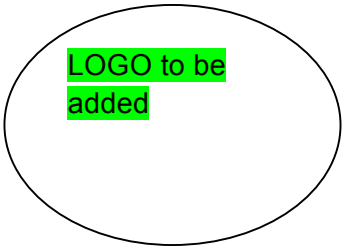
National Guidelines
For Antiretroviral Therapy



National AIDS /STD Program,
Directorate General of Health Services,
Ministry of Health and Family Welfare
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ART Advisory ART Advisory Committee

FOREWORD

List of acronyms

3TC	Lamivudine
AB	Antibody
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ANC	Antenatal Clinic
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate Aminotransferase
ATV	Atazanavir
AZT	Zidovudine (Also Known As ZDV)
BID	Twice Daily
BMI	Body Mass Index
bPI	Boosted Protease Inhibitor
CD4	Cluster of Differentiation 4
CMV	Cytomegalovirus
CNS	Central Nervous System
CXR	Chest X-Ray
DBS	Dried Blood Spot
DNA	Deoxyribonucleic Acid
DRV	Darunavir
EFV	Efavirenz
EIA	Enzyme Immunoassay
EPTB	Extrapulmonary Tuberculosis
ETV	Etravirine
FBC	Full Blood Count
FDC	Fixed-Dose Combination
FPV	Fos-Amprenavir
FSW	Female Sex Worker
FTC	Emtricitabine
GI	Gastrointestinal
Hb	Haemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HIVDR	HIV Drug Resistance
HIVRNA	Human Immunodeficiency Virus Ribonucleic Acid
HSV	Herpes Simplex Virus
IDV	Indinavir
INH	Isoniazid
IRIS	Immune Reconstitution Inflammatory Syndrome
LPV	Lopinavir
LPV/r	Lopinavir/Ritonavir
MSM	Men Who Have Sex With Men
MTCT	Mother-To-Child Transmission (Of HIV)
NASP	National AIDS And STD Program, Bangladesh
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor

NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OI	Opportunistic Infection
OST	Opioid Substitution Treatment
PCP	Pneumocystis Jiroveci Pneumonia
PGL	Persistent Generalized Lymphadenopathy
PI	Protease Inhibitor
PLHIV	People Living With HIV
PML	Progressive Multifocal Leukoencephalopathy
PMTCT	Prevention Of Mother-To-Child Transmission (Of HIV)
PWID	People Who Inject Drugs
r	Low-Dose Ritonavir
RAL	Raltegravir
RBV	Ribavirin
RNA	Ribonucleic Acid
RT	Reverse Transcriptase
RTI	Reverse Transcriptase Inhibitor
RTV	Ritonavir
Sd-NVP	Single-Dose Nevirapine
SJS	Stevens-Johnson Syndrome
SQV	Saquinavir
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TEN	Toxic Epidermal Necrolysis
TLC	Total Lymphocyte Count
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral Load
WBC	White Blood Cell Count
WHO	World Health Organization

SUMMARY OF THE RECOMMENDATIONS

The table below presents an overview of the summary of the recommendations pertaining to various aspects of ART as included in the guidelines. This may not contain entire information necessary to make clinical decision, therefore, all the users are requested to through the main portions of the guideline before making any clinical decision.

Table 1: Summary of the major recommendations

Issue regarding ART	Situation Criteria /definitions
When to start ART in adults and adolescents Initiation of ART in adults and adolescents including pregnant women	· Any HIV positive individuals with CD4 count ≤500 cells/mm3 or any HIV positive individual with WHO clinical staging 3 or 4 irrespective of CD4 cell count · TB and hepatitis B co-infections : ART is started irrespective of CD4 cell count in all HIV positive with active TB disease or HBV infection requiring treatment and for sero discordant couples
When to start ART in infants and children Initiation of ART in infants and children (18 years and below)	· All HIV infected children up to 5 years of age irrespective of CD4 count or WHO clinical stage · All HIV-infected children more than 5 years of age with a CD4 count of ≤500 cells/mm3 (as in adults), irrespective of WHO clinical stage. · All HIV-infected children with WHO clinical stages 3 and 4, irrespective of CD4 count.
How to Monitor ART Laboratory monitoring	· Baseline tests: CD4 count, creatinine clearance for TDF, Hb for AZT, ALT for NVP · During ART: CD4 count, creatinine clearance for TDF, Hb for AZT, ALT for NVP preferably every 6 months
How to detect treatment failure Failure of ART	· Clinical failure : emergence of new or recurrent WHO stage 4 condition or certain WHO clinical stage 3 conditions (e.g. pulmonary TB , severe bacterial

	infections) · Immunological failure: fall of CD4 count to baseline (or below) OR 50% fall from on-treatment peak value OR persistent CD4 levels below 100cells/mm3, without concomitant infection to cause transient CD4 cell decrease. · Virological failure: Plasma viral load above 1000 copies/ml
How to Switch ART Switching of ART	A single drug should not be changed or added to a failing regimen. · The new regimen should have minimum of three active drugs, one of them drawn from at least one new class · The PI class is thus reserved for second-line treatments and ritonavir-boosted protease inhibitors (RTV-PIs) are preferred

Section 1: Introduction

This section contains following topics:

1. **Background**
2. **Objectives of National ART Guidelines**
3. **Rationale of the guidelines**
4. **Targeted users of the guidelines**

1.1 Background

According to global report of UNAIDS 2013, around 35 million people are estimated to be living with HIV globally. Sub Saharan Africa shares the biggest burden of HIV in the world with 24.7 million people living with HIV. Second highest number of HIV is in our part of the world- South and South East Asia where the estimated number of people living with HIV is 4.1 million. According to UNAIDS the number of new infections with HIV is decreasing mainly due to the increase in the levels of awareness about HIV, implementation of various HIV prevention related activities and universal access to ART.

According to National AIDS and STD Program (NASP), the prevalence of HIV in Bangladesh is less than 0.1% in the general population and has remained less than 1% over the years. The surveillance data suggests that there are two key groups in the country that need focused attention viz. People Who Inject Drugs (PWID) and International return migrant workers. The prevalence of HIV among PWID has declined from 7% in 2007 to 5.3% in 2011 as a result of effective intervention programme by NGOs but the epidemic is still concentrated in this group of people.

The estimated number of people living with HIV in the country is around 9,500 (range 4,000 to 97,000) as per spectrum estimates. So far a total of 3,241 persons have been diagnosed with HIV of whom 1299 are AIDS cases and 472 have died. HIV has been detected in 60 out of 64 districts. Of these 75% are concentrated in 12 districts.

1.2 Objectives of the National ART Guidelines:

1. To provide evidence-based recommendations following a public health approach (in view of 2013 WHO consolidated treatment guidelines) for the delivery of ART and monitoring patients on ART in general population and specific groups like (pregnant women, children, HIV- TB co-infected patients, PWID, migrants etc.

2. To provide guidance on the use of potent less toxic more efficacious first line and second line ART regimen.

3. To provide recommendations applicable to the majority of populations regarding the optimal timing of ART initiation, preferred first-line and second-line ARV regimens, improved criteria for ART substitution, switching and managing HIV in special situations in HIV(Pregnancy, pediatric population,, Tuberculosis, hepatitis B and C , occupational exposure etc.)

1.3 Rationale for revision the guidelines

In order to achieve optimal treatment outcomes it is necessary to follow standardized treatment protocols and ensure highest levels of adherence to treatment (> 95%) and these need to be updated periodically based on emerging evidences .

Since the formulation of the first ART guidelines in the country, a number of new developments have occurred in the field of HIV in the world. The 2013 WHO Consolidated Guidelines on the Use of ART for preventing and treating HIV infection follow a public health approach. The focus in these guidelines is to ensure universal access to ART, use of fixed drug combinations, strategic and rational use of medicines and optimizing existing health care systems in order to ensure long term sustainability of HIV treatment activities. WHO has clearly stated in these guidelines that “Implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology, availability of resources, the organization and capacity of the health system and anticipated cost-effectiveness. These revised national ART guidelines for the country are being revised in line with the 2013 WHO guidelines. Besides technical issues, tthese guidelines, for the first time, will also provide guidance on various operational and service delivery issues that will help to increase access to HTC and ART in the public sector health

services. These guidelines will also be useful for the programme managers in NASP and DGHS to take appropriate decisions for smooth roll out of services for PLHIV.

1.4 Targeted audience for these guidelines

The target audiences for these guidelines are national AIDS program managers, partners involved in HIV care and treatment services, and organizations providing technical and financial support to HIV care and treatment programs in Bangladesh. This document will also be of immense help to clinicians who are taking care of the HIV patients, both in public, private or NGO sector. The document will also guide the national HIV program managers and other senior policy-makers who are involved at the policy planning level. These guidelines will continue to evolve according to the evidence and data available nationally and globally and will be updated as and when new evidence becomes available

Section 2: Antiretroviral Drugs

This section includes the followings

1. **Antiretroviral drugs**
2. **Classes of antiretroviral drugs**
3. **Targets of antiretroviral drugs**
4. **Clinical pharmacology of common ARV drugs**

2.1 Antiretroviral drugs

Antiretroviral drugs are the agents which act on the various stages of the life cycle of HIV in the body. These drugs work by interrupting the process of replication of virus and hence reducing the destruction of CD4 cells which leads to delay in progression of HIV infection to AIDS.

To understand the mechanism of action of ARV, one needs to understand the basic steps of the viral replication, in other words life cycle of HIV virus. Virus enters into the CD4 (host) cell involving glycoproteins of the virus and receptors of host cells. The process is called fusion. ARVs interfering with the fusion are called fusion inhibitors. This is the new class of ARV and it includes the drugs like T 20 (Enfuviritide), CCR5 entry inhibitors (Maraviroc) and CXCR4 antagonist. These drugs are currently not available in Bangladesh. After the fusion with the host cell membrane, viral particles including the viral RNA and the enzymes (reverse transcriptase, integrase and protease) enter into the cytoplasm of the host cell. The first process inside the host cell is the reverse transcription in which viral DNA is synthesized from viral RNA. The process involves the reverse transcriptase enzyme. The ARVs interfering with this process are called nucleoside and nucleotide reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). Nucleoside analogue reverse transcriptase inhibitors inhibit the production of proviral DNA by competing with normal nucleotide. Thus in place of normal nucleotide, defective nucleotide

analogue are placed in the DNA fragment thus producing a defective DNA which cannot serve the purpose of proviral DNA in the subsequent stages of HIV replication. In this way the replication of HIV is blocked. Non-nucleosides analogue inhibitor acts by destroying the active site of reverse transcriptase. Individual ARVs in these groups include Zidovudine (ZDV), Lamivudine(3TC), Tenofovir (TDF) – examples of NRTI, Nevirapine (NVP), Efavirenz (EFV)- examples of NNRTI. These groups ARV are available in Bangladesh and recommended as first line ARVs.

The viral DNA synthesized in cytoplasm travels to the nucleus of the host cell, where it integrates with the DNA of the host cell with the help of integrase. Integrase inhibitors are the ARVs that block the process of integration. Example of ARV of this class is Raltegravir and it is not available in Bangladesh. After integration, the DNA of the infected cell converts into the viral DNA and starts to produce copies of viral RNA. For the production of viral particles, the RNA copies thus produced need to be cut into particles of exact size with the help of protease. Protease inhibitors (PI) interrupt this process. The examples of protease inhibitors (PI) are Lopinavir, Saqunavir, Ritonavir, Indinavir, Nelfinavir, Atazanavir etc. The boosted PIs (combination of two types of PI) increase the effectiveness, stability of ARV and minimize the side effects. Lopinavir boosted with ritonavir (LPV/r), and Atazanavir boosted with ritonavir (ATV/r) are some of the boosted PI recommended for Bangladesh.

The viral RNA after the action of protease converts into the viral particles. These particles assemble with the enzymes into a capsule, which eventually leaves the infected cell by the process called budding. The viruses after budding develop into the mature viruses. There are some

ARV inhibiting the process of maturation and are called maturation inhibitors. These ARVs are not available in Bangladesh.

Newer classes of antiretroviral drugs like Fusion inhibitors (FI), Integrate Strand Transfer Inhibitors (INSTI), CCR5 Antagonists act by preventing fusion and entry of the virus to the target cell (CD4), preventing the integration of the HIV proviral DNA into the human DNA and blocking co-receptors needed for the virus to enter the cell.

Although not all antiretroviral drugs mentioned in the guidelines are currently available in Bangladesh, it is the decision of the guideline committee to include some of these drugs so that as more drugs become available in the future, clinicians and program managers can utilize these drugs fully.

2.2 Classes of Antiretroviral drugs

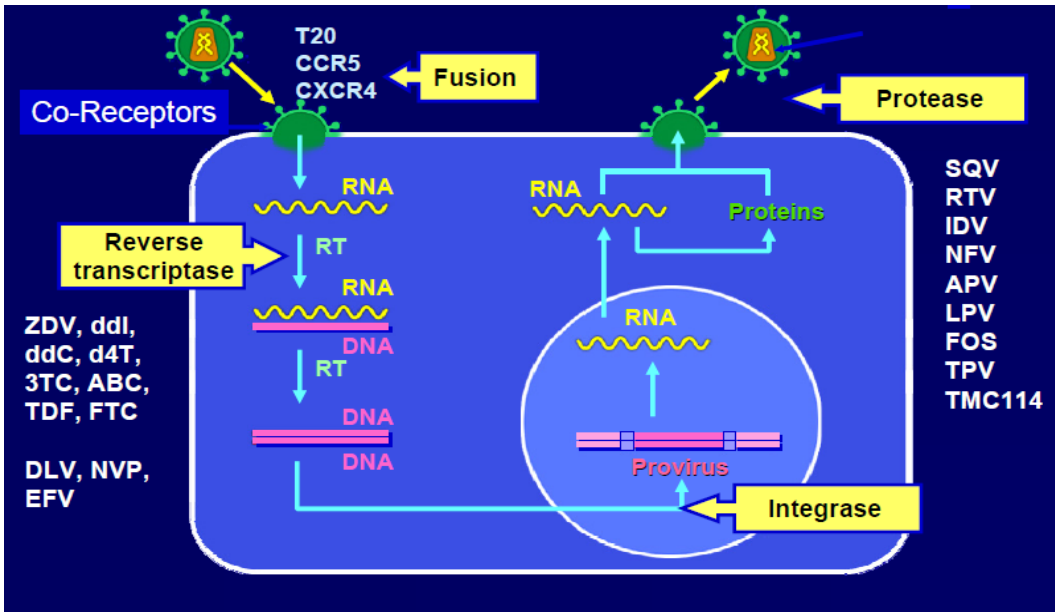
Depending on the mechanism of action the ARVs are categorized into following classes:

1. Nucleoside and nucleotide analogs
   a. Nucleoside reverse transcriptase inhibitors (NRTI)
   b. Nucleotide reverse transcriptase inhibitors (NtRTI)
   2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
   3. Protease inhibitors (PIs)
   4. Integrase Strand Transfer Inhibitors (INSTI)
   5. Fusion Inhibitors
   6. Cellular Chemokine Receptor (CCR5) Antagonist

Only first three groups of drugs are used in the programme presently

The mechanism of the action of ARV is shown graphically below:

2.3 Targets of anti-retroviral drugs (see explanation above)



Currently available antiretroviral drugs are shown in Table 2 below:

Table 2 : Classes of ARV 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)

2.4 Clinical Pharmacology of Commonly Used ARV drugs

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

The first effective class of antiretroviral drugs was the **Nucleoside analogues** which act by incorporating themselves into the DNA of the virus, thereby stopping the building process. The resulting DNA is incomplete and cannot create new virus. **Nucleotide analogues** work in the same way as nucleosides, but they have a non peptidic chemical structure. All nucleoside analogs have been associated with lactic acidosis and hepatic steatosis as their common side effects. **The details of individual ARV of this class are in table 3 below:**

Table 3 : Commonly used NRTIs

Generic Name	Dose	Food related advices	Adverse effects
Zidovudine (ZDV, AZT)	300 mg twice daily	Take without regards to meals	Anaemia, neutropenia, bone marrow suppression, gastrointestinal intolerance, headache, insomnia, myopathy, lactic acidosis1, skin & nail hyperpigmentation.
Tenofovir (TDF)	300mg once daily	Take without regards to meals	Renal toxicity, Bone demineralization
Lamivudine (3TC)	150 mg twice daily Or 300 mg once daily	Take without regards to meals	Minimal toxicity, rash though very rare
Emtricitabine (FTC)	200 mg once daily	Take without regards to meals	Unusual, the most common treatment-related adverse events are mild to moderate in severity diarrhea, headache, nausea, and rash. Skin discoloration, which is typically reported as hyperpigmentation

Generic Name	Dose	Food related advices	Adverse effects
			and usually affects either the palms of the hands or the soles of the feet. Among the more severe side effects patients may experience is hepatotoxicity or lactic acidosis.
Abacavir (ABC)	300 mg twice daily or 600mg OD	Take without regards to meal	Hypersensitivity reaction in 3 to 5% (can be fatal), fever, rash, fatigue, nausea, vomiting, anorexia, respiratory symptoms (sore throat, cough, shortness of breath) Re challenging after reaction can be fatal. Some studies show that ABC has been associated with increased cardio-vascular risk;

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) stop HIV production by binding onto reverse transcriptase and preventing the conversion of RNA to DNA. These drugs are called "non-nucleoside" inhibitors because even though they work at the same stage as nucleoside analogues, they are not nucleoside analogues. **The details of individual ARV of this class are in table 4 below:**

Table 4 : Commonly used NNRTIs

Generic Name	Dose	Food related advices	Adverse Effect
Nevirapine (NVP)	200 mg once daily for 14 days followed by 200 mg twice daily	Take without regards to meals	Hepatitis (usually within 12 wks), life-threatening hepatic toxicity. Skin rash occasionally progressing to severe conditions including Stevens Johnson syndrome5 and TEN5. Patients who develop hepatic toxicity while treated with Nevirapine should not be restarted.
Efavirenz (EFV)	600 mg once daily (bed time administration is suggested to decrease CNS side effects)	Avoid taking after high fat meals	CNS symptoms (dizziness, somnolence, insomnia, confusion, hallucinations, agitation), and personality change. Rash occurs, but less common than NVP

Protease Inhibitors (PIs)

Protease inhibitors work at the last stage of the viral reproduction cycle. They prevent HIV from being successfully assembled and released from the infected CD4 cell. All PIs can produce increased bleeding in hemophilia, GI intolerance, altered taste, increased liver function test and bone disorder, and all have been associated with metabolic abnormalities, such as hyperglycemia, insulin resistance, and increase in triglycerides, cholesterol and body fat distribution (lipodystrophy). **The details of individual ARV of this class are in table 5 below:**

Table 5 : Commonly used PIs

Generic Name	Dose	Food related advices	Adverse Effect
Atazanavir/ ritonavir	300mg Atazanavir + 100mg ritonavir once daily	Take with food	Hyperbilirubinaemia. Less lipid problems than LPV/r Hyperglycemia, Fat maldistribution, Nephrolithiasis Interaction with acid blocking agents. Dosing changes when given with acid-blockers. Do not co-administer with Proton pump inhibitors such as Omeprazole.
Lopinavir /ritonavir (LPV/r) Heat stable tablets	200mg Lopinavir/50 mg Ritonavir Fixed dose tablet 2 tablets twice daily	With or without food	Diarrhea, nausea, vomiting, abnormal lipid profiles, glucose intolerance. Any PI should not be prescribed with Simvastatin, as all PI significantly increase the level of simvastatin in blood leading to the condition called rhabdomyolysis6 resulting into severe kidney failure.

Some notes on adverse effects of ARV drugs

1. Lactic acidosis is a physiological condition characterized by low pH in body tissues and blood (acidosis) accompanied by the buildup of lactate and is considered a distinct form of metabolic acidosis. The condition typically occurs when cells become hypoxic, for example during vigorous exercise. In this situation, impaired cellular respiration leads to lower pH levels. Simultaneously, cells are forced to metabolize glucose anaerobically, which leads to

lactate formation. Therefore, elevated lactate is indicative of tissue hypoxia, hypoperfusion, and possible damage. Lactic acid lactic acidosis includes rapid breathing, drowsiness, fast/irregular heartbeat, unusual weakness, feeling cold especially in the arms/legs etc.

2. Renal insufficiency described as a decrease in the glomerular filtration rate. is typically detected by an elevated serum creatinine level.

3. Fanconi syndrome (also known as Fanconi's syndrome) is a disease of the proximal renal tubules of the kidney in which glucose, amino acids, uric acid, phosphate and bicarbonate are passed into the urine, instead of being reabsorbed. Fanconi syndrome can affect different functions of the proximal tubule, and result in different complications. The loss of bicarbonate results in Type 2 or proximal renal tubular acidosis. The loss of phosphate results in the bone disease rickets (even with adequate vitamin D and calcium).

4. Osteomalacia is the softening of the bones due to defective bone mineralization secondary to inadequate amounts of available phosphorus and calcium. Osteomalacia in children is known as rickets, and because of this, use of the term osteomalacia is often restricted to the milder, adult form of the disease. It may show signs as diffuse body pains, muscle weakness, and fragility of the bones. The most common cause of the disease is a deficiency in vitamin D, which is normally obtained from the diet and/or sunlight exposure.

5. Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two forms of a life-threatening condition affecting the skin in which cell death causes the epidermis to separate from the dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes. Although the majority of cases are idiopathic (no known cause), the main class of known causes is medications, followed by infections and, rarely, cancers.

6. Rhabdomyolysis is a condition in which damaged skeletal muscle tissue breaks down rapidly. Breakdown products are released into the blood stream; some of these, such as protein myoglobin, are harmful to the kidneys and may lead to kidney failure.

Section 3: Antiretroviral Therapy

This section includes the followings topics

1. Goals of ART
2. Provision of ART for Adults and Adolescents
3. Prophylaxis of opportunistic Infections including CPT and IPT
4. Criteria for initiating ART
5. Choice of ARV drugs/regimen
6. What to expect in first six months of ART
7. Immune reconstitution inflammatory syndrome
8. Management of adverse effects of antiretroviral drugs
9. Monitoring of ART
10. ART Adherence
11. Criteria for treatment success
12. Failure of Antiretroviral Therapy
13. Switching ARV in case of treatment failure
14. Considerations for ART in Adolescents

3.1 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 in table 6 below:

Table 6: Goals of ARV therapy
• Clinical goals : Prolongation of life and improvement in quality of life
• Virological goals : Greatest possible sustained reduction in viral load
• 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
• Prevention Goals : Reduction of HIV transmission in individuals : Reduction of HIV transmission by suppression of viral load

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 all eligible patients,
- To monitor and report treatment outcomes on a quarterly basis,
- To attain individual drug adherence rates of 95% or more

The national programme shall provide 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.
- The National programme will work closely with NGOs and other organizations currently working for Care support and Treatment of PLHIV.

3.2 Provision of ART for Adults and Adolescents

Not all people living with HIV are eligible for ART and, of those eligible, many may not be aware of the importance of timely initiation of ART. Therefore it is critical for people living with HIV to enroll in care as early as possible and this can only happen when there is good quality of pre test and post test counselling. All patients diagnosed with HIV at HTC should be registered in HIV care at the earliest. This not only ensures timely initiation of ART but also regular monitoring for other co morbities and minimizes the chances of lost to follow up.

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 HIV testing and counselling (HTC) for confirmatory testing and diagnosis. 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 on the same blood sample.

Assessment of Adults and Adolescents with HIV Infection for Pre - ART Care and follow up in Pre ART Care

Clinical Assessment and other tests

At the beginning of HIV care at the time of enrollment for HIV a comprehensive clinical assessment is done to:

- Determine the clinical stage of HIV infection
- Identify history of past illnesses (especially those related to HIV like TB, STIs, Hepatitis)
- Identify current HIV-related illnesses that require treatment
- Determine the need for ART and OI prophylaxis
- Do CD4 count and other baseline investigations
- Identify coexisting medical conditions and treatments that may influence the choice of ARV drugs.

Medical History

It is important to elicit those risk factors which may influence the counselling as well as drugs to be used for ART. One has to look for

- 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, TB)
- Past or present recipient of blood or blood products
- Injections, tattoos, ear piercing or body piercing using non-sterile instruments

Table 7 : History taking

Table : 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 Previous CD4 cell counts (if available) • Previous viral load (if available)	• Unprotected sexual contact • Injection drug use • Men having sex with men • 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 esophagitis • Persistent diarrhea • Tuberculosis • Varicella zoster (Shingles) • Oral hairy leukoplakia • Pneumocystis juroveci pneumonia (PCP) • Recurrent bacterial pneumonia Cryptococcal meningitis • Toxoplasmosis • Kaposi sarcoma • Disseminated Mycobacterium avium complex • Cytomegalovirus(CMV) infection • Invasive cervical cancer
Tuberculosis history	ART history
• Last chest X-ray • History of past TB • Treatment given (drugs and duration) • History of exposure to TB	• Current and past exposure to ARVs • ARV use during pregnancy of PMTCT Use of PEP in the past • Which drugs taken and for how

	long • Understanding of and readiness to commence ART • Partner's ART history (if HIV-positive)
Sexually transmitted infections (STIs)	Substance use
• Genital ulcer or other lesion • Genital discharge (abnormal vaginal discharge in women) • Lower abdominal pain	• Alcohol, stimulant, opiate and other drug use • Smoking history
General medical history	Allergies
• Any other past medical condition such as diabetes, hypertension, coronary artery disease, hepatitis B, hepatitis C, hyperlipidemia • Mental health issues, e.g. depression	• Known allergies to drugs or other substances or materials
Medication	Vaccination history
• Past use of drugs and reasons for taking • Current use of drugs and reasons • Current use of traditional / herbal remedies • Opioid substitution therapy (OST)	• BCG • Hepatitis A vaccine • Hepatitis B vaccine
Psychosocial history	Functional history
• Family history, e.g. other immediate family members with known HIV infection • Social history e.g. marital status, education, occupation, source of income.	• Financial and family support status • Disclosure status, readiness to disclose • Availability of care and treatment supported supporter • Able to work, go to school, do housework • Ambulatory but not able to work • Bed ridden

	• Amount of day-to-day care needed
Gynecological history	Pregnancy and contraception history
• Last PAP smear • Menstrual irregularities • Pelvic pain or discharge	• 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

Physical Examination

It is essential to have a thorough physical examination for clinical staging and screening. Table 8 details the specific physical signs related to HIV/AIDS which should be screened.

Table 8 : Physical examination

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 other than HIV
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, other than axillary or inguinal nodes • Tuberculous lymph nodes typically present 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 cracking at the corners of the mouth (angular cheilitis) • Difficulty in swallowing is commonly caused by esophageal 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 of viral hepatitis
Neurological	• Focus on visual fields and the signs of neuropathy (bilateral peripheral examination or localized mono-neuropathies) • Assess focal neurological deficit
Ano-genital	• Herpes simplex and other genital sores / lesions, vaginal or penile discharge • Perform PAP smear, if possible
Note : During each consultation, patient is to be clinically screened for TB (history and physical examination)	

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 other concomitant infections and
(iii) Determine baseline safety parameters.

The following investigations are recommended for monitoring of PLHAs at ART centres:

Table 9 : Laboratory Monitoring for patients on ART	
Essential tests for all patients registering in HIV care	Tests for Special Situation
• Haemogram/CBC, • Urine for routine and microscopic examination, • fasting blood sugar, • blood urea, • Serum creatinine • ALT (SGPT), • VDRL, • CD4 count, • X-ray Chest PA view. • Pregnancy test(if required) • Symptoms and signs directed investigations for ruling out OIs. • PAP smear	• 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 • Fundus exam in those with low CD count
Additional tests	Tests for monitoring purpose
For patients to be started on ART (as per the physician's decision depending on clinical presentation) • USG abdomen, • sputum for AFB,	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

• CSF analysis etc. Efforts to be made to fast track these investigations so that ART initiation is not delayed.	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 clinician's assessment/ discretion Other investigations during follow up as per requirement /availability.

However absence of certain investigations should not be a deterrent to starting ART

Table 10: Assessment and initial management after HIV diagnosis is confirmed

Visit 1	Initiation of ART based on CD4 and WHO clinical staging
	• Medical history • Symptom checklist • Screen for TB • Physical examination • Chest X-ray if chest symptoms present • Behavioral/ psychosocial assessment: • Social support, family/household structure • Disclosure status, readiness to disclose • Understanding of HIV/AIDS, transmission, risk reduction, treatment options • Nutritional assessment

	• Investigation: baseline Blood profile, CD4 count, other test as necessary	
	Eligible for ART	Not eligible for ART
Visit 2 (within 3 to 5 days after first visit)	• History (new problems) • Symptom check-list • Screen for TB • Physical examination • Co-trimoxazole prophylaxis • Psychosocial support • Adherence counselling on at least 2 occasions	• History (new problems) • Symptom check-list • Physical examination • Psychosocial support Plan for next visit after 6months for repeat CD4 and clinical evaluation
Visit 3 (2 weeks after previous visit)	• Screen for TB • Commence ART if stable on Co-trimoxazole and patient is ready	To visit only if symptomatic or being treated for an OI
Visit 3 (2 weeks after previous visit)	• History (new problems) and clinical examination • Screen for TB • Adherence assessment / support	To visit only if symptomatic or being treated for an OI
Subsequent Visits (4 weeks after previous visit)	• History (new problems) • Symptom check-list • Screen for TB • Clinical examination • Adherence assessment / support	To visit only if symptomatic or being treated for an OI

Pre-ART Care:

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 500 cells.

- Comprehensive medical history and physical examination (see Tables 7, 8)
- Baseline laboratory tests for pre-ART care patients include: (Table 9)
  1. Baseline screening of CD4 to determine eligibility for starting ART (see Table)
  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 every six months or earlier if some new symptoms are noticed
- Register patients in the national Pre-ART Register

Table 11 : CD4 monitoring and follow-up schedule	
CD4 Count	**Follow up**
CD4 of any value and on ART	Every 6 months
>500 and not on ART	Repeat at 6 months

3.3 Prophylaxis of opportunistic Infections

Cotrimoxazole Prophylaxis Therapy (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.

Cotrimoxazole, a fixed-dose combination of sulfamethoxazole and trimethoprim, is a broad spectrum antimicrobial agent that targets a range of aerobic gram-positive and gram-negative organisms, fungi and protozoa. The drug is widely available in both syrup and solid formulations at low cost in most places. Providing co-trimoxazole is part of the standard of care for preventing Pneumocystis jiroveci pneumonia (PCP) (formerly Pneumocystis carinii pneumonia) and toxoplasmosis.

A. Cotrimoxazole prophylaxis in adults and adolescents

Cotrimoxazole prophylaxis is recommended to

- HIV infected adults with CD4 count less than 200 cells/mm3
- All adults who have had an episode of PCP
- All adults with symptomatic HIV disease or Clinical stage 3 or 4

Recommended dose

One double strength tablet (160mgTMP/800 mg SMX) every day

OR

Two single strength tablets (80mg TMP/ 400 mg SMX) every day

Duration

- If on ART the CD4 is >200 on two consecutive samples 6 months apart, Cotrimoxazole can be discontinued.
- If prophylaxis has been stopped because of immune improvement, Cotrimoxazole prophylaxis (or Dapsone) should be restarted if CD4 cell count falls below 200 or if new or recurrent WHO clinical stage 3 or 4 conditions occur

Cotrimoxazole prophylaxis and ART initiation

Since the most common initial side effect of cotrimoxazole and antiretroviral therapy (especially Nevirapine and efavirenz) is rash, it is recommended to start cotrimoxazole prophylaxis first and to initiate antiretroviral therapy two weeks later if the individual is stable on cotrimoxazole and has no rash. Do NOT start Cotrimoxazole and ART at the same time.

Cotrimoxazole intolerance

If the patient reports a history of hypersensitivity to sulpha-containing drugs, start him/ her on a desensitization regimen as an in-patient.

In cases of non-life -threatening adverse reactions, stop treatment for two weeks; then re-challenge the client with TMP/ SMX in a gradually increasing dose of an oral suspension of TMP/SMX. Co-trimoxazole desensitization has been shown to be successful and safe in approximately 70% of patients with previous mild to moderate

hypersensitivity. 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.

Table12: Protocol for cotrimoxazole desensitization among adults and adolescents

STEP	DOSE
DAY 1	80 mg sulfamethoxazole + 16 mg trimethoprim (2 ml of oral suspensiona)
DAY 2	160 mg sulfamethoxazole + 32 mg trimethoprim (4 ml of oral suspensiona)
DAY 3	240 mg sulfamethoxazole + 48 mg trimethoprim (6 ml of oral suspensiona)
DAY 4	32 320 mg sulfamethoxazole + 64 mg trimethoprim (8 m of oral suspensiona)
DAY 5	One single-strength sulfamethoxazole-trimethoprim tablet (400 mg sulfamethoxazole + 80 mg trimethoprim)
DAY 6 ONWARDS	Two single-strength sulfamethoxazole-trimethoprim tablets or one double strength tablet (800 mg sulfamethoxazole + 160 mg trimethoprim)

Note: A cotrimoxazole oral suspension is 40 mg trimethoprim + 200 mg sulfamethoxazole per 5 ml.

Follow-up of clients on Cotrimoxazole prophylaxis:

- Monitor for toxicity, clinical events and adherence.
- Lab tests of hemoglobin and white blood counts, only as indicated.
- Adherence counseling on Cotrimoxazole can be useful to prepare clients for ART in the future and address barriers to medication adherence.
- Use an alternative antibiotic for treating breakthrough bacterial infections among individuals living with HIV receiving cotrimoxazole prophylaxis, while continuing cotrimoxazole.
- For toxoplasmosis and PCP infections, prophylaxis should be suspended and full active treatment initiated. Cotrimoxazole prophylaxis should be recommenced after the treatment course.

B. Cotrimoxazole prophylaxis among infants and children

PCP has been identified as the leading cause of death in infants with HIV infection. The incidence peaks in the first six months of life. Because of difficulty in diagnosing HIV infection in infants, cotrimoxazole prophylaxis is recommended for all HIV-exposed children born to mothers living with HIV starting at 4–6 weeks after birth and continuing until HIV infection has been ruled out and the infant is no longer at risk of acquiring HIV through breastfeeding.

Table 13: Recommendations for starting Cotrimoxazole in infants and children:

	Age	Recommendations
HIV Exposed Infants And Children	Any Age	All exposed babies start at 4-6 weeks after birth and continue until at least 3 months after stopping breastfeeding with negative HIV test
HIV Infected Infants and Children (confirmed)	< 1 year of age	All regardless of CD4 or clinical status
	1- 4 years of age	Those with symptomatic HIV disease and / or CD4 count < 25%
	> 5 years of age	Those with symptomatic HIV disease and / or CD4 count < 200/mm3

Duration

Primary cotrimoxazole prophylaxis for children can be stopped in older children on ART after at least 12 months of ART with good adherence, no Stage 2, 3 or 4 conditions and high CD4 count on 2 measurements 6 months apart (>25% between 1-5 years, > if > 5 years of age).

Table 14: Recommended dose of Cotrimoxazole (once daily dose)

Recommended daily dosage	Suspension (5 ml syrup 200mg/40mg)	Pediatric tablet (100mg/20mg)	Single strength adult tablet (400mg/ 80mg)	Double strength adult tablet (800mg/160mg)
< 6 months 100mg SMX/ 20mg TMP	2.5 ml	One tablet	---	---
6 months – 5 years 200mg SMX/ 40mg TMP	5 ml	Two tablets	Half tablet	---
6 - 14 years 400mg SMX/ 80mg TMP	10 ml	Four tablets	One tablet	Half tablet
> 14 years 800mg SMZ/ 160mg TMP	---	---	Two tablets	One Tablet

Initiation of CTX in relation to of ART in children

Since the most common initial side effect of CTX and ART (especially nevirapine and efavirenz) is rash, it is recommended to start CTX prophylaxis first and initiate ART two weeks later if the individual is stable on CTX and has no rash.

Cotrimoxazole intolerance in children

- In case of adverse reactions, desensitization using small doses of cotrimoxazole is not recommended in children
- Dapsone is the best alternative for prophylaxis at 2mg/kg/day orally, maximum dose 100mg/day.
- Dapsone is less effective in the prevention of toxoplasmosis and also lacks the broad antibacterial activity of cotrimoxazole.

Monitoring of CTX prophylaxis

- Clinical monitoring of children on CTX should be performed by health staff at the site of CTX provision at regular intervals, followed by laboratory investigations or referral, as required.
- Caregivers should be provided with information on how to recognize common CTX reactions such as jaundice and rash and to stop the drug and report to the nearest clinic, should they occur.
- For those children who are already under laboratory monitoring for HIV care or ART, no additional laboratory tests are needed.

C. Cotrimoxazole prophylaxis among pregnant women

- Women who fulfill the criteria for co-trimoxazole prophylaxis should stay on co-trimoxazole throughout their pregnancy.

If a woman requires co-trimoxazole prophylaxis during pregnancy, it should be started regardless of the stage of pregnancy.

- Some OIs may require secondary prophylaxis as detailed in table

Table 15: Recommended schedule for starting and stopping OIs prophylaxis

Opportunistic Infections	Primary prophylaxis indicated when CD4 is	Drug of choice	Discontinue primary Prophylaxis when CD4 is	Discontinue secondary prophylaxis is when CD4 is
Toxoplasmosis	**< 100**	TMP-SMX 1 DS od	**>200**	
CMV retinitis	Not indicated	Secondary: ganciclovir	Not applicable	**>100**
Cryptococcal Meningitis	Not indicated	Secondary: ganciclovir	Not applicable	**>100**

Isoniazid Preventive Therapy (IPT)

Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT

Duration of IPT

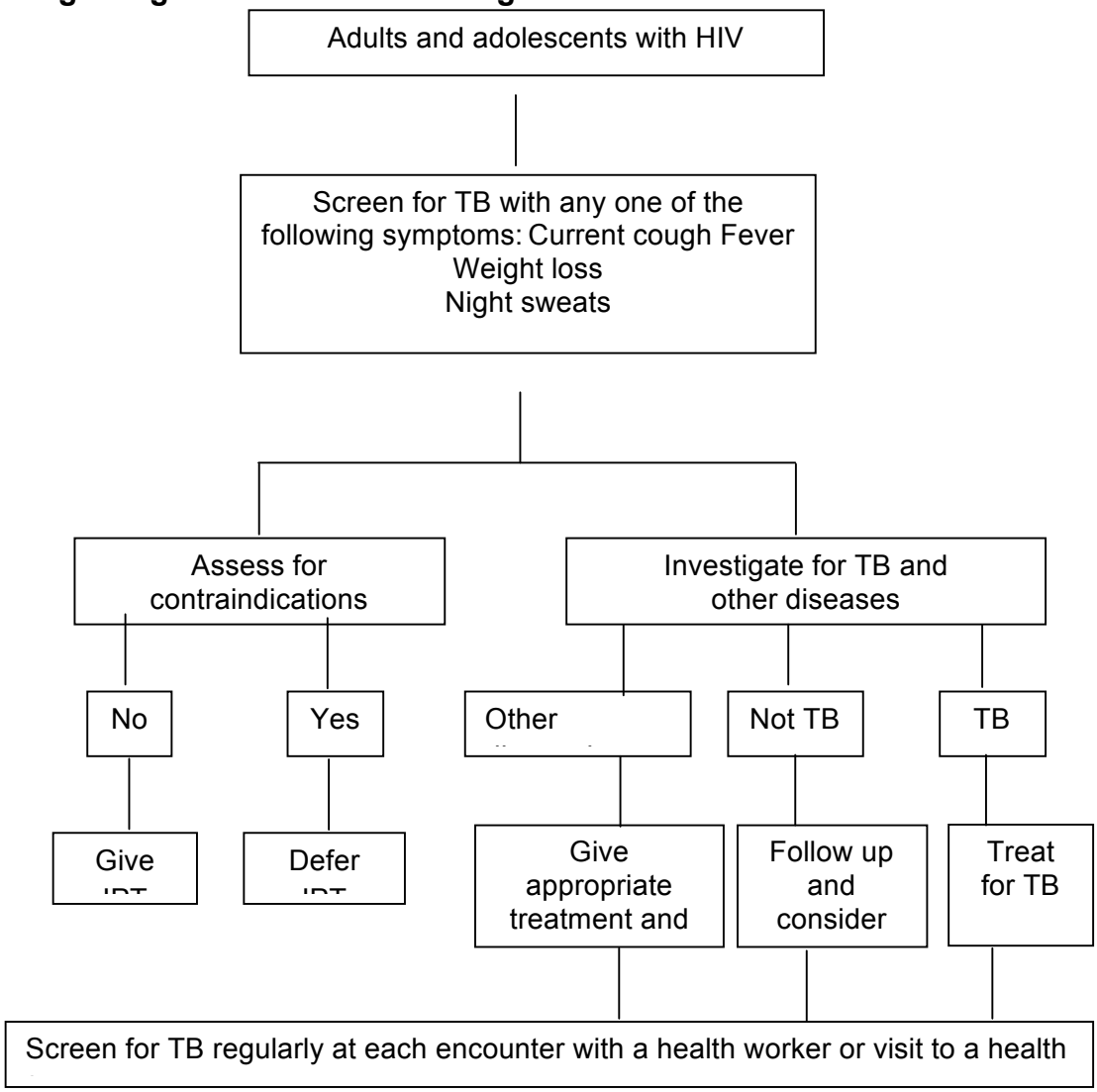
Adults and adolescents who are living with HIV have unknown or positive tuberculin skin test (TST) status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women

Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care services.

In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease

All children living with HIV, after successful completion of treatment for TB disease, should receive isoniazid for an additional six months.

Fig 1 .Algorithm for TB screening



3.4 Initiation of ART

All persons registered for care and treatment at CST centres should have their full history taken and undergo clinical examination, including determining the clinical stage of HIV. 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.

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 500 cells/mm^3.

The CD4 count should be assessed after stabilization of any concurrent illness because the absolute CD4 count can vary with illness.

Criteria for initiating ART

The decision to initiate ART is based on the CD 4 count and clinical stage of patient and is summarized in table 16 below:

Table16: Initiation of ART based on CD4 count & WHO clinical staging

WHO Clinical Stage	Recommendations
HIV infected Adults & Adolescents	
Clinical Stage I and II	Start ART if CD4 <500 cells/mm^3
Clinical Stage III and IV	Start ART irrespective of CD4 count
For Women	
Pregnant and breastfeeding women	Start ART irrespective of CD4 count and continue life long
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 BUT 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 severe liver disease	Start ART if CD4 < 500 cells/mm3
HIV and HBV / HCV co-infection - with evidence of severe liver disease	Start ART irrespective of CD4 count
Others	
Sero-discordant couple	Offer ART irrespective of CD4 count

Ensuring good adherence to the treatment is imperative for the success of the ART programme as well as for the prevention of drug resistance. To achieve this, counselling by the clinical team must start from the first visit itself. These counselling sessions should be aimed at preparing the patient for treatment and providing psychosocial support through an identified guardian/treatment buddy or 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.

Table17: Treat OIs first before starting ART

Clinical Picture	Action
Any undiagnosed active infection with fever	Diagnose and treat first; start ART when patient is 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 patient is stable
Invasive fungal diseases: esophageal 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 patient is stable
Acute diarrhoea which may reduce absorption of ART	Diagnose and treat first; Start ART when diarrhea is stabilized or controlled
Cytomegalovirus infection	Treat if drugs available for CMV; if not, start ART
Toxoplasmosis	Treat; start ART after 6 weeks of treatment and when patient is stabilized

Non-severe anaemia (Hb < 8 g/litre)	Start ART if no other causes for anaemia is found (HIV is often the cause of anaemia); avoid AZT
Malaria	Treat malaria first; start ART when treatment is completed

As a principle ART should not be initiated 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.

3.5 Choice of Antiretroviral Drugs /Regimen

Antiretroviral therapy with single or dual drug regimen is not recommended in any circumstances except for post exposure prophylaxis (PEP) of HIV in certain situations.

The basic principle remain that we have to use a triple drug combination from two different classes of ARVs. An NNRTI or a protease inhibitor with 2 NRTIs is potent combination and results in durable suppression of viral replication. Combination of ritonavir with another PI results in boosting by increasing it's plasma concentration, thereby reducing it's dose frequency and pill burden. Also 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
Some of the recommended ARV combinations are:

Principles of combination:

1. 2 NRTI + 1 NNRTI
   or
2. 2NRTI + 1 boosted PI
   or
3. 3NRTI *

Possible NRTI combination include:
Tenofovir + Emtricitabine (or Lamivudine)
Zidovudine + Lamivudine
Abacavir + Lamivudine

* Triple NRTI combinations are not very potent and are recommended only for individuals who are unable to tolerate or have contraindications to use of both NNRTI and PI based regimens, particularly in the following situations:

- HIV/TB co-infections
- Chronic viral hepatitis
- HIV 2 infection

Only two such combinations are recommended: ZDV+3TC+ABC, ZDV +3TC+TDF, use other triple NRTI options is not recommended

Choice of Initial Regimen

The 2010 guidelines recommended use of 2NRTI with NVP (or EFV in patients on concomitant) + 2 NRTI, which could be AZT or TDF. The guidelines also recommended phasing out d4T because of its long term toxicity. In 2010, there was no evidence that AZT is superior to d4T, AZT is superior to TDF or TDF superior to ABC or EFV is superior to NVP.

The guiding principle remain the same i.e. use fixed dose combination of three antiretroviral drugs, use simplified, less toxic and more convenient regimen. The first line ART essentially comprises of a NRTI backbone, preferably Non Thymidine and one NNRTI, preferably EFV.

Based on evidence supporting better efficacy and fewer side effects, it is now recommended to use TDF + 3TC + EFV as Fixed Dose Combination (FDC) in a single pill . This regimen also has advantage of harmonization

among all adults, adolescent, pregnant women, HIV TB and HIV Hepatitis co infected patients

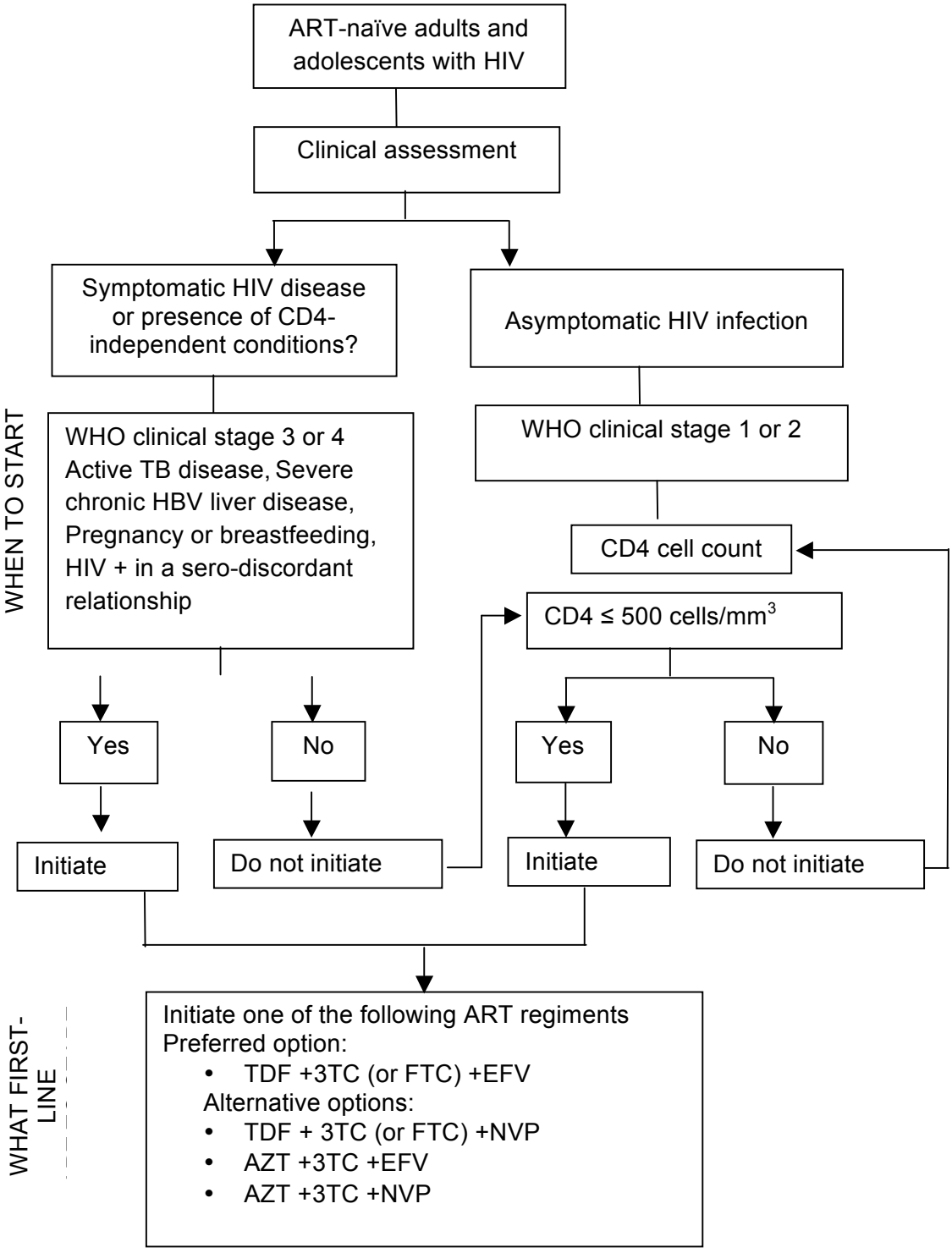
In cases where non Thymidine NRTI or EFV are contra indicated or have adverse events, the other combinations of AZT and NVP can be used as alternative first line.

The recommended regimens are in Table 18 below:

Table 18: Choice of first line ART regimen

First-line ART	Preferred first-line regimens	Alternative first-line regimens[a b]
Adults (including pregnant and breastfeeding women and adults with TB and HBV coinfection)	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Adolescents (10 to 19 years) ≥35 kg		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP ABC + 3TC + EFV (or NVP)

Fig 2. Algorithm for ART initiation in Adults and adolescents



Anti-retroviral regimen and combinations not recommended

Some antiretroviral (ARV) regimens or components are not generally recommended because of suboptimal antiviral potency, unacceptable toxicities, or pharmacologic concerns. These are summarized below.

Mono therapy with nucleoside reverse transcriptase inhibitor (NRTI): No potent and sustained antiviral activity

Dual-NRTI regimens: no potent and sustained antiviral activity

Triple-NRTI regimens except (ABC+3TC+ZDV) and (3TC+ZDV+TDF): suboptimal anti virologic activity

Two-non-nucleoside reverse transcriptase inhibitor (2-NNRTI) combinations: A higher frequency of clinical adverse events.

Lamivudine (3TC) +Emtricitabine (FTC) similar resistance profiles and minimal additive antiviral activity

d4T is no longer recommended as first line treatment due to long term irreversible and life threatening toxicities and is only used in rare situation where patients is anemic (hence cannot use AZT) and has renal failure (cannot use TDF) and has ABC hypersensitivity of ABC is not available.

3.6 What to expect in first six months of ART

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 especially among patients with very low CD4 counts. 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 the immune function of the patient recovers, 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.

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 patients 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).

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

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.

3.7 Immune reconstitution inflammatory syndrome: This is a condition that can occur shortly after a person starts HIV therapy for the first time. It can also occur in people who restart their ARVs after a time being off them. It is a spectrum of clinical signs and symptoms resulting from the body's ability to mount an inflammatory response associated with immune recovery. The suppression of CD4 T cells by HIV causes a decrease in the body's normal response to certain infections. Antiretroviral therapy partially restores immune defects caused by chronic HIV infection, including the restoration of protective pathogen-specific immune responses. If the CD4 count rapidly increases (due to effective treatment of HIV) a sudden increase in the inflammatory response produces nonspecific symptoms such as fever, and in some cases a paradoxical worsening of pre-existing symptoms of infective or non-infective conditions, e.g. TB, MAC or CMV. In general, people with more severely damaged immune systems before starting HIV therapy are most at risk for IRIS.

Possible risk factors for IRIS are listed below:

1. People with CD4 counts below 100 before starting therapy
2. People who start HIV therapy for the first time, or re-start therapy
3. People with greater drops in HIV viral loads due to therapy
4. People with a diagnosis of another infection before starting therapy, the closer the appearance or diagnosis is to starting therapy, the higher the risk
5. Severity of TB disease, especially high pathogen burden, and less than 30-day interval between initiation of TB and HIV treatments

IRIS occurs in two forms, "unmasking" and "paradoxical". It is explained with an example of tuberculosis.

Unmasking IRIS refers to the initial clinical expression of active TB occurring soon after ARV agents are started. Paradoxical IRIS refers to the worsening of TB clinical manifestations after ARV agents are started in patients who are receiving TB treatment.

Symptoms of IRIS may improve and resolve on their own. For others, the symptoms may persist or get worse and become life-threatening in which case it may be necessary to stop ARV and treat the underlying infection before restarting the ARV. Some of the examples are expanding Tuberculoma in the brain causing raised intracranial pressure, or rapidly enlarging lymph nodes in the neck causing respiratory distress due to airway compromise.

Most IRIS in HIV/TB disease occurs within 3 months of the start of TB treatment. Delaying the start of ART for 2–8 weeks may reduce the incidence and severity of IRIS but must be weighed against the potential benefit of earlier ART in improving immune function and preventing progression of HIV disease and mortality.

Milder or moderately severe cases of IRIS can be managed symptomatically or treated with non steroidal inflammatory agents. More severe cases can be successfully treated with corticosteroids.

In the presence of IRIS, neither TB therapy nor ART should be stopped because both therapies are necessary for the long-term health of the patient unless there are some life- threatening conditions as mentioned above.

3.8 Management of adverse effects of antiretroviral drugs

ARVs are not without adverse effects, adverse effects should be recognized as early as possible and resolved. Adverse events of major first line ARVs and recommendations to follow are given below. Please also see in the annex for the ARV to be replaced in case of adverse effect or intolerance:

Drug eruptions -mild to severe, including Stevens-Johnson syndrome or toxic epidermal necrolysis (NVP; less commonly -EFV): In mild cases, symptomatic care. EFV rash often stops spontaneously after 3−5 days without need to change ART. If moderate rash, non-progressing and without mucosal involvement or systemic signs, consider a single NNRTI substitution (i.e. from NVP to EFV). In moderate and severe cases, discontinue ART and give supportive treatment.

Renal toxicity (renal tubular dysfunction- TDF): Consider substitution with AZT.

Anaemia and neutropaenia (AZT): If severe (Hb <9.0 g/dl and/or ANC <750 cells/ mm3), replace with an ARV with minimal or no bone marrow toxicity (e.g. TDF) and consider blood transfusion.

Hepatitis (all ARVs -particularly NVP) : If ALT is at more than five times the basal level, discontinue ART and monitor. After resolution, restart ART, replacing the causative drug (e.g. EFV replaces NVP).

Lactic acidosis (all NRTIs): Discontinue ART and give supportive treatment. After resolution, resume ART with TDF.

Lipoatrophy and lipodystrophy (all NRTIs) :Early replacement of the suspected ARV drug (e.g. TDF or AZT).

Neuropsychiatric changes (EFV): Usually self-limited, without the need to discontinue ART. If intolerable to the patient, replace EFV with NVP or boosted PI. Single substitution recommended without cessation of ART.

Table 19: Suggested substitutes for toxicities

ARV Drug	Common associated toxicity	Suggested substitutes
Tenofovir (TDF)	Renal toxicity (renal tubular dysfunction)	AZT or ABC
Zidovudine (ZDV)	Severe anaemia or neutropenia Severe gastrointestinal intolerance	TDF or ABC
	Lactic acidosis	TDF or ABC
Abacavir (ABC)	Hypersensitivity reaction	AZT or TDF
Efavirenz (EFV)	Persistent and severe central nervous system toxicity	NVP or a boosted PI)
Nevirapine (NVP)	Hepatitis	EFV or a boosted PI)
	Hypersensitivity reaction	a boosted PI
	Severe or life-threatening rash Stevens Johnson syndrome	

3.9 Monitoring of ART

ART monitoring includes clinical monitoring and laboratory monitoring. Clinical monitoring includes monitoring of the ART adherence also. The client should be monitored in the regular interval for clinical progress, for the side effects of the ARV and the adherence counseling. Clinical and laboratory evaluations are carried out in these visits. The follow up intervals for ART are recommended as below:

First month: follow up visit in every two weeks

Second month onward: follow up visit every month

Once stabilized and CD starts improving (after 6 months on ART) and patient does not have any OI or adverse events, the visit frequency can be once in 2 or 3 months depending on drug stocks, distance patient has to travel to reach CST Centre

More frequent visits will be required, if the patient develops symptoms, side effects of the ARVs or experiences difficulties in adherence to ARVs because of any reason.

Monitoring of patients started on Nevirapine based regimen

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.

Table 20:. Guidance for starting NVP based regimen

	Morning	**Evening**
lead-in NVP dose for the first 2 weeks	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)

Laboratory Monitoring:

Symptom-directed laboratory monitoring for safety and toxicity is recommended for those on ART. If resources permit, use viral load in a targeted approach to confirm suspected treatment failure based on immunological and/or clinical criteria.

If resources permit, use viral load in a routine approach, measured every 6 months, with the objective of detecting failure earlier than would be the case if immunological and/or clinical criteria were used to define failure.

Table 21: Recommended laboratory test in different phases of ART

Tests	Baseline Day 0	At 15 days	At 1 month	At 2 month	At 3 month	At 6 month
CBC/Hb	Y	Y (if on AZT)	Y (if on AZT)	Y (if on AZT)	Y	Y
Creatinine	Y				Y	Y (if on TDF)
LFT/ALT	Y	Y(if on NVP)	Y(if on NVP)		Y	Y
Urea	Y					Y
CD4 count/%	Y					Y
Urine R/M/E Esp for albumin and sugar	Y					Y (if on TDF)
Lipid profile	Y					Y
Random Blood sugar	Y					Y
Gene Xpert	Y (If TB Suspect)					
CXR	Y					
Viral load If facility available						Y(If available)
Pregnancy test	Y					
Pap smear (for females)	Y					

The estimation of the CD4 count for patients receiving ART is recommended at six months to document immunological improvement.

For patients on TDF, random blood sugar, urine sugar and albumin is mandatory while Serum creatinine be done wherever available and Creatinine Clearance be calculated using CG formula

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 hematological 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 is diabetes.

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 IRIS and new episodes of OIs.

Patients who are not yet eligible for ART should have CD4 count measurement every six months. In PLHIV with drug use background, test for Hepatitis B and Hepatitis C should be performed in order to identify people with HIV/Hepatitis co-infection and who, therefore, should initiate TDF-containing ART.

For a patient who is not responding to treatment, a viral load test and resistance testing will be requested whenever feasible. Ideal viral load testing schedule would be if virologic failure is suspected and every 6 months after starting ART.

3.10 ART adherence

A high degree of adherence to ARV drugs is necessary for optimal virological suppression. Studies indicate that over 95% of the doses should be taken for optimal viral suppression. Lesser degree of adherence is more often associated with virological failure. Adherence should be assured before initiation of antiretroviral therapy. The patient should fully understand the importance of adherence. Adherence counseling and patient education should be done at every follow-up visit.

At least two to three preparatory adherence counselling visits should be made before the start of ART.. After the final preparatory visit, the treating physician and counselor should jointly consider the patient's readiness to start treatment.

Suggested contents of the pre ART adherence in each visit include the following.

Visit 1

1. Clinical assessment by a doctor.
2. Exploring the client's knowledge and understanding of HIV and his or her own health status.
3. Introduction of the concept of ART and other treatments (OI) to the client.
4. Explaining the consequences of non-adherence.
5. Exploring potential barriers to adherence.
6. Explaining the transmission of resistance and review the client's personal plans for reducing transmission risk.
7. Discussing the concept of having a "treatment buddy" selected by the client or a trained volunteer appointed to assist with the client's permission.

Visit 2

1. Feedback by the doctor to the client on the medical assessments conducted during the previous visit.
2. Review of the client understanding of information provided in the previous visit and assessing the client's understanding of the feedback provided by the doctor.
3. Reviewing the potential barriers that the client anticipated in the previous visit and offering strategies for addressing these barriers
4. Reviewing the treatment plan with the client (the correct dose in the correct way at the correct time).

Visit 3

1. Reviewing the client's understanding of information provided in the previous two sessions. Reinforcing the fact that there is a much to remember and it is not easy.

2. Reviewing client problem-solving strategies and familiarizing the client with the counselling treatment reminder cue cards and adherence recording tools (if any).
3. Reviewing the treatment plan again, as in visit 2.
4. Assessing the client's readiness by simply asking the client to answer the questions about the regimen and what the client proposes to do when there are problems.
5. Providing feedback on the client's readiness to the medical team.
6. Meeting with the client's"treatment buddy" to review his or her role and to for follow-up arrangements with clients. A start date for" buddy support" should be established.

After starting ART follow up visit ideally should be in two wks and in one month after the start of ART. After a month adherence measurement and counseling should be done every month or whenever patient comes to collect ARV.

During each visit some of the information provided in the previous visit can be reviewed and the client's understanding should be assessed.

Ongoing ART Adherence counseling

The individual should have a follow-up adherence counselling visit within one to two weeks and continuous adherence counselling at regular intervals throughout ART. Adherence barriers can change over time and individual patients will need different levels of support as their life circumstances change and they become accustomed to their treatment.. Adherence support therefore needs to change over time as well. Ongoing adherence counselling and continuing interactive communication are the keys to providing effective adherence support to the patient on ART.

A typical follow-up counselling session involves:

1. reviewing the treatment experience of the client;
2. assessing any need for referral back to the doctor (usually related to side-effects);
3. monitoring adherence (over a defined period);
4. reviewing and finding solutions to barriers to adherence;
5. reviewing adherence to transmission risk reduction; and
6. conducting a psychosocial assessment.

Calculating Adherence:

Pill count is recommended to calculate the adherence. In each follow up visit, patient should be asked to bring the remaining pills provided in the previous visits. Following formula is used to calculate the adherence.

Adherence in percent = Total number of pills the patient has actually taken/ total number of pills should have taken in that time period X100.

Adherence should be above 95%

3.11 Criteria for treatment success

Some suggested criteria for evaluating the treatment success of the ART regimen; the clinician should use his or her own judgment for the final decision.

Clinical criteria: By 12 weeks of the treatment initiation patient should become asymptomatic or has only few symptoms, suggested range of the WHO clinical staging is the clinical stage 1 or 2.

Immunological criteria: CD4 count of the patient increases from the baseline by 50-100 cells/mm3 within 6-12 months of the initiation of the ART. In patients with optimal antiretroviral therapy CD4 count increases by more than 100 cells/mm^3 in the first 6-12 months in ARV naive who are adhere to their treatment

Virological criteria: Suggested viral load in 24-48 weeks after the initiation of ART is less than 1000 copies/ml

3.12 Failure of Antiretroviral Therapy

An individual must be on regular ART with good adherence for at least 6 months before it can be determined whether the regimen has failed. Apart from this, adherence has to be assessed and optimized, intercurrent opportunistic infections have to be treated and resolved, and IRIS has to be excluded.

Table22: Criteria for Treatment failure

Failure	Definition	Comments
Clinical failure	New or recurrent WHO stage 4 condition	Condition must be differentiated from immune reconstitution inflammatory syndrome (IRIS)[a] Certain WHO clinical stage 3 conditions (eg pulmonary TB, severe Bacterial infections may be an indication of treatment failure[b.]
Immunological failure	Fall of CD4 count to baseline (or below)OR 50% fall from on-treatment peak value OR persistent CD4 levels below 100cells/mm^3	Without concomitant infection to cause transient CD4 cell decrease[c.]
Virological failure	Plasma viral load above 1000 copies/ml	

Notes:

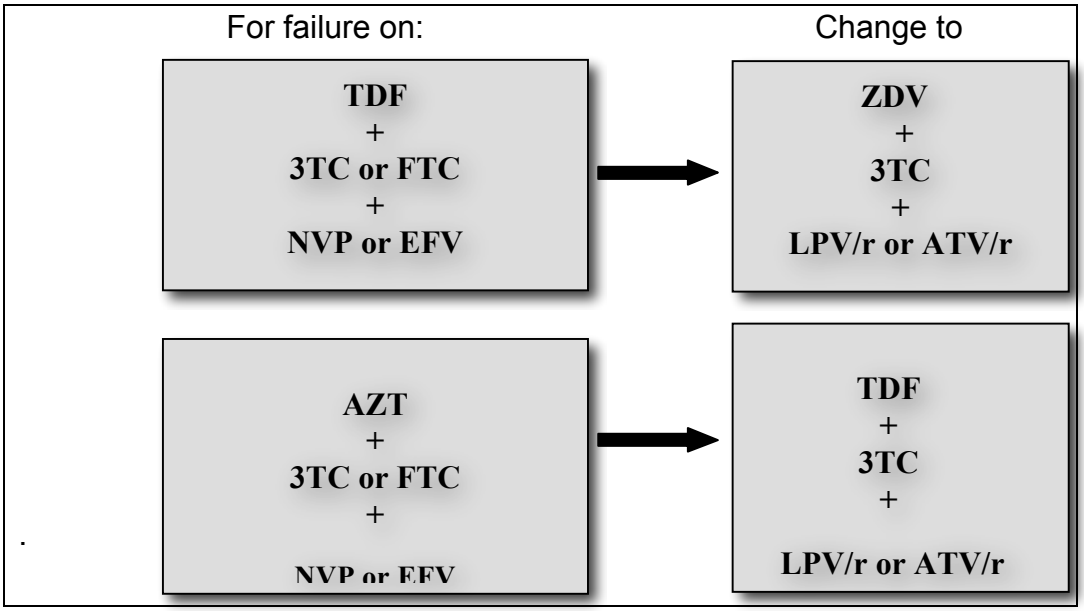
- **a.** See related section below for details.
- **b.** TB can occur at any CD4 level and does not necessarily indicate ART failure. The response to TB therapy should be used to evaluate the need to switch ART. With pulmonary TB and some extra pulmonary TB diagnoses (e.g. lymph node TB or patients with uncomplicated pleural disease), where a good response to TB therapy is frequently seen, the decision to switch ART can be postponed and monitoring can be increased. This also applies if severe and/or recurrent bacterial infections or oesophageal candidiasis, which respond well to therapy.
- **c.** As a general principle, intercurrent infections should be managed, time should be allowed for recovery and the CD4 cell count should be measured before ART is switched. If resources permit, a second CD4 cell count should be obtained to confirm immunological failure. In general, switching should not be recommended if the CD4 cell count is above 200 cells/mm^3
- **d.** An undetectable viral load mandates that ART should not, in general, be switched irrespective of the CD4 cell count or the clinical stage.

3.13 Switching ARV in case of treatment failure

In case of treatment failure, the entire regimen should be changed from a first to a second line combination regimen. A single drug should not be added or changed to a failing regimen. The new second-line regimen will need to use drugs which retain activity against the patient's virus strain and a minimum of three active drugs, one of them drawn from at least one new class, in order to increase the likelihood of treatment success

and minimize the risk of cross-resistance. The PI class is thus reserved for second-line treatments. Ritonavir-boosted protease inhibitors (RTV-PIs) are preferred. They should be supported by two new agents from the NRTI class. Patients should not switch from one NNRTI to the other at the time of failure, as there is a high chance of cross-resistance (i.e. do not give EFV after NVP or vice versa).

Table 23: Recommended second-line regimens in adults and adolescents:



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3.14 Considerations for ART in Adolescents

According to WHO, adolescence is the period between 10-19 years of age. During this period, healthy HIV infected adolescents pass through well-described stages of physical, psychological and sexual maturation for which appropriate care and treatment is 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 ofappropriate ART regimens
- Adherence issues
- Psychosocial support needs
- Physical and sexual issues

Section 4
Anti retroviral drugs treating pregnant women and preventing HIV infection in infants

This section contains following topics:

1. **Options for ARVs for HIV-Positive Pregnant Women**
2. **National Guidance on Use of ARVs for Pregnant Women**
3. **Special situations in pregnancy and related recommendations:**

4.1 Options for ARVs for HIV-Positive Pregnant Women

In the consolidated guidelines on the use of Antiretroviral drugs for treating and preventing HIV infection published in June 2013, the WHO recommended two options:

(i) providing lifelong ART to all pregnant and breastfeeding women living with HIV regardless of CD4 count or clinical stage; or

(ii) providing ART (ARV drugs) for pregnant and breastfeeding women with HIV during the mother-to-child transmission risk period and then continuing lifelong ART for those women eligible for treatment for their own health.

Table 24: WHO ART Option for Pregnant and Lactating Women

<table>
<tr><th>National PMTCT Program Option</th><th colspan="2">Pregnant and Breastfeeding Women with</th><th colspan="2">HIV-Exposed Infant</th></tr>
<tr><td rowspan="2">Use lifelong ART for all pregnant and breastfeeding women (“Option B+”)</td><td colspan="2">Regardless of WHO clinical stage or CD4 cell count</td><td>Breastfeeding</td><td>Replacement feeding</td></tr>
<tr><td colspan="2">Initiate ART and maintain after delivery and cessation of breastfeeding</td><td rowspan="3">6 weeks of infant prophylaxis with once-daily NVP</td><td rowspan="3">4-6 weeks of infant prophylaxis with once-daily NVP (or twice-daily AZT)</td></tr>
<tr><td rowspan="2">Use lifelong ART only for pregnant and breastfeeding women eligible for treatment (“Option B”)</td><td>Eligible for treatment [a]</td><td>Not eligible</td></tr>
<tr><td>Initiate ART and maintain after delivery and cessation of breastfeeding [b]</td><td>Initiate ART and stop after delivery and cessation</td></tr>
</table>

a CD4 count ≤500 cells/mm3 or clinical stage 3 or 4 disease at the time of ART initiation on in accordance with national guidelines.

b Patients who develop clinical or laboratory criteria indicating failure during pregnancy or the breastfeeding period should be assessed for the second-line therapy.

c In the case of breastfeeding stop ART one week after breastfeeding ends. In case of replacement feeding stop ART after delivery.

4.2 National Guidance on Use of ARVs for Pregnant Women

In line with the Third National Strategic Plan for HIV and AIDS Response (2011-2015) and Implementation Plan of National Strategic Plan as well as to achieve the goal of the global plan for the elimination of MTCT of HIV infection by 2015 and keeping their mothers alive, the Ministry of Health and Family Welfare of Bangladesh recommends **the provision of**

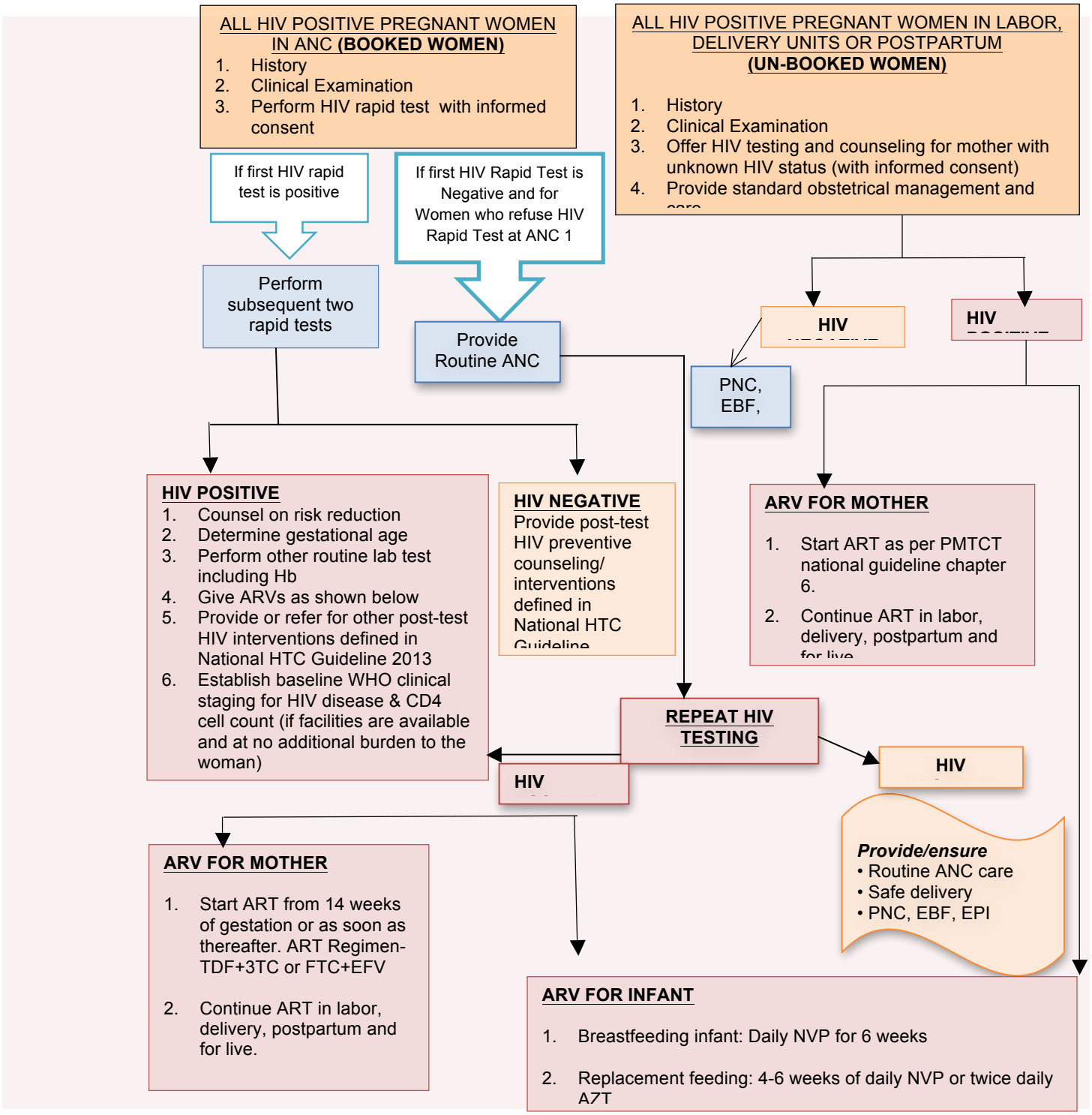
lifelong ART to all pregnant and breastfeeding women living with HIV regardless of CD4 count or clinical stage. (option B+)

However, WHO clinical staging and CD4 testing is recommended at baseline to monitor progress. Infants born to mothers on HAART would be provided with daily NVP or AZT for 6 weeks regardless of feeding options. Later on, these mothers should be transferred for continuous care and monitored accordingly.

4.2 ART Regimens for HIV-Positive Pregnant Women and ARV Prophylaxis for Infants

ART should be started for life-long for all HIV positive pregnant women from as soon as found positive irrespective of duration of pregnancy (including first trimester) or as soon as possible thereafter if women present later in pregnancy, in labor or at delivery. Irrespective of mode of infant feeding, all infants exposed to HIV are to be provided with NVP or AZT from birth (within 6-12 hours) or as soon as feasible thereafter until 4 to 6 weeks of age.

Figure 3 (below) shows the *Clinical Algorithm for Use of Anti-Retroviral (ARV) for Treatment and PMTCT of HIV in ANC, Labour and Delivery and Postpartum Period in Bangladesh.*



The recommended first-line ART regimen for pregnant and breastfeeding women, including women in the first trimester of pregnancy and women of childbearing age is presented in table 4.2 the prophylactic regimen for exposed infant is in table 4.3 and the maternal and exposed infant prophylaxis in different scenario is presented in table 4.4:

Table 25: Recommended First – Line ART for HIV positive pregnant and breastfeeding women

REGIMEN	
Preferred	TDF+3TC (or FTC)+EFV****(TDF-based first-line regimen in conjunction with EFV has more favorable clinical profile)***
	AZT+3TC+EFV (to be used if TDF cannot be used for some reason)
Alternative	AZT+3TC+LPV/r
	AZT+3TC+ABC

***** EFV is clinically superior to NVP, as it provides better long-term viral suppression, has fewer adverse events and less risk of resistance.

Table 26. Prophylactic Regimen for Exposed Infants

Birth Weight	Nevirapine Dose*	AZT Dose (Only recommended in
<2000 g	2 mg/kg body weight once daily	2 mg/kg body weight twice daily
2000 – 2499 g	10 mg per day once daily	10 mg two times a day
2500 g and above	15 mg per day once daily	15 mg two times a day

*Recommended for 6 weeks, but 4 weeks may be considered in settings with replacement feeding.

Table 27: Summary of Maternal ART and Infant ARV Prophylaxis for different Clinical Scenario

Clinical Scenario	Maternal ART[a]	Infant ARV	Duration of infant ARV prophylaxis
Mother diagnosed with HIV	Initiate maternal ART	NVP [c]	6 weeks [c]
Mother diagnosed with HIV during labour or immediately postpartum and	Initiate maternal ART	NVP	6 weeks; consider extending this to12 weeks
Mother diagnosed with HIV during labour or immediately postpartum and plans replacement	Refer mother for HIV care and evaluation for treatment	NVP [c]	6 weeks [c]
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is breastfeeding	Initiate maternal ART	NVP	Perform infant PCR early infant diagnosis test and then immediately initiate 6 weeks of NVP – strongly consider extending this to 12 weeks
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody	Refer mother for HIV care and evaluation for treatment	No prophyl actic drug	Do HIV DNA PCR test for early infant diagnosis; no infant ARV prophylaxis;

Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to	Determine an alternative ART regimen or solution;	NVP	Until 6 weeks after maternal ART is restarted or until 1 week after breastfeeding has

[a] *Ideally, obtain the mother's CD4 cell count at the time of initiating or soon after initiating ART;*

[b] *If infant NVP causes toxicity or NVP is not available, 3TC can be substituted.*

[c] *If the mother is using replacement feeding, infant AZT can be substituted for infant NVP; if there is documented maternal viral suppression near delivery for a mother receiving ART and using replacement feeding, four weeks of infant ARV prophylaxis may be considered.*

[d] *If it is known that the mother has initiated ART less than 4 weeks before delivery, consider extending infant NVP for infants who are breastfeeding to 12 weeks.*

4.3 Special situations in pregnancy and related recommendations:

Women with Anaemia in Pregnancy/Postpartum period

Pregnant or breastfeeding women taking ART who develop clinically significant or severe anaemia (Hb<9g/dl) should be started on a non-AZT containing regimen while anaemia is being corrected. In such cases, AZT can be replaced with TDF.

For women who have clinically significant or severe anaemia and need to start ART, a non-AZT containing regimen should also be considered, e.g. TDF + 3TC (or FTC) + EFV.

Women already exposed to NVP in previous pregnancy

In such cases the initial regimen should consist of a boosted PI along with a TDF+3TC backbone. The preferred PI will be LPV/r in such cases

Women with HIV/Tuberculosis (TB) co infection

a) Women with active TB

HIV-infected pregnant women with active TB should start ART irrespective of the CD4 cell count. The TB treatment should be started first, and followed by ART as soon as clinically possible (within 8 weeks after the start of TB treatment). In case of profound immunosuppression (such as CD4 counts less than 50 cells/mm3), the woman should receive ART immediately within the first two weeks of initiating TB treatment.

Drug interactions between Rifampicin and some of the antiretroviral drugs (i.e. the boosted protease inhibitors) complicate simultaneous treatment of the two diseases. As for all adults, EFV is the preferred NNRTI for HIV/TB co-infected pregnant women. For those HIV/TB coinfected women not able to tolerate EFV, a triple NRTI regimen e.g. AZT + 3TC + ABC can be used.

b) Women without active TB

All pregnant women as of adults and adolescents living with HIV should be clinically screened for TB. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered Isoniazid Preventive Therapy (IPT) until IPT is contraindicated. It is contraindicated in case of active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. In such situations IPT has to defer and follow-up regularly.

Women who have unknown or positive tuberculin skin test (TST) status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. A TST is not a

requirement for initiating IPT. Women, as of other adults and adolescents, living with HIV who have a positive TST benefit more from IPT. Providing IPT to people living with HIV does not increase the risk of developing isoniazid resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.

Women with hepatitis B or hepatitis C virus co-infection

ART should be started in all pregnant women co-infected with HIV and HBV when treatment is required for the HBV infection, irrespective of the CD4 cell count or the WHO clinical stage. Co-infected pregnant women requiring ART and HBV treatment should receive a regimen containing TDF and 3TC (or FTC). These recommendations are the same as those for all adults.

When co-infected pregnant women do not require HBV treatment; ART should follow the general recommendation for HIV-infected pregnant women. However, it is important to note that in HIV/HBV-co-infected pregnant women who do not require treatment of HBV and also do not require lifelong ART for their own health, hepatic flares may occur with the use of maternal triple ARV for prophylaxis of MTCT (option B) when the triple ARVs are stopped. Initiating ART among people with HIV and hepatitis C should follow the same general principles as for the people living with HIV but do not have hepatitis C.

Pregnant women living with HIV who are injecting drug users

Methadone substitution treatment is currently recommended for opioid-dependent pregnant women. Evidence are limited on the use of buprenorphine in pregnancy. Opioid substitution therapy (OST) should be combined with psychosocial counseling, including support groups,

community reinforcement, contingency treatment and motivational therapy and similar modalities.

In general, the same recommendations for ART or ARV prophylaxis for pregnant women living with HIV apply to those who are also PWIDs. For pregnant women already on or starting ART, drug interactions may be a concern. Interactions between methadone and ARV drugs are the same in pregnant women as in other patients. Drug interactions may result in decreased methadone levels or raised ARV levels, increasing the risk of methadone withdrawal or ARV-related side-effects. NNRTI decrease methadone levels while methadone raises AZT concentration. Hence close monitoring and titration of dose is needed.

The use of methadone is sufficient to prevent withdrawal symptoms in opioid-dependent women presenting around labour. The neonatal withdrawal syndrome comprises the signs and symptoms exhibited by newborn infants cut off abruptly after prolonged exposure to drugs during pregnancy. The syndrome occurs in about 60% of neonates who have been exposed to these drugs, usually during the first 48−72 hours of life, although methadone withdrawal can occur up to 2 weeks after birth.

Pregnant women living with HIV and malaria

The drugs used to treat malaria and ARV drugs may share toxicities (particularly sulfa-based drugs) and may have clinically important pharmacokinetic interactions (especially artemesinins, lumefantrine, NNRTIs and protease inhibitors). For this reason, women receiving treatment for both HIV and malaria should be monitored closely for adverse drug reactions, and people with HIV receiving AZT, or EFV should, if possible, avoid amodiaquine-containing artemisinin-based

combination regimens because of increased risk of neutropaenia in combination with AZT, and hepatotoxicity in combination with EFV.

Pregnant women with HIV-2 infection

HIV-2 is naturally resistant to NNRTIs. So, treatment-naive people co-infected with HIV-1 and HIV-2 should be treated with a regimen containing three NRTIs -TDF + 3TC (or FTC) + AZT or AZT + 3TC + ABC or a ritonavir-boosted PI plus two NRTIs. If a PI-based regimen is used, the preferred option for first-line therapy should be LPV/r.

Women who acquire primary infection during pregnancy or breastfeeding

Women who become infected with HIV during pregnancy or while breastfeeding have a very high risk of transmitting the virus to their infants. In a meta-analysis the risk of transmission to infants was about 30% among women who acquired HIV infection during breastfeeding (WHO, 2010).

Retesting of women late in pregnancy is therefore important in order to identify those with recent HIV infection who can benefit from access to HIV prevention and care interventions.

In high-prevalence and generalized epidemic settings and **among high risk women in the context of Bangladesh**, women who tested negative early in pregnancy should be systematically offered repeat HIV testing in the third trimester of pregnancy, as recommended in the WHO 2010 HIV counseling and testing guidelines. There are currently no data that indicate which ART is most efficacious for a pregnant woman with primary HIV infection. Consequently, standard ART regimens for prevention of PMTCT should be used (TDF+3TC+EFV)

Section 5

Antiretroviral therapy in Children

This section contains following topics

5.1 Establishing a diagnosis of HIV infection in infants and children

Infants who acquire HIV before or around delivery, disease progression occurs very rapidly in first few months of life, often leading to death. So, early determination of HIV exposure and definitive diagnosis is critical to allow early initiation of potentially life saving ART. However, in the absence of virological testing it is always difficult to establish the diagnosis of HIV infection in infant and children of age less than 18 months. Until the time when virological testing will be easily available in Bangladesh, it is recommended to use the best obtainable laboratory methods and clinical judgments for establishing the diagnosis of HIV infection in children. Given below are the standard recommended ways of diagnosing HIV infection in infant and children:

a. Diagnosis using Antibody testing with serological assays

b. Diagnosis using Virological testing with DNA PCR

c. Presumptive diagnosis of severe HIV disease

Antibody testing using serological assays

It is strongly recommended that children aged 18 months or older, with suspected HIV infection or HIV exposure, have HIV serological testing performed according to the standard diagnostic HIV serological testing algorithm used for adults. It is also strongly recommended that HIV serological assays (HIV antibody testing) used for the purpose of clinical diagnostic testing should have a minimum sensitivity of 99% and specificity of 98%, under quality assured, standardized and validated laboratory conditions. If the rapid tests are used then the test kits should be used following a standard algorithm and results should be provided on the basis of algorithm, not on the basis of the reactivity of the single test kit. The result of the test should be used as follows:

a. Less than 18 months of age –as a screening assay to determine HIV exposure

b. More than 18 months of age –as a diagnostic assay

Virological test

Virological tests are the recommended tests for all HIV-exposed infants and children less than 18 months of age for diagnosing HIV infection. It should be done at 4 to 6 weeks of age or at the earliest opportunity thereafter. ART guideline team recommends HIV DNA PCR on whole blood specimen or dried blood spots (DBS) as virological test for HIV diagnosis in children and infants. If the infant presents at the age of around 9 months and did not have virological test at the age of 4-6 weeks, then virological tests are done only if the infant is reactive to the antibody (serological) testing. Virological testing facilities are not widely available in Bangladesh, so possibilities of collecting sample in the country and sending to the laboratories in the region should be considered. Collecting sample in DBS and sending for the test in the

regional laboratory is one of the ideal options. In infants with an initial positive virological test result, it is strongly recommended that ART be started without delay. In infected infants immediate initiation of ART saves lives and commencement of ART **should not be delayed.**

Presumptive diagnosis of severe HIV disease

In sick infants in whom HIV infection is being considered as an underlying cause of symptoms and signs, and virological testing is not available, it is recommended to do the HIV serological testing and use the clinical algorithm for presumptive clinical diagnosis of HIV infection. See below:

Table 28: Criteria for presumptive diagnosis of severe HIV disease in infants and children <18 months of age where viral testing is not available

<table>
<tr><td colspan="2">A presumptive diagnosis of severe HIV disease should be made if:</td></tr>
<tr><td>1. The child is confirmed as being HIV antibody-positive

AND</td><td>2a. The infant is symptomatic with two or more of the following:
• Oral thrush[1]
• Severe pneumonia[2]
• Severe sepsis[3]
OR
2b. A diagnosis of any AIDS-indicator condition(s)[4] can be made</td></tr>
<tr><td colspan="2">Other findings that support the diagnosis of severe HIV disease in an HIV-seropositive infant include:
• Recent HIV-related maternal death or advanced HIV disease
• Child's %CD4 + <20%</td></tr>
<tr><td colspan="2">Confirm the diagnosis of HIV infection as soon as possible</td></tr>
</table>

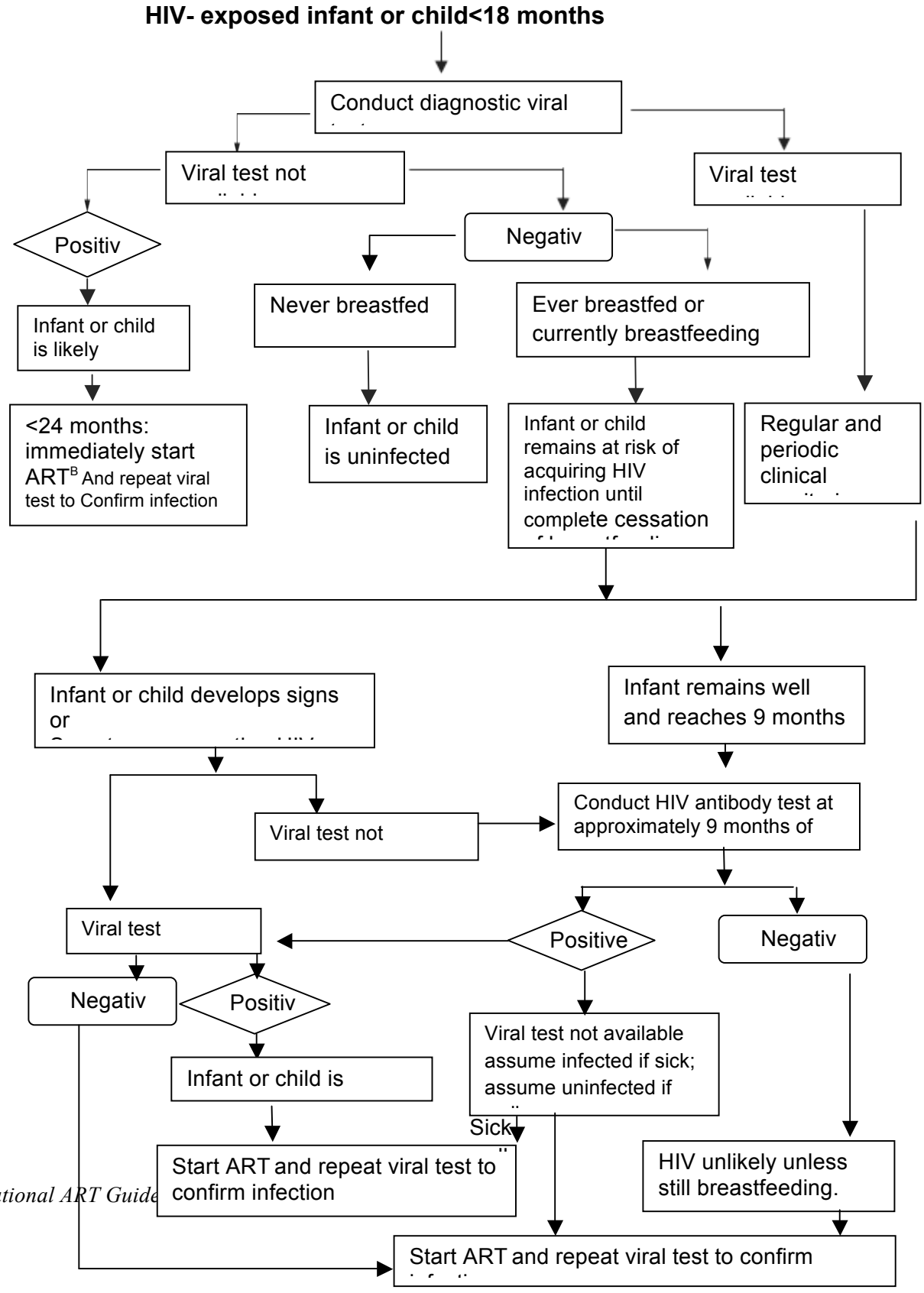
Notes: As per the IMCI definition:

1. *Oral thrush: Creamy white-to-yellow soft small plaques on red or normally coloured mucosa which can often be scraped off (pseudomembranous), or red patches on the tongue, palate or lining of mouth, usually painful or tender.*
2. *Severe pneumonia: Cough or difficult breathing in a child with chest indrawing, stridor or any of the IMCI general danger signs; i.e. lethargic or*

unconscious, not able to drink or breastfeed, vomiting, and presence or history of convulsions during current illness; responding to antibiotics.

3. *Severe sepsis: Fever or low body temperature in a young infant with any severe sign, e.g. fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions.*
4. *AIDS-indicator conditions include some but not all HIV paediatric clinical stage 4 conditions such as Pneumocystis pneumonia,cryptococcal meningitis, severe wasting or severe malnutrition, Kaposi sarcoma, extrapulmonary TB.*

Fig 4: Algorithm for early infant diagnosis



Addressing loss to follow up

The purpose of HIV diagnosis in children is to provide quick treatment and to save life. Since the process of diagnosing infant and children is time consuming and often children are lost before getting the final result. Similarly keeping children in the continuous therapy is often a challenge. So all the chances of meeting these children and doing follow up should be used. Government immunization clinics, NGOs, PLHIV networks and other volunteers should be mobilized for this purpose.

ART for infants and children

Initiation of Antiretroviral Therapy (ART) at the earliest is crucial in reducing mortality and morbidity of infants and children. Recommendations for the care of those who are HIV-infected will change over time, but the challenges of providing this care are the major hurdles in managing both acute and chronic conditions. ART is a life-long therapy, and HIV-infected infants and children are surviving till adolescence and adulthood today. The decision to start ART, depends on, the age of the child, clinical and immunological staging.

5.2 When to start ART in infants and children

Recent WHO consolidated guideline recommends the initiation of ART regardless of clinical and immunological status to children younger than five years. Such expansion eliminates the need for determining the CD4 count to initiate treatment in this age group and avoids delaying ART in settings without access to CD4 testing. However, the availability of CD4 testing, including determining the baseline CD4 count and percentage, remains important to ensure appropriate treatment monitoring in the absence of viral load monitoring.

Recommendations for initiation of ART are as follows:

 ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count.

 ART should be initiated in all HIV-infected children **five years of age and older** with CD4 cell count ≤ 500 cells/mm3, regardless of WHO clinical stage

 ART should be initiated in all children infected with HIV with **severe or advanced symptomatic disease** (WHO clinical stage 3 or 4) regardless of age and CD4 cell count

 ART should be initiated in any **child younger than 18 months of age who has been given a presumptive clinical diagnosis** of HIV infection.

Table 29 : Summary of recommendations on when to start ART in infants and children

Age	When you start
Infants (<1year)	Treat all individuals
1 year to less than 5 years	Treat all individuals
5 years and above	WHO stage 3 or 4 or CD4 ≤500 cells/mm^3

ART should generally be deferred until acute infections have been treated, whenever possible.

In the case of confirmed or presumptive TB disease, initiating TB treatment is the priority. Any child with active TB disease should be started on TB treatment immediately and ART should be started between 2 to 8 weeks of TB treatment, preferably as early as possible, irrespective of the CD4 count and clinical stage. When decided to start ART, one should also consider the child's social environment, including

identification of a clearly defined caregiver who understands the prognosis of HIV and the requirements of ART.

5.3 What to start- ART Regimens for infant and childen

First-line ART for children younger than three years of age

A LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than three years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with a NVP-based regimen. For infants and children infected with HIV younger than three years, the NRTI backbone for an ART regimen should be ABC or AZT + 3TC.

For infants and children infected with HIV younger than three years, **ABC+3TC+AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r.** Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be re-started.

First-line ART for children three years and older (including adolescents)

For children infected with HIV, who are three years and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative. For children infected with HIV three years to less than 10 years old (or adolescents less than 35 kg), the NRTI backbone for an ART regimen should be one of the following, in preferential order:

• ABC + 3TC
• AZT+3TC or TDF + 3TC (or FTC)

Special note: Consideration should be given to the relative merits of ABC versus TDF versus AZT for this population. There is no definitive evidence to make a preferred recommendation, and each option has its respective risks and benefits. ABC can be used once daily, is available across age groups as a fixed-dose combination with 3TC and harmonizes with TDF from a resistance perspective. AZT has been widely used and is available as dual and triple fixed-dose combinations with NVP but is dosed twice daily and can cause severe anaemia. TDF has recently been approved for use in children, and the advantages include once-daily dosing. However, paediatric TDF formulations are not widely available, experience with TDF in children is limited and there are concerns about the long-term effects of bone toxicity.

For adolescents infected with HIV (10 to 19 years old) weighing 35 kg or more, the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in preferential order:

• TDF + 3TC (or FTC)
• AZT + 3TC
• ABC + 3TC

Special note: TDF-containing fixed-dose combinations are currently only available in adult, unscored tablets for once-daily use. At or above 35 kg, the dose of TDF in adult dual and triple fixed-dose combinations and the dose of EFV in adult triple fixed-dose combinations are acceptable for use in adolescents. ABC or boosted PIs can be used in special circumstances.

Fig 5: Algorithm for ART in children

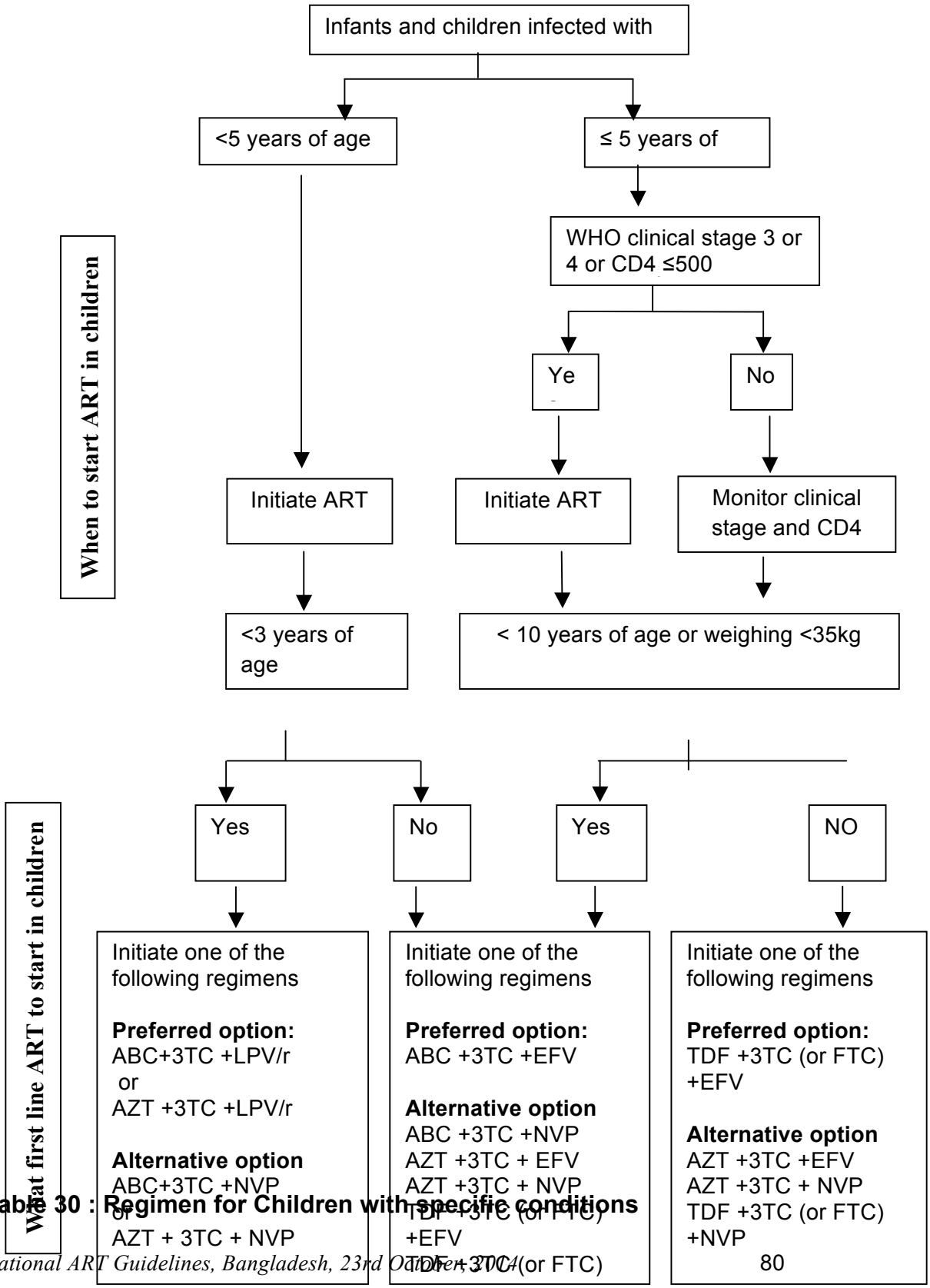


Table 30 : Regimen for Children with specific conditions

Condition	Preferred regimen	Alternative regimen
Children more than 3 years of age with tuberculosis (TB)	EFV+AZT+ 3TC	AZT+3TC+ABC
Infants and children less than 3 years of age with TB	AZT+3TC+NVP	AZT+3TC+ABC
Child or adolescent with severe anaemia (<7.5 g/dl) or severe neutropenia (<0.5/mm3), (avoid AZT).	ABC+3TC+NVP	
Adolescents more than 12 years of age with hepatitis	TDF+3TC(FTC)+EFV	

Table 31:Dosage of first line ARVs for infants and children

Body weight		3-6 kg		6-10 kg		11-14 kg		15-20 kg		21-25 kg	
Drug	Strength	am	pm	am	pm	am	pm	am	pm	am	pm
AZT syrup	10 mg/ml	6ml	6ml	9ml	9ml	12ml	12ml				
AZT tablet	300 mg							½ tab	½ tab	1 tab	½ tab
3TC syrup	10 mg/m	3ml	3ml	4ml	4ml	6ml	6ml				
3TC tablet	150 mg							½ tab	½ tab	1 tab	½ tab
LPV/r syrup	80/20 mg/ml	1ml	1ml	1.5ml	1.5ml	2ml	2ml				
NVP syrup	10 mg/ml	5ml	5ml	8ml	8ml	10ml	10ml				
NVP tablet	200 mg							1 tab	½ tab	1 tab	½ tab

5.4 Clinical and Laboratory Monitoring of Children

The baseline evaluation of HIV-infected infants and children includes clinical assessment and basic laboratory tests, where available. Once an infant or child is on ART, the frequency of clinical monitoring will depend on their response to ART. Routine clinical assessment should include addressing the child's and/or caregiver's understanding of and adherence to therapy, along with their need for additional support.

Clinical monitoring include assessment of signs of infant/child's response to ART, addressing the child's or caregiver's understanding of and adherence to therapy, as well as addressing their need to additional support.

Growth, development and nutrition should be monitored monthly. It can be done as per the standard practice followed for children and infants not infected with HIV.

Laboratory assessment of CD4 values is desirable at a minimum of six months after the initiation of ART, and every six months thereafter. More frequent CD4 monitoring is indicated in cases of new or recurrent clinical staging events, growth faltering or neurodevelopmental delay. Routine monitoring for viral load is not essential where capacity and resources are constrained; however, viral load should be used whenever possible to confirm suspected clinical or immunological failure. Laboratory monitoring for toxicity should be symptom directed.

Table 32:Timing for various laboratory tests for monitoring is shown in table below

Laboratory Test for Diagnosis and Monitoring	Baseline (At entry into care)	At Initiation of First Line or Second-Line ART Regimen	Every Six Months	As Required of Symptoms Directed
HIV diagnostic testing	Y			
Haemoglobin	Y	Y		Y
WBC and differential count				Y
%CD4+ or absolute CD4 cell countb	Y	Y	Y	Y
Full chemistry (including, but not Restricted to liver enzymes, renal function, glucose, lipids, amylase, lipase and serum electrolytes)c				Y
HIV Viral Load measurement d,e				Y
OI screening (where possible)	Y			Y

a. Haemoglobin monitoring at week 8 after initiation of ART is recommended if AZT is used.

b HIV-infected children not yet eligible for ART should be monitored with CD4 count every six months. For infants and children who develop new or recurrent WHO stage 2 or 3 events, or whose CD4 count approaches threshold values, the frequency of CD4 measurement can be increased.%CD4+ is preferred in children <5 years of age.

c Routine monitoring (every six months) of full chemistry, particularly lipid levels, liver enzymes and renal function, should be considered for infants and children on second line drugs.

d. At present, Viral Load measurement is not a prerequisite for initiation or regular monitoring of ART in resource-limited settings. VL can be used to diagnose HIV infection, and to confirm clinical or immunological failure prior to switching treatment regimen.

e. Viral Load should be assessed in infants on NNRTI-based regimens who are known to have been exposed to NNRTIs intra partum or through breastfeeding.

Special considerations for children

These guidelines aim to harmonize monitoring approaches for children with those recommended for adults. As more and more children start ART earlier and at higher CD4 counts, viral load monitoring to detect treatment failure and lack of adherence will be increasingly beneficial. In addition, viral load may be instrumental for implementing treatment strategies to preserve second-line options as children age (such as switching from LPV/r to an NNRTI once virological suppression is sustained).

The recommendation to initiate ART for all children younger than five years of age regardless of clinical and immunological criteria means that CD4 cell count testing at baseline is not required for initiating ART. However, where viral load monitoring capacity is limited or unavailable, CD4 monitoring – including baseline measurement and CD4 percentage for children younger than five years of age – will still be important for monitoring treatment response. As in the case of adults, lack of viral load or CD4 capacity should not prevent children from starting ART.

5.5 Switching the regimen in First-line regimen treatment failure

A switch to a second-line regimen is recommended when clinical and/or immunological and/or virological failure is recognized. These conditions are defined as below:

1. **Clinical failure** is defined as the appearance or reappearance of WHO clinical stage 3 or stage 4 events after at least 24 weeks on ART in a treatment-adherent child.

2. **Immunological failure** is defined as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child:

a. For children aged 2 to less than 5 years: CD4 count of is less than 200 cells/mm3 or CD4% less than 10%

b. For children aged 5 years and older**:** CD4 count is less than 100 cells/mm3

3. **Virological failure** is defined as a persistent viral load above 1000 RNA copies/ml, after at least 24 weeks on ART, in a treatment-adherent child.

5.6 Choice of second-line regimens in the event of treatment failure

Using a boosted PI + two NRTI combination is recommended as the preferred strategy for second-line ART for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART. In children using a PI-based regimen for first-line ART, switching to NNRTI or maintaining the PI regimen is recommended according with age

Table 33: Summary of recommended first- and second-line ART regimens for children (including adolescents)

	Children (including adolescents)	First line ART regimen	second line ART regimen
LPV/r-based first line	< 3years	ABC + 3TC + LPV/r	No change
		AZT + 3TC + LPV/r	
	3 years and older	ABC + 3TC + LPV/r	
		AZT + 3TC + LPV/r	
NNRTI-based first line	All ages	ABC + 3TC + EFV (or NVP)	AZT + 3TC + LPV/r
		TDF + 3TC + EFV (or NVP)	
		AZT + 3TC + EFV (or NVP)	ABC or TDF + 3TC (or FTC) + LPV/r

a *No change is recommended unless in the presence of advanced clinical disease progression or lack of adherence specifically because of poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered. Based on the recent approval of the use of EFV in children less than 3 years, an EFV-based regimen could be considered as an alternative. However, more data are needed to inform how best to use EFV in this population.*

b TDF may only be given to children >2 years.

c ATV/r can be used as an alternative to LPV/r in children older than 6 years.

Isoniazid preventive therapy

1. All HIV-infected infants and children exposed to TB through household contacts, but with no evidence of active disease, should begin isoniazid preventive therapy (IPT).
2. Children living with HIV (older than 12 months of age and including those previously treated for TB), who are not likely to have active TB, and are not known to be exposed to TB, should receive 6 months of IPT as part of a comprehensive package of HIV care.
3. Infants living with HIV, who are unlikely to have active TB and are not known to have been exposed to TB, should not receive IPT as part of a comprehensive package of HIV care.
4. The recommended dose of isoniazid (INH) for preventive therapy in HIV coinfection is 10 mg/kg/ daily for 6 months (maximum 300 mg/day).

5.7 Infants and children diagnosed with TB and HIV

1. Any child with active TB disease should begin TB treatment immediately, and start ART as soon as tolerated in the first 8 weeks of TB therapy, irrespective of CD4 count and clinical stage.

2. The preferred first-line ARV regimen for infants and children less than 3 years of age, who are taking a rifampicin-containing regimen for TB, is 2 NRTIs + NVP or a triple NRTI regimen.
3. The preferred first-line ARV regimen for children more than 3 years of age who are taking a rifampicin- containing regimen for TB is 2 NRTIs + EFV.
4. The preferred first-line ARV regimen for infants and children less than 2 years of age, who have been exposed to NVP and are taking a rifampicin-containing regimen for TB is a triple NRTI regimen.

5.8 Nutrition considerations for HIV-infected infants and child

Breast feeding and HIV

Considering the overall risk of malnutrition and diarrhea related diseases, breast feeding is the best choice of infant feeding for HIV exposed infant in Bangladesh. Exclusive breast feeding up to six months of age and starting introduction of complementary feeding under the full coverage of ARV treatment after 6 months of age minimizes the risk of MTCT. It is recommended to continue breast feeding up to one year of age with the coverage of ARV. It is also recommended to gradually stop breast feeding, preferably starting at eleven month of age and completing by the time infant reaches one year.

Nutritional monitoring and other feeding related issues:

1. HIV-infected children should be assessed routinely for nutritional status, including weight and height at scheduled visits, particularly after the initiation of ART. This can be done during regular growth monitoring and the immunization visits.

2. HIV-infected children on or off ART who are symptomatic, have conditions requiring increased energy (e.g. TB, chronic lung disease, chronic OIs or malignancies) or have weight loss or have evidence of poor growth, should be provided with additional energy. Energy requirements depending on the presence or absence of symptoms are as follow:

· ***Asymptomatic***: Require 10% more energy to maintain growth than healthy children.

· ***Symptomatic with no weight loss***: Require 20 - 30% more energy than healthy children.

· ***Symptomatic with weight loss***: Require about 50 - 100% more energy than healthy children.

3. HIV-infected children who are severely malnourished should be managed as per the guidelines for uninfected children. Energy and protein requirements are the same as those for an uninfected severely malnourished child. It should be based on an individual's symptoms and needs.

4. HIV-infected children should receive one recommended daily allowance (RDA) of micronutrients daily. If this cannot be assured through the diet, or there is evidence of deficiency, then supplementation should be given. Micronutrient requirements are the same as those for an uninfected child. It should consider possible deficiencies.

5. HIV-infected infants and children should receive high-dose vitamin A supplementation every 6 months between 6 and 59 months of age, as per the guidelines for uninfected children.

6. HIV-infected children who have diarrhoea should receive zinc supplementation as a part of management, as per the guidelines for uninfected children.

7. For infants and young children known to be HIV infected, mothers are strongly encouraged to exclusively breastfeed for 6 months and to continue breastfeeding as per recommendations for the general population (i.e. up to two years of age and beyond).

5.9 Immunization for children living with HIV

All HIV affected infants are encouraged having HIV testing during their regular immunization visits. (e.g. at 4-6 weeks etc). Virological testing at 4-6 weeks may not be possible currently in Bangladesh; however, antibody testing, regular check-ups for danger signs should be carried out.

1. All infants and children living with HIV and infants born to mothers with HIV should receive all standard vaccinations according to the national vaccination plan, exceptBCG-vaccination. Infants and children living with HIV should not receive Bacille Calmette-Guérin (BCG)-vaccination for TB.

2. There is no contraindication for giving OPV in HIV positive children. Although this is not recommended in settings where Polio has been eradicated or the transmission risk is very low (e.g., according to WHO EURO guidelines, OPV is contraindicated and IPV is recommended). However, in the context where transmission risk is high or chances of importation are high, OPV is recommended and the fear of prolonged excretion of the virus is questionable. Please refer to the table in annex 4 for details.

3. Infants and children living with HIV or exposed to HIV and unclear HIV-status should receive an extra dose of measles vaccine at the age of 6 months.

4. Children with symptomatic or severe immunodeficiency (%CD4 cell less than 15%) should receive ART before vaccinations with attenuated alive vaccines (measles, mumps, rubella)

5.10 Adherence to ART

Adherence preparation should begin as soon as possible and before initiation of ART, but should not put the child at risk of disease progression or death through delaying the initiation of ART. Adherence should be assessed at each visit. Parental, caregiver and child related issues should always be addressed to support the adherence. Intervene early if problems with adherence are identified, and before switching therapy. Local programmes should select the most efficacious regimens and preparations, which are easiest for caregivers to administer to young children and adolescents. Child-friendly formulations are needed to facilitate adherence.

Pill boxes/calendars/diaries or other practical tools should be used to support adherence.

Section 6

Anti-retroviral Therapy in special situations

This section includes the following topics:

1. ART and Tuberculosis
2. ART and Hepatitis B
3. ART and Hepatitis C
4. ART in IDU's- interaction with methadone and Buprenorphine
5. Post exposure prophylaxis of HIV
6. Managing HIV 2

6.1 ART and Tuberculosis

Tuberculosis is one of the most common co-infection with HIV. Without the proper treatment, mortality in TB patient infected with HIV is very high

Recommendations:

1. Start ART in all HIV-infected individuals with active TB, irrespective of the CD4 cell count.
2. Start TB treatment first, followed by ART as soon as possible afterwards (and within the first eight weeks). It is recommended that ART be initiated as soon as TB therapy is tolerated. Ideally, this may be as early as 2 weeks and not later than 8 weeks.
3. Use efavirenz (EFV) as the preferred NNRTI in patients starting ART while on TB treatment.
4. EFV is recommended because of less interaction with rifampicin compared to NVP. No increase in the dose of EFV is recommended (as was previously the case), the standard dose is 600 mg /day.
5. For those HIV/TB co-infected individuals who are unable to tolerate EFV, an NVP-based regimen or a triple NNRTI (AZT + 3TC + ABC or AZT + 3TC + TDF) are alternative options. In the presence of rifampicin, no lead-in dose of NVP is required.

6. Drug interactions between rifampicin and boosted protease inhibitors (bPIs) prohibit the concomitant use of standard therapies for both HIV and TB. Rifampicin induces the cytochrome P450 enzyme system, lowering standard-dose bPI plasma concentrations by 75−90%. All bPIs (at standard doses) are contraindicated with rifampicin.
7. Rifabutin is the alternative if rifampicin is contraindicated. The recommended dose of rifabutin in the presence of a boosted PI is 150 mg three times per week. However, it should be noted that this dose has been reported to result in inadequate rifabutin levels and acquired rifabutin resistance. Now the HIH recommends use of Rifabutin in dose on 300mg thrice a week. The most common adverse events associated with rifabutin are neutropenia, leucopenia, elevations of hepatic enzymes, rash and upper gastrointestinal complaints, and, more rarely uveitis.

6.2 ART and Hepatitis B

HIV-infected persons especially those with a history of blood transfusion, injecting drug use and a history suggestive of hepatitis need to be screened for baseline HBV/HCV status. 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 34 :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 + 3TC + 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	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

1. Start ART in all HIV/HBV co-infected individuals who require treatment for their HBV infection, (chronic active hepatitis), irrespective of the CD4 cell count or the WHO clinical stage.
2. Start TDF and 3TC (or FTC)-containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.
3. Use at least two agents with activity against HBV (TDF plus 3TC or FTC).
4. Use approved criteria for the diagnosis of chronic active hepatitis in Bangladesh (see Annexes)

6.3 ART and Hepatitis C

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 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 35 : HIV and HCV co infection related issues	
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 coinfection 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
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 • 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 antiHCV 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/ddl: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	

6.4 ART for PWID on Methadone Substitution

A comprehensive package of interventions to prevent the transmission of HIV must include measures to reduce unsafe injecting of opioids, including the treatment of opioid dependence and antiretroviral therapy. To improve adherence, directly administered/observed therapy of HIV and TB should be integrated with opioid agonist maintenance treatment and given in the same location as far as possible. Some ARVs interact with commonly used opoid substitution drugs, mainly methadone. Interactions of ARVs with methadone and the related recommendations for use are given in Table 36 below:

Table 36 : OST and ART Interactions

Opioid Substitution Drugs	Antiretroviral Drugs	Interactions Recommendations
Methadone	AZT	Monitor for ZDV-related adverse effects. Methadone significantly increases the blood concentration of ZDV related adverse events. Watch for possible increases in AZT toxicity: anemia, myalgia, bone marrow suppression, fatigue, headache and vomiting.
	EFV	Opioid withdrawal common; increased methadone dose often necessary. EFV can significantly decrease the concentration of methadone in the blood and can cause methadone withdrawal. Withdrawal can be delayed and possibly not seen until 2–3 weeks after starting the EFV. May require a methadone dose increase.
	3TC, TDF,	No significant effect, no dosage adjustment necessary.
	FTC	No data
	ATV/r, LPV/r	Opioid withdrawal unlikely but may occur. No adjustment in methadone dose usually required; however, monitor for opioid withdrawal and increase methadone dose if clinically will be indicated.
	NVP	NVP can significantly decrease the blood concentration of methadone. Methadone withdrawal is common. Withdrawal can be delayed and possibly not seen until 2–3 weeks after starting NVP. May need increase in methadone dose.
	ABC	No dosage adjustment necessary.

6.5 Post Exposure Prophylaxis (PEP) of HIV

The risk of HIV transmission following skin puncture from a needle or other sharp object that was contaminated with a blood from a person with "documented" HIV infections is about 0.3%. The risk of HIV transmission is less with injuries sustained with solid bore (e.g. suture) needles than with hollow bore (e.g. blood drawing) needles. There have been rare reports of health workers who have become infected by exposure of mucous membrane (of eyes, nose or mouth) or abraded (broken) skin to HIV-infected material; the risk, is estimated to about 0.09%. HIV is not transmitted through healthy intact skin.

1. First aid immediately after potential exposure:

The aim of first aid is to reduce contact time with the source person's blood, body fluids or tissues and to clean and decontaminate the site of the exposure.

If the skin is broken following an injury with a used needle or sharp instrument, the following is recommended.

- Do not squeeze or rub the injury site.
- Wash the site immediately using mild soap

After a splash of blood or body fluids on broken skin, the following is recommended:

- Wash the area immediately.
- Do not use strong disinfectants.

After a splash contacts the eye, do the following.

- Irrigate the exposed eye immediately with water .
- If contact lenses are worn, leave these in place while irrigating the eye, as they form a barrier over the eye and will help protect it.

Once the eye has been cleaned, remove the contact lenses and clean them in the normal manner.

- Do not use soap or disinfectant on the eye.

After a splash contacts the mouth, do the following.

- Spit the fluid out immediately.
- Rinse the mouth thoroughly with water, and spit again. Repeat this process several times.
- Do not use soap or disinfectant in the mouth

2. Indications for Post Exposure Prophylaxis

1. The exposed person is HIV-negative
2. The source person is HIV positive, or at high risk of recent infection and thus likely to be in the window period.
3. The exposure poses a risk of transmission, that is:
    a. Percutaneous exposure to potentially infectious body fluids (non-infectious body fluids include faeces, saliva, urine and sweat)
    b. Exposure to non-intact skin or mucus membranes to potentially infectious body fluids
4. The exposure occurred within 72 hours.

2. Choice of PEP and its regimen:

If the HIV status of the source is not known, HIV testing of the source could be done after necessary counseling. In any case, if the risk is high, PEP should be started immediately. If the HIV test results of the source are found to be negative, PEP can be discontinued**.**

Table 37: PEP for skin injuries

Exposure	Status of Sources		
	Low Risk*	High Risk*	Unknown
Not severe: Solid needle, superficial	2 drug PEP•	3 drug PEP•	Usually none: Consider 2 drug PEP
Severe: Large bore, deep injury, visible blood on device, needle in patient's artery/vein	3 drug PEP•	3 drug PEP•	Usually none: Consider 3 drug PEP

*Low risk: Asymptomatic HIV or VL < 1500 c/ml. High risk: Symptomatic HIV/AIDS, acute seroconversion, high VL.
Concern for drug resistance: Initiate prophylaxis without delay and consult an expert.
Consider 3 drug PEP if source is high risk for HIV or exposure from unknown source but likely to be HIV infected.

Table 38: PEP for Mucous Membrane and Non-Intact Skin Exposures*

Exposure	Status of Sources		
	Low Risk*	High Risk*	Unknown
Small volume (drops)	consider 2 drug PEP	2 drug PEP	Usually no PEP: Consider 2 drug PEP
Large volume (major blood splash)	2 drug PEP	3 drug PEP	Usually no PEP Consider 2 drug PEP

*Non-intact skin = dermatitis, abrasion, wound
Low risk = Asymptomatic or VL < 1500 c/ml High, risk = symptomatic HIV, AIDS acute seroconversion, high HIV viral load.
Consider 3 drug PEP, if source has HIV risk factors or exposure from unknown source where HIV infected source is likely. Can we make it simple? Use 3 drugs in any injury…

Drug Selection

There are two types of regimens recommended for PEP. They are the basic regimen of two drugs combination and expanded regimen of three drugs as given in Table 39 below:

Table 39: Recommended PEP regimens

2 Drug Combinations (Basic Regimen)
TDF+ 3TC (LPV/r treatment experience pt)
3 drug combinations (expanded regimen)
2 NRTI + EFV
Alternative to TDF is ZDV
Alternatives to EFV include: LPV/r or ATV/r.
Note: NVP should not be used for PEP due to the risk of hepatotoxicity.

- Baseline Hemoglobin test is needed if ZDV is prescribed
- Serostatus is recommended to monitor by HIV Antibody testing (rapid or ELISA), performed at start of PEP, at 6 weeks, at 3 months and at 6 months duration of the exposure.
- Testing for other bloodborne diseases – such as hepatitis B and C – is also recommended done as per the judgments of the clinician managing PEP.

3. PEP following rape

There are no available data about the use of PEP following rape. But if the risk of transmission of HIV is considered to be present, PEP, as used for health workers after occupational exposure, can be used.

5. PEP for non-occupational exposure other than rape:

For non-occupational exposure other than rape, clinician will decide on a case-by-case basis whether PEP should be provided. It should not be provided in the case of chronic HIV exposure or cases of "recreational exposure". Provider may decide to provide PEP in some cases, such as an episode of condom breakage in a discordant couple.

6.6 Management of HIV 2

HIV2 is mainly reported from West Africa, some of the nations are Cape Verde, Côte d'Ivoire (Ivory Coast), Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria, and Sierra Leone etc. There are no provisions of the diagnosis of HIV2 in Bangladesh. These recommendations are for

managing accidental cases who have been diagnosed outside and then travelled to Bangladesh.

Both HIV-1 and HIV-2 have the same modes of transmission and are associated with similar opportunistic infections and AIDS. In persons infected with HIV-2, immunodeficiency seems to develop more slowly and to be milder. Compared with persons infected with HIV-1, those with HIV-2 are less infectious early in the course of infection. As the disease advances, HIV-2 infectiousness seems to increase; however, compared with HIV-1, the duration of this increased infectiousness is shorter.

Few recommendations regarding HIV 2 are below:

- In vitro (laboratory) studies suggest that nucleoside analogs are active against HIV-2, though not as active as against HIV-1. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are not active against HIV-2
- Protease inhibitors should be active against HIV-2.
- Triple NRTI with AZT+3TC+ABC can also be used if PI are not available, but this combination has higher virological failure rate than boosted PI.
- Response to treatment for HIV-2 infection may be monitored by following $CD4^+$ T-cell counts and other indicators of immune system deterioration, such as weight loss, oral candidiasis, unexplained fever, and the appearance of a new AIDS-defining illness. or HIV-2.
- The recommendations on viral load monitoring and the use of NNRTIs would not apply to patients with HIV-2 infection.

Section 7

Guidance on Operations and service delivery at Care and Support Centers (CSC)

This section includes the following topics:

7.1 Operations and service delivery at Care and Support Centers (CSC)

As it is planned to initiate provision of ART at some of the CSC being established in the public sector health facilities, it is important that there be defined standard operating procedures for the same so as to provide services in an efficient and coordinated manner. A public health approach for the provision of ART implies that ART regimen should be standardized, easy to use and have minimal adverse affects. Scaling up ARV treatment also calls for active involvement of a range of stake-holders, including those living with HIV, other community members and civil society at large. Bangladesh has the distinct advantage of civil society and NGO being involved in ART right from beginning now and in the new phase when NASP starts ART in government facilities, the experience of these organizations is fully utilized and they continue to be partners in this endeavor by the DGHS and Govt. of Bangladesh.

It is desirable to have certain specific services, facilities and protocols in place before starting ART. These are necessary due to the complexity of accessing and continuing the therapy, the need for close clinical and laboratory monitoring and the cost of therapy. These services include:

1. Easy access to an ART centre, ideally located in the medical OPD of the hospital with adequate space and privacy for examination and counselling
2. Medical services with trained physicians and other health care personnel capable of identifying and treating common HIV-related illnesses and OIs.Duly trained health care providers should provide Care and support services,, adherence counselling and psychosocial support to PLHIV and their families.
3. Reliable laboratory and radiological services capable of performing routine laboratory investigations such as HIV antibody testing, pregnancy testing, complete blood count, serum bio-chemical tests, X rays etc. Access to a laboratory capable of performing CD4 count which is essential to monitor therapy
4. Reliable and affordable access to quality antiretroviral drugs and drugs to prevent and treat OIs and other related illnesses

7.2 Objectives of ART centres

The main objective of Care and Support Centers (CSC) is to provide comprehensive package of Care, Support and Treatment services to persons living with HIV/AIDS (PLHIV). The specific objectives of an ART centre are to:

1) Register and provide Care, Support and Treatment services to all PLHIV and monitor patients in HIV care (Pre- ART) regularly
2) Identify eligible PLHIV requiring ART and initiate them on ART in a timely manner as per the National ART guidelines
3) Provide ARV & OIs drugs to eligible PLHIV
4) Provide treatment adherence and counselling services before and during treatment to ensure high levels of drug adherence
5) Counsel and educate PLHIV, care givers, guardians and family members on nutritional requirements, hygiene, positive living and also on measures to prevent further transmission of infection
6) Refer patients requiring specialized services (including admission) to other departments or higher facilities
7) Provide comprehensive package of services including condoms and prevention education with a view towards "Positive Prevention"
8) Ultimately integrating HIV care into general health system for long term sustainability.

7.3 Functions of ART Centre

PLHIV should be given holistic care at ART centres. This is possible only if the team at the centre is committed and has a comprehensive understanding of the programme. Functions of ART centre can be categorized as medical, psychological, social and programmatic as indicated below:

Medical Functions

1) To monitor, manage and follow up Pre ART patients
2) To screen PLHIV for HIV-TB co-infection for early diagnosis of TB and appropriate linkages with the NTP
3) To diagnose and treat Opportunistic Infections including primary and secondary prophylaxis as per the guidelines.
4) To provide baseline investigations and CD4 cell count
5) To screen PLHIV for clinical eligibility and to initiate ART as per National ART guidelines
6) To provide ART to eligible PLHIV and counsel them on 100% adherence to therapy for long term effectiveness of ART
7) To monitor patients on ART and manage side-effects, IRIS etc (if any)
8) To facilitate easy access to specialist care as and when necessary
9) To provide in-patient care as and when necessary
10) To refer patients suspected for drug toxicity and/or treatment failure to expert group for review and initiation of alternative first line or second line ART, if eligible
11) Sample collection and transportation to reference lab for Blood sample for confirmation of status of children below 18 months found reactive for HIV with Dried Blood Spot (DBS) testing/ rapid test and initiation of ART in children as per guidelines
12) To provide appropriate intervention for PPTCT as per the National guidelines on PPTCT (both technical and operational)

Psychological Functions

1) To provide psychological support to PLHIV accessing the ART centre
2) To provide counselling to "Pre ART" and "On- ART" patients on regular follow up visits and CD4 testing
3) To provide counselling for adherence to ARV drugs and issues related to toxicity
4) To educate PLHIV on proper nutrition and measures to prevent further transmission of infection
5) To educate patients on sexual health and positive living
6) To advice for risk reduction behaviour including usage of condoms
7) Encouraging, educating and counselling to help patients to disclose the HIV results to Spouse/ children/family/care giver.

Social Functions

To facilitate linkages between Governmental and Non Governmental Organisations and service providers like **Ashar Alo, CAAP and Mukto aakash, icddrb,** save the children etc.

Programmatic functions

1) Tracking of “On-ART” and “Pre ART” Lost to Follow Up cases in co-ordination with Governmental and Non Governmental Organisations
2) To work in close coordination with the CSTs to ensure that all the patients detected positive at HTC get registered at the ART centres.

3) To assess the HIV status of spouse and children through HTC and link them to CST services
4) To sensitize the hospital staff on universal work precaution, PEP, ART, medical waste management and other CST services through education and training
5) To work in close coordination with the National TB programme to ensure that all the patients with HIV/TB co infection are registered at the ART centre and started on ART.
6) To establish functional linkages with CST and PPTCT centres, and respond to the needs to be addressed at ART centre
7) Participation in operational research, mentoring other health care facilities.

7.4 Selection Criteria for ART Centre

The following criteria can be used to set-up ART Centres in Government Sector and Non-government organisations:

1) Regions with HIV prevalence
2) Proposed site should be accessible and well connected by public transport
3) Services provided and human resource available in critical departments in the hospital (Medicine, Microbiology, Obstetrics & Gynecology, Paediatrics, Dermatology /Venereology) to be taken into consideration
4) Availability of adequate space for setting up ART centre within the hospital campus, preferably in/near Medicine OPD

5) Willingness to assign minimum one faculty from Departments of Medicine, Paediatrics, Obstetrics & Gynecology and Microbiology to support the ART centre on a daily basis and also involve other faculty members/residents in the functioning of the centre
6) Willingness and preparedness to provide necessary investigations free of cost to the PLHIV and the basic drugs for the treatment of OI available in the hospital pharmacy and essential drugs required for dealing with the side effects of ART
7) Commitment to regularly provide information on facilities, services and outcomes in prescribed formats

Infrastructure

Location and Access to ART Centre

The ART centre should ideally be located near the Medicine OPD. If this is not feasible, a suitable place should be identified within the same campus which is accessible to patients keeping in mind cross-referral to and from various departments. Signage depicting directions to the ART centre should be clearly placed in the institution at strategic locations, including ICTC, so that there is no difficulty in locating the centre within the hospital.

Space for ART Centre

A minimum of 500 square feet area is required for an ART centre expecting on an average 100 patients on ART with scope for expansion. It should have 3 rooms/ cabins each measuring at least

ten feet by ten feet (10' x 10') for the following staff/services listed below:

1) Examination room: One room for medical officer to examine the patients
2) Counselling Room: for individual, group and family counselling (1 counsellor per room) and maintaining records
3) Nursing room: for general examination, taking blood samples and drug dispensing
4) Store Space: for storing drugs and other stationary
5) Waiting Area: There should be adequate area where patients and accompanying persons can wait and where group counselling can also be conducted. Television and other audio-visual facilities should be installed here for educational purposes. IEC material should also be displayed in this common waiting area. Attention should be paid to avoid the air borne infection by adequate ventilation/windows etc
6) Adequate space should be individually identified and provided for different ART centres taking into consideration the need of the particular centre
7) It must also be ensured that adequate toilet facility is made available for the clients visiting the centre
8) Provision for clean drinking water also needs to be ensured.

The ART centre should be kept neat and tidy and should maintain highest standards of cleanliness and hygiene, have proper ventilation, lighting, electric supply and water supply for effectively carrying out examination, counselling, laboratory tests and record

keeping while helping to prevent the spread of nosocomial infections.

Furniture and general equipment

The ART centre should be furnished adequately and must have the following:

1) Tables, chairs and other seating facilities for staff and patients
2) Examination table with side screens, pillow, rubber sheet etc
3) Office shelves for supplies, records and stationery, drugs storage, etc
4) Appropriate furniture for computer and printer and office stationeries
5) Secured cupboards for storing patient records, ARV drugs and other medicines, laboratory kits, consumables and other equipment. These cupboards should have locks to prevent theft of material and data
6) Waste disposal systems

Medical equipment and accessories

A set of general medical equipment like a weighing machine, height measurement pole, blood pressure (BP) apparatus, stethoscope, tuning fork, hammer, Ophthalmoscope, pulse oxymeter, torch, tongue depressor should be available for each medical officer at the ART centre. Digital camera can also be purchased. These items should ideally be provided by the hospital but if not possible, then can be purchased from the one time grant as well as the recurring grant for the centre.

CD4 machines

Each ART centre should have access to CD4 tests either by having a CD machine or by a clear linkage mechanism for conducting regular and uninterrupted CD4 counts at a designated centre. The reagents and other consumables needed for CD4 test would be procured by NASP and supplied to the centres. The machines should be utilized optimally to ensure that there is minimal waiting period for CD4 test. All PLHIV in "Pre ART" and "On ART" should get the CD4 count done at least once in six months or more, if required clinically.

Communication Tools

All ART centres should have desktop computers along with peripheral accessories- printers, scanner, and internet connections. Apart from internet connection, ART centre should have phone connections for external and internal (hospital) communication. The phone number and email of the centre should be displayed at a prominent place in the waiting area.

Display of Information

Proper display of the following in the ART centre should be ensured:

1) Name and designation of all the staff in the centre
2) The timings of the ART centre along with list of holidays displayed in bold letters in Bangla
3) List of facilities/ services available in the ART centre
4) The list of nearby ART centres, DICs and other facilities

5) Information on fast tracking of cough symptomatic, pregnant women and children
6) Request patients to report to the ART centre in case of change of contact details
7) IEC materials related to care, support & treatment and other services
8) Instruction to the patients to report to the "Emergency" in case of any complication/emergency situation

Installation of Complaint/ Suggestion Box

A complaint/ suggestion box must be installed in the ART centre. It should be opened in the presence of the nodal officer weekly. A register should be maintained where in all complaints received and action taken should be entered. PLHIV Network members should be involved in the meetings for review of grievances at the centre.

Working Hours & Holidays

Working hours for ART centre are from 9 am to 4 pm or (8:00- 3:00 pm) with a lunch break for half-an-hour. In case the OPD closes at 2 PM, the ART centre should still be open till 4 PM for updation of records. All records should be completed on the same day after disposal of patients. The ART centre will observe same holidays as the medicine OPD of the institution. The ART centre shall remain closed on Fridays and other gazetted holidays.

7.5 Human Resources

ART Team

All institutions with ART centre are requested to constitute a multi-disciplinary ART team headed by the Head of the institution (Dean/Principal/Medical Superintendent/CMO). It should consist of trained faculty from the departments of Medicine, Pediatrics, Microbiology, Obstetrics & Gynecology, Biochemistry, Community Medicine, Surgery, Psychiatry, TB-Chest, Dermatology and Venereology. This team should meet at least once in two months under chairpersonship of head of institution (Dean/Superintendent) and discuss the functioning of the ART centre and other relevant cross cutting issues.

Staffing Pattern for ART centres

All ART centres are provided with manpower in proportion to the number of patients on ART at each centre. However, manpower structure for ART centres will be periodically reviewed and revised by NASP based on the increase in patient load and other requirements in the programme.

Keeping in mind low PLHIV load in the beginning, the existing Medical officer in the institution be trained for ART services. However it would be in interest of patients to appoint full time additional nurse, counselor cum data manger for the designated ART centre. These staff can be supported from the World Bank funds ear marked for CSC services

Human Resources & their Job Responsibilities:

Nodal Officer of ART centre (Head, Dept. of Medicine/ another faculty member nominated by the HOD)

1) Overall responsibility of the functioning of the ART centre, reporting to NASP, participation in review meeting, coordinate and develop referral system and linkages with other departments of the hospital
2) Ensure that PLHIV are not discriminated in the hospital and are not denied admission/ care
3) All administrative matters relating to the centre including sanctioning of leave of contractual staff, annual performance appraisal of the staff etc
4) Establish links with other facilities developed under NASP, NGOs, Positive Network Groups etc
5) Ensure adherence to the highest standards of quality and excellence in patient care
6) Review and monitor the functioning of the centre periodically and in depth and ensure submission of reports as required. Once in a week the Nodal Officer should sit with the ART staff to review the functioning of the centre, record completion, computerization, etc. Also meetings should be minuted and adequate action be taken as per the minutes
7) Scrutinize the monthly ART centre report, approve it and send to NASP. Also ensure that the softwares are properly installed and working on the computers at the ART centre
8) Ensure posting of other faculty members and resident doctors in the department to ART centre on rotation basis in order to ensure that every member is oriented in the functioning of the centre. A roster indicating name of faculty

deputed on day to day basis and PG students rotation to ART centre should be prepared every month and displayed at the centres

9) Ensure multidisciplinary ART team meeting once in two months under the supervision of Head of the institution
10) All ART centres should have a attendance register where all staff should sign daily at the time of coming and leaving along with time
11) Physical verification of the ARV drug stocks (once in 3 months) and signatures in stock register
12) Review the actions initiated on the complaints received in the complaint box from the PLHIV every fortnight
13) Focal point for interaction with NASP/NTP etc
14) Act as a team leader to constantly guide and mentor the ART staff (Medical Officers, Counsellor, Laboratory Technician, Staff Nurse, Pharmacist and Data manager).

Medical Officer (ART Centre)

The eligibility criteria to be followed while appointing MO for ART centre are as follows:

- First preference should be given to candidates with MD in Medicine or any other clinical discipline. If no candidate as per para 1 above is available, candidates with MBBS + Diploma in any clinical discipline having minimum 3 years of experience can be considered
- In the event of unavailability of candidates as per para 1 & 2 above, candidates with MBBS + Diploma in Public Health having 3 years of experience can be considered for the post of SMO.

Job responsibilities of Medical Officer (MO)

1) He/she is the functional team leader of the ART centre under the overall guidance of the Nodal officer. The MO has to supervise the administrative and medical functions of the ART centre on a day- to- day basis and provide leadership to staff to work as a cohesive team and deliver the services effectively
2) He/she should examine the patients, advise required investigations including CD4 count, review the investigations and prescribe the treatment. It includes referrals to other departments for treatment of TB, STI, OIs, etc
3) Refer difficult/ complicated cases to the Nodal Officer or other specialist for further expert opinion and interventions including admission and inpatient care, if required
4) Monitor the consumption and availability of ARV, OI and other drugs, CD4 kits, other consumables and alert the concerned authorities in case of impending shortage well in advance so as to enable adequate replenishment without disruption of ART care and support to PLHIV.
5) He/she must ensure that all records, registers, cards and PLHIV software are updated on a daily basis and reports are sent to the concerned authorities on time. All reports should be checked by the SMO before taking approval from the Nodal Officer for sending them to the concerned authorities
6) He/she must update the prescribed columns in patient cards and registers
7) He/she must attend or ensure appropriate representatives are sent for monthly coordination meetings held at the

district level, ART centre-CCC coordination meetings. The MO must attend review meetings by NASP and training programs conducted for medical officers.

8) He/she has to ensure that the guidelines for running and maintaining the ART centre are abided by
9) He/she must be aware of all communications sent from NASP to the ART centre and should update the nodal officer about them on a day to day basis
10) He/she has to verify the staff attendance register daily and get it approved by the Nodal Officer at the end of the month
11) The MO must appraise the annual performance of the contractual staff based on the PMDS format which should then be approved by the nodal officer
12) The MO should also monitor the linkages with other department, NGO's and other networks and attend monthly coordination meetings

Counsellor cum Data Manager

Qualification: He/ she should hold a Masters degree in Social Work (preferably specialized in medical & psychiatric social work). If no candidate with the above qualification is available candidates with degree in sociology may be considered. Qualified and competent PLHIV, if available, should be given preference while appointing counselors. Alternatively, a qualified graduate nurse can be appointed as counselor but he/she must undergo training on ART as well as on counselling issues.

Job responsibilities of Counselor:

1) He/she has to work under the guidance and supervision of MO/ Nodal officer
2) He/she must assess / assist the staff nurse in triaging the new patients eligible for Pre-ART registration and refer others to the nearest HTC for confirming HIV status
3) Complete the Pre-ART registration (HIV care) register on first visit of the PLHIV and provide adherence counseling
4) Counselor to maintain the HIV exposed/ infant child register
5) Provide necessary counseling on subsequent visits to the "Pre ART" patients and adherence counseling to "On ART" patients
6) Referral and linkages with other community based organizations, rehabilitation centres and various support groups
7) Address issues related to ARV treatment:
    - Pre ART or treatment preparedness exercises, encourage and help in finding guardian Support Explain the details of treatment and its importance, including side effects of ARV drugs
    - Adherence counseling and monitoring, identification of barriers to adherence and suggestions to remove these barriers
    - Pill counting for PLHIV on ART and assess adherence
8) Provide emotional, social, and psychological support to patients and/or direct them to the concerned person or organization that can do so
9) Explain to the patients, care givers, guardians and other family members about palliative and home-based care,

hygiene and nutrition

10) Counsels patients on positive living, prevention proper condom usage; and dispense condoms
11) Complete the required sections in the recording and reporting tools maintained by the ART centre
    - Issue patient book for the first time to the new patients (Pre-ART)
    - Pre-ART Registers (fill in prescribed columns)
    - ART Enrollment register: (fill in prescribed columns)
12) Counselors must ensure all the registers are filled appropriately and updated
13) Collect and update address of PLHIV
14) Counseling of Pre ART patients on follow up visits and repeat CD4 count. CD4 report of Pre ART patients is to be given by counselor after proper counseling
15) Follow up for testing of spouse and children of the PLHIV
16) Contact the Lost to Follow Up (LFU) cases through telephone and outreach workers and bring them back to ART centre for drug collection
17) Attend HTC counselors monthly meeting for feedback on HTC- ART referral and LFU cases
18) Provide counseling on family planning and breast feeding, particularly for pregnant women coming for PPTCT. The counselor should ensure appropriate advise and counseling to link the pregnant women to appropriate services including ANC and post natal services, immunization and EID for infant
19) Ensure that all data recording and reporting software's are properly installed, functioning and updated
20) Print and share all circulars/information sent by NASP to the

Nodal Officer/MO and maintain a file for the important orders/communication

21) Maintain the attendance register for the ART centre staff and get it verified by the MO every day and by the Nodal Officer at the end of the month
22) Maintain the performance appraisal report, training details, remuneration etc
23) Prepare and send all the monthly reports prescribed by NASP after approval of Nodal Officer
24) Assist in analysis of data under the supervision of the Nodal Officer of the ART centre
25) Maintain the accounts of the ART centre and the fixed assets register
26) Besides all the above, any other responsibilities / instructions related to the programme given by the supervisors need to be discharged / followed from time to time.

In case pharmacist is not available/on leave, staff nurse shall do the job of the pharmacist.

Laboratory Technician

Qualification: The Laboratory Technician should be a graduate/diploma holder in Medical Laboratory Technology from a recognized institute. He/she must be registered in the concerned council. He/she should be trained by NASP in ART related laboratory work, including CD4 count testing.

Job responsibilities of Laboratory Technician:

1) He/she has to work under the guidance and supervision of SMO/MO
2) Collect the specimen for CD4 counts at the ART centre and take these samples to the Department of Microbiology, test them and give the report to the counselor at the ART centre.
3) In case the ART centre does not have a CD4 machine or CD4 testing is not possible at the same centre due to any reason, the LT is expected to transport samples of blood to a linked CD4 laboratory and to collect the results when ready
4) Prepare and provide CD4 monthly report to ART centre
5) Maintain the stock of the CD 4 kits, consumables and inform the ART SMO / In-charge MO / Nodal Officer of the centre as and when the stocks come to critical levels
6) Generate the “Due list” for CD4 testing for all the Pre-ART & On ART patients as specified norms
7) Address confirmation on CD4 test date every six monthly
8) Incase the LT is on leave sample collection and transportation should be done by the staff nurse. In some situations where the staff nurse is unable to travel, then the staff nurse should collect the sample, pack it as per the protocols and the care coordinator or another staff under shall carry the sample to the testing lab
9) The additional laboratory staff provided at select sites can also be used for laboratory work
10) Any other duty assigned by ART Centre In-charge.

Staff Nurse cum Pharmacist cum Phlebotomist

Nurse will be a very crucial HR for the ART center. Each centre should appoint a contractual staff nurse full time for the centre. In addition one should be deputed to the ART centre by the hospital (institution). Nurses play a very important role at the ART centre and their responsibilities include the following:

1) Assist in all the clinical and paramedical functions of the centre as per requirement
2) Perform baseline assessment of the patient including pulse, BP, weight, height etc
3) Provide need based nursing care and support to the patients
4) Focal point for all issues related to pregnant positive women and HIV exposed child and early Infant Diagnosis (EID) incase counselor not there
5) Maintain the daily OI summary sheet, compile it on monthly basis and give it to the data manager
6) Coordinating and tracking the referrals made within the hospital by establishing linkages with various departments and in-patient wards
7) Streamlining and guiding patients at the ART centre and helping in the efficient and orderly functioning of the centre
8) Assist the counselor in record keeping and maintenance of patient documents
9) Counselling of patients as and when required
10) Collection of blood samples for CD4 testing and arrange/perform its transportation to the linked lab
11) Provide reports to the doctor and other members of the ART centre multidisciplinary team

12) Ensure implementation of the UP and proper waste disposal at the centre
13) To monitor and ensure the implementation of various infection control measures

Role of Nurse as a pharmacist

1) Dispense ARV and OI drugs with proper counseling
2) Advise the patients and family about the importance of adherence during each visit
3) Counsel the patient on possible drug toxicities and report the same, if significant
4) Do pill count and report any adverse effects of drugs or any OIs. Also, confirm the next visit date given by the MO and inform the patient
5) Prepare a "Daily Due" list of patients who are scheduled for their appointment and provide the list of “LFU” patients to the counselor
6) Maintenance of the drug stores
7) Maintain and update drug stock and drug dispensing registers regularly every day. Inform the concerned medical officer in case of any discrepancy. Duly take his signature every fortnightly in the stock register
8) Physical verification of the drugs under the supervision of the nodal officer and the SMO

Role of nurses at the ART centre in HIV-TB coordination:

1) Do regular screening of the patients for symptoms of pulmonary/extra pulmonary TB
2) The lab form given to the TB suspect to be stamped by the

nurse with the ART centre stamp to facilitate fast tracking of the patient for sputum testing

3) Reinforce cough and hand hygiene practices among the suspects/diagnosed pulmonary TB cases
4) Keep a record of the patients referred from ART centre to Designated Microscopy Centre for the diagnosis of TB with the help of line list.
5) Attend the monthly NTP meeting along with the completed line list for the month to be shared
6) Maintain the TB/HIV register at the ART centre ensuring timeliness, accuracy and completeness
7) Prepare and submit the monthly TB/HIV report to NTP through ART centre in charge.

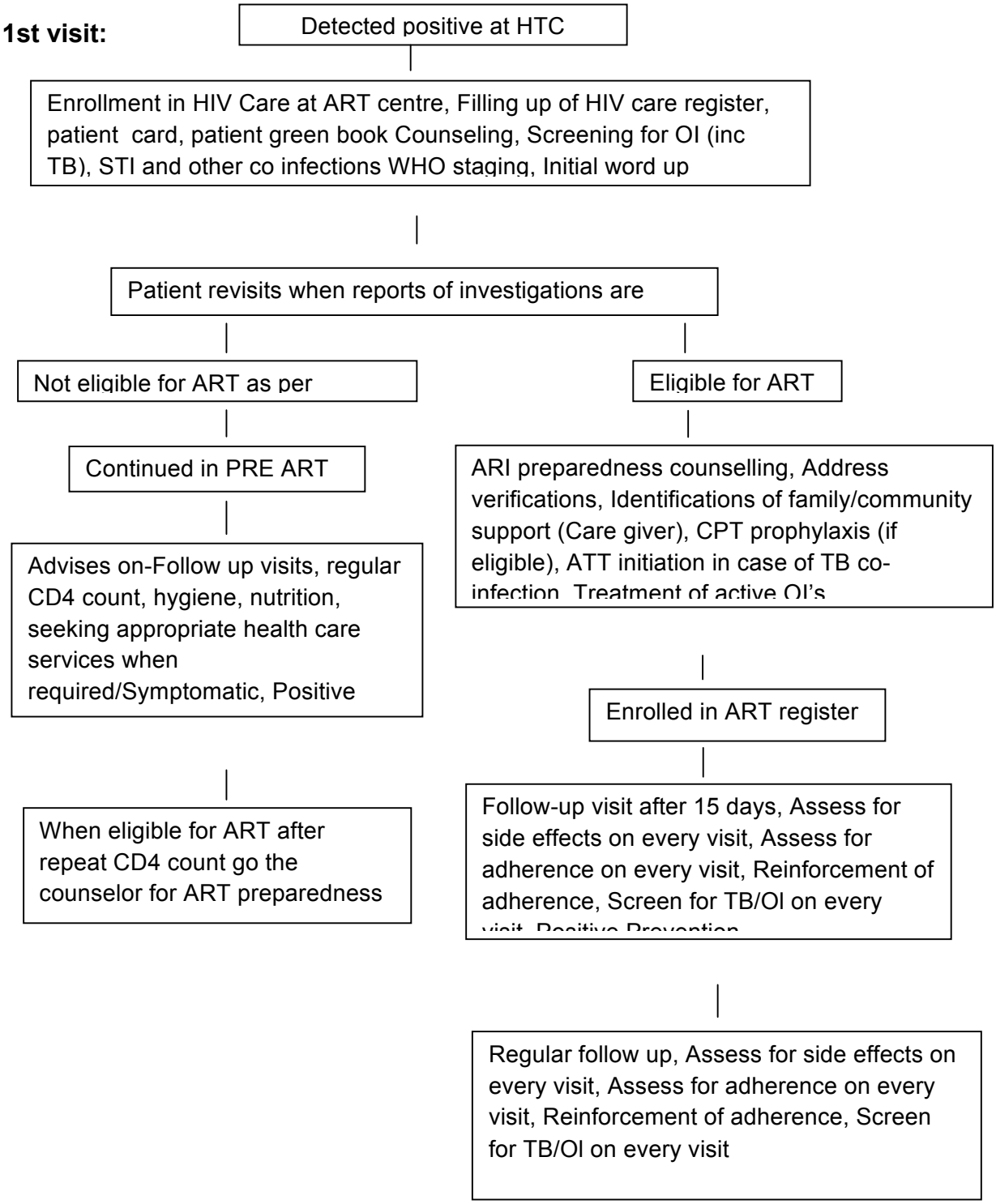
Capacity Building of ART Centre Staff

To ensure uniform standards of services, adherence to operational guidelines and treatment protocols, induction training is provided to various personnel using standard curriculum, training module and tools at identified institutions. Various training programmes organized for ART staff include:

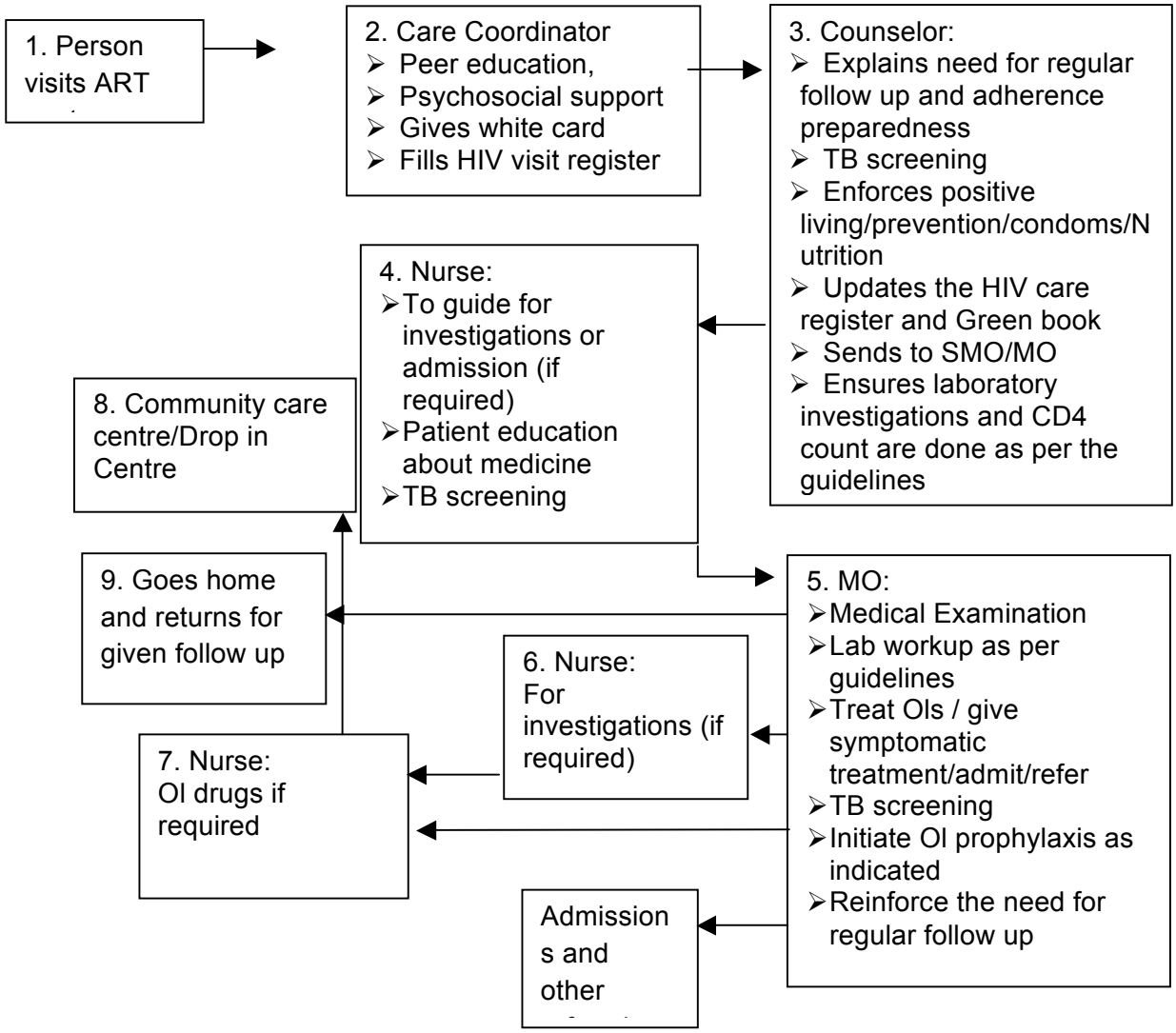
1) Orientation of "ART team" members from the institution (4 days)
2) Training of Medical Officers of ART centres (12 days)
3) Training of counselors (12 days)
4) Training of nurses (6 days)
5) Refresher/ re- orientation programme for ART centre team

7.6 Operating procedure at ART centre

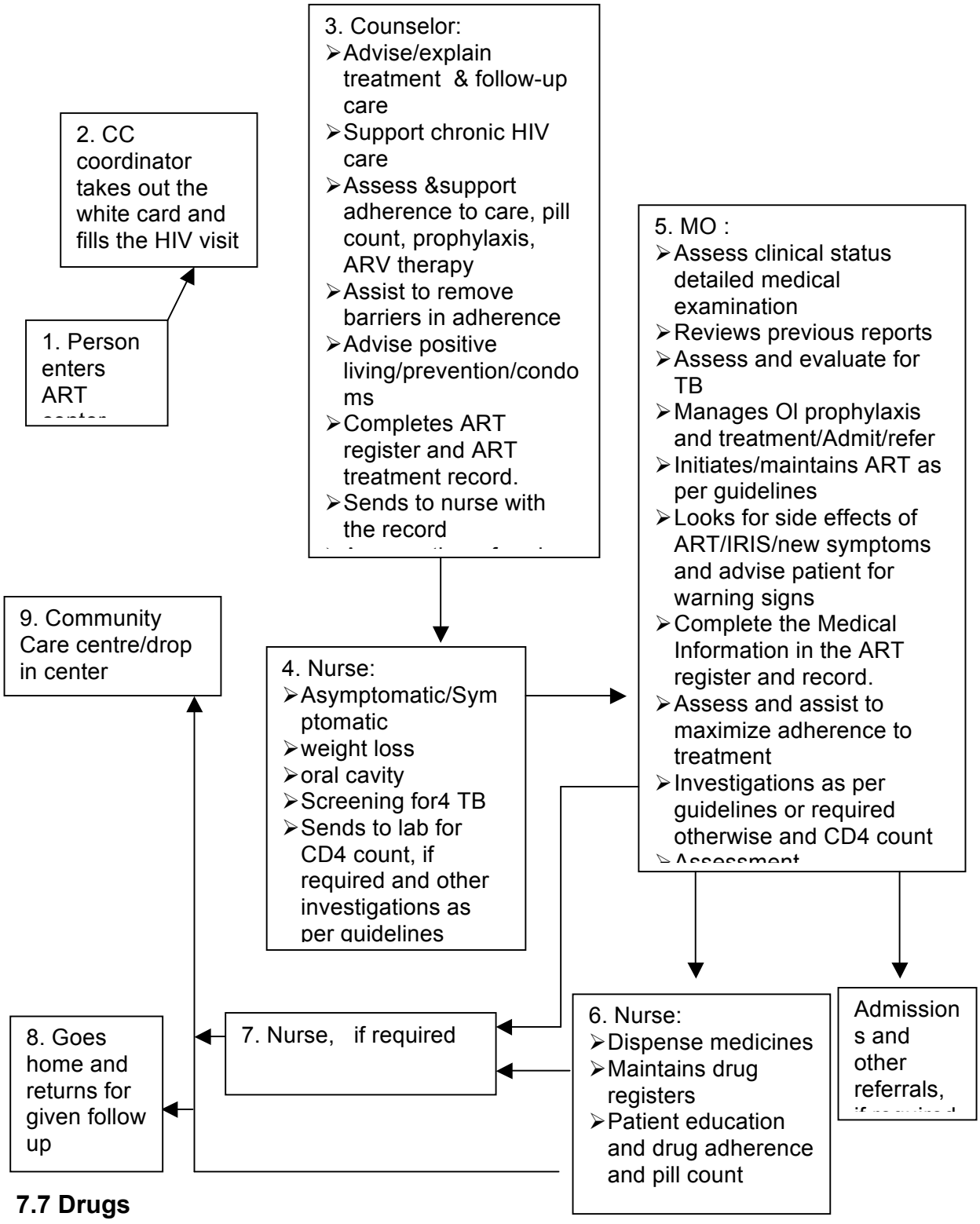
Flow chart at ART centre:



2nd visit:



Follow up visit:


1. Person enters ART
2. CC coordinator takes out the white card and fills the HIV visit
3. Counselor:
Advise/explain treatment & follow-up care
Support chronic HIV care
Assess &support adherence to care, pill count, prophylaxis, ARV therapy
Assist to remove barriers in adherence
Advise positive living/prevention/condoms
Completes ART register and ART treatment record.
Sends to nurse with the record
4. Nurse:
Asymptomatic/Symptomatic
weight loss
oral cavity
Screening for4 TB
Sends to lab for CD4 count, if required and other investigations as per guidelines
5. MO :
Assess clinical status detailed medical examination
Reviews previous reports
Assess and evaluate for TB
Manages OI prophylaxis and treatment/Admit/refer
Initiates/maintains ART as per guidelines
Looks for side effects of ART/IRIS/new symptoms and advise patient for warning signs
Complete the Medical Information in the ART register and record.
Assess and assist to maximize adherence to treatment
Investigations as per guidelines or required otherwise and CD4 count
6. Nurse:
Dispense medicines
Maintains drug registers
Patient education and drug adherence and pill count
Admissions and other referrals,
7. Nurse, if required
8. Goes home and returns for given follow up
9. Community Care centre/drop in center

7.7 Drugs

ARV Drugs:

All ART centres shall be provided with ARV drugs by NASP through CMSD. The drugs are generally procured annually and supplied in 2 - 3 installments. The drugs required for all ART centres are supplied to respective drug store which, in turn, send it to the ART centres and monitor the same. All centres should ensure that they have a minimum stock of three months at their centre. In case of near expiry ARV/OI drugs stock that may not be consumed, the centre should inform drug store well in advance (4 month before expiry) so that necessary arrangement can be done to relocate the same. In case of shortage of drugs, information should be sent to the CMSD and NASP (NASP_CSTC@gmail.com)

The drugs should be stored in the main pharmacy of the institution and shall be indented by the centre on monthly basis from the main store. The centre should utilize them following “first expiry first out” principle.

Drugs for Opportunistic Infections

Drugs for Opportunistic infections should be available at all the ART centres. The common drugs that are required for the management of OI’s are as below:

Sl#	Drugs to be supplied by	Drugs to be procured by	Drugs to be procured by ART

	the Institution where ART centre is located	NASP and supplied to ART centres	centres as and when required
1	Metronidazole 400mg	Nitozoxanide	Fluconazole IV-200mg
	Inj. Ceftriaxone	Azithromycine	Acyclovir
	Ciprofloxacin 500mg	Fluconazole	Gancyclovir
	Cotrimoxazole	Cefotaxime	Amphotericine B
	Other common drugs like Paracetamol, Anti-allergic, Anti-diarrhoel, Antacids, etc.	Levofloxacine	

Universal Work Precautions

Universal precautions should be followed by all people involved in patient care (like the doctors, nurses etc) and those handling blood and blood products (eg the lab technicians). Staff working in the blood collection room and laboratory should observe universal work precautions while handling blood and blood products. Gloves, disposable needles and syringes for drawing blood and puncture resistant containers for disposal of sharp instruments should be used. In addition, the safety kits consisting of plastic disposable gowns, disposable goggles, face mask, disposable shoe cover and two pair of long gloves should be available in all ART centres.

Post Exposure Prophylaxis (PEP)

The health care providers have potential risk of getting occupational exposure to various blood borne infections. Occupational exposure refers to exposure to potential blood-borne infections (HIV, HBV and HCV) that occurs during performance of duties. The average risk of acquiring HIV infection after different types of occupational exposure is 0.3%. Appropriate post exposure management guidelines, therefore, form an important element of work place safety. Comprehensive medical management to minimise the risk of infection due to exposure to blood-borne pathogens (HIV, HBV, HCV) in Health Care Personnel (HCP) to be ensured. This includes counselling, risk assessment, relevant laboratory investigations based on informed consent of the source and exposed person, first aid, and depending on the risk assessment, the provision of short term (four weeks) of antiretroviral drugs, with follow up and support. Post exposure prophylaxis (PEP) is a standard protocol for preventing chances of getting HIV infection when a health care worker is exposed to a source patient known to be / possibly HIV-infected (i.e., occupational exposure). PEP aims to inhibit the replication of the initial inoculums of virus and thereby prevent establishment of chronic HIV infection.

PEP drugs are required on an urgent basis after accidental exposure and should be available and accessible round the clock. In all cases, the first dose of PEP should be offered as soon as possible, preferably within 2 hours, once the decision to give PEP is made. The basic PEP regimen (2-drug combination) should be made available from ARV drug stocks, in the casualty, OT, Labour Room, ICU and

Emergency Ward.

7.8 Linkages and Referrals

Mechanisms for establishing linkages and referral systems are necessary to meet immediate and long-term needs of the persons enrolled in a comprehensive HIV care programme. PLHIV need a wide range of services during the course of HIV infection and stage of the disease. These needs are related to:

1) Physical health
2) Psycho-social and spiritual health
3) Nutrition
4) Financial stability and security
5) Quality of life

There is, therefore, need to develop linkages and referral systems to take care of these needs. Following steps would help in establishing linkages within a district/region:

1) Identification of organisations and facilities dealing with HIV/AIDS;
2) Mapping of such organisations in the district/region;
3) Consultation for setting up linkages and referrals systems including procedures and schedules; and
4) Evolving mechanisms for referrals and feedbacks.

The care coordinator/counselor shall serve as focal points for dissemination of information regarding these services.

It is desirable if representatives of all the ART centres in the state meet regularly to discuss problems, if any, so that the

referral system is made effective and user-friendly. Looking at the various needs of the PLHIV, linkages and referral system need to be set up with other departments within the institution where ART centre is located and with service providers and organisations outside the institution.
The ART centre team also needs to have regular meetings in order to identify and resolve programmatic issues.

Referrals within the Institute

For comprehensive care, people need access to various departments/services depending upon disease stage and occurrence of opportunistic infections. To facilitate effective referral system, the “ART team” constituted at the time of the establishment of the ART centre with specialists from the departments of Medicine, Microbiology, Obstetrics & Gynaecology, Paediatrics, Dermatology / Venereology and Chest diseases should meet once in two months to review ART services and interdepartmental linkages. This ART team meeting can be clubbed with other meetings of institution that are held periodically.

ART centre should have referral linkages with at least following and nurse should be responsible for tracking the referrals within the hospital.

1) Antenatal clinics and Gynaecology Department
2) Microbiology Department (for CD4 count and other investigations)
3) Paediatric Department
4) Dermatology and Venereology Department
5) Chest Diseases / Tuberculosis centre

6) Other departments as per requirement

Referrals outside the Institutions

Certain conditions may need a referral to facility that is outside the institution where ART centre is located. The counsellor/ nurse may be the right person to identify such needs and suggest the place of referrals. Hence, it is important that the counsellor has a list of centres for referrals and is also acquainted with the person to whom referral is to be made. The various possible places for linkages and referral may include the following:

1) NGOs actively working in the field of HIV/AIDS including those involved in Targeted Intervention for High Risk Groups (FSW, Migrants, Truckers, IDU, MSM etc.)
2) Other Government Hospitals
3) Community Care Centres
4) Drop -in Centres
5) Home Based Care Organisations
6) Local PLHIV networks
7) Rehabilitation centres

It is important to track and document the result of referrals. Counsellor/community care coordinator would be responsible to keep track of referrals made outside the hospital. ART centre should maintain account of all the referrals made to the facilities outside the hospital. If feasible, PLHIV network or a drop in centre may be given the responsibility to coordinate linkages and referrals.

Confidentiality and Discrimination Issues

Irrespective of HIV status of a person, all patients are entitled to receive general and specialty out-patient and in-patient services in a hospital. Confidentiality should be maintained at all levels irrespective of HIV status as per accepted medical ethics and the law. Maintenance of confidentiality should help to reduce discrimination against PLHIV during the management of the patient in the hospital. It may also be noted that hospital infection control policies and measures, are properly maintained at all levels and Post Exposure Prophylaxis (PEP) is available for all the staff members. If norms are followed, it will create a safe environment for health care providers to manage PLHIV appropriately.

7.10 Supports from NGOs and Positive Network Groups

In order to improve the quality of care provided to HIV/AIDS patients, the hospital should have effective linkages with Community Based Organisations (CBO), and with Positive Network Groups in the region. Rapport building and development of positive relationships with these organisations will also help reduce the burden on the hospital. Such NGOs may provide vocational (or occupational) rehabilitation to deserving PLHIV and family members and support children affected by AIDS by providing educational support and care homes. They could also provide legal support when PLHIV or their family members are deprived of their rights. In addition, they are often well equipped to provide psychosocial support and even nutritional support.

Continuous supervision of activities carried out at ART centres is essential for monitoring effectiveness and quality of services provided under the programme. To facilitate a uniform and systematic monitoring, systems and tools have been developed.

7.11 Monitoring Tools

Standardised reporting and recording tools used for data collection and supervision have been classified under the following categories:

1. Care and Treatment Records
2. Stock management registers, drugs,CD4 and consumable records
3. Referrals formats
4. Monitoring & Evaluation Formats
    1. ART Centre Supervisory Visit Format
    2. CST Monthly Report Format
5. Programme Performance Monitoring Reports
    1. Monthly ART Centre Report (Including CD4)
    2. TB-HIV monthly report from ART centre

These tools are under development and separate guidance shall be provided on the type of tools and also guidance on filling these tools.

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National ART Guidelines, National Center for AIDS and STD Control, Nepal , 2009 (Unpublished)

Annex 1: WHO clinical staging of HIV disease in adults, adolescents and children

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

Adults and adolescents	**Children**
Clinical stage 1	
Asymptomatic Persistent generalized lymphadenopathy	Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2	
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Seborrhoeic dermatitis	Unexplained persistent hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Herpes zoster Lineal gingival erythema Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Extensive wart virus infection Extensive molluscum contagiosum Unexplained persistent parotid enlargement

Clinical stage 3	
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than 1 month Unexplained persistent fever (intermittent or constant for longer than 1 month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 109/l) and/or chronic thrombocytopaenia (<50 x 109/l)	Unexplained moderate malnutritionb not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month) Persistent oral candidiasis (after first 6 weeks of life) Oral hairy leukoplakia Lymph node tuberculosis Pulmonary tuberculosis Severe recurrent bacterial pneumonia Acute necrotizing ulcerative gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 109/l) or chronic thrombocytopaenia (<50 x 109/l) Symptomatic lymphoid interstitial pneumonitis, Chronic HIV-associated lung disease, including bronchiectasis

Clinical stage 4	
HIV wasting syndrome Pneumocystis (jirovecii) pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 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 meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis	Unexplained severe wasting, stunting or severe malnutritiond not responding to standard therapy Pneumocystis (jirovecii) pneumonia Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) Chronic herpes simplex infection (orolabial or cutaneous of more than 1 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 with onset at age more than 1 month) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy Extrapulmonary cryptococcosis,

Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis) Lymphoma (cerebral or B-cell non-Hodgkin) Symptomatic HIV-associated nephropathy or cardiomyopathy Recurrent septicaemia (including nontyphoidal Salmonella) Invasive cervical carcinoma Atypical disseminated leishmaniasis	including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) Cerebral or B-cell non-Hodgkin lymphoma HIV-associated nephropathy or cardiomyopathy

Annex 2: Diagnostic criteria for HIV-related clinical events (adults)

Clinical events	Clinical diagnosis	Definitive diagnosis
Clinical stage 1		
Asymptomatic	No HIV-related symptoms reported and no signs on examination	Not applicable
Persistent generalized lymphadenopathy	Painless enlarged lymph nodes >1 cm, in two or more noncontiguous sites (excluding inguinal), in absence of known cause and persisting for 3 months or longer	Histology
Clinical stage 2		

Clinical events	Clinical diagnosis	Definitive diagnosis
Moderate unexplained weight loss (under 10% of body weight)	Reported unexplained weight loss. In pregnancy, failure to gain weight	Documented weight loss (under 10% of body weight)
Recurrent bacterial upper respiratory tract infections (current event plus one or more in last 6 months)	Symptoms complex, e.g. unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media), or tonsillopharyngitis without features of viral infection (e.g. coryza, cough)	Laboratory studies if 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 cheilitis	Splits or cracks at the angle of the mouth not attributable to iron or vitamin deficiency, and usually responding to antifungal treatment	Clinical diagnosis
Recurrent oral ulcerations (two or more episodes in last 6 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 postinflammatory 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 nail from 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
Severe unexplained weight	Reported unexplained weight loss (over	Documented loss of more

Clinical events	Clinical diagnosis	Definitive diagnosis
loss (more than 10% of body weight)	10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass index below 18.5. In pregnancy, weight loss may be masked.	than 10% of body weight
Unexplained chronic diarrhoea for longer than 1 month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than 1 month	Not required but confirmed if three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens
Unexplained persistent fever (intermittent or constant and lasting for longer than 1 month)	Reports of fever or night sweats for more than 1 month, either intermittent or constant with reported lack of response to antibiotics or antimalarials, without other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Documented fever exceeding 37.6 oC with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection
Oral candidiasis	Persistent or recurring creamy white curd-like plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Clinical diagnosis
Oral hairy leukoplakia	Fine white small linear or corrugated lesions on lateral borders of the tongue, which do not scrape off	Clinical diagnosis
Pulmonary TB	Chronic symptoms (lasting at least 2 to 3 weeks): cough, haemoptysis, shortness of	Isolation of M. tuberculosis on sputum

Clinical events	Clinical diagnosis	Definitive diagnosis
	breath, chest pain, weight loss, fever, night sweats, plus EITHER positive sputum smear OR negative sputum smear AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, cavitation, pulmonary fibrosis and shrinkage). No evidence of extrapulmonary disease.	culture or histology of lung biopsy (together with compatible symptoms)
Severe bacterial infection (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease)	Fever accompanied by specific symptoms or signs that localize infection, and response to appropriate antibiotic	Isolation of bacteria from appropriate clinical specimens (usually sterile sites)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, rapid loss of bone and/or soft tissue	Clinical diagnosis
Unexplained anaemia (below 8g/dl), neutropenia (below 0.5 x 109/l) and/or chronic (more than 1 month) thrombocytopenia (under 50 x 109/l)	No presumptive clinical diagnosis	Diagnosed on laboratory testing and not explained by other non-HIV conditions. Not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in relevant national treatment guidelines, WHO IMCI guidelines or

Clinical events	Clinical diagnosis	Definitive diagnosis
		other relevant guidelines.

HIV wasting syndrome	Reported unexplained weight loss (over 10% of body weight) with obvious wasting or body mass index below 18.5, plus EITHER unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than 1 month OR reports of fever or night sweats for more than 1 month without other cause and lack of response to antibiotics or antimalarials. Malaria must be excluded in malarious areas.	Documented weight loss (over 10% of body weight) Plus two or more unformed stools negative for pathogens OR documented temperature exceeding 37.6 oC 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 CXR evidence of diffuse bilateral interstitial infiltrates, AND no evidence of bacterial pneumonia. Bilateral crepitations on auscultation with or without reduced air entry.	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue
Recurrent bacterial Pneumonia (this episode plus one or more episodes in	Current episode plus one or more episodes in last 6 months. Acute onset	Positive culture or antigen test of a

Clinical events	Clinical diagnosis	Definitive diagnosis
last 6 months)	(under 2 weeks) of symptoms (e.g. fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or CXR. Response to antibiotics.	compatible organism
Chronic herpes simplex virus (HSV) infection (orolabial, genital or anorectal) of more than 1 month, or visceral at any site or any duration	Painful, progressive anogenital or orolabial 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 in 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 lymphadenopathy, osteitis. Miliary TB: diffuse uniformly distributed small miliary shadows or micronodules on CXR. Discrete cerv ical lymph node M.tuberculosis infection is usually considered a less severe form of extrapulmonary tuberculosis.	M. tuberculosis isolation or compatible histology from appropriate site, together with compatible symptoms/ signs (if culture/histology is from respiratory specimen there must be other evidence of extrapulmonary disease)
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat patches with a pink or blood-bruise	Macroscopic appearance at endoscopy or bronchoscopy, or by

Clinical events	Clinical diagnosis	Definitive diagnosis
	colour, skin lesions that usually develop into violaceous plaques or nodules	histology
Cytomegalovirus disease (retinitis or infection of other organs, excluding liver, spleen and lymph nodes)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Compatible histology or CMV demonstrated in CSF by culture or DNA (by PCR)
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 neuroimaging (CT or MRI)
HIV encephalopathy	Clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily 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, neuroimaging (CT or MRI)
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasingly severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Isolation of Cryptococcus neoformans from extrapulmonary site or positive cryptococcal antigen test (CRAG) on CSF/blood
Disseminated non-tuberculous	No presumptive clinical diagnosis	Diagnosed by finding

Clinical events	Clinical diagnosis	Definitive diagnosis
mycobacteria infection		typical mycobacterial species from stool, blood, body fluid or other body tissue, excluding lung
Progressive multifocal leukoencephalopathy (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 neuroimaging or positive polyomavirus JC (JCV) PCR on CSF
Cryptosporidiosis (with diarrhoea lasting more than 1 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 septicemia (including non-typhoid salmonella)	No presumptive clinical diagnosis	Blood culture
Lymphoma (cerebral or B cell non-Hodgkin) or other solid HIVassociated tumours	No presumptive clinical diagnosis	Histology of relevant specimen or, for CNS tumours, neuroimaging techniques

Clinical events	Clinical diagnosis	Definitive diagnosis
Invasive cervical carcinoma	No presumptive clinical diagnosis	Histology or cytology
Atypical disseminated leishmaniasis	No presumptive clinical diagnosis	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 Clinical staging and immunological classification of HIV and case definition of HIV for surveillance. 2006.

Annex 3: Chronic Hepatitis B Virus Infection Case Definition

Clinical description:

Persons with chronic hepatitis B virus (HBV) infection may be asymptomatic or may have no evidence of liver disease or may have a spectrum of disease ranging from chronic hepatitis to cirrhosis or liver cancer.

Laboratory criteria for diagnosis:

IgM antibodies to hepatitis B core antigen (anti-HBc) negative

AND

A positive result on one of the following tests:

i. Hepatitis B surface antigen (HBsAg),

ii. Hepatitis B e antigen (HBeAg),

iii. or Hepatitis B virus (HBV) DNA

OR

HBsAg positive or HBV DNA positive or HBeAg positive two times at least 6 months apart (Any combination of these tests performed 6 months apart is acceptable.)

Case classification:

Confirmed: A case that meets either laboratory criteria for diagnosis.

Probable: A case with a single HBsAg positive or HBV DNA positive or HBeAg positive lab result when no IgM anti-HBc results are available.

Multiple laboratory tests indicative of chronic HBV infection may be performed simultaneously on the same patient specimen as part of a “hepatitis panel”. Testing performed in this manner may lead to seemingly discordant results, e.g., HBsAg-negative AND HBV DNA-positive. For the purposes of this case definition, any positive result among the three laboratory tests mentioned above is acceptable, regardless of other testing results. Negative HBeAg results and HBV DNA levels below positive cutoff level do not confirm the absence of HBV infection.

Classification of HBV infections

The clinical outcome of HBV is a result of a combination of the level of replication attained by the virus and the nature of the patient’s immune response.

Patients with persistent hepatitis B generally exhibit one of four major clinical patterns of infection:

1. Profound immunotolerance and mild hepatitis B despite high levels of replication of the virus (HBeAg-positive immunotolerant chronic hepatitis B).
2. Active infection (sustained high levels of replication of HBV and raised ALT) in which the 'wild-type' HBeAg-positive HBV is predominant (chronic HBeAg-positive hepatitis B).
3. Active infections in which variant forms of HBV unable to secrete HBeAg are predominant (chronic HBeAg-negative or 'precore mutant' chronic hepatitis B).
4. Inactive HBV infection (HBeAg-negative inactive disease).

Occult HBV infection: A profile, of uncertain clinical significance, which is characterized by the persistence of HBV DNA in liver tissue in HBsAg negative patients.

It is important to note that these phases are by no means static and can change from one to the other.

The virological pattern of chronic hepatitis B is changing in many parts of the world. A few decades ago the disease was characterised primarily by wild-type (HBeAg-positive chronic hepatitis B) infection. In recent years the prevalence of HBeAg-positive relative to HBeAg-negative infection has diminished. A substantial proportion of HBV infection is now characterised by HBV variants unable to secrete HBeAg.

All the above tests are being done in Bangladesh. In Dhaka Medical College and in Bangabandhu Sheikh Mujib Medical

University IgM antibodies to hepatitis B core antigen (anti-HBc), Hepatitis B surface antigen (HBsAg) and Hepatitis B e antigen (HBeAg) are done using ELISA method. Hepatitis B Virus (HBV) DNA is done by PCR in Bangabandhu Sheikh Mujib Medical University.

Annex 4 :Summary of first line ART for Adult, adolescents and children

First-line ART	Preferred first-line regimens	Alternative first-line regimens
Adults (including pregnant and breastfeeding women and adults with TB and HBV coinfection)	TDF +3TC (or FTC) +EFV	AZT +3TC +EFV AZT +3TC +NVP TDF +3TC (or FTC) +NVP
Adolescents (10 to 19 years) ≤35kg		AZT +3TC +EFV AZT +3TC +NVP TDF +3TC (or FTC) +NVP ABC +3TC + EFV (or NVP)
Children 3 years to less than 10 years and adolescents <35kg	ABC +3TC +EFV	ABC +3TC + NVP AZT +3TC +EFV AZT +3TC +NVP TDF +3TC (or FTC) +EFV TDF +3TC (or FTC) +NVP
Children <3 years	ABC or AZT + 3TC + LPV/r	ABC +3TC + NVP AZT +3TC +NVP

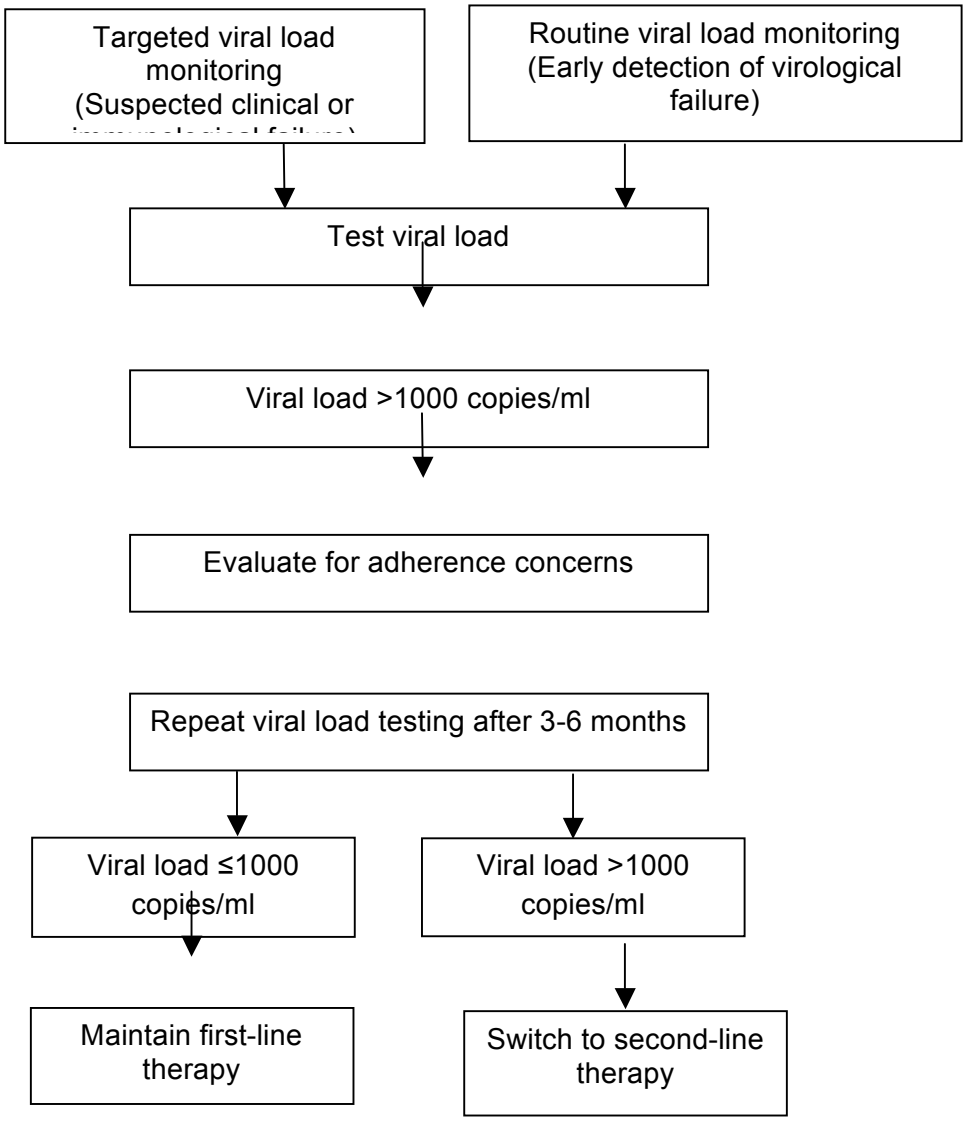
Annex 5: Currently available antiretroviral drugs

There are more than 20 approved antiretroviral drugs across six mechanistic classes. These six classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors, CCR5 antagonists, and integrase inhibitors. Following table shows FDA approved ARV:

Nucleoside Reverse Transcriptase Inhibitors (NsRTIs)	**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**	**Protease Inhibitors (PIs)**	**Fusion Inhibitor**	**CCR5 Antagonists**	**Integrate Inhibitor**
- Zidovudine (ZDV, AZT) - Didanosine (ddI) - Stavudine (d4T) - Lamivudine (3TC) - Abacavir (ABC) - Emtricitabine (FTC)	- Nevirapine (NVP) - Efavirenz (EFZ) - Delavirdine (DLV) - Etravirine (ETV)	- Indinavir (IDV) - Nelfinavir (NFV) - Lopinavir/ritonavir (LPV/r) - Ritonavir (RTV) (as pharmaco-enhancer) - Atazanavir (ATV) - Fosamprenavir (FPV) - Tipranavir - Darunavir - Saquinavir (SQV)	Enfuvirtide (T-20)	Maraviroc	Raltegravir

-Tenofovir (TDF)		Soft gel (SGC)			

Annex 6: Algorithm for detecting virological failure



Annex 7: Summary of second line ART for Adult

Target population		Preferred second-line regimen
Adults, adolescents (>10 years) and Pregnant women	If d4T or AZT was used in first – line ART	TDF + 3TC (or FTC) + ATV/r or LPV/r
	If TDF was used in first-line ART	AZT + 3TC + ATV/r or LPV/r
HIV and TB co-infection	If rifabutin is available	Standard PI-containing regimens as recommended for adults and adolescents
	If rifabutin is not available	Same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800 mg/200mg twice daily)

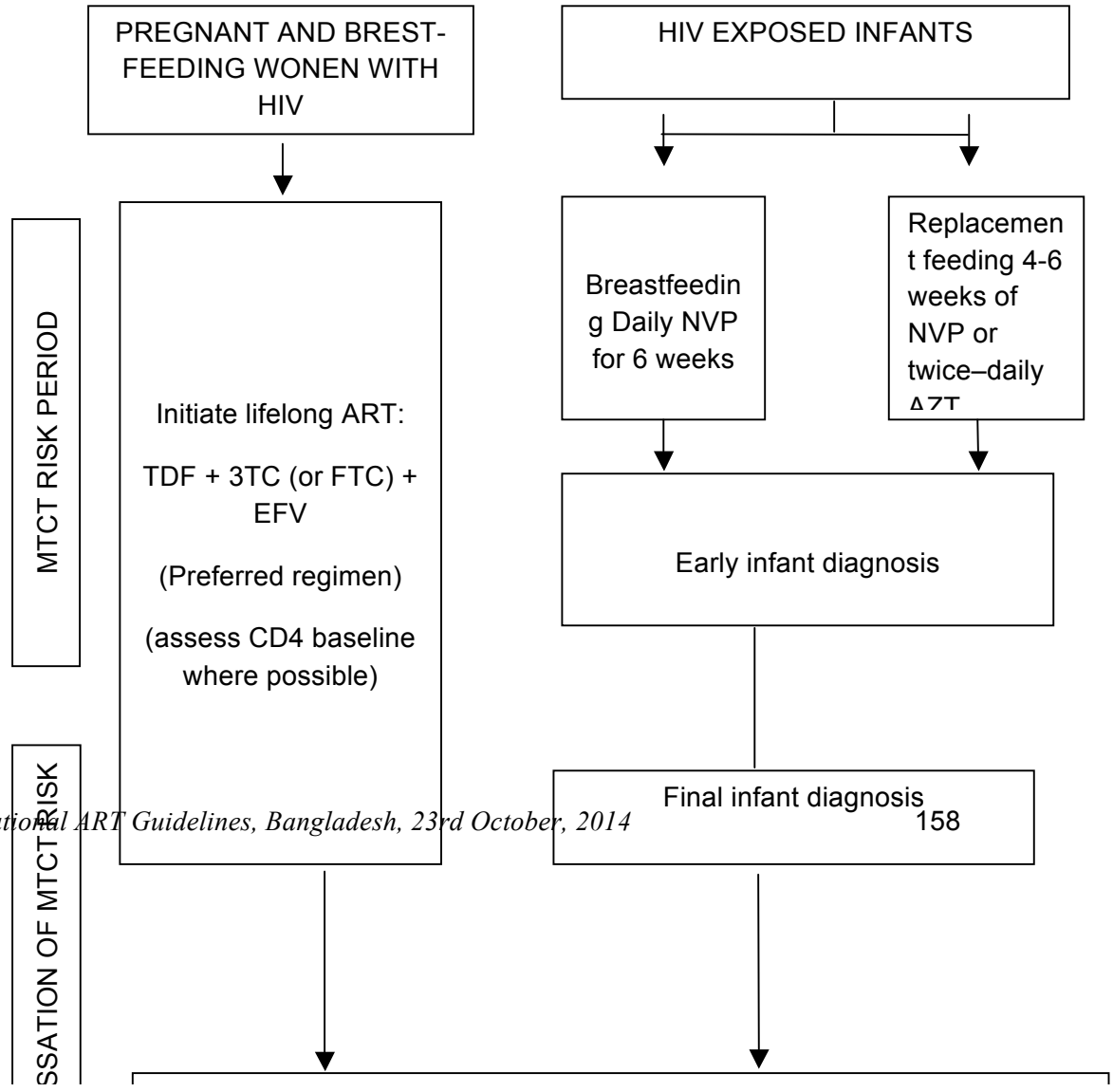
		or standard LPV dose with an adjusted dose of RTV (that is, LPV/r 400 mg/400 mg twice daily)
HIV and HBV coinfection	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)	

Annex 8 :Summary of preferred second-line ART regimens for adults, adolescents, pregnant women and children

Second-line ART Alternative regimens	Preferred regimens	
Adults and adolescents (>10 years) including pregnant and breastfeeding women	AZT + 3TC + LPV/r AZT + 3TC + ATV/r[a] ABC +3TC +LPV/r	TDF + 3TC (or FTC) +ATV/r TDR + 3TC (or FTC) + LPV/r
If a NNRTI-based first-line regimen was used		ABC +3TC +LPV/r TDR + 3TC (or FTC) + LPV/r
Children <3 years If a PI-based First-line Regimen was use	No change from first line regimen in use[c]	AZT (or ABC) +3TC +NVP
3 years to less	AZT (or ABC) +3TC +EFV	ABC (or TDF) +3TC +NVP

Annex 9 :Algorithms for the 2013 recommendations for pregnant and breastfeeding women

Lifelong ART for all pregnant and breastfeeding women with HIV (Option B+)

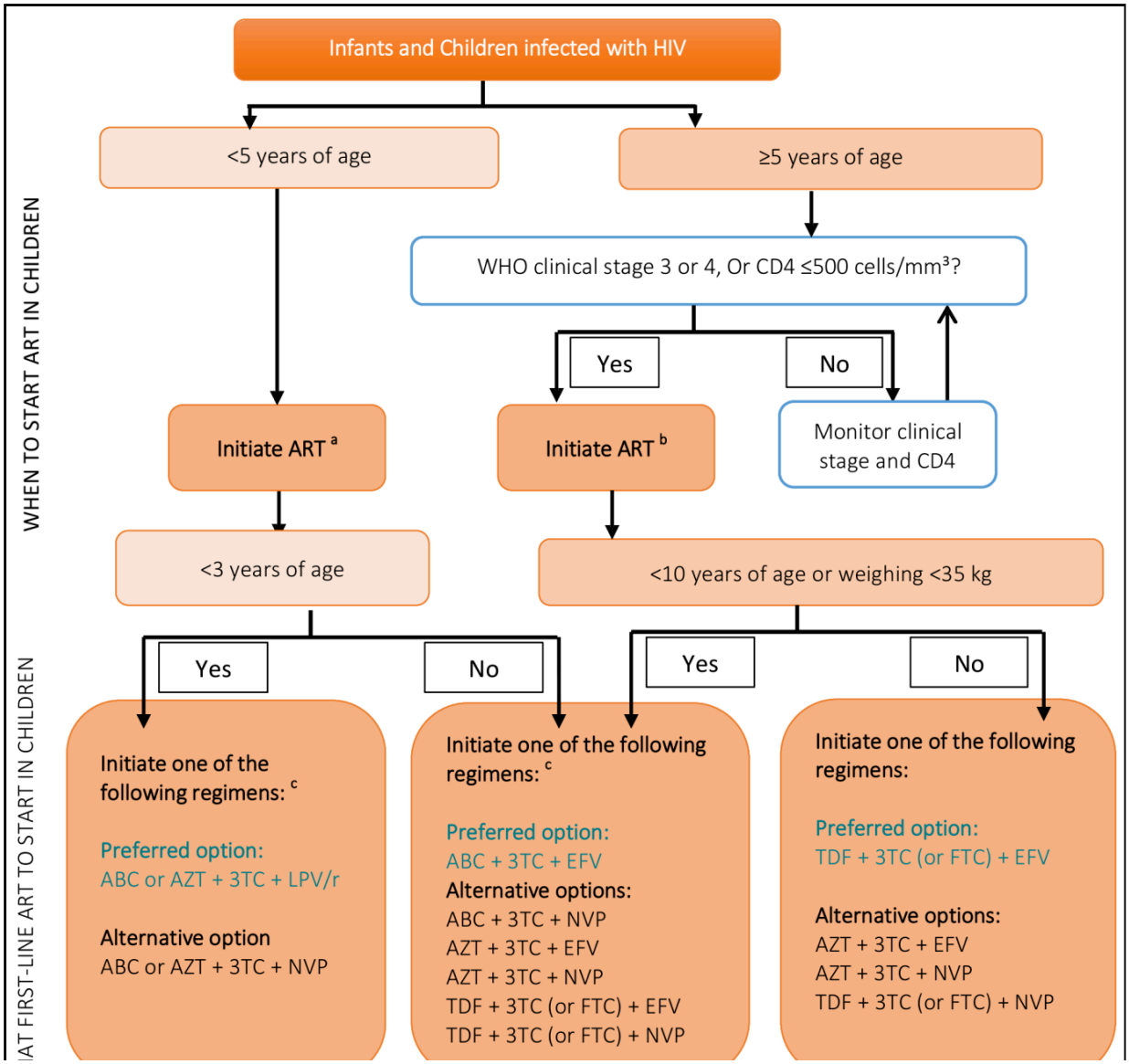


Annex 10: Common Adverse Effect of ARV

ARV/Class	Adverse Effects	Counseling and Follow-up Tips
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)		
Zidovudine (AZT) **Lamivudine (3TC)** **Abacavir (ABC)** **Tenofovir (TDF/TFV)** **Emtricitabine (FTC)**	· Nausea · Diarrhea · Hypersensitivity (ABC) · Anaemia, neutropaenia, myopathy, lipoatrophy or lipodystrophy (AZT) · Nephrotoxicity (TDF) and limited data available on potential maternal and infant bone toxicity with use of	Clinical follow-up for anaemia and hypersensitivity Reassure and manage for nausea and diarrhea Lab follow-up: CBC, LFTs and creatinine
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz (EFV)	· CNS effects- confusion, abnormal thinking, impaired concentration, depersonalization, abnormal dreams, dizziness, feeling of disengagement, insomnia, amnesia, hallucination. · Hepatotoxicity · Hypersensitivity reaction, Stevens-Johnson syndrome · Convulsions · Teratogenicity- Potential risk (probably <1% of neural tube defect	Should be taken initially at bed time. Patient should be warned about the side- effects and re-assured that with continued dosing these rarely persist longer than 2 to 4 weeks. Caution: Avoid driving and not to operate heavy machinery when experiencing side- effects.
Protease Inhibitors (PIs)		

Lopinavir/ritonavir (LPV/r)	· Well tolerated · Hypergylcaemia · Hyperlipidemia · Insulin resistance · Gastro-Intestinal intolerance	Ask regularly for symptoms of hyperglycaemia particularly during the first 18 weeks of therapy when this toxicity is most likely, take following measures: · Take with food · Antiemetics · Antimotility Lab follow-up: glucose level, lipid profile

Annex 11: Anti-Retroviral Treatment Algorithm for Children



Annex 12: Dosages of recommended antiretroviral drugs

Dosages of antiretroviral drugs for adults and adolescents

Generic name	Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily lor 300 mg once daily
Zidovudine (AZT)	250 – 300 mg twice daily
Nucleotide reverse – transcriptase inhibitors (NtTTIs)	
Tenofovir (TDF)	300 mg once daily
Non – nucleoside reverse – transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	600 mg once daily
Etravirine (ETV)	200 twice daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily
Proteases inhibitors (PIs)	
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg once daily
Darunavir + ritonavir (DRV/r)	800 mg + 100 mg once daily or 600mg + 100mg twice daily
Lopinavir/ritonavir (LPV/r)	400mg/100mg twice daily

	Considerations for individuals receiving TB therapy In the presence of rifabutin, no dose adustment required. In the presence of rifampicin, adjusted dose of (LPV 800mg+RTV200mg twice daily or LPV 400mg+RTV400mg twice daily) or SQV/r (SQV 400mg+RTV 400mg twice daily), with close monitoring.
Integrase strand transfer inhibitors (NSTIs)	
Raltegravir (RAL)	400 mg twice daily

Annex 13: Key drug interactions and suggested management

ARV drug	Key interactions	Suggested management
AZT	Rifampicin	Substitute rifampicin with rifabutin Adjust the PI dose or substitute with three NRTIs (for children)
	Ribavirin and peg-interferon alfa-2a	substitute AZT with TDF
Boosted PI (ATV/r, LPV/r)	Estrogen based contraception	Use alternative or additional contraceptive methods
	TDF	Monitor renal function
	Astemizole and terfenadine	Use alternative antihistamine agent
	Methadone	Adjust the methadone dose as appropriate
	Lovastatin and simvastatin	Use an alternative dyslipidaemia agent (for example pravastatin)
EFV	Amodiaquine	Use an alternative antimalarial agent
	Astemizole and	Use alternative antihistamine agent

	terfenadine	
	Methadone	Adjust the methadone dose as appropriate
	Estrogen based contraception	Use alternative or additional contraceptive methods
NVP	Rifampicin	Substitute NVP with EFV
	Itraconazole and ketoconazole	Use an alternative antifungal agent (for example fluconazole)

This table was developed using the University of Liverpool's drug interaction charts, a resource which can be found online at www.hiv-druginteractions.org. A more comprehensive table of ARV drug interactions is available on the Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes).

Annex 14: Recommended Routine Immunizations for all Children - Summary of WHO Position Papers *(updated October 21, 2010)*

(need to retyped)

Antigen		Age of 1st Dose	Doses in Primary Series	Interval Between Doses 1st to 2nd	2nd to 3rd	3rd to 4th	Booster Dose	Considerations (see footnotes for details)
Recommendations for all children								
BCG [1]		*As soon as possible after birth*	1					Exceptions HIV
Hepatitis B [2]	Option 1	*as soon as possible after birth (<24h)*	3	4 weeks (min) with DTP1	4 weeks (min) with DTP3			Premature and low birth weight Co-administration and combination vaccine High risk groups
	Option 2	*as soon as possible after birth (<24h)*	4	4 weeks (min) with DTP1	4 weeks (min) with DTP2	4 weeks (min),with DTP3		
Polio [3]	OPV	6 weeks *(See footnote for birth dose)*	3	4 weeks (min) with DTP2	4 weeks (min) with DTP3			OPV birth dose Transmission and importation risk criteria IPV booster needed for early schedule
	IPV/OPV Sequential	*8 weeks (IPV 1st)*	1-2 IPV 2 OPV	4-8 weeks	4-8 weeks	4-8 weeks		
	IPV	8 weeks	3	4-8 weeks	4-8 weeks		*(see footnote)*	
DTP [4]		6 weeks (min)	3	4 weeks (min) - 8 weeks	4 weeks (min) - 8 weeks		1-6 years of age *(see footnote)*	Delayed/ interrupted schedule Combination vaccine
Haemophilus influenzae type b [5]		6 weeks (min) with DTP1, 24 months (max)	3	4 weeks (min) with DTP2	4 weeks (min) with DTP3		*(see footnote)*	Single dose if >12 months of age Delayed/ interrupted schedule Co-administration and combination vaccine
Pneumococcal (Conjugate) [6]		6 weeks (min) with DTP1	3	4 weeks (min) with DTP2	4 weeks (min) with DTP3		*(see footnote)*	Single dose if 12-24 months of age Delayed/interrupted schedule Co-administration
Rotavirus [7]	Rotarix	6 weeks (min) with DTP1 15 weeks (max)	2	4 weeks (min) with DTP2 no later than 32 weeks of age				Maximum age limits for starting/completing vaccination
	RotaTeq	6 weeks (min) with DTP1, 15 weeks (max)	3	4 weeks (min) - 10 weeks with DTP2	4 weeks (min) with DTP3 no later than 32 weeks of age			
Measles [8]		9-15 months (6 months min, see footnote)	2	4 weeks (min) (see footnote)				Combination vaccine; HIV early vaccination.
HPV [9]		Quadrivalent 9 -13 years of age Bivalent 10- 13 years of age	3	Quadrivalent - 2 mos (min 4 wks) Bivalent - 1 mos (max 2.5 mos)	Quadrivalent - 4 mos (min 12 wks) Bivalent - 5 mos			Vaccination of males for prevention of cervical cancer not recommended currently

For other details and explanation of footnotes mentioned in the table please refer to *http://www.who.int/immunization/documents/positionpapers*

Annex 14: **ADDITIONAL GUIDANCE ON DRUG INTERACTION/TOXICITY**

1. TDF RELATED RENAL TOXICITY

TDF is now preferred first line ART for all new patients to be enrolled in national programme. It has a good overall safety profile, with fewer metabolic side-effects & mitochondrial toxicities. TDF has a relatively long half-life, allowing once daily dosing and making compliance easier for patients. The major side effects of TDF are:

- Renal toxicity
- Decrease in Bone marrow density

However out of these, most significant is TDF related renal toxicity, though overall incidence may by only 3-5%. The renal proximal tubule (PT) is the main target of TDF toxicity but; although the pathogenesis is incompletely elucidated mitochondria appear to be a major target. [1,2].

Effect on glomerular function

In a pooled analysis comparing TDF with zidovudine a modest but significant decline in eGFR was observed in the TDF-exposed patients. [3] A meta-analysis that included data from 17 studies concluded that TDF exposure is associated with a mean difference in estimated CrCl of −3.9 ml/ min over the course of treatment. However, this meta analysis also found a high degree of statistical heterogeneity in the published data, due to variability in parameters such as follow-up time, previous anti-retroviral therapy (ART) exposure, and concomitant usage of protease inhibitors (PIs) [4].

Effect on tubular function

Serum creatinine and eGFR are predominantly measurements of glomerular function, however, the main target of TDF nephrotoxicity is the PT and in severe cases leading to a breakdown of solute transport in this nephron segment (renal Fanconi syndrome—FS) or acute kidney injury (AKI). Fanconi syndrome include aminoaciduria, glycosuria, tubular proteinuria, and uricosuria and also bone demineralization due to phosphate wasting. This may lead to acute renal failure and this renal toxicity can usually present after 20 weeks or more of Tenofovir therapy, with resolution typically within 10 weeks after the discontinuation of the therapy.

Numerous case reports and case series have described FS or AKI in HIV-infected patients taking TDF [5-12]. The exact incidence of TDF-induced FS is unknown, and attempts at accurate estimates are hampered by underreporting and a lack of clear diagnostic criteria, but based on the available data it is probably <1 % [10]. Renal biopsy specimens from patients with TDF toxicity typically show acute tubular damage, with misshapen and swollen mitochondria in the PT on electron microscopy [10,12]. While cases of FS and AKI are relatively infrequent in patients taking TDF, these represent the most severe end of the scale of PT toxicity [15-18]. Studies have [19-21] demonstrated that generally it is mild or sub-clinical PT dysfunction in patients on TDF. The reported prevalence varies among studies, partly because of a lack of standardized definitions, but may be greater than 20 % [17]. It is currently unknown whether mild PT toxicity will lead to progressive CKD over time in these patients, but one credible concern is that chronic phosphate wasting might cause a decrease in bone mineral density.

Effect on tubular secretion of creatinine

Serum creatinine is widely used to calculate CrCl/eGFR, however, in addition to glomerular filtration, about 10-40 % of creatinine clearance occurs by secretion across the PT epithelium. Decline in CrCl/eGFR within the first 2–3 months of commencing therapy, with very little further change over time, has been seen in many studies [13,14,22]. Therefore, given the pattern of CrCl/eGFR changes reported in patients taking TDF, it is plausible that they might be due to impaired PT creatinine secretion, rather than alterations in actual GFR. To explore this hypothesis, a recent small study of 19 HIV-infected patients, either remaining on zidovudine therapy or switching to TDF, looked in detail at changes over time in actual GFR, calculated CrCl, and urine excretion of tubular [23]. In the patients switching to TDF, mean CrCl was significantly decreased, while urine excretion of tubular protein was significantly increased after 48 weeks; however, there was no corresponding change in actual GFR, and no changes in any of the three parameters were observed in the zidovudine group which helps to conclude that decrease in CrCl in the TDF patients was more likely to be due to impaired PT creatinine secretion rather than a change in glomerular function.

Guidance for treatment

The main target of TDF toxicity is the proximal tubule and hence for the suspicion of Renal toxicity, the presence of tubular proteinuria is thought to be the most sensitive test for proximal tubule dysfunction. For monitoring the renal tubular dysfunction which often results in Fanconi Syndrome, the urine routine showing pH as acidic along with glycosuria and albuminuria will be sufficient for the diagnosis though a 24 hours urine sample for Phosphate (hypophosphatemia and hypokaleamia) and protein, calcium are confirmatory. If feasible the creatinine clearance may

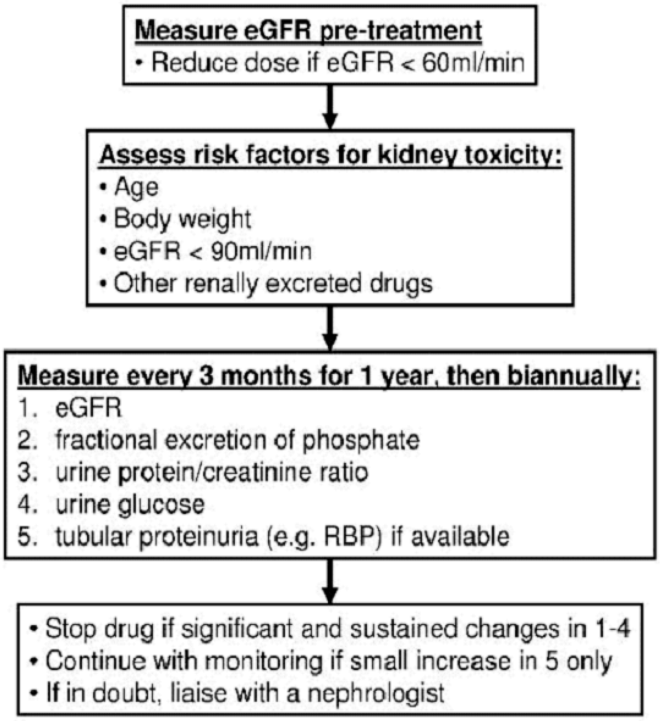
also be calculated and any adverse raise in the level of serum creatinine should raise suspicion for early signs of renal damage.

For initiating on TDF-containing regimens, creatinine clearance calculation is recommended, if feasible, before initiation and every 6 months. Especially in patients of high risk situations like underlying renal disease, Age > 40 years, BMI < 18.5 (or body weight < 50 kg), diabetes mellitus, Hypertension, concomitant use of nephrotoxic drugs, doing a creatinine clearance is strongly recommended for this population before opting for TDF. The inability to perform creatinine clearance is not a barrier to TDF use. Hence in a resource limited settings, TDF can even be started without a creatinine clearance level however the above mentioned risk factors should be assessed. TDF dose should be reduced in patients with pre-existing decreased kidney function

CG (Cockroft- Gault) formula: eGFR = (140 – age) X (Wt in kg) X 0.85 (if female)/(72 X Cr in mg%).

Do not continue TDF when the estimated glomerular filtration rate is <50 ml/min. In patients suspected with Fanconi syndrome, treatment should be stopped and resolution typically occurs within 10 weeks after discontinuation of the therapy. Patients receiving TDF and meet any one of the four criteria below mentioned should have kidney function (eGFR) and serum phosphate measured every 6 months and be analyzed for proteinuria and glycosuria.(24)

1. GFR <90 mL/min
2. use of other medications eliminated through renal secretion (eg, adefovir, acyclovir, ganciclovir, or cidofovir),
3. other co morbid diseases (eg, diabetes or hypertension), and
4. Following a ritonavir-boosted protease inhibitor regimen.


Measure eGFR pre-treatment
• Reduce dose if eGFR < 60ml/min
Assess risk factors for kidney toxicity:
• Age
• Body weight
• eGFR < 90ml/min
• Other renally excreted drugs
Measure every 3 months for 1 year, then biannually:
1. eGFR
2. fractional excretion of phosphate
3. urine protein/creatinine ratio
4. urine glucose
5. tubular proteinuria (e.g. RBP) if available
• Stop drug if significant and sustained changes in 1-4
• Continue with monitoring if small increase in 5 only
• If in doubt, liaise with a nephrologist

2. ATAZANAVIR INDUCED UNCONJUGATED HYPERBILIRUBINAEMIA

Background

The recommended prescribed dose of Atazanavir (ATV)is ATV 300 mg + Ritonavir (RTV) 100mg once daily. No dosage adjustment is required for patients with renal dysfunction unless they are on haemodialysis. Considering the widespread use of Atazanavir, clinicians caring for HIV-infected patients should have familiarity with the entity of protease inhibitor-associated hyperbilirubinaemia.

Isolated unconjugated hyperbilirubinaemia is the most common laboratory abnormality associated with the use of Atazanavir and this is not associated with hepatocellular injury. Although not considered a serious adverse effect, the higher levels of unconjugated hyperbilirubinaemia associated with this drug can manifest as jaundice with a high colored urine. The onset of Atazanavir associated hyperbilirubinaemia typically occurs within several months, and bilirubin levels generally peak within 4 months (range 1 to 8 months); the subsequent natural history on therapy is notable for a non-progressive course, with bilirubin levels remaining generally stable in patients on further follow-up. Routine monitoring of bilirubin is acceptable.

An isolated elevation in total bilirubin should be confirmed as predominantly unconjugated by testing the indirect fraction of bilirubin. The presence of elevated conjugated bilirubin or changes in serum hepatic aminotransferases or alkaline phosphatase warrant further investigation for other causes of hyperbilirubinaemia, such as other drug hepatotoxicity, viral hepatitis, alcoholic hepatitis or cholestasis. It is

important to recognize that patients who are on Atazanavir but with acute hemolysis will also develop increased indirect bilirubin levels.

Management

For patients who develop clinically-evident jaundice, the decision of whether to discontinue the offending protease inhibitor (Atazanavir) usually depends on how severe and noticeable the jaundice is, and whether the patient is willing to tolerate it. Additional work-up is not required if liver enzymes are not raised and consistent with baseline values. The patient require proper counseling on this development of yellowish discoloration of eye which is not associated with liver damage and reemphasized that was physiological and need not get alarmed.

Dose reduction of Atazanavir is not recommended in this setting. In most cases, a change to an alternative regimen is necessary only for patients who develop an unacceptable level of jaundice with Grade 3 (5-10 times of ULN) & 4 (>10 times of ULN) elevation of serum ALT & AST.

In case of Hepatic insufficiency dosage adjustment is recommended. Child-Pugh Score is utilized to assess the severity and prognosis of chronic liver disease and to identify patients who require liver transplantation. This score is to be used only in those HIV infected subjects who have concomitant chronic liver disease e.g. chronic hepatitis B & C, alcoholic liver disease, NASH and other chronic liver diseases.

ATV/r (300/100 mg) can only be used in patients with chronic liver disease in Child Pugh Class A. It should not be used on second line patients with Child Pugh Class B or C. Please refer the following tables for the scores and classifications.

	Child-Pugh Score		
Component	**Points 1**	**Points 2**	**Points 3**
Encephalopathy	**none**	Grade 1–2	Grade 3–4
Ascites	**none**	Mild or controlled by diuretics	Moderate or refractory despite diuretic
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
Total bilirubin or	<2 mg/dL (<34 µmol/L)	2–3 mg/dL (34 µmol/L to 50 µmol/L)	>3 mg/dL (>50 µmol/L)
Modified total bilirubin (for patients of Gilbert Disease and patients on Atazanavir&Indinavir)	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin time (seconds prolonged) or	<4	4–6	>6
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3

Encephalopathy Grades

Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination

Grade 2: Drowsiness, disorientation, asterixis

Grade 3: Somnolent but arousable, marked confusion, incomprehensible speech, incontinence, and hyperventilation

Grade 4: Coma, decerebrate posturing, flaccidity

Child-Pugh Classification

Child-Pugh Classification *	Total Score
Class A	5-6 points
Class B	7-9 points
Class C	>9 points

3. DRUG INTERACTION WITH ATAZANAVIR

Avoid concurrent use of the following drugs:

Astemizole, Cisapride, fluticasone, Indinavir, Lovastatin, Simvastatin, Midazolam, Terfenadine etc

Unique drug interaction involving Atazanavir:

In addition to all the drug interactions involving PI class, Atazanavir has significant drug interaction with antacids, H2 Receptor antagonists and proton pump inhibitors.

S No	Patient on following drugs concomitantly	Recommendation / points to remember for ATV
1	Antacids	Give ATV at least 2 hours before or 1 hour after antacids or buffered medications
2	H2 Receptor Antagonist	1. H2 receptor antagonist dose should not exceed a dose equivalent to Famotidine 40 mg BID in ART-naïve patients or 20 mg BID in ART-experienced patients. 2. Give ATV 300 mg + RTV 100 mg simultaneously with and/or >10 hours after the H2 receptor antagonist. ***Example:*** *If a PLHIV on Zidovudine +*

		Lamivudine + Atazanavir/ Ritonavir (Regimen IV) requires to be treated with Famotidine 20 mg BID or Ranitidine 150 mg BID, S/he should be instructed to take Tab. Famotidine / Ranitidine with Zidovudine + Lamivudine at 8.00 AM and again Tab. Famotidine / Ranitidine with Zidovudine + Lamivudine + Atazanavir / Ritonavir at 8.00 PM.(after dinner)
3	Proton pump Inhibitor	1. **H2 receptor antagonist is not recommended with** Tenofovir + Lamivudine + Atazanavir/Ritonavir 2. PPIs should not exceed the dose of Omeprazole 20 mg daily or equivalent dose of Esomeprazole 20mg / Pantoprazole 40 mg / Rabeprazole 20 mg in PI-naïve patients, along with Ritonavir boosted Atazanavir. PPIs should be administered at least 12 hours prior to Atazanavir/Ritonavir. 3. **PPIs are not recommended in PI-experienced patients**. ***Example:*** *If a PLHIV is on Tenofovir + Lamivudine + Atazanavir / Ritonavir requires to be treated with PPI, S/he should be instructed to take Tab. Omeprazole 20 mg / Esomeprazole 20mg / Pantoprazole 40 mg / Rabeprazole 20 mg OD at 8 AM and Tenofovir + Lamivudine + Atazanavir/Ritonavir after 8 PM.*

Important consideration in pregnancy

ATV/r is not to be used for pregnant HIV seropositive women requiring a PI based regimen or HIV-2 infected patients where LPV/r should be used

Toxicities of ATV/r

a. Prolongation of P-R and Q-Tc interval in the ECG can occur. So PR interval need to be monitored in patients with known conduction defects or with concurrent use of other drugs that alter conduction abnormalities (like diltiazem, clarithromycin, , cisapride, ketoconazole etc.). However, routine ECG before starting Atazanavir based ART is not recommended.
b. Atazanavir induced urolithiasis is also reported; presumably due to precipitation of the drug resulting in crystalluria in a manner analogus to Indinavir.
c. If the serum total Bilirubin is > 7 mg/dl or the Child-Pugh Score is ≥ 7, then ATV/Ritonavir can not be used and the details of such cases should be refereed for expert consultation

Counseling issues:

There is a need for enhanced counseling of the PLHIV on these regimens particularly unique side effects of Atazanavir/ Ritonavir. So, the patients need to be counseled that they may appear to be jaundiced with yellow eyes but they should not be afraid as it is only a cosmetic problem. It should not be taken as hepatotoxicity. However, LFT has to be done should someone appears to have jaundice. Also, they should be advised to consume plenty of water.

4. GUIDANCE ON SKIN RASH WITH ARVS

The ART MO should remember the following important points about drug rash

1. Cotrimoxazole prophylaxis needs to be initiated 7-10 days before ART initiation. This interval is essential to rule out co-trimoxazole hypersensitivity which may be a delayed phenomenon in some individuals.

2. If CPT and ART are started simultaneously or within a short interval and the patient presents with rash, assess the severity of the rash. If it is of grade 1 or 2, stop co-trimoxazole, provide symptomatic treatment, continue ART under close supervision. If rashes resolves, then co-trimoxazole should be presumed to be the offending agent. Once the patient gets stabilized on ART, slow co-trimoxazole desensitization or Dapsone can be tried later on.

3. Although Nevirapine is the commonest agent incriminated in adverse cutaneous drug reactions, many other antiretroviral drugs used in the National programme (e.g. efavirenz, lamivudine, abacavir, atazanavir, ritonavir, lopinavir etc.) as well as drugs frequently used to treat PLHIV/CLHIV (e.g. cotrimoxazole, Anti-TB drugs, Fluconazole etc.) can also give rise to skin rash.

4. It is very important to grade the rash appropriately.
   Mucocutaneous drug rashes are typically graded in 4 grades;

Grade -1	Grade -2	Grade -3	Grade -4
Erythema, pruritus	Diffuse maculopapular rash or dry desquamation	Vesiculation or moist desquamation or ulceration	Any one of the following; mucous membrane involvement, Stevens Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema multiforme, Exfoliative dermatitis

Source: Division of AIDS, National Institute of Allergy and Infectious Diseases, USA (modified)

(For appropriate clinical diagnosis, the ART MO should take the help of the Dermatologist.)

Stop Nevirapine immediately if anyone the following is present; (1) mucosal involvement (buccal, nasal, conjunctival or genital mucosa), (2) Fever, (3) Erythema multiforme/urticaria/vesicles/blisters, (4) jaundice, (5) rise of ALT/AST > 5 times of upper limit of normal

5. The general guideline regarding management of ART associated cutaneous side-effects is as follows;

Grade	Severity	Advice on ART
1	Mild	Changes of ART should be avoided, offer symptomatic treatment but close clinical monitoring is warranted
2	Mild to moderate	
3	Moderate	It will usually be necessary to discontinue the suspected drug until the condition resolves. Subsequently, it may be possible to cautiously substitute the offending drug with another drug from the same class (e.g. NVP → EFV)
4	Severe	Discontinue all drugs and hospitalise the patient. The offending drug should never be re-challenged. After the patient improves clinically, an alternate regimen involving drugs of different class is used (e.g. NVP or EFV →ATV/r or LPV/r)

6. Considering the long half lives of NNRTI, whenever a decision is taken to stop NVP or EFV in case of non-severe (Grade 4) rash, a tail of NRTI (AZT + 3TC) should be given for 7-14 days to reduce the possibility of development of NNRTI resistance. However, if the rashes continue to evolve while having AZT + 3TC, the tail should immediately be stopped and the dermatologist consulted. For patients on TDF + 3TC based regimen, similar NRTI tail is not needed as the intra-cellular half-live of TDF metabolite is long. For severe rashes, all ARVs should immediately be stopped without any NRTI tail. All other concomitant drugs like cotrimoxazole, anti-TB drugs, fluconazole etc. should also be discontinued immediately and the patient should be managed under the guidance of a dermatologist &/or physician as an in-patient.