OCTOBER, 2019

National Anti Retroviral Therapy (NRT) Guidelines, Bangladesh

National AIDS /STD Programme

Directorate General of Health Services,
Ministry of Health and Family Welfare

World Health Organization
Bangladesh

NATIONAL ART GUIDELINES, BANGLADESH

Updated on October, 2019

National AIDS /STD Programme
Directorate General of Health Services
Old DGHS Building (4th Floor), Mohakhali, Dhaka-1212

TABLE OF CONTENTS

ABBREVIATIONS/ACRONYMS

3TC	Lamivudine
AB	Antibody
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ANC	Antenatal Clinic
ART	Antiretroviral Therapy
ARV	Antiretroviral
ASP	AIDS and STD Programme, Bangladesh
AST	Aspartate Aminotransferase
ATV	Atazanavir
AZT	Zidovudine (Also Known As ZDV)
BID	Twice Daily
BMI	Body Mass Index
bPI	Boosted Protease Inhibitor
CD4	Cluster of Differentiation 4
CMV	Cytomegalovirus
CNS	Central Nervous System
CXR	Chest X-Ray
DBS	Dried Blood Spot
DNA	Deoxyribonucleic Acid
DRV	Darunavir
EFV	Efavirenz
EIA	Enzyme Immunoassay
EPTB	Extrapulmonary Tuberculosis
ETV	Etravirine
FBC	Full Blood Count
FDC	Fixed-Dose Combination
FPV	Fos-Amprenavir
FSW	Female Sex Worker
FTC	Emtricitabine
GI	Gastrointestinal
Hb	Haemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HIVDR	HIV Drug Resistance
HIVRNA	Human Immunodeficiency Virus Ribonucleic Acid
HSV	Herpes Simplex Virus
HTC	HIV Testing and Counselling
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)
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

LIST OF CONTRIBUTORS:

1. Dr. Mohammad Aminul Islam Mian, Director, National AIDS/ STD Control, DGHS
2. Dr. Md. Belal Hossain, Deputy Director and Programme Manager, AIDS/ STD Programme, DGHS
3. Dr. Fuad Abdul Hamid, DPM (TCS), AIDS/ STD Programme, DGHS
4. Dr. Salimuzzaman, PSO, IEDCR
5. Prof. Dr. Shakil Ahmed, Shahid Shuhrawardi Medical College Hospital, Dhaka
6. Dr. Shahidul Islam, Save the Children
7. Dr. Nilufar Begum, Ashar Alo Society
8. Dr. Mahmudul Hasan, NIDCH
9. Dr. Saidur Rahman, ART Focal Point and Associate Prof. Dept of Skin-VD, Shahid Ziuar Rahman medical College, Bogura
10. Dr. Rahat Nazma, Infectious Disease Hospital, Mohakhali
11. Dr. Rizwanul Ahsan, Assistant Prof. pediatrics, RP, Dhaka Shishu Hospital
12. Dr. Ferdousur Rahman, Associate Prof. Internal Medicine, BSMMU
13. Dr. Md. Sahikh Abdullah, RP, General, Dhaka Medical College Hospital
14. Dr. Saima Khan, Country Manager, UNAIDS
15. Dr. Sabera Sultana, NPO, WHO
16. Dr. Shahnaz Begum, UNICEF Bangladesh
17. Dr. Mohammed Moshtaq Pervez, Consultant

Overall Guidance:

Prof. Dr. Md. Shamiul Islam, Director (MBDC) and Line Director, TB-Leprosy and AIDS/ STD Programme, DGHS

FOREWARD

Since the formulation of the first ART guidelines in the country in 2006, a number of new developments have occurred in the field of HIV. In 2013 WHO Consolidated Guidelines on the Use of ART for preventing and treating HIV infection followed a public health approach. The focus in these guidelines was to ensure universal access to ART, use of fixed drug combinations, strategic and rational use of medicines and optimizing existing health care systems in order to ensure long term sustainability of HIV treatment activities. The national ART guidelines for the country were revised in line with the 2013 WHO guidelines in October 2014 & May 2016. Based on evidence from some new studies, WHO revised these guidelines on when to start and released these updated guidelines on 2017 & policy brief on 2018. The present revision of 2016 National guideline is based on evidence in this 2017/2018 WHO guidelines & July 2019 policy brief.

Reaching the global strategy "Fast Track" 90-90-90 Bangladesh has been taken so many initiatives among its one of the major interventions is to scale up of the ART services across the country where the there is a significant number of PLHIV. As per differentiated ART delivery strategy ASP expanding the ART and refill center in the country considering geographical presence of the PLHIV. The aim of this scale up is to enroll all patient in ART services through reducing the distance of the patient. These initiatives will also help to reach second and third 90 of the fast track strategy. Trained physicians are providing the ART services for the affected people. Ensuring quality of the treatment for the providers this guideline will play important role to maintain the standard, this guideline will be used by hospitals based physician, NGOs physicians and private sector health service providers. Other hand, this standard guideline will also help to the hospital manager, programme manager of the national programme, NGOs manager and management of the private sector health service providers for monitoring the treatment procedure as part of the quality assurance. I congratulate all the stakeholders who contributed for updating this guideline also expressing my good wishes to the users of this guideline in advance. I hope, we will able to reach our target "Ending AIDS by 2030".

Professor Dr. Abul Kalam Azad
Director General
Directorate General of Health Services

World Health Organization
Bangladesh

MESSAGE FROM WHO REPRESENTATIVE

The Government of Bangladesh is collaborating closely with national partners and technical experts to accelerate efforts in order to maintain its status of low prevalence of HIV in general population as well as to sustain the achievements of HIV prevention and control in the country. Recently, the National AIDS/STD Control (NASC) updated the strategic plan to accelerate the national response to HIV and AIDS to achieve the global commitment of 'Ending AIDS by 2030' and treatment targets of '90-90-90' by 2020.

To reinforce the national efforts on HIV response, WHO is providing technical assistance to NASC for developing and updating manuals, guideline and capacity building of health care providers. As part of the collaborative effort, WHO provides technical assistance for updating this antiretroviral treatment (ART) guideline in accordance with recent scientific evidence and the latest WHO guidelines.

According to WHO's recommendation, access to testing, link with appropriate treatment will enable people living with HIV to lead healthy, productive lives as well as prevent HIV transmission to other people. It also works as an effective prevention, reducing the risk of onward transmission by 96%.

I believe that these guidelines along with other national implementation guidelines, will be instrumental in accelerating and scaling up ART uptake throughout the country. It is my sincere wish that health care providers all health care facilities across the board will use these guidelines to offer quality services to the people of Bangladesh.

Moreover, it will be a resource guide for policy makers and managers at different levels to plan the required commodities and human resources to deploy the appropriate treatment plan for HIV. This action will contribute strengthening health system and reaching a broader agenda of Universal Health Coverage.

I take this opportunity to appreciate the efforts of the AIDS/STD program, DGHS, MOH&FW and all the internal and external stakeholders who actively contributed to the development of this new edition of the National ART Guidelines as a part of the ongoing effort to rapidly scale up antiretroviral therapy.

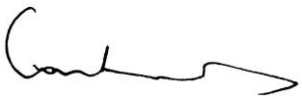
WHO will continue to support Bangladesh to reach the unreached and underserved, and ensure all people living with HIV know their status, can access treatment and achieve viral suppression. Together we must act reaching the Sustainable Development Goal target of ending AIDS as a public health threat by 2030.

Dr. Bardan Jung Rana
WHO Representative, Bangladesh

ACKNOWLEDGEMENT

Treatment is the key component of the HIV Programme in Bangladesh, it's also help to prevent new cases. Recently, AIDS/ STD Programme expanded the care, treatment as well as testing services covering all the divisional based medical college and district hospitals. Initially all 23 priority districts hospital introduced testing service among its 11 center developed with treatment facility, gradually it will be expanded in the country to reach all the PLHIV under treatment programme. The last ART guideline was developed in 2016 by adopting WHO and other regional treatment protocol considering country context. Different approaches require in order to enhance access to available of treatment support to reach the global target 90-90-90. ASP given emphasis the quality of the treatment service in the public, NGOs and private health sector with adopting recent changes made by WHO and other competent agencies. Considering all those importance, ASP was taken the initiative to update the exiting ART guideline. The global decision "Test and Treat" adopted in this guideline after analysis of the country capacity as well as context.

A technical working committee was formed to update this guideline consisting the members of different technical expertise including. Several consultations were organized to review the existing document as well as relevant updates. Finally, WHO and UNAIDS reviewed the updated guideline and made few comments which were addressed in this version, I am sincerely expressing thanks to all the working group members who contributed for updating the ART guideline. I am also expressing my gratefulness to the World Health Organization (WHO), Bangladesh for supporting the updating process.



Professor Dr. Md. Shamiul Islam
Director (MBDC) and Line Director, TB – Leprosy and ASP
Directorate General of Health Services

Section 1: Introduction

This section includes the followings

1. Background
2. Objectives of the national ART guideline
3. Rationale for revision the guidelines
4. Targeted audience for these guidelines

1.1 BACKGROUND

Since the identification of initial cases of HIV/AIDS in June 1981 in Los Angeles, USA, there have been tremendous advances in the field of HIV prevention, diagnosis, care and treatment globally. This global progress is not only limited to identification of newer molecules that are more robust and less toxic but includes a significant reduction in the cost of therapy, and innovative approaches to service delivery that increase access to treatment, literally transforming the disease from a virtual death sentence, a few years ago, to a chronic manageable disease now.

Globally, 37.9 million [32.7 million–44.0 million] people were living with HIV at the end of 2018[1]. An estimated 0.8% [0.6-0.9%] of adults aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. Approximately 1.8 million new infections occurred in 2016 worldwide and approximately 1.0 million people died of AIDS-related illnesses. Currently, there are 19.5 million patients on ART globally. Albeit a great achievement, the challenge remains to put the rest on ART to reduce mortality and co-morbidities, and to prevent further transmission of HIV.

In Bangladesh the first HIV case was detected in 1989. HIV prevalence remains less than 0.01% among general population. Estimated people living with HIV are 11,700. So far, a total of 5,586 persons have been diagnosed with HIV[2]. HIV has been detected in 61 out of 64 districts[3]. Most of who were concentrated in Dhaka (37.5%), Chittagong (23.5%), Khulna (17.0%) and Sylhet divisions (14.0%)[4]. In 2017, total numbers of new cases were 856. Reported cases for Rohingya crises from 25th August 2017 till 31st December 2019 is 425. In 2019, treatment was given among 6,132 people living with HIV and in the last year total no of ARV receiver was 4,078[5].

To respond to this challenge, the Government of Bangladesh established The National AIDS Committee (NAC) in 1985, four years before the first case of HIV was detected in the country. Bangladesh was the first country in the region to adopt a comprehensive national policy on HIV/AIDS and STIs (in 1997), and then also developed the first National Strategic Plan for HIV/AIDS, 1997-2002. Current 4th NSP 2018-2022 is developed in alignment with the 4th Health, Nutrition and Population Sector Program, 2017-2022 as well as other national, regional and global commitments, namely the 2016 Political Declaration to End AIDS by 2030.

In 2005, ART programme was started by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) with its own funding for a small number of patients. Under the Global Fund Round 6 project, Ministry of Health and Family Welfare (MOHFW)/National AIDS/STD Programme (NASP) as Principal Recipient (PR) and Save the children as Management Agency (MA) initiated ART programme for PLHIV. Before 2008, 100% of ART was managed by INGOs and their implementing partners in the country. Central Medical Stores Depot of MOHFW has started ARV

[1] Global HIV & AIDS statistics — 2019 fact sheet, UNAIDS; https://www.unaids.org/en/resources/fact-sheet

[2] ASP and UNAIDS 2017

[3] National AIDS/STD programme (NASP). Investment case: prioritizing investment options in HIV response in Bangladesh to end AIDS by 2030, with financial and technical assistance from UNAIDS, 2015

[4] Funding request application form, Global Fund, https://www.icddrb.org/dmdocuments/Funding%20Request%20_Application%20form_BCCM.PDF and NASP 2016, World AIDS Day slide# 13 and 12

[5] National AIDS/STD Program. Bangladesh country situation and national response of HIV/AIDS. Workshop proceedings of coordination & monitoring of HIV/AIDS programme in priority district. Director General Health Sector. Dhaka: March 20, 2018.

procurement in 2012. Before that, Save the Children has provided ART to 911 PLHIV in past 4 years with grants from the Global Fund. Beginning of 2013, 88.28% of PLHIV were provided ARV through Public-Private Partnerships (PPP). To provide direction to the national ART programme, MOHFW developed ART guidelines (2006, updated in 2016), Management of Opportunistic Infection (2009) and developed Standard Operating Procedures (SOP) for Services to PLHIV in 2009. Simultaneously NASP installed CD+4 counters and additional laboratory equipment in eight tertiary government health institutes for HIV management.

The success is encouraging, and gains are to be consolidated. Yet it is not the time to be complacent. Among various priorities, reaching the unreached, early diagnosis, need to improve linkages and retention across the continuum of HIV care, maintaining a high level of adherence, and ensuring treatment as prevention is well understood are a few key priorities. The country is committed to achieving the SDG of ending AIDS as a public health threat by 2030 and is signatory to the UN strategy of 90-90-90 by 2020 which aims at ending AIDS epidemic by achieving that-

- 90% of the estimated PLHIV know their status, of which
- 90% PLHIV are on ART, of which
- 90% PLHIV have viral suppression

To achieve this aim, standardized and uniform national ART guidelines remain the mainstay to standardize treatment practices and thereby improve the quality of HIV care across all sectors of health care in our country context, especially when many other guidelines with a wide spectrum of recommendations already exist.

These guidelines will continue to evolve and will be revised and updated on regular basis as per national and global evidence and recommendations.

1.2 OBJECTIVES OF THE NATIONAL ART GUIDELINES

1. To provide evidence-based recommendations following a public health approach (in view of WHO Policy brief of 2019 & When to start guideline 2017) for the delivery of ART and monitoring patients on ART in general population and specific population groups like (pregnant women, children, HIV- TB co-infected patients, PWID, migrants etc.)
2. To provide guidance on the use of potent less toxic more efficacious first line and second line ART regimen.
3. To provide recommendations applicable to the majority of populations regarding the optimal timing of ART initiation, preferred first-line and second-line ARV regimens, improved criteria for ART substitution, switching and managing HIV in special situations in HIV (Pregnancy, pediatric population, Tuberculosis, hepatitis B and C , occupational exposure etc.)

1.3 RATIONALE FOR REVISION OF THE GUIDELINES

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

Since the formulation of the first ART guidelines in the country in 2006, a number of new developments have occurred in the field of HIV. The 2013 WHO Consolidated Guidelines on the Use of ART for preventing and treating HIV infection followed a public health approach. The focus in

these guidelines was to ensure universal access to ART, use of fixed drug combinations, strategic and rational use of medicines and optimizing existing health care systems in order to ensure long term sustainability of HIV treatment activities. WHO has clearly stated in these guidelines that "Implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology, availability of resources, the organization and capacity of the health system and anticipated cost-effectiveness. The national ART guidelines for the country were revised in line with the 2013 WHO guidelines in October 2014 & May 2016. Based on evidence from some new studies (African Temprano & START), WHO revised these guidelines on when to start and released these updated guidelines on 2017 & policy brief on 2018/2019. The present revision of 2016 National guideline is based on evidence in this 2017/2018 WHO guidelines & July 2019 policy brief.

1.4 TARGET AUDIENCE

National AIDS program managers, partners involved in HIV care and treatment services, and organizations providing technical and financial support to HIV care and treatment programs in Bangladesh- are the targeted audiences for these guidelines. This document will also be of immense help to clinicians who are taking care of the HIV patients, both in public, private or NGO sector. The document will also guide the national HIV program managers and other senior policy-makers who are involved at the policy planning level for necessary logistic, infrastructure, HR & funding related issues.

Special Note:

These National ART guidelines are subject to be revised in the event of any significant change in management of patient. The National ART Committee has decided to use the TDF+3TC+DTG as preferred regimen, as currently DTG based combination is not available in the country. Till then TDF+3TC+EFV based combination will be used as 1st line ART.

For details on HIV testing, please see the national testing and counseling guidelines.

Since beginning prevention, treatment, care and support services provided through NGOs/SHGs in Bangladesh for people living with HIV. Almost all countries including Bangladesh, the delivery of HIV care in the initial phase of scale-up was based on hospital / clinic-based model and largely undifferentiated for individual needs. But now the cohort of patients who are on treatment for several years is growing up and timely access of ART felt to expand for those who have yet to start.

Therefore, differentiated care services across the cascade conceptualized to adapt service provision for various groups of people living with HIV reflecting their preferences and expectations. Clients will be the center of service delivery with an aim to enhance the quality of the clientele experience and ensure health system to remain medically accountable and efficient in sustaining treatment as prevention.

Table 1: Summary of the major recommendations on ART

Issue	Situation Criteria /definitions
Initiation of ART	
When to start ART in adults including pregnant and breast-feeding women, Adolescents, and Infants and children	Any HIV positive individuals irrespective of CD4 count or clinical stage as soon as found positive.

Monitoring ART	
Clinical monitoring Laboratory monitoring	On every visit, weight, clinical stage, adherence monitoring Baseline tests: CD4 count, S. creatinine for TDF, Hb for AZT, ALT for NVP, Pregnancy test (adult & adolescent female) & Screening of STIs e.g; RPR/TPHA. During ART: S. creatinine for TDF, Hb for AZT, ALT for NVP preferably every 6 months, routine Viral Load to be preferred approach- 6 months after initiation and every 12 months thereafter, CD4 count every 6 months in case viral load is not available
Detecting treatment failure	
Failure of ART	Clinical failure: emergence of new or recurrent WHO stage 4 condition or certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections) Immunological failure: fall of CD4 count to baseline (or below) OR 50% fall from on-treatment peak value OR persistent CD4 levels below 100cells/mm3, without concomitant infection to cause transient CD4 cell decrease. Virological failure: Plasma viral load consistently above 1000 copies/ml
Switching ART	A single drug should not be changed or added to a failing regimen. **1.1.1 The new regimen should have minimum of three active drugs, one of them drawn from at least one new class**

Section 2: Antiretroviral Drugs

This section includes the followings

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

2.1 ANTIRETROVIRAL DRUGS

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

To understand the mechanism of action of ARV, one needs to understand the basic steps of the viral replication, in other words life cycle of HIV virus. Virus enters into the CD4 (host) cell involving glycoproteins of the virus and receptors of host cells. ARVs interfering with Entry are called Entry inhibitors. One class of Entry inhibitors is the fusion inhibitor class which includes T 20 (Enfuviritide). CCR5 entry inhibitors (Maraviroc) and CXCR4 antagonist block entry through a different mechanism. After the fusion with the host cell membrane, viral particles including the viral RNA and the enzymes (reverse transcriptase, integrase and protease) enter into the cytoplasm of the host cell. The first process inside the host cell is the reverse transcription in which viral DNA is synthesized from viral RNA. The process involves the reverse transcriptase enzyme. The ARVs interfering with this process are called nucleoside and nucleotide reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). Nucleoside analogue reverse transcriptase inhibitors inhibit the production of proviral DNA by competing with normal nucleotide. Thus, in place of normal nucleotide, defective nucleotide analogue is placed in the DNA fragment thus producing a defective DNA which cannot serve the purpose of proviral DNA in the subsequent stages of HIV replication. In this way the replication of HIV is blocked. Non-nucleosides analogue inhibitor acts by destroying the active site of reverse transcriptase. Individual ARVs in these groups include Zidovudine (AZT), Lamivudine (3TC), Tenofovir (TDF) – examples of NRTI, Nevirapine (NVP), Efavirenz (EFV)- examples of NNRTI.

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 Dolutegravir. After integration, the DNA of the infected cell converts into the viral DNA and starts to produce copies of viral RNA. To produce viral particles, the RNA copies thus produced need to be cut into particles of exact size with the help of protease. Protease inhibitors (PI) interrupt this process. The examples of protease inhibitors (PI) are Lopinavir, Saqunavir, Ritonavir, Indinavir, Nelfinavir, Atazanavir etc. The boosted PIs (combination of two types of PI) increase the effectiveness, stability of ARV and minimize the side effects.

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

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

Although not all antiretroviral drugs mentioned in the guidelines are currently available in Bangladesh, some of these may become available in the future hence the list of the drugs needs to be expanded so that clinicians and program managers can utilize these drugs fully.

2.2 CLASSES OF ANTIRETROVIRAL DRUGS

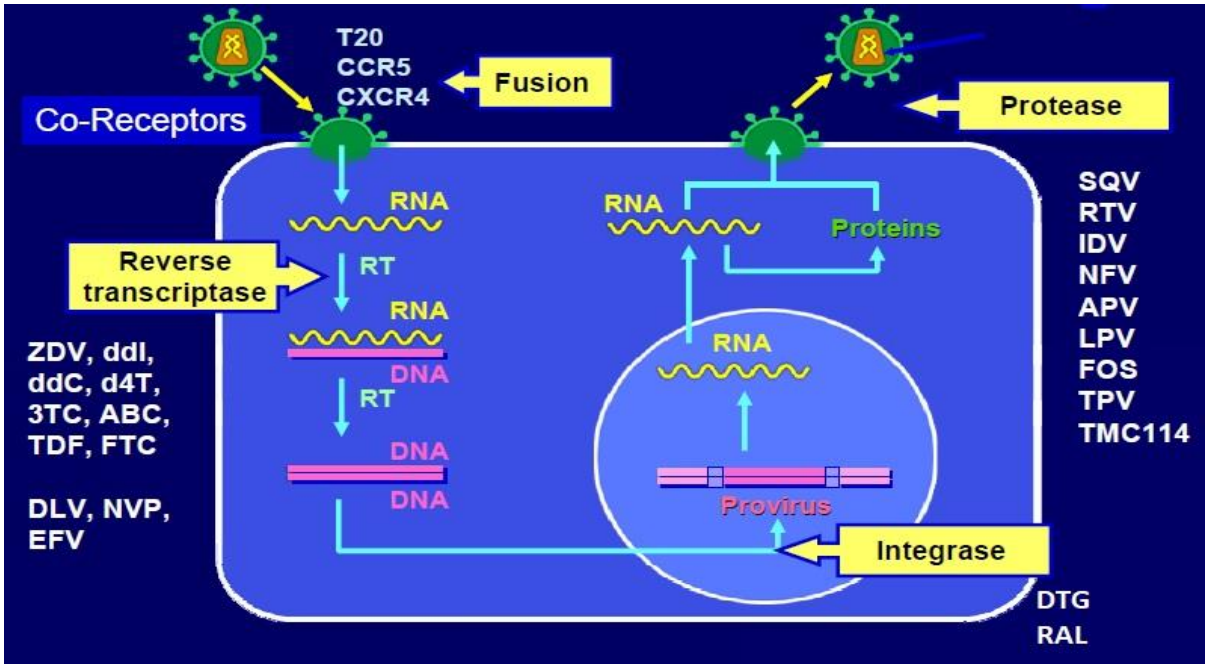
Depending on the mechanism of action the ARVs are categorized into following classes:

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

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

2.3 TARGETS OF ANTI-RETROVIRAL DRUGS

(see explanation above)



Currently available antiretroviral drugs are shown in Table 2 below:

Table 2.1: Classes of ARV Drugs Available			
Nucleoside reverse Transcriptase inhibitors (NRTI)	**Non-nucleoside reverse transcriptase inhibitors (NNRTI)**	**Protease inhibitors (PI)**	**Fusion inhibitors (FI)**
Zidovudine (AZT/ZDV)	Nevirapine (NVP)	Saquinavir (SQV)*	Enfuviritide (T-20)
*Stavudine (d4T)	Efavirenz(EFV)	Ritonavir (RTV)	**Integrase Inhibitors**
Lamivudine (3TC)	Etravirine	Nelfinavir (NFV)*	Raltegravir (RAL) Dolutegravir (DTG)
Abacavir (ABC)		Lopinavir/Ritonavir	CCR5 Entry

		(LPV)	Inhibitors
Emtricitabine (FTC)		Darunavir Darunavir	Maraviroc
		Atazanavir (ATV)	
(NtRTI)			
Tenofavir (TDF)			

* These drugs are no longer used in clinical practices

2.4 CLINICAL PHARMACOLOGY OF COMMONLY USED ARV DRUGS

2.4.1 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

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

Table 2.2: Commonly used NRTIs

Drug name	Dose (in adults)	Dietary restrictions	Comments
Zidovudine (AZT or ZDV) Available in 300mg tablets and as FDC with 3TC and 3TC/ NVP	300mg/ dose BD	No food restrictions	Monitor for anaemia in the first 3 months of treatment
Lamivudine (3TC) Available in 150mg tablet and as FDC with AZT and AZT/NVP, and with TDF and TDF/ EFV	150mg/ dose BD OR 300mg/dose OD	No food restrictions	A well-tolerated drug. Adjust dose in renal impairment.
Abacavir (ABC) Available in 300mg tablets and in combination with 3TC and DTG	300mg/ dose BD or 600mg OD	No food restrictions. Alcohol increases ABC levels by 41%	Educate patient on hypersensitivity reaction. Once hypersensitivity has occurred, the patient should never be re-challenged with ABC. Avoid alcohol while on ABC.
Emtricitabine Available in 200mg and as FDC with TDF and TDF/EFV	200mg/ dose OD	No food restrictions.	Effective against hepatitis B. Ideally patients should be screened for hepatitis B virus (HBV) before starting therapy; exacerbation of Hepatitis B reported in patients on discontinuation of FTC. Decrease dosage in patients with renal impairment. Monitor renal function if combined with TDF. When

			combined with TDF, should not be given to patients with a creatinine clearance of <30ml/min. Should not be used with or after failure of 3TC.
Tenofovir disoproxil fumarate (TDF) Available in 300mg tablet and as FDC with 3TC and FTC/EFV	300mg/dose OD	No food restrictions.	Renal function should be monitored while on TDF. Ideally patients should be screened for hepatitis B virus (HBV) before starting therapy; exacerbation of Hepatitis B reported in patients on discontinuation of TDF. When combined with 3TC, should not be given to patients with a creatinine clearance of <30ml/min. When use with ATV, levels of ATV reduced significantly, therefore combine with RTV.
Tenofovir alafenamide (TAF) Available as co-formulation of FTC or rilpivirine +FTC/TAF	As TAF 25mg+FTC 200mg OD	No food restrictions	DRV decreases TAF levels. Boosted PI increase TAF levels but the PI levels are not affected. Avoid co-administration with rifabutin, rifampicin, phenytoin.

2.4.2 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 to DNA. These drugs are called "non-nucleoside" inhibitors because even though they work at the same stage as nucleoside analogues, they are not nucleoside analogues. The details of individual ARV of this class are in table below:

Table 2.3: Commonly used NNRTIs

Drug name	Dose (in adults)	Dietary restrictions	Comments
Nevirapine (NVP) available in 200mg tablet and as FDC with AZT/3TC	200mg/dose OD for first 14 days and then 200 mg/dose BD	No food restrictions.	Use with caution in women with baseline CD4 >250 and in men with baseline CD4 >350. Check LFT in the 1st 3 months. Should not be used with rifampicin in TB patients. Avoid NVP in patients requiring prolong treatment with fluconazole because of increased NVP levels with possibility of increased toxicity. Use alternative antifungal drugs for treatment of oral candidiasis in patients

			on NVP.
Efavirenz (EFV) available in 200mg, 400mg & 600mg tablet and as FDC with TDF/FTC	400mg/600mg OD Best taken at bedtime	Preferably taken on empty stomach. Can be given with food but avoid high fat meals	Can be used with Rifampicin in TB patients **400mg is preferable as per WHO recommendations

2.4.3 Protease Inhibitors (PIs)

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

Table 2.4: Commonly Used PIs

Drug name	Dose (in adults)	Dietary restrictions	Comments
Lopinavir/ritonavir (LPV/r) Available as 200mg + 50mg RTV	[LPV 400 mg + RTV 100 mg] 2 tablets BD	Take with food. Moderate fat increases bioavailability.	Tablets should be swallowed whole
Atazanavir (ATV) Available in 100mg, 150mg, 200 mg capsules Available as FDC with RTV	ATV 300mg / RTV 100mg OD	Take with food. Take 2 hours before or 1 hour after antacids and buffered medications such as buffered ddI (reduced ATV concentrations if administered together)	Indirect hyperbilirubinemia. When used with TDF should always be given with RTV. Experienced patients should also be given ATV/RTV.
Ritonavir (RTV) Available as 100mg capsules Capsules should be refrigerated until dispensed; stable at room (up to 25ºC) for 30 days	Recommends for use as a booster of other PIs	Administration with food increases absorption and helps reduce gastrointestinal side effects.	Potent CYP450 inhibitor, thus its use as a booster of other PIs

Darunavir (DRV)	DRV 600 mg/ RTV 100 mg BID OR DRV 800 mg/RTV 100 mg OD (only if PI naïve)	Take with a meal to limit ADR	Metabolized by CYP3A and is an inhibitor of CYP3A. Contains sulphur moiety. Monitor liver functions especially in patients at risk or with pre-existing liver disease. May cause hormonal contraceptive failure.

2.4.4 Integrase Strand Transfer Inhibitors - INSTIs

HIV integrase is one of three enzymes (reverse transcriptase, protease, and integrase) that are encoded by the virus and are essential for HIV replication. After entry into CD4+ T cells, viral RNA is reverse transcribed into DNA by HIV reverse transcriptase. The integrase enzyme catalyzes the process by which viral DNA is integrated into the genome of the host cell. This process is essential for maintenance of the viral genome and viral gene expression. The details of individual ARV of this class are in table below:

Table 2.5: Commonly used INSTIs

Drug name	Dose (in adults)	Dietary restrictions	Comments
Dolutegravir (DTG) Available FDCs as ABC/3TC/DTG (600/300/50mg) and TDF/3TC/DTG (300/300/50mg)	50 mg once daily If co- administering with EFV, carbamazepine, or rifampicin, use DTG 50 mg BD If suspected or confirmed INSTI resistance (e.g; Raltegravir) use DTG 50 mg BD	No food restrictions	Interacts with carbamazepine, phenobarbital and phenytoin, use alternative anticonvulsants. Administer DTG at least 2 hours before or 6 hours after taking supplements or antacids containing Mg, Al, Fe, Ca and Zn. For Ca or Fe, if DTG is taken with a meal then dose separation is not required
Raltegravir (RAL)	ADULT and CHILD over 16 years, 400 mg BD	No food restrictions	Contraindicated in breast- feeding mothers Safety in paediatric patients has not been established

Section 3: Antiretroviral Therapy in Infants, Children, Adolescents and Adults

This section includes the followings

1. Goals of antiretroviral therapy
2. Provision of ART for infant, children, adolescents and adults
3. Timing of ART initiation
4. Choice of antiretroviral drugs/regimen
5. What to expect in first six months of ART
6. Monitoring of ART
7. Management of adverse effects of antiretroviral drugs
8. Criteria for treatment success
9. Failure of antiretroviral therapy
10. ART adherence
11. Prophylaxis for opportunistic infections

3.1 Goals of Antiretroviral Therapy

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

The goals of therapy are:

Table 6: Goals of ARV therapy
• Clinical goals: Prolongation of life and improvement in quality of life
• Virological goals: Greatest possible sustained reduction in viral load
• Immunological goals: Immune reconstitution that is both quantitative and qualitative
• Therapeutic goals: Rational sequencing of drugs in a manner that achieves clinical, virological and immunological goals while maintaining future treatment options, limiting drug toxicity and facilitating adherence
• Prevention goals: Reduction of HIV transmission due to suppression of viral load

3.2 Provision of ART for Infant, Children, Adolescents and Adults

Eligibility:

All individuals with confirmed HIV infection are eligible for ART irrespective of CD4 cell levels, WHO clinical stage, age, pregnancy or breastfeeding status, co-infection status, risk group, or any other criteria.

3.3 Timing of ART Initiation

ART should be started in all patients as soon as patient is ready, preferably within 7 days of confirmation of HIV status. ART initiation on the same day as testing HIV-positive has additional benefits for HIV prevention (e.g. for pregnant and breastfeeding women, and the HIV positive partner in a discordant relationship), and is associated with improved retention, viral suppression, and survival. Special considerations for timing of ART initiation are listed in Table 3.1.

Table 3.1: Special Considerations for Timing of ART Initiation

Population	Timing of ART Initiation
Pregnant and breastfeeding women	Support ART initiation on the same day as testing positive for HIV
Patients with strong motivation to start ART immediately	Support ART initiation as soon as they meet ART Readiness Assessment criteria, even if on the same day as testing positive for HIV
Infants (< 12 months old)	Support ART initiation on the same day as testing positive for HIV
Patients with newly diagnosed TB	Start anti-TB treatment immediately and initiate ART as soon as anti-TB medications are tolerated, within 2 weeks to 2 months, (2 weeks for those with low CD4 count). For TB meningitis consider

	delaying ART for up to 8 weeks
Patients with cryptococcal meningitis	Defer ART until after completing 5 weeks of CM treatment and symptoms have resolved
Patients for whom adherence will be particularly challenging	Start ART while adequate support systems are being put in place for adherence (e.g. enrolling a PWID into a methadone program; psychiatric treatment for a patient with mental illness; caregiver identified for an orphan)
All other patients	Start ART within 7 days of HIV diagnosis, once they are ready for ART

Pre- and Post-ART Care for PLHIV:

All persons registered for care and treatment at HTC should have their full history taken, undergo clinical examination (**see table below**), including determining the clinical stage of HIV (see annex for details) and baseline investigations (see annex for details). The CD4 count and viral load are recommended to guide treatment and follow-up the patients on ART. However, the lack of CD4 result or viral load should not delay the initiation of ART.

Ensuring good adherence to the treatment is imperative for the success of the ART as well as for the prevention of drug resistance. To achieve this, counselling by the clinical team must start from the first visit itself **(for details, see annexes 2 and 7).**

Table 3.2: Assessment and management for initiation of ART

Visit 1	For initiation of ART/Pre- ART assessment
	• Medical history (including allergy or drug hypersensitivity) • Immunization status • Clinical Features checklist (see annexure for details) • Screen for TB & initiate IPT (TBPT)- "in those who do not have active TB". • Physical examination (including height and weight) • Pregnancy status • Chest X-ray if chest symptoms present • Behavioral/ psychosocial assessment: • Social support, family/household structure and support • Disclosure status, readiness to disclose • Understanding of HIV/AIDS, transmission, risk reduction, treatment options • Nutritional assessment • Investigation: baseline Blood profile, CD4 count, other test as necessary
Visit 2	Within 3 to 5 days after visit 1

	• History (new problems including Pregnancy status) • Clinical features check-list • Physical examination (including weight) • Co-trimoxazole prophylaxis • Psychosocial support Adherence counselling on at least 2 occasions & assessment clients/caregivers' preparedness to initiate ART. **Initiate ART if counselor feels that patient is adequately prepared.**
Follow up visits	Monthly post ART assessment
	• History (new problems including Pregnancy status) • Clinical Features check-list • Screen for TB • Clinical examination (including weight) • Adherence assessment / support • Looking for side effects, if any

Table 3.3: Treat OIs first before starting ART

Clinical Picture	**Action**
Any undiagnosed active infection with fever	Diagnose and treat first; start ART when patient is stable
TB	Treat TB first; start ART as recommended in TB section
PCP	Treat PCP first, start ART when patient is stable
Invasive fungal diseases: esophageal candidiasis, cryptococcal meningitis, penicilliosis, histoplasmosis	Treat esophageal candidiasis first; start ART as soon as the patient can swallow comfortably Treat cryptococcal meningitis, penicilliosis, histoplasmosis first; start ART when patient is stabilized or OI treatment is completed
Bacterial pneumonia	Treat pneumonia first; start ART when patient is stable
Acute diarrhoea which may reduce absorption of ART	Diagnose and treat first; Start ART when diarrhea is stabilized or controlled
Cytomegalovirus infection	Treat if drugs available for CMV; if not, start ART
Toxoplasmosis	Treat; start ART after 6 weeks of treatment and when patient is stabilized
Non-severe anaemia (Hb < 8 g/litre)	Start ART if no other causes for anemia is found (HIV is often the cause of anaemia); avoid AZT Correction for anemia may be required, if Hb <7g/litre
Malaria	Treat malaria first; start ART when treatment is completed

ART should not be initiated in the presence of an active OI. In general, OIs should be treated or stabilized before commencing ART.

3.4 Choice of Antiretroviral Drugs /Regimen

The BASIC PRINCIPLE is to use a triple drug combination from two different classes of ARVs. Single or dual drug regimens are not recommended under any circumstances.

The recommended ARV combinations are:

Principles of combination:

1. 2 NRTI + 1 II (Integrase Inhibitor)
2. 2 NRTI + 1 NNRTI
   or
3. 2 NRTI + 1 boosted PI
   or
   3 NRTI *

For example, recommended NRTI backbone includes:

Tenofovir + Emtricitabine (or Lamivudine)
Zidovudine + Lamivudine
Abacavir + Lamivudine

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

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

**ART needs to be started promptly in coinfected patients with a CD4 count < 50*

Only two such combinations are recommended: ZDV+3TC+ABC; ZDV +3TC+TDF), use of other triple NRTI options is not recommended.) The recommended regimens are in Table below:

Table 3.4: Preferred and alternative first-line regimens in infants, children, adolescents and adults (including Pregnant and Breastfeeding Women)- see annex for age, weight based doses, drug-drug interactions etc.

Populations	Preferred first line regimen	Alternative first line regimen	Special situation
Adult men and adolescents	TDF + 3TC (or FTC) + DTG[b]	TDF + 3TC (or FTC) + EFV*	AZT + 3TC + EFV* - TDF (or TAF) + 3TC (or FTC) + PI/r
Children (3 to 10 years)	ABC + 3TC + DTG[c]	ABC + 3TC + LPV/r	AZT + 3TC + LPV/r (or RAL)
	TAF[g] (or TDF) + 3TC + RAL[d]	ABC + 3TC + EFV	ABC or AZT + 3TC + EFV[e]
Children (< 3 years to < 28 days)	ABC + 3TC + LPV/r	AZT + 3TC + LPV/r	AZT+3TC+ ----- ABC
Neonates (0 to 28 days)	AZT + 3TC + RAL	AZT + 3TC + NVP	AZT + 3TC + LPV/r[f]

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; PI/r: protease inhibitor boosted with ritonavir; RAL: raltegravir; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

**EFV 400mg is preferable but if not available, 600mg can be used.*

b. Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy

c For age and weight groups with approved DTG dosing.

d RAL can be used as an alternative regimen if LPV/r solid formulations are not available.

e EFV should not be used for children younger than three years of age.

f If starting after 2 weeks of age.

g TAF may be considered for people with established osteoporosis and/or impaired kidney function.

All patients must have their weight documented at every visit. Children and adolescents must have correct weight-based dosing of ARVs confirmed at every visit. (For details see annex)

Infants and children depend on their caregivers for adherence to medication. Caregivers should be adequately prepared for their role of administering ARVs to infants and children, including addressing anticipated challenges such as drug palatability.

Caregivers should always be shown and then asked to demonstrate how to measure and administer ARVs. This should be done at the time of prescribing the ART (by the clinician) and at the time of dispensing the ART.

Special notes on DTG:

DTG is preferred in first line ART in combination with two other ARVs for adolescents and adults. DTG is well tolerated, has a high genetic barrier to resistance and fewer drug-drug interactions.

Recommended Dosing of DTG

- ≥ 15 years (**or** ≥ 35 kg body weight): DTG 50 mg once daily, preferably as a morning dose (Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy)
- **For patients taking rifampicin: increase dose to DTG 50 mg twice daily until 2 weeks after completion of TB treatment, then reduce to DTG 50 mg once daily again (the additional 2 weeks of higher-dose DTG is to counter the ongoing liver enzyme induction effect of rifampicin, which continues for a short period after TB treatment is completed)**
- For patients with suspected or confirmed INSTI resistance (e.g. patients with prior history of failing a RAL-based regimen): use DTG 50 mg twice daily
- DTG can be taken with or without food

Contraindications for use of DTG
• DTG is contraindicated for any patient with a history of hypersensitivity reaction to DTG • DTG is not currently recommended for patients with end-stage renal disease or end-stage liver disease because it has not been evaluated in these populations

Table : Considerations for changing or transitions of 1st line ARV drugs

Current ARV that is being changed	Preferred ARV to switch to	Alternative, if contraindication or intolerance to preferred ARV
EFV	DTG* (if currently on rifampicin-containing TB treatment then continue EFV until TB treatment is completed before switching to DTG)	Continue on EFV
NVP	DTG*	Switch to ATV/r
LPV/r	DTG*	Switch to ATV/r
ATV/r	DTG*	Continue on ATV/r
DTG	EFV	Switch to ATV/r
AZT	TDF	If pre-existing renal disease (with eGFR < 50 ml/min): switch to ABC instead of TDF[1]

[1] TDF + 3TC should be used despite renal impairment (with renal dose adjustments) for patients who have HIV/HBV co-infection

• If DTG is not available, alternative should be used

3.5 What to expect in first six months of ART

The first six months of ART are critical. Although clinical and immunological improvement is expected, it is not always apparent, and the drugs may have side-effects. Some patients may not respond as expected or may even deteriorate clinically at first. Complications are the most common in the first few weeks after the initiation of ART especially among patients with very low CD4 counts. It takes time for HIV viral replication to be controlled by ART and for the immune system to be strengthened. It also takes time for the reversal of the catabolism associated with HIV infection, particularly in patients with HIV-associated wasting. As the immune function of the patient recovers, there may be exacerbation of previously sub-clinical co- existing infection (e.g. TB), resulting in an apparent worsening of the disease. This is NOT due to failure of the therapy, but to the success of ART and the resulting immune reconstitution **(For details see annex)**. It is important to allow for sufficient time on therapy before judging the effectiveness of ART and considering the possibility of IRIS in patients with worsening disease in the first few months of ART.

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

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

3.6 Monitoring of ART

ART monitoring includes clinical monitoring and laboratory monitoring. The objectives of monitoring during ART are to identify and treat inter- current illnesses, assess for and manage adverse drug reactions, and evaluate response to treatment. Routine laboratory monitoring recommendations are described in Table 3.4; however, additional investigations should be ordered whenever there is clinical suspicion for which a laboratory test result may alter patient management.

Clinical monitoring:

Clinical monitoring includes monitoring of the ART adherence also. Patients starting ART should be educated on the potential side effects of ART and all other prescribed medication. ADRs can have a significant impact on patient adherence and must be identified early and managed aggressively. The client should be monitored on regular interval for clinical progress, for the side effects of the ARV and the adherence counseling. The follow up intervals for ART are recommended as below:

First month: follow up visit in every two weeks

Second month onward: follow up visit every month

Once stabilized and CD4 starts improving (after 6 months on ART) and patient does not have any OI or adverse events, the visit frequency can be once in 2 or 3 months depending on drug stocks, distance patient has to travel to reach ART/CST Centre, etc.

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

Laboratory Monitoring:

Table 3.5: Recommended laboratory test at different timelines in ART monitoring

Tests	Baseline Day 0	At 15 days	At 1 month	At 2 months	At 3 months	At 6 months
CBC/Hb	Y	Y (if on AZT)	Y (if on AZT)	Y (if on AZT)	Y	Y
Creatinine	Y				Y	Y (if on TDF)
LFT/ALT	Y	Y (if on NVP)	Y (if on NVP)		Y	Y
Urea	Y					Y
CD4 count/%*	Y					Y
Urine R/M/E Esp for albumin and sugar	Y					Y (if on TDF)
Fasting Lipid profile	Y					Y
Random Blood sugar	Y					Y

Gene Xpert	Y (If TB Suspect)					
CXR	Y					
Viral load If facility available	Y					Y
Pregnancy test (for female)	Y					
Pap smear (for females)	Y					Y

** Once routine viral load monitoring is available there is no need for routine CD4, although it remains important at baseline, for those failing treatment and those returning to care after disengagement from care.*

3.7 Management of Adverse Effects Of Antiretroviral Drugs

ARVs are not without adverse effects, adverse effects should be recognized as early as possible and resolved. Adverse events of major first line ARVs and recommendations to follow are given below.

Table 3.6: Common toxicities of ARV drugs and management

ARV drug	Major types of toxicity	Risk factors	Suggested management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 gene	Do not use ABC in presence of the HLA-B*5701 gene. Substitute with AZT or TDF.
ATV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome	Use with caution in people with pre-existing conduction disease or who are taking concomitant drugs that may prolong the PR or QRS intervals.
	Indirect hyperbilirubinaemia (clinical jaundice)	Presence of UDP-glucuronosyltransferase 1-1 enzyme (UGT1A1*28 gene)	This phenomenon is clinically benign but potentially stigmatizing. Substitute only if adherence is compromised.
	Nephrolithiasis	History of nephrolithiasis	Substitute with LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first- line ART, consider substituting with integrase inhibitors.
AZT	Anaemia, neutropaenia	Baseline anaemia or neutropaenia CD4 cell count of □200 cells/mm3	Substitute with TDF or ABC. Consider using low-dose zidovudine.

	Lactic acidosis or severe hepatomegaly with steatosis lipoatrophy, lipodystrophy myopathy	BMI >25 (or body weight >75 kg) Prolonged exposure to NRTIs	Substitute with TDF or ABC.
DTG	Hepatotoxicity Hypersensitivity reactions	Coinfection with hepatitis B or C Liver disease	Substitute with another therapeutic class: EFV or boosted PIs.
	Insomnia	Older than 60 years Female	Consider morning dose or substitute with EFV, boosted PI or RAL.
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	Substitute with another therapeutic class: EFV or boosted PIs
ARV drug	**Major types of toxicity**	**Risk factors**	**Suggested management**
EFV	Persistent central nervous system toxicity (such as dizziness, insomnia and abnormal dreams) or mental symptoms (anxiety, depression and mental confusion)	Depression or other mental disorder (previous or at baseline) Daytime dosing	For central nervous system symptoms, dosing at bedtime. Consider using EFV at a lower dose (400 mg/day or an integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms.
	Convulsions	History of seizure	
	Hepatotoxicity	Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs	For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
	Severe skin and hypersensitivity reactions	Risk factors unknown	
	Gynaecomastia	Risk factors unknown	Substitute with another therapeutic class (integrase inhibitors or boosted PIs).
LPV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome Hypokalaemia	Use with caution for people with pre-existing conduction disease or taking concomitant drugs that may prolong the PR or QRS intervals.
	Hepatotoxicity	Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs	If LPV/r is used in first-line ART for children, substitute with RAL or DTG if younger or older than 6 years respectively. If integrase inhibitors are not available EFV, NVP or boosted ATV can be used. If LPV/r is used in second-line ART for adults and the

			person has treatment failure with NNRTIs in first-line ART, consider integrase inhibitors.
	Pancreatitis	Advanced HIV disease, alcohol	Substitute with another therapeutic class (integrase inhibitors).
	Dyslipidaemia	Cardiovascular risk factors such as obesity and diabetes	Substitute with another therapeutic class (integrase inhibitors).
	Diarrhoea	Risk factors unknown	Substitute with atazanavir/r, darunavir/r or integrase inhibitors.

ARV drug	Major types of toxicity	Risk factors	Suggested management
NVP	Hepatotoxicity Severe skin rash and hypersensitivity reaction, including Stevens-Johnson syndrome	Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs High baseline CD4 cell count (CD4 count >250 cells/mm3 for women or >400 cells/mm3 for men)	If hepatotoxicity is mild, consider substituting with EFV, including for children three years and older. For severe hepatotoxicity and hypersensitivity, and for children younger than three years, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
RAL	Rhabdomyolysis, myopathy and myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis, including statins	Stop ART. When symptoms are resolved, substitute with another therapeutic class boosted PIs).
	Hepatitis and hepatic failure Severe skin rash and hypersensitivity reaction	Risk factor(s) unknown	
TDF	Chronic kidney disease Acute kidney injury and Fanconi syndrome	Underlying renal disease Older than 50 years old BMI <18.5 or low body weight (<50 kg), notably in females Untreated diabetes Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	Substitute with AZT or ABC Do not initiate TDF at an estimated glomerular filtration rate of <50 mL/min, uncontrolled hypertension, untreated diabetes or kidney failure
	Decreases in bone mineral density	History of osteomalacia (adults) and rickets (children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss	

		Vitamin D deficiency	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity Liver disease	

Table 3.7: Management of AZT-Associated Bone Marrow Suppression

Test	Result	Action
Hb (g/dL)	> 8.5 (and decrease from pre-AZT baseline)	Retain AZT, repeat Hb at week 1, 2, 4 and 12 (if accessing follow-up Hb is difficult then consider substituting to an alternative ARV immediately)
	≤ 8.5	Switch from AZT to an alternative ARV
Neutrophils (x 109/L)	1.0 – 1.5 (and decrease from pre-AZT baseline, if available)	If receiving cotrimoxazole consider withholding unless essential. Retain AZT, repeat at week 1, 2, 4 and 12 (if accessing follow-up neutrophils is difficult then consider switching to an alternative ARV immediately)
	≤ 1.0	Switch from AZT to an alternative ARV

Notes:

- Patients with baseline Hb of < 9.5 g/dL should not be initiated on AZT; patients who develop anaemia while on AZT should be managed as per this table.
- AZT-associated bone marrow suppression occurs early in the course of treatment, usually within 3 months of initiating ART.
- All patients with anaemia and/or neutropenia, whether on AZT or not, should be evaluated for other likely causes of anaemia/neutropenia and managed appropriately.

Table 3.8: Management of Drug-Related Hepatotoxicity

ALT	<2.5 x Upper Limit of Normal (ULN)	2.5 – 5 x ULN	> 5 x ULN
Action	Retain regimen, repeat in 2 weeks	Retain regimen, repeat in 1 week	Discontinue offending drug/s

Note: All patients with acute increase in liver enzymes should be evaluated for other likely causes of hepatitis/hepatotoxicity and managed appropriately

Changing ARVs:

Indications for changing ART include optimizing therapy for patients who have undetectable viral load, managing adverse drug reactions or toxicity, drug-drug interactions, co-morbidity and treatment failure, and responding to pregnancy intention

Changing ARVs Due to Drug-Drug Interactions

Patients must be asked about other medications (including non-prescription and herbal medicine) they are taking at every visit. Some common drugs have specific drug-drug interactions that may require dose adjustment or substitution of the ARV or the other interacting drugs. Common medications that interact with specific ARVs include: rifampicin, rifabutin, antacids, multivitamin/mineral supplements, methadone, several anti-fungals, anti-convulsants, calcium- channel blockers, some anti-

depressants, some statins, and some anti-malarial. Annex provides common drug-drug interactions and management recommendations.

DTG co-administered with rifampicin among people coinfected with HIV and TB showed that the dose of DTG needs to be increased to 50 mg twice daily because of drug–drug interactions with rifampicin.

Changing ARVs Due to Treatment Failure Viral load is the test of choice for monitoring response to ART and identifying treatment failure.

Note: Treatment failure should be suspected when a new or recurrent HIV associated condition indicating severe immunodeficiency (WHO stage III or IV condition) develops after at least 6 months on ART (excluding IRIS occurring after initiation of ART), or when CD4 count fails to rise as expected or when CD4 count drops while on ART. Treatment failure should always be confirmed with VL testing.

Clinical and immunological criteria for identifying treatment failure have low sensitivity and specificity for diagnosing treatment failure. Every effort should be made to obtain a viral load test.

Non-adherence is one of the causes of treatment failure. All adherence issues must be resolved before switching to a new regimen otherwise the patient will quickly fail the new regimen as well, and soon run out of viable ART options. An exception to this may be when the regimen itself is the primary cause of poor adherence (e.g. side effects from one of the ARVs are not manageable such as severe diarrhea with LPV/r that does not improve with symptom management), in which case the regimen may need to be modified to allow for perfect adherence.

3.8 Criteria For Treatment Success

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

Clinical criteria: By 12 weeks of the treatment initiation patient should become asymptomatic or has only few symptoms, suggested range of the WHO clinical staging is the clinical stage 1 or 2. (Treatment staging, T1 to T4)

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

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

3.9 Failure of Antiretroviral Therapy

For any patient showing evidence of treatment failure, it is important to ensure that patient has received at least 6 months of ART, has good adherence & no OIs and IRIS has been ruled out.

The criteria for treatment failures are defined below:

Table 3.9: Criteria for Treatment failure

Failure	Definition	Comments
Clinical failure	New or recurrent WHO stage 4 condition	Condition must be differentiated from immune reconstitution inflammatory syndrome (IRIS) Certain WHO clinical stage 3 conditions (eg pulmonary TB, severe Bacterial infections may be an indication of treatment failure
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 as it can cause transient CD4 cell decrease In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed
Virological failure	Plasma viral load above 1000 copies/ml	Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure. Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, two consecutive viral load measurements within a 3-month interval, with adherence support between measurements) after at least 6 months of starting a new ART regimen. Enhanced adherence interventions may be needed following the first high viral load.

Switching ARV in case of treatment failure

In case of treatment failure, the entire regimen should be switched from a first to a second line combination regimen. A single drug should not be added or changed to a failing regimen. The new second-line regimen should use drugs which retain activity against the patient's virus strain and a minimum of three active drugs, one of them drawn from at least one new class, in order to increase the likelihood of treatment success and minimize the risk of cross-resistance. The PI class is thus reserved for second-line treatments. Ritonavir-boosted protease inhibitors (RTV-PIs) are preferred. They should be supported by two new agents from the NRTI class. Patients should not switch from one NNRTI to the other at the time of failure, as there is a high chance of cross-resistance (i.e. do not give EFV after failure on NVP or vice versa).

TABLE 3.10: PREFERRED AND ALTERNATIVE SECOND-LINE ART REGIMENS

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents	TDF + 3TC (or FTC) + DTG	AZT + 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/r
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT + 3TC + DTG	AZT + 3TC + ATV/r (or LPV/r or DRV/r)
	AZT + 3TC + EFV (or NVP)	TDF + 3TC (or FTC) + DTG	TDF + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)

Children and infants	ABC + 3TC + DTG[e]	AZT+ 3TC + LPV/r (or ATV/r[f])	AZT + 3TC + DRV/r[g]
	ABC (or AZT) + 3TC + LPV/r	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) + 3TC + RAL
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) + 3TC + LPV/r (or ATV/r[f])
	AZT + 3TC + NVP	ABC + 3TC + DTG[e]	ABC + 3TC + LPV/r (or ATV/r[f] or DRV/r[g])

3TC: lamivudine; ABC: abacavir; ATV/r: atazanavir/ritonavir; AZT: zidovudine; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ ritonavir; NVP: nevirapine; RAL: raltegravir; TDF: tenofovir disoproxil fumarate.

[e]The European Medicines Agency currently only approves DTG for children weighing at least 15 kg and more widely for children weighing more than 20 kg who can take adult 50- mg film-coated tablets. Studies are ongoing to determine dosing for younger children, with approval expected in early 2020, (PI-based for children for whom NNRTIs have failed and RAL for children for whom LPV/r has failed), TAF (tenofovir alafenamide) can be used as an alternative NRTI in children weighing at least 25 kg.

[f]ATV/r can be used as an alternative to LPV/r for children older than three months, but the limited availability of suitable formulations for children younger than six years, the lack of a fixed-dose formulation and the need for separate administration of the ritonavir booster should be considered when choosing this regimen.

[g]DRV should not be used for children younger than three years and should be combined with appropriate dosing of ritonavir.

Second-line ART Treatment Failure

The following general principles apply to managing patients failing 2nd line ART

- Patients failing second-line ART have limited options left. Agents used to construct a third- line regimen are often more expensive, will have increased pill burden and more side effects. These factors will exacerbate pre-existing poor adherence.

Second-line treatment failure should be confirmed by viral load testing, assess for and address all causes of poor adherence, assess for all other possible causes of viremia. Repeat the VL after 3 months of good adherence (preferably with daily witnessed ingestion of the ARVs by a treatment buddy, relative, CHV, etc). If the second VL is still is detectable (above LDL) then continue the failing second-line regimen and consult the experienced ART provider.

Table 3.11: Possible Third-line ART in Children, Adolescents and Adults

	Possible 3rd Line Regimen	Comments
Children	RAL (or DTG) + 3TC (FTC) + DRV/r	DTG can be substituted for RAL in children once pediatric formulations of DTG are available and weight-based dosing bands are defined
	AZT + RAL (or DTG) + 3TC + DRV/r	
	ABC (or TDF) + RAL (or DTG) + 3TC + DRV/r	
	ETV + 3TC + DRV/r	

Adults	DTG + 3TC + DRV/r	It may be recommended reusing some of the ARVs the patient has already failed, even when resistance is present
	DTG + AZT + 3TC + DRV/r	
	DTG + TDF + 3TC + DRV/r	
	DTG + TDF (or AZT) + 3TC	
	ETV + 3TC + DRV/r	

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. The patient should fully understand the importance of adherence. Adherence counseling and patient education should be done at every follow-up visit and attempt should be made to understand potential barriers to adherence by patient which may differ from patient to patient The intervention should be tailored accordingly.

After patient readiness, the treating physician and counselor should jointly consider the patient's readiness to start treatment.

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

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

However, these are suggested protocols but these need to be tailored according to patient profile as many patients who come from another city may find difficult to make many visits.

A typical follow-up counselling session involves:

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

Calculating Adherence:

There are number of ways of measuring adherence like patient recalls, pill count, home visit, patient diary etc. Pill count is most commonly used method to calculate the adherence. In each follow up visit, patient should be asked to bring the remaining pills provided in the previous visits. Following formula is used to calculate the adherence.

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

Adherence should be above 95% on all visits, if less, counselling needs to be reinforced.

3.11 Prophylaxis for Opportunistic Infections

Cotrimoxazole Prophylaxis Therapy (CPT) is effective against several organisms, like PCP, Toxoplasma and several organisms causing diarrhoea in HIV- infected persons. Evidence has shown

that CPT helps prevent morbidity and mortality in adults with both early and advanced HIV disease. Providing co-trimoxazole is part of the standard of care for preventing Pneumocystis jiroveci pneumonia (PCP) (formerly Pneumocystis carinii pneumonia) and toxoplasmosis.

Table 3.12: Recommendations for starting Cotrimoxazole in Adult:

	Adult	**Children**
Recommended for	• CD4 count less than 350 cells/mm3 • All who have had an episode of PCP • All symptomatic HIV disease or Clinical stage 3 or 4	• All exposed babies start at 4-6 weeks after birth and continue until at least 3 months after stopping breastfeeding with negative HIV test • All regardless of CD4 or clinical status • Those with symptomatic HIV disease and / or CD4 count < 25% • Those with symptomatic HIV disease and / or CD4 count < 350 /mm3
Doses	One double strength tablet (160mgTMP/800 mg SMX) every day OR Two single strength tablets (80mg TMP/ 400 mg SMX) every day	
Duration	• If on ART the CD4 is >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 3 or 4 conditions occur	

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.

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.

Some OIs may require secondary prophylaxis as detailed in table

Table 3.13: Recommended schedule for starting and stopping OIs prophylaxis

Opportunistic Infections	Primary prophylaxis indicated when CD4 is	Drug of choice	Discontinue primary Prophylaxis when CD4 is	Discontinue secondary prophylaxis when CD4 is
Toxoplasmosis	< **100**	TMP-SMX 1 DS Tablet od	**>350**	
CMV retinitis	Not indicated	Secondary: ganciclovir	Not applicable	**>100**
Cryptococcal Meningitis	Not indicated	Secondary: fluconazole (should continue for at least one year)	Not applicable	**>200**

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

This section includes the followings

1. Use of ART for pregnant and breastfeeding women
2. ART in some specific conditions of women

4.1 Use of ART for Pregnant and Breastfeeding women

The goal of ART for HIV positive pregnant women is two-fold: to restore and maintain the mother's immune function and therefore general health, and secondly, to prevent transmission of HIV in utero, at labour and delivery and during breastfeeding.

To achieve this goal, the mother must take effective antiretroviral therapy to achieve viral suppression.

Table 4 summarizes recommendations for use of ART for HIV positive pregnant women

Table 4.1: Summary of Use of ART for HIV Positive Pregnant and Breastfeeding Women

Overall recommendations	
When to start	Same as for non-pregnant adults (section 3): ART should be initiated in all pregnant and breastfeeding women living with HIV, regardless of gestation, WHO clinical stage and at any CD4 cell count and continued lifelong. ART should be started, ideally, on same day as HIV diagnosis with ongoing enhanced adherence support including community-based case management and support.
What to start with (first-line ART)	Start on TDF+3TC (or FTC)+DTG TDF+3TC (or FTC)+EFV
Monitoring	Review monthly until after delivery. Offer adherence support
Scenario	
Pre-conception planning for women already on ART (not yet pregnant)	Maintain ART unless using an ARV that is contraindicated in pregnancy*
Not on ART at the time of confirming pregnancy	Prepare the patient and start on ART as soon as possible. Preferably on the same day HIV infection is confirmed.
Not on ART at during labour and delivery	Start on ART during labour. After delivery, continue treatment preparation and support and continue ART
Not on ART during post-partum/breastfeeding	Prepare and start on ART as soon as possible preferably on the same day HIV infection is confirmed
Managing labour and delivery	Minimize vaginal examinations, use aseptic techniques to conduct delivery, avoid artificial rupture of membranes, monitor labour and avoid prolonged labour by use of the partograph, avoid unnecessary genital tract trauma.

*****Women on DTG based ART need to be counselled about consistent use of contraceptives and possible side effect of DTG in form of neural tube defects

Table 4.2: ARV Prophylaxis for HIV-Exposed Infants

Infant Scenario	Infant Prophylaxis	Maternal Scenarios
HIV Exposed Infant	• Infant prophylaxis ○ NVP (and or AZT) for 6 weeks, and should be continued until 6 weeks after complete cessation of breastfeeding ○ Infant prophylaxis can be discontinued after a minimum of 12 weeks on NVP if the child is not breastfeeding (death of mother or separation with mother) ○ The infant prophylaxis regimen applies to all infants irrespective of age when identifying HIV exposure (e.g. mother diagnosed HIV-positive in the postpartum period)	If mother not on ART, initiate ART as soon as possible (preferably same day) If mother is on ART for ≥ 3 months and the VL is detectable, intensify adherence, repeat the VL after 3 months of excellent adherence and if VL ≥ 1,000 copies/ml, change to an effective regimen.
Note: If child has contraindication or unable to tolerate NVP or AZT then give tolerated drug to complete a minimum of 12 weeks of infant prophylaxis and continue until maternal viral load suppression is confirmed.		

Table 4.3: Dosing of ARVs for Infant Prophylaxis from Birth to 12 Weeks of Age

Age/Weight	NVP Dose	AZT Dose (Only recommended in settings with replacement feeding)
Birth to 6 weeks		
Birth weight < 2,000 g	2 mg/kg body weight once daily	2 mg/kg body weight twice daily
Birth weight 2,000-2,499 g	10 mg once daily	10 mg two times a day
Birth weight ≥ 2,500 g	15 mg once daily	15 mg, two times a day
> 6 weeks to 12 weeks of age*		
Any weight	20 mg once daily	60 mg two times a day

*Dose adjustment required once child reaches 6 weeks of age.

4.2 ART in some specific conditions of women

Women with HIV/Tuberculosis (TB) co infection

HIV-infected pregnant women with active TB should start ART irrespective of the CD4 cell count (For details- see section 3).

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/DTG is the preferred ARV drug for HIV/TB co-infected pregnant women. For those HIV/TB coinfected women

not able to tolerate EFV/DTG, a triple NRTI regimen e.g. AZT + 3TC + ABC can be used or a PI based regime.

Women with hepatitis B or hepatitis C virus co-infection

ART should be started in all pregnant women. Co-infected pregnant women requiring ART and HBV treatment should receive a regimen containing TDF and 3TC (or FTC) and EFV/DTG (NVP should be avoided for risk of additive hepatic toxicity). These recommendations are the same as those for all adults.

Initiating ART among people with HIV and hepatitis C should follow the same general principles as for the people living with HIV but do not have hepatitis C. However now the Hepatitis C treatment is become simpler & cheaper, hence same should be offered, if available.

Pregnant women living with HIV who are injecting drug users

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

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

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

Pregnant women living with HIV and malaria

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

Pregnant women with HIV-2 infection

HIV-2 is naturally resistant to NNRTIs. So, treatment-naive people co-infected with HIV-1 and HIV-2 should be treated with a regimen containing TDF+ 3TC + DTG alternative options can be TDF+ 3TC + LPV/r or three NRTIs -TDF + 3TC (or FTC) + AZT or AZT + 3TC + ABC, though this is slightly inferior to LPV/r based regimen.

Section 5: Anti-Retroviral Therapy in special situations

This section includes the followings

1. ART for HIV/TB Co-infection
2. HIV/Hepatitis B Co-infection
3. HIV/Hepatitis C Co-infection
4. ART in HIV positive PWID
5. ARVs for post exposure prophylaxis
6. Management of HIV 2

5.1 ART FOR HIV/TB CO-INFECTION

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

Recommendations:

As with all PLHIV, those who are diagnosed with HIV/TB co-infection should be on ART and CPT as part of the comprehensive package of care for PLHIV.

Timing of ART for TB/HIV Co-infection

- Patients who are not yet on ART
  - Start TB treatment immediately
  - Initiate ART as soon as anti-TB medications are tolerated, preferably within 2 weeks; for TB meningitis consider delaying ART for up to 8 weeks
  - Monitor closely for IRIS (Annex 16)

- Patients who are already on ART
  - Start TB treatment immediately
  - Continue ART, making any required adjustments to the ART regimen based on drug-drug interactions (Table)
  - Monitor closely for IRIS (Annex 16)

- Patient being treated concurrently for TB and HIV require close monitoring for toxicity
  - MDR TB and HIV co-infection should be managed in settings where close toxicity monitoring and follow up by experienced clinicians is possible
  - Patients on TDF and aminoglycosides are at high risk for renal toxicity and require close monitoring

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 300 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.

Table 5.1: Preferred ART Regimens for TB/HIV Co-infection for Patients Newly Initiating 1st Line ART [1]

Age	1st Line if HIV/TB Co-infection
< 4 weeks	Start anti-TB treatment immediately; start ART after 4 weeks of age, once tolerating anti-TB drugs (follow the regimen recommendations for children 4 weeks to < 3 years of age)

4 weeks - < 3 years	• ABC + FTC + LPV/r + RTV[2] • After completion of TB treatment revert to the recommended first line regimen (ABC + 3TC + LPV/r)
3-14 years (and < 35 kg body weight)	ABC + FTC + EFV
≥ 15 years (**or** ≥ 35 kg body weight)	• Preferred regimen is TDF + FTC + DTG and alternative regimen is TDF + FTC + EFV[3] • Give TDF/3TC(or FTC)/DTG FDC at morning + DTG 50mg at evening for duration of rifampicin-containing TB treatment and for an additional 2 weeks after TB treatment is completed, then revert to TDF/3TC(or FTC)/DTG FDC OD
PWID/HIV ≥ 15 years	• Give TDF/3TC(FTC)/ EFV or DTG; if DTG[4] used, give FDC am + DTG 50mg pm for duration of rifampicin-containing TB treatment and for an additional 2 weeks after TB treatment is completed, then revert to TDF/3TC(FTC)/DTG FDC OD

1. Refer to Annex for weight-based ARV dosing
2. Use "super-boosted" LPV/r by adding additional ritonavir suspension to manage the drug interaction between LPV/r and rifampicin (see Table 8.8 for dosing recommendations). **Two weeks after TB treatment is completed the child should go back to standard LPV/r dosing**. For children ≥ 2 year who cannot tolerate LPV/r + RTV (usually because of GI side-effects), the alternative regimen is RAL at x2 standard weight-based BD dosing until 2 weeks after TB treatment then continue with RAL standard weight-based BD dosing.
3. EFV is no longer being recommended for children < 3 years old because of highly variable EFV metabolism at this age group
4. DTG co-administered with rifampicin among people coinfected with HIV and TB showed that the dose of DTG needs to be increased to 50 mg twelve hourly because of drug–drug interactions with rifampicin.

Table 5.2: Ritonavir Dosing for Super-Boosting LPV/r in Children Taking Rifampicin

Weight Range (kg)	Standard Dosing of Lopinavir/ritonavir (LPV/r) (Twice Daily)				Additional dosing of ritonavir for children taking rifampicin (Twice Daily)
	LPV/r 80/20 mg/ml solution	LPV/r 40/10mg pellets (number of pellets)	LPV/r 100/25mg tablets	LPV/r 200/50mg tablets	Ritonavir liquid (80mg/ml, in 90 ml bottle). Ritonavir dose is adjusted to nearest mark for the ease of measurement
3 - 5.9	1 ml BD	2 BD	Not recommended	Not recommended	1 ml BD

6 - 9.9	1.5 ml BD	3 BD	Not recommended	Not recommended	1 ml BD
10 - 13.9	2 ml BD	4 BD	2 am 1 pm	Not recommended	1.5 ml BD
14 - 19.9	2.5 ml BD	5 BD	2 BD	1 BD	2 ml BD
20 - 24.9	3 ml BD	6 BD	2 BD	1 BD	2.5 ml BD
25 - 29.9	Not recommended	7 BD	3 BD	2 am 1 pm	4 ml am 2 ml pm
30-34.9	Not recommended	8 BD	3 BD	2 am 1 pm	4 ml am 2 ml pm
≥35	Not recommended	10 BD	4 BD	2 BD	4 ml BD

Patients taking isoniazid containing regimen should also be given Pyridoxine (Vitamin B6) daily to reduce the risk of developing peripheral neuropathy

For anti TB drugs please see/follow National anti TB guidelines

5.2 HIV/HEPATITIS B CO-INFECTION

HIV and HBV have shared transmission routes. Acute HBV infection in HIV positive people is associated with increased risk of chronicity, reduced chances of spontaneous clearance, higher rates of replication and reactivation and therefore increased incidence of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). Additionally, HIV/HBV co-infection has been associated with rapid HIV disease progression and poorer HIV treatment outcomes. Other complications of HIV/HBV co-infection include increased incidence of drug-related hepatotoxicity, drug-toxin interactions and ART-related immune reconstitution hepatitis.

When to start ART

All HIV infected patients who are co-infected with hepatitis B should be started on ART irrespective of CD4 cell count, WHO clinical stage or stage of liver disease

The general recommendations for treatment preparation, adherence counselling and support and monitoring of therapy for PLHIV apply. However, because HBV positive patients are at higher risk of hepatotoxicity, closer monitoring of liver function (with ALT) is advised. Table provides a summary of areas of focus during initial evaluation for HIV/HBV co-infected patients initiating therapy.

Recommended first-line ART in HIV/HBV co-infection

The recommended first-line ART in adolescents and adults with HIV/HBV co-infection is TDF + FTC/3TC + EFV (DTG) or (TDF + FTC/3TC + EFV for women and adolescent girls of childbearing potential)

Treatment with both TDF and FTC/3TC is recommended as FTC/3TC alone will result in rapid emergence of resistance. In case of renal impairment (as assessed by creatinine clearance), the dose of TDF and FTC/3TC should be adjusted (refer to Table).

Table 5.3: Summary of Initial Clinical and Laboratory Evaluation in HIV/HBV Co-infection

	Findings	Action
History	Alcohol use, cigarette smoking, intravenous drug use, unsafe sexual practices, anorexia, right upper quadrant pain, jaundice, early satiety, haematemesis, dark stool, bleeding, pruritus	Assess, counsel and support to stop taking alcohol; counsel and support smoking cessation; counsel and provide or refer for harm reduction interventions
Physical examination	Enlarged liver, enlarged spleen, ascites, scratch marks	Evidence of established chronic liver disease, closer follow-up due to increased risk of hepatotoxicity, discuss or refer to a consultant for additional evaluation and management
LFT	If elevated, may point to active liver disease. Exclude other causes of elevation of liver enzymes	Every effort should be made to assess for liver function (albumin and INR), especially in symptomatic patients. However, this should not delay initiation of ART
Creatinine	Calculate creatinine clearance	In HIV/HBV co-infection, TDF is indicated even in patients with CrCl < 50 ml/min. In such patients, avoid FDCs. Instead administer the ART as single drugs to allow for dosage adjustment as shown in Table
Comorbidities	HCV antibody, random blood sugar, Fasting lipid profile, alcoholic and non-alcoholic liver disease, hepatocellular carcinoma (family history)	Refer the patient for additional investigations where these are suspected

Table 5.4: Dose Adjustment of TDF in Patients with Impaired Renal Function[1]

Drug	Creatinine clearance (ml/min)			Haemodialysis
	50 - 80	30-49	10-29	
TDF 300 mg	Unchanged: 300 mg once daily	300 mg every	300 mg every 72 to 96 hours (twice weekly). For patients getting HD, administer 300	

		48 hrs	mg once weekly after completion of dialysis sessions [2]

1 Patients with impaired renal function in whom the benefits of continued use of TDF outweighs the risks (such as in the management of HIV/HBV co-infection) should be managed with input from a specialist in internal/paediatric or renal medicine

2 Assuming 3 haemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative haemodialysis

Follow-up, Monitoring

Follow-up of HIV/HBV co-infected patients should be as for all other patients on ART. However, consider more frequent monitoring (using ALT) for patients with active liver disease (jaundice, liver cirrhosis and features of portal hypertension) at baseline. The presence of co- infection also increases the risk of drug-related hepatotoxicity from all ARV drugs by 3-5 times, especially when anti-TB and ART are given simultaneously. Also, hepatic flare (AST > 5 times normal value) can occur, often in the initial 3 months. **ALT elevations 5-10 times normal can be tolerated in the first 3 months of ART as long as the patient is not severely symptomatic, remains stable without progression, and there is no evidence of synthetic dysfunction (INR normal, glucose normal, albumin normal)**. Subsequent laboratory monitoring after baseline should be conducted every 6 months. Patients should be counselled and supported to abstain from consuming alcohol.

Stopping treatment, treatment interruptions

TDF-containing ART should not be stopped in a patient with HIV/HBV co-infection as this may result in a flare-up of the hepatitis. If the regimen must be stopped and another alternative for suppressing hepatitis B cannot be found, liver enzymes should be monitored and treatment reinstated as soon as possible.

Second line for HIV/ HBV co-infected

Maintain TDF + FTC/3TC in the ART regimen for patients switching from TDF-based-therapy.

The recommended second-line ART regimen in HIV/HBV co-infection is

TDF + FTC/3TC + ATV/r

5.3 HIV/HEPATITIS C CO-INFECTION

HIV/ HCV co- infection is associated with-

- Rapid progression of liver fibrosis
- Higher risk of deteriorating liver disease even in the presence of controlled HIV disease
- Worsened hepatotoxicity as a result of ART and other drugs used in the treatment of co-morbidities

Thus, HIV-positive persons at risk of HCV co-infection should be identified and offered HCV treatment. The recent introduction of direct acting antiviral therapies (DAAs) for treatment of HCV has simplified the management of HIV/HCV co-infection; making it possible to manage uncomplicated HIV/HCV infection safely even in primary care settings.

> However, treatment for HCV is a rapidly evolving field of therapeutics. Providers are encouraged to seek regular updates on the subject and, when in doubt, to discuss individual cases with experienced providers.

HCV serology should be offered to individuals at risk of HCV infection. These include

- People who inject or use intranasal drugs
- Persons who have had tattoos, body piercing or scarification procedures from settings of doubtful infection prevention precautions
- Children born to HCV positive mothers

Up to 45% of individuals who are infected with HCV spontaneously clear the infection. To confirm chronic HCV infection, HCV positive individuals should be offered nucleic acid HCV RNA testing to establish presence of chronic HCV infection.

Treatment of HIV/HCV Co-infection

Table 5.5: Summary of Initial Clinical and Laboratory Evaluation in HIV/HCV Co-infection

	Findings	Action
History	Alcohol use, cigarette smoking, intravenous drug use, unsafe sexual practices, anorexia, right upper quadrant pain, jaundice, early satiety, haematemesis, dark stool, bleeding, pruritus	Assess, counsel and support to stop taking alcohol, counsel and support smoking cessation; counsel provide and refer for harm reduction interventions

Physical examination	Enlarged liver, enlarged spleen, ascites, scratch marks	Evidence of established chronic liver disease, closer follow-up due to increased risk of hepatotoxicity, discuss or refer to a consultant for additional evaluation and management
HCV RNA PCR	For confirmation of chronic HCV infection	If available, at baseline
HCV genotype		Important for selecting appropriate DAA regimen
LFT	If elevated, may point to active liver disease. Exclude other causes of elevation of liver enzymes	Every effort should be made to assess for liver function (albumin and INR), especially in symptomatic patients. However, this should not delay initiation of ART
Comorbidities	HBV, random blood sugar, Fasting lipid profile, alcoholic and non-alcoholic liver disease, hepatocellular carcinoma (family history)	Refer the patient for additional investigations where these are suspected

Table 5.6: Recommended DAA for the Treatment of HCV without Cirrhosis

Genotype	DAA Regimen*	Duration of treatment	ART considerations
Pan genotype (All)	Velpatasvir (100mg) + Sofosbuvir (400mg)	12 weeks	TDF+FTC+(DTG)
	Sofosbuvir (400mg) + Declatasvir (90mg)	12 weeks	TDF+FTC+EFV

***Start DAA HCV therapy under specialist supervision**

**Treatment duration is extended to 12 - 24 weeks in patients with compensated cirrhosis

5.3 A. HIV/Hepatitis B & C co-infections

Recommended treatment for HIV/HBV+ HCV co-infections

> **The recommended ART in adolescents and adults with HIV/HBV+HCV co-infections is TDF + FTC+ DTG**

And DAA for HCV will be same as table 5.6

5.4 ART IN HIV POSITIVE PWID

The use of ART for HIV in key populations should follow the same general principles and recommendations as for all adults. People in key populations may experience discrimination and marginalization that can impede their access to health care, including treatment for HIV, and frequently present late for treatment. It is important to ensure that people from key populations have equitable access to HIV treatment and care. Programs should ensure that missed opportunities are minimized and every single encounter with someone from a key population is optimally used. ART service delivery includes decentralization of HIV care and treatment and integrating ART services into other clinical services such as Medically Assisted Therapy and drop in centers where appropriate capacity exists.

PWID have complex needs related to drug dependency, psychosocial and medical complications of injection and other substance use. When they require ART, anti-TB or any other therapy, they are at increased risk of adverse drug reactions and drug interactions and non-adherence. These patients are best comprehensively managed by providers who have received specific training in the management of injection drug users. Once identified, PWID should be counselled and linked to programs with the capacity to offer comprehensive care for such patients

Table 5.7: Summary of ART Recommendations for PWID

Care and Support	Recommendation/Additional Information
When to start ART in HIV positive PWID	ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count
What to start with (first-line ART)	Irrespective of OST, PWID with HIV infection should be initiated on a first-line regimen of TDF + 3TC (FTC) + DTG or EFV or ATV/r
	For PWID with TB/HIV co-infection on DTG, give TDF/3TC(FTC)/DTG FDC am (morning) + DTG 50mg pm (evening) for duration of rifampicin-containing TB treatment and for an additional 2 weeks after TB treatment is completed, then revert to TDF/3TC/DTG FDC OD.
Second-line ART	Patients failing DTG-based first line ART (including PWID) should switch to ATV/r-based second ART as per Table

Treatment preparation and adherence counselling and support	Injecting drug use is not a contra-indication to ART initiation. OST, though important in contributing to the success of ART in PWID, should not be a pre-requisite to initiation of ART. However, these patients benefit from additional preparation and support to increase their chances of successful treatment including: Harm reduction interventions Thorough baseline assessment for important comorbid conditions like hepatitis, renal impairment, TB and depression or other psychiatric disorders Negotiation for, and access to directly observed therapy Community outreach
Preventing and managing drug-drug interactions	ARV interactions with methadone (see annex for details) NRTIs TDF, 3TC, FTC: no significant interactions AZT levels are increased, with higher risk of AZT toxicity ABC levels are decreased and methadone levels are decreased NNRTIs EFV and NVP: methadone levels are decreased, and may induce withdrawal symptoms PI/r: all boosted PIs decrease methadone levels LPV/r and methadone increase risk for prolonged QT syndrome and sudden cardiac death INSTIs: no significant interactions ARV interactions with buprenorphine ATV/r and DRV/r increase concentrations of buprenorphine or its active metabolites and may increase risk of toxicity EFV decreases buprenorphine levels substantially No known significant interactions with other ARVs
Monitoring	PWID on ART require more frequent monitoring and support to ensure adherence to treatment and harm reduction interventions, assess for and manage adverse drug reactions or drug-drug interactions. Ongoing monitoring should also include screening for other illicit substance/drug use.

5.5 ARVs FOR POST EXPOSURE PROPHYLAXIS (PEP)

Post-exposure prophylaxis (PEP) is short-term use of antiretroviral treatment to reduce the likelihood of HIV infection after potential exposure. People can be accidentally exposed to HIV through healthcare work or due to exposures outside healthcare setting, for example, through

unprotected sex or sexual assault among adults and children. Healthcare workers are at increased risk of exposure to HIV through contact with contaminated blood and other body fluids containing HIV through needle stick injuries and injuries by other sharp objects or through non-intact skin and mucous membranes.

To avoid exposure to HIV, precautions should be taken when handling possibly contaminated body fluids including the use of appropriate barriers such as gloves, gowns and goggles; care with sharps including minimizing blind surgical procedures and proper handling and disposal of sharps; safe disposal of contaminated waste; safe handling of soiled linen; adequate disinfection procedures and universal Hepatitis B vaccination of non-immune at risk groups including HCWs, police, prison staff and rescue workers.

PEP should always be offered as soon as possible, preferably within 2 hours (and within 72 hours) after a high-risk exposure (as defined in Table 10.1) or if exposure is from an unknown status. Three-drug regimens are preferred for PEP. However, if a person is unable to tolerate a drug (usually the PI/r), then 2 drugs can be used. Patients should be counselled and **strongly encouraged to complete the full 28-day course of PEP** once a decision has been made to initiate PEP. For occupational exposure, immediate care of the exposure site includes: wash the site with soap and water, and allow the wound to bleed freely for several minutes (but do not do anything that will increase tissue damage such as squeezing, scrubbing or cutting the site further).

Table 5.8: Post-exposure Prophylaxis

Considerations	Recommendation

Eligibility: Must meet all of the following criteria	• Exposed individual is HIV negative at baseline or unknown status
	• Exposure must have occurred within the past 72 hours
	• Exposure must be high-risk (high-risk type AND material)
	  ◦ Type: mucous membrane; non-intact skin, or; percutaneous injury
	  ◦ Material: blood or bloody body fluids; breast milk; semen; vaginal secretions; synovial, pleural, pericardial, amniotic fluids; CSF, or; HIV cultures in lab
	Note: HIV status of the source is no longer part of the risk stratification for PEP, because even if the source tests HIV negative by rapid antibody test they may still be in the window period of acute HIV infection so should be assumed to be positive
	Note: if a breastfeeding mother starts PEP because of HIV exposure, the infant does **not** require PEP or infant prophylaxis as well. The infant should continue breastfeeding.

Management at initial contact	• Counsel on risks and benefits of PEP and obtain verbal consent for HIV testing • Voluntary testing for both exposed and source individuals • Offer PEP as soon as high-risk exposure is established and exposed individual tests HIV- negative at baseline (if HIV testing not available, can provide 1-2 days of PEP to cover until HIV test performed) • Pregnancy testing

	• Cr (if TDF-containing regimen) and Hb (if AZT-containing regimen), however PEP should be offered even when lab tests are not available. Do not delay administration of PEP while waiting for lab results • Hepatitis B vaccination (if not previously immunized & not known HBV positive)

ARV regimen for PEP	≥ 15 years old (or ≥ 35 kg body weight): TDF + 3TC/(FTC) + DTG as 1st choice and alternatively TDF + 3TC/(FTC) + PIs (or TDF + 3TC/(FTC) + ATV/r for women and adolescent girls of childbearing potential) can be used	• AZT can be used as an alternative when TDF or ABC cannot be used • For children who cannot tolerate LPV/r: RAL or DRV/r can be used instead
	0-14 years and < 35 kg: ABC + 3TC + LPV/r	
Time of initiation	As soon as possible after exposure, preferably within 2 hours, but no later than after 72 hours	
Duration of PEP	28 days (dispense all 28 days of treatment at the first visit)	
Dose of PEP	Same as indicated for ART; use weight-based dosing for children	
Follow-up	• Follow up client at 7 days, 14 days, 28 days, and 12 weeks after starting PEP • Follow-up HIV testing at 12 weeks, if negative, test again at 6 months after which test as per risk category • Assess for and manage side effects due to PEP	
Counselling	Adherence counselling, risk reduction, trauma and mental health counselling, social support and safety, safe sex practices	
Other services for sexual assault	• STI prophylactic treatment to all (treat for vaginal/urethral discharge syndrome following the national STI algorithms) • Emergency contraception for non-pregnant women • Tetanus toxoid for any physical injury of skin or mucous membranes • Hepatitis B immunization • Documentation of clinic evidence of assault and collection of forensic evidence • Refer to post-rape care guidelines for additional details	

Note: DTG is recommended as the preferred third drug for HIV post-exposure prophylaxis

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. Provider may decide to provide PEP in some cases, such as an episode of condom breakage in a discordant couple.

5.6 ORAL PRE-EXPOSURE PROPHYLAXIS

Pre Exposure Prophylaxis (PrEP) is the use of ARV medication to prevent the acquisition of HIV infection by an uninfected person at substantial risk of acquiring HIV infection.

Currently PrEP is not recommended in Bangladesh. However, some NGOs working with PWID, MSM, etc. are considering PrEP as a trial. If the results show positive outcome, PrEP can be used as follow:

Indications and Criteria for PrEP

INDICATIONS

PrEP is offered to sexually active HIV-negative individuals who are at substantial risk of acquiring HIV infection as defined by any of the following

- Sexual partner is known HIV positive and: not on ART, or on ART < 6 months, or suspected poor adherence to ART, or most recent VL is detectable
- Sexual partner/s are of unknown HIV status and are at high-risk for HIV infection (has multiple sexual partners, has had STIs, engages in transactional sex, injects drugs, from high HIV burden settings)
- Engaging in transactional sex
- History of recent sexually transmitted infection
- Recurrent use of post-exposure prophylaxis
- History of sex whilst under the influence of alcohol or recreational drugs as a habit
- Inconsistent or no condom use or unable to negotiate condom use during intercourse with persons of unknown HIV status
- Injection drug use where needles and syringes are shared
- Sero-discordant couples trying to conceive

Criteria

To qualify for PrEP, patients must meet ALL of the following criteria

- Confirmed HIV negative (rapid antibody testing following the HIV testing algorithm on the day of PrEP initiation is adequate confirmation of HIV-negative status)
- Assessed as ready to adhere to PrEP and willing to attend follow-up evaluations including repeat HIV testing and monitoring for side effects
- No contraindication to use of TDF +/- FTC (or 3TC)

PrEP does not eliminate the risk of HIV infection and it does not prevent STIs or unintended pregnancies. It should, therefore, be offered as part of a combination prevention package that includes risk reduction counselling, HIV testing, condoms and lubricants, STI screening and treatment, contraception, needle exchange and opioid replacement therapy.

RECOMMENDED ARVs FOR PREP

The recommended ARV regimen for use as PrEP is: TDF 300 mg and Emtricitabine 200 mg once daily (given as FDC). Alternatively, TDF 300 mg once daily or TDF 300 mg/ 3TC 300 mg may be used.

PrEP should only be offered after thorough assessment to establish eligibility, readiness for effective use, required follow-up and absence of contraindications to TDF +/- FTC (or 3TC).

MINIMUM REQUIRED LABORATORY EVALUATION FOR PREP

Before initiating PrEP, the following investigations should be performed:

- Rapid HIV antibody test
- Baseline creatinine is recommended but should not delay initiation of PrEP.
- Where available: HBsAg and HCV serology;

The following investigations should be done for monitoring patients on PrEP

- Rapid HIV antibody test every 3 months
- Annual serum creatinine

CONTRA-INDICATIONS TO ORAL PREP

- HIV infection or suspected acute HIV infection (i.e. flu-like symptoms in the last 4 weeks in combination with a preceding high-risk exposure for HIV)

Adolescents < 35 kg or age < 15 years
Impaired renal function
Unable or unwilling to adhere to prescribed PrEP or follow-up schedule

CRITERIA FOR DISCONTINUING PREP

PrEP should be discontinued if ANY of the following criteria are met

- Becomes HIV positive
- Renal dysfunction with creatinine clearance below 50 ml/min
- Client request to stop
- Sustained non-adherence
- The HIV positive partner in a discordant relationship achieves confirmed undetectable viral load. But the couple should continue consistent condom use

Users discontinuing PrEP -- should continue PrEP for at least 28 days after the last potential exposure to HIV. Reasons for discontinuation should be documented in the client's record.

WHO SHOULD PROVIDE PREP AND WHERE

PrEP must be prescribed by a healthcare professional who has completed training on the national guidelines for the use of ARVs as PrEP.
PrEP can potentially be offered in any setting that has trained healthcare professionals

who have been trained on the national guidelines for use of ARVs as PrEP, and with systems and tools in place for the monitoring, documentation, and reporting of PrEP use.

PrEP implementation can be integrated in any setting that meets the conditions for initial evaluation and initiation including

- Drop-in Centers (DICEs) for key populations (including community and facility settings)
- HIV clinics (for HIV-negative partners before the HIV-positive partner achieves viral suppression)
- ANC/MNCH/RH and STI clinics
- Community settings meeting the criteria for initial client assessment and evaluation,
  e.g. integrated prevention centers and youth friendly outlets

5.7 MANAGEMENT OF HIV 2

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

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

Few recommendations regarding HIV 2 are below:

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

Section 5: Annexure

This section includes the followings

1. WHO clinical staging of HIV diseases in adults, adolescents and children
2. Assessment of adults and adolescents with HIV infection clinical assessment and other test
3. History taking
4. Cotrimoxazole intolerance
5. Recommended dose of cotrimoxazole
6. Isoniazid preventive therapy
7. ART adherence
8. Dosing of Solid and Liquid Formulations for Twice-Daily Dosing in Infants and Children 4 Weeks of Age and Older
9. Simplified Dosing of Child-Friendly Solid and Oral Liquid Formulations for Once-Daily Dosing in Infants and Children 4 Weeks of Age and Older
10. Drug Dosing of Liquid Formulations for Twice-Daily Dosing in Infants Less than 4 Weeks of Age
11. Simplified Dosing of INH and CTX Prophylaxis for Infants and Children Who Are at Least 4 Weeks of Age
12. Drug-drug Interactions: Overlapping Drug Toxicity
13. Drug-Drug Interactions - NNRTIs
14. Drug-Drug Interactions – PIs
15. Drug-Drug Interactions – INSTIs
16. Immune Reconstitution Inflammatory Syndrome
17. Additional guidance on drug interaction/toxicity
18. ARV,CTX and Fluconazole Adjustments in Renal and Hepatic Impairment

ANNEX 1: WHO CLINICAL STAGING OF HIV DISEASE IN ADULTS, ADOLESCENTS AND CHILDREN

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

Adults and adolescents	Children
Clinical stage 1	
Asymptomatic Persistent generalized lymphadenopathy	Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2	
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Seborrheic dermatitis	Unexplained persistent hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis, tonsillitis) Herpes zoster Lineal gingival erythema Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Extensive wart virus infection Extensive molluscum contagiosum Unexplained persistent parotid enlargement
Clinical stage 3	
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea for longer than 1 month Unexplained persistent fever (intermittent or constant for longer than 1 month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anemia (<8 g/dl), neutropenia (<0.5 x 109/l) and/or chronic thrombocytopenia (<50 x 109/l)	Unexplained moderate malnutrition not adequately responding to standard therapy Unexplained persistent diarrhea (14 days or more) Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month) Persistent oral candidiasis (after first 6 weeks of life) Oral hairy leukoplakia Lymph node tuberculosis Pulmonary tuberculosis Severe recurrent bacterial pneumonia Acute necrotizing ulcerative gingivitis or periodontitis Unexplained anemia (<8 g/dl), neutropenia (<0.5 x 109/l) or chronic thrombocytopenia (<50 x 109/l) Symptomatic lymphoid interstitial pneumonitis, Chronic HIV-associated lung disease, including Bronchiectasis

Clinical stage 4	
HIV wasting syndrome Pneumocystis (jirovecii) pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site) Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis, including meningitis Disseminated non-tuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis) Lymphoma (cerebral or B-cell non-Hodgkin) Symptomatic HIV-associated nephropathy or cardiomyopathy Recurrent septicemia (including nontyphoidal Salmonella) Invasive cervical carcinoma Atypical disseminated leishmaniasis	Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy Pneumocystis (jirovecii) pneumonia Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site) Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis (with diarrhea) Chronic isosporiasis Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) Cerebral or B-cell non-Hodgkin lymphoma HIV-associated nephropathy or cardiomyopathy

ANNEX 2: ASSESSMENT OF ADULTS AND ADOLESCENTS WITH HIV INFECTION CLINICAL ASSESSMENT AND OTHER TESTS

As soon as a person enrolls for HIV care, a comprehensive clinical assessment should be done as baseline status and to rule out opportunistic infections. This helps to:

- Determine the clinical stage of HIV infection
- Identify history of past illnesses (especially TB, STIs, Hepatitis)
- Identify current HIV-related illnesses that may require treatment
- Determine the need for OI prophylaxis
- Do CD4 count and other baseline investigations as per protocol
- Identify coexisting medical conditions like diabetes, hepatitis etc and treatments that may influence the choice of ARV drugs.
- Determine nutritional status and needs.
- Need for psychosocial support

It is important to elicit those risk factors which may influence the type of counselling requirement as well as drugs to be used for ART. One must look for -

- Past or present use of injecting drugs
- Present or past unprotected sex, with female or male sex worker
- Past or present sexually transmitted infection (STI, TB)
- Past or present recipient of blood or blood products
- Risk factors like MSM, FSW, PWID etc as this may require special counselling and ART delivery mechanisms
- Injections, tattoos, ear piercing or body piercing using non-sterile instruments

ANNEX 3: HISTORY TAKING

Medical History Checklist	
HIV Testing	**HIV risks (can have multiple factors)**
• Ever tested for HIV in the past? • Date and place of first HIV test • Reason for the test • Documentation of the result- • Previous CD4 cell counts (if available) • Previous viral load (if available)	• Unprotected sexual contact • Injecting drug use • Men having sex with men • Perinatal transmission • Recipient of blood products • Unknown Partner's HIV status being positive
System Review	**Past history of HIV related illnesses**
• Unexplained weight loss • Swollen lymph nodes • Night sweats and fever • Unusual headaches or poor concentration • Changes in appetite • Skin rashes • Sores or white spots in mouth • Painful swallowing • Chest pain, cough or shortness of breath • Stomach pain, vomiting or diarrhea • Numbness or tingling in hand or feet • Muscular weakness and changes in vision	• Oral candidiasis or candida esophagitis • Persistent diarrhea • Tuberculosis • Varicella zoster (Shingles) • Oral hairy leukoplakia • Pneumocystis juroveci pneumonia (PCP) • Recurrent bacterial pneumonia Cryptococcal meningitis • Toxoplasmosis • Kaposi sarcoma • Disseminated Mycobacterium avium complex • Cytomegalovirus(CMV) infection • Invasive cervical cancer
Tuberculosis history	**ART history**
• Last chest X-ray • History of past TB • Treatment given (drugs and duration) • History of exposure to TB in the family/close contacts • Ask the four TB screening questions "4 S Screening "(any cough, fever or weight loss and night sweat).	• Current and past exposure to ARVs • ARV use during pregnancy of PMTCT • Use of PEP in the past • Which drugs taken and for how long • Understanding of and readiness to commence ART • Partner's ART history (if HIV-positive)
Sexually transmitted infections (STIs)	**Substance use**
• Genital ulcer or another lesion • Genital discharge (abnormal vaginal discharge in women) • Lower abdominal pain	• Alcohol, stimulant, opiate and another drug use • Smoking history
General medical history	**Allergies**
• Any other past medical condition such as diabetes, hypertension, coronary artery disease, hepatitis B, hepatitis C,	• Known allergies to drugs or other substances or materials

hyperlipidemia • Mental health issues, e.g. depression	
Medication	**Vaccination history**
• Past use of drugs and reasons for taking those drugs • Current use of drugs and reasons • Current use of traditional / herbal remedies • Opioid substitution therapy (OST)	• BCG • Hepatitis A vaccine • Hepatitis B vaccine
Psychosocial history	**Social history**
• Family history, e.g. other immediate family members with known HIV infection • Social history e.g. marital status, education, occupation, source of income.	• Financial and family support status • Disclosure status, readiness to disclose • Availability of care and treatment supported supporter • Able to work, go to school, do housework • Ambulatory but not able to work • Bed ridden • Amount of day-to-day care needed
Gynecological history	**Pregnancy and contraception history**
• Last PAP smear • Menstrual irregularities • Pelvic pain or discharge	• Previous pregnancies and MTP (years) • Children and HIV status of children (living and dead) • Exposure to ARVs during pregnancy • Drugs and duration of ART • Contraception used • Last menstrual period

Physical examination checklist	
Record vital signs, body weight, height and body mass index (BMI), temperature, blood pressure, pulse rate, respiratory rate	
Appearance	• Unexplained moderate or severe weight loss, HIV wasting • Rapid weight loss in suggestive of active Ol, especially if associated with fever • Gradual weight loss (not caused by malnutrition or other obvious illness) is suggestive of HIV infection • "Track marks" and soft tissue infections which are common among IDUs
Consider conditions other than HIV	• Malaria, tuberculosis, syphilis, gastrointestinal infections, bacterial pneumonia, pelvic inflammatory disease, viral hepatitis other than HIV
Skin	• Look for signs of HIV-related and other skin problems. These include diffuse dry skin, typical lesions of PPE, especially on the legs, seborrheic dermatitis on face and scalp • Look for herpes simplex and herpes zoster or scarring of previous herpes zoster (especially multi-dermatome)
Lymph nodes	• Start with posterior cervical nodes • PGL (persistent glandular lymphadenopathy) that typically presents as multiple

	bilateral, soft, non-tender, mobile cervical nodes, other than axillary or inguinal nodes • Tuberculous lymph nodes typically present with constitutional symptoms such as fever, night sweats and weight loss
Mouth	• Look for signs suggestive of HIV infection including white plaques on tongue, cheeks and roof of mouth (oral candida), white stripped lesions on the side of the tongue (OHL) and cracking at the corners of the mouth (angular cheilitis) • Difficulty in swallowing is commonly caused by esophageal candida
Chest	• The most common problems will be PCP and TB • Signs and symptoms are cough, shortness of breath, hemoptysis, weight loss, fever, congestion or consolidation • Perform a chest X-ray, if symptomatic
Abdomen	• Hepatosplenomegaly, masses and local tenderness • Jaundice may indicative of viral hepatitis
Neurological	• Focus on visual fields and the signs of neuropathy (bilateral peripheral examination or localized mono-neuropathies) • Assess focal neurological deficit
Ano-genital	• Herpes simplex and other genital sores / lesions, vaginal or penile discharge • Perform PAP smear, if possible
Note: During each consultation, patient is to be clinically screened for TB (history and physical examination)	

Laboratory Monitoring for patients on ART
Baseline Tests --Essential tests for all patients registering in HIV care • Hemogram/CBC, • Urine for routine and microscopic examination, • fasting blood sugar, • blood urea, Serum creatinine • ALT (SGPT), • VDRL/RPR/TPHA, • CD4 count, • Sputum for Gene xpert • X-ray Chest PA view. • Pregnancy test (if required) • Symptoms and signs directed investigations for ruling out Ols. • PAP smear • Viral Load test as preferred test if available
Additional tests at baseline as per the physician's decision depending on clinical presentation
• USG abdomen, • Sputum for C/S • CSF analysis etc. • Any other test required to rule out OIs Efforts to be made to fast track these investigations so that ART initiation is not delayed.
Tests for Special Situations at baseline
• HBsAg: for all patients if facility is available but mandatorily for those with history of IDU, multiple blood & blood products transfusion, ALT > 2 times of ULN, on strong clinical suspicion.

But ART not to be withheld if HBsAg testing is not available.

- Anti - HCV antibody: Especially for those with history of IDU, multiple blood & blood products transfusion, ALT >2 times of ULN, on strong clinical suspicion.
- For patients with Hepatitis B or C co-infection: further tests may be required to assess for chronic active hepatitis
- Fundoscopic examination of eyes in those with low CD4 count
- CMV antibody- IgG, IgM with low CD4 cell count

Tests for monitoring patients on ART (Follow up tests)
• For all patients on ART, need to do CD4, Hb, TLC, DLC, ALT (SGPT). For those on TDF based regimen: S. Creatinine, every 6 months or earlier if required. • It is preferable /desirable to monitor patients with CD 4 and viral load at 6 & 12 months after initiation of ART & then viral load every 12 months. For stable patients with virological suppression, frequency of CD4 can be reduced. • CD4 test is required for CPT initiation/stopping CPT, and for primary and secondary prophylaxis for some OIs • For those on AZT based regimen: Hb at 15 days, then every month for initial 3 months, 6 months and then every 6 months/ as & when indicated. • For those on NVP based regimen: ALT (SGPT) at 15 days, 1 month and then every 6 months. • For those on EFV based regimen: lipid profile should also be done yearly, if available. • For those on ATV based regimen: LFT to be done at 15 days, 1 month, 3 months, 6 months and then every 6 months. • Blood sugar and Lipid profile every 6 months for patients on PI based regimen. Any other can be done earlier based on clinician's assessment/ discretion and as per availability. • Drug resistance test in case of treatment failure, if available

ANNEX 4: COTRIMOXAZOLE 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. Co-trimoxazole desensitization has been shown to be successful and safe in approximately 70% of patients with previous mild to moderate hypersensitivity. Desensitization should not be attempted in individuals with a history of severe co-trimoxazole or other sulphonamide reaction. If a reaction occurs, the desensitization regimen should be stopped. Once the patient recovers fully, Dapsone at a dosage of 100 mg per day may be tried.

Protocol for cotrimoxazole desensitization among adults and adolescents:

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

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

Follow-up of clients on Cotrimoxazole prophylaxis:

- Monitor for toxicity, clinical events and adherence.
- Lab tests of hemoglobin and white blood counts, as indicated.
- Adherence counseling on Cotrimoxazole can be useful to prepare clients for ART 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.

ANNEX 5: RECOMMENDED DOSE OF COTRIMOXAZOLE (ONCE DAILY DOSE)

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

ANNEX 6: ISONIAZID PREVENTIVE THERAPY (IPT)

Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats (known as "4S") are unlikely to have active TB and should be offered IPT

Duration of IPT

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

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

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

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

ANNEX 7: ART ADHERENCE

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

Visit 1

1. Clinical assessment

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

Visit 2

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

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

However, these are suggested protocols but these need to be tailored according to patient profile as many patients who come from another city may find difficult to make many visits. Also, some patients have good understanding of ART & may not require three sessions.

Ongoing ART Adherence counseling

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

A typical follow-up counselling session involves:

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

ANNEX 8: DOSING OF SOLID AND LIQUID FORMULATIONS FOR TWICE-DAILY DOSING IN INFANTS AND CHILDREN 4 WEEKS OF AGE AND OLDER

Drug	Strength of tablets	Number of tablets by weight band morning and evening										Strength of adult tablet	Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
AZT/3TC	Tablet (dispersible) 60/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 /150 mg	1	1
AZT/3TC/ NVP[2]	Tablet (dispersible) 60/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 /150 /200 mg	1	1
ABC/3TC	Tablet (dispersible) 60/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600 /300 mg	0.5	0.5
ABC/3TC	Tablet (dispersible) 120/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600 /300 mg	0.5	0.5
ABC/3TC/ LPV/r	30/15/40/10 mg	2	2	3	3	4	4	5	5	6	6			
SOLID SINGLE FORMULATIONS														
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
NVP[2]	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200 mg	1	1
	Tablet 200 mg	–	–	–	–	0.5	0.5	1	0.5	1	0.5	200 mg	1	1
LPV/r[3]	Tablet 100/25 mg	–	–	–	–	2	1	2	2	2	2	100/25 mg	3	3
	Tablet 200/50 mg	–	–	–	–	–	–	1	1	1	1	200/50 mg	2	1
	Pellets[4] 40/10 mg	2	2	3	3	4	4	5	5	6	6			

RAL[6]	Chewable tablets 25 mg	–	–	–	–	3	3	4	4	6	6	400 mg	1	1
	Chewable tablets 100 mg	–	–	–	–	–	–	1	1	1.5	1.5	400 mg	1	1
	Granules (100 mg/sachet)	0.25	0.25	0.5	0.5	–	–	–	–	–	–		–	–
LIQUID SINGLE FORMULATIONS														
AZT	10 mg/ml	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	–	–	–	–	–	–	–
ABC	20 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	–	–	–	–	–	–	–
3TC [2]	10 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	–	–	–	–	–	–	–
NVP	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	–	–	–	–	–	–	–
LPV/r[3]	80/20 mg/ml	1 ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml	–	–	–
DRV[5]	100 mg/ml	–	–	–	–	2.5 ml	2.5 ml	3.5 ml	3.5 ml	–	–			

Notes

[1] For infants younger than 4 weeks of age refer to Table 10C for more accurate dosing information

[2] NVP dose escalation with half dose for 2 weeks when initiating ART is still recommended for infants > 2 weeks of age and not already on NVP prophylaxis to avoid toxicity from high initial NVP levels. HEI already on NVP prophylaxis who are confirmed positive can initiate full dose (twice daily) NVP without dose escalation

[3] LPV/r liquid requires a cold chain during transport and storage. The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. The adult 200/50 mg tablet could be used for patients 14-24.9kg (1 tab am and 1 tab pm) and for patients 25-34.9kg (2 tabs am and 1 tab pm). The 100/25 mg tablet is smaller than the adult formulation and may be used by children of lower weight bands able to swallow tablets.

[4] LPV/r pellets formulation should not be used in infants younger than 3 months and should not be used by children able to swallow tablets.

[5] DRV must be administered with 0.5 ml of RTV 80 mg/mL oral suspension if less than 15 kg and with RTV 50 mg solid formulation in children 15 to 30 kg

[6] RAL granules are approved for used in children as young as 4 weeks, however feasibility and acceptability of such formulations has not been widely investigated. Additional guidance will be provided as evidence becomes available. If this RAL must be used, consult the regional/national clinical support center

ANNEX 9: SIMPLIFIED DOSING OF CHILD-FRIENDLY SOLID AND ORAL LIQUID FORMULATIONS FOR ONCE-DAILY DOSING IN INFANTS AND CHILDREN 4 WEEKS OF AGE AND OLDER

Drug	Strength of tablet	Number of tablets or capsules by weight band once daily					Strength of adult tablet	Number of tablets or capsules by weight band once daily
		3–5.9 kg	**6–9.9 kg**	**10–13.9 kg**	**14–19.9 kg**	**20–24.9 kg**		**25–34.9 kg**
EFV 2	Tablet (scored) 200 mg	–	–	1	1.5	1.5	200 mg	2
ABC /3TC	Tablet (dispersible) 60/30 mg	2	3	4	5	6	600 mg/ 300 mg	1
ABC /3TC	Tablet (dispersible) 120/60 mg	1	1.5	2	2.5	3	600 mg/ 300 mg	1
ATV 3	Capsules 100 mg	–	–	1	2	2	300 mg	2 (100 mg) or 1 (300 mg)
TDF[4]	Oral powder 40 mg/scoop	–	–	3	–	–	300 mg	1 (200 mg) [d] or 1 (300 mg)
	Tablets 150 mg or 200 mg	–	–	–	1 (150)	1 (200)		

Notes [1]For infants younger than 4 weeks of age refer to Table 10C for more accurate dosing information

[2]EFV is not recommended for children younger than 3 years and weighing less than 10 kg. Where there are no suitable alternatives, EFV may be used in children less than 3 years weighing more than 3.5 kg (3.5-5 kg two 50 mg capsules; 5-7.5 kg three 50 mg capsules; 7.5-15 kg one 200 mg capsule). A pediatric triple FDC containing ABC/3TC/EFV (150/75/150 mg) will be available soon, which can replace the use of single and dual formulations where appropriate.

[3]ATV is only approved for use in children 3 months and older. ATV single strength capsules should be administered with RTV 100 mg for all weight bands. ATV powder formulation enables administration of ATV to infants and children as young as 3 months. Infants and children 5-10 kg should be given 200 mg of ATV powder (4 packets, 50 mg/ packet) with 80 mg of RTV oral solution (1 ml)

[4]TDF is can be used in children 2 years and older. Target dose: 8 mg/kg or 200 mg/m^2 (maximum 300 mg)

ANNEX 10: DRUG DOSING OF LIQUID FORMULATIONS FOR TWICE-DAILY DOSING IN INFANTS LESS THAN 4 WEEKS OF AGE

Drug	Strength of oral liquid	2-3 kg	3-4 kg	4-5 kg
AZT	10 mg/mL	1 mL	1.5 mL	2 mL
NVP[1]	10 mg/mL	1.5 mL	2 mL	3 mL
3TC	10 mg/mL	0.5 mL	0.8 mL	1 mL
LPV/r[2]	80/20 mg/mL	0.6 mL	0.8 mL	1 mL

Notes:

1 NVP for treatment can be initiated with twice daily dosing for infants < 2 weeks of age (they do not require once-daily lead-in dosing).

2 Do not use LPV/r solution in infants aged <2 weeks of age. LPV/r pellets should not be used in infants younger than 3 months.

ANNEX 11: SIMPLIFIED DOSING OF INH AND CTX PROPHYLAXIS FOR INFANTS AND CHILDREN WHO ARE AT LEAST 4 WEEKS OF AGE

Drug	Strength of tablet or oral liquid	Number of tablets or ml by weight band once daily					Strength of adult tablet	Number of tablets by weight band
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg		25–34.9 kg
INH	100 mg	0.5	1	1.5	2	2.5	300 mg	1
CTX	Suspension 200/40 per 5 ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	–	–
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	–	–
	Tablets (scored) 400/80 mg	–	0.5	0.5	1	1	400 mg/80 mg	2
	Tablets (scored) 800/160 mg	–	–	–	0.5	0.5	800 mg/ 160 mg	1

ANNEX 12: DRUG-DRUG INTERACTIONS: OVERLAPPING DRUG TOXICITY

Bone marrow suppression	Peripheral neuropathy	Pancreatitis	Nephrotoxicity	Hepatotoxicity	Rash	Diarrhoea	Ocular effects
Cotrimoxazole Dapsone Ganciclovir Pyrimethamine Zidovudine	Isoniazid Vincristine	Lamivudine (esp in children) Stavudine Cotrimoxazole Ritonavir Pentamidine	Aminoglycosides Amphotericin B Tenofovir	Atazanavir Atovaquone Cotrimoxazole Efavirenz Nevirapine	Abacavir Cotrimoxazole Dapsone Efavirenz Nevirapine Sulfadiazine	Clindamycin LPV/r Ritonavir	Ethambutol Voriconazole

ANNEX 13: DRUG-DRUG INTERACTIONS - NNRTIS

Drugs Affected	Nevirapine (NVP)	Efavirenz (EFV)
ANTIRETROVIRALS		
Dolutegravir	Co-administration not recommended because NVP decreases levels of DTG	Co-administration not recommended because EFV decreases levels of DTG. If must be used together then increase DTG to 50 mg BD when co-administered with EFV
Raltegravir	No interaction or not studied	Efavirenz decreases RAL plasma levels but it is unlikely to be clinically significant
Atazanavir/ritonavir	Co-administration not recommended because ATV/r may increase the serum concentration of NVP leading to increased risk of toxicity, and NVP decreases the serum concentration of ATV/r which may lead to resistance and treatment failure	Co-administration not recommended because EFV decreases the serum concentration of ATV/r which may lead to resistance and treatment failure
Lopinavir/ritonavir	Co-administration not recommended because NVP decreases levels of LPV/r	AVOID: this combination increased risk of prolonged-QT syndrome and sudden cardiac death

ANTI-MYCOBACTERIALS	Nevirapine (NVP)	Efavirenz (EFV)
Rifampicin	Levels of NVP ↓. Virologic consequences are uncertain; the potential for additive hepatotoxicity exists. Use of this combination is not recommended; however, if used, co administration should be done with careful monitoring	Levels of EFV ↓ Dose: Consider ↑ EFV to 800 mg QD
METHADONE	Levels: NVP unchanged. Methadone significantly ↓. Opiate withdrawal common when this combination is used. Increased methadone dose often necessary. Titrate methadone dose to effect	Levels: Methadone ↓ Opiate withdrawal common, increase methadone dose often necessary. Titrate methadone dose to effect

ANNEX 14: DRUG-DRUG INTERACTIONS – PIS

Drugs Affected	Atazanavir (ATV)	Darunavir (DRV)	Lopinavir (LPV)
EFV	Co-administration not recommended because EFV decreases the serum concentration of ATV/r which may lead to resistance and treatment failure	Co-administration not recommended because DRV/r may increase the serum concentration of EFV leading to increased risk of toxicity, and EFV decreases the serum concentration of DRV/r which may lead to resistance and treatment failure	AVOID: this combination increased risk of prolonged-QT syndrome and sudden cardiac death
ETR	No significant interaction	No significant interaction	No significant interaction
DTG	No significant interaction	No significant interaction	No significant interaction
RAL	ATV/r may increase RAL levels but interaction in not clinically significant	No significant interaction	No significant interaction
ANTI-MYCOBACTERIALS	**Atazanavir (ATV)**	**Darunavir (DRV)**	**Lopinavir (LPV)**
Rifampicin	↓ levels of Atazanavir	↓ levels of DRV	↓ levels of LPV
OTHER DRUG	**Atazanavir (ATV)**	**Darunavir (DRV)**	**Lopinavir (LPV)**
Methadone	No interaction with unboosted ATV Increased metabolism of methadone with boosted ATV	↓ levels of methadone	↑levels of Methadone. Opiate withdrawal may occur Monitor and titrate dose if needed. May require ↑ methadone dose

ANNEX 15: DRUG-DRUG INTERACTIONS – INSTIS

Drugs Affected	Dolutegravir (DTG)	Raltegravir (RAL)
Efavirenz	Co-administration not recommended because EFV decreases levels of DTG. If must be used together then increase DTG to 50 mg BD when co-administered with EFV.	Efavirenz decreases RAL plasma levels but it is unlikely to be clinically significant
Rifampicin	Increase DTG to 50 mg BD when co-administered with rifampicin (for children, use double the standard weight-based DTG dose). There is no known drug interaction between DTG and rifabutin.	Increase RAL to 800 mg BD when co-administered with rifampicin (for children, use double the standard weight- based RAL dose; there is no data to guide dose adjustment for children below 2 years of age). Rifabutin may alter RAL plasma levels but it is unlikely to be clinical significant.
Mineral supplements and antacids containing cations (e.g. calcium, iron, zinc, magnesium, aluminum), including prenatal vitamins	Administer DTG at least 2 hours before or 6 hours after taking any of these supplements (note: if taking DTG with a meal then it is safe to take at the same time as prenatal vitamins, calcium, or iron) There is no drug-drug interactions between DTG and proton pump inhibitors or H2 blockers used for gastritis.	Do not use calcium, magnesium and aluminum containing antacids with RAL.
Methadone	No interaction	No interaction

ANNEX 16: IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Immune Reconstitution Inflammatory Syndrome (IRIS)

Definition:

IRIS is a paradoxical inflammatory reaction against a foreign antigen (alive or dead) in patients who have started ART with reconstitution (improved functioning) of their immune system. The immune system, once it regains some function, is now able to respond against the foreign antigen.

Classification:

- **Unmasked IRIS:** appearance of a previously undiagnosed opportunistic infection (OI) following ART initiation (or switch of ART to a suppressive regimen)
- **Paradoxical IRIS:** worsening of a previously diagnosed disease after ART initiation (or switch of ART to a suppressive regimen)

Risk Factors for IRIS:

- 10-20% of patients who start ART with advanced immunosuppression (refer to section 3) experience clinical deterioration during the first few months due to IRIS
- High risk patients include:
    - Advanced immunosuppression (WHO Stage 3 or 4, or CD4 count ≤ 200 cell/mm3 (or CD4% ≤ 25% for children ≤ 5 years old))
    - Patients with a diagnosed opportunistic infection like TB, MAC, CMV, and PCP
    - Low baseline CD4 (CD4 count ≤ 50 cell/mm^3 or CD4% ≤ 10%)
    - High baseline viral load
    - Substantial increase is CD4 count and drop in viral load after starting ART

Diagnosis of IRIS

- IRIS should be suspected any time a patient has clinical deterioration weeks to months after starting ART (or switching to a suppressive ART regimen)
- Clinical deterioration usually occurs within 4-8 weeks of initiation or change of ART (but can be months afterwards)
- IRIS has varied clinical presentations due to multiple possible pathogens that the immune system may be reacting to, and various immune system reactions; there are generally clinical manifestations consistent with an inflammatory condition
- A high level of suspicion is required when making a diagnosis of IRIS, which is generally one of exclusion
- Rule out the possibility of drug reaction, patient non-adherence to OIs treatment, persistently active infection and/or drug resistance to OI treatment
- There could be localized tissue inflammation with or without systemic inflammatory response

Patient evaluation:

In addition to the clinical evaluation for PLHIV outlined in Table 3.1, emphasis should be placed on the following areas during the patient evaluation:

History:

Symptoms and current ARV history:

- Specific systemic symptomatology
- Date of ARV initiation
- Regimen

- Reason for substitution / switch from previous ART if not first line
- Adherence to ART and other ongoing treatment
- HIV viral load
- CD4 count

Prior History:	**History of treatment of opportunistic infections:**
• ARV toxicity • Drug-drug interaction • CD4 count • HIV viral load	• Date of initiation of treatment • Duration of therapy • Clinical response to treatment • Adherence to the OI treatment • Any default to treatment • Resistance to treatment

Physical examination:

Vital signs assessment: Temperature, Heart rate, Blood pressure, Respiratory rate
Conduct a detailed systemic examination: • Emphasis should be placed on the system(s) which are primarily affected.

Investigations:

- All patients with advanced HIV disease should be screened for common OIs including TB, cryptococcal meningitis and other common OIs depending of their presenting signs and symptoms

Major and Minor presentations of IRIS:

Major presentation	**Minor presentation**
Tuberculosis (TB) Mycobacterium avium complex (MAC) Cryptococcal meningitis Cytomegalovirus (CMV) retinitis Hepatitis B or C virus Progressive multifocal leukoencephalopathy (PML) Kaposi's sarcoma Cerebral toxoplasmosis Autoimmune diseases	Herpes simplex virus (HSV) and varicella zoster virus (VZV) Nonspecific dermatologic complications such as folliculitis and oral and genital warts

Management of IRIS

IRIS management is dependent on severity of symptoms and the following general guidance is recommended:

Severity of IRS	**Definition**	**Management**
Mild	• Resolves over	• Treat the OI and manage the associated symptoms

	time in most patients • Symptomatic treatment is often sufficient	• Treat IRIS-associated inflammation: o NSAIDS for discomfort associated with mild inflammation / fevers o Inhaled steroids for bronchospasm or cough associated with mild pulmonary inflammation	
Severe	• Threatens a patient's functional state • Cause permanent disability • Potentially lead to death Examples: • Decline in pulmonary capacity from TB or MAC infection • Neurologic complications from cryptococcal infection • Loss of vision from CMV retinitis infection	• Treat the OI and manage the associated symptoms • Manage the IRIS-associated inflammation: o If NOT cryptococcal meningitis or KS: give 1 to 2 mg/kg prednisone for 1 to 2 weeks. Follow with a period of individualized tapering of the dose o Do not use corticosteroids for the management of CM or KS- related IRIS • Closely monitor patients on corticosteroid therapy for: o Hyperglycemia o Hypertension o Mental status changes o Avascular necrosis o Worsening of an existing infection o Predisposition to a new infection (e.g. TB and CMV)	

ANNEX 17: ADDITIONAL GUIDANCE ON DRUG INTERACTION/TOXICITY

TDF RELATED RENAL TOXICITY

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

- Renal toxicity
- Decrease in Bone marrow density

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

Effect on glomerular function

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

Effect on tubular function

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

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

Effect on tubular secretion of creatinine

Serum creatinine is widely used to calculate CrCl/eGFR, however, in addition to glomerular filtration, about 10-40 % of creatinine clearance occurs by secretion across the PT epithelium. Decline in CrCl/eGFR within the first 2–3 months of commencing therapy, with very little further change over time, has been seen in many studies [13,14,22]. Therefore, given the pattern of CrCl/eGFR changes reported in patients taking TDF, it is plausible that they might be due to impaired PT creatinine secretion, rather than alterations in actual GFR. To explore this hypothesis, a recent small study of 19 HIV-infected patients, either remaining on zidovudine therapy or switching to TDF, looked in detail

at changes over time in actual GFR, calculated CrCl, and urine excretion of tubular [23]. In the patients switching to TDF, mean CrCl was significantly decreased, while urine excretion of tubular protein was significantly increased after 48 weeks; however, there was no corresponding change in actual GFR, and no changes in any of the three parameters were observed in the zidovudine group which helps to conclude that decrease in CrCl in the TDF patients was more likely to be due to impaired PT creatinine secretion rather than a change in glomerular function.

Guidance for treatment

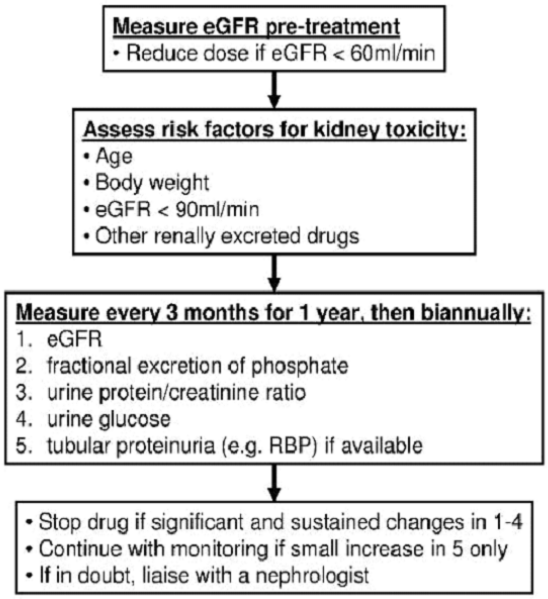
The main target of TDF toxicity is the proximal tubule and hence for the suspicion of Renal toxicity, the presence of tubular proteinuria is thought to be the most sensitive test for proximal tubule dysfunction. For monitoring the renal tubular dysfunction which often results in Fanconi Syndrome, the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

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

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

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

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



ATAZANAVIR INDUCED UNCONJUGATED HYPERBILIRUBINAEMIA

Background

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

Isolated unconjugated hyperbilirubinemia is the most common laboratory abnormality associated with the use of Atazanavir and this is not associated with hepatocellular injury. Although not considered a serious adverse effect, the higher levels of unconjugated hyperbilirubinemia associated with this drug can manifest as jaundice with a high colored urine. The onset of Atazanavir associated hyperbilirubinemia typically occurs within several months, and bilirubin levels generally peak within 4 months (range 1 to 8 months); the subsequent natural history on therapy is notable for a non-progressive course, with bilirubin levels remaining generally stable in patients on further follow-up. Routine monitoring of bilirubin is acceptable. An isolated elevation in total bilirubin should be confirmed as predominantly unconjugated by testing the indirect fraction of bilirubin. The presence of elevated conjugated bilirubin or changes in serum hepatic aminotransferases or alkaline phosphatase warrant further investigation for other causes of hyperbilirubinemia, such as other drug hepatotoxicity, viral hepatitis, alcoholic hepatitis or cholestasis. It is important to recognize that patients who are on Atazanavir but with acute hemolysis will also develop increased indirect bilirubin levels.

Management

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

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

In case of Hepatic insufficiency dosage adjustment is recommended. Child-Pugh Score is utilized to assess the severity and prognosis of chronic liver disease and to identify patients who require liver transplantation. This score is to be used only in those HIV infected subjects who have concomitant chronic liver disease e.g. chronic hepatitis B & C, alcoholic liver disease, NASH and other chronic liver diseases. ATV/r (300/100 mg) can only be used in patients with chronic liver disease in Child Pugh Class A. It should not be used on second line patients with Child Pugh Class B or C. Please refer the following tables for the scores and classifications.

Important consideration in pregnancy

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

Counseling issues:

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

Annex 18: ARV, CTX and Fluconazole Adjustments in Renal and Hepatic Impairment[1]

Drug	CrCl (ml/min)		Haemodialysis	Liver impairment
	10-50	<10		
ABC	No change			Reduce adult dose to 200 mg BD for moderate to severe liver impairment. AVOID in severe hepatic impairment
AZT	No change	300 mg/day	300 mg/day	Reduce dose by 50% or double interval of administration in moderate to severe impairment
TDF[2]	AVOID	AVOID	300 mg every 7 days	No change
3TC	150 mg OD	50 mg OD	50 mg first dose, then 25 mg daily	No change
LPV	No change			No change, use with caution in moderate to severe impairment
RTV				
ATV				
DRV				
RAL	No change			No change in mild to moderate impairment. Use with caution in severe impairment
DTG				
EFV	No change			Use with caution in mild to moderate liver impairment, avoid in severe impairment
NVP	No change			AVOID
ETV	No change			Use with caution in severe liver impairment
CTX	If CrCl > 30 ml/min then no dose adjustment required; if 15-30 ml/min then use 50% of normal recommended dose; if CrCl < 15 ml/min then CTX should be avoided			Use with caution in mild to moderate liver impairment, avoid in severe impairment
Fluconazole	If CrCl ≤ 50 ml/min then use 50% of normal recommended dose (no dose adjustment required for CrCl > 50 ml/min)			Use with caution

1 Patients with evidence of renal or hepatic impairment should have access to regular monitoring of renal and liver function

2 TDF and renal impairment:

- In acute kidney injury (AKI), interrupt TDF administration until the cause of AKI is established and corrected. Patients with baseline CrCl of ≤ 50 mL/min should not be initiated on TDF; patients who develop renal impairment (CrCL ≤ 50 mL/min) while on TDF should be switched to an alternate ARV (preferably ABC). For patients with HBV co-infection, the benefit of TDF for treating HBV often outweighs the risks of renal impairment, so more severe levels of renal impairment are tolerated. See Table 5.4 for TDF dose adjustments for patients with HBV/HIV co-infection. These patients should be managed in consultation with an experienced clinician

Notes on common adverse effects of ARV drugs

1. Lactic acidosis is a physiological condition characterized by low pH in body tissues and blood (acidosis) accompanied by the buildup of lactate and is considered a distinct form of metabolic acidosis. The condition typically occurs when cells become hypoxic, for example during vigorous exercise. In this situation, impaired cellular respiration leads to lower pH levels. Simultaneously, cells are forced to metabolize glucose anaerobically, which leads to lactate formation. Therefore, elevated lactate is indicative of tissue hypoxia, hypoperfusion, and possible damage. Lactic acid lactic acidosis includes rapid breathing, drowsiness, fast/irregular heartbeat, unusual weakness, feeling cold especially in the arms/legs etc.

2. Renal insufficiency described as a decrease in the glomerular filtration rate. is typically detected by an elevated serum creatinine level. In case of elevated creatinine need to calculate creatinine clearance in using CG formula and adjust dosage of drugs accordingly

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

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

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

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

Bibliography:

1. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019 (WHO/CDS/HIV/19.15). Licence: CC BY-NC-SA 3.0 IGO.
2. Policy brief on HIV treatment- An interim guidance. UPDATED RECOMMENDATIONS ON FIRST-LINE AND SECOND-LINE ANTIRETROVIRAL REGIMENS AND POST-EXPOSURE PROPHYLAXIS AND RECOMMENDATIONS ON EARLY INFANT DIAGNOSIS OF HIV- JULY 2018, World Health Organization
3. Ministry of Health, National AIDS & STI Control Program. Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya 2018 Edition. Nairobi, Kenya: NASCOP, August 2018.
4. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Clinical guidelines: Antiretroviral Therapy 2017, World Health Organization
5. Consolidated Guidelines on the Use of Anti retroviral Drugs for Treating and Preventing HIV infection, recommendations for public health approach, June 2013, World Health Organization Updated version 2015
6. National guidelines for PMTCT HIV and congenital Syphilis 2013, NASP, Directorate General of Health Services, Ministry of Health and Family Welfare, Dhaka, Bangladesh
7. 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 updated on 2015
8. Antiretroviral therapy guidelines for HIV infected adults and adolescents, NACO, Ministry of Health and Family Welfare, government of India, 2013
9. Operational guidelines for ART services, NACO, Ministry of Health and Family Welfare, government of India, 2012 Anti retroviral therapy for HIV infections in adults and adolescents, recommendations for public health approach, 2010 revision, World health Organization, 2010

10. Antiretroviral drugs for treating pregnant women and preventing, HIV infections in infants, recommendations for a public health approach, 2010 version, World Health Organization, 2010
11. Antiretroviral therapy for HIV Infections in infants and Children : Towards universal Access, recommendations for a public health approach , 2010 revision, World Health organization, 2010
12. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Department of Health and Human Services. January 10, 2011
13. 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
14. Antiretroviral therapy guidelines for HIV infected adults and adolescents including post-exposure prophylaxis, NACO, Ministry of Health and Family Welfare, government of India, 2007
15. National ART Guidelines, National Center for AIDS and STD Control, Nepal , 2009 (Unpublished)