nutrition in the context of HIV and TB: https://www.wfp.org/content/nutrition-assessment-counselling-and-support-adolescents-and-adults-living-hiv

b. Calculation of daily energy needs and nutritional management plan

On average, the daily energy intake to meet basic energy expenditure for adults is 30 kcal/kg/day. This is then multiplied by a stress factor of 1.1 for asymptomatic HIV and then by their weight. For example, for a 70 kg man, the daily kcal needs would be:

30 x 1.1 x 70 = 2 300 kcal/day

For a symptomatic patient (HIV-related) the stress factor increases to 1.2–1.3, depending on how significant the symptoms are.

www.nutval.net

Once you know the energy needs per day, you can try and help the patient design meal plans. These are very context-specific, but there are useful tools, such as **NutVal 4.1,** which can be used. Ask your nutrition advisor for help in this area if you have trouble with the tool. NutVal 4.1 website: http://www.nutval.net/2015/12/nutval-41-released.html

This tool is accompanied by simple training on how to use it.

Protein intake should be the same as for non-infected adults, at 10–12% of total energy intake, but usually when patients increase the energy intake, the total amount of protein will increase too. If possible, there should be a variation of the sources of protein in the diet, including some with a high protein digestibility such as soybeans or foods from animal sources, including dairy products.

Fat intake recommendations are also the same as for non-infected adults at 15–30% of total energy intake. Many HIV-positive adults in high incidence areas already struggle to meet these recommendations, so, if possible, oil/butter/ghee should be added to meals for these individuals. Oil, especially, can be an easy food to offer as a supplement, even in primary healthcare settings.

Although it is widely accepted that **micronutrients** are important for the immune system and many vital body functions, there is currently no clear evidence as to the exact amounts and compositions most useful for HIV-positive adults. The WHO currently still recommends the consumption of one recommended nutrient intake (RNI) per day. (The South African Academy of Science, however, recommends an intake of 1–2 RNI per day because of higher needs during infection and the likelihood of pre-existing deficiencies.) If it is clear that the patient's diet lacks dietary diversity, then a daily multivitamin tablet can be prescribed. This should always be weighed up with the risk that just one more tablet could make a patient feel overwhelmed and decide not to take any/fewer ARTs, in which case the ARTs should obviously be prioritised.

3.2 Management of the adult at risk of acute malnutrition

Follow guidelines for nutrition counselling and calculation of daily energy needs as above in 3.1 for adults with 'normal' nutritional status.

In addition:

Further action will depend on a case-by-case evaluation of the patient's nutritional status and social situation. The patient may be close to a BMI/MUAC cut-off for acute malnutrition or may have severe food insecurity at home.

An important first step may simply be more frequent follow-ups, if it is feasible for the patient to come more often. If you have resources for a home visit by a community health worker, this could also assist in a closer follow-up of the patient.

A key moment of vulnerability for many patients is when they initiate treatment. If that patient seems at risk of acute malnutrition at that time, it could be beneficial to provide some sort of food supplementation and review the situation 4–8 weeks after they have been on the ART, looking for signs of improvement in their nutritional status and overall condition.

3.3 Management of the adult with moderate acute malnutrition (MAM)

Follow guidelines for nutrition counselling and calculation of daily energy needs as above for adults with 'normal' nutritional status. In addition:

There is no direct evidence to show that all untreated MAM leads to severe acute malnutrition (SAM), but in practical terms, we can see the logic of treating this group to prevent such progression, with its much higher associated mortality.

At present, there is not enough strong evidence for internationally agreed guidelines on the management of MAM in HIV-positive or non-infected adults with MAM, with respect to which food supplements should be given. WHO recommends nutrition counselling as the cornerstone of any intervention. We know HIV increases energy requirements, so, since an adult with MAM already has a nutritional deficit, some kind of food supplement is encouraged, whether given directly or via referral to a food supplementary programme.

This could be a local product (beans, flour, rice, oil) or a specific fortified product, such as Super Cereal, which can be consumed daily as a porridge or gruel. Local products are obviously cheaper than fortified products, but depending on the level of MAM and food insecurity in your patient cohort, this might be an important element of their treatment that you decide to prioritise budget on.

Practical tip

How to make a Super Cereal porridge for adults:

1. Wash hands and all utensils with detergent and water.
2. Mix 40 g of Super Cereal with 250 ml of water, bring to the boil, then let simmer 5–10 minutes.
3. Serve while still warm.

1–2 teaspoons of sugar and/or oil/butter can be added to improve palatability.

There is no direct evidence to show that all untreated MAM leads to severe acute malnutrition (SAM), but again, from a practical approach, we can see the logic of treating this group to prevent such progression with its much higher associated mortality.

3.4 Management of the adult with severe acute malnutrition (SAM)

Follow guidelines for nutrition counselling and calculation of daily energy needs as above in 3.1 for adults with ‘normal’ nutritional status.

In addition, adults with SAM have a high risk of mortality, so must be referred ***immediately*** into a therapeutic feeding service, whether in your health facility or elsewhere. If you are able to treat these patients in your health facility, then follow your section’s protocol or the national protocol for the management of SAM in adults.

Important: Most existing protocols still use therapeutic milks (F75 and F100) and RUTF (e.g. PlumpyNut, eeZee Paste, Insta Paste, Chiponde, BP100). These products were initially designed with children in mind, so adults, with their more refined taste, may not tolerate them as readily. In addition, they become bored with food more quickly than children. As a result, you may need to be more creative in your advice on how to consume these foods – maybe make porridge from the BP100, mix the RUTF pastes with water to make a pap, etc.

Practical tip

A month’s supply of RUTF can be very heavy for a person already suffering from weakness to carry long distances home, so think about what is **most practical in terms of frequency** of visits and other delivery mechanisms for therapeutic foods.

Malnutrition in the HIV-positive child (1 month–10 years old)

1. Nutritional status assessment

Anthropometric measurements

There is much debate as to whether WHZ or MUAC is better for assessing a child for acute malnutrition. In practice, one or the other may be more suited to the capacities of the health facility and the context, and using both can give us operational flexibility. A child can, thus, be admitted to an outpatient or inpatient nutrition service if their WHZ *and/or* MUAC fit the admission criteria. In addition, although anthropometrics are a vital part of a nutritional status assessment, they must not be used in isolation, but along with a clinical assessment of the child.

Height and weight are frequently measured incorrectly. See **Chapter 10**, page 155 for details.

Weight-for-height Z-score (WHZ)

This is calculated in clinical practice by taking the weight and height of the child and then using the WHO reference tables. See Appendix 24.1 at the end of the chapter to see which column (-3, -2 or -1) the child falls into.

Table 24.4 WHZ and interpretation for children

Malnutrition classification	WHZ category (children 1 month to 10 years)
Normal	>-2
Moderate acute malnutrition (MAM)	>-3 and ≤-2
Severe acute malnutrition (SAM)	<-3

Figure 24.3 shows two worked examples of this.

- For a boy 50 cm in length and 2.5 kg, we can see that his weight, if plotted on the table would be less than the reference for -3. On Table 24.4, he is therefore suffering from SAM.
- For a girl with a length of 48.5 cm and a weight of 2.5 kg, we see her weight falls between -2 and -3, so she is suffering from MAM.

Figure 24.3 Example of calculation of a WHZ category

WHO 2006 new references in Z-score

Weight for Length (Lying down)

BOYS								GIRLS
- 3	- 2	- 1	Median	cm	Median	- 1	- 2	- 3
1,9	2	2,2	2,4	45	2,5	2,3	2,1	1,9
1,9	2,1	2,3	2,5	45,5	2,5	2,3	2,1	2
2	2,2	2,4	2,6	46	2,6	2,4	2,2	2
2,1	2,3	2,5	2,7	46,5	2,7	2,5	2,3	2,1
2,1	2,3	2,5	2,8	47	2,8	2,6	2,4	2,2
2,2	2,4	2,6	2,9	47,5	2,9	2,6	2,4	2,2
2,3	2,5	2,7	2,9	48	3	2,7	2,5	2,3
2,3	2,6	2,8	3	48,5	3,1	2,8	2,6	2,4
2,4	2,6	2,9	3,1	49	3,2	2,9	2,6	2,4
2,5	2,7	3,0	3,2	49,5	3,3	3,0	2,7	2,5
2,6	2,8	3,0	3,3	50	3,4	3,1	2,8	2,6
2,7	2,9	3,1	3,4	50,5	3,5	3,2	2,9	2,7
2,7	3	3,2	3,5	51	3,6	3,3	3	2,8

Weight 2.5 kg

Weight 2.5 kg

Mid-upper arm circumference (MUAC)

There are significant data to show that children 6 months to 5 years of age with a MUAC <115 mm have an increased risk of mortality. Although there are no internationally agreed MUAC cut-offs for children 5 years and older, there is enough evidence for us to have confidence in the values below:

Table 24.5 MUAC value and interpretation for children

Malnutrition classification	65–110 cm (6–59 months)	110–140 cm (5–10 years)
Normal	≥125 mm	≥140 mm
Moderate acute malnutrition (MAM)	≥115 and <125 mm	≥ 130 and <140 mm
Severe acute malnutrition (SAM)	<115 mm	<130 mm

There is always the possibility that in discussion with the team and a nutrition advisor, these cut-offs may be tailored to the specific context and therapeutic approach (see below).

Important: If a child with a MUAC <115 mm is referred by any kind of community nutrition screening programme to your health facility, regardless of their WHZ, they should be admitted into an inpatient or outpatient nutrition service, depending on the presence of medical complications and appetite. Failure to do so will cause distrust in these screening services and in the health facility receiving the referral.

Assessment for oedema

Children with bilateral pitting oedema must be treated for SAM irrespective of their WHZ or MUAC. Oedema in children is classified as follows:

Table 24.6 Classification of oedema in children

Feet	+
Feet and legs	++
Feet, legs and other parts of the body	+++

Note that infants below one year may have fatty feet that can be easily mistaken for oedema.

Dietary/food security history

To get an overall picture of the food security situation in the household, follow the guideline in the Dietary/food security history box on page 473. In addition, there are a number of specific questions that should be asked for children, many of which can be put to the child directly, or to their caregiver. If they are not old enough, make sure the caregiver you ask questions of is the person primarily in charge of feeding the child.

Questions not to be missed include:

- Breastfeeding: Was this done, and for how long was breastfeeding exclusive (no other foods given)?
- Weaning: At what age was the child weaned and what complementary foods were first introduced?
- What is a normal day of food for the child? (24-hour recall of all meals)
- Meal time practices: Does the child share a plate and with how many other children? Does the child eat alone, or are they supervised?
- Dietary preferences: What does the child like to eat? What does the child refuse to eat?

Additional resources to assess the infant and young child feeding practices (IYCF) can be found in the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

samumsf.org/en/
resources

2. Classification of nutritional status

Classify into one of the four categories:

- Normal;
- At risk of acute malnutrition (this includes patients who have normal anthropometric measurements, but are at the lower end of normal and/or patients who are assessed as experiencing significant food-insecurity);
- Moderate acute malnutrition (MAM); or
- Severe Acute Malnutrition (SAM).

3. Specific management plan

Follow the management guidance below, tailored to the nutritional classification.

3.1 Management of the child with normal nutritional status

a. Nutrition counselling

Follow the core guidance for nutrition counselling in the nutrition counselling box on page 474, and if the child is old enough you can involve them in the counselling, as well as their caregiver.

More detailed information on IYCF counselling, which can be adapted to your context, can be found in the **additional resources** folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018; and https://www.fantaproject.org/sites/default/files/resources/NACS-Module-3-Counseling-May2016.pdf

samumsf.org/en/
resources
www.fantaproject.org

b. The calculation of a daily energy needs management plan

Daily energy needs vary greatly with age. Although there may be other factors leading to poor growth (OIs, social problems), the only way to try and assess if children are getting suitable energy requirements is by regular weight, height and head circumference monitoring.

For children less than 6 months, the most important message for nutrition is exclusive breastfeeding on demand, taking care to ensure the mother is in the best health to be able to support this.

samumsf.org/en/resources

More detailed advice on HIV and infant feeding can be found at can be found in the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

For children older than 6 months, caregivers should be counselled on the importance of appropriate complementary foods (see IYCF counselling guidelines above). The following table can be used as a guide on extra energy requirements.

Table 24.7 Examples of ways to increase energy intake by 10% using food

Give in addition to the meals and snacks appropriate for the child's age.

Age	Kcal/day	Local adaptation
6–11 months	Additional 60–75 kcal = Total ~760 kcal/day	Give examples and quantities of local foods that can be used to increase energy density of other foods e.g. 2 tsp margarine/oil and 1–2 tsp sugar to porridge or that can be given in addition to normal diet.
12–23 months	Additional 80–95kcal = Total ~990 kcal/day	Give examples and quantities of local foods that can be used to increase energy density of other foods e.g. margarine/oil and sugar to porridge or that can be given in addition to normal diet.
2–5 years	Additional 100–140 kcal = Total ~1 390 kcal/day	Give examples and quantities of local foods that can be used to increase energy density of other foods or that can be given in addition to normal diet e.g. extra cup of full cream milk/fermented milk.
6–9 years	Additional 130–190 kcal = Total ~1 815 kcal/day	Give examples and quantities of local foods that can be used to increase energy density of other foods or that can be given in addition to normal diet e.g. extra cup of full cream milk/fermented milk.
10–14 years	Additional 170–230 kcal = Total ~2 200 kcal/day	Give examples and quantities of local foods that can be used to increase energy density of other foods or that can be given in addition to normal diet. e.g. extra cup of fruit yoghurt or cheese/peanut butter sandwich

The full document can be found in the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

3.2 Management of the child at risk of acute malnutrition

Refer above to the management of the child with normal nutritional status for nutrition counselling and the calculation of daily energy needs. In addition, always be quicker to act and review children at risk, compared to adults, as they can deteriorate much quicker. When in doubt, treat as MAM (see below).

One option for a food supplement specifically for children 6–24 months is a Lipid-Based Nutrient Supplement (LNS Small Quantity) such as EnovNutributter or eeZee20, which can be mixed with a child's normal complementary food. The goal of using this product is to prevent acute malnutrition by using this for 4–6 months.

3.3 Management of the child with moderate acute malnutrition (MAM)

Refer above to the management of the child with normal nutritional status for nutrition counselling and the calculation of daily energy needs. In addition, as with adults, at present there is not enough strong evidence for internationally agreed guidelines on the management of MAM in HIV-positive or non-infected children, with respect to which food supplements should be given. WHO recommends nutrition counselling as the cornerstone of any intervention. From a more clinical (and perhaps practical) approach, we know HIV increases energy requirements and a child with MAM already has a nutritional deficit, so if it is possible to either give a food supplement directly, or refer to a food supplementary programme, some kind of food supplement is encouraged. This is even more important for children, as they are quicker to deteriorate than adults.

This could be a local product (beans, flour, rice, oil), depending on age, or a specific fortified product, such as Super Cereal Plus (designed specifically for children 6 months to 5 years old), which can be consumed daily as a porridge or gruel. Other options are ready-to-use supplementary foods – RUSF, also known as Lipid Based Nutrient Supplement (LNS) Large Quantity – such as eeZeeBAR and PlumpySup. There are varying protocols for amounts to use, but usually 1–2 sachets of RUSF can be eaten directly from the packet, in addition to a balanced diet.

Local products are obviously cheaper than fortified products and RUSF, but, depending on the level of MAM and food insecurity in your patient cohort, this might be an important element of their treatment that you decide to prioritise budget on.

Practical tip

How to make a Super Cereal Plus Porridge for children (6 months to 5 years old):

1. Wash hands and all utensils with detergent and water.
2. Mix 50 g of Super Cereal Plus with 250 ml of water, bring to the boil then let simmer for 5–10 minutes.
3. Serve while still warm.

1–2 teaspoons of sugar and/or oil/butter can be added to improve palatability.

3.4 Management of the patient with severe acute malnutrition (SAM)

Refer above to the management of the child with normal nutritional status for nutrition counselling and the calculation of daily energy needs. In addition, children with SAM have a high risk of mortality. If you assess a patient as having SAM, they must be **referred immediately** into an inpatient/outpatient nutrition service, whether that is in your health facility or in another one. If, however, you are able to treat these patients yourself, follow the national protocol for the management of SAM in children or that of your MSF operational section.

Important: TB in children often presents in atypical ways, including significant weight loss. Always ensure therefore that you have also screened SAM cases for TB.

Malnutrition in the HIV-positive adolescent (10–19 years old)

1. Nutritional status assessment

This is a special group of individuals who need to be treated with sensitivity, acknowledging that they are in a difficult phase between childhood and adulthood. For more information on approaches to this group see **Chapter 10**.

Anthropometric measurements

No anthropometric measurement gives a diagnosis of acute malnutrition in adolescents. There is debate as to which index to use for this age group, and more evidence is likely to come to light in the coming years. For now, one option is presented below.

Criteria for malnutrition using WHZ and oedema in adolescents

See adolescent WHZ chart (Appendix 24.2 at the end of this chapter), which gives a value of -1 to -3 as a % or the median. Using the chart and the table below, classify the malnutrition.

Table 24.8 Adolescent malnutrition assessment

% of the median or bilateral oedema	Malnutrition classification
>80%	Normal
≥70% to <80%	Moderate acute malnutrition (MAM)
<70 % or bilateral oedema	Severe acute malnutrition (SAM)

Dietary/food security history

Take a comprehensive history as outlined in the Dietary/food security history box on page 473. Try to establish if the adolescent is treated more like an adult or a child, when it comes to mealtimes in the household.

Daily energy needs vary greatly with age. As a rough guide, use Table 24.7 above for adolescents 10–14 years and use adult calculations for adolescents 14–19 years.

2. Classification of nutritional status

Classify into one of the four categories:

- Normal;
- At risk of acute malnutrition (this includes patients who have normal anthropometric measurements, but are at the lower end of normal and/or patients who are assessed as experiencing significant food-insecurity);
- Moderate acute malnutrition (MAM); or
- Severe Acute Malnutrition (SAM).

3. Specific management plan

Regarding the management of the different categories of malnutrition in the adolescent, follow the management guidance for adults, but use the adolescent-friendly approaches described in **Chapter 10**.

Malnutrition in HIV: Key points

- Malnutrition is a recognised independent risk factor for morbidity and mortality in HIV-positive adolescents and adults.
- The assessment of the nutritional status of the HIV-positive patient needs to be part of the comprehensive care package offered.
- All HIV-positive patients need to be started on ART as soon as possible, as it is the combination of medical treatment and improved nutrition that has greatest impact for an individual.
- Nutrition management needs to be tailored specifically to the classification of malnutrition and the age of the patient.
- Patients of all ages with severe acute malnutrition have a significant mortality rate and require urgent medical and nutritional attention.

B. The patient presenting with persistent weight loss

The purpose of this section is not to give the full differential diagnosis of all the causes of persisting weight loss, nor is it to make recommendations regarding the different investigations to be done and treatment to be given, as this information is provided in specific chapters elsewhere in this book.

The intention here is to provide a checklist of the common conditions likely to be seen in the HIV primary care clinic, for the clinician to consider when encountering a patient with persisting weight loss, where the common illnesses do not appear to be the cause. The information is presented in Table 24.9 below, with additional tips given where appropriate.

Asthenia merely means that the patient is thin and wasted. Asthenia is not a diagnosis, so the cause needs to be actively looked for.

Table 24.9 Possible causes of weight loss seen in the primary care HIV clinic

Category	Illness	Tips/comments
Infections	TB, both DS and DR	There is no test that can exclude TB! If clinical suspicion is high, start TB treatment. If patient is seriously ill, has a poor functional state, prolonged illness or is rapidly declining – start empiric treatment and refer to hospital, in parallel with investigations. (See **Chapter 11**, The ambulatory patient presenting with advanced HIV disease.)
	Non-tuberculous mycobacteria (NTM or MOTT)	More common in SE Asia. Not detailed in this book. See MSF guidelines.
	Disseminated fungal infections	Consider, especially if CD4 <100. Do serum CrAg and if skin lesions, perform skin scrapings or biopsy if available (**chapters 11, 14 and 20**). Skin lesions, together with pulmonary involvement suggest histoplasmosis or penicilliosis: these are common in some regions (SE Asia, for example).
IRIS	TB IRIS is the most common and can involve any organ system	Consider, especially within the first 3 months of starting ART or switching to a new regimen (**Chapter 5**).
GIT	Chronic diarrhoea, with or without vomiting	Need to ask about this, as patients may not volunteer this information. A low potassium is a pointer to chronic diarrhoea. Empiric treatment for chronic diarrhoea is often indicated (see **Chapter 15**).

Category	Illness	Tips/comments
Metabolic	Diabetes mellitus (DM) (See **Chapter 21** for more detail.)	Always check the serum glucose. Some ARVs increase incidence of DM (DM is an independent risk factor for TB).
Poor nutrition	Food scarcity	Any patient with a BMI <18 needs a more comprehensive nutritional status assessment, with the provision of food supplements (see this chapter, above).
	Depression	Significant loss of appetite associated with depression can lead to weight loss (**Chapter 22**).
Malignan-cies	Kaposi's sarcoma	Do a full skin check and check CXR for nodes and signs of pulmonary infiltrates. Also, check Hb, as there may be occult blood loss via the bowel. (See **chapters 15** and **20**.)
	Lymphoma	Examine carefully for peripheral lymph nodes and do CXR to look for mediastinal nodes.
	Other sites	Consider other malignancies not necessarily related to HIV (e.g. lung, colon, stomach).
Rarer causes	EFV toxicity	Can cause generalised slowing, physically and mentally, and can be associated with weight loss or inadequate weight gain (see **Chapter 4**).
	Hyperthyroidism	Check TSH.

- **HIV wasting syndrome** is a stage 4 WHO diagnosis that relies on the exclusion of all possible causes. **It should not be used as a diagnosis in our settings,** as this type of presentation is far more likely to be due to TB or other opportunistic infections.
- Weight loss is rarely caused by a low CD4 count and/or an elevated viral load alone. It is far more likely that these have resulted in an OI, which is the real cause of weight loss.

CHAPTER 25

Patient support

A senior national healthcare leader in the 1980s once famously said, ‘Drugs don’t work in people who don’t take them’.

Supporting HIV and TB patients to take their medication correctly is the foundation of our work as healthcare providers. Whether it is about ARVs, TB or other drugs, treatment adherence is arguably the biggest challenge in the management of HIV and TB today. Patient Support (PS) is the cornerstone of care to patients with such diseases requiring long or lifelong treatment(s).

Consider the following two scenarios:

SCENARIO 1

How good are you at completing a 5-day course of antibiotics, with virtually no side effects, and especially when you feel fine after 3 days? Consider, therefore, how difficult it must be for our HIV patients to take a combination of drugs every day, often with side effects, for the rest of their lives, and with no ‘permission’ ever to forget them or even just take a break?

SCENARIO 2

Imagine a situation in which you visit your doctor with a cluster of symptoms that you think may represent a serious illness. At the end of the brief encounter he/she gives you a prescription and hurries you out of the room with minimal explanation of the diagnosis reached, the medication prescribed or the prognosis for the condition. What questions do you have as you leave the room?

You will find that you can categorise your questions into two broad groups:

1. Feelings and concerns about your illness (fear, shock, anxiety: am I going to die? is this going to hurt? what if others find out?).
2. Expectations of the treatment (am I going to get sick or cured? how and for how long will I have to take pills?).

All people, regardless of education and socio-economic status, have questions, fears or other feelings about any illness they may have. Moreover, they have expectations and personal ways of coping with what is going to happen to them. This applies all the more to a disease like HIV, with its potentially devastating consequences – not only for physical health, but also for its psychosocial impact. The degree to which these concerns, feelings and behaviours are identified and addressed determines the likelihood of our patients taking their medication and staying in care. A trusting relationship between the HCW and the patient is therefore necessary, so that patients feel at ease to express their real challenges in dealing with a chronic health condition.

Patient support for treatment adherence describes the various processes used by a team of people, mostly clinicians and counsellors, who attempt to understand and address the feelings, concerns, behaviours and expectations with a patient-centred approach.

ART adherence support is often based on the Information-Motivation-Behaviour skills (IMB) model. This entails information/education on ART, motivation to take ARVs correctly and for life, and practical ways/skills to be adherent; adapted to patients' needs and daily lives.

As the busy clinician rarely has the time needed to address these many different issues, this critical role is passed on to counsellors. The counsellor is most a peer or lay-counsellor, or sometimes a professional, with some training in the technicalities of HIV and TB, along with some education in counselling. Despite the significant skill and dedication that many of them bring to their work, it is important that **the full burden of this essential function is not left to counsellors to carry alone**. Patient support also relies on a healthy collaboration between the counsellor and the clinician.

Patient support should always be a collaborative effort between the clinician and the counsellor, with neither party left to fulfil this key function alone. There should be constant communication between them, either via notes, or in person.

This chapter covers key PS interventions **by medical staff in HIV and TB care**. Following the HIV and TB cascades of care in the charts below, you will find the PS key points to be taken into consideration by medical staff when dealing with HIV/ART and TB patients.

For further information and detailed PS guidance, refer to MSF's *Patient Support, Education & Counselling Guideline for Children and Adolescents Living with HIV* in the additional resources section for this chapter on the **SAMU website**: https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018/

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018/

More PS resources can be also found in the Patient and Community Support section of the SAMU website, https://samumsf.org/en/resources

Table 25.1 Context-specific patient support guidelines

Step in HIV care	Patient support key interventions by medical staff
HIV prevention (PEP, PrEP, VMMC)	**General** • Conduct an HIV risk evaluation (e.g. ask if person knows modes of HIV transmission, whether there was a recent exposure, or if they consider themselves to be of high risk), and when necessary, propose PEP, PREP or VMMC. • Always recommend safe sex practices and condom use. **PEP:** • For people starting PEP, reassure about its benefits and motivate to take it. • Highlight: importance of taking the full course of 28-days treatment, and the risks of not completing the course. • Ask the person if they foresee any difficulties taking medication every day for a month. • Inform about side effects and reassure these are normal. Encourage patient to return to health facility if it's difficult to deal with side effects or there are any other concerns. • Plan return for re-testing after the completion of treatment. • Be sensitive, especially in case of sexual assault. • Refer for counselling, based on the needs of patient (e.g. for psychological support or adherence support) and encourage safe sex/condom use. **PrEP:** • Where PrEP is available, it should be promoted for people at substantial high risk (see **Chapter 8**). • During PrEP follow-up visits, assess and encourage adherence to PrEP, in addition to support provided by counsellors. • Ask the person if they have missed any doses since last visit or experienced any unpleasant effects. • Always encourage use of contraception and condoms to avoid STIs, unplanned pregnancies, etc. • Ensure patient returns for re-testing, PrEP refills and follow-up. • Pay attention to your attitude. It should not imply any criticism regarding the person's work, sexual identity, social or other habits (e.g. when PrEP is given to a CSW, MSM or PWID); this can discourage people from continuing PrEP and returning for follow-up. **Voluntary Medical Male Circumcision (VMMC)** • When VMMC is available and recommended, medical staff should offer the option, promote VMMC and refer young boys and men to relevant services. Key messages: • VMMC considerably decreases risk of acquiring HIV. • It does not remove the need for safe sex practices and condom use.

Step in HIV care	Patient support key interventions by medical staff
HIV testing services (HTS)	Remember to promote and/or propose HIV testing in: • TB, viral hepatitis, STI clinics; • In ANC and MCH settings and in children under 5 years; • Clinical settings/IPD when condition of patient indicates HIV infection; • Malnutrition clinics; and • Health services for key populations. All staff need to ensure HTS counselling guidelines and the '5 Cs principles' (Consent, Confidentiality, Counselling, Correct results, Connection) are followed. Key points to be covered (whether voluntary or PITC): • The benefits of HIV testing; • Explanation of positive or negative results; • Prevention in future; • Access to immediate and free treatment; and • Emotional support if result is positive. In addition, in case of HIV-positive result: • Retest to confirm HIV status; • Active referral for ART initiation as soon as patient is ready; • Important to recommend index testing, with partner notification when possible; • Screen for TB and STIs; and • Prevention of transmission and contraception planning. In addition, if negative result: • Risk reduction, PEP, PrEP or VMMC (depending on HIV exposure/risk); • Screen STIs; and • Contraception planning. Guidelines: • Pre-test information can be given in groups, but the result must always be given during an individual post-test counselling session, so that confidentiality is respected. • Never forget to ask for consent (verbal or written) from the person undergoing HIV testing or the caregiver (e.g. in case of child). Especially in PITC in inpatient hospital settings, explain that an HIV test will help HCWs to decide about the best treatment and care to offer for the patient's specific condition. Promote **oral self-test** when available. Key points: • Emphasise linkage to care if result is positive. • Remind the person a positive self-test requires confirmation by a HCW. • In HIV-positive people on ART it will most likely show a negative result. Thus, to avoid confusion, it should not be performed on known HIV-positive people.

Step in HIV care	Patient support key interventions by medical staff
Entry/re-entry into ART care	Entry into ART care should be a welcoming service, whether this is for a newly diagnosed patient, someone lost-to-follow-up or an advanced HIV patient returning to care. **Caution with attitude towards the patients returning to care.** A positive and welcoming attitude can significantly increase the chance of discussing the following questions with the patient: • What were the reasons for previous interruptions/defaulting? • When was the treatment interrupted and for how long? • What psychosocial needs could affect the patient's adherence from now onwards?
ART initiation	When prescribing ART, check that the patient understands key ART information provided through ART education and counselling. Key points: • Establish why treatment is necessary. • Emphasise why adherence is important. • Explain the risks of not taking daily, lifelong treatment. • Describe how to take medication (when, what…), especially if other treatments are also prescribed (e.g. TB medication or IPT). • Rather than imposing a specific time for taking meds, encourage patient to decide the best time, based on their daily schedule. • Clarify that ARVs can be taken on empty stomach. • Clarify that, though not advisable to take ART with alcohol, it will not make the patient ill, nor will it stop the ART from working. • Explain the most common side effects of treatment, and what steps to take/not to take, if side effects are present. • Teach danger signs to patients and family, and when and how to access healthcare if concerned. Patient's answers will guide you to where to reinforce ART key messages.
Dealing with patients refusing ART initiation	If a patient refuses to start ART, gently and non-judgmentally assess the reasons: • Are there misunderstandings about ARVs (e.g. side effects, ART and food or alcohol)? • Has the patient been counselled on ART? • Is there fear of discrimination? • Are there social factors influencing the ART initiation? Address the different issues accordingly, engaging the counsellors as needed.

Step in HIV care	Patient support key interventions by medical staff
ART follow-up from month 1 to month 6	At every follow-up visit: • Evaluate and support adherence and side effects. • Assess and discuss how to manage side effects. • Between ART months 1 and 3 explain what VL is, why we do VL tests, what VL results mean and that the goal is for it to be undetectable. At the time the first VL sample is taken, check patient's VL knowledge. • Ensure patients who missed appointment(s) are traced; welcome patients who return to care. Disclosure issues for children above 5 years of age (**Chapter 10**) • Ensure that the child is referred/followed up by a counsellor for full or partial disclosure counselling sessions. • When child's status is disclosed, remember to engage him/her in the discussions about his treatment and care.
ART follow-up from M6 onwards	Propose differentiated service delivery (e.g. CAG/clubs, fast track with longer ARV refills). Assess and support adherence in every follow-up visit: • Stable adherence for life is not guaranteed. • Regular follow-up by counsellors stops after ART M6, unless there is a problem. Refer for counselling if you suspect any problems with adherence. When booking next appointments: • Assess if patient has travelling plans. • Verify the next visit date is convenient for the patient. • Be flexible in providing longer ARV refills when the patient is travelling or cannot return to health facility on the appointment day. VL testing plans: • Ensure patients are referred for VL tests according to VL algorithms. • Try and get the patient to ensure they get their own result. • Congratulate patients when VL is suppressed. • Ensure correct management, including EAC, according to VL algorithm if VL >1 000 copies. • Ensure patients who missed appointment(s) are traced and welcome those who return to care. **Disclosure issues for children** (see **Chapter 10** page 177 and in the **PSEC guideline** in the additional resources section for this chapter on the SAMU website: https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018/) • Ensure that the child is referred/followed up by a counsellor for full or partial disclosure counselling sessions. • When child's status is disclosed, remember to engage him/her in the discussions about treatment and care.

<table>
<tr><th>Step in HIV care</th><th>Patient support key interventions by medical staff</th></tr>
<tr><td>VL monitoring and care for patients with high VL</td><td>In follow-up visits, always remember to check patient's files/cards to ensure all patients have had VL tests done at the correct times (routine or catch-up).

<u>With high VL results,</u> ensure:
• The patient is informed of the result;
• The patient is referred for Enhanced Adherence Counselling (EAC) the same day the high VL result is given to the patient. (Ideally there are two subsequent EAC sessions, but if this is not feasible, remember that one good EAC session is often adequate).

<u>In the period between the first high VL and the follow-up VL:</u>
• Give additional support to the patient regarding the adherence issues addressed in the EAC.
• Schedule follow-up appointments and ARV refills according to patient feasibility. Be prepared to be flexible, considering ability to get to the clinic and the size of the ART refill already provided. Ideally, the visits should be monthly, but compromises can be made, provided the patient has attended at least one EAC session and will return to repeat the VL test at the correct time.
• If the repeated VL test is still high, follow the local guideline, which probably recommends a switch to a second or third line regimen. IMPORTANT: Do not delay this switch just because the patient has not completed two EAC sessions. The clinical indication is far more important than strictly complying with the guidelines for EAC sessions (see Chapter 6). The counsellor can easily continue adherence support after the switch has been made.
• Remember to record VL information in the VL register and follow up till an outcome is documented in the register.</td></tr>
</table>

Step in HIV care	Patient support key interventions by medical staff
Switching to a second or third line regimen	Verify that the patient understands: • The reasons for switching to a different regimen (the treatment you have been taking is no longer working for you); • The effectiveness of the new treatment (the new treatment is safe, will stop HIV from multiplying in your body and will protect you from getting sick), and importance of adherence (it will work well for you if you take it every day); • Exactly how to take the new regimen (which tablets and when taken); • The possible side effects (it is normal to experience some side effects, such as … (give examples of most common side effects of the specific medication prescribed to the patient); and • **That if there are side effects, not to stop medication but rather return to the clinic for review.** If a patient refuses to start a new regimen: • Do not be aggressive in your manner towards the patient as there are likely to be genuine reasons for this. • Explore the patient's concerns. • Explain the risks of delaying the regimen switch. ('Without a treatment that is effective for you, HIV will continue multiplying in your body and damage your ability to fight infections. Sooner or later you will get sick. You need new medication to strengthen your ability to fight infections.') • Verify there are no misconceptions about second (or third) line treatment. Sometimes a patient may think this is the very last treatment option and, lacking self-confidence, may feel afraid to start it. Encourage patient and refer for further counselling and motivation. From M1 on the new regimen to follow-up VL: • Give monthly ARV refills and highlight the importance of returning for regular health monitoring. • Explain possible reasons for retuning sooner to the health facility (e.g. if patient cannot tolerate a side effect; in case of an unplanned trip; and where there is a need for ARV refill earlier than next appointment). • Ensure patient understands when to have the follow-up VL (usually 6 months after change of regimen) and action that will be taken when VL $<$ or $>$ 1 000. • Similar to first line ART follow-up, evaluate and encourage adherence in every follow-up visit. Refer to a counsellor if a problem is identified.

Step in PMTCT care	PMTCT patient support messages to be considered by medical staff

HTS	HIV testing and retesting should be offered at ANC/MCH clinics for all women who are pregnant, in labour or breast-feeding, if their HIV status is unknown or negative more than 3 months previously.
	Explain the following:
	• HIV can be also transmitted during pregnancy, at delivery and during breastfeeding, hence the need for testing at any of these stages.
	• Emphasise that if test is positive:
	  • ART needs to be started as soon as possible (ideally same day) to prevent HIV transmission to the baby.
	  • Plan to deliver in a health facility.
	  • Baby should be given preventative treatment as soon possible after delivery.
	  • Baby should be exclusively breastfed for 6 months, starting from birth.
	  • Recommend index testing with partner notification; encourage (but do not force) disclosure of HIV status to partner.

ART initiation and follow-up at ANC	Ensure the woman understands the benefits of starting ART, both for her own health and to prevent HIV transmission to her baby. Details includes the following: • Explain that PMTCT programme should be followed not only during pregnancy, but also after delivery, until HIV status of the baby is confirmed (at approximately 18 months or 3 months after cessation of breastfeeding). • Explain the importance of coming back to the health facility for follow up of her health condition and for the health of her future baby. • Motivate, assess and support treatment adherence at every ANC visit. • Discuss how she can deliver in a health facility. • Refer eligible women for VL testing, explain VL results and refer for EAC if VL is high. • Before delivery, ensure the woman understands the details of giving treatment to the baby right after birth. • Highlight the importance of coming to the health facility after the delivery for HIV testing and to continue the baby's treatment. • Recommend exclusive breastfeeding for 6 months. Do not suggest feeding options, other than breastfeeding, unless there is a clinical indication.

Step in PMTCT care	PMTCT patient support messages to be considered by medical staff
Early infant diagnosis (EID) and ART follow-up during postnatal care	Ensure that the mother understands the importance of EID, the HIV testing procedures for the baby and their timing over the next 18 months. • Discuss the meaning of each test result. • A positive test requires confirmation and will require the baby to be on ART. • A negative test also requires confirmation and is not definitive unless it is a confirmatory test after stopping breastfeeding. Explain the need for the baby to take daily medication to prevent or treat HIV, depending on the results of the tests done. Explain the principles of feeding over the first 18 months: • Exclusive breastfeeding for the first 6 months after birth; • What and how to give additional food after 6 months in addition to breastfeeding; and • How to wean when the time comes. In addition: • Closely monitor adherence of both mother and baby at every postnatal visit and under a one-stop service. Ensure a tracing system is in place for those missing appointment(s). • Remember to refer the eligible for VL testing and to take actions in case of high VL test results. • Discuss contraceptive options with the mother as early as possible.

Steps in TB care	TB patient support key interventions by medical staff
Prevention and screening	Do not forget TB screening, especially for HIV patients, and offer IPT as per WHO recommendations. Educate patients and families on infection control of transmission: • Educate on when and how to use the mask (demonstrate if possible). • Explain in detail about ventilation, cough hygiene and when to avoid crowded places. For people undergoing a sputum exam: • Educate patient on how to produce sputum. • Educate patient on how to use the sputum card. • Give key messages, as illustrated in MSF TB flipchart. (See the MSF TB flipchart in the additional resources section for this chapter on the **SAMU website**: https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018/)
Drug-sensitive TB treatment	Ensure patient understands the basics on TB, its treatment and follow-up procedures: • The benefits of treatment, highlighting that TB can be cured; • When and how to take medication during intensive and continuation phases; • The length of treatment; • Most common side effects; and • Laboratory tests. In every follow-up visit: • Evaluate and support treatment adherence throughout full course. • Explain risks of non-adherence and that, when adherence is good, the patient will feel better more quickly. • Ensure that medication is never stopped without HCW advice. Encourage patient rather to return to the health facility if there are any problems with side effects or other treatment issues. • Refer accordingly for adherence counselling and support. • Don’t forget about contact tracing, home visits, patient tracing and referring for social support services. In case of HIV-TB co-infection, facilitate/ensure one-stop services.

<table>
<tr><th>Steps in TB care</th><th>TB patient support key interventions by medical staff</th></tr>
<tr><td>Drug resistant TB treatment</td><td>The treatment of DR TB is long, has many potential side effects and requires closer monitoring. As such, the risk of loss to follow-up is very high. Patient support is a key part of the full treatment strategy.

In collaboration with the counsellors, ensure that the patient understands the following:

The details of DR TB treatment (pills vs injections, when to take them, how long for);
Possible side effects and how these can be managed; and
The importance of follow-up and SAT or DOT services (depending on what is implemented in the specific context); and
The risks of treatment interruptions/not completion of treatment.

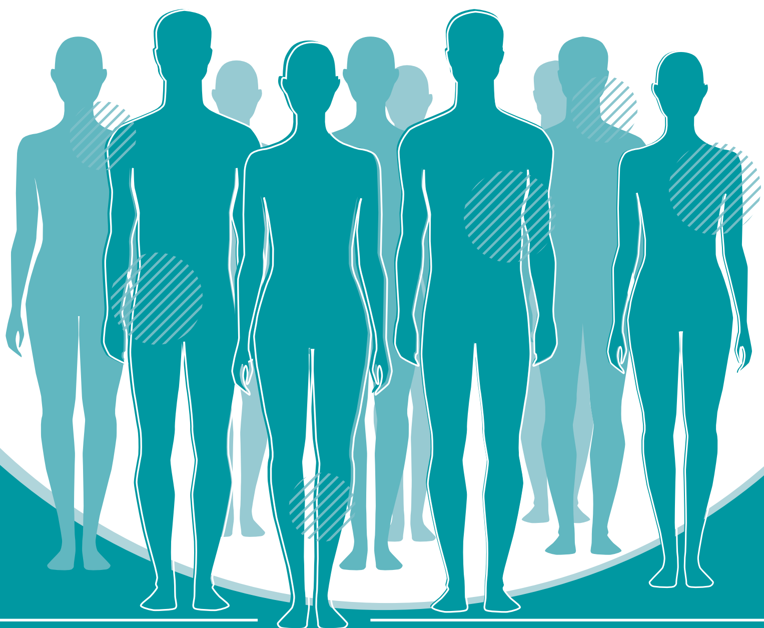
Reasons for possible previous treatment interruptions and their possible impact on treatment adherence in the present.
Propose a mental health screening (the prevalence of mental illness in DR TB is high). Refer to relevant services when needed.
Invite patient (but do not force) to identify a caregiver that can provide support throughout treatment.
Ensure measures to prevent transmission are well understood and practised.
Motivate patient and support adherence in every follow-up visit throughout the intensive and continuation phases, until completion of treatment.
Have a patient tracing system in place and ensure an HCW is tracing patients who miss appointment(s).
</td></tr>
</table>

Patient support: Key messages

- All patient support interventions are ultimately about promoting prevention, supporting adherence and retaining patients in care by addressing their psychosocial needs and reinforcing their skills to deal with the specifics of their health condition.
- For the busy clinician, it is necessary to shift some of this task to counsellors but the full burden of patient support should never be left to the counsellor to carry alone.

CHAPTER 26

Key populations



In most countries, investment in HIV care has tended to focus on the general population. However, in both concentrated and generalised epidemics, **key populations often account for a large share of HIV prevalence**. In addition, incidence in certain key populations has continued to rise, even when rates in the general population have stabilised or declined. This ongoing high risk is closely related to criminalisation of their behaviour and resultant exclusion or limitation of access to health care. World-wide it is thought that up to 50% of new infections among adults may occur among people from key populations and their immediate partners, and in Africa this ranges from 10–40%. As many people from key populations engage in more than one high risk behaviour, there is also a tendency for HIV to be more readily transmitted between the different key population groups, resulting in a multiplier effect on the incidence.

The solution for these populations lies in structural changes and investment to improve access to prevention and care for high-risk and excluded populations. This is beyond the scope of this clinically oriented handbook. However, as people from key populations are all seen in our clinics, regardless of the existence of specific programmes, it is essential that clear guidelines are given for the specifics of clinical care required.

The focus of this chapter is, therefore, on the **clinical information** necessary to provide an optimal service during a consultation with members of key population groups.

Who are key populations?

Five categories are recognised by WHO:

1. Commercial sex workers (CSWs)
2. Men who have sex with men (MSM)
3. People in prisons and other closed settings
4. People who inject drugs
5. Transgender people

In addition, for a variety of biological and psychosocial reasons, **adolescents and young people** from key populations have consistently been shown to be more vulnerable to STIs, HIV and other sexual and reproductive health problems than cohorts with older people. Therefore, an adolescent in one or more key population groups needs particularly focused attention.

WHO guidelines

Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations 2016 update: http://www.who.int/hiv/pub/guidelines/keypopulations-2016/en/

What the clinician needs to know in a consultation with people in key populations:

Much of this is generic to all, while there is some that is specific to a particular group. The generic information is presented first, followed by group-specific guidelines.

Generic guidelines: People in key populations

All have a right to the basic respect due to all populations:

a. **Voluntary HIV testing and counselling.** They have the right to decide on their own treatment and to refuse services. Healthcare providers should explain all procedures and respect the sex worker's choice if he or she refuses examination or treatment.

b. They have a right to the same **confidentiality** afforded to others. This refers to patient information, including clinical records and laboratory results.

c. Healthcare providers should be **discreet, non-judgmental, non-stigmatising** and trained to address the special needs of sex workers. Specific training (e.g. EVA) may be needed to develop this in health staff.

Core needs to be addressed

Key populations may be less likely than other groups to access care after a referral or to return to a clinic as requested. For this reason, wherever possible, deal with all health issues in an integrated, one-stop shop approach.

1. Prevention strategies

Ensure constant availability of condoms and compatible lubricants.

Ensure availability of PEP and PrEP, and in some situations, the active promotion of PrEP (see details for specific groups).

Promote voluntary male medical circumcision (VMMC) to decrease the acquisition of HIV.

2. ART

(**Chapters 2–7**)

The requirements for ART are the same as for all the other infected people, with a **greater degree of urgency for either starting it or detecting treatment failure,** so that the viral load can be suppressed as soon as possible and thus decrease infectivity.

There are also greater challenges to retention in care, due to stigma and discrimination, along with other factors specific to a particular key population group (see later in chapter).

All women in key population groups should have the same access to **PMTCT** (**Chapter 9**) as all other population groups.

Inherent in their key population status is a higher risk of acquiring HIV. The clinician therefore needs to be fully aware not only of the availability of local **PEP and PrEP** services, but also all the technical medical details regarding how to administer it (see **Chapter 8**).

3. TB treatment

(**Chapter 12**)

HIV-positive persons are 30 times more likely to get TB, further compounded if they use IV drugs or are prisoners. Increased focus needs to be given, therefore, to regular screening for TB and the issuing of IPT if negative. Since people in one key population group are often part of one or more other groups, this applies to the group as a whole.

4. STIs

(**Chapter 19**)

For the same reasons noted above in the ART section, all people in key population groups are at a higher risk of acquiring a wide range of STIs. A consultation should, therefore:

- Include regular screening, including history and examination (vaginal and anal), especially for syphilis, gonorrhoea and chlamydia, but also including other regionally prevalent STIs.
- If testing is not available, use the WHO syndromic approach, adapted for high-risk population as appropriate.
- Where access is poor and risk is high, offer **presumptive treatment**. Also to be considered is **periodic presumptive treatment (PPT)** to all. PPT is the periodic treatment, regardless of the presence or absence of signs or symptoms, of curable STIs, based on a particular key population's high risk and prevalence of infection. It is an effective short-term measure that can reduce the prevalence of STIs amongst high risk populations, such as sex workers.
- Ideally implement PPT, together with peer intervention and measures to increase condom and lubricant use. Consult local MSF or MoH guidelines for implementation details. See also page 380 in **Chapter 19**.
- Screen for HBV, far more infectious than HIV, if national policy allows, and vaccinate all negative patients. If there is doubt about vaccination status and it cannot be tested, a vaccination should be given, anyway. Efforts should also be made to ensure that infants receive birth dose vaccination against hep B.
- Test for HCV, though not as readily sexually transmitted, and refer patients if a local treatment protocol is present.

5. Sexual and reproductive (SRH) needs

(**Chapter 19**)

People in key populations have the same SRH needs, and indeed the same right to have them met, as anyone else. Clinicians need to be aware of the availability of these services and readily use them as required. These include:

- Family planning and contraception;
- Planning for a safe pregnancy;

- Access to ToP and post-ToP care;
- Screening for reproductive tract cancer (cervix, ano-rectal, prostatic);
- Management of reproductive tract cancer, especially of the cervix; and
- Management plans, including PEP, for survivors of sexual assault.

6. Mental health and alcohol/substance abuse

See **Chapter 22** for detail.

Mental health, including alcohol and substance abuse, is often influenced by social circumstances and environment. People in key populations are especially vulnerable because of poverty, criminalisation, marginalisation, discrimination or violence. Poor mental health may be a barrier both to seeking testing or treatment for HIV and for continuation in HIV care.

As with all HIV-positive patients, but especially so with these groups of people, periodic screening for mental health and alcohol/substance abuse should be performed.

Group-specific guidelines

All of the above generic guidelines are important for all key population groups. Noted here are additional guidelines specific to a particular population group.

1. Commercial sex workers (CSWs)

There is a large variation within regions in prevalence for HIV infection amongst sex workers, often substantially higher than in the general population. Sex workers are at an increased risk, due to exposure to multiple sexual partners, and, sometimes, inconsistent condom use, often due to clients unwillingness or coercion.

All of the above generic guidelines are important for sex workers. Below are specific extra points for attention for the clinician:

ART

Due to the nature of CSWs' work, and with greater likelihood of sexual violence and condom breakage, the need for the preventative benefits of PEP and PrEP is significantly higher. Clinicians should pro-actively offer PEP, which could also be a route to offering PrEP, a more stable, longer-term strategy.

As local policies incorporate WHO guidelines for the use of PrEP into their guidelines for all sex workers, clinicians will need to be familiar with its detailed use.

STIs

Please note that the periodic presumptive treatment (PPT) referred to above in section 4, STIs, is specifically recommended by WHO in the management of CSWs.

Support for PWID

Many sex workers often also use IV drugs and other substances, so consideration should be given to the specific needs of this population group (see later).

2. Men who have sex with men

For MSM in general:

- In major urban areas, HIV prevalence among MSM is, on average, 13 times greater than in the general population. A key reason is that HIV transmission through anal intercourse without a condom is more efficient than through vaginal intercourse without a condom.
- Individual-level risks for HIV acquisition among MSM include unprotected receptive anal intercourse, high number of male partners and concomitant injecting drug use.

Specific challenges to MSM healthcare in Africa:

- In many countries, homosexuality is considered simply to be un-African. This, therefore, lays a strong social foundation for increased discrimination and stigma.
- One of the consequences of homosexuality being considered taboo, is laws that criminalise MSM and further entrench rejection of them across society as a whole.
- The majority of MSM also have sex with women (MSMW) and identify as heterosexual. This compounds the problem, as it makes them invisible to the healthcare system.

All of the above generic guidelines are important for MSM. Below are specific extra points for attention for the clinician.

PrEP and PEP in MSM

Unprotected anal intercourse (UAI) has a 20 times greater risk of HIV transmission than unprotected vaginal sex. This makes the need for additional protection higher than in the normal population. As tenofovir levels in the rectal mucosal have been observed to be particularly high, PrEP is a particularly effective intervention and should be promoted for MSM. As with sex workers, clinicians should pro-actively offer PEP, which could also be a route to offering PrEP, a more stable, longer-term strategy.

STIs in MSM

- **Many STIs are asymptomatic** in men. Apart from those that are frequently asymptomatic in both males and females (e.g. syphilis, hepatitis, HIV) the majority of gonococcus and chlamydia infections in men are also asymptomatic. This is then likely to increase transmission risk. The incorporation of presumptive periodic treatment into guidelines needs to be considered.

- The risk of sexual transmission of **Hepatitis C**, known to be much lower than for hepatitis B, carries the highest risk in HIV-positive MSM. Screening this key population group is, therefore, a higher priority.
- Along with generous availability of condoms, ensure equally generous provision of a **compatible lubricant**.

SRH needs in MSM

Screening and treatment of abnormalities related to HPV infection in women is becoming increasingly available, but similar management in MSM for anal lesions (CIN and anal carcinoma) is rarely present in national programmes. Clinicians should, therefore, have a high index of **suspicion for any anal lesion** presenting in MSM.

3. People in prisons and other closed settings

- Unsafe sexual activities, overcrowding, poor ventilation, injecting drug use and tattooing contribute significantly to the considerably higher prevalence of HIV, STIs, hepatitis B and C and TB in prison settings.
- Because sex work, drug use and same-sex behaviour is illegal in many countries, many people from key population groups spend some time in prison at some time in their lives.
- In addition, with the movement globally of about 30 million people between prisons and the community, focused attention on this population group is not only critical for individual health, but also for communities as a whole.

All of the above generic guidelines are important for this key population group. Additionally, for the clinician’s attention:

- The key message, more programmatic than clinical, regarding people in prisons and closed settings is that access to all the services is likely to be more limited, if present at all.
- Though clinicians’ hands are often tied in their ability to address many of these deficiencies, understanding of this will tailor the treatment to these realities.

4. People who inject drugs (PWID)

Data on IV drug use in Africa is generally poor, but where statistics are better recorded, the prevalence of HIV is shown to be substantially higher than in the general population. IV drug users are more likely to engage in high-risk sexual behaviour and are more likely to spend time in prison. In addition, the sharing of needles and drug use paraphernalia substantially increases the risk of transmission, not only of HIV but also of hepatitis B and C.

WHO has described a **comprehensive harm reduction guideline** for PWID, the details of which can be found in the full document (abbreviated title is Care package for PWID) in the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018.

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

The following are specific drug-related interventions that contribute to harm reduction in PWID:

- Needle and syringe programmes (NSPs) to decrease the spread of disease via unsterile needles;
- Opioid substitution therapy (OST) to provide a regular supply of a safer opiate and thus decrease the exposure to more toxic opiates, and the infectious delivery systems often associated with them.
- The focus on injectable drugs should not cause the clinician and programme manager to overlook the need to address other forms of substance abuse, such as methamphetamines, alcohol and others.

5. Transgender people

The estimated worldwide prevalence of HIV in transgender women is 19% and they are nearly 50 times more likely to be living with HIV than other adults of reproductive age. The data for other transgender populations is more limited.

Due to violence, legal barriers, stigma and discrimination, transgender people have lower rates of access to health and HIV services. In addition, transgender people are frequently exposed to other risks relating to sex work and substance use.

All of the above generic guidelines are important for transgender individuals. Below are specific extra points for the clinician's attention.

Preventative therapy

Due to likely lack of natural lubricant for penetrative sex, special care needs to be given for the provision of condoms and compatible lubricants.

SRH

Hormonal therapy is used both for contraception and for gender-affirmative therapy in both transwomen and transmen. The clinician looking after these people needs to be familiar with its use, including side effects and drug interactions.

Mental health

Due to much higher levels of discrimination and stigma, there needs to be a higher index of suspicion for mental illness, coupled with skill and sensitivity in managing it.

For more detailed information see a more comprehensive document by the UNDP on implementing comprehensive HIV and STI programmes with transgender people in the additional resources folder at https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018. The document is filed as 'TRANSIT-1'

samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Adolescents and young people from key populations: Summary

Adolescents and young people are significantly more vulnerable to STIs, HIV and other sexual and reproductive health problems than are older adults in key populations. This vulnerability is further increased by their rapid physical, emotional and mental development, complex psychosocial and socio-economic factors, poor access to services and the compounding factors of legal restrictions of their ability to make independent decisions.

Because of all of the above, and the fact that they face more stigma, discrimination and violence, they tend not to attend diagnostic and treatment facilities, and, as a result, are invisible on most data sets. This further isolates them because the lack of data results in their specific needs not being addressed by policy developers.

All of the above generic guidelines are important for this key population group. Below are specific extra points for attention for the clinician:

The complexities of dealing in general with adolescents living with HIV management are covered in more detail in **Chapter 10**. However, in the context of this chapter, the clinician needs to be particularly aware of the special attention needed for the patient who is part of one or more key populations who is also an adolescent. Both the generic and specific guidelines apply to an adolescent in any of the different population groups principles, only amplified due to the higher prevalence of disease seen in this particular age group.

Preventative strategies

All adolescents should be considered for HPV vaccine (see **Chapter 8**).

Sexual and reproductive (SRH) needs

Adolescents are more likely to need more comprehensive advice on all aspects of SRH, contraception, access to ToP and post-ToP care, cervical screening and management for sexual assault.

Summary: Management of key populations

In any country the investment of resources in the effective management of key populations is a wise move. Not only is it in these populations that the prevalence of HIV and STIs is highest but also the nature of the high-risk sexual behaviour associated with these people results in greater rates of spread. While much of the intended impact on this prevalence needs to be driven by changes in health policy, individual clinicians taking all the appropriate clinical steps in managing these patients will go a long way in contributing to the necessary change needed.

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