National Guidelines of Antiretroviral Therapy Bangladesh

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

2011

ART Advisory ART Advisory Committee

Prof. Dr. Khondoker Md Shefyetullah, Director General, DGHS, Directorate General of Health Services (DGHS)
Dr. Md.Abdul Waheed, Line Director, NASP, Directorate General of Health Services
Dr. S.M. Idris Ali, Programme Manager, NASP
Senior Consultant, Infectious Diseases Hospital (IDH)
Prof. Kazi Zulfiqur Mamon, Microbiology, DMCH
Prof. Dr. AQM Sirajul Islam-HIV Clinical Specialist
Prof. Aga Masud Choudhury- Head of Dermatology Department and Venerology, BSMMU
Dr. Nizam Uddin Ahmed, Director, HIV Sector and South Asia Program Advisor, Save the Children USA
Dr. Salil Panakadan, Country Coordinator, UNAIDS
Dr. Tasnim Azim, Head, HIV/AIDS Program and Virology Laboratory, ICDDR,B
Mr. Helmut Raelhlmann, Country Representative, Swiss Red Cross
Ms. Misti McDowell, Country Director, FHI
Ms. Habiba Akhter, Executive Director, Ashar Alo Society and President, PLHIV Network
Dr. Halida Hanum Khandaker, Executive Director, CAAP.
Ms. Mukti, Executive Director, Mukto Akash Bangladesh.

Technical & Financial Support
World Health Organization (WHO)
Save the Children-USA
Eminence

Published by: National AIDS/STD Programme (NASP)

Printed by

Technical Specialist
Dr.Durga Prasad Bhandari, World Health Organization (WHO)

Contributors
Dr. Anisur Rahman, Deputy Programme Manager –NASP
Dr. Mahmud Hasan, Deputy Programme Manager –NASP
Dr. Sayedur Rahman, Deputy Programme Manager –NASP
Prof. Dr. Kazi Zulfikar Mamun.—Dhaka Medical College
Prof. Dr.Abid Hossain Mollah—Dhaka Medical College.
Prof. Dr.Nazmul Ahasan—Dhaka Medical College.
Dr. Iffat Ara—Dhaka Medical College.
Dr. Rabeya Sharmin—Dhaka Medical College.
Dr. Parveen Sultana—Technical Specialist, Save the Children-USA

Dr. Fadia Sultana—Save the Children-USA
Dr. Samina Choudhury—Save the Children -USA
Bridget Job Jhonson—UNICEF
Dr Nashaba Matin—ICDDR'B
Dr. Shamim Jahan—Family Health International (FHI)
Dr. Md. Shahidul Islam—CAAP
Dr. M. Salim uzzaman- SSMC & Mitford Hospital
Dr. Nilufar Begum—AAS
Dr. Enamul Haque—WHO
Dr. Rabeya Sharmin—DMCH
Dr. Mohsina Ahmed—IDH
Dr. Mostaq Parvez—ICDDR,B

Table of Contents

F O R E W O R D

According to global report of UNAIDS, 2010 on average 33 million people in the world are living with HIV. Sub Saharan Africa shares the biggest burden of HIV in the world with 22.5 million people living with HIV. South and South East Asia is the region with second highest number of PLHIV with the estimated number of 4.1 million. Bangladesh is not the high HIV burden country in the region, however HIV vulnerability is high concern. According to National AIDS and STD Program Bangladesh, the estimated number of HIV positives is 7500. The cumulative numbers of PLHIV reported until December 2010 was 2088 and out of these 574 PLHIV were on ART by May 2011(NASP).

Bangladesh is taking all the possible measures to halt the epidemic. Along with the prevention in the targeted group, care, support and treatment are also provided to the identified PLHIVs. To ensure standard and rational treatment NASP took initiative to develop National ART guideline. The first ART guideline was developed in 2006 incorporating 2006 recommendations of WHO. This has streamlined the ART services in the country. Since the development of the ART guidelines in 2006, many new developments have occurred in the field of HIV. In Bangladesh, the pattern of HIV epidemic has also changed. The incidence rate along with identification rate has also increased, thus increasing the number of HIV positive people requiring care and treatment. In 2010, World Health Organization updated the guidelines to include new evidences and developments in the field of HIV. To provide optimum care to PLHIV in Bangladesh, it was an immediate need of the country to adopt the new guidelines by revising the existing one and allowing the care providers to treat PLHIV with the updated internationally accepted regimens.

This revised guideline includes all the recommendations made by WHO in 2010. It includes the areas, which were not addressed fully by the previous version. Extensive sections on Antiretroviral Drugs, Prevention of Mother to Child Transmission, Pediatric ART, special situations, cotrimoxazole prophylaxis have been added and are the highlights of the revised version.

We hope, clinical service providers as well as the beneficiaries both will be benefitted from the clear instructions provided in these sections of the guideline. We also expect that program mangers, senior policy makers and donors will also equally be benefitted from these guidelines, as these will serve as framework of the ART services in the country.

This is also worthy of mentioning that National AIDS and STD Program followed a fully participatory process to revise the guideline. A technical working group was formed under the guidance of National ART Advisory Committee. This working group was comprised of technical experts working in the field of ARV service delivery. NASP would like to acknowledge the efforts of technical experts of the ART Guideline Committee. Our sincere thanks go to all the reviewers who provided their valuable comments on the draft of the guidelines, which helped to bring this document to the current shape. We would also like to express our acknowledgements to World Health Organization, Save the Children USA, Eminence Bangladesh and implementing partners along with PLHIV- Self Help Group for providing technical support for the revision of the guideline.

Dr. Md. Abdul Waheed
Line Director
National AIDS / STD Program
Directorate General of Health Services
Ministry of Health and Family Welfare, Bangladesh

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 cell	T-Lymphocyte Bearing CD4 Receptor, 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 presents the summary of the recommendations included in the guidelines. This may not contain all the 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.

Summary of the major recommendations

Situation	Criteria /definitions
Initiation of ART in adults and adolescents including pregnant women	• **Any HIV positive individuals with CD4 count ≤ 350 cells/mm^3 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**
Initiation of ART in infants and children (18 years and below)	• **All HIV infected children up to 24 months of age irrespective of CD4 count or WHO clinical stage** • **In the absence of virological tests, any child less than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection** • **All HIV infected children 24 to 59 months with CD4 count of ≤750 cells/mm3 or %CD4+ ≤25, whichever is lower, irrespective of WHO clinical stage.** • **All HIV-infected children more than 5 years of age with a CD4 count of ≤350 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.**
Laboratory monitoring	• **Baseline tests: CD4 count, Hb for AZT, creatinine clearance for TDF, ALT for NVP** • **During ART: CD4 count, Hb for AZT, creatinine clearance for TDF, ALT for NVP preferably in every 6 months**
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 5000 copies/ml**
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
ARV Prophylaxis in PMTCT (Pregnant women not requiring treatment due to their own health)	**Option B** • **This is preferred option for Bangladesh** • **Mother: Triple ARV prophylaxis starting from as early as 14 weeks of gestation and continued until delivery, or if breastfeeding, continued until 1 week after all infant exposure to breast milk has ended.** • **Infant: Irrespective of mode of infant feeding, daily NVP or twice daily AZT from birth until 4 to 6 weeks of age** • **Option A** • **This option is for HIV positive mother with HBV co infection not requiring treatment** • **It should be started as early as 14 weeks of pregnancy** • **Mother: Ante partum twice-daily AZT, plus sd-NVP at the onset of labour plus twice daily AZT + 3TC during labour and delivery and continued for 7 days postpartum.** • **Infant (on breastfeeding):Daily administration of NVP from birth until 1 week after all exposure to breast milk has ended, or for 4 to 6 weeks if breastfeeding stops before 6 weeks** • **Infants (with no breast-feeding): Daily administration of NVP from birth or sd-NVP at birth plus twice-daily AZT from birth until 4 to 6 weeks of age is recommended.**

SECTION 1: INTRODUCTION

This section contains following topics:

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

1.1 Background

According to global report of UNAIDS 2010 on average 33 million people in the world are living with HIV. Sub Saharan Africa shares the biggest burden of HIV in the world with 22.5 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 global number of people living with HIV is decreasing. It may be due to the efforts of prevention and care programs implemented all over the world in the previous years. Even with the available efforts, it is becoming difficult to tackle HIV in the high burden countries of Asia and Africa due to existing poverty, illiteracy and overall ignorance.

There have been efforts at the global and regional level for effective control of HIV. Some of the global and regional commitments and initiatives include:

1. UNAIDS strategy "Getting to Zero" – particularly "zero AIDS-related deaths", where ART is one of the specific objectives
2. 2011 Political Declaration on HIV and AIDS – Intensifying Our Efforts to Eliminate HIV and AIDS
3. Treatment 2.0 (UNAIDS & WHO)
4. 2010 WHO guidelines on ART, PMTCT, Pediatrics

According to National AIDS and STD Program Bangladesh, the estimated number of HIV positives is 7500 Bangladesh is a low-level epidemic country but with a concentrated epidemic in certain clusters of PWID. Prevalence of other groups of MARP (FSW, MSM, Hijra, and Transgender) and in general population is less than one percent. The cumulative number of PLHIV reported until December 2010 was 2088 and AIDS cases were 850(NASP). Out of these over 574 PLHIV were on ART as of May 2011(NASP). Revision of National ART Guidelines 2006 is one of the efforts of Bangladesh in response to global and regional initiatives.

1.2 Objectives of the National ART Guidelines

1. To provide recommendations based on WHO 2010 guidelines using a public health approach to the delivery of ART within the context and setting of Bangladesh
2. To identify the most potent, effective and feasible first-line and second-line treatment regimens for expanded national response to HIV care in Bangladesh.
3. To recommend the optimal timing of ART initiation, preferred first-line and second-line ARV regimens, improved criteria for ART switch and managing HIV in special situations (pregnancy, pediatric, tuberculosis, hepatitis, occupational exposure etc)

1.3 Rationale of the guidelines

Since the development of the first ART guidelines in the country in 2006, many new developments have occurred in the field of HIV. In Bangladesh, the pattern of HIV epidemic has also changed. The incidence rate in Bangladesh has increased by more than 25% since 2001, increasing the number of HIV positive people requiring care and treatment. World Health Organization updated the guidelines in 2010 to include new evidence and developments in the filed of HIV.

To provide optimum care to PLHIV in Bangladesh, it was the immediate need of the country to adopt the new guidelines and allow all the care providers to treat PLHIV with the updated internationally accepted regimens. It is equally important to have updated national recommendations that are in line with recognized international guidelines, so that policy makers and the program mangers can put forward rational and evidence-based proposals for resource mobilization on program implementation to the relevant donors.

The role of the antiretroviral treatment for prevention of HIV transmission has also been demonstrated. This underlines the need of ensuring access to quality treatment for all people living with HIV. The development of current ART guidelines is based on two fundamental principles of HIV care- to provide standardized treatment regimens and to promote more than ninety-five percent adherence to the regimens. This will ensure effective antiretroviral therapy with minimal possibilities of resistance development to ARV, and reduce chances of further HIV transmission

1.4 Target audience of the guidelines

The target audiences of these guidelines are national treatment advisory board, national AIDS program managers, partners implementing HIV care and treatment, and organizations providing technical and financial support to HIV care and treatment programs in Bangladesh. This document will be useful to clinicians in Bangladesh who are directly taking care of the PLHIV. All the available regimens in Bangladesh are included and updated with the most recent international recommendations. National HIV program managers and other senior policy-makers in Bangladesh can use these guidelines for planning of national HIV care strategies and activities. The treatment guidelines will serve as a framework for selecting the most potent and feasible ARV regimens as components of expanded national responses for the care of HIV-infected individuals.

SECTION 2: ANTI–RETROVIRAL DRUGS

This section includes the followings

1. ***Anti- retroviral drugs and their mechanisms of action***
2. ***Classes of anti-retroviral drugs***
3. ***Recommended antiretroviral drugs***

2.1 Antiretroviral drugs and their mechanisms of action

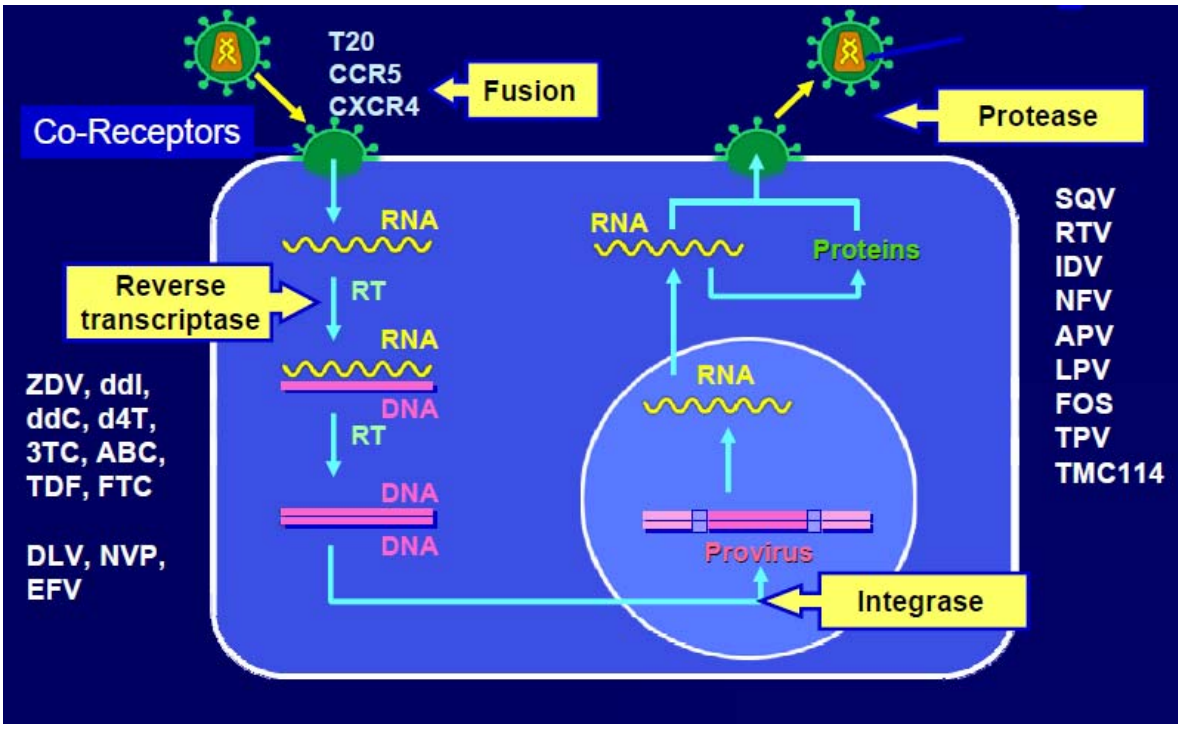
To understand the mechanism of action of ARV, one needs to understand the basic steps of the viral replication, in other words life cycle of HIV virus. Virus enters into the CD4 (host) cell involving glycoproteins of the virus and receptors of host cells. The process is called fusion. ARVs interfering 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 (Marraviroc) 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 trancriptase enzyme. The ARVs interfering with this process are called nucleoside and nucleotide reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). 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, Atazanvir 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), Saquinavir boosted with ritonavir (SQV/r) and Atazanovir boosted with ritonavir (ATV/r) are some of the boosted PI recommended for Bangladesh.

The viral RNA after the action of protease convert 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. The following graphic represents the process viral replication and the action of the ARV in different stages of the replication.



2.2 Classes of Antiretroviral drugs

This classification does not represent all the ARV drugs described above, these are the drugs currently recommended by guideline development team for the use in Bangladesh. Depending on the mechanism of action, ARVs are categorized into following classes:

1. Nucleoside and nucleotide analogs (NRTI)
    B. Nucleoside reverse transcriptase inhibitors
    C. Nucleotide reverse transcriptase inhibitors
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)

2.3 Recommended Antiretroviral drugs

2.3.1 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

The first effective class of antiretroviral drugs was the Nucleoside analogues. These are structural analogues of nucleosides and mimic the DNA building blocks there by stopping the viral replication process. The resulting DNA is incomplete and cannot create new virus. Nucleotide analogues work in the same way as nucleosides. All nucleoside analogs have been associated with lactic acidosis as their common side effects. For the details of individual ARV of this class, refer the table below:

Generic Name	Dose	Food related advices	Adverse effects
Zidovudine (ZDV, AZT)	300 mg twice daily	No food related restrictions	Anaemia, neutropenia, bone marrow suppression, gastrointestinal intolerance, headache, insomnia, myopathy, lactic acidosis[1], skin & nail hyperpigmentation.
Lamivudine (3TC)	150 mg twice daily or 300mg once daily	No food related restrictions	Minimal toxicity
Tenofovir (TDF)	300 mg once daily	No food related restrictions	Asthenia, headache, diarrhea, nausea, vomiting, and flatulence Renal insufficiency[2], Fanconi syndrome[3]Dosage adjustment in renal insufficiency recommended Osteomalacia[4] Potential to decrease mineral density of bone Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF.
Abacavir (ABC)	300 mg twice daily or 600mg once daily	No food related restrictions	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;
Emtricitabine(FTC)	200 mg once daily	No food related restrictions	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 and usually affects either the palms of the hands or the soles of the feet. More severe side effects may be hepatotoxicity or lactic acidosis.

2.3.2 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 into DNA. These are called "non-nucleoside" inhibitors because they are not nucleoside analogues and act by physically blocking the reverse transcriptase For the details of individual ARV of this class refer the table below:

Generic Name	Dose	Food related advices	Adverse Effect
Nevirapine(NVP)	200 mg once daily for 14 days followed by 200 mg twice daily	No food related restrictions	Hepatitis (usually within 12 wks), life-threatening hepatic toxicity; Skin rash occasionally progressing to severe conditions including Stevens Johnson syndrome[5] and TEN[5]; Patients who develop hepatic toxicity while on

Generic Name	Dose	Food related advices	Adverse Effect
			treatment with Nevirapine, the drug should not be restarted.
Efavirenz (EFV)	600 mg once daily (bedtime administration is suggested to decrease CNS side effects). It is not recommended to increase dose in TB/HIV coinfection	Avoid taking after high fat meals	CNS symptoms (dizziness, somnolence, insomnia, confusion, hallucinations, agitation), and personality change; Rash occurs but less common than NVP; not recommended in first trimester of pregnancy[6].

2.3.3 Protease Inhibitors (PIs)

Protease inhibitors work at the last stage of the viral reproduction cycle. These drugs prevent HIV from being successfully assembled and released from the infected CD4 cell. PIs can cause increased bleeding in hemophilia, GI intolerance, altered taste, increased liver function and bone disorder. All PIs are associated with metabolic abnormalities, such as hyperglycemia, insulin resistance, increased triglycerides, cholesterol level and abnormal body fat distribution (lipodystrophy).

For the details of individual ARV of this class, refer the table below:

Generic Name	Dose	Food related advices	Adverse Effect
Lopinavir/ritonavir (LPV/r) Heat stable tablets	200mg Lopinavir/50mg Ritonavir Fixed dose tablet 2 tablets twice daily	No food related restrictions	Diarrhea, nausea, vomiting, abnormal lipid profiles, glucose intolerance; PIs should not be prescribed with Simvastatin, as all PI significantly increase the level of Simvastatin in blood leading to the condition called rhabdomyolysis[7] resulting into severe kidney failure.
Saquinavir/ritonavr (SQV/r) Requires refrigeration Less potent PI	1000mg saquinavir + 100 mg ritonavir twice daily	No food related restrictions	Diarrhea, nausea, vomiting, headache, photosensitivity
Atazanavir/ritonavr (ATV/r)	300mg Atazanavir + 100mg ritonavir once daily	Recommended to take with food	Hyperbilirubinemia; Less lipid problems than LPV/r Hyperglycemia, Fat maldistribution, Nephrolithiasis Interacts with acid blocking agents. Dose adjustments are necessary when given with acid-blockers. Do not co-administer with proton pump inhibitors such as Omeprazole.

2.3.4 Some notes on adverse effects from various sources

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 acidosis causes 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 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. *EFV is not recommended in pregnant women during the first trimester of pregnancy or in women with high pregnancy potential (women of childbearing potential who are trying to conceive or who are sexually active with men and are not using effective and consistent contraception). However, it is not recommended to discontinue EFV if a woman on it becomes pregnant.*
7. *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:ANTI–RETROVIRAL THERAPY

This section includes the followings topics:

1. ***Requirements for establishing ART Services***
2. ***Goals of antiretroviral therapy***
3. ***WHO Clinical staging of HIV in adults and adolescents***
4. ***Criteria for initiating ART***
5. ***Choice of ART regimens***
6. ***Preferred first line ART regimens***
7. ***Anti-retroviral regimen and combinations not recommended***
8. ***Management of adverse events of antiretroviral drugs***
9. ***Monitoring of ART***
10. ***ART adherence***
11. ***Criteria for treatment success***
12. ***Failure to antiretroviral therapy***
13. ***Switching ARV in case of treatment failure***

3.1 Requirements for establishing ART Services

3.1.1 Training and Infrastructure

1. Availability of voluntary and confidential counseling and reliable, inexpensive tests to diagnose HIV infection , provisions of ART adherence counseling
2. Adequate health services infrastructure for the management of opportunistic infections and availability of affordable drugs for their treatment and prophylaxis
3. Laboratory facilities to monitor CD4 count, viral load (HIV RNA levels)if available ; liver function test (liver enzymes), urea, creatinine and electrolytes: complete blood count, pregnancy test, acid fast bacilli and chest X ray
4. Appropriate training for clinicians and nurses in the correct use and adherence of ART and managing HIV patients including the capability to perform a basic clinical assessment including documentation of past medical history, identification of current and past HIV related illnesses, identification of coexisting medical conditions and current signs and symptoms
5. Support of a social network including PLHIV support groups, PLHIV networks, NGO etc to help patient's adherence to the regimen
6. If the social network is not present, then provision of psycho-social services (including psycho social counseling, supportive counseling, adherence counseling etc) through government, NGOs or private and philanthropic sector.
7. Strengthening of health and psycho-social services in a continuum of care, from the home, through community health centers, to district/ city hospitals, with flexible and timely referral coordination procedures.
8. Provisions of material and psycho-social support for those taking ART at various levels of the continuum of care
9. Reliable, long-term and regular supply of ARV drugs, reagents and test kits

3.1.2 Baseline Laboratory Tests

The necessary baseline laboratory investigations are listed below, the choice depends on the requirements of patient and clinical judgment of the ART clinician.

1. CD4 cell count
2. Complete Blood Count, Hemoglobin percent
3. ALT/SGPT – If needed other LFT (Liver function test)
4. Serum creatinine – If needed other Kidney function test (Urea, Electrolytes)
5. Chest X ray, Sputum for AFB
6. Hepatitis B and Hepatitis C screening test (for current or past PWID)
7. Urine for pregnancy test (if indicated in female)
8. Urine for Routine & Microscopic examination; Urinalysis to assess proteinuria
9. Blood Sugar level
10. For women, cervical pap smear or other method of cervical cancer screening, if available.

.

3.2 Goals of Antiretroviral Therapy

3.2.1 Major goals of ART are given below

1. Maximal and durable suppression of viral load
2. Restoration and/or preservation of immunologic function
3. Reduction of HIV-related morbidity and mortality
4. Improvement of quality of life of HIV infected persons
5. Prevention of Mother to Child Transmission (PMTCT)
6. Providing Post Exposure Prophylaxis (PEP)

3.3 WHO Clinical staging of HIV in adults and adolescents

Note: Please see annex I for WHO Clinical staging of HIV in children and annex II for diagnostic criteria of the conditions mentioned in staging.

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (under10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular chelitis

Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections
Clinical stage 3
Unexplained severe weight loss (over 10% of presumed or measured body weight) Unexplained chronic diarrhea for longer than one month Unexplained persistent fever (intermittent or constant, for longer than 1 month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (e.g. pneumonia, empyema, meningitis, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory diseases) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (below 8 g/dl), neutropaenia (below 0.5×10^9/l) and/or chronic thrombocytopaenia (below 50×10^9 /l)
Clinical stage 4
HIV wasting syndrome Pneumocystis jiroveci pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extra pulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs excluding liver spleen and lymph nodes) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis including meningitis Disseminated non-tuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extra pulmonary histoplasmosis or coccidiomycosis) Recurrent septicemia (including non-typhoidal *Salmonella*) Lymphoma (cerebral or B-cell non-Hodgkins) Invasive cervical carcinomas Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

Source: Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance, 2006

3.4 Criteria for initiating ART

Recommendations for initiating antiretroviral therapy in adults and adolescents with documented HIV infection are given in the box below:

Target population	Clinical condition	Recommendation
Asymptomatic individuals (including pregnant women)	WHO clinical stage 1	Start ART if CD4 ≤350
Symptomatic individuals (including pregnant women)	WHO clinical stage 2	Start ART if CD4 ≤350
	WHO clinical stage 3 or 4	Start ART irrespective of CD4 cell count
TB and hepatitis B co-infections	Active TB disease	Start ART irrespective of CD4 cell count
	HBV infection requiring treatment*	Start ART irrespective of CD4 cell count

**Note:*

1. *Please refer to the diagnostic criteria used by Dhaka Medical College for diagnosis of hepatitis in Bangladesh (annex 3)*
2. *In co-infection with other diseases, treatment of tuberculosis and some other opportunistic infections priority may be to start OI treatment before antiretroviral therapy. However, recent evidences suggests that ART should be started early in the setting of acute AIDS-related OIs if there are no major contraindications to doing so. Waiting to complete OI treatment before initiating ART appears to be associated with a higher risk of AIDS-related disease progression and/or death without any significant benefit in terms of safety or virological response.*

3.5 Choice of Antiretroviral Therapy

Antiretroviral therapy with single or dual drug regimen is not recommended except for post exposure prophylaxis (PEP) of HIV. 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 the plasma concentration, thereby reducing dose frequency and pill burden. PI based combination is currently recommended as second line option for Bangladesh. These regimens are composed of three or four drugs. The principles of combinations recommended in Bangladesh for first line ART regimen are given in the box below:

Principles of combination	Possible NRTI combination include
1. 2 NRTI + NNRTI or 2. 2NRTI + PI or 3. 3NRTI *	1. Zidovudine + Lamivudine 2. Abacavir + Lamivudine 3. Tenofovir + Lamivudine 4. Tenofovir + Emtricitabine

**Only two such combinations are recommended: ZDV+3TC+ABC, ZDV +3TC+TDF, do not use other triple NRTI options. Triple NRTI combination are recommended for individuals who are unable to tolerate or have contraindications NNRTI-based regimens, particularly in case of HIV/TB co-infection, pregnant women, chronic viral hepatitis and HIV 2 infection*

3.6 Preferred first-line ART regimens for treatment -naive adults and adolescents

Target Population	Preferred Options	Comments
Adults and adolescents	1. AZT + 3TC + EFV or NVP 2. TDF + 3TC + EFV or NVP	• Make the choice of between EFV and NVP depending on the tolerance of the client on ARV • Use fixed-dose combinations
Pregnant women	1. AZT + 3TC+ NVP 2. AZT + 3TC+ EFV	• Do not initiate EFV during first trimester • TDF acceptable alternative of AZT • In women with prior exposure to PMTCT regimens, see below

HIV/TB co infection	1. AZT + 3TC + EFV 2. TDF + 3TC + EFV	• Initiate ART as soon as possible (within the first 8 weeks) after starting TB treatment • NVP is acceptable alternative of EFV. • Triple NRTI can also be in case both EFV and NVP can not be used (see below)
HIV/HBV co infection	1. TDF + 3TC +EFV 2. TDF + 3TC +NVP	• Consider HBsAg screening before starting ART, especially when TDF is not the preferred first- line NRTI • Use of two ARVs with anti- HBV activity required

**Note:*

1. *The regimens are numbered according to preference of the regimen in Bangladesh, number 1 is the preferred regimen and number 2 is an alternative to preferred regimen*
2. *For the dose of each ARV please refer to the previous chapter on ARV drugs*
3. *FTC is currently not in supply in Bangladesh, when available, it can be used as an alternative to 3TC.*

3.7 Anti-retroviral regimen and components 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.

Anti-retroviral regimen and components not recommended	Reason
Monotherapy 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
Efavirenz (EFV) in first trimester of pregnancy and in women with significant childbearing potential	Possible teratogenic effect
Lamivudine (3TC) an Emtricitabine (FTC) combination	Similar resistance profiles and minimal additive antiviral activity

3.8 Management of adverse effects of antiretroviral drugs

ARVs are not without adverse effects and these should be recognized and resolved as early as possible. Given below are key adverse events of major first line ARVs and recommended actions. Please also see the table below for replacement ARV in case of adverse effects 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. After resolution, resume ART with a bPI-based regimen or triple NRTI if no other choice.

Anaemia and neutropaenia (AZT): If severe (Hb <7.0 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.

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

Suggested substitutes for toxicities

ARVs	Common associated toxicity	Suggested substitutes
Abacavir (ABC)	Hypersensitivity reaction	AZT or TDF
Zidovudine (AZT)	Severe anaemia or neutropenia Severe gastrointestinal intolerance	TDF or ABC
	Lactic acidosis	TDF or ABC
Tenofovir (TDF)	Renal toxicity (renal tubular dysfunction)	AZT or ABC or
Efavirenz (EFV)	Severe central nervous system toxicity	NVP or ABC (or any PI)
	Potential neural tube abnormalities if used in first trimester of pregnancy	NVP or ABC (or any PI)
Nevirapine (NVP)	Hepatitis	EFV or ABC (or any PI)
	Hypersensitivity reaction, severe or life-threatening rash Steven Johnson syndrome	ABC (or any PI)

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 at regular intervals for clinical progress, side effects of the ARV and adherence. After initiation of ART, clinical and laboratory evaluations are done during follow up visits that are recommended as follows:

- ***First month:*** every two weeks
- ***Second and third month:*** every one month
- ***Fourth month onwards:*** every three months

More visits are required, if the patient develops symptoms, side effects of the ARVs or experiences difficulties with adherence to ARVs due to any reason. These follow up visits can be used for the resupply of ARVs to the patient.

3.9.1 Laboratory Monitoring

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

If resources permit, use viral load as 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. Following table provides recommended laboratory test in different phases of ART

Laboratory monitoring after initiation of ART

Phase of HIV management	Recommended test	Desirable test
At start of ART	CD4	Hb for AZT[1] Creatinine clearance for TDF[2] ALT for NVP[3]
On ART	CD4 preferably every 6 months	Hb for AZT[1] Creatinine clearance for TDF[2] ALT for NVP[3]
Women exposed to PMTCT interventions with sd-NVP with a tail4 within 12 months and without a tail within 6 months of initiating ART	Viral load 6 months after initiation of ART (depends on its availability)	

**Notes:*

1. *Recommended test in patients with high risk of adverse events associated with AZT (low CD4 or low BMI).*
2. *Recommended test in patients with high risk of adverse events associated with TDF (underlying renal disease, older age group, low BMI, diabetes, hypertension and concomitant use of a boosted PI or nephrotoxic drugs).*
3. *Recommended test in patients with high risk of adverse events associated with NVP (ART-naive HIV+ women with CD4 of >250*
4. *Due to the longer half life of Nevirapine it remains in the blood for a longer duration sufficient for virus to develop resistance, and to minimize the chances of resistance development due to monotherapy, other ARVs(AZT+3TC) are provided for one week after stopping NVP, these two ARVS provided for extra one week are 'tail' in this example.*

Patients who are not yet eligible for ART should have CD4 count measurement every six months. In PLHIV with drug use background, tests 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 is recommended whenever feasible. If viral load testing becomes readily available, ideal testing schedule would be every 6 months after starting ART. Additional pediatric recommendation for viral load monitoring include those babies under 12 months requiring ART containing NVP after exposure to NVP through maternal or infant PMTCT prophylaxis.

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.

Preparatory adherence counselling visits should be made before the start of ART with mock pills and other medications,if possible. After the final preparatory visit, the treating physician and counsellor will jointly consider the patient's readiness to start treatment.

Suggested contents and visits of the pre ART adherence in each visit include the following:

Visit 1

1. Clinical assessment by a clinician
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 plan 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 clinician 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 clinician.
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).
5. Offering the client an opportunity to conduct a test run of the treatment regimen using empty capsules and by asking the client to record missed doses,reason for missing the doses (e.g., forgetting to take pills on out-of-town travel for work).

Visit 3

1. Reviewing the client's understanding of information provided in the previous two sessions. Reinforcing the fact that there is 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 first follow up visit ideally should be in 48–72 hours, and then in two weeks and in one month after the start of ART. After the first 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.

3.10.1 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 as they become accustomed to their treatment, experience side effects, feel better or worse, and face new challenges. Adherence support therefore needs to change over time as well. Ongoing adherence counselling and continuing interactive communication is key to providing effective adherence support to the patient on ART.

A typical follow-up counselling session involves:

- Reviewing the treatment experience of the client
- Assessing any need for referral back to the clinician (usually related to side-effects)
- Monitoring adherence (over a defined period)
- Reviewing and finding solutions to barriers to adherence
- Reviewing adherence to transmission risk reduction; and
- Conducting a psychosocial assessment

3.10.2 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. Then the remaining pills are counted and deducted from the amount supplied in the previous visits. Following formula is used to calculate the adherence.

$$\text{Adherence (\%)} = \frac{\text{Total no. of pills the patient should have taken} - \text{No pills missed}}{\text{Total no of pills patient should have taken}} \times 100$$

Adherence should be above 95%

3.11 Criteria for treatment success

Here are suggested criteria for evaluating the treatment success of the ART regimen, the clinician should use his or her own judgment for the final decision. Virological examination currently may not be available in Bangladesh, in such situation consider clinical and immunological criteria.

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/mm^3 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, adherent patient with drug susceptible virus.

Virological criteria: Suggested viral load in 24-48 weeks after the initiation of ART is less than 5000 copies/ml

3.12 Failure of Antiretroviral Therapy

An individual must be taking ART at least 6 months before it can be determined that the regimen 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.

Criteria for failure are given below

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 (e.g. 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 5000 copies/ml	• The optimal viral loads threshold for defining virological failure has not been determined. Values of >5000 copies /ml are associated with clinical progression and a decline in the CD4 cell count[d].

**Notes:*

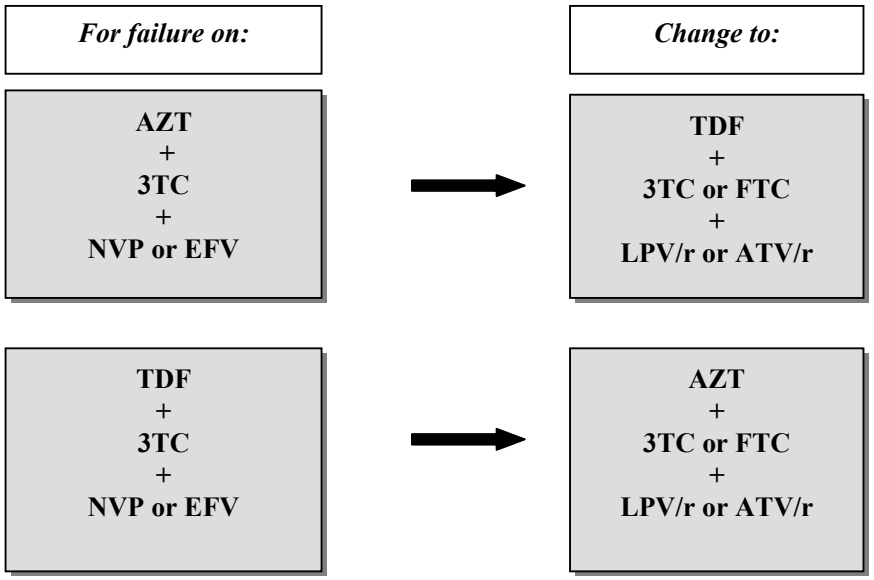
1. *See related section below for details.*

2. *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 extrapulmonary 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.*
3. *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*
4. *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 changed to a failing regimen or added 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 the new regimen should have 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. For example , if you fail on AZT you should go to TDF and vice versa. The PI class is thus reserved for second-line treatments. Ritonavir-boosted protease inhibitors (RTV-PIs) are preferred. Boosted PIs 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 (ie. do not give EFV after NVP or vice versa).

Recommended second-line regimens in adults and adolescents, in Bangladesh:



.

SECTION 4: ANTIRETROVIRAL DRUGS TREATING PREGNANT WOMEN AND PREVENTING HIV INFECTION IN INFANTS

This section contains following topics:

1. Lifelong ART for HIV- Infected women in need of treatment for their own health

2. Maternal and infant ARV prophylaxis to prevent MTCT for HIV-infected pregnant women who do not need treatment for their own health

3. Special situations in pregnancy and related recommendations:

- ***a. Pregnant women who require treatment and have had prior exposure to anti-retroviral drugs for PMTCT***
- ***b. Women receiving ART and planning to become pregnant***
- ***c. Women receiving ART who become pregnant***
- ***d. Women diagnosed with HIV infection in labour***
- ***e. Women diagnosed with HIV infection immediately postpartum***
- ***f. Women with anaemia***
- ***g. Women with active tuberculosis***
- ***h. Women with hepatitis B or hepatitis C virus co-infection***
- ***i. Pregnant women living with HIV who are injecting drug-users***
- **j.** ***Delivery in women living with HIV***

The current recommendations of providing ARV to the pregnant women emphasize the need to have a unified approach to preventing MTCT throughout pregnancy, labour and delivery, postpartum, and the breastfeeding period. This allows more effective and safer postpartum interventions. This also emphasizes that PMTCT is not an intervention that stops at delivery, but includes postpartum and breast feeding follow up and interventions for both mother and infant. To maximize prevention of HIV transmission and maternal and infant survival, it is critical that care of both the mother and the infant is optimized. These recommendations are based on two key approaches:

1. Lifelong ART for HIV-infected women in need of treatment for their own health, which is also safe and effective in reducing MTCT(mother to child transmission).
2. ARV prophylaxis to prevent MTCT during pregnancy, delivery and breastfeeding for HIV-infected women not in need of treatment

4.1 Lifelong ART for HIV- Infected women in need of treatment with their own health

For HIV-infected pregnant women, the initiation of ART for their own health is recommended for all women who have CD4 cell counts of ≤350 cells/mm3, irrespective of WHO clinical staging, and for all women in WHO clinical stage 3 or 4, irrespective of the CD4 cell count. These criteria for initiating ART for pregnant women are the same as for non-pregnant women. The maternal ART continued during pregnancy and breastfeeding is the most effective intervention for maternal health and is also efficacious in reducing the risk of HIV transmission

and infant death in the group of women with the highest risk of MTCT. Therefore, HIV-infected pregnant women in need of treatment for their own health should start ART irrespective of gestational age and should continue with it throughout pregnancy, delivery, during breastfeeding (if breastfeeding) and thereafter. The timing of ART initiation for HIV-infected pregnant women is the same as for non-pregnant women, i.e. as soon as the eligibility criteria are met.

4.1.1 Antiretroviral treatment options recommended for HIV – infected pregnant women who are eligible for treatment

Maternal ART and infant prophylaxis
Mother
Maternal antepartum daily ART, starting as soon as possible irrespective of gestational age, and continued during pregnancy, delivery and thereafter. Recommended regimens include the following, these are numbered according to the preferences: 1. AZT + 3TC + NVP or 2. AZT + 3TC +EFV* or 3. TDF + 3TC (or FTC) + NVP or 4. TDF + 3TC (or FTC) +EFV*
Infant
Daily NVP or twice daily AZT from birth until 4 to 6 weeks of age(irrespective of the mode of infant feeding)

**Note: Avoid use of EFV in the first trimester and use NVP instead*

Doses of NVP and AZT according to birth weight for infants are given below:

Birth weight	Nevirapine	AZT
<2000 g	2 mg/kg body weight one times a day	2 mg/kg body weight two times a day
2000g – 2499 g	10 mg per day	10 mg two times a day
2500 g and above	15 mg per day	15 mg two times day

4.2 Maternal and infant ARV prophylaxis to prevent MTCT for HIV-infected pregnant women who do not need treatment for their own health

All HIV-infected pregnant women who do not need ART for their own health require an effective ARV prophylaxis to prevent HIV transmission during pregnancy, labour and delivery, postpartum *and* during the breastfeeding period. ARV prophylaxis should be started from as early as 14 weeks of gestation (second trimester) or as soon as possible thereafter if women present later in pregnancy, in labour or at delivery.

For all HIV-infected pregnant women who are not in need of ART for their own health, a choice of one of two equally efficacious ARV prophylaxis options is recommended.. There is a strong benefit in providing effective and sustained ARV prophylaxis to women not eligible for ART during pregnancy, labour and delivery, and to either the women or their infants throughout breastfeeding.

WHO recommends two options, but guideline development team in Bangladesh considering the epidemiological situation and trends, capacity of the country as well as advantages and disadvantages of the two options, have decided to select the 'Option B – triple ART'. In this option, Nevirapine is not recommended considering hepatotoxicity in women with CD4 count more than 350/mm3. Option A of maternal AZT and infant ARV prophylaxis is discussed later under special considerations. Recommended option B regimen for ARV prophylaxis is given below:

Mother triple ARV prophylaxis (option B)
Mother
Triple ARV prophylaxis starting from as early as 14 weeks of gestation and continued until delivery, or if breastfeeding, continued until 1 week after all infant exposure to breast milk has ended. Recommended regimens include: 1. AZT +3TC +LPV/r or 2. AZT +3TC +ABC or 3. AZT +3TC +EFV or 4. TDF + 3TC (or FTC) + EFV
Infant
Irrespective of mode of infant feeding Daily NVP or twice daily AZT from birth until 4 to 6 weeks of age

4.3 Special situations in pregnancy and related recommendations:

4.3.1 Pregnant women who require treatment and have had prior exposure to anti-retroviral drugs for PMTCT

Resistance to NNRTI drugs is an important concern for PMTCT regimens. The long half-life of NVP and its low genetic barrier to resistance means that detectable drug levels persist for 2−3 weeks in the presence of active viral replication following a single maternal dose .EFV also has a long half-life, with detectable drug levels for more than 21 days following discontinuation. Additionally, NNRTI resistance can develop in women receiving NNRTI-based triple drug prophylaxis regimens following discontinuation of prophylaxis, particularly if all drugs are stopped simultaneously. In most women, resistant virus can no longer be detected 6 to 12 months after exposure. Recommended ART regimens for women with prior exposure to ART are given below:

Recommendations for women with previous exposure to ART

Characteristics of previous PMTCT ARV exposure	**Recommendation**
sd-NVP (+/-short-course AZT) with no NRTI tail within the last 12 months	• Initiate a 3 NRTI regimen • 2NRTIs + PI (preferred over 3 NRTIs)
sd-NVP(+/-short course AZT) with a NRTI tail	• Initiate an NNRTI regimen

Characteristics of previous PMTCT ARV exposure	Recommendation
in the last 12 months	• If available check viral load at 6 months and if >5000 copies/ml, switch to second-line ART with PI
sd-NVP(+/-short course AZT) with or without an NRTI tail more than 12 months before	• Initiate an NNRTI regimens • If available check viral load at 6 months and if>5000 coupies/ml, switch to second-line ART with PI
All triple ARV regimens, irrespective of duration of exposure and time since exposure	• Initiate NNRTI regimens • If earlier triple ARV regimen was NNRTI-based and was stopped without administration of an NRTI tail, check viral load (if available) at 6 months, if it >5000 copies/ml, switch to second-line ART with PI

4.3.2 Women receiving ART and planning to become pregnant

Preferred ART regimens in such situations should have minimal teratogenic potentials for infants. Women who are planning to become pregnant should use a regimen that does not include EFV, in order to avoid the highest risk period of in utero EFV exposure -conception to day 28 of gestation). If taken during first trimester of pregnancy there have been some reports of neural tube abnormalities. For women receiving an EFV-based regimen and who plan to become pregnant, substitution of NVP in the place of EFV during peri-conception period and during first three months of pregnancy is recommended. Pharmacokinetic data indicate that women should immediately start NVP at 200 mg twice a day (i.e; no need to have an initial 2-week period of NVP 200 mg once a day).

Alternatively, a triple NRTI or PI-based regimen can be given. Some concerns exist about exposure to TDF in utero and the risks of abnormal fetal bone development. However, for women requiring ART and receiving TDF who become pregnant, the benefits of continuing treatment are likely to outweigh the theoretical risks of toxicity for the infant. All PLHIV women should have access to appropriate family planning services with the counseling on choice of methods, child bearing and methods of dual protection.

4.3.3 Women receiving ART who become pregnant

Most women are not enrolled in antenatal care during the early stages of pregnancy, when most organogenesis occurs (i.e. the first trimester). Since the neural tube closes at approximately 28 days of gestation, fetal exposure to EFV during the risk period for neural tube defects will have occurred before the recognition of pregnancy in the vast majority of women. If a woman receiving EFV is recognized as pregnant before 28 days of gestation, EFV should be stopped and substituted with NVP or a PI. If a woman is diagnosed as pregnant after 28 days of gestation, EFV should be continued.

There is no indication for abortion in women exposed to EFV in the first trimester of pregnancy

4.3.4 Women diagnosed with HIV infection in labour

Mother: Triple ARV prophylaxis during labour until 1 week after all exposure to breast milk has ended.

Infant: daily NVP from birth until 6 weeks of age (since the infant is breastfeeding and immediate protection is desirable, NVP would be the preferred infant prophylaxis and given for a full 6 weeks).

A clinical assessment should be done postpartum and a CD4 count obtained. Women who are found to require ART for their own health should not discontinue their triple drug ARV regimen but continue on an appropriate life-long ART regimen.

4.3.5 Women diagnosed with HIV infection immediately postpartum

Mother: triple ARV prophylaxis until 1 week after all exposure to breast milk has ended, or for 4 to 6 weeks if breastfeeding ceases before 6 weeks (always continue for 1 week after all exposure to breast milk has ended).

Infant: daily NVP from birth until 6 weeks of age (since the infant is breastfeeding and immediate protection is desirable, NVP would be the preferred infant prophylaxis and given for a full 6 weeks).

A clinical assessment should be done postpartum and a CD4 count obtained. Women who are found to require ART for their own health should not discontinue their triple drug ARV regimen but continue on an appropriate life-long ART regimen.

4.3.6 Women with anaemia

Pregnant or breastfeeding women eligible for ART who have clinically significant or severe anaemia 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 not eligible for ART who have clinically significant or severe anaemia (Hb <7g/dl), a non- AZT-containing regimen should also be considered, e.g. TDF + 3TC (or FTC) + EFV. Alternatively, AZT-based prophylaxis could be initiated after the severe anaemia has been corrected.

4.3.7 Women with active tuberculosis

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). 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 (starting after the first trimester). For those HIV/TB coinfected women not able to tolerate EFV, an NVP-based regimen or a triple NRTI regimen e.g. AZT + 3TC + ABC or AZT + 3TC + TDF can be used.

4.3.8 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 or ARV prophylaxis 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.

Option A (maternal AZT and extended infant prophylaxis), which does not contain drugs with anti-HBV activity, may therefore be preferred if HBV treatment is not needed and lifelong ART is not planned.

Option A: maternal AZT + infant ARV prophylaxis

- Option A consists of ante partum twice-daily AZT, plus sd-NVP at the onset of labour plus twice daily AZT + 3TC during labour and delivery and continued for 7 days postpartum. It should be started as early as 14 weeks of gestation or as soon as feasible during pregnancy, labour and delivery or thereafter.
- In breastfeeding infants, daily administration of NVP to the infant from birth until 1 week after all exposure to breast milk has ended, or for 4 to 6 weeks if breastfeeding stops before 6 weeks (but at least 1 week after the early cessation of breastfeeding), is recommended.
- In infants receiving only replacement feeding, daily administration of NVP from birth or sd-NVP at birth plus twice-daily AZT from birth until 4 to 6 weeks of age is recommended.

4.3.9 Pregnant women living with HIV who are injecting drug-users

Methadone substitution treatment is currently recommended for opioid-dependent pregnant women. Data are limited on the use of buprenorphine in pregnancy. Opioid substitution therapy should be combined with psychosocial counselling, 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.

4.3.10 Delivery in women living with HIV

WHO recommends vaginal delivery in all conditions except during obstetric emergencies. Prophylaxis (mother and baby) should be started immediately on the first contact. However, to reduce MTCT during normal vaginal delivery, it is important to minimize both the duration of labour and obstetric interventions (including minimizing vaginal examinations, episiotomies, tears, and instrumental delivery)

Operative or manipulative vaginal delivery (including forceps or vacuum extraction, breech extraction and manipulations during vaginal delivery of multiple pregnancies) increase the risk of mixing of fetal and maternal blood. These manipulations should be avoided.

Some international recommendations suggest elective caesarean section for HIV infected women who have failed to achieve adequate viral suppression through ARV prophylaxis or treatment by 38 weeks of gestation. Elective CS must be seen in light of availability, accessibility and quality of institutional pregnancy childbirth and postpartum care.

Viral load testing facilities are limited in Bangladesh at present and so it is difficult to provide hard and fast recommendations on mode of delivery depending on viral load. It is recommended that obstetrician and ART clinician will make the joint decision for the operative delivery considering the duration of the ARV prophylaxis or treatment, clinical and immunological findings, and obstetric conditions requiring manipulation.

SECTION 5: ANTIRETROVIRAL THERAPY IN CHILDREN

This section contains following topics

1. ***Establishing a diagnosis of HIV infection in infants and children***
2. ***When to start antiretroviral therapy in infants and children***
3. ***What to start − recommended first-line ART regimens for infants and children***
4. ***Clinical and laboratory monitoring***
5. ***First-line regimen treatment failure; when to switch regimens***
6. ***Choice of second-line regimens in the event of treatment failure***
7. ***Considerations for infants and children with tuberculosis and HIV***
8. ***Considerations for the nutrition for HIV-infected infants and children***
9. ***Adherence to ART***

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

5.1.1 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

5.1.2 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 viroligical 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.** Every possible effort should be made for fast tracking of positive results from the laboratory to mother-baby pairs

5.1.3 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:

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

A presumptive diagnosis of severe HIV disease should be made if
1.The child is confirmed as being HIV antibody-positive
AND
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

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%

Confirm the diagnosis of HIV infection as soon as possible

**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. *It is unclear how often CD4 is lowered in the above conditions in HIV-uninfected children.*
5. *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.*

5.1.4 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.

5.2 Criteria for starting antiretroviral therapy in infants and children

5.2.1 Infants

Initiate ART for all HIV-infected infants diagnosed in the first year of life, irrespective of CD4 count or WHO clinical stage.

5.2.2 Children

1. Initiate ART for all HIV-infected children between 12 and 24 months of age irrespective of CD4 count or WHO clinical stage.
2. Initiate ART for all HIV-infected children between 24 and 59 months of age with CD4 count of ≤750 cells/mm3 or %CD4+ ≤25, whichever is lower, irrespective of WHO clinical stage.
3. Initiate ART for all HIV-infected children more than 5 years of age with a CD4 count of ≤350 cells/mm3 (as in adults), irrespective of WHO clinical stage.
4. Initiate ART for all HIV-infected children with WHO clinical stages 3 and 4, irrespective of CD4 count.
5. In the absence of virological or serological tests, initiate ART for any child under 18 months of age who has been given any presumptive diagnosis of HIV infection. In this case, treatment should be closely monitored and confirmation of HIV infection should be obtained as soon as possible using age-appropriate testing methods.

5.3 Recommended first-line ART regimens for infants and children

5.3.1 Infants

Groups of infants	Preferred regimen	Alternative regimen
Not exposed to ARVs, or whose exposure to maternal or infant ARVs is unknown; start ART with nevirapine (NVP) + two nucleoside reverse transcriptase inhibitors (NRTIs)	NVP+AZT+ 3TC	NVP+ ABC+3TC

Groups of infants	Preferred regimen	Alternative regimen
Not exposed to ARVs, or whose exposure to maternal or infant ARVs is unknown; start ART with nevirapine (NVP) + two nucleoside reverse transcriptase inhibitors (NRTIs).	LPV/r+AZT+3TC	NVP+AZT+3TC (alternative only when PIs are not available and not feasible)
Exposed to maternal or infant NVP or other NNRTIs used for maternal treatment or PMTCT.	LPV/r+AZT+3TC	NVP+AZT+3TC (alternative only when PIs are not available and not feasible)

Notes:

1. *EFV is not recommended to children below 3 years due to lack of information on appropriate dosing*
2. *FTC can be used as alternative to 3TC to the children above 3 months of age*
3. *TDF is not recommended in young children due to lack of data on pediatric safety*

5.3.2 Children

Groups of children	Preferred regimen	Alternative regimen
Between 12 and 24 months of age exposed to maternal or infant NVP or other NNRTIs used for maternal treatment or PMTCT	LPV/r+AZT+3TC	NVP+AZT+3TC
Between 12 and 24 months of age not exposed to NNRTIs	NVP+AZT+ 3TC	NVP+ ABC+3TC
More than 24 months and less than 3 years of age	NVP+AZT+ 3TC	NVP+ ABC+3TC
3 years of age and older,	1. NVP+AZT+ 3TC 2. EFV+AZT+ 3TC	NVP+ ABC+3TC

5.3.3 Infants and 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	NVP+AZT+ 3TC	AZT+3TC+ABC
Child or adolescent with severe anaemia (<7.5 g/dl) or severe neutropenia (<0.5/mm3), (avoid AZT).	NVP+ABC+3TC	
Adolescents more than 12 years of age with hepatitis	TDF+3TC(FTC)+EFV	

5.3.4 Dosage of first line ARVs for infants and children

Body weight		3-6 kg		6-10 kg		10-14 kg		15-20 kg		20-25 kg	
Drug	Strength	a.m.	p.m	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
AZT syrup	10 mg/ml	6ml	6 ml	9 ml	9 ml	12ml	12ml				
AZT tablet	300 mg							½ tab	½ tab	1 tab	½ tab
3TC syrup	10 mg/ml	3ml	3 ml	4 ml	4 ml	6 ml	6 ml				
3TC tablet	150 mg							½ tab	½ tab	1 tab	½ tab
NVP syrup	10 mg/ml	5ml	5 ml	8 ml	8 ml	10ml	10ml				

Body weight		3-6 kg		6 10 kg		10 14 kg		15 20 kg		20 25 kg	
NVP tablet	200 mg							1 tab	½ tab	1 tab	½ tab
LPV/r syrup	80/20mg/ml	1 ml*	1 ml*	1.5ml	1.5ml	2 ml	2 ml	2.5ml	2.5ml	3 ml	3 ml

**in infants/children 4-6 kg WHO recommends to use already 1.5 ml bid.*

5.4 Clinical and laboratory monitoring

5.4.1 For children who are NOT yet eligible for ART

- Because of the rapid rate of disease progression in infants and young children, more frequent clinical and laboratory monitoring is indicated for them than for adults.
- *Clinical evaluation* of children who are not yet eligible for ART should be performed at every 3 to 6 months, at minimum, and should include the same parameters as are used in the baseline evaluation.
- *CD4 monitoring* should be performed every six months in order to determine whether the child has become eligible for treatment and/or co-trimoxazole prophylaxis. Percent CD4 is preferred for children under 5 years old rather than absolute CD4 count.

5.4.2 For children on ART

- The monitoring will depend on child's response to ART. Nevertheless, at minimum, after starting ART, follow up visit should occur;
    - For infants: at weeks 2, 4, 8 and then every 4 weeks for the first year
    - For children: at weeks 2, 4, 8, 12 and then every 2-3 months once the child has stabilized on therapy.
- *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.
- *CD4 monitoring* is recommended at 6 month after the initiation of ART and every 6 months thereafter.
- Though not essential for Bangladesh, *viral load* should be used whenever possible to confirm suspected treatment failure.
- Other laboratory tests- baseline haemoglobin level (and white cell count, if available) and haemoglobin level at week 8 after initiation of AZT-containing regimens, or more frequently if symptoms indicate
- Growth, development and nutrition should be monitored monthly. It can be done as per the standard practice followed for chidren and infants not infected with HIV.
- Laboratory monitoring for toxicity (if available) should be symptom directed.

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 percent
    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 5 000 RNA copies/ml, after at least 24 weeks on ART, in a treatment-adherent child. As per the current facilities available in Bangladesh, viral load measurement may not be possible and clinicians need to rely on clinical and immunological criteria.

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

After failure on a first-line NNRTI-based regimen, a boosted PI plus 2 NRTIs are recommended for second-line ART. LPV/r is the preferred boosted PI. After failure on a first-line regimen of AZT+3TC; ABC + 3TC is the preferred NRTI backbone option for second-line ART and vice versa.If the child had been started on a PI regime, due to previous NNRTI exposure, then NNRTI plus 2NRTIs would be the preferred second –line regimen. Please refer to the table below preferred second line regimens.

5.7 Recommended II line regimens in the event of first line regimen treatment failure

Situation	First line regimen	Preferred Second line regimen
Infants and children less than 24 months		
Not Exposed to ARV	NVP+2NRTIs: 1. NVP+AZT+ 3TC 2. NVP+ ABC+3TC	LPV/r +2NRTIs: 1. LPV/r+ ABC+3TC 2. LPV/r + AZT+3TC
Exposed to NNRTI	LPV/r +2NRTIs: LPV/r+AZT+3TC (preferred)	NNRTI+2NRTIs: NVP+AZT+ 3TC
Unknown ARV exposure	NVP+2NRTIs: 1. NVP+AZT+ 3TC 2. NVP+ ABC+3TC	LPV/r +2NRTIs: 1. LPV/r+ ABC+3TC 2. LPV/r + AZT+3TC
Children		
24 months or more	1. NVP+AZT+ 3TC (preferred) 2. EFV+AZT+ 3TC (preferred, over 3 yrs) 3. NVP+ ABC+3TC	1. LPV/r+ ABC+3TC 2. LPV/r + AZT+3TC
Concomitant conditions of Children and adolescents		
With Severe anemia	NVP+ABC+3TC	LPV/r +3TC+ NRTI*
With TB	1. EFV+AZT+ 3TC (preferred for > 3 years of age) 2. NVP+AZT+ 3TC (for < 3 years of age) 3. AZT+3TC+ABC	1. LPV/r+ ABC+3TC 2. LPV/r + AZT+3TC
With Hepatitis B	TDF+3TC+EFV	LPV/r + AZT+3TC

** Decide consulting with pediatrician and considering the availability*

5.8 Nutrition considerations for HIV-infected infants and children

5.8.1 Breast feeding and HIV

Considering the overall risk of malnutrition and diarrhoea 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 or prophylaxis 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. Mothers are advised to continue ARV till one week after stopping of breast feeding, if they are on prophylaxis.

5.8.2 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).

5.8.3 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, except

BCG-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)

5.9 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 PWIDs- interaction with methadone***
5. ***ART for PLHIV with severe anemia***
6. ***Post exposure prophylaxis of HIV***
7. ***Immune Reconstitution Inflammation Syndrome***
8. ***Cotrimoxazole prophylaxis***
9. ***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 almost 100 percent. Recommendations for the management HIV in Tuberculosis coinfected individuals are as below:

a. Screen all people living with HIV for active tuberculosis. Screening should be done as per National TB HIV Guidelines.

b. Start ART in all HIV-infected individuals with active TB, irrespective of the CD4 cell count.

c. 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.

d. Use efavirenz (EFV) as the preferred NNRTI in patients starting ART while on TB treatment. 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. For those HIV/TB coinfected 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. The ART regimens recommended in Bangladesh to treat HIV in people infected with TB are as follow:

   Preferred regimen- AZT+3TC+ EFV

   Alternative regimens:

   i. AZT+3TC+NVP
   ii. AZT + 3TC + ABC or
   iii. AZT + 3TC + TDF

e. 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. 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. The most common adverse events associated with rifabutin are neutropenia, leucopenia, elevations of hepatic enzymes, rash and upper gastrointestinal complaints, and, more rarely uveitis.

f. An exception of the beneficial outcome of early initiation is TB meningitis. In case of TB meningitis, sequenced therapy (ART-initiation after completion of TB treatment) is recommended.

6.2 ART and Hepatitis B

a. 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.

b. Start TDF and 3TC (or FTC)-containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.

c. Use at least two agents with activity against HBV (TDF plus 3TC or FTC).

d. Use following criteria given in annex(no.) for the diagnosis of chronic active hepatitis in Bangladesh:

6.3 ART and Hepatitis C

a. Hepatitis C (HCV) co-infection is significantly associated with increased risk of death and advanced liver disease in HIV-positive individuals. HIV infection accelerates HCV-related disease progression and mortality.

b. Considering the significant level of uncertainty on these topics and the importance of hepatitis C management in the context of HIV co-infection, WHO is planning to revise the recommendations for the prevention and treatment of major HIV-related opportunistic infections and co-morbidities, including hepatitis C.

c. Meanwhile, the initiation of ART in HIV/HCV coinfected people should follow the same principles and recommendations as for its initiation in HIV mono-infected individuals.

6.4 ART for PWIDs 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 below:

Antiretroviral Drugs	Interactions and recommendations
ABC	No dosage adjustment necessary.
ZDV	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.
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.
ATV/r, LPV/r, SQV/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.
3TC, TDF	No significant effect ,no dosage adjustment necessary.
FTC	No data

6.5 Post Exposure Prophylaxis (PEP) of HIV

Post Exposure Prophylaxis is for providing prophylaxis of HIV to the health care workers who get exposures to the risk of HIV while providing medical care to PLHIV. Commonest form of occupational exposure among the health workers is needle stick injury. The risk of HIV transmission following skin puncture from a needle or other sharp object 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 infection transmission to a health worker by exposure of mucous membrane (of eyes, nose or mouth) or abraded (broken) skin to HIV-infected material; the risk is about 0.09%. HIV is not transmitted by exposure-infected materials to healthy intact skin.

PEP, if indicated, should be started as soon as possible, preferably within 2 hours of the exposure. PEP is not recommended after 72 hours of exposure.

Recommendations in case of occupational exposure

a. Provide first aid by washing the exposed area thoroughly with running water and mild soap. It is not recommended to squeeze the wound with intention to express the blood out and it is also recommended not too apply any antiseptic to the injury area; squeezing the wound or application of any antiseptic increases the chances of HIV transmission by enhancing the local inflammation.

b. Testing for HIV source person and the exposed person is essential to make the decision of starting PEP. The source should always be HIV positive or the person at high risk of recent infection (likely to be in the window period). The exposed person should always be HIV negative. Considering the anxiety of the health worker exposed, the counseling for testing should be short, It should include the risk of occupational exposure, side effects of ARV and adherence, and follow up during PEP..

c. Depending on the exposure received, risk of HIV transmission is evaluated. All occupational exposures considering the risk of transmission of HIV are divided into three categories - no risk, low risk and high risk exposure. Use of Only two ARVs is recommended for low risk exposure, and three for the high-risk exposure. ART clinician should do the risk assessment and decide the level of risk of HIV transmission related to the exposure. Following table provides the criteria for level of risk and recommended prophylaxis.

Recommended HIV regimen according to the risk of HIV transmission

Risk of HIV transmission	Type of exposure	Recommended prophylaxis regimen
No Risk	• Exposure to intact skin • Exposure with urine, saliva, feces, tears, sweat with no blood contamination	Not recommended
Low risk	• Blood on mucous membrane - eye, nose, mouth • Splash of blood on abraded skin • Solid needle superficial injury	AZT 300 mg and 3TC 150 mg, two times a day for 28 days
High Risk	• Exposure to large quantity of blood (device with visible blood on it) • Exposure to body fluids- pleural, pericardial, and ascetic fluid, semen and vaginal secretions, amniotic fluid, CSF, synovial fluids and body secretion contaminated with blood • Exposure to a needle that had been placed in a vein or artery • Deep injury • Hollow bore needle stick injury • Source-terminally ill with AIDS	AZT 300 mg and 3TC 150 mg, two times a day Plus LPV/r (200mg/50 mg) two tablets two times a day for 28 days

**Note: Alternatives of ZDV is TDF and and substitute for LPV/r are ATV/r, SQR/r or APV/r.*

d. Follow up
- Follow up HIV Antibody testing (rapid or ELISA is recommended to perform at 6 weeks, at 3 months and at 6 months after the exposure. Negative result of HIV antibody testing at 6 months after the exposure confirms that no transmission occurred.
- Baseline Hemoglobin test is recommended when AZT is prescribed
- Tests for other blood-borne diseases (eg. hepatitis B and C) are also recommended.

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

f. 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 Immune reconstitution inflammatory syndrome (IRIS)

Immune reconstitution inflammatory syndrome (IRIS) 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. IRIS happens as the immune system recovers following initiation of ARV. The suppression of CD4 T cells by HIV causes a decrease in the body's normal response to certain infections. 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-exisiting symptoms. Though most cases of IRIS resolve after a few weeks, when IRIS does occur, it happens more often in people with TB and other mycobacterial infections.

In general, people with more severely damaged immune systems before starting HIV therapy are most at risk for IRIS. Possible risk factors 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 nonsteroidal 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.

This subsection includes:

1. *Cotrimoxazole prophylaxis in adults and adolescents*
2. *Cotrimoxazole prophylaxis among infants and children*
3. *Cotrimoxazole prophylaxis among pregnant women*

6.7 Cotrimoxazole Prophylaxis

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. Cotrimoxazole is in list of essential medicines of Bangladesh. Providing co-trimoxazole has been part of the standard of care for preventing Pneumocystis jiroveci pneumonia (PCP) (formerly Pneumocystis carinii pneumonia) and toxoplasmosis since the early 1990s.

6.7.1 Cotrimoxazole prophylaxis in adults and adolescents

Cotrimoxazole prophylaxis in adults and adolescents is recommended to:

- HIV infected adults with CD4 count <350 cells/mm3
- All adults who have had an episode of PCP
- All adults with symptomatic HIV disease or Clinical stage 2, 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

- Lifelong, if not on ART
- If on ART the CD4 is >350 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 350 or if new or recurrent WHO clinical stage 2, 3 or 4 conditions occur

a. 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.

b. Cotrimoxazole intolerance

Consider Dapsone 100 mg once daily as the first choice the in case of cotrinoxazole intolerance. 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. After desensitization under surveillance, up to 70 percent of clients may again tolerate TMP/SMX.

c. Cotrimoxazole desensitization chart for adults and adolescents

Day	Dose of Cotrimoxazole		Equivalent preparations
	Sulfamethoxazole	Trimethoprim	
I	80 mg	16 mg	2 ml of oral suspension
II	160 mg	32 mg	4 ml of oral suspension
III	240 mg	48 mg	6 ml of oral suspension
IV	320 mg	64 mg	8 ml of oral suspension
V	400 mg	80 mg	One single-strength sulfamethoxazole-trimethoprim tablet
VI and after	800 mg	160 mg	Twosingle-strength sulfamethoxazole-trimethoprim tablets or one double strength tablet

Note: Each 5 ml cotrimoxazole oral suspension in contains 40 mg trimethoprim and 200 mg sulfamethoxazole

d. 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.

6.7.2 Cotrimoxazole prophylaxis for 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 6 weeks after birth and continuing until HIV infection has been excluded and the infant is no longer at risk of acquiring HIV through breastfeeding.

a. Recommendations for starting Cotrimoxazole in infants and children:

Group of 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)	Less than 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% (or absolute 1000/mm3)
	> 5 years of age	Those with symptomatic HIV disease and / or CD4 count < 350/mm3

Duration

Primary cotrimoxazole prophylaxis can be stopped in older children on ART at least after 12 months of good adherence, no stage 2, 3 or 4 conditions and high CD4 on two measurements done in six months apart (>25% between 1-5 years, > 350 for children above 5 years of age).

Dose of cotrimoxazole prophylaxis in children

Age of the children	Recommended Dose	Doses of the commonly available preparations			
		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 SMX/ 160mg TMP			Two tablets	One Tablet

b. Initiation of cotrimoxazole in relation to ART in children

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

c. Cotrimoxazole intolerance in children

- In case of adverse reactions desensitization using small doses of cotrimoxazole in children is not recommended.
- 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.

d. Side effects of cotrimoxazole, grading of toxicity and the recommendations

Clinical descriptions	Toxicity	Recommendations
Erythema	Grade 1	Continue CPT Monitor closely Consider antihistamines
Maculopapular rash Dry desquamation	Grade 2	
Vesiculation Ulceration	Grade 3	Stop CPT Try desensitization after return to the normal condition, not recommended for children
Exfoliative dermatitis Stevens-Johnson-Syndrome Erythema multiforma Moist desquamation	Grade 4	Stop CPT permanently and Document the reason

e. Monitoring of Cotrimoxazole 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.

6.7.3 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.
- Folic acid is provided in a higher dose to pregnant PLHIV taking cotrimoxazole. Recommended dose of folic acid in this situation is 5 mg daily.

6.8 Management of HIV- 2

HIV- 2 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 HIV-2 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:

a. 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
b. Protease inhibitors should be active against HIV-2.
c. 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.
d. 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.
e. The recommendations on viral load monitoring and the use of NNRTIs would not apply to patients with HIV-2 infection.

Bibliography

1. Anti Retroviral Therapy for HIV Infections in Adults and Adolescents, Recommendations for Public Health Approach, 2010 Revision, World Health Organization, 2010
2. Antiretroviral Drugs for Treating Pregnant Women and Preventing, HIV Infections in Infants, Recommendations for a Public Health Approach, 2010 Version, World Health Organization, 2010
3. Antiretroviral Therapy for HIV Infections In Infants And Children : Towards Universal Access, Recommendations For a Public Health Approach, 2010 Revision, World Health Organization, 2010
4. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, US Department o Health and Human Services, January 10, 2011
5. National Guideline on TB/HIV Program Collaboration National Tuberculosis Control Program, Mycobacterial Disease Control, Directorate General of Health Services, Ministry of Health and Family Welfare, Dhaka, Bangladesh, 2007
6. Antiretroviral Therapy Guidelines for HIV Infected Adults and Adolescents Including Post-Exposure Prophylaxis, NACO, Ministry of Health and Family Welfare, Government of India, 2007
7. National ART Guidelines, National Center for AIDS and STD Control, Nepal, 2009 (unpublished)
8. Guidelines on Co-Trimoxazole Prophylaxis for HIV-Related Infections among Children Adolescents and Adults, Recommendations for Public Health Approach, World Health Organization, 2006
9. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, National Institute of Health, USA, August 2010
10. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States, National Institute of Health, USA, May 2010
11. Northern Ireland Guidelines For Antenatal, Intrapartum And Postpartum Care Of HIV Positive Women and Management of the HIV-Exposed Infant, North Ireland, July 2010
12. Recommended Routine Immunizations for Children - Summary of WHO Position Papers, WHO, October 2010

Annex 1 WHO Clinical Staging of HIV for Infants and Children with Established HIV Infection

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Unexplained persistent hepatosplenomegaly Papular pruritic eruptions Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Unexplained persistent parotid enlargement Lineal gingival erythema Herpes zoster Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Fungal nail infections
Clinical stage 3
Unexplained moderate malnutrition not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5 oC, intermittent or constant, for longer than one month) Persistent oral Candidiasis (after first 6 weeks of life) Oral hairy leukoplakia Acute necrotizing ulcerative gingivitis/periodontitis Lymph node TB Pulmonary TB Severe recurrent bacterial pneumonia Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease including bronchiectasis Unexplained anaemia (<8.0 g/dl), neutropenia (<0.5x109/L3) or chronic thrombocytopenia (<50 x 109/L3)
Clinical stage 4
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy Pneumocystis pneumonia Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration, or visceral at any site) Extrapulmonary TB Kaposi sarcoma Oesophageal candidiasis (or candiadisis of trachea, bronchi or lungs) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age more than 1 month Extrapulmonary cryptococcosis including meningitis

Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)
Chronic cryptosporidiosis (with diarrhoea)
Chronic isosporiasis
Disseminated non-tuberculous mycobacterial infection
Cerebral or B cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
HIV-associated cardiomyopathy or nephropathy
Penicillinosis

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		
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 loss (more than 10% of body weight)	Reported unexplained weight loss (over 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.	Documented loss of more than 10% of body weight

Clinical events	Clinical diagnosis	Definitive diagnosis
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 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.	Isolation of M. tuberculosis on sputum 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

Clinical events	Clinical diagnosis	Definitive 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 other relevant guidelines.
Clinical stage 4		
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 last 6 months)	Current episode plus one or more episodes in last 6 months. Acute onset (under 2 weeks) of symptoms (e.g. fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or CXR. Response to antibiotics.	Positive culture or antigen test of a compatible organism
Chronic herpes simplex 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	M. tuberculosis isolation or compatible histology from appropriate site, together with

Clinical events	Clinical diagnosis	Definitive diagnosis
	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.	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 colour, skin lesions that usually develop into violaceous plaques or nodules	Macroscopic appearance at endoscopy or bronchoscopy, or by 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 mycobacteria infection	No presumptive clinical diagnosis	Diagnosed by finding 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

Clinical events	Clinical diagnosis	Definitive diagnosis
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
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 characterized 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.

References:

1. New Chronic Hepatitis B Virus 2007 Case Definition (www.cdc.gov/epo/dphsi/print/hepatitisbcurrent.htm).
2. Division of Viral Hepatitis. Guidelines for Viral Hepatitis Surveillance and Case Management. Centers for Disease Control and Prevention. January 2005.
3. British *Liver Trust (www.britishlivertrust.org.uk).*

Annex 4 Recommended Routine Immunizations for all Children - Summary of WHO Position Papers *(updated October 21, 2010)*

Antigen		Age of 1st Dose	Doses in Primary Series	Interval Between Doses 1st to 2nd	Interval Between Doses 2nd to 3rd	Interval Between Doses 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*