Antiretroviral Therapy Guidelines for HIV-Infected Adults and Adolescents

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NACO

Department of AIDS Control
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Ministry of Health & Family Welfare
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Table of Contents

Chapter

Acronyms & Abbreviations 5

Introduction 7

Objectives of the guidelines 9

Section A: Management of Anti Retroviral Therapy for Adults and Adolescents 10

Section A1: Diagnosis of HIV Infection in Adults and Adolescents 10

Section A2: Assessment of Adults and Adolescents with HIV Infection and Pre ART Care and Follow up 14

Section A 3: Prophylaxis of opportunistic Infections 22

Section A4: ART in Adults and Adolescents 25

Section A5: Routine Monitoring of Patients on ART 33

Section A6: ART in Pregnant Women, PPTCT and Previous Exposure to NVP 35

Section A7: Considerations for Co-infection of Tuberculosis and HIV 38

Section A8: What to Expect in the First Six Months of Therapy 41

Section A9: Antiretroviral Drug Toxicity 45

Section A10: ART Treatment Failure and when to switch 50

Section A11: Choice of ARV Regimens in the Event of Failure of First-line Regimens 55

Section A12: Considerations for ART in IDUs or PLHA under Substitution Programmes 57

Section A13: HIV and Hepatitis Co-infection 61

Section A14: Considerations for ART in Adolescents 63

Section A15: Adherence to ART 64

Section A16: Nutritional Aspects of HIV 66

Section A17: Palliative Care in HIV 72

Section A18: NACO Standardized Reporting and Recording System 81

Section B: Annexes 87

Annex 1: Presumptive and Definitive Criteria for Recognising HIV-Related Clinical Events in Adults and Adolescents 87

Annex 2: ARV Drug Combinations and Strategies not to be used 91

Annex 3: Dosages of Antiretroviral Drugs for Adults and Adolescents 92

Annex 4: Clinical signs and Symptoms and Management of Adverse Effects of Antiretroviral Drugs 93

Annex 5: Drug Interactions with ARVs 96

Annex 6: Summary of Methadone and ART 99

Annex 7: Patient Information Sheets: Treatment Education Cards 102

Annex 8: Checklist for Adherence Counseling 106

Annex 9: Barriers to Adherence and ways to address them 109

Annex 10: Tools for HIV 2 Testing 110

Annex 10a: Designated HIV-2 referral laboratories 110

Annex 10b: Referral Slip for HIV 2 Testing 112

Annex 10 c: National HIV 2 Testing Algorithm 113

Annex 10 d: Report Format to be used by HIV-2 Referral Laboratories 115

Annex 10 e: PCR Requisition Form 116

Annex 10 f: Inventory for kit utilization 117

Annex 10 g: HIV-2 Referral Laboratory Cumulative Monthly Reporting Format 118

Annex 10 h: ICTC HIV Test Reporting Format 119

Acknowledgements 120

Acronyms and Abbreviations

ABC	Abacavir
AFB	Acid-Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Sminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral (drug)
AST	Aspartate Aminotransferase
ATV	Atazanavir
AZT	Zidovudine (also known as ZDV)
bid	Twice Daily
CD4	T-lymphocyte CD4+
CNS	Central Yervous System
CPK	Creatinine Phosphokinase
CPT	Cotrimoxazole Preventive Therapy
CXR	Chest X-ray
d4T	Stavudine
ddI	Didanosine
EFV	Efavirenz
FBC	Full Blood Count
FDC	Fixed-Dose Combination
GI	Gastrointestinal
Hgb	Haemoglobin
HIV	Human Immunodeficiency Virus
HIVDR	HIV Drug Resistance

Acronyms and Abbreviations

HIVNET	HIV Network for Prevention Trials
HIVResNet	Global HIV Drug Resistance Network
IDV	Indinavir
IRS	Immune Reconstitution Syndrome
NACO	NationalAIDS Control Organisation
NFV	Nelfinavir
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Analogue Reverse Transcriptase Inhibitor
NVP	Nevirapine
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PGL	Persistent Generalized lymphadenopathy
PI	Protease Inhibitor
PLHA	People Living With HIV/AIDS
PMTCT	Prevention of Mother-to-Child Transmission (of HIV)
/r	Low dose Ritonavir
RDA	Recommended Daily Allowances
RNA	Ribonucleic Acid
SQV	Saquinavir
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TLC	Total lymphocyte Count
WHO	World Health Organization

1. Introduction

Government of India launched the free ART programme on 1st April 2004, starting with eight tertiary-level government hospitals in the six high-prevalence states of Andhra Pradesh, Karnataka, Maharashtra, Tamil Nadu, Manipur, and Nagaland. As on March 2013, there are around 18.13 lakhs People Living with HIV (PLHIV) registered at the 400 ART Centres functioning all around the country. Currently near 6.5 lakhs are on first line ART. Along with this 840 Link ART Centres primarily established for dispensing ARV drugs, monitoring side effects and treating minor OIs. Among this 154 LACs have been upgraded as LAC plus centres to provide Pre ART services additionally.

India is estimated to have around 1.16 lakhs annual new HIV infections among adults and around 14,500 new HIV infections among children in 2011. Of the 1.16 lakhs, estimated new infections in 2011 are among adults. The six high prevalence states account for only 31% of new infections, while the ten low prevalence states of Odisha, Jharkhand, Bihar, Uttar Pradesh, West Bengal, Gujarat, Chhattisgarh, Rajasthan, Punjab & Uttarakhand together account for 57% of new infections. The greater vulnerabilities in these states are being given higher focus in the AIDS control programme.

The total number of PLHIV in India is estimated at 21 lakhs in 2011. Children (<15 yrs) account for 7% (1.45 lakhs) of all infections, while 86% are in the age group of 15-49 years. Of all HIV infections, 39% (8.16 lakhs) are among women. The estimated number of PLHIV in India maintains a steady declining trend from 23.2 lakhs in 2006 to 21 lakhs in 2011. The four high prevalence states of South India (Andhra Pradesh, Karnataka, Maharashtra, and Tamil Nadu) account for 53% of all HIV infected population in the country.

HIV epidemic in India is concentrated among High Risk Groups and heterogeneous in its distribution. The vulnerabilities that drive the epidemic are different in different parts of the country. Overall trends of HIV portray a declining epidemic at national level, though inter-state variations exist. Both prevention and treatment strategies have yielded good impacts as reflected in the reduction in new infections as well as AIDS-related deaths in the country.

It is estimated that the scale up of free ART since 2004 has saved over 1.5 lakhs lives in the country till 2011 by averting deaths due to AIDS-related causes. Greater declines in estimated annual deaths are noted in states where significant scale up of ART services has been achieved. In high prevalence states, estimated AIDS-related deaths have decreased by around 42% during 2007 to 2011. At the current pace of scale up of ART services, it is estimated around 50,000 to 60,000 deaths annually will be averted in the next five years. With increasing coverage of treatment & decreasing AIDS-related mortality, a significant number of people are likely to require first and second line ART treatment in the coming years.

1.1 The key goals of the national ART programme:

The Clinical goals of ART are:

- To improve quality of life,
- To reduce HIV-related morbidity and mortality,
- To provide maximal and durable suppression of viral load and,
- To restore and/or preserve immune function.

These goals are achieved by completely suppressing viral replication for as long as possible using well-tolerated and sustainable treatment. With prolonged viral suppression, the CD4 lymphocyte count usually increases, which is accompanied by partial restoration of pathogen-specific immune function. For most patients, this results in a dramatic reduction in the risk of HIV-associated morbidity and mortality.

The Programmatic goals of ART are:

- To provide long-term ART to eligible patients,
- To monitor and report treatment outcomes on a quarterly basis,
- To attain individual drug adherence rates of 95% or more,
- To increase life span, so that at least 50% of patients on ART are alive 3 years
- after starting the treatment, and
- To ensure that at least 50% of patients on ART are engaged in or can return to their previous employment.

1.2 Eligibility for ART:

The national programme offers ART to the following groups of persons:

- All persons with HIV infection who are medically eligible to receive ART (as per national guidelines)
- Those who are already on ART (outside the national programme) and want to enroll with the National programme for the available ART regimens, after written informed consent

Strengthening of linkages and referrals to the prevention of parent-to-child transmission (PPTCT) programme is being carried out so that women and children living with HIV/AIDS have greater access to treatment. The national programme will also link with other programmes, such as the Revised National Tuberculosis Control Programme (RNTCP), Reproductive and Child Health (RCH) Programme and National Rural Health Mission (NRHM).

2. Objectives of the Guidelines

While many ART guidelines are available internationally, these guidelines have been written to address issues relevant to India. These guidelines are intended to assist physicians prescribing ART, as well as the teams in the ART centres, with the practical issues regarding the treatment of HIV/AIDS.

Following general principles underpinned the writing process:

- India is a Low-income country and only treatment and diagnostic options available in the country were included.
- The need to bridge the gap in treatment recommendations between public and private sector programmes has been taken into account, considering that many patients transition between the two sectors for treatment.
- The guidelines are intended to reflect 'best practice' – while it is acknowledged that certain recommendations are inspirational for poorly resourced settings, the unavailability of diagnostic/monitoring tests should not be a barrier to providing ART to those in need.

The present guidelines have been finalized in December 2012, following the meetings of the ART Technical Resource Group (TRG) and online consultations with national and international experts on ART. This includes the national consultation with clinicians and medical practitioners from the public and private sectors, technical experts from the Director General of Health Services (DGHS), Government of India, WHO and other UN agencies, bilateral donors, Confederation of Indian Industry (CII), pharmaceutical industries, Network of Positive People and non-governmental organizations (NGOs) involved in the care and treatment of PLHA. These guidelines will continue to evolve according to the evidence and data available nationally as well as globally and will be updated when needed.

These guidelines are part of a series of NACO guidelines:

- National guidelines on Post Exposure Prophylaxsis
- National Guidelines for HIV Care and Treatment in Infants and Children
- Guidelines for Prevention and Management of Common Opportunistic Infections
- National Guidelines for Prevention of Parent-to-Child Transmission (PPTCT)

Section - A: Management of ART for Adults and Adolescents

Section A1: Diagnosis of HIV Infection in Adults and Adolescents

Confirmatory diagnosis of HIV infection is essential for ensuring access to care and treatment services. It is recommended that if there is any doubt regarding the diagnosis of HIV, the individual should be referred to the integrated counselling and testing centre (ICTC) for confirmatory testing and diagnosis. An excerpt from the national strategies on HIV testing follows.

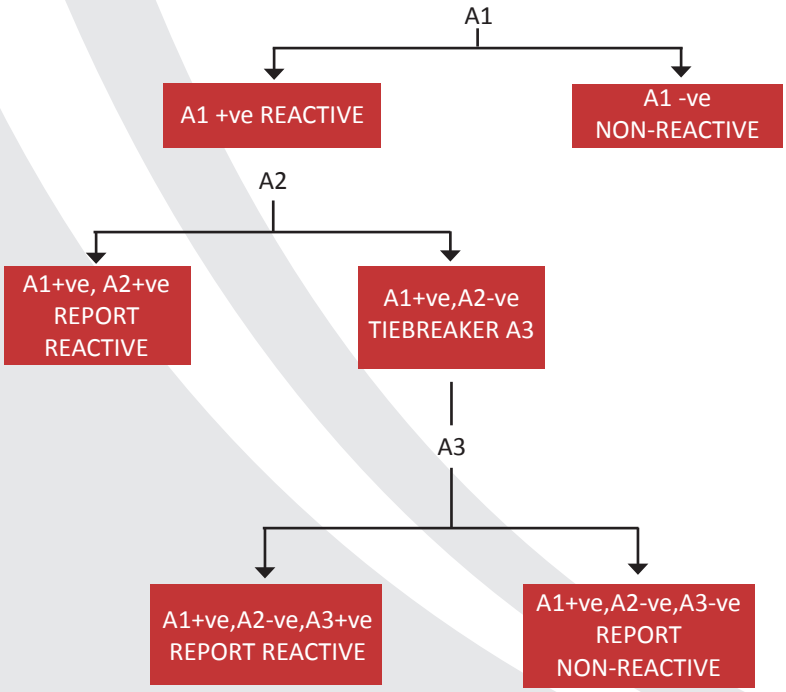
1.1 National Guidelines on Testing Adults

- For symptomatic persons: the sample should be reactive with two different kits.
- For asymptomatic persons: the sample should be reactive with three different kits

The blood sample collected at one time is tested with the first kit. If it is reactive, it is then retested sequentially with the second and third kits.

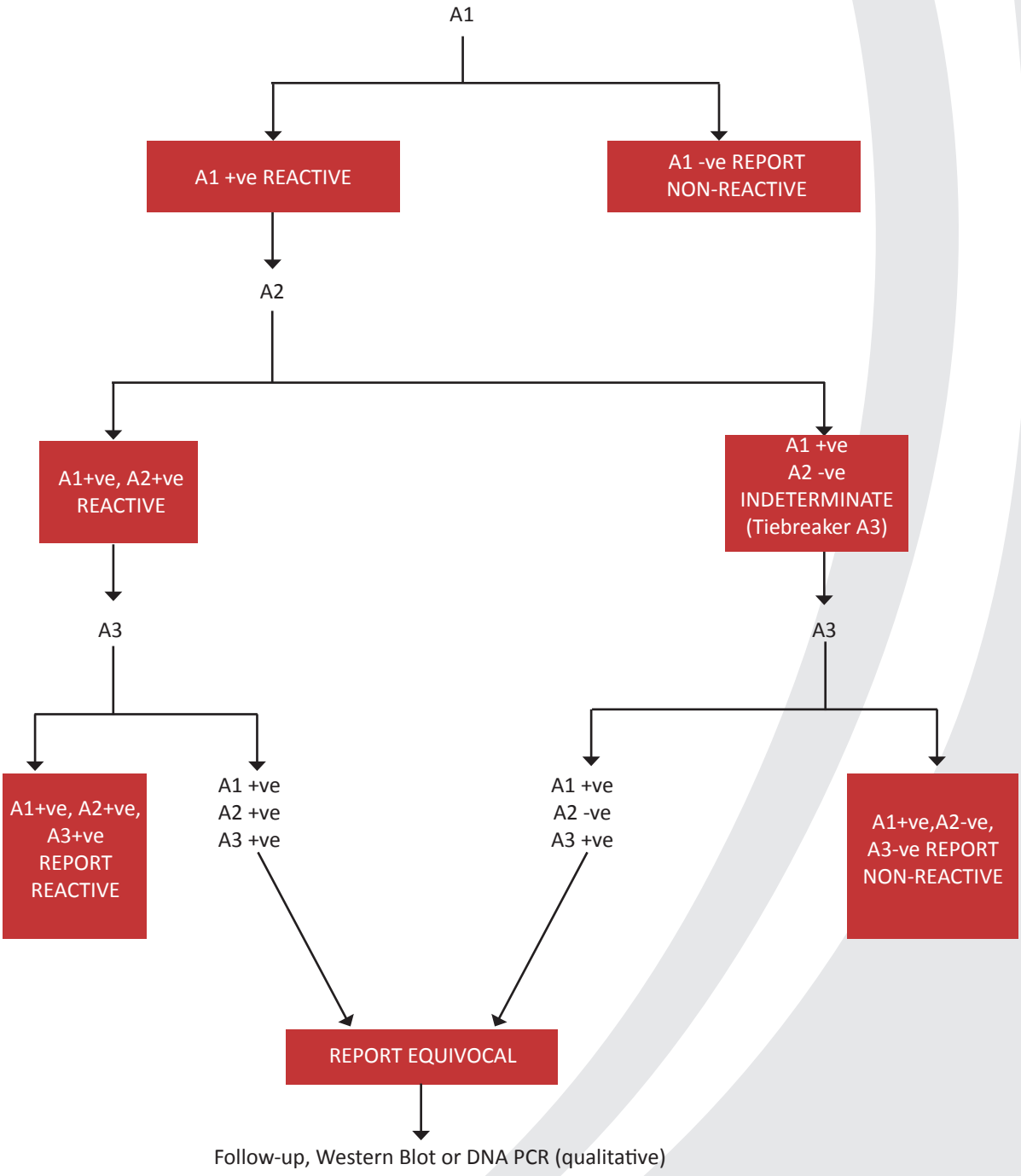
For asymptomatic persons:

1.1.1 HIV testing strategy II B (Blood/Plasma/Serum)



For asymptomatic persons:

1.1.2 HIV testing strategy III



Operational Guidelines for HIV 2 Diagnosis

Introduction:

There are 2 types of Human immunodeficiency virus (HIV) viz. HIV type I (HIV-1) and HIV type 2 (HIV-2). The most common cause of HIV disease throughout the world is HIV-1 which comprises of several subtypes with different geographic distributions. HIV type 2 (HIV-2) is endemic in West Africa and has spread in the last decade to India and Europe.

Natural history studies indicate that HIV-2 is less pathogenic than HIV-1. Those infected with HIV-2 have slower disease progression, a much longer asymptomatic stage, slower decline in CD4 count, lower rates of vertical transmission, lower viral loads while asymptomatic and smaller gains in CD4 count in response to antiretroviral treatment (ART).

It is observed and well documented that infection with HIV 2 does not protect against HIV 1 and dual infection. Dually infected patients tend to present at a more advanced stage of disease than those with HIV-2 only. Infection with both HIV-1 and HIV-2 generally carries the same prognosis as HIV-1 single infection.

Information on the epidemiology of HIV-2 and dual infection in India is limited. However, some cases of HIV2 infection have been reported.
Although HIV-1and HIV-2 are related, there are important structural differences between them. Accurate diagnosis & differentiation of HIV-1 & HIV-2 is crucial for treatment, as HIV-2 is intrinsically resistant to NNRTI, the pillar of national first line ART regimen. This information is crucial for treatment of infected individuals as well as for understanding extent of HIV2 infections in India. Discriminating rapid kits are being used at ICTCs. However, HIV2 positivity shown in these tests needs confirmation which cannot be done at ICTCs.

NACO has established a network of laboratories which includes ICTCs, State reference laboratories (SRLs) and National Reference laboratories (NRLs). Designated NRLs & SRLs will be responsible to confirm the presence of HIV 2 infection.

Instructions to be followed by ART centers for referring clients/patients for HIV 2 diagnosis (Refer to Flow chart):

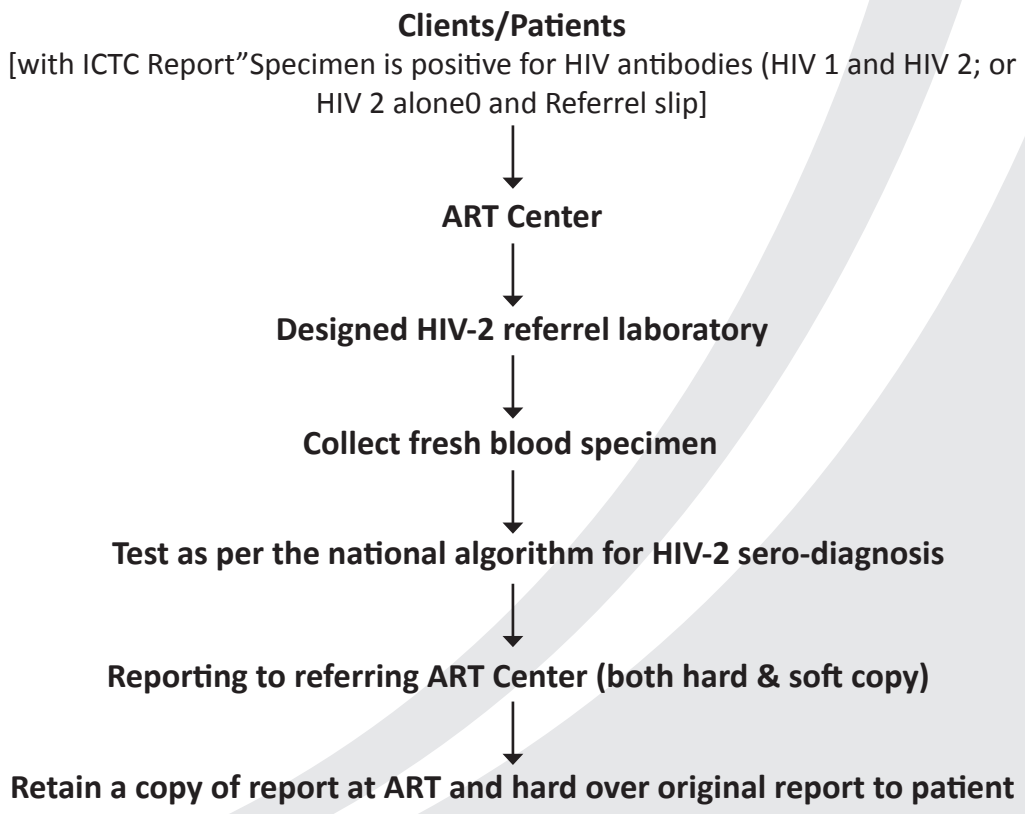
- Clients/Patients with the following report from the ICTC **"Specimen is positive for HIV antibodies (HIV 1 and HIV 2; or HIV 2 alone)"** (Annexure 8) will be referred to the nearest ART centre for registration.
- The ART centre will then refer the said client/patient to the designated HIV-2 referral laboratory
- The patient must carry ICTC report and a referral slip (Annexure-2) duly signed by the ART Medical Officer along with a photo ID to the referral lab on any working day from Monday to Friday between 9:00 AM to 2:00 PM.
- The HIV-2 referral lab will collect fresh blood specimen (serum + plasma) for HIV serostatus confirmation

- Specimen will be tested by referral laboratory as per the national algorithm for HIV-2 sero diagnosis
- Two copies of report will be sent to the referring ART center (both hard & soft copy) within 4 weeks
- Copy of the report to be retained by the referring ART center & original to be handed over to patient/client

Instructions to be followed at HIV 2 Referral Laboratories:

- Check ICTC report, Referral slip from ART center, photo ID and related details in the forms
- Collect 5 ml blood each in two tubes - one plain and one EDTA vacutainer tube
- Separate the serum from blood collected in plain vacutainer. Proceed as per the algorithm for HIV 2
- Store the blood collected in EDTA vacutainer at -200C. Only those samples will be send to Apex laboratory whose result is indeterminate either for HIV 1, HIV 2 or HIV1 & 2 by Western blot (Annexure 5 : PCR requisition form). These samples will be tested at Apex laboratory by Molecular tests.
- Reports to be sent to referring ART center by both as soft copy (e- mail) and a hard copy. Hard copy of the report to be prepared in triplicate. Original and a copy to be sent to the referring ART centre and one copy to be retained in the Referral lab for records.
- VI. Utilization of kit details to be submitted to Apex laboratory every quarterly

Flow chart referring the patient for HIV2 Testing



Section A2:
Assessment of Adults and Adolescents with HIV Infection and Pre – ART Care and Follow up

2.1 Clinical Assessment

At the beginning of HIV care and prior to starting ART, a clinical assessment should be performed to:

- Determine the clinical stage of HIV infection
- Identify history of past illnesses (especially those related to HIV)
- Identify current HIV-related illnesses that require treatment
- Determine the need for ART and OI prophylaxis
- Identify coexisting medical conditions and treatments that may influence the choice of therapy

The recognition of HIV-related clinical events helps to determine the stage of a patient's disease and decisions on when to initiate OI prophylaxis and ART.
WHO stage 1, 2 and 3 conditions, with the exception of moderate anaemia, can be readily recognized clinically. For WHO stage 4 conditions, where clinical diagnosis is not possible, definite diagnostic criteria are recommended in the case of conditions such as lymphoma and cervical cancer ***(See Table 1).***

2.2 Medical History

Many individuals with HIV infection may have concurrent risk behaviours. It is important to elicit these risk factors, which may influence how a person will be counselled and supported. These risk factors for HIV infection include:

- Past or present use of injecting drugs
- Male or female sex worker
- Men who have sex with men (MSM)
- Present or past unprotected sex, in particular with female or male sex worker
- Past or present sexually transmitted infection (STI)
- Past or present recipient of blood or blood products
- Injections, tattoos, ear piercing or body piercing using non-sterile instruments
  See Table 2

Table 1: WHO clinical staging of HIV/AIDS for adults & adolescents 2010
Clinical Stage 1
Asymptomatic Persistent generalized lumphadenopathy
Clinical Stage 2
Unexplained moderate 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 eruptions Seborrhoeic dermatitis Fungal nail infections
Clinical Stage 3
Unexplained 2 servere weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than one onth Unexplained persistent fever (above 37.5OC intermittent or constant for longer than one month) Persistent oral candidiais Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropenia (<0.5 x 109/litre) and or chronic thrombocytopenia (<50 x 109/litre3)
Clinical stage 4[3]
HIV wasting syndrome Pneumocystis 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) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis including menigitis Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis) Recurrent septicaemia (including non-typhoidal salmonella) Lymphoma (cerebral or B cell non Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or symptomatic HIV – associated cardiomyopathy
1 Assessment of body weight in pregnant women needs to consider expected weight gain of pregnancy. 2 Unexplained refers to where the condition is not explained by other conditions. 3 Some additional specific conditions can also be included in regional classifications (e.g. reactivation of American trypanosomiasis (meningoencephalitis and / or myocarditis) in Americas region, Penicillionsis in Aisa)

Table 2 : Medical History Checklist	
HIV Testing	**HIV risks (can have multiple factors)**
• Ever tested for HIV in the past? • Date and place of first HIV test • Reason for the test • Documentation of the result • Date of last negative HIV test result • Previous CD4 cell counts (if available) • Previous viral load (if available)	• Unprotected sexual contact • Injection drug use • Men having sex with men • Occupational exposure • Perinatal transmission • Recipient of blood products • Unknown • Partner's HIV status being positive
System Review	**Past history of HIV related illnesses**
• Unexplained weight loss • Swollen lymph nodes • Night sweats and fever • Unusual headaches or poor concentration • Changes in appetite • Skin rashes • Sores or white spots in mouth • Painful swallowing • Chest pain, cough or shortness or breath • Stomach pain, vomiting or diarrhea • Numbness or tingling in hand or feet • Muscular weakness and changes in vision	• Oral candidiasis or candida oesophagitis • Persistent diarrhoea • Tuberculosis • Varicella zoster (Shingles) • Oral hairy leukoplakia • Pneumocystis juroveci pneumonia (PCP) • Recurrent bacterial pneumonia • Cyptococcal meningitis • Toxoplasmosis • Kaposi sarcoma • Disseminated Mycobacteriumvium complex Cytomegalovirus (CMV) infection • Invasive cervical cancer
Tuberculosis history	**Sexually transmitted infections (STIs)**
• Last chest X-ray • History of past TB • Treatment given (drugs and duration) • History of exposure to TB	• Genital ulcer or other lesion • Genital discharge (abnormal vaginal discharge in women) • Lower abdominal pain
Gynaecological history	**General medical history**
• Last PAP smear • Menstrual irregularities • Pelvic pain or discharge	• Any other past medical condition, such as diabetes, hypertension, coronary artery disease, hepatitis B, heptatis C, hyperlipidaemia • Mental health issues, e.g. depression

Table 2 : Medical History Checklist	
Pregnancy and contraception history	**Vaccination history**
• Previous pregnancies and terminations • Children and HIV status of children (living and dead) • Exposure to ARVs during pregnancy • Drugs and duration of ART • Contraception used • Last menstrual period	• BCG • Hepatitis A vaccine • Hepatitis B vaccine
Medication	**Allergies**
• Past use of drugs and reasons for taking them • Current use of drugs and reasons for taking them • Current use of traditional / herbal remedies • Opioid substitution therapy (OST)	• Known allergies to drugs or other substances or materials
ART history	**Psychosocial history**
• Current and past exposure to ARVs • ARV use during pregnancy of PMTCT • Which drugs taken and for how long	• Family history, e.g. other immediate family members with known HIV infection • Social history e.g. maritial status, education, occupation, source of income.
Substance use	**Functional status**
• Understanding of and readiness to commence ART • Partner's ART history (if HIV-positive)	• Financial and family support status • Disclosure status, readiness to disclose • Availability of care and treatment supporter
• Alcohol, stimulant, opiate and other drug use • Smoking history	• Able to work, go to school, do housework • Ambulatory but not able to work • Bed ridden • Amount of day-to-day care needed

2.3 Physical Examination

It is essential to have a thorough physical examination for clinical staging and screening. Table 3 details the specific physical signs related to HIV/AIDS which should be screened

Table 3 : Physical examination checklist	
Record vital signs, body weight, height and body mass index (BMI), temperature, blood pressure, pulse rate, respiratory rate	
Appearance	• Unexplained moderate or severe weight loss, HIV wasting • Rapid weight loss in suggestive of active OI, especially if associated with fever • Gradual weight loss (not caused by malnutrition or other obvious illness) is suggestive of HIV infection • "Track marks" and soft tissue infections which are common among IDUs
Consider conditions other than HIV	• Malaria, tuberculosis, syphilis, gastrointestinal infections, bacterial pneumonia, pelvic inflammatory disease, viral hepatitis
Skin	• Look for signs of HIV-related and other skin problems. These include diffuse dry skin, typical lesions of PPE, especially on the legs, seborrhoetic dermatitis on face and scalp • Look for herpes simplex and herpes zoster or scarring of previous herpes zoster (especially multi-dermatome)
Lymph nodes	• Start with posterior cervical nodes • PGL (persistent glandular lymphadenopathy) typically presents as multiple bilateral, soft, non-tender, mobile cervical nodes, Similar nodes may be found in the armpits and groins • Tuberculous lymph nodes typically present as unilateral, painful, hard enlarging nodes, with constitutional symptoms such as fever, night sweats and weight loss
Mouth	• Look for signs suggestive of HIV infection including white plaques on tongue, cheeks and roof of mouth (oral candida), white stripped lesions on the side of the tongue (OHL) and craking at the corners of the mouth (angular cheilitis) • Difficulty in swallowing is commonly caused by oesophageal candida
Chest	• The most common problems will be PCP and TB • Signs and symptoms are cough, shortness of breath, haemoptysis, weight loss, fever, congestion or consolidation • Perform a chest X-ray, if symptomatic
Abdomen	• Hepatosplenomegaly, masses and local tenderness • Jaundice may indicative viral hepatitis
Ano-genital	• Herpes simplex and other genital sores / lesions, vaginal or penile discharge • Perform PAP smear, if possible
Neurological examination	• Focus on visual fields and the signs of neuropathy (bilateral peripheral or localized mono-neuropathies) • Assess focal neurological deficit
Note : During each consultation, patient is to be clinically screened for TB (history and physical examination)	

2.4 Comprehensive Laboratory Evaluation in HIV/AIDS

The purpose of the baseline laboratory evaluation is to (i) determine the stage of the disease, (ii) rule out concomitant infections and (iii) determine baseline safety parameters. The following are recommended tests for monitoring of PLHAs at ART centres (See also table 18).

Table 4: Laboratory Monitoring for patients at ART centres

Essential tests	Additional tests
• Haemogram/CBC, • Urine for routine and microscopic examination, • fasting blood sugar, • blood urea, • ALT (SGPT), • VDRL, • Serum creatinine (when considering TDF) • CD4 count, • X-ray Chest PA view. • Pregnancy test (if required) • Symptoms and signs directed investigations for ruling out OIs.	For all patients to be started on ART (as per the physician's decision depending on clinical presentation) • USG abdomen, • sputum for AFB, • CSF analysis etc. Efforts to be made to fast track these investigations so that ART initiation is not delayed. PAP smear & Fundus examination also to be done but ART initiation not to be delayed for these tests.
Tests for Special Situation	**Tests for monitoring purpose**
• HBsAg: for all patients if facility is available but mandatorily for those with history of IDU, multiple blood & blood products transfusion, ALT > 2 times of ULN, on strong clinical suspicion. But ART not to be withheld if HBsAg testing is not available. • Anti - HCV antibody: only for those with history of IDU, multiple blood & blood products transfusion, ALT >2 times of ULN, on strong clinical suspicion. • For patients with Hepatitis B or C co-infection: further tests may be required to assess for chronic active hepatitis • For patients to be switched to a PI based regimen: Blood Sugar, LFT and Lipid profile to be done at baseline.	**Essential:** CD4, Hb, TLC, DLC, ALT (SGPT). **TDF based regimen:** Creatinine/ creatinine clearance, every 6 months or earlier if required. **AZT based regimen:** Hb at 15 days, then every month for initial 3 months, 6 months and then every 6 months/ as & when indicated. **NVP based regimen:** ALT (SGPT) at 15 days, 1 month and then every 6 months. **EFV based regimen:** lipid profile should also be done yearly. **ATV based regimen:** LFT to be done at 15 days, 1 month, 3 month, 6 months and then every 6 months. Blood sugar and Lipid profile every 6 months for patients on PI based regimen. All the above tests can be done earlier based on clinicians assessment/ discretion Other investigations during follow up as per requirement /availability.
Note: All above investigations other than C04 and viral load estimations (when required), shall be done from the health facility where the centre is located, with support from State Health Department	

2.5 Revised WHO Clinical staging of HIV Disease for Adults and Adolescents, 2010

Table 5: Assessment and initial management after HIV diagnosis is confirmed		
Visit 1	** Refer to Table 13: Initiation ofARTbasedon CD4 and WHO clinical staging*	
	• Medical history • Symptom checklist • Screen for TB • Physical examination • Chest X-ray if chest symptoms present Behavioural/psychosocial assessment: Educational level, employment history,financial resources • Social support, family/household structure • Disclosure status, readiness to disclose • Understanding of HIV/AiDS, transmission, risk reduction, treatment options • Nutritional assessment • Family/household assessment to determine if there are other HIV-infected family members who may need care • Recommend condom use during every visit • **Investigation**: baseline Blood profile, CD4 count, other test as necessary	
	Eligible for ART	**Not eligible for ART**
Visit 2 (Anytime)	• History (new problems) • Symptom check-list • Screen for TB • Physical examination • Co-trimoxazole prophylaxis • Psychosocial support • Adherence counselling (more than one session may be needed before commencing ART)	• History (new problems) • Symptom check-list • Physical examination • Psychosocial support
Visit 3 (2 weeks after previous visit)	• Screen for TB • Commence ART if stable on Co-trimoxazole and patient is ready . • Commence lead in dose of NVP 200 mg once daily	
Visit 4 (2 weeks after previous visit)	• History (new problems) and clinical examination • Screen for TB • If on NVP, note any side-effects (rash, fever, signs of liver toxicity) • Dose escalation of NVP to 200 mg 2 times a day • Adherence assessment / support	
Subsequent visits (4 weeks after previ-ous visit, or as necessary)	• History (new problems) • Symptom check-list • Screen for TB • Clinical examination • Adherence assessment / support	Follow-up visit for CD4 monitoring (see Table 6) History (new problems) Screen for TB during each visit
See table IB (p 25) foi routine monitoring aftet ART has been initiated.		

2.6 Pre-ART Care:

With the scaling up of treatment nationally, as well as increased awareness of HIV and access to counselling and testing services, it is envisioned that there would be a decrease in the number of PLHIV requiring ART as many more would present in the earlier stages of the infection. The recent experience of ART centres has shown that there is a need to emphasize good HIV (pre-ART) care and support so as to maintain well-being.

Pre-ART care is defined as the ***period where an HIV positive person does not medically require the initiation of ART.*** PLHIV who do not need ART (or are not medically eligible for the initiation of ART) should be counselled to maintain healthy/positive living and be linked to care and support services. The following steps are recommended for monitoring patients who are not yet eligible for ART for the early detection of OIs and initiation of ART before the CD4 count falls below 200 cells.

- Comprehensive medical history and physical examination (*see Tables 2,3,4*)
- Baseline laboratory tests for pre-ART care patients include:
    1. Baseline screening of CD4 to determine eligibility for starting ART (*see Table 13*)
    2. Baseline laboratory assessment, including CBC, ALT/AST, ALP, urinalysis
    3. For women: Annual PAP smear screening or acetic acid cervical screening at district health care facilities
    4. HBsAg and HCV screening for IDUs/those with transfusion-associated infections or elevated liver enzyme levels
    5. Any other relevant investigations (symptom-driven) and screening for TB at every visit
- Follow-up visit for pre-ART care and CD4 screening
- Educate patient to return to ART centre if unwell or new symptoms arise
- Other services for pre-ART care patients including family screening and testing/ counselling of partners (couple counselling) and children, as well as follow-up of discordant couples and referral for care and support services
- Register patients in the NACO Pre-ART Register

Table 6: CD4 monitoring and follow-up schedule

CD4 Count	Follow up
CD4 of any value and on ART	Every 6 months
Between 350 and 500 and not on ART	Repeat at 3 months
>500 and not on ART	Repeat at 6 months
Note: If the CD4 count is between 350 to 400 cells/mm3 and the patient is not on ART; repeat CD4 assessment after 4 weeks and consider treatment in asymptomatic patients. *See Table 13 for more details p19.*	

Section A3: Prophylaxis of opportunistic Infections

Routine prophylaxis with co-trimoxazole is provided under the national programme. CPT is effective against several organisms, including *Toxoplasma*, PCP and several organisms causing diarrhoea in HIV- infected persons. Recent evidence has shown that CPT helps prevent morbidity and mortality in adults with both early and advanced HIV disease.

Under the national programme, CPT may be initiated in the following scenarios:

- HIV infected adults with CD4 <250 cells/mm3 ***or***
- WHO clinical stage 3 or 4 irrespective of CD4 count

It is currently recommended that prophylaxis for OI be given as per the schedule below.

Table 7: Co-trimoxazole prophylaxis recommendations

Commencing primary CPT	**CD4 awaited**	**CD4 available**
	WHO clinical stage 3 or 4 (This includes all patients with TB)	Any WHO clinical stage and CD4 <250 cells/mm3 or Any WHO clinical stage, CD4 <350 cells/mm3 and if patient is symptomatic or WHO stage 3 or 4 irrespective of CD4 count
Commencing secondary CPT	For all patients who have completed successful treatment for PCP until CD4 is >200 (at least on two occasions, done 6 months apart)	
Timing the initiation of co-trimoxazole in relation to initiating ART	Start co-trimoxazole prophylaxis first. Start ART about two weeks later if the patient can tolerate co-trimoxazole and has no symptoms of allergy (rash, hepatotoxicity) Meanwhile, make use of the time for adherence and treatment preparation	
Dosage of cotrimoxazole in adults and adolescents	One double-strength tablet or two single-strength tablets once daily– total daily dose of 960 mg (800 mg SMZ + 160 mg TMP)	
Cotrimoxazole for pregnant women	Women who fulfill the criteria for CPT should continue on it throughout pregnancy. If a woman requires CPT during pregnancy, it should be started regardless of the stage of pregnancy Breastfeeding women should continue CPT where indicated	
Patients allergic to sulpha-based medications	Dapsone 100 mg per day, if available Co-trimoxazole desensitization may be attempted but not in patients with a previous severe reaction to CTX or other sulpha-containing drugs	
Monitoring	No specific laboratory monitoring is required in patients receiving co-trimoxazole	

Table 8: When to stop Cotrimoxazole Prophylaxis	
When to stop prophylaxis (cotrimoxazole or Dapsone) in patients on ART	If CD4 count >250 for at least 6 months and If patient is on ART for at least 6 months, is asymptomatic and well
Notes: * If CPT is started at CD4 levels between 250–350 cells/mm^3: CD4 counts should have increased, patient is on ART for at least 6 months, is asymptomatic and well; before CPT is stopped.	

Note:

- Start co-trimoxazole when CD4 count is less than 250 or WHO Clinical Stage 3 or 4, irrespective of CD4. This includes all HIV-TB co-infected patients
- Discontinue when two consecutive CD4 counts are more than the respective levels, the patient is on ART more than 6 months and adherence is good
- Reintroduce prophylaxis if CD4 count falls below 250 again
- Secondary prophylaxis is indicated to prevent recurrent OI

Co-trimoxazole desensitization

If the patient reports a history of hypersensitivity to sulpha-containing drugs, start him/her on a desensitization regimen as an in-patient. Desensitization can be attempted two weeks after a non-severe (grade 3 or less) co-trimoxazole reaction which has resulted in a temporary interruption in the use of the drug.

Co-trimoxazole desensitization has been shown to be successful and safe in approximately 70% of patients with previous mild to moderate hypersensitivity.[1,2,3] Desensitization should not be attempted in individuals with a history of severe co-trimoxazole or other sulphonamide reaction. If a reaction occurs, the desensitization regimen should be stopped. Once the patient recovers fully, Dapsone at a dosage of 100 mg per day may be tried. Some patients may be allergic to both co-trimoxazole and Dapsone. There are no other prophylaxis drug options in resource-limited settings.

Table 10: Protocol for Co-trimoxazole desensitization		
Step	**Dosage**	
Day 1	80 mg SMX + 16 mg TMP	(2 ml oral suspension)
Day 2	160 mg SMX + 32 mg TMP	(4 ml oral suspension)
Day 3	240 mg SMX + 48 mg TMP	(6 ml oral suspension)
Day 4	320 mg SMX + 64 mg TMP	(8 ml oral suspension)
Day 5	One single – strength SMX-TMP tablet	(400 mg SMX + 80 mg TMP)
Day 6	Two single-strength SMX-TMP tablets or one double-strength tablet	(800 mg SMZ + 160 mg TMP)
Reference : Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings : Recommendations for a public health approach. World Health Organization, 2006. *Note : Co-trimoxazole oral suspension contains 40 mg TMP + 200 mg SMX per 5 ml*		

Some OIs may require secondary prophylaxis as detailed in table 9.

Table 9: Recommended schedule for starting and stopping OL prophylaxis				
Opportunistic	**Primary prophylaxis indicated when CD4 is**	**Drug of choice**	**Discontinue primary prophylaxis when CD4 is**	**Discontinue secondary prophylaxis when CD4 is**
Toxoplasmoxix	<100	TMP-SMX 1 DS od	> 200	
CMV retinitis	Not indicated	Secondary : oral ganciclovir	Not applicable	> 100
Cryptococcus meningitis	Not indicated	Secondary : fluconazole	Not applicable	> 100
Oral and oesophageal candidiasis	Not indicated	Not applicable	Not applicable	Not indicated

Section A4: ART in Adults and Adolescents

Antiretroviral drugs are medications for the treatment of infection by retroviruses, primarily HIV. Different classes of antiretroviral drugs act on different stages of the HIV life cycle. These drugs act at various stages of the life cycle of HIV in the body and work by interrupting the process of viral replication. Theoretically, ARV drugs can act in any of the following ways during different stages of viral replication. These include:

(i) Block binding of HIV to target cell (*fusion inhibitors*)
(ii) Block viral RNA cleavage and one that inhibits reverse transcriptase (*reverse transcriptase inhibitors*)
(iii) Block the enzyme, integrase, which helps in the incorporation of the proviral DNA into the host cell chromosome (*integrase inhibitors*)
(iv) Block the RNA to prevent viral protein production
(v) Block the enzyme protease (*protease inhibitors*)
(vi) Inhibit the budding of virus from host cells

Table 11: Classes of drugs available

Nucleoside reverse transcriptase inhibitors (NRTI)	**Non-nucleoside reverse transcriptase inhibitors (NNRTI)**	**Protease inhibitors (PI)**
Zidovudine (AZT/ZDV)*	Nevirapine* (NVP)	Saquinavir* (SQV)
Stavudine (d4T)*	Efavirenz*(EFV)	Ritonavir* (RTV)
Lamivudine (3TC)*	Delavirdine (DLV)	Nelfinavir* (NFV)
Didanosine (ddI)*	Fusion inhibitors (FI)	Amprenavir (APV)
Zalcitabine (ddC)*	Enfuviritide (T-20)	Indinavir* (INV)
Abacavir (ABC)*	Integrase Inhibitors	Lopinavir/Ritonavir (LPV)*
Emtricitabine (FTC)	Raltegravir	Foseamprenavir (FPV)
(NtRTI)	CCR5 Entry Inhibitor	Atazanavir (ATV)*
Tenofavir (TDF)*	Maraviroc	Tipranavir (TPV)
** Available in India*		

4.1 Goals of Antiretroviral Therapy

The currently available ARV drugs cannot eradicate the HIV infection from the human body. This is because a pool of latently infected CD4 cells is established during the earliest stages of acute HIV infection and persists within the organs/cells and fluids (e.g., liver and lymphoid tissue) even with prolonged suppression of plasma viraemia to <50 copies/ml by antiretroviral therapy. The goals of therapy are as follows.

Table 12: Goals of ARV therapy
• Clinical goals : Prolongation of life and improvement in quality of life
• Virological goals : Greatest possible reduction in viral load for as long as possible
• Immunological goals : Immune reconstitution that is both quantitative and qualitative
• Therapeutic goals : Rational sequencing of drugs in a fashion that achieves clinical, virological and immunological goals while maintaining treatment options, limiting drug toxicity and facilitating adherence
• Reduction of HIV transmission in individuals : Reduction of HIV transmission by suppression of viral load

In general, the clinical management of an HIV patient revolves around optimizing the treatment regimen, reducing drug toxicity, reducing the pill burden and increasing adherence to the treatment.

4.2 When to start ART in Adults and Adolescents

4.2.1. All persons registered for care and treatment at ART centres should have their full history taken and undergo clinical examination, including determining the clinical stage of HIV (see Table 1). The initiation of ART is based on the clinical stage and the CD4 count is used to guide treatment and follow-up. The lack of a CD4 result should not delay the initiation of ART if the patient is clinically eligible according to the WHO clinical staging, but a CD4 test should be done as soon as possible.

4.2.2 All HIV-positive persons are eligible for CD4 testing for the purpose of screening for ART eligibility, under the national programme.

Table 13: Initiation of ART based on CD4 count and WHO clinical staging

WHO Clinical Stage	Recommendations
HIV infected Adults & Adolescents (Including pregnant women)	
Clinical Stage I and II	Start ART if CD4 < 350 cells/mm3
Clinical Stage III and IV	Start ART irrespective of CD4 count
For HIV and TB co-infected patients	
Patients with HIV and TB co-infection (Pulmonary/ Extra-Pulmonary)	Start ART irrespective of CD4 count and type of tuberculosis (Start ATT first, initiate ART as early as possible between 2 weeks to 2 months when TB treatment is tolerated)
For HIV and Hepatitis B and C co-infected patients	
HIV and HBV / HCV co-infection – without any evidence of chronic active Hepatitis	Start ART if CD4 < 350 cells/mm3
HIV and HBV / HCV co-infection – With documented evidence of chronic active Hepatitis	Start ART irrespective of CD4 count

Starting ART by using CD4 guidance: The optimum time to start ART is before the patient becomes unwell or presents with the first OI. **The patients should be started on ART as soon as possible when CD4 falls below 350**

The CD4 count should be assessed after stabilization of any concurrent illness because the absolute CD4 count can vary with illness. The CD4 count should be used as a *supplement to clinical assessment* for determining the stage of the disease in matters of decision-making. **All HIV-confirmed persons should be referred to ART centres for registration into care and screening for medical eligibility for ART by CD 4 test and other baseline investigation.**

Do NOT delay ART initiation if the patient is clinically eligible according to the WHO Clinical Staging criteria, in absence of a CD4 count

4.2.3 Ensuring good adherence to the treatment is imperative for the success of the national programme as well as for the prevention of drug resistance. To achieve this, counselling must start from the first contact visit by the clinical team and should include preparing the patient for treatment and providing psychosocial support through an identified guardian/treatment buddy and through support networks. All patients should undergo **at least two counselling sessions** before the initiation of ART. The period of investigations should be utilized for counselling and treatment preparation. All efforts should be made to trace patients who have defaulted or are lost to follow-up. NGO and positive network linkages should be established by each ART centre for the respective locality.

4.3 Manage OIs before Starting ART

4.3.1 Commencing ART in the presence of active OIs

Do not start ART in the presence of an active OI. In general, OIs should be treated or stabilized before commencing ART. *Mycobacterium Avium Complex* (MAC) and progressive multifocal leukoencephalopathy (PML) are exceptions, in which commencing ART may be the preferred treatment, especially when specific MAC therapy is not available. For details on starting ART in patients with HIV-TB co-infection, see the section on the management of HIV-TB. Some conditions which may regress following the commencement of ART include candidiasis and cryptosporidiosis.

The following OIs and HIV-related illnesses need treatment or stabilization before commencing ART.

Table 14: Managing OIs before starting ART

Clinical Picture	Action
Any undiagnosed active infection with fever	Diagnose and treat first; start ART when stable
TB	Treat TB first; start ART as recommended in TB section (within 2 weeks to 2 months)
PCP	Treat PCP first; start ART when PCP treatment is completed
Invasive fungal diseases: oesophageal candidiasis, cryptococcal meningitis, penicilliosis, histoplasmosis	Treat esophageal candidiasis first; start ART as soon as the patient can swallow comfortably Treat cryptococcal meningitis, penicilliosis, histoplasmosis first; start ART when patient is stabilized or OI treatment is completed
Bacterial pneumonia	Treat pneumonia first; start ART when treatment is completed
Malaria	Treat malaria first; start ART when treatment is completed

Table 14: Managing OIs before starting ART	
Drug reaction	Do not start ART during an acute reaction
Acute diarrhoea which may reduce absorption ofART	Diagnose and treat first; start ART when diarrhoea is stabilized or controlled
Non-severe anaemia (Hb < 8 g/litre)	Start ART if no other causes for anaemia are found (HIV is often the cause of anaemia); avoid AZT
Skin conditions such as PPE and seborrhoeic dermatitis, psoriasis, HIV-related exfoliative dermatitis	Start ART (ART may resolve these problems)
Suspected MAC, cryptosporidiosis and microsporidiosis	Start ART (ART may resolve these problems)
Cytomegalovirus infection	Treat if drugs available; if not, start ART
Toxoplasmosis	Treat; start ART after 6 weeks of treatment and when patient is stabilized

4.4 Antiretroviral Therapy Regimens

4.4.1 Currently, the national programme provides the following drugs/ combinations for first-line regimens

(i) Zidovudine (300 mg) + Lamivudine (150 mg)
(ii) Tenofovir (300mg) + Lamivudine (150 mg)
(iii) Zidovudine (300 mg) + Lamivudine (150 mg) + Nevirapine (200 mg)
(iv) Efavirenz (600 mg)
(v) Nevirapine (200 mg)

Fixed-dose combinations (FDCs) are preferred because they are easy to use, have distribution advantages (procurement and stock management), improve adherence to treatment and thus reduce the chances of development of drug resistance. The current national experience shows that bid (twice a day) regimens of FDCs are well tolerated and complied with.

4.4.2 Recommended choices of first-line regimens

Principles for selecting the first-line regimen

1. Choose 3TC (Lamivudine) in all regimens
2. Choose one NRTI to combine with 3TC (AZT **or** TDF)
3. Choose one NNRTI (NVP **or** EFV)

Table 15: Revised NACO ART Regimen 2012		
Regimen I	Zidovudine + Lamivudine + Nevirapine	First line Regimen for patients with Hb ≥9 gm/dl and not on concomitant ATT
Regimen I (a)	Tenofovir + Lamivudine + Nevirapine	First line Regimen for patients with Hb <9 gm/dl and not on concomitant ATT
Regimen II	Zidovudine + Lamivudine + Efavirenz	First line Regimen for patients with Hb ≥9 gm/dl and on concomitant ATT
Regimen II (a)	Tenofovir + Lamivudine + Efavirenz	First line Regimen for patients with Hb <9 gm/dl and on concomitant ATT First line for all patients with Hepatitis B and/or Hepatitis C co-infection First line Regimen for pregnant women, with no exposure to sd-NVP in the past
Regimen III	Zidovudine + Lamivudine + Atazanavir/ Ritonavir	Regimen for patients on AZT Containing first line regimen, who develop toxicity to both NVP and EFV Also Second line regimen for those who are on TDF containing first line regimen if Hb ≥ 9 gm/dl
Regimen III(a)	Zidovudine + Lamivudine + Lopinavir / Ritonavir	For patients of Regimen III who develop severe Atazanavir toxicity First line regimen for patients with HIV-2 infection with Hb ≥ 9 gm/dl
Regimen IV	Tenofovir + Lamivudine+ Atazanavir/ Ritonavir	Second line regimen for those who are on AZT/d4T containing regimen in the first line. Also for patients on TDF containing first line regimen who develop toxicity to both NVP and EFV
Regimen IV (a)	Tenofovir + Lamivudine+ Lopinavir/ Ritonavir	For patients on Regimen IV who develop severe Atazanavir toxicity First line Regimen for patient with HIV 2 infection with Hb < 9 gm/dl First line Regimen for all women exposed to sd-NVP in the past
Regimen V	Stavudine+ Lamivudine+ Atazanavir/ Ritonavir	Second line for those who are on TDF containing regimen in the first line if Hb < 9 gm/dl
Regimen V(a)	Stavudine+ Lamivudine+ Lopinavir/ Ritonavir	For patients on Regimen V who develop severe Atazanavir toxicity

Table 16: Choice of NRTIs		
NRTI	**Advantages**	**Disadvantages**
3TC	Good safety profile, non-teratogenic Once daily Effective against hepatitis B Widely available, including In FDCs	Low genetic barrier to resistance
FTC**	An alternative to 3TC Good safety profile Same efficacy as 3TC against HIV and hepatitis B and the same resistance profile	No added advantage over 3TC except as daily dose Can be used as once-a-day dose in combination with TDF and EFV.(i.e. reduced pill burden and dosing schedule)
TDF*	Good efficacy, safety profile Once daily regimens Metabolic complications, such as lactic acidosis and lipoatrophy, are less common than with d4T	Renal dysfunction has been reported Safety in pregnancy not established Adverse effects on foetal growth and bone density reported Limited availability at SACS on case-to-case basis
AZT	Generally well tolerated Widely available, including in FDCs Metabolic complications less common than with d4T	Initial headache and nausea Severe anaemia and neutropenia Haemoglobin monitoring recommended
ABC**	Good efficacy profile Once daily Causes the least lipodystrophy and lactic acidosis	Severe hypersensitivity reaction in 2-5% of adults
D4T	Good efficacy profile and cheap No or limited laboratory monitoring Widely available in FDCs	Most associated with lactic acidosis, lipoatrophy and peripheral neuropathy
** Shall be available on case to case basis* *** Not supplied by NACO at present*		

Note: D4T is no longer used in programme (except in exceptional circumstances) due to its long term, irreversible, and life threatening toxicities

Table 17: Starting NVP-based regimen		
lead-in NVP dose for the first 2 weeks	**Morning**	**Evening**
	FDC: AZT or TDF + 3TC (one pill) + NVP (one pill)	FDC: AZT or TDF + 3TC (one pill)
Escalate to full NVP dose after 2 weeks	FDC: AZT + 3TC + NVP (one pill) or FDC: TDF + 3TC (one pill) + NVP (one pill)	FDC: AZT + 3TC + NVP (one pill) or FDC: TDF + 3TC (one pill) + NVP (one pill)

4.4.3 The lead-in period for NVP dosing at 200 mg once daily for the first two weeks produces adequate NVP levels. Due to enzyme auto-induction, NVP levels decline over two weeks and an increase in the dosage to 200 bid is required to maintain adequate levels. Starting with the full NVP dosage without a lead-in period results in a very high serum concentration of the drug and increases the risk of hepatotoxicity and rash. If NVP is restarted after more than 14 days of treatment interruption (due to whatever reason, e.g. elevated liver enzymes), the lead-in dosing is again necessary. PIs are not recommended in first-line regimen because their use in an initial treatment regimen essentially rules out second-line regimen options.

4.4.4 Efavirenz (EFV) should be given to the following groups of persons:

- In PLHIV receiving concurrent rifampicin-containing anti-TB regimen (ATT) for the duration of the anti-TB treatment
- In cases with clinical or laboratory evidence of hepatic dysfunction, e.g. due to hepatitis B/C coinfection or other causes
- In patients with significant NVP side-effects/toxicity and in whom NVP re-challenge cannot be done.

4.4.5 Patients on an NVP regimen who have been switched over to EFV because of rifampicin-containing anti-TB treatment should be shifted back to NVP after completion of the TB treatment5 (unless other contraindications to NVP exist).

- The change from EFV to NVP should be made two weeks after completing the anti-TB treatment.
- In this particular scenario, the lead-in dose/period is not necessary while shifting from EFV to NVP (i.e. should start immediately on bid NVP dosage).
- Patients should be monitored closely for NVP toxicity (hepatotoxicity), particularly if the CD4 count is >250 cells/mm3, especially in women.

4.4.6 For women of the reproductive age group, screening for pregnancy should be carried out. Testing for pregnancy is essential if EFV is being considered for use. For women who are of the child-bearing age and have been started on EFV, counselling and support on consistent contraception use is needed.

EFV is contraindicated in pregnant HIV-infected women during the first trimester of pregnancy because of concerns of teratogenicity

See Annex 2: Drug combinations and strategies not to be used

Section A 5: Routine Monitoring of Patients on ART

5.1 Follow-up and monitoring is essential in patients initiated on ART to track clinical progress and monitor wellbeing. The routine monitoring and follow-up schedule for patients on ART under the national programme is detailed in table 18.

Table 18: Monitoring and follow-up schedule for patients on ART

Tests	Day 0 (baseline)	At 15days	At 1 month	At 2 month	At 3 month	At 6month &
Hb/CBC	✓	✓ (if on AZT)	✓ (if on AZT)	✓ (if on AZT)	✓	✓
Urea	✓					✓
LFT	✓	✓ (if on ATV)	✓ (if on ATV)		✓ (if on ATV)	✓
ALT @	✓	✓ (if on NVP)	✓ (if on NVP)			✓ *
Urinalysis	✓					✓ (if on TDF)
Creatinine	✓ (If planning for TDF)					✓ (if on TDF)
Lipid profile	✓ (if on EFV and PI)					✓ (if on d4T, EFV or PI)
Random Blood sugar	✓					✓ (if on PI)
CD4	✓					✓
Pregnancy testing	✓ (if planning for EFV)					
XrayChest & Mx	✓					
CD 4 % or counts ^	✓					✓
Plasma Viral Load#	Not recommended under national programme					

- The estimation of the CD4 count for patients receiving ART is recommended at six months to document immunological improvement.
- After the initiation of an NVP-based regimen, ALT measurement is recommended in the first month to detect drug-induced hepatitis.
- With an AZT- based regimen, it is important to monitor CBC for the early detection of haematological toxicity
- The prevalence of lipid abnormalities is significantly frequent in patients on ART, particularly if they are on d4T, EFV or PIs. In the case of such patients and those with significant risk factors for coronary artery disease, a fasting lipid profile should be done at six months. Otherwise, yearly estimations suffice.
- Random blood sugar is recommended as part of the baseline screening of all patients to be started on ART, as currently one of the major causes of morbidity in India is diabetes.
- (See also table 4)

Scheduled follow-up is necessary during the initial months of ART to diagnose and manage acute adverse events efficiently, work with the patient on adherence issues, and diagnose clinical conditions like IRS and new episodes of OIs.

Section A 6: ART in Pregnant Women, PPTCT and Previous Exposure to NVP

Parent-to-child transmission of HIV is a major route of new HIV infections in children. Children born to women living with HIV acquire HIV infection from their mother, either during pregnancy, labour/delivery or through breastfeeding which is largely preventable with appropriate intervention, by providing Anti-retroviral (ARV) prophylaxis or Anti-retroviral therapy (ART) depending on her immunological status and CD4 count.

There has been a significant scale-up of HIV counseling & testing, PPTCT and ART services across the country over the last five years. The number of pregnant women tested annually under the Prevention of Parent-to-Child Transmission (PPTCT) programme, increased from 0.8 million to 8.5 million between 2004 and 2012 and the reach of the services has extended to the rural areas to a large extent. Concurrently, there has also been a significant decentralization and scale-up of the ART services, with 5,16,412 persons including 29,000 children receiving free ART across the country through 408 ART centers and 809 Link-ART centers (LAC) as on Dec 2012. Early initiation of ART, is associated with improved survival and reduced HIV-related morbidity. In pregnant women, early initiation of ART, will not only benefit her health, but will also have a significant reduction of HIV transmission from mother-to-child.

PPTCT Services:

In line with WHO standards for a comprehensive strategy, the National PPTCT programme recognizes the 4 elements integral to preventing HIV transmission among women and children. These include:

Prong 1: Primary prevention of HIV, especially among women of childbearing age
Prong 2: Prevention of unintended pregnancies among women living with HIV
Prong 3: Prevention of HIV transmission from pregnant women infected with HIV to their child
Prong 4: Provide care, support and treatment to women living with HIV, her children and family.

The National PPTCT programme adopts a public health approach to provide these services to pregnant women and their children. Currently, the major activities focused under PPTCT services have been Prong- 3 and 4. However, Prongs 1 & 2 too are also emphasized, to achieve the overall results of the PPTCT Programme.

The major goals of PPTCT programme are:

- Primary prevention of HIV, especially among adolescents and women in the child-bearing age.
- Integration of PPTCT interventions with general health services such as basic antenatal care (ANC), sexual reproductive health and family planning, EID and Paediatric ART, Adolescent Reproductive and Sexual Health (ARSH), ART, TB and STI/RTI services.
- Strengthening postnatal care of the HIV-infected mother and her exposed infant.
- Provide the essential package of PPTCT continuum of care services.

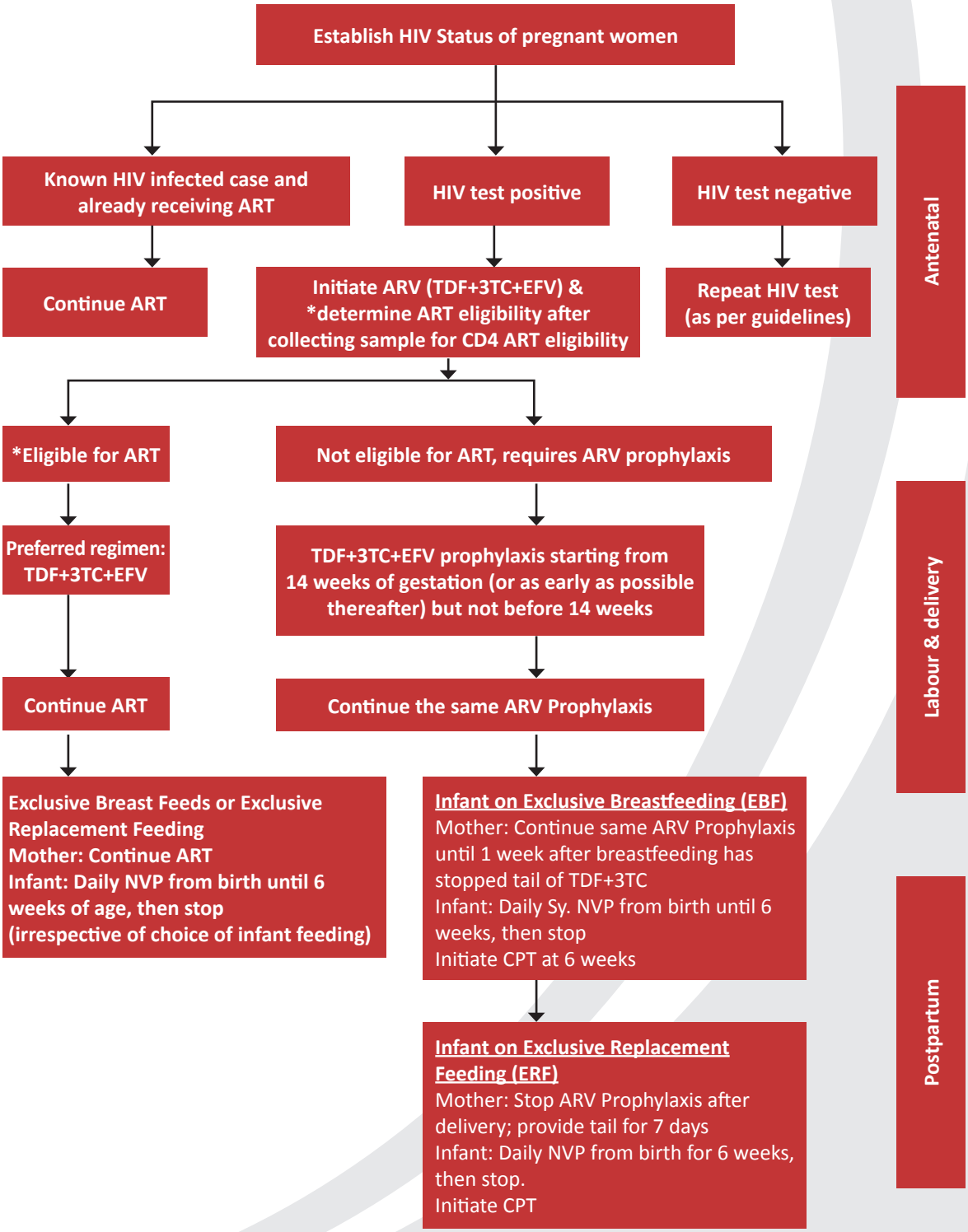
Currently, single dose Nevirapine (Sd NVP) is being given as prophylaxis to ANCs at the onset of labour pains/delivery and Syp NVP to the baby soon after birth. This significantly reduces peri-partum HIV transmission, may be 10%. However, it does not reduce risk of HIV transmission during the ante-natal or breast-feeding periods. To bring down the transmission levels further to less than 5% it is essential that ARV Prophylaxis is started as early as 14 weeks of gestation and continued during the entire breast-feeding period of at-least 12 months.

Therefore, the National PPTCT Programme has launched the New PPTCT Guidelines in August2012, and is moving from the single-drug prophylaxis to multi-drug prophylaxis (Option B of WHO guidelines) in a phased manner. As part of the roll -out of the programme, it was decided to scale- up the programme in Karnataka and Andhra Pradesh initially. The recommended regimen for the HIV infected pregnant woman is TDF+3TC+EFV (FDC, single pill, once daily). Under these new guidelines, the baby is also given Syp. Nevirapine for 6 weeks birth. These recommendations are in accordance with the WHO 2010 guidelines and have the potential to reduce the risk of mother- to -child transmission to 5% or less. The Nation-wide implementation of these guidelines will also help in achieving the Millennium Development Goal (MDG 5) of elimination of new HIV infections among children. This has been launched in three states and a national strategic plan has been made to cover all states by March 2014

Technical guidelines and options for the more efficacious PPTCT regimen

*To "Determine ART eligibility"—the treatment will be the same irrespective of CD4 count or clinical stage at baseline. CD4 count is necessary to guide duration (life-long (ART) or during breastfeeding) of ARVs.

Technical guidelines and options for the more efficacious PPTCT regimen



Section A7: Considerations for Co-infection of Tuberculosis and HIV

HIV-TB co-infection is one of the most challenging issues in the effort to scale up ART since more than 60% of PLHIV develop TB. Patients with TB merit special consideration because the co-management of HIV and TB is complicated by drug interactions between rifampicin and NNRTIs and PIs; IRIS; pill burden; adherence; and drug toxicity. Active TB is the commonest OI among HIV-infected individuals and is also the leading cause of death in PLHIV.

The management of patients with HIV and TB poses many challenges, including patient acceptance of both diagnoses. HIV-infected persons with TB often require ART and WHO recommends that ART be given to: all HIV TB co infected (pulmonary/Extra pulmonary) regardless to the CD4 count.

ART reduces the incidence and recurrence of TB, as well as the fatality rates. Co-trimoxazole prophylaxis should be given to HIV-TB patients as per the guidelines.

When to start first-line ART in patients with active TB:

If a patient with active TB is diagnosed with HIV and requires ART, the first priority is to start TB treatment in accordance with the RNTCP guidelines. ART may need to be started later; keeping in mind the pill burden, time needed for acceptance of the diagnosis, counselling needs, drug interactions, toxicity and IRIS (see Table 20)

Table 20: Initiation of first-line ART in relation to anti-TB therapy (Based on 2011 WHO guidelines)

CD4 cell count (cells/mm3)	Timing of ART in relation to initiation of TB treatment	ART recommendations
CD4 count of any value	Start ATT first Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months)	Recommend ART EFV-containing regimens
Rationale for ART recommendation during TB treatment (References 6,7,8,9,10,11) : In the absence of ART, TB therapy alone does not significantly increase the CD4 cell count. Nor does it significantly decrease the HIV viral load. Thus, CD4 counts measured during active TB are likely to reflect the actual level of immunosuppression The use of HAART in patients with TB can lead to a sustained reduction in the HIV viral load. It can also facilitate immunological reconstitution, and decrease AIDS-defining illness and mortality. This benefit is seen across different ranges of CD4 counts		

7.1 The use of the standard 600 mg/day dose of EFV is recommended for patients receiving EFV and Rifampicin.

7.2 IRIS may occur in up to one-third of patients who have been diagnosed with TB and who have started ART. It typically presents within three months of the initiation of ART but can occur as early as five days. Patients with TB-associated IRIS most commonly present with fever and worsening of pre-existing lymphadenopathy or respiratory disease. The symptoms are similar to the paradoxical reactions seen in immuno-competent patients on ATT, but occur more frequently. Most cases resolve without any intervention and ART can be safely continued. Serious reactions, such as tracheal compression caused by massive adenopathy or respiratory difficulty, may occur. Therapy may require the use of corticosteroids

7.3 There are two issues to be considered if TB is diagnosed in patients already receiving ART.

The first is modification of ART (see Table 21).

Table 21: ART recommendations for patients who develop TB within six months of starting a first-line or second-line ART regimen

First-line or second-line ART regimen	ART regimen at the time TB occurs	Management options
First-line ART	(AZT or TDF) + 3TC + EFV	Continue with two NRTIs + EFV
	(AZT or TDF)+ 3TC + NVP	Substitute NVP with EFV(i),(ii)
Second-line ART	Two NRTIs + PI	Substitute Rifampicin with Rifabutin in the ATT

Notes:
i) Shifting back to the original regimens once the rifampicin-containing regimen is completed is recommended. When substituting back from EFV to NVP, no lead-in dose is required.
ii) EFV should not be used in the first trimester of pregnancy. In women of child-bearing age, the use of contraceptives should be ascertained.

The second issue is whether when a patient on ART presents with active TB, it can be said to constitute ART failure.
WHO recommends the following guiding principles in this context:

- **If an episode of TB occurs within the first six months of the initiation of ART**, it should not be considered as failure of the treatment, and the ART regimen should be adjusted for co-administration with rifamipicin-containing regimens.
- **If an episode of TB develops more than six months after the initiation of ART**, and data on the CD4 count (and viral load), is available, the decision on whether the diagnosis of TB represents ART failure should be based on the CD4 count (and viral load, if available) data. The development of an episode of PTB after six months of ART, without other clinical and immunological evidence of disease progression, should NOT be regarded as representing ART failure. Extrapulmonary TB should be considered as indicative of ART failure, although simple lymph node TB or uncomplicated pleural disease may be less significant than disseminated TB. If the response to TB therapy is good, the decision on switching to a second-line regimen can be delayed until ATT has been completed. Close monitoring is needed and adherence support should be reinforced.

7.4 Second-line ART in Patients with TB

Tuberculosis is the most commonly detected serious opportunistic infection among PLHIV in India. While tuberculosis has to be treated appropriately and on priority, in the context of second-line ART drug-drug interactions must be considered. Rifampicin alters the metabolism of Protease Inhibitors, including Lopinavir, Atazanavir and Ritonavir, and reduces effectiveness of standard doses. However, rifamycin-class drugs are highly efficacious in treatment of tuberculosis.

7.5 Another rifamycin, **rifabutin**, can be administered in the presence of PI-containing second line ART regimen without compromising the efficacy of ART or Anti TB treatment. Therefore NACP and RNTCP have recommended the substitution of rifabutin for rifampicin for the duration of TB treatment. In the presence of the boosting drug like Ritonavir (PI), rifabutin metabolism is altered, and less rifabutin is needed than would be without ritonavir. Therefore, the dosage of rifabutin during the administration of Second line regimen containing LPV/r shall be 150 mg thrice weekly for all patients, weighing >30 kg weight. The remainder of the TB treatment regimens, including dosing and duration, remain unchanged as per RNTCP guidelines

TB-HIV coordination is an integral component of HIV management. The coordination linkages encompass referral of TB suspects from counselling and testing centres to RNTCP, referral from RNTCP to ICTC for HIV testing, and referral and cross-referral of patients to/from ART centres to/from RNTCP for ATT and for HIV care and treatment.

See Annex- 5: Common drug interactions with ARVs

Section A 8: What to Expect in the First Six Months of Therapy

The first six months of ART are critical. Although clinical and immunological improvement is expected, it is not always apparent and the drugs may have side-effects. Some patients may not respond as expected or may even deteriorate clinically at first. Complications are the most common in the first few weeks after the initiation of ART in patients with severe immunodeficiency. It takes time for HIV viral replication to be controlled by ART and for the immune system to be strengthened. It also takes time for the reversal of the catabolism associated with HIV infection, particularly in patients with HIV-associated wasting. As a patient with advanced disease recovers immune function, there may be exacerbation of previously sub-clinical co- existing infection (e.g. TB), resulting in an apparent worsening of the disease. This is NOT due to failure of the therapy, but to the success of ART and the resulting immune reconstitution. It is important to allow for sufficient time on therapy before judging the effectiveness of ART and considering the possibility of IRIS in patients with worsening disease in the first few months of ART.

8.1 **CD4 recovery:** In most patients, the CD4 cell count rises with the initiation of ART and immune recovery. However, this may be blunted if the baseline CD4 count is low. In general, the lower the baseline CD4 count is at the start of ART, the longer it will take for the count to increase with time. In some patients, the count may never exceed 200 cells/mm3 even with clinical improvement. In those who have achieved a substantial peak response, a subsequent progressive decline in the CD4 count in the absence of intercurrent illness indicates an immunological failure (determined by the trend of regular six-monthly CD4 counts).

8.2 **Early ARV toxicity:** First-line drug toxicities fall into two categories. Early toxicity usually presents in the first few weeks to months of ART. Early and potentially severe toxicities such as hypersensitivity to NNRTIs (EFV and NVP) normally occurs within the first few weeks of therapy and AZT-related anaemia and neutropenia typically presents in the first few months of therapy (See section 9.0).

8.3 **Mortality on ART:** While ART significantly decreases mortality; the risk of death is higher in the first six months than during the subsequent period on therapy, particularly when patients start ART with clinical stage 4 events, severe immunosuppression and very low CD4 counts.

8.4 Immune reconstitution inflammatory syndrome: This is a spectrum of clinical signs and symptoms resulting from the body's ability to mount an inflammatory response associated with immune recovery. Antiretroviral therapy partially restores immune defects caused by chronic HIV infection, including the restoration of protective pathogen-specific immune responses. The protective response sometimes causes (atypical) inflammatory manifestations to concurrent infective or non-infective conditions, e.g. TB, MAC or CMV. Clinically, IRIS manifests itself as the occurrence or worsening of clinical and/or laboratory parameters, despite a favourable CD4 count (and viral load). The temporal association between the commencement of HAART (or change from a previously failing regimen) and the development of an unusual clinical phenomenon often provides a strong clue to the diagnosis of IRIS.

Experience has shown IRIS can manifest itself in a variety of ways. **In India, the agreed practical definition of IRIS would be the "occurrence or manifestations of new OIs or existing OIs within six weeks to six months after initiating ART; with an increase in CD4 count".**

8.4.1 The following points help in the diagnosis of IRIS:

- Temporal association between the initiation of ART and the development of clinical phenomena (mostly within 3 months).
    1. Typically, IRIS occurs within 2–12 weeks of the initiation of ART, although it may present later (usually between 6 weeks to 6 months)
    2. The incidence of IRIS is estimated to be 10% among all patients in whom ART has been initiated; and up to 25% among those who have started ART and who have a CD4 cell count of below 50 cells/mm3
- Unusual clinical manifestations in patients responding to ART include:
    1. Unexpected localized disease, e.g. lymph nodes (appearance or enlargement and/or suppuration), or involving liver or spleen
    2. Exaggerated inflammatory reaction, e.g. severe fever, with exclusion of other causes
    3. Painful lesions
    4. Atypical inflammatory response in affected tissues, e.g. granulomas, suppuration, necrosis
    5. Perivascular lymphocytic inflammatory cell infiltrate
    6. Progression of organ dysfunction or enlargement of pre¬-existing lesions
    7. Development or enlargement of cerebral space-occupying lesions after treatment for cerebral cryptococcosis or toxoplasmosis
    8. Progressive pneumonitis or the development of organizing pneumonia after treatment forpulmonary MTB or PCP
    9. Onset or worsening of uveitis/vitritis after the resolution of CMV retinitis
    10. Fever and cytopenia after treatment for disseminated MAC

8.4.2 The identified risk factors for infectious IRIS are

- An active or sub-clinical infection by opportunistic pathogens
- The antigens of non-viable microorganisms (e.g. Cryptococus and CMV) are all possible targets for an immunopathological response
- A CD4 count of below 50/mm3 prior to the initiation of HAART
- Being ART naïve
- Starting ART in close proximity to the diagnosis and initiation of treatment for an OI (should first treat and stabilize the OI, then start ART)

Non-infectious IRIS includes Guillain-Barre Syndrome, autoimmune thyroiditis and sarcoidosis. The differential diagnosis for IRIS includes active OI, ARV drug failure, ARV drug toxicity or failure of antimicrobial therapy if the patient is already on the treatment. Culturing the microorganism in body fluids may provide clues to an active OI, which would warrant antimicrobial therapy.

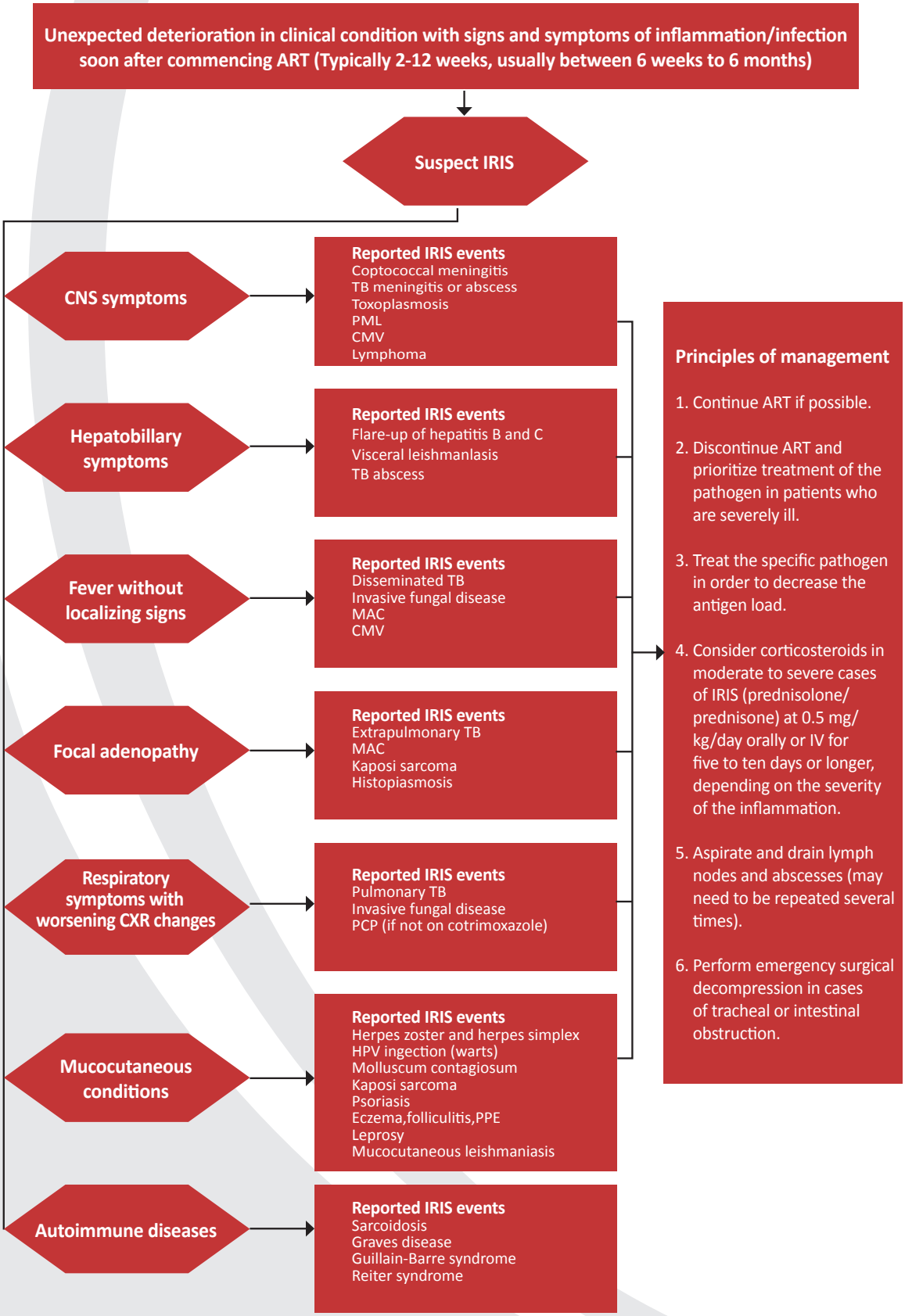
8.4.3 Treatment of IRIS

Treatment of IRIS should be referred to a tertiary setting/experienced HIV physician for management.

There are no standard guidelines for the treatment of IRIS. There is very limited information on the effectiveness of various interventions for managing it and little evidence from randomized clinical trials. Most cases resolve without any additional treatment. Milder forms of IRIS resolve with continuing anti-infective therapy and HAART. In the majority of cases, HAART can be safely continued and need not be interrupted. In general, most clinicians prefer to continue ART if the CD4 count is below 100/mm3 or if the patient presents with IRIS months after the initiation of HAART. However, the discontinuation of ART should be considered if the inflammatory responses are considered life-threatening (e.g. intracranial IRIS leading to encephalitis, cerebritis, perilesional cerebral oedema and pulmonary IRIS with ARDS/acute respiratory distress syndrome), or are unresponsive to steroids. Discontinuation of the treatment should also be considered if the pathogens involved are not amenable to specific antimicrobials (e.g. Parvovirus B19, polyomavirus JC casuing PML/progressive multifocal leukoencephalopathy), or if ART toxicity is the main differential diagnosis (e.g. hepatitis).

Non-steroidal anti-inflammatory drugs (NSAIDs) are helpful in controlling inflammation and fever associated with IRIS. However, in severe IRIS, a short course of oral prednisolone is required to alleviate the symptoms. The dosage and duration of treatment required is variable and should be judged clinically. Severe disease requires at least 1–2 mg of prednisolone per kg body weight. Thalidomide has also been tried effectively in some patients.

Suspect and diagnose IRIS



Section A 9: Antiretroviral Drug Toxicity

9.1 ARV drugs are associated with a broad range of toxicity, ranging from low-grade intolerance, which may be self-limiting, to life-threatening side-effects. Differentiating between complications of HIV disease and ART toxicity is sometimes difficult. Alternative explanations should be considered before it is concluded that the symptoms are related to ART toxicity. The factors to be considered include intercurrent illness (e.g. hepatitis A and malaria) and reactions to medications other than ARV drugs (e.g. Isoniazid-induced hepatitis or cotrimoxazole-induced rash). Most of the toxicity/side-effects can be adequately co-managed with efficient clinical monitoring at all levels of the health care system.

9.2 As a general principle, mild toxicities do not require the discontinuation of ART or drug substitution. Symptomatic treatment may be given. Moderate or severe toxicities may require substitution of the drug with another, of the same ARV class, but with a different toxicity profile. Severe life-threatening toxicity requires discontinuation of all ARV drugs until the patient is stabilized and the toxicity is resolved.

9.3 Regardless of Regardless of severity, toxicities may affect adherence to therapy. A proactive approach is required to manage toxicity.

- Discuss potential side-effects of the ART regimen with the patient before initiation and during the early stages of treatment.
- Offer support during minor and major adverse events.
- Ensure that the patient is familiar with the signs and symptoms of toxicities that are serious and require immediate contact with the clinical team, especially in the case of NVP-associated Stevens–Johnson syndrome, hepatitis, lactic acidosis or ABC-associated hypersensitivity reaction.

The side-effects of ARVs need to be differentiated from manifestations of a new OI and IRIS. The management of ART toxicities is based on clinical and laboratory monitoring.

9.4 What Toxicities to Expect after Commencing First-line ART

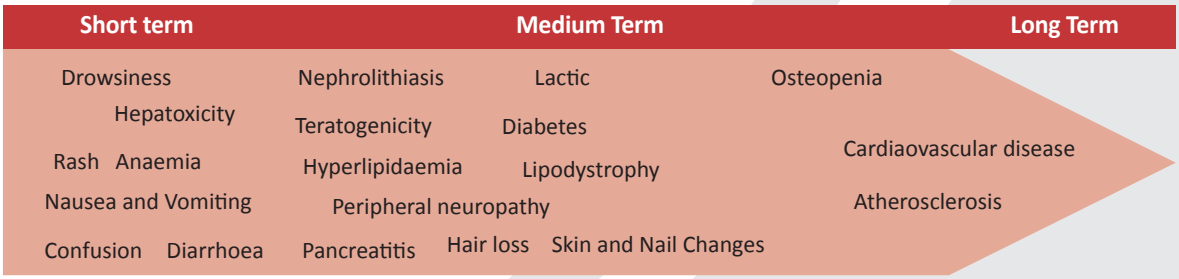


Table 22: Side-effects and common causes		
Time	**Side-effects and toxicities**	**Common causes**
Short term (the first few weeks)	Gastrointestinal toxicities, including nausea, vomiting, diarrhea, Anaemia and neutropenia	AZT, TDF, PIs
	Rash (Most rashes occur within the first 2-3 weeks.)	NVP, EFV, Abacavir PIs (rarely)
	Hepatotoxicity (More common in hepatitis B or C co-infection)	NVP, EFV, PIs
	Drowsiness, dizziness, confusion and vivid dreams (Normally self-resolving but can take weeks to months)	EFV
Medium term (the first few months)	Anaemia and neutropenia Sudden and acute bone marrow suppression can occur within the first weeks of therapy or present as a slow onset of progressive anaemia over months	AZT
	Hyperpigmentation of skin, nails and mucous membranes	AZT
	Lactic acidosis (More common after the first few months, most commonly associated with d4T)	d4T, ddI, AZT
	Peripheral neuropathy (More common after the first few months)	d4T, ddI
	Pancreatitis (Can occur at any time)	ddI
Long term (after 6–18 months)	Lipodystrophy and lipoatrophy	d4T, ddI, AZT, PIs
	Dyslipidaemia	d4T, EFV, PIs
	Diabetes	IDV
	Skin hair and nail abnormalities PIs,	especially IDV
	Renal Tubular Dysfunction	TDF
	Bone Mineral Toxicity	TDF
(See Annex 4: Clinical signs and symptoms and management of adverse effects of antiretroviral drugs)		

ARV	Most frequent significant toxicity For the ARV drug	Suggested first line ARV drug substitution
AZT	Severe anemia(b) or neutropenia(c)	**d4T or ABC**
	Lactic acidosis	**ABC**
	Severe gastrointestinal intolerance(d)	**d4T or ABC**
TDF	Renal tubular Dysfunction(l) (Fanconi's syndrome)	**AZT/ABC**
	Bone Mineral Density loss(m)	
EFV	Persistent and severe central nervous system toxicity(g)	**NVP**
	Potential teratogenicity (adolescent girl in 1st trimester pregnancy or of childbearing potential not receiving adequate contraception)	
NVP	Acute symptomatic hepatitis(h)	**EFV(i)**
	Hypersensitivity reaction	**Preferred substitution by PI (disadvantage, premature start of 2nd line ARV drug)(k)**
	Severe or life-threatening rash (Stevens-Johnson Syndrome)(j)	
ABC	Fatal hypersensitivity reaction(n)	**AZT**
D4T	Lactic acidosis	**ABC(e)**
	Peripheral neuropathy	**AZT or ABC**
	Pancreatitis	
	Lipoatrophy/metabolic syndrome(f)	

Notes:

a) 3TC - associated pancreatitis has been described in adults, but is considered very rare in children.

b) Exclude malaria in areas of stable malaria.

c) Defined as severe haematological abnormality that can be life-threatening and that is refractory to supportive therapy.

d) Defined as severe, refractory gastrointestinal intolerance that prevents ingestion of ARV drug regimen (e.g., persistent nausea and vomiting).

e) ABC is preferred in this situation as it is the least likely of the NRTIs to cause lactic acidosis; however, where ABC is not available AZT may be used.

f) Substitution of d4T may not reverse lipoatrophy, but may prevent further lipoatrophy. In children, ABC or AZT can be considered as alternatives.

g) Defined as severe central nervous system toxicity such as persistent hallucinations or psychosis. Symptomatic NVP-associated hepatic toxicity is very rare in HIV-infected children prior to adolescence.

h) EFV is not currently recommended for children <3 years of age or < 10kg, and should not be given to post pubertal adolescent girls who are either in 1st trimester of pregnancy or are sexually active and not using adequate contraception.

i) Severe rash is defined as extensive rash with desquamation, angioedema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema, conjunctivitis; Stevens - Johnson syndrome can be life-threatening. In most cases of non life-threatening NVP-associated rash, EFV may be re-introduced with caution and monitored for adverse events. For life-threatening rash, most clinicians would not substitute EFV due to the potential for NNRTI-class specific toxicity.

j) The premature introduction of the PI class of drugs in first-line regimens leads to limitations in the choice of drugs in the event of treatment failure

k) Regular monitoring of proximal tubular dysfunction and serum creatinine in high-risk patients is required to minimize nephrotoxicity.

l) Careful monitoring of BMD (e.g., DXA at baseline and every 6–12 months) is indicated.

m) Hypersensitivity is strongly associated with presence of HLA-B*5701 allele .Any patient with a positive test for HLA-B*5701 should not receive abacavir.

9.5 Substituting within a First-line Antiretroviral Drug Regimen due to Drug Toxicity

A drug may need to be substituted to simplify the regimen so as to improve adherence, manage side-effects/toxicities and/or reduce the cost of the regimen. The commonest example of substitution for avoiding long term toxicity is substituting from d4T and AZT to ABC or TDF.

Regimen	Toxicity	Alternative Regimen	Level of Substitution
Zidovudine + Lamivudine + Nevirapine	AZT induced Anemia/ severe intolerance	Tenofovir + Lamivudine + Nevirapine	At ART Centre level
	NVP-related severe hepatotoxicity (Other than severe Grade IV)	Zidovudine + Lamivudine + Efavirenz	
Tenofovir + Lamivudine + Nevirapine	TDF related Renal Tubular Dysfunction/Bone Mineral Toxicity	Zidovudine + Lamivudine + Nevirapine	
	NVP-related severe hepatotoxicity (Other than severe Grade IV)	Tenofovir + Lamivudine + Efavirenz	
Zidovudine + Lamivudine + Efavirenz	AZT induced Anemia/ severe intolerance	Tenofovir + Lamivudine + Efavirenz	
	EFV-related persistent CNS toxicity	Zidovudine + Lamivudine + Nevirapine	
Tenofovir + Lamivudine + Efavirenz	TDF related Renal Tubular Dysfunction/Bone Mineral Toxicity	Zidovudine + Lamivudine + Efavirenz	
	EFV-related persistent CNS toxicity	Tenofovir + Lamivudine + Nevirapine	
Zidovudine + Lamivudine + Atazanavir / Ritonavir	AZT induced Anemia/ severe intolerance	Tenofovir + Lamivudine+ Atazanavir/Ritonavir	At ART plus/ CoE level
	ATV induced Hyperbilirubinemia	Zidovudine + Lamivudine + Lopinavir /Ritonavir	
Zidovudine + Lamivudine + Lopinavir / Ritonavir	AZT induced Anemia/ severe intolerance	Tenofovir + Lamivudine+ Lopinavir/Ritonavir	
	LPV induced Triglycerdemia	Zidovudine + Lamivudine + Atazanavir /Ritonavir	

Guidance on Toxicity to ARV drugs

The general principle is that single-drug substitution for toxicity should be made within the same ARV class. If a life-threatening toxicity occurs, all ART should be stopped until the toxicity has resolved and a revised regimen commenced when the patient has recovered.

Toxicity to	Substitute with
AZT	TDF
TDF	AZT, if not anaemic. d4T, if anaemic
Both TDF and AZT	d4T
NVP(except grade 4)	EFV
EFV	NVP
Both NVP & EFV	ATV/r
ATV/r	LPV/r

The suspected cases of rare Lamivudine Toxicity should be refererred to SACEP for further opinion on management.

Section A 10: ART Treatment Failure and when to switch

10.1 The clinical goals of HIV treatment are optimally accomplished through consistent high-level adherence to HAART and sustained suppression of the viral load. However, as a result of the need for lifelong therapy and HIV's prodigious replication rate and error-prone reverse transcriptase, varying amounts of drug resistance are common in individuals undergoing treatment. It is now well known that even with good adherence levels, resistance occurs. HIV drug resistance evolves naturally due to the selective pressure from drugs or from the immune system.

10.2 Drug resistance occurs when HIV replication is not fully suppressed. This is frequently linked to non-adherence to ARV therapy. Resistant viruses can spread and affect ARV therapy. The transmission of ARV-resistant strains is of increasing concern in countries where ARV is widely used. Resistance can be contained. Its occurrence can be reduced or prevented by an appropriate and careful choice of treatment, intense support to ensure adherence, monitoring for resistance and reinforcing positive prevention with condom use.

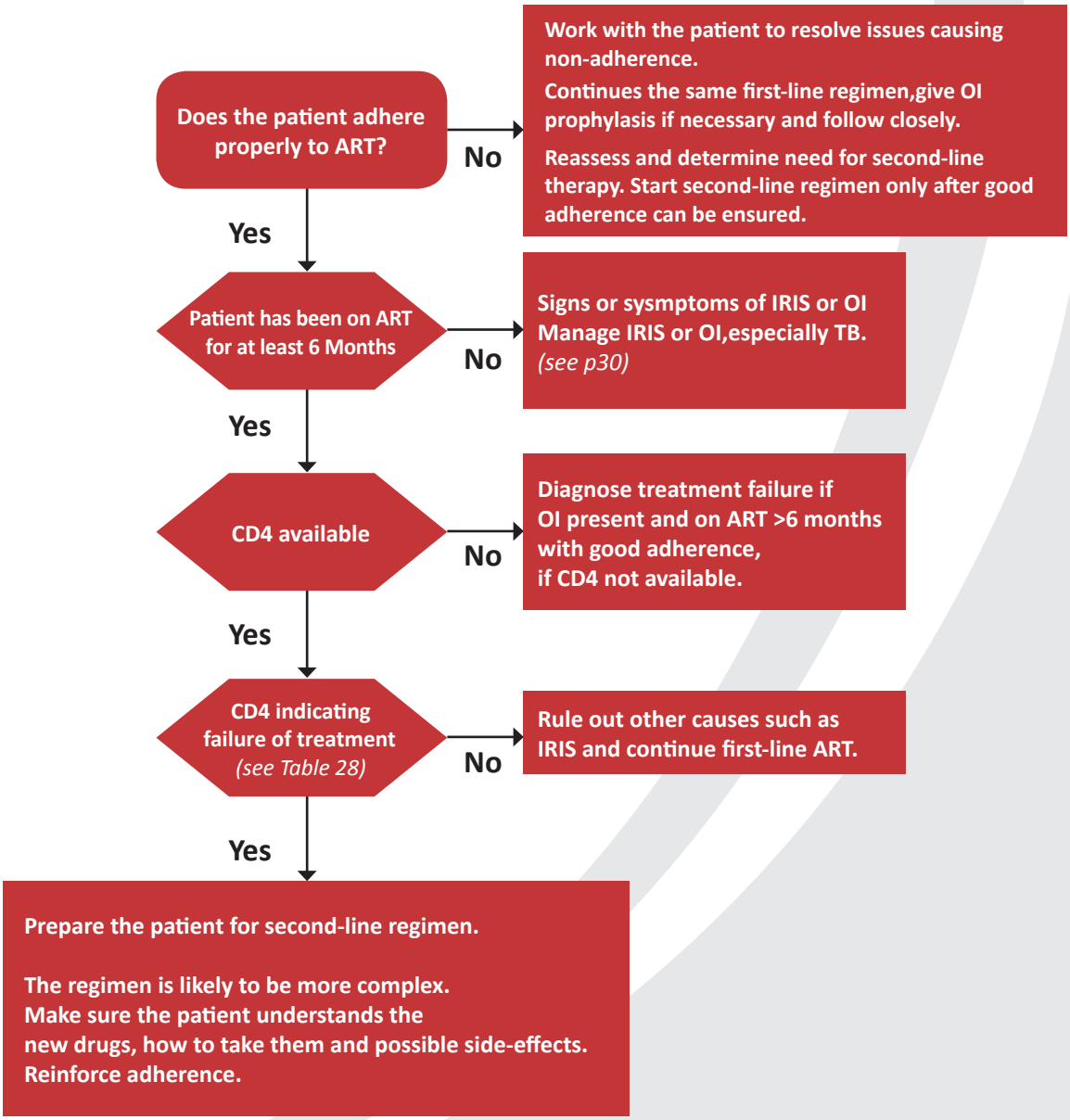
10.3 Failure to access care and discontinuation of or non-adherence to ART are the most important factors associated with the progression of HIV disease. Nationally, there is a need to define drug resistance qualitatively and quantitatively through surveillance and monitoring conducted in accordance with international standards. Such studies have already been initiated by NACO and WHO. The outcome of these studies will be used to guide programmatic and treatment options.

Prevention of the emergence of HIV drug resistance (HIV DR) is accorded a high priority and is a crucial component of the National ART Programme

10.4 Identifying Treatment Failure

The decision on when to switch from first-line to second-line therapy is critical. If the decision is made too early, the months or years of any potential survival benefit from an effective first-line therapy may be lost. If the decision is made too late, the effectiveness of second-line therapy may be compromised and the patient may be put at an additional risk of death. The time of switching drugs is dictated by the failure of treatment, which can be measured in three ways: clinically, immunologically and virologically. However, the definitions of these criteria represent different biological endpoints. It is not clear which criterion is optimal, individually or together with others. There is a need for consensus and standardization on the different ways of identifying failure. (WHO,2006). In ALL cases, adherence counselling and clinical judgment must form a part of the decision-making.

10.4.1 Determining ART failure



Notes:

- Switching to second-line regimen is not an emergency. Review the patient's OI prophylaxis management. Patients on a failing regimen with WHO stage 2, 3, 4 disease or with a CD4 count <250 cells/mm3 need to restart cotrimoxazole.
- While a failing regimen may retain some anti-HIV activity; the longer the patient remains on a failing regimen, the more resistance mutations accumulate, reducing the chances of success of the second-line regimen. The decision to switch drugs is based on clinical, immunological or virological definitions of failure (presented below) and the availability of second-line ARV drugs.

10.4.2 As mentioned earlier, antiretroviral treatment failure can be defined virologically, immunologically or clinically, and in most instances, one type of failure follows the other. There is a delay between virological and immunological failure, which increases the risk of exposing the HIV virus to a failing regime, leading to the development of further cross-resistance and compromising the efficacy of the second-line regimen.

10.4.3 The progression of clinical disease should be differentiated from IRIS, which is characterized by the appearance of signs and symptoms of an OI a few weeks after the initiation of HAART in the setting of advanced immunodeficiency. These symptoms are an inflammatory response to previously subclinical OI. It is also possible to have atypical presentations of some OIs.

10.4.4 The failure of treatment cannot be diagnosed on the basis of clinical criteria in the first six months of ART. Clinical events that occur before the first six months of therapy often represent IRIS and not failure.

10.5 The following definitions of Art failure are used:

Table 25: Clinical, immunological and virological definitions of treatment failure for first-line regimen (WHO, 2010)

Clinical failure	New or recurrent WHO stage 4 condition, after at least 6 months of ART
Immunological failure	• Fall of CD4 count to pre-therapy • 50% fall from the on-treatment peak value • Persistent CD4 levels below 100 cells/mm
Virological Failure	Plasma viral load >5,000 copies/ml after at least 6 months of ART

Notes:

i) Current event must be differentiated from IRIS.

ii) Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections) may indicate treatment failure and thus requires second-line therapy to be considered.

iii) Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not indicate treatment failure and thus second-line therapy need not be considered.

iv) Without any concomitant infection causing transient CD4 cell count decrease.

v) Some experts consider persistent CD4 cell counts of below 50/mm3 after 12 months of ART to be more appropriate.

vi) The optimal viral load value at which ARV drugs should be switched has not been defined. However, values of more than 5,000 copies/mL have been associated with subsequent clinical progression and an appreciable decline in the CD4 cell count.

10.5.1 Clinical failure:

There should be a reasonable trial of first-line therapy, lasting at least 6–12 months, before concluding that the ARV regimen is failing on the basis of clinical criteria. Adherence should be assessed and optimized, intercurrent OI treated and resolved, and IRIS excluded before drawing such a conclusion.

The development of a new or recurrent WHO stage 3 or 4 condition while on treatment (after the first six months) is considered functional evidence of the progression of HIV disease. This is referred to as T staging, where T refers to the staging event on treatment. The assumption is that with immune restoration on ART and the subsequent progressive immunodeficiency with a failing ART regimen, the clinical events signaling immune failure will be the same as those marking advanced and then severe immunodeficiency without ART eg. WHO Clinical stage 3 and 4. Table 26 indicates how clinical staging on ART can be used as an indicator of failure and may facilitate the decision on whether to switch therapy.

Table 26: Clinical and CD4 cell count definitions of treatment failure in adults and adolescents

Clinical signs of treatment failure	CD4 cell criteria for treatment failure
• Occurrence of new OIs or malignancy signifying clinical disease progression. This must be differentiated from IRIS, which can occur in the first 3 months of ART[i] • IRIS does not signify treatment failure and the OI should be treated as usual, without changes in the ART regimen • Recurrence of previous OI[ii] • Onset or recurrence or WHO stage 3 conditions (including but not restricted to HIV wasting, chronic diarrhoea of unknown aetiology, prolonged fever of unknown aetiology, recurrent invasive bacterial infections, or recurrent / persistent mucosal candidiasis)	• Return of CD4 count to pre-therapy baseline or below, without other concomitant infection to explain transient CD4 count decrease iii • > 50% (2006 WHO guidelines) fall from on-treatment CD4 peak level without other concomitant infection to explain transient CD4 count decrease[iii]

Notes :

i. IRIS is characterized by the appearance of signs and symptoms of OIs a few weeks after the start of HARRT in the setting of advanced immunodeficiency, as an inflammatory response to previously subclinical OI. This immunological reconstitution may also lead to the development of atypical presentations of some OIs

ii. The recurrence of TB may not represent HIV disease progression as re-infection can occur. Clinical evaluation is necessary.

iii. If the patient is asymptomatic and treatment failure being defined by the CD4 count alone, consider taking a confirmatory CD4 count, if resources permit.

TB can occur at any CD4 level and does not necessarily indicate ART failure. The response to TB therapy should be used to evaluate the need to switch ARV drugs. In the case of pulmonary TB and some types of extrapulmonary TB (e.g. simple lymph node TB or uncomplicated pleural disease), the response to TB therapy is often good and the decision to switch ARV drugs can be postponed and monitoring can be stepped up. This also applies if severe and/or recurrent bacterial infections (as stage 3 or 4 events) or oesophageal candidiasis respond well to therapy.

10.5.2 Immunological failure:

The working definitions of immunological failure are:

- A return to, or fall below, the pre-therapy CD4 baseline after at least 6 months of therapy
- A 50% decline from the on-treatment peak CD4 value (if known)
- A persistent CD4 count of less than 100 cells/mm3 after 6–12 months of therapy

The CD4 cell count is the strongest predictor of HIV-related complications, even after the initiation of therapy. The baseline pre-treatment value is informative: lower CD4 counts are associated with smaller and slower improvements in the count over time. CD4 cell counts can also be used to determine when not to change therapy. For example, in a patient with a new clinical stage 3 event, switching is not be recommended if the CD4 cell count is greater than 200 cells/mm3.
Even though the declining CD4 count helps in suspecting the treatment Failure, the Virological failure should complement the decision-making on switching over to second line ART.

10.5.3 Virological failure:

This is an incomplete suppression of the virus and is defined as a PVL value of more than 5,000 copies/mL at six months after the initiation of ART. Viral rebound after being undetectable is also considered as virological failure. A low-level viral rebound (<500–1000 copies/mL), termed blips, usually indicates a statistical variation in the determination of PVL and not the need to alter therapy. The viral load remains the most sensitive indicator of ART failure. Recognizing early failure facilitates the decision to switch drugs before multiple resistance mutations develop to drugs of the first-line regimen.

In general, the clinical status, CD4 cell count and PVL (if available) can be used in an integrated fashion to determine whether HIV disease is progressing while a patient is on ART; and whether a change should be made from first-line to second-line therapy. Although the national programme does not have provision for second-line drugs at present, guidance is essential, considering that patients may seek advice from the private sector or buy drugs out-of-pocket. Table 27 provides guidance on deciding when to change the treatment regimen on the basis of clinical status in relation to the CD4 count alone or to the CD4 count plus viral load data. Clinical judgment is an important part of the decision-making process.

10.6 Managing Failure

Identifying the cause of failure is important before deciding to modify the ART regimen. The following points need to be assessed.

Adherence: A detailed assessment of adherence needs to be made. The reasons for non-adherence need to be explored. Unless these reasons are identified, a patient will also find it difficult to adhere to the second-line regimen.
Drug-drug interactions: Assessing whether the patient is concomitantly taking medications which interfere with ARV activity is important. For example, many patients may not reveal that they take herbal treatments along with the prescribed ART regimen.
Continuing high-risk behaviour: If a patient continues to engage in high-risk behaviour, superinfection with a drug resistant virus may lead to treatment failure.

Refer to NACO guidelines on Second line and Alternate First line ART for more details on treatment failure and its management protocols

Section A 11: Choice of ARV Regimens in the Event of Failure of First-line Regimens

11.1 During the development of the NACO technical guidelines, it was acknowledged that the private sector too provide ARV therapy. With second-line regimens are currently available under the national programme, experience has shown that the private sector concurrently uses second-line ARV drugs, such as ABC and PIs as first line, and this has resulted in a cohort of non-naïve treatment experience patients. It is, therefore, important to provide guidance on the choices of second-line regimens in the event of the failure of first-line regimens. A second-line regimen should be recommended only by CoE/ ART plus Centre after the SACEP review, after he/she has confirmed that it is a case of true treatment failure.

11.2 When failure has been identified clinically or immunologically, many patients can be expected to have significant NRTI resistance at the time of switching. Thus, in the decision-making for a second line regimen with maximal antiviral activity, one has to consider nucleoside class cross-resistance and drug interactions (see table 29). Several points to note are:

- Cross resistance exists between d4T and AZT; thus NRTI-component in the second-line regimens should be either ddI/ABC or TDF/ABC.
- High level AZT/3TC resistance reduces susceptibility to ABC.
- TDF can be compromised by multiple nucleoside analogue mutations (NAMs) but often retain activity against nucleoside-resistant viral strains.
- ddI/ABC and TDF/ABC may facilitate evolution of the K65R drug resistance mutation, which mediates resistance to non-AZT NRTIs.
- NNRTI (such as EFV and NVP): usually there is complete cross-resistance.

Table 29 : Expected resistance mutations with different NRTI backbone	
Failing NRTI backbone	**Mutations**
AZT or d4T + 3TC and AZT + 3TC + ABC	M 184V and then successive NAMs (cumulative, the longer one waits to switch)
TDF + 3TC	K65R and / or M184V
ABC + 3TC	L74V > K65R and / or M184V
AZT or d4T + ddI	TAMs, Q151M, T69ins
TDF + ABC and TDF + ddI	K65R

11.3 Ideally, second-line regimens should include at least three active drugs; one of them from a new class, in order to increase the likelihood of the success of the treatment and to minimize the risk of cross-resistance. The PI class should be reserved for second-line treatments.

Common First line Regimen and preferred Second line Regimen

First Line Regimen	Preferred second line
Zidovudine + Lamivudine + Nevirapine/ Efavirenz	Tenofovir + Lamivudine+ Atazanavir/ Ritonavir
Tenofovir + Lamivudine + Nevirapine/ Efavirenz	
Zidovudine + Lamivudine + Atazanavir /Ritonavir	
Zidovudine + Lamivudine + Lopinavir /Ritonavir	
Tenofovir + Lamivudine + Nevirapine/ Efavirenz (if Hb <9 at the time of Switching)	Stavudine+ Lamivudine+ Atazanavir/Ritonavir

11.4 Decide What to Give for Second-line Regimen

Second-line regimens should be prescribed by experienced HIV physicians or in consultation with them. The following flow chart provides guidance.

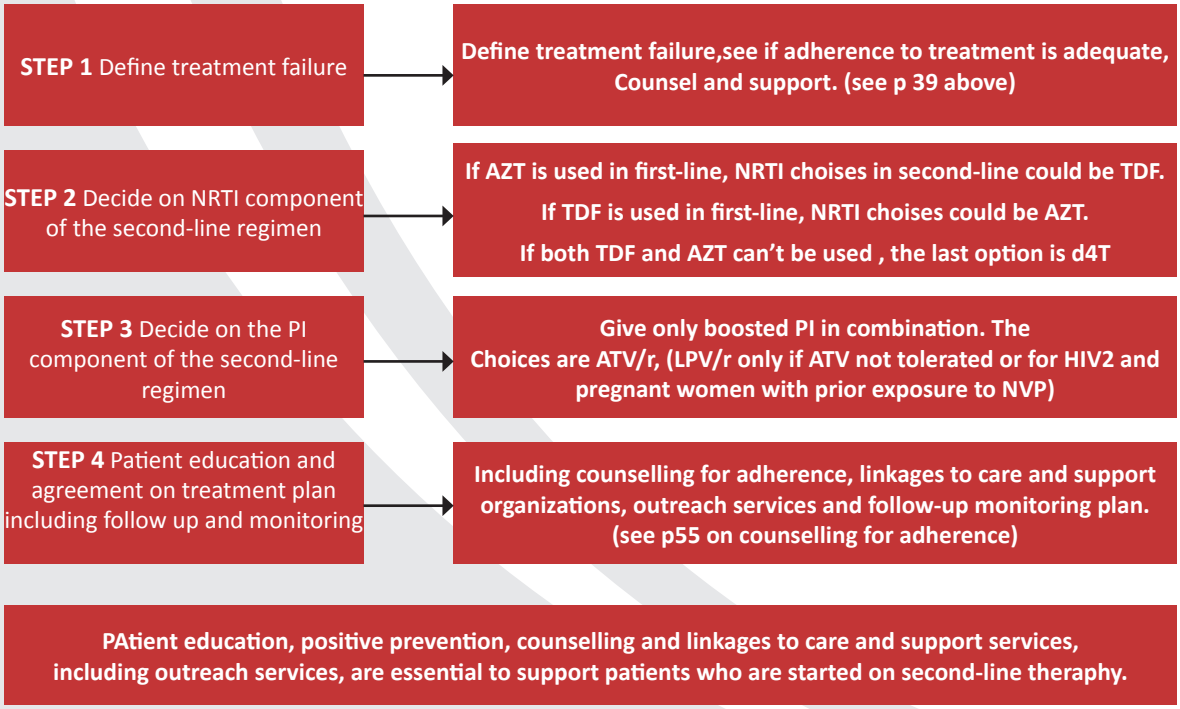


Table 30: List of regimens and alternatives			
First-line regimen		Second-line regimen	
		NRTI component	PI component
Standard Regimens	AZT + 3TC + NVP	Choices: 1st- TDF + ABC or 2nd- ddI + ABC or 3rd- TDF + AZT (± 3TC)(ii)	Choices: 1st - ATV/r 2nd- LPV/r 3rd- SQV/r 4th- IND/r 5th- NLF
	AZT + 3TC + EFV		
	TDF+ 3TC + NVP		
Special circumstances	D4T + 3TC + NVP	Choices: 1st- ddI/ABC 2nd- ddI/AZT (± 3TC)(ii)	
	TDF + 3TC + NVP		
	TDF + 3TC + EFV		

Notes:

(i) A ritonavir-boosted PI is the core of the second-line regimen. NLF can be used but is considered less potent than an RTV-boosted PI.

(ii) 3TC can be considered to be maintained in the second-line regimen to potentially reduce viral fitness, confer residual antiviral activity and maintain pressure on the M184V mutation to improve viral sensitivity to AZT or TDF. AZT may prevent or delay the emergence of the K65R mutation. The disadvantage is the very high pill burden, which may create practical difficulties.

Section A 12: Considerations for ART in IDUs or PLHA under Substitution Programmes

12.1 Principles of Comprehensive Care for IDUs

The key components of comprehensive care for IDUs are:

- Assessment and management of physical and psychological co-morbidities, including viral hepatitis and psychiatric conditions (such as depression).
- Assessment of the patient's treatment priorities, goals and readiness to start ART if it is medically indicated.
- Opioid substitution therapy (OST).

Since the clinical and CD4 criteria for initiating ART in substance-dependent patients are no different from other PLHAs, IDUs (current or previous) who are eligible for ART should receive care and treatment as per the national protocol.

12.2 Linkage between Harm-reduction programmes and ART centres

As HIV-infected IDUs have special needs with regard to drug use, ART should be given as part of a comprehensive package of prevention (including harm reduction), care and support, and treatment. Harm reduction programmes have trained staff (social workers, counsellors and outreach workers), who are experienced in reaching out to and communicating with IDUs, and have established credibility and trust. The linkage between ART centres and harm reduction programmes and Opioid Substitution Therapy (OST) clinics should be established for the following:

- Outreach to potential clients for HIV testing and prevention of transmission of HIV.
- Support for ART adherence.
- Follow-up of patients who drop out of care or default on scheduled visits.
- Implementation of OST for suitable patients.
- Patient education and peer support.

12.3 ART for HIV-infected IDUs

Substance-using PLHA (current or previous) who are medically eligible for ART should be given care and treatment as per the national guidelines. Refer to the harm reduction programme if required.

Table 31: Initiating ART in substance-using patients

Initiating ART	The criteria for initiating ART in substance-using patients are the same as in the case of other patients with HIV • Before starting ART, specific factors that may affect the timing of initiation and the choice of ART should be considered: social instability, active use of illicit drugs and the presence of co-morbidities, such as mental problems and co-infection with hepatitis viruses • Unavailability of OST or active use of illicit drugs should not hinder access to ART for those in need of treatment • Effective links between ART and harm-reduction programmes are essential. • Initiate ART once the patient has been adequately prepared and counseled for treatment adherence • Spending adequate time on preparing patients for ART, and helping them understand the treatment goals, need for adherence and lifelong nature of ART will maximize treatment outcomes
Choice of ART	National regimens can be chosen for the majority of IDUs. The choice of specific ARV drugs depends on: • Co-morbidities (especially hepatitis B/C and psychiatric disorders). • Drug interactions (methadone) • Adherence.

Table 31: Initiating ART in substance-using patients	
Preferred first line regimen	**TDF + 3TC + EFV** for all patients with Hepatitis B and /or Hepatitis C co-infection. With this combination, there are two drugs active against HBV
Alternative first-line regimen	**AZT + 3TC + EFV** TDF may be replaced by AZT in any regimen in case of toxicity or other contraindications eg. Renal Tubular Dysfunction/ Bone Mineral Toxicity **d4T+ 3TC + (EFV or NVP)** in special circumstances, for example, if the patient is intolerant to both TDF and AZT
Second-line regimen	The recommendations are the same as those for other patients with HIV
Adherence	Given a good patient–clinical team relationship and adequate support, IDUs can adhere to ART and have clinical outcomes comparable with those of HIV patients who do not use drugs13,14
Buprenorphine	There is no significant drug interaction between the first-line ARV drugs and buprenorphine
Methadone	Methadone is not available as OST in India. WHO has included methadone as part of the Essential Drug List. *See Annex 6* for details on ART and methadone

12.4 Viral Hepatitis and Chronic Liver Disease

Co-infection with HCV is common among HIV-infected IDUs. Chronic, active hepatitis B and alcoholic liver disease are also common. **Hepatotoxicity associated with these conditions complicates the choice of ART.** The NRTIs associated with the greatest hepatotoxicity are AZT, ddI and d4T. Both the NNRTIs available under the national programme can cause hepatotoxicity. Of these, NVP is more commonly associated with severe hepatotoxicity and should be avoided if possible in all patients with chronic liver disease and liver dysfunction. EFV can be administered in full doses in patients with liver insufficiency. PIs are also associated with hepatotoxicity, and the dosing is complex in patients with hepatic insufficiency.

Drugs for treating hepatitis C, such as pegylated interferon (IFN) and ribavirin (RBV), are not currently provided by the national programme. Newer drugs are being developed globally. Patients should be stabilized on ART at a CD4 count of above 200 cells/mm3 before pegylated IFN and RBV are started. RBV increases AZT levels, and patients should be closely monitored for hepatic toxicity, neutropenia and anaemia.

Causes of hepatic dysfunction other than viral hepatitis need to be considered. Alcohol use/ dependency has the same implication for treatment options and monitoring as does viral hepatitis. Where possible, the least hepatotoxic ARV should be used and hepatic enzymes monitored in all patients with hepatic dysfunction.

See section A13

12.5 Opioid Substitution Therapy

OST is the most effective treatment for opioid dependence, and results in substantially higher retention rates, suppression of drug use and improved psychosocial functioning. Its use in the context of HIV treatment has been associated with improved adherence to and outcomes of treatment. Detoxification and abstinence-based programmes are unlikely to achieve similar levels of clinical effectiveness and may prove counterproductive in the context of ART. If possible, stabilization of substance use with substitution treatment is recommended prior to the commencement of ART.

- The outcomes of OST in a structured programme include:
- Decreased heroin use and reduced chaotic drug-taking
- Decreased needle-sharing
- Stabilization of clients' lives
- Improved quality of life and the chance to lead a productive life in the community
- Improved ability to commence and adhere to ART

OST programmes in India use buprenorphine sublingual tablets. Methadone and buprenorphine are both included in the WHO Essential Drugs List.

12.5.1 Buprenorphine

Buprenorphine is administered as a single daily dose in the range of 8–34 mg/day. The average dose for most patients is 16 mg/day, but doses up to 34 mg/day may be required. Tablets should be placed under the tongue until they dissolve. Swallowing the tablets reduces the bioavailability of the drug. There are two sublingual formulations, buprenorphine alone and buprenorphine combined with naloxone. The addition of the opioid antagonist, naloxone, is intended to discourage injecting of the dissolved tablets.

Interactions between ART and buprenorphine are not as well researched as those involving methadone. Serum levels of buprenorphine are reduced by EFV and some PIs (e.g. IND and SQV), but **no dosage adjustment** of buprenorphine is recommended. However, emerging evidence indicates that certain PIs, including RTV and ATV, inhibit buprenorphine metabolism, resulting in a clinically significant effect. The dose of buprenorphine may need to be reduced in this context.

Table 32: Interactions between buprenorphine and ARVs

ARV	Effect On Bruprenorphine	Effect on ARV	Comments
NRTIs			
No significant interactions reported			
NNRTIs			
EFV	Buprenorphine concentrations decreased but not significantly [15]	None reported	No dose adjustment of EFV required
PIs			
RTV	Inhibition of buprenorphine metabolism, resulting in a clinically significant increase in buprenorphine levels	None reported	Buprenorphine dose may need to be reduced.

Section A 13: HIV and Hepatitis Co-infection

13.1 Hepatitis B Co-infection

As Hepatitis B is endemic in India, with varying geographical prevalence, HIV-infected persons especially those with a history of blood transfusion, injecting drug use and a history suggestive of hepatitis will be screened for baseline HBV/HCV status under the national programme. Vaccination may be considered for those attending STI clinics and HIV-infected persons who are found to be HbsAg-negative.

HIV modifies the natural history of HBV infection: higher rates of progression to advanced liver disease occur among persons with HIV/HBV co-infection. The presence of HIV infection is associated with greater rates of progression to cirrhosis. The impact of HBV on the natural history of HIV is less known.

Table 33: Principles of ART in hepatitis B co-infection	
Choice of ART	ARVs with anti-HBV activity such as 3TC (or FTC) and TDF should be included in the first-line ART regimen for HIV-infected patients who are HBsAg-positive (and HBeAg-positive, if known)
Preferred first line ART	**TDF + TC + EFV** TDF may be replaced by AZT in any regimen in case of toxicity or other contraindications
Alternatives	**AZT + 3TC +** **EFV** TDF may be replaced by AZT in any regimen in case of toxicity or other contraindications eg. Renal Tubular Dysfunction/ Bone Mineral Toxicity **d4T+ 3TC + (EFV or NVP)** in special circumstances, for example, if the patient is intolerant to TDF and AZT
Second-line regimen	3TC should be continued as part of the second-line ART following initial ART failure, even if it was used in the first-line regimen
HBV Resistance	• Ideally, 3TC should be used either with TDF or not at all, because HBV resistance to 3TC develops quickly • HBV resistance to 3TC develops in 50% of patients after two years and in 90% after four years of treatment if 3TC is the only active anti-HBV drug in the ART regimen
Therapy outcomes	HBV seroconversion (loss of HBeAg and development of HBeAg) occurs in 11–22% of HBeAg-positive HIV-infected patients who are treated with 3TC for one year.
Hepatic flares	• HBV flares on ART start soon after the initiation of ART as a manifestation of IRIS • Discontinuation of 3TC may also result in hepatic flares

Table 33: Principles of ART in hepatitis B co-infection	
FTC	The rate of suppression of HBV and safety profile and resistance pattern with FTC are similar to those with 3TC.FTC is not provided by the national ART programme
Notes : Hepatic flares typically present as an unexpected increase in ALT / AST levels and symptoms of clinical hepatitis (fatigue, nausea, abdominal pain and jaundice) within 6-12 weeks of commencing ART. The flares may be difficult to distinguish from ART – induced hepatic toxicity. Drugs active against HBV should preferably be continued during a suspected flare. If it is not possible to distinguish serious hepatitis B flare from grade 4 drug toxicity. ART should be stopped until the patient stabilizes	

Choice of NNRTIs (NVP or EFV) in hepatitis co-infection: Patients who have hepatitis B or C and/or abnormal liver function at the start of therapy with NVP are at a greater risk of symptomatic events (at six weeks or more of NVP) and asymptomatic increases in AST or ALT. The risk of symptomatic hepatic events, regardless of severity, is the greatest in the first 6 weeks of therapy. However, hepatic events may occur at any time during the treatment. In some cases, patients present with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initial abnormal serum transaminase levels. Serious psychiatric events have been reported in patients treated with EFV. These include severe depression (2.4%), suicidal ideation, aggressive behaviour, paranoid reactions and manic reactions.

Chronic active hepatitis describes any progressive inflammatory process within the liver. It is a histopathologic diagnosis in which there is evidence of sustained, aggressive, chronic liver disease. The histologic diagnosis is often cholangiohepatitis because the inflammatory response is mainly in the periportal areas. Histologic examination of a liver biopsy is needed for a definitive diagnosis. The tissue should also be cultured, although in most cases significant isolates are not identified.

13.2 Hepatitis C Infection

Co-infection with Hepatitis C increases the risk of hepatotoxicity with ART. However, the majority of patients with HCV are able to tolerate ART. Where there is a previous history of injecting drug use, HCV and HBV screening should be included in the baseline testing.

The progression of liver disease is greater in the setting of HIV–HCV co-infection. However, as with HBV, the effect of HCV on HIV disease progression is uncertain.

Table 34 : Principles of ART in HCV Co-infection	
HCV therapy	No ARV drugs are directly active against HCV. However, ART has been shown to delay the progression of HCV liver disease in HCV-HIV co-infection The only effective treatment consists of pegylated IFN and RBV, which are generally not available widely
HCV therapy outcomes	Clinical trial outcomes • HCV genotype 1:15-28% sustained virological response rates • HCV genotypes 2 and 3:60-70% virological response rates

Table 34 : Principles of ART in HCV Co-infection	
Side-effects of IFN	Up to 60% of individuals treated with IFN experience psychiatric problems, mostly commonly depression. Monitor mental health closely
Timing of HCV therapy in relation to ART	• Commence anti-HCV therapy before the CD4 count drops to levels where ART is required, i.e. <200 cells/ mm^1 • If ART is required, the patient should be stable on ART with a CD4 count >200 cells/mm^3 before anti-HCV therapy is considered, in order to get better anti-HCV response rates after immune recovery
Preferred first-line ART regimen	• The choice of NRTI is the same as that for patients without HCV • EFV is the preferred NNRTI where liver dysfunction is noted • NVP should be used with care and regular monitoring in patients who have known • HIV-HBV/HCV co-infection and grade 1,2 or 3 increase in ALT/AST • NVP is not recommended for patients with a grade 4 or higher increase in ALT/AST
Drug interactions	• RBV and d4T/ddI:do not co-administer as there is a risk of pancreatitis/lactic acidosis/liver decompensation • RBV and AZT : monitor closely for anaemia • IFN and EFV : monitor closely for depression
Hepatic flares	Soon after initiation of ART, as part of IRIS
Notes : It is recommended that HBV and HCV disease be co-managed with specialized departments (gastroenterology / hepatology). As prevention is the mainstay of HCV management, treatment should be made available to IDUs as a part of a package of services, including harm reduction and substitution programmes	

Section A 14: Considerations for ART in Adolescents

According to WHO, adolescence is the period between 10–19 years of age. During this period, healthy HIVinfected adolescents pass through well-described stages of physical, psychological and sexual maturation for which appropriate care and treatment are required. Physicians giving care and treatment to such adolescents should consider the following issues:

- Disclosure
- Developmental delays
- Transition difficulties from childhood to adulthood which may influence choice of appropriate ART regimens
- Adherence issues
- Psychosocial support needs
- Physical and sexual issues

Refer to National Guidelines for HIV Care and Treatment in Infants and Children, NACO December 2012, for more details.

Section A 15: Adherence to ART

The most common cause of ART failure is **poor adherence**. Adherence should be assessed and routinely reinforced by everyone in the clinical team (physicians, counsellors, nurses, pharmacists, peer educators, NGO workers, etc) at each of the patient's visits to the clinic. Studies indicate that 90–95% of the doses should be adhered to for optimal suppression. Lesser degrees of adherence are often associated with virological failure. Maintaining the optimum level of adherence is difficult.

Factors associated with poor adherence include a poor patient–clinician relationship, high pill burden, forgetfulness, mental depression, lack of patient education, inability of patients to identify their medications, drug toxicity, cultural factors (e.g. religious fasting), beliefs about treatment and the impression of being too ill for treatment.

Table 35: Counselling for treatment preparation and adherence

Step 1: Establish rapport and relationship of trust with the patient

Provide necessary information and guidance

- Encourage peer participation and help identify treatment support persons.
- Encourage disclosure
- Develop an individual treatment plan, fitting ART into the patient's lifestyle/daily events and identifying treatment reminders
- Assess patient's readiness for and commitment to ART. Readiness to commence ART may be assessed by:
  - past ability to attend clinic regularly and not miss appointments
  - past ability to take 01 prophylaxis, such as cotrimoxazole
  - past ability to complete a full course of TB therapy
  - adequate understanding
- There should be strict adherence to treatment. Adherence to recommended regimens should be > 95% to avoid development ofARV drug resistance. This means that missing > 3 doses per month is associated with an increased risk of drug resistance and failure
- If patients have difficulty in adhering to regular doses, reinforce adherence counselling. List barriers to adherence and develop strategies to overcome these barriers. Enlist community outreach teams and peer support groups of PLHA, as appropriate
- Treatment is lifelong
- The timing of drug intake is critical (e.g. drugs taken twice daily must betaken every 12 hours + one hour) Missed doses can be taken up to 6 hours later in a twice-daily regimen. If > 6 hours elapse, skip the dose and take next normal dose
- Dietary requirements with ARV drugs: Some drugs are taken with food, some on an empty stomach, and some require an increased intake of water
- The side-effects of the drugs have to be explained to and understood by the patient before commencing ART

- Give an information sheet to patients about the ART regimen they are taking. See Annex 7
- People on ART need to continue to use condoms regularly and practise safe injecting drug use
- Other medications, including herbal/traditional products, may interact with ART. Patients need careful counselling about which medications are allowed and which are not with their ART
- Regular clinic attendance for monitoring of efficacy, side-effects and adherence is essential
- If patients cannot keep the appointment, they should call or a home visit should be made

Step 2: Counselling - in one or more individual sessions

- Help the patient explore his/her feelings. Many patients are preoccupied with problems related to familyjob, relationships, etc. and cannot focus on strict adherence until negative feelings about these problems are sorted out
- Many have no private place to store their medicines and are not able to take them in privacy. Not wanting others to know their HIV status is by far the commonest reason for poor adherence by patients. Patients must be realistic about who :o confide in about their HIV status and how to tell them
- Check for any financial difficulties the patient may be experiencing. Some patients may not follow up if they do not have money to travel to the centre, or their health maybe affected by a poor diet. Help patients develop secondary support systems for themselves

Step 3: Solving practical problems and creating a treatment plan

- Where will the ARV drugs be stored?
- At what time will they be taken?
- How will the patient remember or who will remind him/her to take the medication if he/she forgets?
- What will the patient do if his/her normal routine is interrupted?
- A time should be agreed upon to meet or telephone the patient within a few days of starting ART to discuss any problems

Table 36: Checklist to assess treatment adherence

- Number of doses missed in the past 3 and 15 days
- Number of doses missed since the last visit
- Whether doses are taken at correction time (if not, ask about delay in hours/ days)
- If correction dose is taken
- Reasons for missing / incorrect dosing / non-adherence
- Estimated proportion of doses taken using a visual analogue scale

The key to successful adherence is educating the patient before the initiation of therapy, supporting ARV initiation as the patient first starts taking medications, and continuously monitoring and supporting adherence. The reinforcement of the principles of adherence by treatment supporters (guardian), relatives, friends and community support personnel is of great help. Providing PLHA with an **information sheet on the ART regimen** they are taking will facilitate adherence and education. *See Annexes 7 & 8.*

Refer to HIV Counselling Training Modules for ICTC, PPTCT and ART Counsellors, NACO for more details

Section A 16: Nutritional Aspects of HIV

16.1 In India, the HIV/AIDS epidemic is occurring in populations in which malnutrition is already endemic. Opportunistic infections and related syndromes, such as TB and diarrhoea, affect the nutritional status as well as physical factors such as appetite and weight.

- Barriers to good nutrition include the following:
- Barriers related to information: provider barriers, client barriers, system barriers
- Barriers related to food choices: economic, geographical, physical, time constraints
- Barriers related to cooking and supplying: who will cook/supply
- Cultural, social and religious barriers: vegetarians
- Personal barriers: depression, loss of appetite, concurrent substance abuse, alcohol use

Depending upon the stage of the disease, HIV/AIDS produces

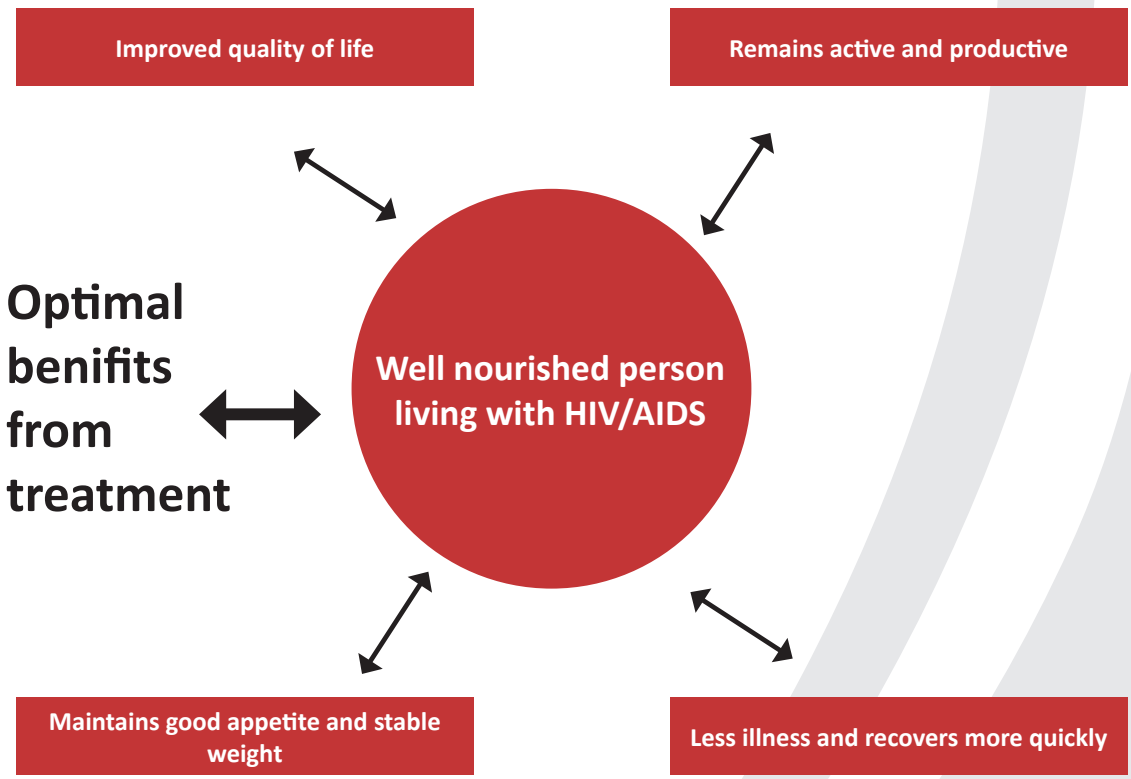
- Reduction in food intake
- Difficulties related to digestion
- Difficulties related to absorption
- Altered metabolism of nutrients (e.g. metabolism of carbohydrates/lipids may be different in HIV)
- Altered body functions: inability to produce saliva, other juices
- Improper utilization of fats

16.2 Increased Resting Energy Expenditure (REE) is Observed in HIV-infected Adults

- Energy requirements are likely to increase by 10% to maintain body weight and physical activity in asymptomatic HIV-infected adults, and maintain growth in asymptomatic children.
- During symptomatic HIV, and subsequently during AIDS, energy requirements increase by approximately 20–30% to maintain adult body weight.

Table 37: Relationship between HIV and malnutrition	
Effect of malnutrition on HIV	Effect of good nutrition on HIV
Increased mouth ulcers, sores, etc., which facilitate transmission of infections	Reduced complication of HIV (diarrhoea, fever muscle wasting, weight loss)
Reduced immunity to OIs, TB, pneumonia, etc.	Stronger immune system (proteins, antioxidants, zinc, selenium)
Rapid progression from HIV infection to AIDS	maintenance of required body weight, improving energy level, productivity, sense of wellbeing
	Supports the effective action of OI treatment and ART
Nutrition is an investment that has both physical and psychological benefits	

Effect of nutrition on HIV/AIDS



16.3 Nutritional counselling is necessary every time the PLHA visits the clinic. Give practical advice on nutrition to PLHA and their care-givers:

(1) Simple steps on food handling and safety:

- Cook food thoroughly.
- Eat cooked food immediately.
- Store food carefully.
- Re-heat cooked food thoroughly.
- Avoid contact between raw and cooked food.
- Wash your hands thoroughly before and after cooking.
- Keep kitchen surface clean.
- Protect food from rodents, insects and animals.
- Use clean water.

(2) Commonly available food items and their nutritional content (Table 37).

(3) Recommendations on which food items to avoid:

- Raw eggs
- Food that has not been thoroughly cooked, especially meat and chicken
- Unboiled water or juices made with unboiled water
- Alcohol and coffee
- Stale food

(4) Symptom-based nutritional care and support (Table 38)

(5) Nutrition and ART, including food–drug interactions

- Paying greater attention to diet and nutrition may enhance the acceptability and effectiveness of ART, as well as adherence to it. Give counselling on correct nutrition and foods which can enhance the well-being of PLHIV. Food can affect the absorption metabolism, distribution and excretion of medication. Medication too can affect the metabolism of food.
- High fat meals reduce the absorption of Indinavir (unboosted).
- High fat meals increase bioavailability of Tenofovir.
- Ritonavir causes changes in fat metabolism.
- The side-effects of medication may adversely affect the consumption and absorption of food, e.g. AZT causes nausea, anorexia and vomiting; didanosine causes vomiting, diarrhoea and dryness of mouth.
- The combination of certain medications and alcohol can produce side-effects, e.g. taking didanosine together with alcohol may result in pancreatitis.
- Take AZT with low-fat meals.
- Take didanosine on an empty stomach.
- Avoid alcohol with any medication.

Table 38: Commonly available food items and their nutritional content	
Item	Nutritional Value
Cereals	Carbohydrates, vitamin B
Pulses	Protein, vitamin B
Nuts and oil seed	Protein, energy, vitamin B
Fats and Oil	Fat
Fruits and vegetables	Vitamins C,A, carbohydrates, iron and pectin
Roots and tubers	Carbohydrates, carotene, calcium and fibre
Milk and milk products	Protein, calcium, vitamin B
Flesh foods, e.g., meat	Protein, vitamin B, calcium and iron
Condiments and spices	Beta carotene and vitamin C
Salt	Helps maintain electrolyte balance
Fibre	Soluble Fibre • Helps people who have loose stools • Available in - fruit like apples, oranges, plums - vegetables like carrots, potatoes - legumes and grains like kidney beans, soya, barley, oats, split peas
	Insoluble Fibre • Adds bulk to stool • Helps prevent constipation Found in whole grain cereals, brown rice, potatoes with skin, apples with skin, raisins, bananas
Special effects : • Garlic : contains Allicin, which has antibacterial, antiviral and antioxidant properties (2-3 cloves a day). • Turmeric : contains polyphenol compounds that have antioxidant properties and ability to fight inflammation.	

Table 39: Symptom-based nutritional care	
Symptoms	**Management**
Loss of appetite	• Eat small, frequent meals (5—6 meals/day) • Eat nutritious snacks • Drink plenty of liquids • Take walks before meals—the fresh air helps to stimulate appetite • Have family or friends assist with food preparation • Take light exercise and do light activity • Add flavour to drink and food
Mouth ulcer	• Avoid citrus fruits and acidic and spicy foods • Eat food at room temperature • Eat soft and moist food • Avoid caffeine and alcohol
Candidiasis	• Eat soft, cool and bland foods (like rice porridge, oat meal, mashed vegetables, apple juice, milk)
	• Add garlic (optional) • Avoid sugar (glucose,cane sugar),yeast, caffeine, spicy food, carbonated drinks and alcohol
Nausea and vomiting	• Eat small, frequent meals • Avoid an empty stomach as this makes the nausea worse. • Eat bland food • Avoid food with strong or unpleasant odours • Drink plenty of liquids • Rest and relax after meals • Avoid lying down im mediately after eating • Avoid coffee and alcohol
Constipation	• Eat fibre-rich food and sprouted food • Take light exercise and do light activity • Drink plenty of water • Take warm drinks
Anaemia	• Eat meat and fish • Eat cereals like rag/' and bajra • Eat a variety of green leafy vegetables (radish greens, mint.paruppu keerai/kulfa kan, cauliflower leaves and sune/a/faa/).The best way for the body to utilize iron from plant sources is to combine food rich in iron with a food rich in vitamin C, like oranges, lemons, tomatoes and papaya. • Take jaggery and dates between meals

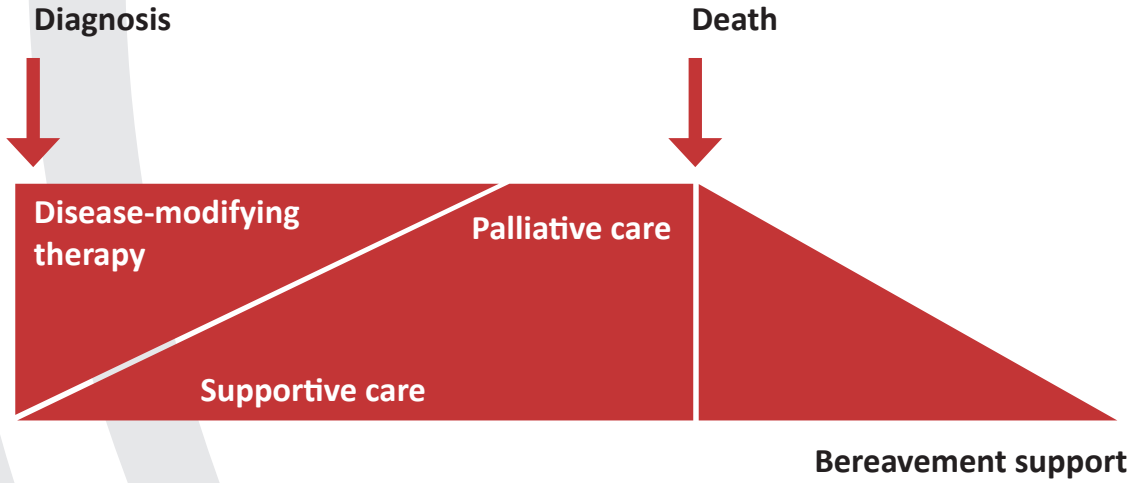
Table 39: Symptom-based nutritional care	
Symptoms	Management
Loss of appetite	• Eat small, frequent meals (5—6 meals/day) • Eat nutritious snacks • Drink plenty of liquids • Take walks before meals—the fresh air helps to stimulate appetite • Have family or friends assist with food preparation • Take light exercise and do light activity • Add flavour to drink and food
Mouth ulcer	• Avoid citrus fruits and acidic and spicy foods • Eat food at room temperature • Eat soft and moist food • Avoid caffeine and alcohol
Candidiasis	• Eat soft, cool and bland foods (like rice porridge, oat meal, mashed vegetables, apple juice, milk)

Table 40: Managing Side Effects the role of diet	
Side-effects	**Preferred diet**
Neuropathy-tingling and numbness	More vitamin 812 (fish, liver, poultry, dairy products)
Gas, bloated feeling, discomfort	Drink plenty of water May take curd Avoid pulses and legumes
Constipation	Drink plenty of water, high fi bre, nuts, fruits, popcorn
Weakness, anaemia	Iron-rich food (beans, peas, dry fruits,dates, liver); food rich in folic acid and vitamin B12 (fortified cereals, orange juice, fish, liver,dairy products)

Section A 17: Palliative Care in HIV

17.1 The Government of India has adopted WHO's definition of palliative care, which is *the active total care of patients whose disease is not responsive to curative treatment* (*Manual on Palliative Care, MOHFW, November 2005*). Palliative care is an "approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual". Palliative care extends, if necessary, to support in bereavement.

Relationship between disease-modifying,supportive and palliative care:



17.2 Palliative care in HIV:

- Is family and patient-centred
- Optimizes the quality of life by active participation, prevention and treatment of suffering
- Involves an inter-disciplinary team approach throughout the continuum of illness, placing critical importance on the building of respectful and trusting relationships
- Addresses physical, intellectual, emotional, social and spiritual needs

The availability of ART and palliative care has made HIV a chronic, manageable disease for many. Apart from regular pain management, nutritional support and OI management, palliative care includes giving support for drug failure and severe toxicities due to ART.

Special attention needs to be given to the following HIV-related conditions, which may present as terminal illness. These conditions can be managed with proper medical care and support.

Severe oral and oesophageal candidiasis, leading to severe pain and weight loss
Cryptococcal meningitis and Toxoplasma encephalitis.

17.3. The Main Components of Palliative Care Include

- Pain management.
- Symptom management
- Nutritional support
- Psychosocial support
- Spiritual support
- End-of-life care
- Bereavement counselling

17.3.1. Management of Pain

Step 1: Assess the patient for pain

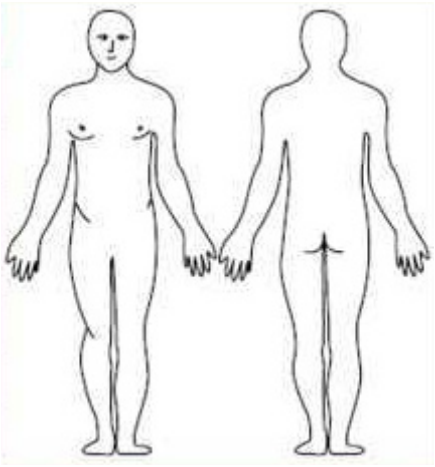
- Determine the severity, site and nature of the pain (bone pain, mouth pain, shooting nerve pain, colicky pain, severe muscle spasms).
- If there is infection, prompt management of infection is the main step in controlling the pain (e.g. treating severe oral and oesophageal candidiasis with fluconazole relieves the pain).
- The severity of the pain can be graded with the help of the tools below.

GO BY WHAT THE PATIENT SAYS IS HURTING: Do not disregard the patient's complaint of pain just because there is no apparent physical cause.

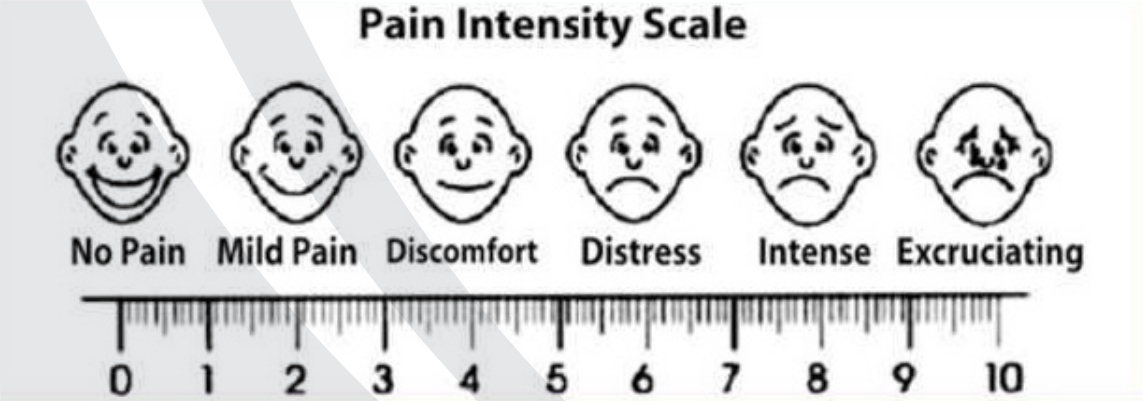
Pain can be assessed using the PQRST characteristics	
P- Palliative factors **Provocative factors**	**'What makes it better?'** **'What makes it Worse?'**
Q- Quality	**'What exactly is it like?'**
R- RAdiation	**'Does it spread anywhere?'**
S -Severity	**'How severe is it?'** **'How much does it affect your life?'**
T- Temporal factors	**'Is it there all the time or does it come and go?'** **'Is it worse at any particular time of the day of night?'**

PQRST Characteristics

Pain Assesment						
Pain site	Pain site	Pain site	Pain site	Pain site	Pain site	Pain site



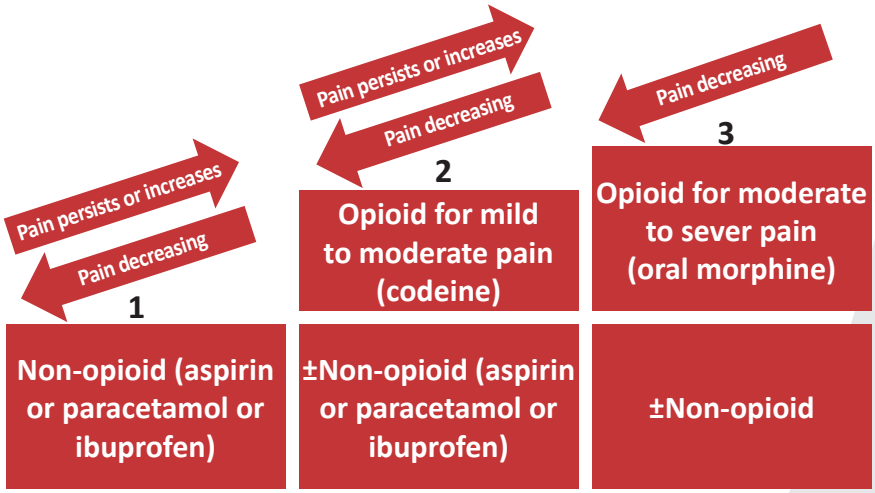
Various scales for pain assessmant are	
• Descriptive Scale • Numeric Scale • Visual analogue Scale	• Percentage Scale • Coin Sclae • Face Scale
The following format may be used for assessing pain in any given patient.	



Step 2: Decide the treatment strategies for pain

Table 41: Strategies for treatment of pain	
By mouth	**By the Clock**
If possible, administer painkiller by mouth (rectal administration is an alternatiove- avoid intramuscular route).	• Give painkillers aat fixed time intervals(by clock or radio or sun). • Start with a small dose, then titrate the dose against the patient's pain, until the patient is comfortable. • The next dose should be iven before the effects of the previous one wears off. • For breakthrough pain,give an extra"rescue" dose,in addition to the regular schedule.

By the analgesic ladder:



The right dose is the dose that relieves the patient's pain

Step 3: Prescribe analgesics – use of opioid and non-opioid

Give only one drug from the opioid and non-opioid groups at a time. The exception is if codeine cannot be given, use aspirin every four hours combined with paracetamol every four hours—overlap so one is given every two hours.

Table 42: Use of analgesics in pain relief				
	Analgesics	Starting dose in adults	Range	Side effects / cautions
	Non-opioid			
	Paracetamol (also lowers fever)	2 tablets of 500 mg every 4-6 hours (skip dose at night or give another analgesic to keep total to 8 tablets)	Only 1 tablet may be required in elderly or very ill, or when combined with opioid. Mild pain might be controlled with 6 hourly dosing	Do not exceed eight 500 mg tablets in 24 hours (more can cause serious liver toxicity)
STEP1	Aspirin (acetylsalicylic acid) (also anti-inflammatory and lowers fever)	600 mg (2 tablets of 300 mg) every 4 hours		Avoid use if gastric problems. Stop if epigastric pain, indigestion, black stools petechiae or bleeding Avoid if presence of any bleeding
	Ibuprofen (also antiinflammatory, lowers fever, for bone pain)	400 mg every 6 hours		Max. 8 tablets per day
	Opioid for mild to moderate pain (give in addition to aspirin or paracetamol)			
STEP 2	Codeine (if not available, consider alternating aspirin and paracetamol')	30 mg every 4 hours	30-60 mg every 4 to 8 hrs. Maximum daily dose for pain 180-240 mg due to constipation— switch to morphine	Give laxative to avoid constipation unless diarrhoea
	Opioid for moderate to severe pain			
STEP 3	Oral morphine 5 mg/5 ml or 50 mg/5 ml. Drop into mouth. Can also be given rectalfy (by syringe)	2.5-5 mg every 4 hours (dose can be increased by 1.5 or doubled after 24 hours if pain persists)	According to need of patient and breathing. There is NO ceiling dose	Give laxative to avoid constipation unless diarrhoea

17.3.2 Give medications to control special pain problems

There are nerve injury pains and pains from special conditions which can be relieved by specific medications. Provide specific treatment in combination with drugs from the analgesic ladder.

Table 43: Medications for special pain problems

Special pain problems	Medication—adolescent/adult
For burning pains; abnormal sensation pains; severe, shooting pains with relatively little pain in between; pins and needles	Low dose amitriptyline (25 mg at night or 12.5 mg twice daily; some start 12.5 mg daily)—wait 2 weeks for response, then increase gradually to 50 mg at night or 25 mg twice daily
For muscle spasms in end-of-life care or paralyzed patient	Diazepam 5 mg orally or rectally 2-3 times per day
Herpes zoster (or the shooting pain following it) Refer patients with ophthalmic zoster	Low dose amitriptyline Early eruption: aciclovir if available; apply gentian violet if ruptured vesicles
Gastrointestinal pain from colic only after intestinal obstruction has been excluded (ie. vomiting, no stool and gas passing, visible bowel movements)	Codeine 30 mg every 4 hours or Hyoscine 10 mg three times daily (can increase up to 40 mg three times daily)
Bone pain or renal colic or dysmenorrhoea	Ibuprofen (or other NSAID)
If pain from: • Swelling around tumour • Severe esophageal ulceration and cannot swallow • Nerve or spinal cord compression • Persistent severe headache (likely from increased intracranial pressure)	When giving end-of-life care and referral not desired, can consider use of steroids under careful clinical supervision

17.3.3 Additional methods for pain control

Combine these with pain medications if patient agrees and it helps:

- Emotional support.
- Physical methods: Touch (stroking, massage, rocking, vibration). Ice or heat. Deep breathing
- Cognitive methods: distraction such as radio, music, imagining a pleasant scene.
- Prayer (with respect to patient's practice).
    - Traditional practices which are helpful and not harmful—get to know what can help in the local setting.

17.3.4 Symptom Management

Table 44: Management of Symptoms with Medications and home care		
Symptoms	Medications to give	Home care
Nausea and Vomiting:	Give Anti-emetic: metoclopromide (10 mg every 8 hours). Give only for a day at a time or haloperidol (1 -2 mg once daily) or chlorpromazine (25-50mg every 6-12 hours).	• Eat small, frequent meals • Avoid an empty stomach as this makes the nausea worse • Eat bland foods • Avoid foods with strong or unpleasant odours. • Drink plenty of liquids. • Rest and relax after and between meals. • Avoid lying down immediately after eating. • Avoid coffee and alcohol.
Painful mouth ulcers or pain on swallowing:	• If Candida: give fluconazole, nystatin or miconazole orally. Topical anesthetics can provide some relief. Pain medication may be required according to analgesic ladder • For Aphthous ulcers: crush one 5 mg prednisone tablet and apply a few grains. • Smelly mouth/breath (halitosis) from oral cancer or other lesions: metronidazole 400mg bd or chlorhexidine Gluconate 1% 10 ml qid mouthwash or hexetidine 0.1% 10 ml qid or Benzydamine 0.5 mouth wash or sodium bicarbonate mouthwash (1 tsp in 1 pint warm water) • For Herpes simplex: 5 ml nystatin solution (500,000 U) + 2 tablets metronidazole + 1 capsule aciclovir (if available)—paint on lesions.	• Remove bits of food stuck in the mouth with Cotton wool,gauze or soft cloth soaked in salt water. • Rinse the mouth with diluted salt water (a finger pinch of salt or 1/2 teaspoon sodium bicarbonate in a glass of water) after eating and at bedtime. • Mix 2 tablets of aspirin in water and rinse the mouth up to 4 times a day. • Soft diet to decrease discomfort such as rice porridge, oat meals, depending on what the sick person feels is helpful. • More textured foods and fluids may be • swallowed more easily than fluids. • Avoid extremely hot or cold or spicy foods.

Table 44: Management of Symptoms with Medications and home care		
Hiccups:	• First try maneuvers to control. If oral thrush, treat. • If no response or recurrent: metoclopromide (10 mg tablet, 1-2 tablets three or four times daily). OR - haloperidol (5 mg tablet: 1/4 to 1/2 tablets once to three times daily). • If patient has brain tumor, consider anti- epileptic medication.	• Maneuvers to stop hiccups: • Stimulate the throat: • Quickly eat 2 heaped teaspoons sugar, or • Drink cold water or eat crushed ice, or Rub with a clean cloth inside the top of the mouth (feel toward the back, where the top of the mouth is soft). • Interrupt the normal breathing by: • Hold breath or breathe into paper bag - stop when you feel uncomfortable. • Pull knees to chest and lean forward (compress the chest).
Bed Sores:	• All patients need skin care to avoid pressure problems • Check for signs of infection. • For smelly tumours or ulcers, sprinkle metronidazole powder —enough to cover the area and keep dry.	• For small sores, clean gently with salt water and allow to dry. • Apply honey to bedsores that are not deep and leave the wound open to the air. • If painful, give painkillers such as paracetamol or aspirin regularly. • For deep or large sores, every day clean gently with diluted salt water, fill the bedsore area with pure honey and cover with a clean light dressing to encourage healing.

17.4 End-of-life Care

" How people die lives on the memory of those left behind"

The terminal phase is defined as the period when day-to-day deterioration, particularly of strength, appetite and awareness are occurring. Is it difficult to predict when death will occur and it is better not to do so. The aim of care at this stage should be to ensure the patient's comfort holistically, and a peaceful and dignified death.

Provide psychosocial and spiritual support to the patient:

- Other patients active listening, counseling and social/emotional support
- Spiritual support is very important:
- Be prepared to discuss all matters if patient would like to.
- Learn to listen with empathy.
- Understand reactions to the losses in their life (the different stages of grief).
- Be prepared to "absorb" some reactions, for example anger projected onto the health care provider
- Do not impose your own views.
- Share religious beliefs with the appropriate person (e.g. religious leader, spiritual counselor etc.) as required
- Empower the family to provide care: *see table 45*
- Help the family come to terms with the fact that the patient is leaving them soon: let family members be around to see and talk to the patient
- Deal with their anxieties and fears gently
- Give information and skills.

Table 45: Management of end-of-life care issues

Steps	Actions
Preparing for death	• Encourage communication within family • Discuss worrying issues such as custody of children, family support, future school fees, old quarrels, funeral costs • Tell the patient that they are loved and will be remembered • Talk about death if the patient wishes to (keep in mind cultural taboos if not in a close relationship) • Make sure the patient gets help with feelings of guilt or regret • Connect with spiritual counselor or pastoral care as patient wishes
Presence	• Approach, be present with compassion • Outreach visit regularly with home-based care • Someone needs to hold hand, listen, converse with the patient and family. This could be a volunteer, NGO worker, outreach worker,counselor etc
Caring	• Provide comfort and physical contact by light touch, holding hands (if appropriate)

Table 45: Management of end-of-life care issues	
Comfort measures near the end of life	• Moisten lips, mouth, eyes • Keep the patient clean and dry and prepare for incontinence of bowel and bladder • Only give essential medications—pain relief, antidiarrhoeals, treat fever and pain (eg paracetamol round-the-clock) etc • Control symptoms with medical treatment as needed to relieve suffering (including antibiotics and antifungals, especially in HIV/AIDS) • Eating less is OK. Ensure hydration • Skin care/turning every 2 hours or more frequently to prevent bed sores • Make sure pain is controlled
Signs of imminent death	• Decreased social interaction—sleeps more, acts confused, coma • Decreased food and fluid intake—no hunger or thirst • Changes in elimination—reduced urine and bowel movements, incontinence • Respiratory changes—irregular breathing, "death rattle" • Circulatory changes—cold and grayish or purple extremities,decreased heart rate and blood pressure
Signs of death	• Breathing stops completely • Heart beat and pulse stop • Totally unresponsive to shaking, shouting • Eyes fixed in one direction, eyelids open or closed • Changes in skin tone—white to gray

Section A 18: NACO Standardized Reporting and Recording System

The National ART Programme is using a paper-based as well as computerized monitoring system consisting of registers, records and forms. The purpose of maintaining various registers and forms is to record relevant information in an easily retrievable manner and for different purposes. All centres are provided with a computer, a data manager and a broadband internet connection for this purpose. In the long term, NACO may shift to a fully electronic system, wherein ART data will be fed into the CMIS at the state, district or even ART center level. The standardized recording and reporting tools used for data collection and supervision includes:

Form	What information?	For what purpose?	When to complete?	Who will complete?	Overall responsibility
Care and Treatment Records and Registers					
Patient visit register	Standardized and key information about each patient visiting the ART centre	• Optimize patient flow, information about patients having TB, pregnancy & record for OPD register	• For all visits during the day	• Care coordinator (nurse, if CC not in place)	Care coordinator
HIV care (Pre-ART) Register	Standardized and systematic key variables of each patient at time of first visit and registration at ART centre till the time of start of ART	• Patient monitoring and follow up before ART initiation • Patient preparedness & ART initiation • Programme monitoring for planning and assessing demand for ART	• At the 1st visit • At start of tuberculosis treatment and CPT • At ART eligibility • At start of ART	• Counsellor under the supervision of SMO/MO Column 1-13 to be filled at the first visit. Information of Column 14-25 shall be entered later from the patient treatment record (white card), which will be filled in by SMO/MO.	Counsellor under the supervision of SMO/MO
Patient Treatment Record (White card)	Standardized and systematic key variables of each patient on HIV care (Both Pre-ART & ART)	• Patient monitoring to report key variables on each patient • Programme monitoring	• At each visit to ART Centre for all PLHIV	• Section 1 to 3 – Counsellor • Section 4 to 13 – Counsellor	SMO/MO – ART Centre
ART Enrollment Register	Standardized and systematic key variables of each patient on ART	• Patient monitoring to report key variables on each patient • Programme monitoring for planning and assessing demand for ART	• At each visit once ART is starts (from white card)	• Counselor to complete all the sections by transferring the corresponding information from the Patient Treatment Record (white card) under the over all supervision of the ART centre SMO/MO.	Counsellor under the supervision of SMO/MO

Care and Treatment Records and Registers					
Patient Booklet (Green Booklet)	Demographic, HIV care, antiretroviral treatment and monthly follow-up clinical information and CD4 count due dates and review	1. Empower the patient 2. Patient management to ensure appropriate lifelong follow-up	• At each patient visit starting from day of registration at the centre	• The patient details on the cover page are to be filled by counselor. • The counsellor notes are to be entered by counsellor. • The vital parameters and investigation report are to be entered by staff nurse. • The clinical notes, investigation requisition, prescription & next visit date are to be entered by SMO/MO	Counselor, Nurse, Lab technician, SMO/MO
TB-HIV tools	Standard systematic information about HIV – TB co-infected PLHIV being referred to the RNTCP	3. Ensure fast tracking of patients referred to RNTCP and getting feedback of these patients	• As per reporting formats	• ART centre staff nurese and STS	Staff nurse
EID register	Key information about mother and the DNA PCR-HIV results of HIV exposed child	4. Follow up and treatment of HIV exposed child	• As per referrals	• Counsellor	Counsellor
LAC/LAC plus reporting tools	Standard systematic information about patients linked out to link Centres	5. Monitor and track the patient linked out to the Link Centers	• Montly Basis • As & when patient linked	• LAC staff • ART centre staff	ART centre/LAC/ LAC plus M/O incharge
CD4 laboratory register	Key information about PLHIV undergoing CD4 testing	6. Patient monitoring for CD4 testing and to generate CD4 due list	• On a daily basis	• Laboratory technician	Laboratory technician

Care and Treatment Records and Registers					
Post exposure prophylaxis register	Key demographic information and details about occupational exposure to HIV	7. To monitor the health care personnel exposed to HIV and provide treatment and list the modes of exposure	• As per referrals	• ART centre nurese	ART centre nurese
PLHIV Tracker format	Key demographic information about MISSED/ LFU cases	8. To track MISSED/ LFU cases	• Monthly basis	• Data Manager at ART centre and Project coordinator at CCC	ART centre Data Manager
Stock Management Registers (Drugs, CD4 Kits & Consumables etc.)					
ARV Drug Stock Registers	Stocks of each ARV drug	• Programme monitoring : drug consumption and available stocks	• Daily basis	• Pharmacist (if not available, then nurse	Pharmacist
OI drug stock register	Stocks of each OI drug	• Programme monitoring : drug consumption and available stocks	• Daily basis	• Pharmacist (if not available, then nurse	Pharmacist
ARV Drug Dispensing Register	Drugs and no. of tablets dispensed	• Patient monitoring accounting for no. of tablets dispensed	• At time of drug dispensing to each patient	• Pharmacist (if not available, then nurse	Pharmacist
Monthly TB – HIV report	Programme indicators	• Patent monitoring	• Monthly Basis	• Nurse	SMO/MO
OI drug dispensing register	Drugs and no. of tablets dispensed	• Patient monitoring accounting for no. of tablets dispensed	• At time of drug dispensing to each patient	• Pharmacist (if not available, then nurse	Pharmacist
Expired drug stock register	Drugs and no. of tablets expired	• Programme monitoring: Quantity of drug expired	• As and when expiry occurs. Monthly basis, as preapproved procedure for disposal of drugs	• Pharmacist (if not available, then nurse	Pharmacist
CD4 kits & Consumable Stock Register	Stock of CD4 kits & Consumables	• To monitor the consumption and stock of CD4 kits and other consumables	• Daily basis	• Laboratory technician	Laboratory technician
Fixed assets register	Details regarding all fixed assets available at ART centre	To track fixed assets quantity, condition and maintenance records	• Every time a fixed asset is purchased or provided to the centre	• Data Manager	Data Manager

Second Line and Alternate first ART tools				
		Who will complete	**Overall Responsibility**	**Sites**
RRF	SACEP Referral and Reply form	SACEP coordinator at CoE/pCoE & data manager ar ART plus centre/ All ART centres	Nodal Officer/SMO	All ART Centres
1 SL*+ AL**	SACEP register (for patients being referred to SACEP for the first time only)			CoE/pCoE & ART plus centre
2 AL	SACEP Meeting format (alternative first line)			
2 SL	SACEP Meeting format (second line)			
3AL+SL	Monthly reporting format (second line and alternative first line)			
4 AL	Line list (alternative first line)			
4 SL	Line list (second line)			
5 SL	Centre wise (linked centre information) break up for PLHIV initiated on second line ART			
CF	Consent form for second line ART			
Programme performance monitoring reports				
Monthly ART Centre Report	Programme Inficators	Programme monitoring to calculate/ analysis indicators To check ART centre's performance and service utilization	Latest by 4th of every month (preferably earlier)	Prepared by Data Manager with input from counsellor/nurse/ pharmacist Checked by ART SMO/MO

Refer to the NACO Training Module on Monitoring and Evaluation Tools for Anti Retroviral Treatment Facilities, December 2012, for more details

Section B: Annexes

Annex 1: Presumptive and Definitive Criteria for Recognising HIV-Related Clinical Events in Adults and Adolescents

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical Stage 1		
Asymptomatic	No MIV related symptoms reported and no signs on examination	Not applicable
Persistent generalized lymphadenopathy (PGL)	Painless enlarged lymph nodes >1 cm. in two or more non-contiguous sites (excluding inguinal), in absence of known cause and persisting for 3 months	Histology
Clinical Stage 2		
Moderate unexplained weight loss (< 10% of body weight)	Reported unexplained weight loss. In pregnancy failure to gain weight	Documented weight loss <10%of body weight
Recurrent bacterial upper respiratory tract infections (current event plus one or more in last six-month period)	Symptom complex, e.g. unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media), or tonsillo- pharyngitis without features of viral infection (e.g. coryza, cough)	Laboratory studies where available, e.g. culture of suitable body fluid
Herpes zoster	Painful vesicular rash in dermatomal distribution of a nerve supply does not cross midline	Clinical diagnosis
Angular chelitis	Splits or cracks at the angle of the mouth not due to iron or vitamin deficiency, and usually respond to antifungal treatment	Clinical diagnosis
Recurrent oral ulcerations (two or more episodes in last six months)	Aphthous ulceration, typically painful with a halo of inflammation and a yellow-grey pseudomembrane	Clinical diagnosis
Papular pruritic eruption	Papular pruritic lesions, often with marked post-inflammatory pigmentation	Clinical diagnosis
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin)	Clinical diagnosis
Fungal nail infections	Paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails (white discolouration—especially involving proximal part of nail plate - with thickening and separation of nail from nail bed)	Fungal culture of nail/nail plate material

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical Stage 4		
HIV wasting syndrome	Reported unexplained weight loss (>10% body weight), with obvious wasting or body mass index <18.S PLUS EITHER unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month, or Reports of fever or night sweats for more than one month without other cause and lack of response to antibiotics or antimalarials. Malaria must be excluded in malarial areas	Documented weight loss >10%of body weight; plus two or more unformed stools negative for pathogens or Documented temperature of > 37.6 C or more with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged CXR
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past 3 months), tachypnoea and fever; AND Chest x-ray evidence of diffuse bilateral interstitial infiltrates AND No evidence of a bacterial pneumonia. Bilateral crepitations on auscultation with or without reduced air entry	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAD, or histology of lung tissue
Recurrent bacterial pneumonia (this episode plus one or more episodes in last 6 months)	Current episode plus one or more previous episodes in last 6 months. Acute onset (< 2 weeks) of symptoms (e.g. fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or CXR. Response to antibiotics	Positive culture or antigen test of a compatible organism
Chronic herpes simplex (HSV) infection (orolabial, genital or anorectal) of more than one month duration	Painful, progressive anogenital or orolabial virus ulceration; lesions caused by recurrent HSV infection and reported for more than one month. History of previous episodes, Visceral HSV requires definitive diagnosis	Positive culture or DNA (by PCR) of HSV or compatible cytology/ histology
Oesophageal candidiasis	Recent onset of retrosternal pain or difficulty on swallowing (food and fluids) together with oral candidiasis	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy/ histology
Extrapulmonary TB	Systemic illness (e.g. fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated TB varies by site: Pleural, pericardial, peritoneal involvement, meningitis, mediastinal or abdominal rymphadenopathy, osteitis. Miliary TB diffuse uniformly distributed small miliary shadows or micronodules on CXR Discrete cervical lymph node M. tuberculosis infection is usually considered a less severe form of extra pulmonary tuberculosis	M. tuberculosis isolation or compatible histology from appropriate site, together with compatible symptoms/ signs (if culture/histology is from respiratory specimen then must other have evidence of extra pulmonary disease)

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical Stage 4		
Kaposi's sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat patches with a pink or blood-bruise colour, skin lesions that usually develop into violaceous plaques or nodules	Macroscopic appearance at endoscopy or bronchoscopy, or by histology
CNS toxoplasmosis	Recent onset of a focal neurological abnormality or reduced level of consciousness AND response within 10 days to specific therapy	Positive serum toxoplasma antibody AND (if available) single/ multiple intracranial mass lesion on neuro imaging
HIV encephalopathy	Clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of dairy living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection which might explain the findings	Diagnosis of exclusion: and (if available) neuro-imaging (CT or MRI)
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually sub acute, fever with increasing severe headache, meningism, confusion, behavioural changes that responds to cryptococcal therapy	Isolation of Cryptococcus neoformans from extrapulmonary site or positive cryptococcal antigen test (CRAG) on CSF/blood
Disseminated non-tuberculous mycobacteria infection	No presumptive clinical diagnosis	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding lung
Progressive multi focal leukoencephalopathy (PML) PML	No presumptive clinical diagnosis	Progressive neurological disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuro-imaging or positive poiyomavirus (JCV) PCR on CSF

Clinical event	Clinical diagnosis	Definitive diagnosis
Cryptosporidiosis (with diarrhoea lasting more than one month)	No presumptive clinical diagnosis	Cysts identified on modified ZN microscopic examination of unformed stool
Chronic isosporiasis	No presumptive clinical diagnosis	Identification of Isospora
Disseminated mycosis (coccidiomycosis, histoplasmosis)	No presumptive clinical diagnosis	Histology, antigen detection or culture from clinical specimen or blood culture
Recurrent non-typhoid salmonella bacteraemia	No presumptive clinical diagnosis	Blood culture
Lymphoma (cerebral or B cell non-Hodgkin) or other sol id HIV associated tumours	No presumptive clinical diagnosis	Histology of relevant specimen or for CNS tumours neuroimaging techniques
Invasive cervical carcinoma	No presumptive clinical diagnosis	Histology or cytology
Visceral leishmaniasis	No presumptive clinical diagnosis	Diagnosed by histology (amastigotes visualized) or culture from any appropriate clinical specimen
HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography
Source: Revised WHO Cinkal Staging and Immunological Classification of HIV and case definition of HIV for surveillance. May 2006		

Annex 2: ARV Drug Combinations and Strategies not to be used

Some antiretroviral regimens or components are not recommended for HIV-1 infected patients due to sub-optimal antiviral potency, unacceptable toxicity, or pharmacological concerns. These are summarized below:

ARV drug combinations not to use:

ARV combinations	Reason not to use
Monotherapy or dual therapy to treat chronic HIV infection	Rapid development of resistance
d4T + AZT	Antagonism (reduced levels of both drugs)
d4T + ddI	Overlapping toxicities (pancreatitis, hepatitis, lipoatrophy, peripheral neuropathy, lactic acidosis) Deaths reported in pregnant women
3TC + FTC	Interchangeable, but should not be used together
TDF + 3TC + ABC or TDF + 3TC + ddI	Select for K65R mutation and are associated with high incidence of early virological failure
TDF + ddI + any NNRTI	High incidence of early virological failure
Unboosted PIs	Poor bioavailbility and higher pill burden.

Antiretroviral strategies not recommended

- Induction-maintenance: Initiation of three drug ART and then reducing it to a combination of two ARV drugs is not recommended.
- Sequential adding of drugs: A third drug, especially NNRTI should not be added to an on-going two drug regimen, as it can lead to rapid selection of resistance.
- Structured treatment interruptions: Any form of treatment interruptions is not recommended in clinical practice.

Annex 3: Dosages of Antiretroviral Drugs for Adults and Adolescents

Generic name	Dose	
Nucleoside RTIs		
Abacavir (ABC)	300 mg twice daily or 600 mg once daily	
Zidovudine (AZT)	300 mg twice daily	
Emtricitabine (FTC)	200 mg once daily	
Didanosine (ddl)' buffered tabs or enteric coated (EC) caps	>60 kg:400 mg once daily <60 kg:250 mg once daily	
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily	
Stavudine (d4T)	30 mg twice daily	
Nucleotide RTIs		
Tenofovir	300 mg once daily	
Non-nucleoside RTIs		
Efavirenz (EFV)	600 mg once daily	
Nevirapine (NVP)	200 mg once daily for 14 days (lead-in dose);followed by 200 mg twice daily	
Proteases inhibitors		
Atazanavir/ritonavir (ATV/r)	300 mg/100 mg once daily	
Fos-amprenavir/ritonavir (FPV/r)	700mg/100 mg twice daily	
Indinavir/ritonavir (IDV/r)	800 mg/100 mg twice daily	
Lopinavir/ritonavir (LPV/r)[2]	Capsule Lopinavir 133 mg + ritonavir 33 mg	Three capsules twice daily (ie 400/1 OOmg twice daily) Four capsules twice daily when combined with EFV or NVP (533/133 mg twice daily)
	Tablet (heat stable formulation) Lopinavir 200mg + ritonavir 50mg	Treatment naive patients Two tablets twice daily irrespective of coadministration with EFV or NVP (400/100 mg twice daily)
		Treatment experienced patients Three tablets twice daily when combined with EFV or NVP (600/150 mg twice daily)
Nelfinavir(NFV)	1250 mg twice daily	
Saquinavir/ ritonavir (SQV/r)	1000/100 mg twice daily	

ddl dose should be adjusted when co-administered with tenofovir. If weight >60 kg, give ddl at 250 mg once daily. If weight <60 kg, give ddl at 200 mg once daily.
See TB section forTB-specific dose modifications of lopinavir/r.

Annex 4: Clinical signs and Symptoms and Management of Adverse Effects of Antiretroviral Drugs

Adverse effect	Possible offending drugs(s)	Clinical signs / symptoms	Management
Acute hepatitis	Nevirapine (NVP) and PI/r; Efavirenz (EFZ) less common; Uncommon with zidovudine (AZT), didanosine(ddI), stavudine(d4T)(<1%);	Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia)	If possible, monitor serum transaminases and bilirubin. If ALT > 5 times the baseline level, stop ARVs until symptoms resolve. NVP should be permanently discontinued. Substitute the most likely offending ARV drug
Acute pancreatitis	ddI,d4T Lamivudine (3TC) (infrequent)	Nausea, vomiting and abdominal pain	If possible, monitor serum pancreatic amylase, lipase. All ART should be stopped until symptoms resolve. Restart ART with change to different NRTI, preferably one without pancreatic toxicity (e.g. AZT,TDF, ABC)
Lactic acidosis	All nucleoside analogue reverse transcriptase inhibitors (NRTIs) particularly D4Tandddl	Initial symptoms are variable:a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhoea.abdominal pain, hepatomegaly, anorexia, and/ or sudden unexplained weight loss), respiratory symptoms (tachypnoea and dyspnoea) or neurological symptoms (including motor weakness)	Discontinue all ART;symptoms may continue or worsen after discontinuation of ART. Give supportive therapy. Resume ART with replacing the offending NRTI with either ABC, TDF
Hypersensitivity reaction	Abacavir (ABC) Nevirapine (NVP)	ABC: Constellation of acute onset of symptoms including: fever, fatigue, myalgia, nausea/ vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea (with or without rash). While these symptoms overlap those of common infectious illnesses,	Discontinue all ART until symptoms resolve.The reaction progressively worsens with drug administration and can be fatal. Administer supportive therapy. Do not rechalienge with ABC (or NVP),as anaphylactic reactions and death have been reported. Once symptoms resolve, restart

Adverse effect	Possible offending drugs(s)	Clinical signs / symptoms	Management
		the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hypersensitivity reaction NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, eosinophilia with or without rash	ART with a change to different NRTI if ABC-associated or to PI- or NRTI -based regimen if NVP-associated
Rash/drug eruptions-including Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN)	Nevirapine (NVP), Efavirenz (EFV-rarely)	Rash usually occurs during the first two to four weeks of treatment.The rash is usually erythematous, maculopapular, confluent, most prominent on the body and arms, may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis has been reported in ~0.3% of infected individuals receiving NVP	In mild cases,give anti-histamines. If rash is moderate, non-progressing and without mucosal or systemic symptoms, consider substituting NVP to EFV after rash resolves. In moderate and severe cases, discontinue all ARVs until symptoms resolve and give supportive treatment. Permanently discontinue NVP for rash with systemic symptoms such as fever, severe rash with mucosal lesions or urticaria,or Stevens-Johnson syndrome or toxic epidermal necrolysis. Once resolved, switch ART regimen to different ARV class (e.g. three NRTIs or two NRTIs and PI)
Peripheral neuropathy	ddl,d4T,3TC	Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness, and areflexia can occur	Stop suspect NRTI early and switch to different NRTI that does not have neurotoxicity (e.g. AZT, ABC). Symptoms usually resolve in two to three weeks
Diarrhoea	ddl,NLF,LPV/r, SQV/r	Loose or watery diarrhoea	Usually self-limited. No need to discontinue ART. Offer symptomatic treatment
Dyslipidaemia, Insulin resistance and hyperglycaemia	Pis EFV		Consider replacing the suspected PI by drugs with less risk of metabolic toxicity
Gl intolerance	All ARVs	Gastritis, indigestion etc	Usually self-limited. No need to discontinue ARVs. Offer symptomatic treatment
Haematological toxicities eg anaemia and leucopenia	AZT	Fatigue, breathlessness, palpitation	If severe (Hb < 6.5 g/dl and/ or absolute nuetrophil count < 500 cells/mm3) - substitute with an NNRTI which has less effect on bone marrow eg D4T, ABC orTDF. Consider blood transfusion

Adverse effect	Possible offending drugs(s)	Clinical signs / symptoms	Management
Lipoatrophy and Lipodystrophy	All NRTIs (particularly d4T)	Lipodystrophy syndrome: Dyslipidemia consisting of elevated total cholesterol, low high-density lipoprotein (HDL) cholesterol and elevated triglycerides; Insulin resistance with hy perg lycem ia; Ce ntra 1 fat accumulation (visceral, breast, neck) and local fat accumulation (lipomas, "buffalo hump"); Generalized diminution of subcutaneous fat mass (lipoatrophy). Lipoatrophy includes loss of subcutaneous fat in the face, extremities and buttocks	Early replacement of the suspected ARV drugs (eg D4T) with TDF or ABC. Consider aesthetic treatment and physical exercises
Neuropsychiatric changes	EFV	High rates of CNS effects in the first 2-3 weeks eg confusion, abnormal thinking, nightmares, impaired concentration, depersonalization, abnormal dreams, dizziness, insomnia, euphoria, hallucinations. Severe depression has been reported in 2.4%	Usually self-limited. No need to discontinue unless severe psychosis Counsel to take EFV at night before bedtime
Renal Toxicity (nephrolithiasis)	Indinavir (IND)	Acute flank pain, may have systemic signs eg fever	Stop IND and hydrate, monitor renal functions and symptomatic treatement. Consider substituting with another PI
Renal Toxicity (renal tubular dysfunction)	TDF	Features of Fanconi syndrome ie. Hypophosphatemia, hypouricaemia, proteinuria, normoglycaemic glycosuria. Acute renal failure has been reported. Risk factors—low body weight and pre-existing renal disease	Discontinue TDF and give supportive treatment. After resolution, replace with another ARV
Note: Discontinuing the offending agent would mean substituting with an alternative drug to ensure efficacy of HAART regimen.			

Annex 5: Drug Interactions with ARVs

ARV	NVP	EFV	LPV/r	NFV	SQV
Anti-Tuberculous drugs					
Rifampicin	πNVP level by 20-58%. Virological consequences are uncertain; the potential of additive hepatotoxicity exists. Coadministration is recommended only be done with careful monitoring	πEFV level by 25% Standard dosing of EFV recommended	πLPV AUC by 75% Should not co- administer	πNFV level by 82% Should not co-administer	πSQV level by 84% Severe liver impairment with co-administer reported Should not co-administer
Rifabutin	Levels: NVPπ16%. No dose adjustment.*	Levels: EFV unchanged; Rifabutin π35% Dose:vrifabutin dose to 450-600 mg Once daily or 600 mg 3x/ week. EFV: Standard	Levels: Rifabutin AUCv3-fold.25 Decrease rifabutin dose to 150 mg once daily or 3x/ week LPV/r: Standard	Levels: NFV π 82%. Should not be co-administered.	Levels : SQVπ40%. Contraindicated unless SQV/RTV. Dose: Rifabutin iSOmgonce daily or 3x/week
Clarithromycin	None	πClarithromycin by 39% Monitor for efficacy or use alternative drugs	πClarithromycin AUCby 75%, adjust clarithromycin dose if renal impairment	No data	Without RTV, vclarithromycin level by 45%, vSQV level 177% RTV can vClarithromycin level by 75% No clarithromycin dose adjustment needed for unboosted SQV. For boosted SQV if renal impairment-no data
Antifungal					
Ketoconazole	vKetoconazole level by 63% vNVP level by 15-30% Do not recommend co-administer	No significant changes in ketoconazole or EFV levels	πLPVAUC πKetoconazole level 3-fold Do not exceed 200mg/day ketoconazole	No dose adjustment necessary	v SQV level by 3 fold Nodose adjustment necessary if given unboosted. For RTV-boosted SQV - no data (RTV treatment dose can increase ketoconazole level 3-fold)

ARV	NVP	LPV/r	NFV	SQV	SQV
Fluconazole	vNVPCmax, AUCCminby 100% No change in fluconazole level Possible increase hepatotoxicity with co-administer requiring monitoring of NVP toxicity	No data	No data	No data	No data
Itraconazole	No data	No data	itraconazole level Do not exceed 200mg/ day itraconazole	No data but potential for bidirectional inhibition. monitor toxicities	Bidirectional interaction has been observed. May need to decrease itraconazole dose. Consider monitor SQV level (especially if given unboosted with RTV)
Oral Contraceptives res					
Ethinyl oestradiol	π Ethinyl oestradiol by 20%. Use alternative or additional methods	π Ethinyl oestradiol by 37%. Use alternative or additional methods	π Ethinyl oestradiol level by 42% Use alternative or additional methods	π levels of norethindrone by 18% and ethinyl oestradiol by 47%	No data forunboosted SQV. RTV treatment dose can level of ethinyl oestradiol by 41%
Anticonvulsants					
Carbamazepine Phenytoin	Use with caution. One case report showed low EFV concentrations with phenytoin.	Unknown. Use with caution	Many possible interactions: Carbamazepine ilevels when co-administered with RTV. Use with caution Monitor anticonvulsant levels. Phenytoin: π levels of LPVRTV, and π levels of phenytoin when administered together. Avoid concomitant use or monitor LPV level.	Unknown, but may decrease NFV levels substantially. Monitor anticonvulsant levels and virological response.	Unknown, but may markedly .τSQV levels. Monitor anticonvulsant levels and consider obtaining SQV level.

ARV	NVP	EFV	LPV/r	NFV	SQV
Opiod Substitution Treatment (OST)					
Methadone	Levels: NVP unchanged. methadoneπ significantly. Opiate withdrawal common when this combination is used. Increased methadone dose often necessary. Titrate methadone dose to effect.	Levels: methadoneπ 60%. Opiate withdrawal common, increase methadone dose often necessary. Titrate methadone dose to effect.	Methadone AUC π 53%. Opiate withdrawal may occur. Monitor and titrate dose if needed. May requirev methadone dose.	NFV may decrease methadone levels, but opiate withdrawal rarely occurs. Monitor and titrate dose if needed. May require methadone dose.	Methadone AUC π 20%. When co-administered with SQV/ RTV 400/400 mg BID. No adjustment for this PI regimen, but monitor and titrate to methadone response as necessary.
Buprenorphine	Not studied	Buprenorphine levels ττ50% nut no withdrawals reported. No dose adjustment is recommended	No significant interactions	No significant interactions	No significant interactions
Lipid lowering agents					
Simvastatin, Lovastatin	No data	πSimvastatin level by 58% EFV level unchanged Adjust simvastatin dose according to lipid response, not to exceed the maximum recommended dose	Potential large vstatin level Avoid concomitant use	vSimvastatin AUC by 505% Potential largev lovastatin AUC Avoid concomitant use	Potential largev statin level Avoid concomitant use
Atorvastatin	No data	πAtorvastatin AUC by 43% EFV level unchanged Adjust atorvastatin dose according to lipid response, not to exceed maximum recommended dose	vAtorvastatin AUC 5.88 fold Use lowest possible starting dose with careful monitoring	vAtorvastatin AUC74% Use lowest possible starting dose with careful monitoring	vAtorvastatin level by 450% when use as SQV/RTV Use lowest possible starting dose with careful monitoring
Pravastatin	No data	No data	vPravastatin AUC 33% No dose adjustment needed	No data	πPravastatin level by 50% No dose adjustment needed

Anticonvulsants					
Carbama-zepine, Phenobarbital, phenytoin	Unknown. Use with caution Monitor anticonvulsant levels	Use with caution. One case report showed low EFV levels with phenytoin Monitor anticonvulsant and EFV levels	vCarbamazepine from RTV Both phenytoin and LPV/r levelsπ For all, avoid concomitant use or monitor LPV/ anticonvulsant levels	Unknown but may decrease NFV level substantially Monitor NFV/ anticonvulsant levels	Unknown for unboosted SQV but may markedly πSQV level Monitor SQV/ anticonvulsant levels
Proton pump inhibitors : All the PIs and EFV can increase levels of cisapride and non sedating antihistamines (aztemizole, terfenedine) which can cause cardiac toxicity. Co administration is not recommended					
Abbreviations : AUC : area under the curve, Cmax : maximum concentration, Cmin : Minimum Concentration Note : Concomitant use of fluticasone with RTV results in significant reduced serum cortisol concentrations. Coadministration of fluticasone with RTV – boosted PI regimen is not recommended unless the potential benefit outweight the risk of systemic corticosteroid side effects. (Adapted from the Guidelines for the use of antiretroviral agents in HIV infected Adults and Adolescents, May 4,2006, www.aidsinfo.nlh.gov)					

Annex 6: Summary of Methadone and ART

Methadone is part of the WHO essential drug list and is being considered for OST use in India. Administration of methadone with EFV, NVP or RTV decreases plasma levels of methadone, which may precipitate opiate withdrawal. Patients receiving methadone and commencing ART may require increased doses of methadone. **ARV dose adjustments in patients receiving methadone:** Methadone withdrawal syndrome include signs and symptoms of methadone withdrawal typically occur 4–8 days after starting NNRTI-based ART and include chills, sweating, nausea, diarrhoea, abdominal cramping, rhinorrhoea, myalgia and anxiety. Patients receiving methadone replacement therapy and NNRTI-based ART require a step-wise increase in the daily dose of methadone of 5–10 mg until they are comfortable. Precipitating methadone withdrawal may trigger relapse to heroin use, distrust of medical providers, and unwillingness to take ART. Contraindications for methadone are: Known hypersensitivity to methadone Acute asthma Alcoholism (unstable alcohol use) Use of MAOI anti depressants Severe hepatic impairment History of biliamy or renal tract spasm (relative contraindication)

Drug interactions between methadone and ARVs			
ARV	Effect On Methadone	Effect On ARV	Comments
NNRTIs			
Efavirenz(EFV)	Methadone concentrations significantly decreased Methadone withdrawal common	Unknown	Observe for signs of methadone withdrawal and increase dosage as necessary Considerable increase in Methadone dose up to 50% commonly required
Nevirapine(NVP)	Methadone concentrations significantly decreased Methadone withdrawal common	NVP unchanged	
NRTIs			
Zidovudine (AZT)	None reported No dosage adjustments necessary	Concentrations increased Clinical significance unclear Adverse events possible	Monitor for adverse events of AZT Monitor for anaemia, neutropenia, nausea, myalgia, vomiting and headache
Lamivudine (3TC)	None reported	None reported	No known interactions
Emtricitabine (FTC)	Not studied	Not studied	No known interactions
Tenofovir (TDF)	None reported	None reported	No known interactions
Stavudine (d4T)	None reported No dosage adjustments necessary	Concentrations decreased	No dose adjustment of d4T required
Abacavir(ABC)	Methadone levels slightly decreased Risk of opiate withdrawal low Dosage adjustments unlikely but some patients might require increase in methadone dose	Concentrations decreased	Risk of opiate withdrawal low Methadone dose adjustment might be needed No dose adjustment of ABC required
Didanosine (ddl) Buffered tablet Enteric-coated (EC) capsule	None reported No dosage adjustments necessary	Concentrations significantly decreased when buffered tablet taken, but not with EC capsule	Avoid use of ddl buffered tablets Use EC capsule if available

Drug interactions between methadone and ARVs			
Pis			
Lopinavir/ritonavir (LPV/r)	Methadone levels decreased	None reported	Opiate withdrawal may occur May require increase in methadone dose
Saquinavir (SQV)	Methadone slightly decreased when co-administered with SQV/ RTV 400/400 BID	No change	No dose adjustment with this PI regimen, but monitor and titrate to methadone response as necessary
Ritonavir (RTV)	Methadone levels decreased	None reported	Studies limited Observe for signs of methadone withdrawal
Nelfinavir (NFV)	May decrease methadone levels	No dose adjustment required	Opiate withdrawal rarely occurs May require of methadone dose.

Interactions between methadone and other drugs			
Drug	**Indication**	**Effect On Methadone**	**Comments**
Rifampicin	Tuberculosis	Significant decrease in methadone levels May induce methadone withdrawal	Increase in methadone dose required if withdrawal symptoms present
Sertraline	Antidepressant	Increase in methadone levels	Associated with cardiac rhythm disturbances, caution when used with methadone
Carbamazepine and phenytoin	Anticonvulsants	Decrease in methadone levels and may cause opioid withdrawal	Increase in methadone dose may be required
Fluconazole	Antifugal	Increase in methadone levels (35%)	Clinical significance unknown

Physicians should discuss potential drug interactions with patients receiving methadone before initiating ARV therapy. Report all prescribed ART-related drug changes for patients receiving methadone to the patient's OST programme. Monitor for symptoms of withdrawal and/or excess sedation when ARV therapy is initiated or changed.

Annex 7: Patient Information Sheets: Treatment Education Cards

(To be translated at state level)

From: Adherence to treatment for HIV: A Training Curriculum for Counselors, Engender Health 2006

Source: World Health Organization(WHO), 2005 March. Chronic HIV Care with ARV Therapy . Integrated Management of Adolscent and Adult illnesses. Interim Guidelines for Capital Health Workers at Health Center or Clinic at Distirct Hospital Outpatient Draft.Rev.1

1. TREATMENT EDUCATION CARD: D4T-3TC-NVP

Now you are on ART

D4T-3TC-NVP		
Stavudine	**Lamivudine**	**Nevirapine**

Day 1 - 14	Day 15 Onwards
Morning : Staudine Lamivudine Nevirapine	**Morning :** Staudine Lamivudine Nevirapine
Evening : Staudine Lamivudine	**Evening :** Staudine Lamivudine Nevirapine

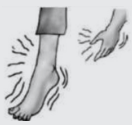
Remember that :

- If you miss doses (even 2 doses in a mouth) **Drug Resistance** can develop. This is bad for you and your community. (These drugs will stop working.)
- Drugs must be taken twice daily, and miss no doses.
- This is very important to maintain blood levels so ART can work.
- If you forget a dose, do not take a double dose.
- If you stop you will become ill within months or year.
- Drugs **MUST NOT** be shared with family and friends.
- If you find it difficult taking your pills twice daily, DISCUSS with health workers. Ask for support from your Treatment supporter, family or friends.

It is common to have side effects. They usually go away in 2-3 weeks.

If you have :	Do the following :
Nausea	Take the pill with food.
Diarrhoea	Keep drinking and eating

If Nausea or diarrhea persists or get worse, or you have any of the following, report to the health worker **AT THE NEXT VISIT.**



- Tingling, numb or painful feet or legs or hands.
- Arms, legs, buttock, and cheeks become THIN.
- Breasts, body, back of neck become FAT

SEEK CARE URGENTLY IF :

- Severe abdominal pain
- Yellow eyes along with high fever, headache running nose and body ache
- Skin rash, along with fever and ulcer in the mouth and lips.

2. TREATMENT EDUCATION CARD AZT-3TC-NVP

Now you are on ART

AZT-3TC-NVP		
Zidovudine	**Lamivudine**	**Nevirapine**

Day 1 - 14	Day 15 Onwards
Morning : Zidovudine Lamivudine Nevirapine	**Morning :** Zidovudine Lamivudine Nevirapine
Evening : Zidovudine Lamivudine	**Evening :** Zidovudine Lamivudine Nevirapine

Remember that :

- If you miss doses (even 2 doses in a mouth) **Drug Resistance** can develop. This is bad for you and your community. (These drugs will stop working.)
- Drugs must be taken twice daily, and miss no doses.
- This is very important to maintain blood levels so ART can work.
- If you forget a dose, do not take a double dose.
- If you stop you will become ill within months or year.
- Drugs **MUST NOT** be shared with family and friends.
- If you find it difficult taking your pills twice daily, DISCUSS with health workers. Ask for support from your Treatment supporter, family or friends.

It is common to have side effects. They usually go away in 2-3 weeks. If you have them, do the following :

If you have :	Do the following :
Nausea	Take the pill with food.
Diarrhoea	Keep drinking and eating
Muscle Pain, Fatigue	These will go away

If Nausea or diarrhea persists or get worse, report to the health worker **AT THE NEXT VISIT.**

SEEK CARE URGENTLY IF :

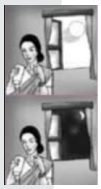
- Severe abdominal pain
- Yellow eyes along with high fever, headache running nose and body ache
- Skin rash, along with fever and ulcer in the mouth and lips.
- Pale or do not have enough blood
- Fatigue and shortness of breath

Note: Zidovudine, ZDV is also called AZT

3. TREATMENT EDUCATION CARD AZT-3TC-EFV

Now you are on ART

AZT-3TC-EFV		
Zidovudine	**Lamivudine**	**Nevirapine**



Daily
Morning : Zidovudine Lamivudine
Evening : Zidovudine Lamivudine Efavirenz

Remember that :

- If you miss doses (even 2 doses in a mouth) **Drug Resistance** can develop. This is bad for you and your community. (These drugs will stop working.)
- Drugs must be taken twice daily, and miss no doses.
- This is very important to maintain blood levels so ART can work.
- If you forget a dose, do not take a double dose.
- If you stop you will become ill within months or year.
- Drugs **MUST NOT** be shared with family and friends.
- If you find it difficult taking your pills twice daily, DISCUSS with health workers. Ask for support from your Treatment supporter, family or friends.

It is common to have side effects. They usually go away in 2 weeks. If you have them, do the following :

If you have :	Do the following :
Nausea	Take the pill with food.
Diarrhoea	Keep drinking and eating
EFV can cause brain effects such as sleepiness, dizziness, bad dreams or problems with sleep or memory	These side effets usually go away. Taking the efavirenz at night is important. Do not take efavirenz immediatly after eating. It is best when take before sleep
Muscle Pain, Fatigue	These will go away

If Nausea or diarrhea persists or get worse, report to the health worker **AT THE NEXT VISIT.**

SEEK CARE URGENTLY IF :

- Bizarre thoughts/confusion
- Severe abdominal pain
- Yellow eyes along with high fever, headache running nose and body ache
- Skin rash, along with fever and ulcer in the mouth and lips.
- Pale or do not have enough blood
- Fatigue and shortness of breath
- Missed periods/possibility of pregnancy

Note: Zidovudine, ZDV is also called AZT

4. TREATMENT EDUCATION CARD d4T-3TC-EFV

Now you are on ART

d4T-3TC-EFV		
Stavudine	**Lamivudine**	**Nevirapine**

Daily
Morning : Stavudine Lamivudine
Evening : Stavudine Lamivudine Efavirenz

Remember that :

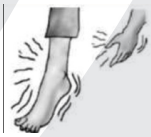
- If you miss doses (even 2 doses in a mouth) **Drug Resistance** can develop. This is bad for you and your community. (These drugs will stop working.)
- Drugs must be taken twice daily, and miss no doses.
- This is very important to maintain blood levels so ART can work.
- If you forget a dose, do not take a double dose.
- If you stop you will become ill within months or year.
- Drugs **MUST NOT** be shared with family and friends.
- If you find it difficult taking your pills twice daily, DISCUSS with health workers. Ask for support from your Treatment supporter, family or friends.

It is common to have side effects. They usually go away in 2 weeks. If you have them, do the following :

If you have :	Do the following :
Nausea	Take the pill with food.
Diarrhoea	Keep drinking and eating
EFV can cause brain effects such as sleepiness, dizziness, bad dreams or problems with sleep or memory	These side effets usually go away. Taking the efavirenz at night is important. Do not take efavirenz immediatly after eating. It is best when take before sleep

If Nausea or diarrhea persists or get worse, or you have any of the following, report to the health worker **AT THE NEXT VISIT.**

- Tingling, numb or painful feet or legs or hands.
- Arms, legs, buttock, and cheeks become THIN.
- Breasts, body, back of neck become FAT



SEEK CARE URGENTLY IF :

- Bizarre thoughts/confusion
- Severe abdominal pain
- Yellow eyes along with high fever, headache running nose and body ache
- Skin rash, along with fever and ulcer in the mouth and lips.
- Pale or do not have enough blood
- Fatigue and shortness of breath
- Missed periods/possibility of pregnancy

Note: Zidovudine, ZDV is also called AZT

Annex 8: Checklist for Adherence Counseling

ADHERENCE COUNSELLING CHECKLIST 1
Counselling Session 1

Name of the Client .....

Date of Counselling session.....

Assess of Patient		
Medical history Knowledge of HIV/AIDS Prior use of ART Determine the social support Disclosure—have they disclosed to anyone? Alcohol/drug use Mental state		
Review the health status		
Ols CD4/viral laod		
Review living conditions and employment		
Housing Employment / Income		
Describe the treatment programme and importance of adherence		
Drug regimen—name/frequency/storage/deitary instructions/not to share pills What ART does—suppresses virus/improves immunity/lessens Ols/not a cure Cost Side-effects and what to do Follow-up Importance of adherence and consequences of non-adherence		
Discuss adherence promotion strategies		
Buddy reminder—discuss role of support person Pill diary Other reminder cues		
Identity barriers to adherence	**Yes**	**No**
Poor communication Low literacy Inadequate understanding about HIV/AIDS Lack of social support Failure to disclose the HIV-positive status Alcohol and drug use Mental state		

ADHERENCE COUNSELLING CHECKLIST 2
Counselling Session 2

Name of the Client .....

Date of Counselling session.....

Review client's understanding of HIV/AIDS
What is HIV and AIDS? What are opprtunistic infections? What do they understand by CD4 counts/viral load? What are the effects of treatment?
Review the treatment programme and importance of adherence
Drug regimen Dummy pill demonstration What ART does—improves immunity/lessens Ols/ART is not a cure? Need for continued prevention—use of condoms Side-effects and what to do Follow-up Importance of adherence and consequences of non-adherence
Review proposed adherence promotion strategies
Buddy reminder—discuss the role of a support person Review all pill diary Other reminder cues—HAART
Review barriers to adherence and the progress made so far
Poor communication skills Low levels of literacy Inadequate understanding about HIV/AIDS Lack of social support Failure to disclose the HIV-positive status Alcohol and drug use Mental state
Take the client's address and establish contact system with a treatment centre
Schedule the next counselling session and complete the appointment card

ADHERENCE COUNSELLING CHECKLIST 3
Counselling Session 3

Name of the Client .....

Date of Counselling session.....

Review client's understanding of HIV/AIDS
What is HIV and AIDS? What are opprtunistic infections? What do they understand by CD4 counts/viral load? What are the effects of treatment? What is their level of commitment of adherence
Review the treatment programme and importance of adherence
Drug regimen Dummy pill demonstration What ART does – improves immunity / lessens Ols / ART is not a cure? Need for continued prevention – condoms use Side-effects and what to do Follow up Link between adherence and successful outcome
Review proposed adherence promotion strategies
Buddy reminder – discuss the role of a support person Review the pill diary Other reminder cues – HAART
Fill the ART register, schedule the next appointment and complete the appointment card
Refer to the Pharmacy / Chemist

Annex 9: Barriers to Adherence and ways to address them

List of Barriers to adherence and ways to address them

1. **Communication** difficulties (language, cultural differences, patient attitudes regarding treatment efficacy, lack of comprehension about treatment plan or regimen)
    (i) Discuss in an open and non-judgmental way
    (ii) Provide patients with scientific basis for treatment
    (iii) Repeat and paraphrase
    (iv) Use counsellors who speak the same language and understand the cultural context of the patient

2. Literacy levels
    (i) Verbal repetition of adherence message, treatment plan and regimen
    (ii) Use patient literacy materials
    (iii) Use dummy pills for demonstration
    (iv) Review information with patient

3. Inadequate knowledge or awareness about HIV disease
    (i) Provide patients with scientific information about HIV disease
    (ii) Review Information with patients
    (iii) Use examples

4. Inadequate understanding about effectiveness of medications - Inform patients and bring change in attitudes and understanding of effectiveness of medications

5. Lack of social support
    (i) Establish contact with PLHA support groups
    (ii) Link with community health workers and home-based care services
    (iii) Link with charitable institutions, faith-based organizations

6. Discomfort with disclosure of HIV status
    (i) Counselling patient to support disclosure
    (ii) Identify other support persons such as friends or peers if patient unable to disclose to the family.

7. Difficult life conditions (lack of income, housing, food, support for childcare)
    (i) Establish contact with PLHA support groups
    (ii) Link with community health workers and home-based care services
    (iii) Link with charitable institutions, church programmes

8. Alcohol and drug use
    (i) Counselling—emphasize link between alcohol, ARV drugs and liver damage
    (ii) Family support
    (iii) Peer group support programmes, church programmes
    (iv) Medical consultation—de-addiction programmes

9. Depression and other psychiatric problems - Refer to physician for treatment

10. Negative or judgemental attitude of providers - Training of providers

11. System barriers (drug stock-out, shortage of staff, health facility closed) **Annex 10: Tools for HIV 2 Testing**

Annex 10: Tools For HIV 2 Testing

Annex 10 a: Designated HIV-2 referral laboratories

Sr. No.	Referring ART centers	Name of laboratory	Contact Name & Address
1	Maharashtra, Mumbai, Dadra & Nagar Haveli, Daman & Diu, Goa	NAR1, Pune	Dr. A. R. Risbud Scientist F National AIDS Research Institute NACO laboratory PlotNo.73, "G "Block, MIDC, Bhosari, Pune-411026 Ph. No: 020-27331200 Ext. E mail: nrl.naril@gmail.com
2	Bihar, West Bengal, Jharkhand, Sikkim,	School of Tropical Medicine (STM), Kolkata	Dr. Bhaswati Bandopadhyay NRLIncharge Dept. of Virology, 4th Floor, School of Tropical medicine, 108, C.R. Avenue, Kolkata-700073. Ph. No: 033-22198538 Email: nrl.stm1@gmail.com
3	Delhi, Haryana, Himachal Pradesh, Jammu &Kashmir, Punjab, Chandigarh, Rajasthan	National Centre for Disease Control (NCDC), Delhi	Dr. R. L Icchpujani NRL In-charge, Centre of AIDS & Related Diseases, National Centre for Disease Control, 22-Shamnath Marg, New Delhi-110054. Tele/Fax: 011-23934517 Email: nrl.nicd@gmail.com
4	Andhra Pradesh	IIPM, Hyderabad	Dr. Uma Devi NRL In-charge Institute of Preventive Medicine, BSQC Department, Narayanguda, Near YMCA, Hyderabad-500029 Ph. No: 040-27568167 Email: nrl.ipm@gmail.com
5	Uttar Pradesh and Uttaranchal	NIB,Noida	Dr. Reba Chabra NRL Incharge National Institute of Bioiogicals A-32, Sec- 62, NOIDA (UP)-201307 Ph. No: 0120-2400022 / 2400072 Ext.2380/2173 Email: nrl.nib@gmail.com
6	Assam, Meghalaya, Arunachal Pradesh	Guwahati Medical College & Hospital	Dr. Naba Kr. Hazarika Dept. of Microbiology, Gauhati Medical College & Hospital, Guwahati-781032 Ph. No: 0361-2529457 Email: sri.assam.gmc@gmail.com

7	Odisha	SCB Medical College & Hospital, Cuttack	Dr. Ashoka Mahapatra SCB Medical College & Hospital, Cuttack, Orissa-751007 Ph. No: 0671-2410041 Email: srl.orissa.scbmc@gmail.com
8	Gujarat	B J Medical College, Ahmedabad	Dr. M. M. Vegad Head & Prof. Dept. of Microbiology, B.J.Medical College, Asarwa , Ahmedabad, Gujarat-380016 Ph. No: 079-22683721 Email: srl.guiarat.bimc(3Rmail.com
9	Kerala, La ksh wad weep	TD medical college, Alapuzha	Dr. Anitha Madhavan SRL, Department of Microbiology. Govt. TD medical college, Alapuzha, Kerala-688005 Ph. No: 04772282015 Email: sri.kerala.mc2[Sigmail.com
10	Madhya Pradesh & Chattisgarh	Gandhi Medical College, Bhopal	Dr. Deepak Dube SRL In-charge, Department of Microbiology, Gandhi Medical College, Barakktullah Vishwavidyalaya, Sultania Road, Bhopal - 462001. Ph. No: 0755-2730502 E-mail: srl.mp.Emc@smail.com
11	Karnataka	NIMHANS, Bangalore	Dr. Anita Desai Assistant Professor Dept. of Neuro-virology, NIMHANS, Hosur Road, Bangalore-560029. Ph. No: 080-26995778 Ext. Fax: 080-26564830 Email: nrl.nimhans8@gmail.com
12	Manipur, Nagaland, Tripura, Mizoram	RIMS, Imphal	Dr. Ng. Brajachand Singh NRL Incharge Department of Microbiology, Regional Institute of Medical Science, P.O. Lamphelpat, Imphal (west), Manipur-795004 Ph. No: 0384-2414750 Ext-181 Email: nrl.rimsl@gmail.com
13	Tamil Nadu& Pondicherry, Andaman & Nicobar islands	Madras Medical College, Chennai	Dr. Vasanthi Prof & Office Incharge, HIV NRL Laboratory, Tower Block-1, Room No. 106, Madras Medical College, Chennai-600003 Ph. No: 044-25383445 Ext. Email: nrl.mmc@gmail.com

Annex 10 b: Referral Slip for HIV 2 Testing

To be filled in duplicate by ART I/C / SMO / MO. Original copy to be sent to HIV-2 referral laboratory Client / Patient to carry ICTC HIV report & Photo ID

Name : Surname _____ Middle Name _____ First Name _____

Date : _____ (DD/MM/YY) Gender M / F / TG Age : _____ Years

ICTC PID # _____ Pre ART Reg. No. _____

Name and postal address of referring ART Centre :

Email ID of referring ART centre / MO in charge :

Name & Signature of Medical Officer ART center :

Annex 10 c: National HIV 2 Testing Algorithm

Test Kits to be used at the referral lab :

Rapid 1 : Determine HIV1 / 2 (FDA Approved) HIV-1 Western Blot : New LAV Blot 1

Rapid 2 : HIV Tridot HIV – Western Blot : New LAV Blot 2

Rapid 3 : Immunocomb Bispot (HIV1 & 2)

Testing Algorithm for HIV-2 Samples

S. No.	T1	T2		T3		Action required	Result – WB HIV-1	Results – WB HIV-2	Final Interpretation
	Determine	HIV Tridot		Imminocomb					
	Screening	HIV-1	HIV-2	HIV-1	HIV-2				
1.	NEG	-	-	-	-	Follow up with ICTC thro SRL	-	-	Negative
2.	POS TEST BY BOTH HIV TRIBOT AND IMMUNIOCOMB	POS	NEG	POS	NEG	No further testing required as both differentiating rapid tests are giving HIV1 result			Report as HIV1 positive
3	POS	POS	POS	POS	POS	Perform HIV-1 & HIV-2 WB (To confirm HIV type)	POS	NEG	HIV-1
							NEG	POST	HIV – 2
							POS	POS	HIV – 1+2
							NEG	NEG	Negative
							POST	IND	Samples giving indeterminate results with WB be referred to Apex Lab for HIV-1 and / or HIV-2 PCR as per the case
							IND	POS	
							IND	IND	
4.	POS	NEG	POS	NEG	POS	Perform HIV-2 WB (To confirm HIV2 status)	-	NEG	Negative
							-	POS	HIV-2
							-	IND	Repeat Testing

5.	POS	POS	NEG	NEG	POS	Perform HIV-1 & HIV-2 WB (To confirm HIV type)	POS	NEG	HIV – 1
							NEG	POS	HIV – 2
							POS	POS	HIV – 1 +2
							NEG	NEG	Negative
							POS	IND	Samples giving Inderterminate results with WB be referred to Apex Lab for HIV-1 and / or HIV-2 PCR as per the case
							IND	POS	
							IND	IND	
6.	POS	NEG	POS	POS	NEG	Perform HIV-1 & HIV-2 WB (To confirm HIV type)	POS	NEG	HIV-1
							NEG	POS	HIV -2
							POS	POS	HIV-1+2
							NEG	NEG	Negative
							POS	IND	Samples giving indeterminate results with WB be referred to Apex Lab for HIV-1 and / or HIV-2 PCR as per the case
							IND	POS	
							IND	IND	
7.	POS	NEG	NEG	NEG	NEG	Perform HIV-1 WB only for confirmation	POS		HIV-1
							NEG		Negative
							IND		Repeat Testing

Annex 10 d:
Report Format to be used by HIV-2 Referral Laboratories

To be filled in triplicate. Two copies to be send to referring ART center (One for Patient and one ART record)

Name of the Referral Laboratory

Name : Surname _____ Middle Name _____ First Name _____

Date : _____ (DD/MM/YY) Gender : M / F / TG Age: _____ Years

ICTC PID# _____ Pre ART Reg. No. _____

Laboratory Sample ID _____

Name of referring ART Center :

Date of sample collection (DD/MM/YY)

Date of sample testing (DD/MM/YY)

Test Name	Rapid 1	Rapid 2	Rapid 3	HIV1 WB	HIV2 WB
Name of the Kit					
Result					

Final Interpretation of Test Result :

Signature of laboratory Incharge : Date :

POS : Positive, Neg : Negative, IND : Indeterminate, ND : Not Done, WB : Western Blot

***** END OF REPORT *****

Annex 10 e: PCR Requisition Form

Name of the Referral Laboratory requesting PCR:
Name : Surname _____ Middle Name _____ First Name _____
Date : _____ (DD/MM/YY) Gender : M / F / TG Age: _____ Years
ICTC PID# _____ Pre ART Reg. No. _____
Laboratory Sample ID _____
Name of referring ART Center :
Address of referring ART Center :
Serological test result at the referral laboratory :
Signature of laboratory Incharge :

Annex 10 f: Inventory for kit utilization

(To be send quarterly to Apex laboratory by Email)

Date :

Name of KIT	Batch No. / Expiry Date	No. of Kits received	No. of Kits used	Balance
Determine ™ HIV1/2				
HIV Tridot				
Immunocomb Bispot HIV1 / HIV2				
New Lav Blot 1				
New Lav Blot 2				

Signature of Laboratory Incharge

Annex 10 g: HIV-2 Referral Laboratory Cumulative Monthly Reporting Format

Name of HIV 2 Referral Laboratory

HIV-2 Referral Laboratory cumulative Monthly Reprting Format									
Month / Year	Number of ART centers referring patients	Number of patients received	Number of primary samples collected	Number that are only HIV-1 Positive	Number that are only HIV-2 Positive	Number that are both HIV-1 & HIV-2 Positive	Number that are referred to Apex lab for further testing	Number that are HIV-Negative	Number of samples that are rejected

Signature of Laboratory Incharge

Annex 10 h: ICTC HIV Test Reporting Format

HIV TEST REPORT FORM

Name and address of ICTC Centre : .....(Form to be filled in duplicate)

Name : Surname _____ **Middle Name** _____ **First Name** _____

Gender : M / F / TG **Age** : _____ Years **PID #** _____ **Lab ID#** _____

Date and the time blood drawn : _____ (DD/MM/YY) _____ (HH:MM)

Test Details :

Specimen type used for testing : Serum / Plasma / Whole Blood

Date and time specimen tested : _____ (DD/MM/YY) _____ (HH:MM)

Note :

- Column 2 and 3 to be filled only when HIV 1 & 2 antibody discriminatory test(s) used
- No cell has to be left blank; indicate as NA where not applicable

Column 1	Column 2	Column 3	Column 4
Name of HIV test kit	Reactive / Nonreactive (R/NR) for HIV-1 antibodies	Reactive / Nonreactive (R/NR) for HIV-2 antibodies	Reactive / Nonreactive (R / NR) for HIV antibodies
Test I :			
Test II :			
Test III :			

Interpretation of the result : Tick (✓) relevant

- ❑ Specimen is negative for HIV antibodies
- ❑ Specimen is positive for HIV – 1 antibodies
- ❑ *Specimen is positive for HIV antibodies (HIV 1 and HIV 2; or HIV 2 alone)
- ❑ Specimen is indeterminate for HIV antibodies, Collect fresh sample in two weeks

* Confirmation of HIV 2 sero – status at identified referral laboratory through ART centres

Name & Signature
Laboratory Technician

Name & Signature
Laboratory In-charge

- End of report -

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