ZAMBIA CONSOLIDATED GUIDELINES

for Prevention and Treatment of HIV Infection

2018

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Republic of Zambia
Ministry of Health

Zambia Consolidated Guidelines

for Treatment and Prevention of HIV Infection

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ACRONYMS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
AFB	Acid Fast Bacilli
ANC	Antenatal Care
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate Aminotransferase
ATC	Advanced Treatment Centre
ATT	Anti-Tuberculosis Treatment
ATV	Atazanavir
AZT	Azidothymidine (Also Known as Zidovudine, or ZDV)
Bdq	Bedaquiline
BID	Twice Daily
BMI	Body Mass Index
cART	Combination Antiretroviral Therapy
CD4	T-Lymphocyte Bearing CD4 Receptor
CD4 %	CD4 Percentage
CDC	Centers For Disease Control and Prevention
Cfz	Clofazimine
CNS	Central Nervous System
CPT	Co-Trimoxazole Preventive Therapy
Cm	Capreomycin
CRAG	Cryptococcal Antigen
CrCl	Creatinine Clearance
CTX	Co-Trimoxazole
Cs	Cycloserine
CSF	Cerebrospinal Fluid
d4T	Stavudine
DBS	Dried Blood Spot
Dlm	Delemanid
DMPA	Depot Medroxyprogesterone Acetate
DNA	Deoxyribonucleic Acid
DOTS	Directly Observed Therapy, Short Course
DRS	Drug Resistance Surveillance
FQ	Fluoroquinolone
H	Isoniazid
H^{HD}	Isoniazid High Dose
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HTS	HIV Testing Services
Km	Kanamycin
Lfx	Levofloxacin
INH	Isoniazid
INSTIs	Integrase Strand Transfer Inhibitors
IPT	Isoniazid Preventive Therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
L&D	Labour and Delivery
LEEP	Loop Electrosurgical Excision Procedure
LPV	Lopinavir
MDR TB	Multidrug – Resistant Tuberculosis
MNCH	Maternal, Newborn, and Child Health
MOH	Ministry of Health
MTCT	Mother-to-Child Transmission (of HIV)
NAT	Nucleic Acid Test
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NUPN	National Unique Patient Number
NVP	Nevirapine
OD	Once Daily
OI	Opportunistic Infection
Ofx	Ofloxacin
PAS	Para – Aminosalicyclic Acid
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PHDP	Positive Health Dignity and Prevention
PI	Protease Inhibitor
PLHIV	People Living With HIV
PO	Per os (Orally)
PNC	Postnatal Care

DR TB	Drug Resistant Tuberculosis
DRV	Darunavir
DST	Drug Susceptibility Testing
DTG	Dolutegravir
E	Ethambutol
EFV	Efavirenz
EMTCT	Elimination of Mother-to-Child Transmission (of HIV)
EPI	Expanded Program for Immunization
ETR	Etravirine
ETV	Entecavir
FDC	Fixed-Dose Combination
FP	Family Planning
FTC	Emtricitabine
GRZ	Government of Republic of Zambia
Hb	Haemoglobin
HBeAg	Hepatitis B E-Antigen
HBsAg	Hepatitis B Virus Surface Antigen
HBV	Hepatitis B Virus
HCW	Health Care Worker
PrEP	Pre-Exposure Prophylaxis
R	Rifampicin
RR	Rifampicin Resistance
-r	Ritonavir (Low-Dose)
RNA	Ribonucleic Acid
R	Rifampicin
RAL	Raltegravir
sd-NVP	Single-Dose Nevirapine
TAF	Tenofovir Alafenamide
FBC	Full Blood Count
TAT	Toxoplasmosis Antigen Test
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
UNAIDS	Joint United Nations Programme on HIV/ AIDS
UNICEF	United Nations Children's Fund
VIA	Visual Inspection with Acetic Acid
XDR - TB	Extensively Drug – Resistant Tuberculosis
XTC	Lamivudine or Emtricitabine
FTC	Emtricitabine
Z	Pyrazinamide

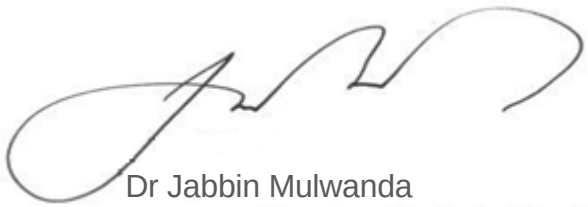
FOREWORD

With this publication, the Ministry of Health issues the first guidelines on universal routine HIV testing, counselling and treatment, HIV self testing and use of better tolerated drugs such as Dolutegravir, Efavirenz-400mg and Tenofovir alafenamide. These ambitious guidelines have followed the recent trends and global approach of fast-tracking towards HIV epidemic control. This will be achieved through, counselling leading to more individuals being tested, implementation of the universal routine HIV testing, improved linkage to care and retention through adoption of the decentralised service delivery models and better tolerated regimens leading to increased HIV treatment coverage and better virological outcomes with virological suppression and eventual reduction in new HIV infections.

A key way to accelerate progress towards HIV epidemic control is to test all consenting individuals, initiate therapy the same day an individual is tested HIV positive, as recommended in these guidelines. This will bring the dual advantage of keeping people healthier longer and reducing the risk of virus transmission to others. These guidelines have also defined individuals at high risk of acquiring HIV and providing those who test HIV negative within these high risk categories with pre exposure prophylaxis (PrEP).

These new guidelines will therefore provide a reference tool to health care providers and support staff on the new trends that do reflect the changes in the diagnosis, care and management of all people living with HIV in Zambia.

The Ministry of Health expects implementation of these guidelines to help fast-track towards HIV epidemic control. I therefore call on all health care workers to take advantage of these new guidelines to accelerate scale up of HIV prevention, treatment and care services to all people living with HIV.



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INTRODUCTION

In July 2017, the World Health Organization released the technical update on transitioning to new antiretroviral drugs and guidelines on managing advanced HIV disease. This version of the Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection provides simplified guidance on a country transition plan, the continued approach that positively affects the continuum of HIV care, while adding to innovative methods that will reduce transmission rates and increase life span for those on treatment. This is all to further accelerate efforts to meet the ambitious Fast-Track target for 2020, including achieving major reductions in the number of people dying from HIV-related causes and the 90–90–90 treatment target: *ensuring that 90% of the people living with HIV know their HIV status; 90% of the people living with HIV who know their HIV status are accessing treatment; and 90% of people living with HIV who are receiving treatment have suppressed viral load*.

Besides the recommendation to provide lifelong cART to all HIV infected populations, regardless of CD4 cell count these guidelines present several new recommendations, including universal routine HIV testing, counselling and treatment in all public and private health facilities in Zambia. The approach of offering Universal Routine HIV Testing gives a window to provide immediate treatment and care to all HIV infected individuals through the "test and treat" strategy. This will accelerate our strides towards HIV epidemic control. Additionally, these guidelines provide the use of better and safer antiretroviral agents such as Dolutegravir, Tenofovir alafenamide, and Efavirenz-400mg and how to transition patients who are on the older regimens.

Our 2016 guidelines have also adopted the recommendations to offer PrEP to selected people at substantial risk of acquiring HIV. Alternative treatment regimens are recommended, including an integrase inhibitor as an option in resource-limited settings and reduced dosage of a key recommended first-line drug. Importantly, there has been introduction of Raltegravir, an integrase inhibitor, as a part of the second-line regimen for children failing Lopinavir-ritonavir-based first-line therapy. These guidelines also highlight the management of patients failing second-line cART with third-line cART, who should be managed at higher-level health facilities called Advanced Treatment Centres (ATCs). All of the recommendations have been adopted because of their anticipated public health effect.

Several significant recommendations from the previous guidelines remain a priority, namely providing lifelong cART regardless of CD4 cell count to all pregnant and breastfeeding women and moving toward viral load testing as the preferred means of monitoring people on cART. Newer developments aim to complement and improve the service delivery of HIV services to our population. Importantly, in the guidance WHO emphasizes the need for differentiated approaches to care for people who are stable on cART, such as reducing the frequency of clinic visits and community ART distribution. Such efficiencies are essential if countries with a high burden of HIV infection are to manage their growing numbers of people receiving cART and reduce the burden on people receiving treatment and on health facilities.

There will be continued concerted efforts required toward implementing these guidelines at district and health facility levels; the 2016 Consolidated Guidelines represent an important step toward achieving the goal of universal access to ARV drugs, treating and preventing HIV, and ultimately ending the HIV epidemic by 2030.

HIV TESTING SERVICES

Recommendations

- **Universal Routine HIV Testing and Linkage to Services**
- **HIV Self-testing for increased access to testing Services**
- **Partner Notification Services and HIV Self Testing (HIV-ST) to complement conventional testing**
- **POC Technologies for early diagnosis of HIV-infected infants and children**

HIV Testing Services (HTS) refers to the full range of services that should be provided with HIV testing, including counseling (pre-test information and post-test counseling). HTS is a gateway to appropriate HIV prevention, treatment, and care, and other clinical services; and coordination with laboratory services to support quality assurance (QA) and the delivery of accurate results.

HTS is primarily conducted by healthcare workers as well as trained, certified and supervised lay providers that can conduct safe and effective HIV testing using recommended test kits.

HTS should be done at all service delivery points (see Table 1) within the facility, as well as in the community, as an efficient and effective way to identify people with HIV, bearing in mind the priority and key populations. Community-based testing embraces a family-centered approach based on the index-patient model and leads to early diagnosis of HIV infection and prompt linkage to care and treatment. Every individual in the index-patient's home and network, regardless of age and risk factors, should be tested with a serological test (also known as antibody test or rapid test), or given an opportunity to self-test (see Figure 1). All individuals testing negative should re-test after 3 months to account for the window period.

UNIVERSAL ROUTINE HIV TESTING

Universal Routine HIV Testing gives an opportunity to provide immediate treatment and care to all HIV infected individuals through the "test and treat" strategy without using CD4 as eligibility criteria for HIV treatment.

Health care workers are therefore mandated to offer routine HIV testing to all individuals presenting to health facilities (in the inpatient department, routine testing should be extended to the caregivers). Routine HIV testing should be offered with the following considerations:

- Provide information in a confidential manner - those who opt out should continue to be counseled and offered an HIV test at each interaction with health care providers, including the opportunity to self-test
- Provide counselling on benefits of HIV testing and other services available for HIV negative and positive individuals
- Provide correct results following the HIV testing algorithms
- Provide linkage or connection to preventive and treatment and care services by issuance of a National Unique Patient Number (NUPN), regardless of test result.

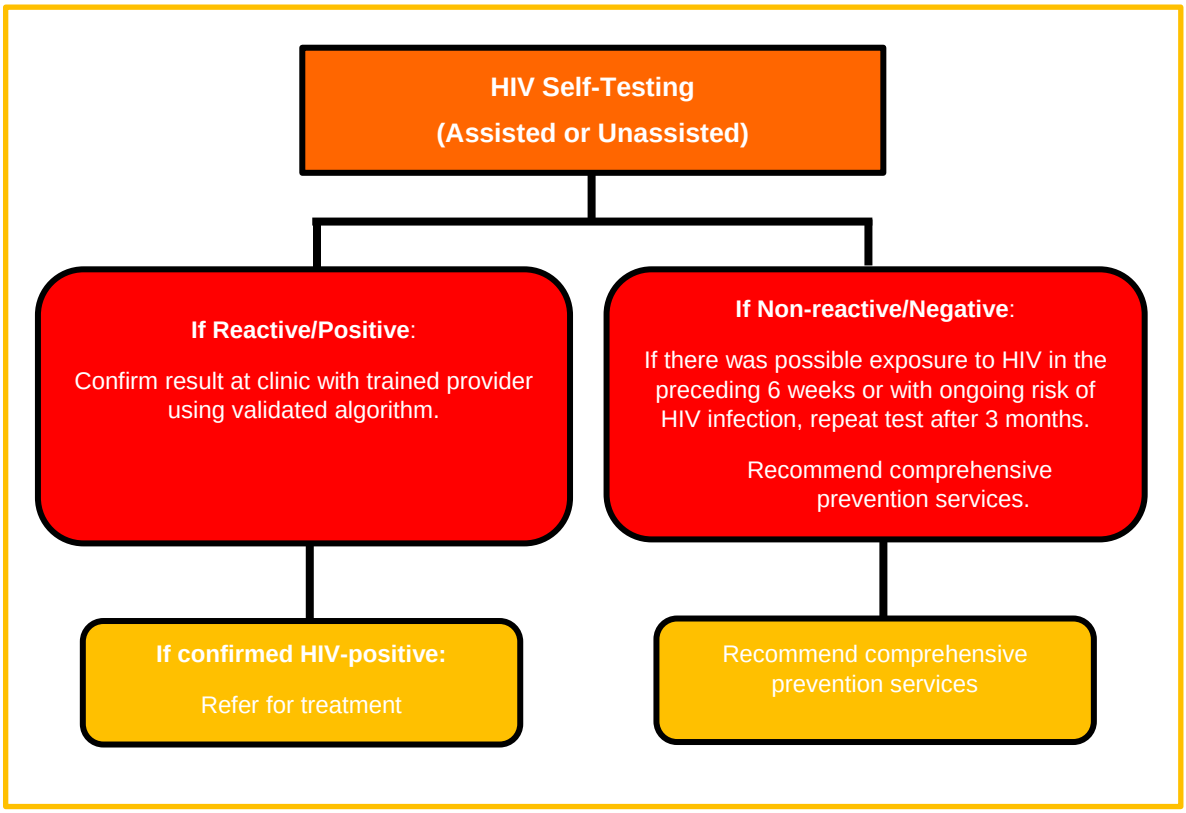
Therefore, *Universal Routine HIV testing*, counselling and treatment should be implemented in all health facilities (public and private) to all without discrimination.

HIV Self-Testing (HIV-ST)

HIVST is a process in which a person collects their own oral fluid or blood and then performs an HIV rapid test and interprets the result. An HIV self-test is a screening test which requires further testing and confirmation for any reactive result. Health care providers should ensure that users receive clear information on:

- How to perform the test and interpret the result correctly
- Where to access HTS and further support services
- How to safely dispose of the used test-kits
- The ethical and legal obligations (no one should test a third party without their consent)

Figure 1: HIV Self Testing Algorithm



PARTNER NOTIFICATION SERVICES THROUGH INDEX CLIENTS

HIV Partner notification is a voluntary process where trained health providers (including lay providers) ask index clients (people diagnosed HIV positive) about their sexual or drug injecting partners (including children under 12 years) and with the consent of the HIV positive client to offer HIV testing to these partners/children who may have been exposed to HIV within the past 12 months.

Partner notification is provided using passive or assisted approaches. (It is recommended to use the best approach for each index client at that time).

Passive HIV partner notification services is where HIV positive clients are encouraged by health care providers to disclose their status to their sexual/drug injecting partners by themselves, and to suggest HTS to the partner(s) given their potential exposure to HIV infection. Being at the discretion of the index client to encourage their contacts to test, this approach is less effective.

Assisted HIV partner notification services is where consenting HIV positive clients are assisted by health care providers to disclose their status or to anonymously notify their sexual/drug injecting partner(s) of their potential exposure to HIV infection. The provider then offers testing to these partner(s).

Assisted partner notification is done using provider contract or dual referral approaches.

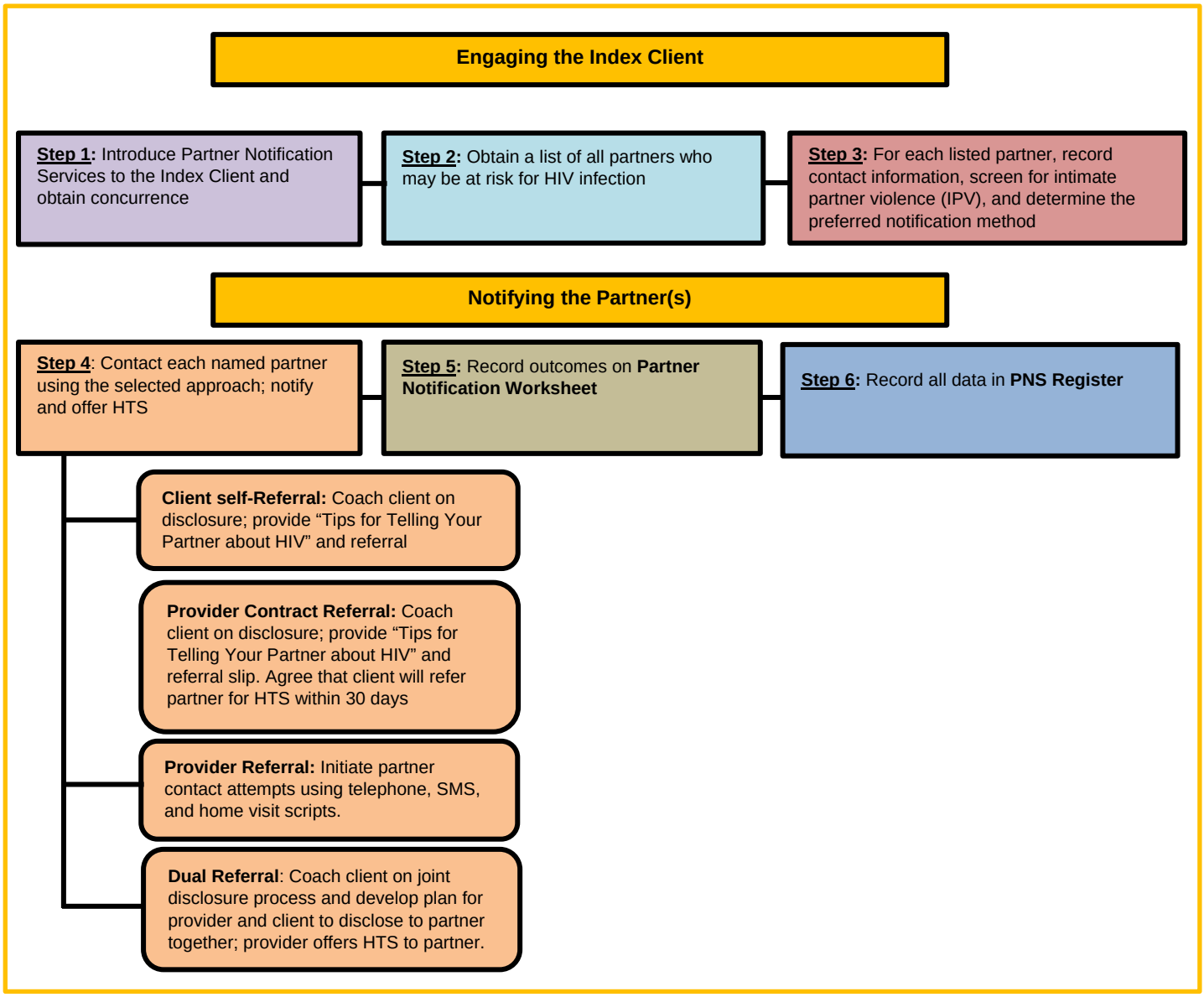
Provider contract is where HIV positive clients enter into a contract with a trained provider and agree to disclose their status (and the potential HIV exposure to their partners) by themselves and to refer their partner(s) to HTS within a specific time period. If the partner(s) of the HIV-positive individual do not access HTS or contact the health provider within that period, then the provider will contact the partner(s) directly and offer voluntary HTS.

Provider referral is when the health care provider confidentially contacts the person's partner(s) directly and offers the partner(s) voluntary HTS.

Dual referral is when a health care provider accompanies and provides support to HIV positive clients when they disclose their status and the potential exposure to HIV infection to their partner(s). The provider also offers HTS to the partner(s).

In partner and family-based index testing, it is critically important to ensure that sexual partners and children under the age of 12 years also offered an opportunity to test for HIV.

FIGURE 2: PARTNER NOTIFICATION SERVICES ALGORITHM



EARLY INFANT DIAGNOSIS

For children <24 months old who are breastfeeding, the mother should be tested first. If she is HIV-positive, perform a Nucleic Acid Test (NAT) which can be done using either a **Dried Blood Spot- DBS (by being sent to a central testing lab) or a Point-of-care machine (POC)** on the HIV-exposed infant (HEI), regardless of age. The advantage of new POC technologies is that they are done at the point of service delivery and offer same-day results. Infants who have HIV detectable by NAT at birth are likely infected in utero, will progress to disease rapidly, and, in the absence of treatment, will experience high mortality in the first few months of life. Infants infected at or around delivery may not have virus detectable by NAT for several days to weeks. The ability of NAT to detect the virus in the blood may be affected by ARV drugs taken by the mother or infant for postnatal prophylaxis, resulting in false-negative results. This includes drugs present in breast milk as a result of maternal ART during breastfeeding.

The rationale behind this recommendation is that infants who are first identified as HIV-exposed postpartum have a high cumulative risk of already having acquired HIV by the time prophylaxis is initiated; thus NAT should be performed around the time of initiating prophylaxis, which would be at birth. This will help to minimize the risk of development of resistance because of extended prophylaxis in infected infants and help to promote linkage to timely initiation of cART.

LINKAGE TO HIV TREATMENT AND SUPPORT SERVICES

Linkage to care is a process of actions and activities that support people testing for HIV and those diagnosed with HIV to engage with prevention, treatment, and care services as appropriate for their HIV status. Linkage to care and treatment is the period beginning with HIV diagnosis and ends when a person enters into HIV care and/ or initiates cART.

For clients who test HIV negative, it is necessary to link them to prevention services including condoms, VMMC, PrEP, and others depending on their individual risk factors. Linkage to treatment is a vital bridge between the first 90 (diagnosis) and the second 90 (treatment initiation).

QUALITY ASSURANCE/IMPROVEMENT

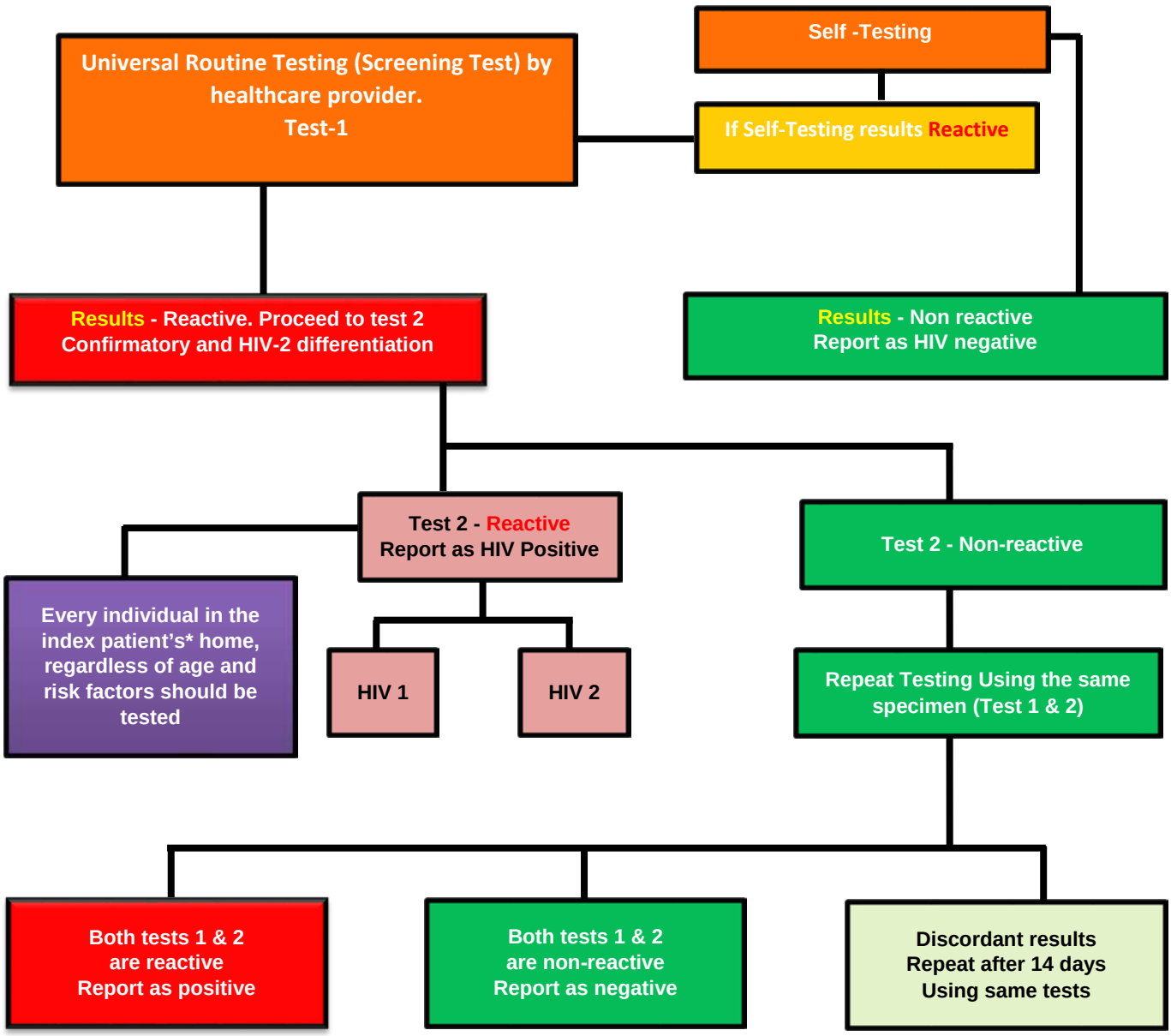
All testing sites should participate in HIV proficiency testing at least twice per year. If testing is performed in the community by community health workers, every 10th sample (10%) should be retested at the nearest health facility.

TABLE 1: TIMING OF HIV TESTING SERVICES FOR SPECIFIC POPULATIONS

Specific populations	Whom to test	When to test	HIV testing
Pregnant women, breastfeeding women (and their sexual partners)	All	During antenatal care (ANC): at first ANC visit and repeat test every 3 months if negative In labour and delivery (L&D): test if last test >6 weeks ago During postnatal care (PNC): test at first contact if unknown status. Serologic test at 6 weeks if negative. If breastfeeding: repeat test every 3 months if negative until cessation of breastfeeding Partner testing: same time points	Serologic test
(0 to <10 years old)	Well, never-breastfed HIV Exposed Infant (HEI)	At birth/first week of life or at first contact	NAT*
		6 weeks old	
		18 months old	Serologic test
	Well, breastfed HEI	At birth/first week of life or at first contact	NAT*
		6 weeks old	
		6 months old	
		9 months old	Serologic test. If positive, follow with NAT. If negative, follow up with serologic test at 18 months
		12 months old	Serologic test, if positive, follow with NAT. If negative, follow up with serologic test at 18 months
		18 months old	Serologic test; if positive, follow up with NAT
		24 months old	Serologic test, if positive, follow up with NAT
	Infant or child who has completely stopped breastfeeding	≥6 weeks after breastfeeding cessation	Serologic test; if positive, follow up with NAT
		≥18 months old	Serologic test
	Asymptomatic infant with unknown HIV exposure	At first contact	Maternal serologic test and/or infant serologic test; follow with NAT for positive serologic child <18 months old
	Infant or child symptomatic for HIV infection	Immediately regardless of age	Serologic test; follow with NAT for positive serologic child <18 months old
	Positive serologic child <18 months old	At first contact	NAT
	All infants and children with unknown HIV status admitted for inpatient care, attending malnutrition clinic, outpatient care or immunization clinics	Routine HIV testing	Age-appropriate tests
Adolescents (10 – 19 years) and adults	All sexually active persons with their partners and any person of unknown HIV status	At first contact, 3 months if negative and every 6 months	Serologic test

* **Where there is no POC NAT a DBS should be sent for HIV PCR.** Where NAT is positive, a repeat test should be done to rule out false-positive results. cART should be initiated without waiting for the receipt of the second test result because of the high risk of mortality with in utero infection; if the second specimen tests negative, a third NAT should be performed before interrupting cART. Although plasma remains the gold standard sample for NAT, DBS will be the preferred mode of sample transportation for both DNA and RNA testing

FIGURE 3: HIV SEROLOGIC TESTING ALGORITHM



- HIV testing for those <18 months, NAT is gold standard. Although plasma remains the gold standard sample for NAT, DBS will be the preferred mode of sample transportation for both DNA and RNA testing
- Index patient refers to the client being tested and identified HIV positive, whether child, adolescent or adult
- Determine is used as a screening test and Bioline as confirmatory test (discriminates between HIV-1 and HIV-2)

Summary/Key Points

- HIV testing services (HTS) include HIV testing, pre-test information, post-test counselling, linkage to appropriate HIV prevention, treatment, care, other clinical services, and coordination with laboratory services to support quality assurance (QA) and delivery of accurate results.
- HTS should be done at all service delivery points within the facility, as well as in the community, as an efficient and effective way to identify people with HIV.
- HIV testing is the gateway to HIV prevention, treatment, care, and other support and clinical services, and Universal Routine HIV Testing, Counselling and Treatment (HTCT) should be offered to all clients and in all service points.
- HIV testing is primarily conducted by health care workers. Lay providers who are trained, certified by MOH, and supervised can conduct safe and effective HIV testing using recommended diagnostic tests.
- All mothers of breastfeeding children <24 months old should be tested. If she tests HIV positive, a Nucleic Acid Test (NAT) should be performed on the HIV-exposed infant (HEI), regardless of age.
- Where NAT is positive, a repeat test should be done to rule out false-positive results at 18months with serological test. cART should be initiated without waiting for the receipt of the second test result because of the high risk of mortality with in utero infection; if the second specimen tests negative, a third NAT should be performed before interrupting cART.
- Where NAT is negative, a repeat test should be done at 6 weeks, 6months, 9months, 12 months and serological tests at 18 and 24 months if the HEI infant is being breast fed.
- Community-based testing embraces a family-centred approach based on the index-patient model and leads to early diagnosis of HIV infection and prompt linkage to care and treatment.

Recommendations

- **PrEP to be used as preventive measure of HIV transmission in key populations**
- **ARVs used for oral PrEP and PEP**
- **Adherence and treatment support for those on PrEP**

PRE-EXPOSURE PROPHYLAXIS (PREP)

Pre-exposure prophylaxis, or PrEP, is when people at high risk for HIV take two HIV medicines daily to lower chances of getting infected. When someone is exposed to HIV through sex or injection drug use, these medicines can work to keep the virus from establishing a permanent infection.

PrEP involves the use of antiretroviral (ARV) drugs before HIV exposure by people who are not infected with HIV to block the acquisition of HIV. Twelve trials on the effectiveness of oral PrEP have been conducted among serodiscordant couples, heterosexual men, women, men who have sex with men, people who inject drugs, transgender men and women. Where adherence has been high, significant levels of efficacy have been achieved, showing the value of this intervention as part of combination prevention approaches. WHO recommends oral PrEP containing Tenofovir (TDF) with either Emtricitabine (FTC) or Lamivudine (3TC) to be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches.

Considerations for PrEP

- The combination of TDF+XTC (Emtricitabine or Lamivudine) is active against Hepatitis B infection thus discontinuation of TDF+XTC requires close monitoring in those infected with Hepatitis B due to the concern for rebound viremia.
- Persons with osteopenia/osteomalacia/osteoporosis may be at risk of bone loss associated with TDF.
- PrEP efficacy has not yet been established in pregnancy and breastfeeding, therefore its use in this population is NOT recommended.
- TDF should not be co-administered with other nephrotoxic drugs, e.g. aminoglycosides.
- Standard TB medication does not interact with PrEP drugs and there is no need for dose adjustments.
- Clients on MDR-TB medications may have increased risk of renal side effects. PrEP should therefore be avoided.
- Other prevention methods should be recommended and PrEP screening should be delayed until the end of MDR-treatment.
- Standard hormonal contraception does not affect PrEP effectiveness, nor does PrEP affect contraceptive effectiveness.
- PrEP clients must be routinely tested for HIV infection, and cART offered immediately if the PrEP user seroconverts.
- PrEP is not 100% effective at preventing HIV and clients need to be counselled that they should use other prevention methods as well.

Eligibility Criteria

- No suspicion of acute HIV infection
- Test HIV negative at health facility
- Interested in PrEP and willing to be adherent
- Able to attend regular 3 month reviews and HIV testing
- Able to concomitantly apply other prevention methods such as barriers to prevent the transmission of other STIs
- Willing to stop taking PrEP when no longer eligible

And: at substantial risk for HIV infection, defined as engaging in one or more of the following activities within the last six months:

- Vaginal/anal intercourse without condoms with more than one partner
- Sexually active with a partner who is known to be HIV positive or at substantial risk of being HIV positive
- Sexually active with an HIV-positive partner who is not on effective treatment (defined as on cART for > 6 months and virally suppressed)
- History of STI
- History of PEP use
- Sharing injection material or equipment

PrEP may also be considered for key populations (as defined by the 2017 NASF) or by persons self-selected as high-risk for HIV acquisition. Such persons should meet the eligibility criteria above.

Recommendations

- PrEP should be taken for a minimum of 7 days in men, 21 days in women to achieve maximal protection from HIV acquisition before engaging in high risk sexual exposure and must be continued as long as risky exposure persists or one remains negative

HIV testing is required before PrEP is offered

- Repeat HIV testing every 3 months is mandatory while a client is on PrEP
- The frequent HIV testing during PrEP use should also ideally become an opportunity for STI screening and management.
- Those who seroconvert while on PrEP should be immediately switched to a standard first line regimen
- PrEP should be provided as part of the combination prevention package (condom use, HTS, family planning, STI screening, etc.)

Lab Tests before PrEP

- HIV test (only HIV-negative partners should be on PrEP)
- Creatinine (or urinalysis if creatinine not available)
- ALT
- RPR/RST
- Repeat HIV testing is recommended while PrEP is taken every three months
- Hepatitis B (those with positive results should be on lifelong TDF+XTC to treat HBV)

ARV regimen to be used for oral PrEP

- Tenofovir in combination with Emtricitabine (TDF+FTC) is preferred for PrEP
- However, if Emtricitabine is not available, Lamivudine in combination with Tenofovir (TDF+3TC) may be used for PrEP

Lab Monitoring while on PrEP

- Creatinine at 1 month, 2 months, every 3 months for first 12 months then annually thereafter
- ALT every 3 months for first 12 months then annually thereafter

TABLE 2: PREP FOLLOW-UP

Activity	Timing of Visit
Confirmation of HIV-negative status	Initial visit, month 1, and then every 3 months
Adherence Counseling	Every visit
Side effects	Every visit
Creatinine Clearance Test	Initial visit, month 1, then every 3 months for the first year, then annually
ALT	Every 3 months for first year, then annually
STI Screening	Every visit
PrEP Drug Dispensation	Initial visit, month 1, and then every 3 months
Behavioral sexual risk reduction counseling	Every visit

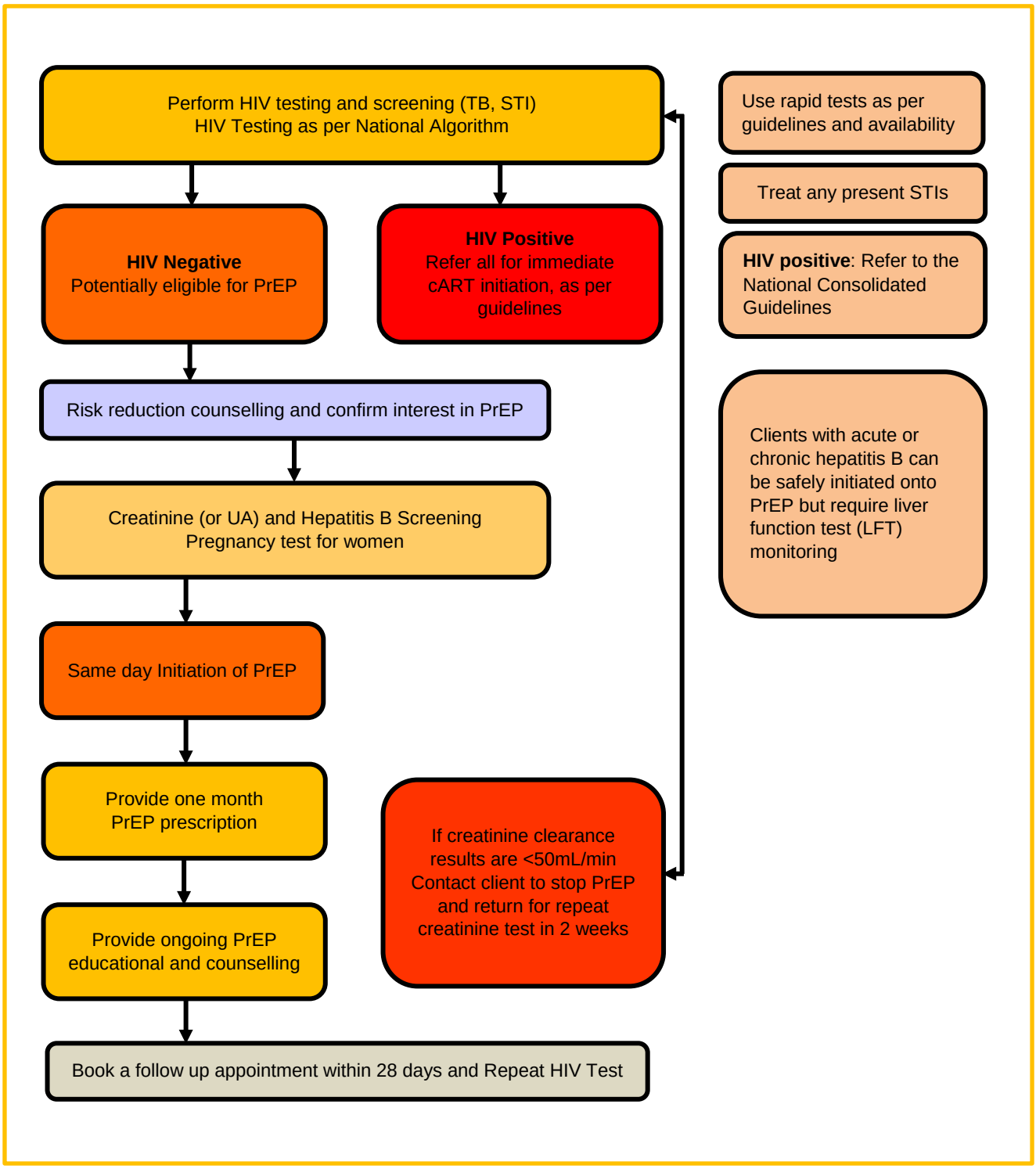
Adherence Support on PrEP

- Support for adherence should include information that PrEP is highly effective when used with strict adherence.
- PrEP users should be advised that **PrEP only becomes effective after 7 days (21 days in women)** and must be continued as long as risky exposure persists or one remains negative.
- Brief client-centred counseling that links daily medication use with a daily habit (such as waking up, going to sleep, or a regular meal) may be helpful.
- Special programmes to facilitate adherence among particular groups—such as young people and women—may be needed.
- Support groups for PrEP users, including social media groups (for example, https://www.facebook.com/groups/PrEPFacts) may be helpful for peer-to-peer sharing of experience and challenges.
- People who start PrEP may report side effects in the first few weeks of use. These side effects include nausea, abdominal cramping, or headache, are typically mild and self-limited, and do not require discontinuation of PrEP. People starting PrEP who are advised of this start-up syndrome may be more adherent.

When to Stop PrEP

- PrEP can be discontinued if a person taking PrEP is no longer at risk and when this situation is likely to be sustained (i.e., no longer engaging in any high-risk behaviors as defined above).
- PrEP can be discontinued after 4 weeks of elimination of the risk exposure.
- Significant side effects or if the creatinine clearance decreases to <50mL/min.
- If in a serodiscordant relationship, the HIV positive partner has been on cART for more than 6 months, is known to be virally suppressed, and there are not other partners, then the HIV negative partner on PrEP may discontinue therapy.

FIGURE 4: PREP FLOW CHART



POST-EXPOSURE PROPHYLAXIS (PEP)

Post-exposure prophylaxis is the use of cART to prevent HIV transmission. Non-occupational exposure to HIV in children is mostly due to sexual abuse. In adults, exposure to HIV is mostly associated with occupational injuries. The risk of acquiring HIV infection after occupational exposure to HIV-infected blood is low (1:300 after percutaneous exposure to <1:1000 after mucocutaneous exposure).

There is no risk of transmission when the skin is intact. Factors associated with an increased risk include: deep injury, visible blood on the device that caused the injury, injury with a large bore needle from artery or vein, and unsuppressed HIV viral load in source patient. Body fluids and materials that pose a risk of HIV transmission are amniotic fluid, cerebrospinal fluid, human breast milk, pericardial fluid, peritoneal fluid, pleural fluid, saliva in association with dentistry, synovial fluid, unfixed human tissues and organs, vaginal secretions, semen, any other visibly blood-stained fluid, and fluid from burns or skin lesions. Other blood-borne infections are hepatitis B and hepatitis C viruses. Thus all HCWs should receive HBV vaccination.

Management of occupational exposure to infectious substances includes the following steps:

Immediately after exposure:

- Clean the site: wash skin wounds with soap and running water. DO NOT squeeze, allow wound to freely bleed. If the exposed area is an eye or mucous membrane, flush with copious amounts of clean water. DO NOT USE BLEACH or other caustic agents/disinfectants to clean the skin.
- Contact your In-Charge or supervisor.
- Consult the clinical officer or medical officer, who does the following:
    - Determine the need for post-exposure prophylaxis (PEP) based on the risk of transmission and risks and benefits of taking (or not taking) cART.

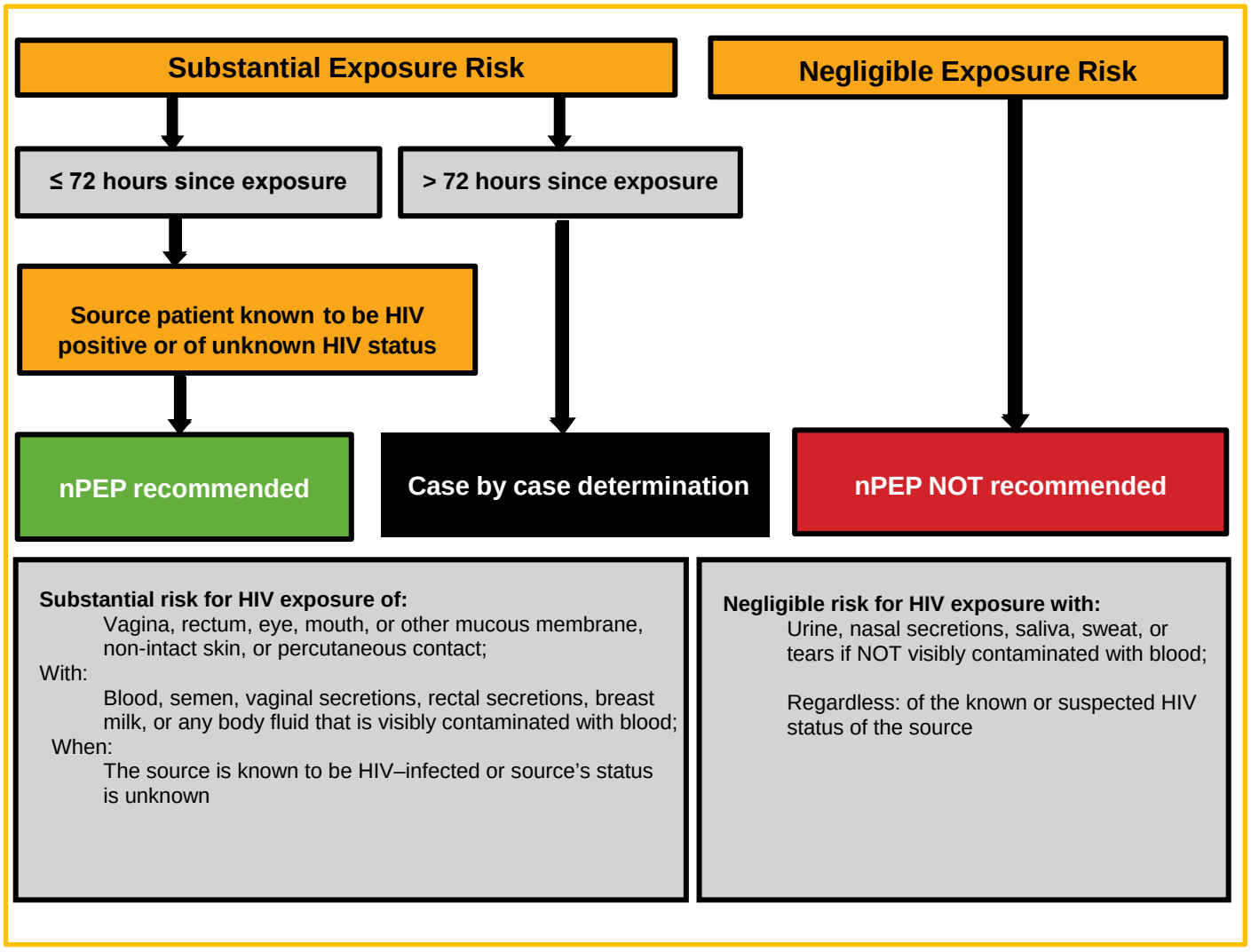
TABLE 3: POST EXPOSURE PROPHYLAXIS RECOMMENDATIONS BY RISK CATEGORY

Risk category	cART	Duration
No risk: intact skin	Not recommended	
Medium risk: invasive injury, no blood visible on needle	Preferred: TDF*+XTC+DTG** Alternative: TDF + XTC + ATV-r** AZT + 3TC + LPV-r (children <10 years)	28 days
High risk: large volume of blood/fluid, known HIV-infected patient, large bore needle, deep extensive injury		
Penetrative sexual abuse		

* For patients with CrCl <50mL/min, replace TDF with AZT
**DTG is effective against both HIV 1 and 2 and prevents integration of the viral DNA into the host DNA. It should be avoided in pregnancy and for HIV/TB patients on Rifampicin, the dose of DTG should be 50mg twice daily instead of the regular 50mg once daily. For intolerance to DTG (such, insomnia, anxiety, depression), use a recommended PI
** For patients who intolerant to ATV-r or if source is HIV-2 infected and cannot tolerate DTG, LPV-r should be used.

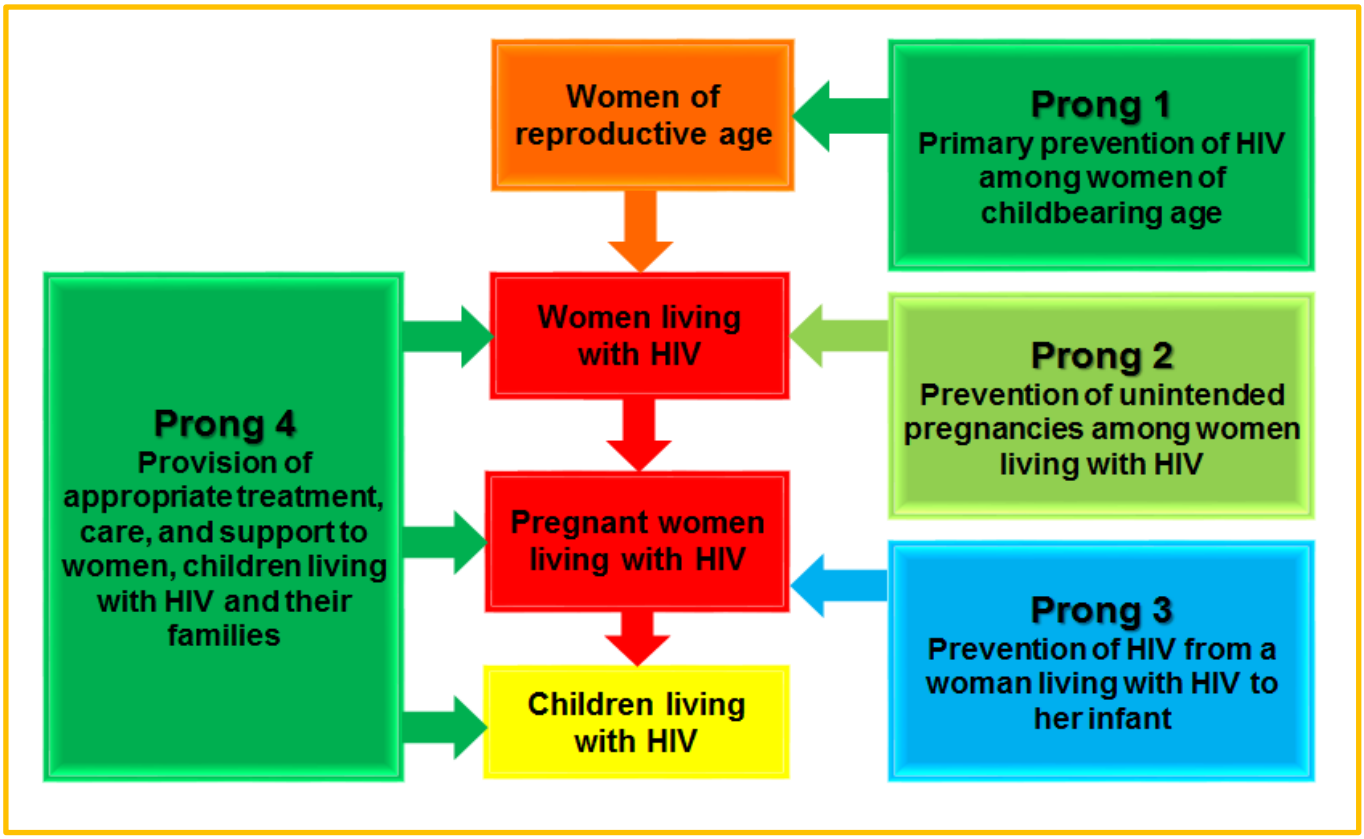
Management of non-occupational exposure to infectious substances should be managed as shown in Figure 5 below:

FIGURE 5: ALGORITHM FOR EVALUATION AND TREATMENT OF POSSIBLE NON-OCCUPATIONAL HIV EXPOSURE



ELIMINATION OF MOTHER TO CHILD TRANSMISSION OF HIV (EMTCT)

FIGURE 6: THE FOUR PILLARS/PRONGS OF EMTCT



Prong 1: Primary HIV Prevention

The drivers of the HIV epidemic include low rates of HIV testing, multiple concurrent sexual partners, low rates of male circumcision, MTCT, commercial sex workers, and migrant workers. Adolescents, especially young female adolescents, are vulnerable to HIV infection. The following interventions should be done in the health facilities and community:

- Counsel regarding STIs and HIV prevention, including post-test information on how to remain HIV negative or to live positively based on the outcome of the HIV test result
- Provide condoms or information on where to access condoms, including female condoms
- Refer to youth friendly services for more comprehensive sexual information, including HIV prevention
- Treatment of discordant couples
- Provide adherence support for adolescents on cART (prevention with positives)

Prong 2: Prevention of Unintended Pregnancies

Prevention of unintended pregnancies in HIV-infected women contributes to elimination of mother-to-child transmission. It includes counseling and provision of a variety of family planning (FP) methods. With timely initiation of cART and adherence to cART in HIV-infected non-pregnant women, planning for pregnancy is encouraged

- Refer patients to Family Planning clinics for further counseling and alternative methods if needed
- Promote mixed methods, also known as dual protection, because condoms alone or hormonal methods alone when the woman is on cART have been associated with unintended pregnancies
- Offer condoms to all men and women ≥15 years old
- Offer long-term FP methods to all women ≥15 years old
- Depot medroxyprogesterone acetate (DMPA) 150mg (1 vial) IM injection in deltoid muscle every 3 months
- Noristerat 200mg IM injection in deltoid or gluteal muscle, every 2 months
- Hormonal implant
- Intrauterine contraceptive device (IUCD)
- Sterilization (male or female) if child-bearing is complete
- Patients have the right to choose their FP method, including declining all method

Prong 3: Prevention of Mother-to-Child Transmission of HIV Using ARVs

In pregnant and breastfeeding women of unknown HIV status should be offered: HIV test & counseling (and depending on the result follow the guidelines) and routine antepartum, intrapartum, and postpartum obstetric care

- For mothers testing positive, immediately initiate cART among all pregnant or breastfeeding women diagnosed with HIV within MNCH under the key steps of:
- Treatment preparation and adherence counseling should be accelerated so that it is completed on the same day where feasible
- Initiation may be done by ART trained HNPs, nurses/midwives within MNCH
- Where there is NO adequate capacity within MNCH to initiate the pregnant woman on cART, she should be fast-tracked through the ART clinic
- Start CTX among all HIV-infected pregnant and breastfeeding women, regardless of CD4 count or WHO stage or gestational age
- Viral load should be performed 1 to 4 weeks before delivery to estimate risk of transmission for all mothers who are pregnant and on cART
- At 6 weeks postnatally, check CD4 count and if >350 cells/µL CTX may be discontinued.
- Continuous counseling
- Positive health, dignity, and prevention
- Promoting safer sex practices

Prong 4: Care and Support to HIV infected women and their infants/families

- Continued treatment and adherence support for HIV infected women on treatment. Both high and low risk infants should be provided with prophylaxis.
- Encourage counseling and provision of a variety of family planning (FP) methods.
- For HIV-positive partners, transfer the sexual partner after cART initiation to ART clinic for further management.
- Refer all HIV-uninfected male partners in serodiscordant relationships to medical male circumcision and encourage routine retesting every 3-6 months.

MANAGEMENT OF HIV EXPOSED INFANTS AND HIV INFECTED POPULATIONS

Recommendations

- ARV Prophylaxis in High-risk Infants = AZT/3TC + NVP for 12 weeks
- Treat ALL regardless of CD4 count or WHO Clinical Stage
- TDF+XTC+DTG as preferred first line in ART naïve or those on TDF+XTC+EFV and are virologically suppressed
- AZT+3TC+RAL for children failing ABC+3TC+LPV-r first line therapy
- Routine Viral Load Monitoring

HIV EXPOSED INFANTS (HEIS)

TABLE 4: HEI ARV PROPHYLAXIS FOR ROUTINE CASES

Case scenario	Management of the mother at delivery and in Postnatal Care (PNC)	Infant ARV prophylaxis and Nucleic acid test (NAT)
High-Risk HIV-Exposed Infants		
1. Born to women with established HIV infection and having received less than 12 weeks of cART at the time of delivery; or: 2. Born to women with established HIV infection with viral load >1000 copies/mL within the four weeks before delivery, if viral load measurement available*	Start or continue cART immediately	All exposed infants to be put on AZT/3TC+NVP for 12 weeks
1. Born to women with established HIV infection not on cART; or: 2. Born to known HIV positive woman who refuses cART	Start or continue cART immediately Continue counseling for need to start therapy. Suggest to start cART with possibility of stopping after delivery (Option B) while counseling continues toward the mother accepting lifelong cART (Option B+)	Prophylactic ART (AZT/3TC+NVP) until confirmed final outcome HIV negative after complete cessation of breastfeeding
Low-Risk HIV-Exposed Infants		
Known HIV-positive women on cART for more than 12 weeks	Continue cART	All exposed infants to be put on AZT/3TC+NVP for 6 weeks
HIV-negative women with known positive partner	Do NAT, if negative, continue PrEP (if woman was already on PrEP before pregnancy) and provide HTS every 3 months	If NAT on the mother is positive do NAT on the baby

***ALL HIV POSITIVE PREGNANT WOMEN ON CART SHOULD HAVE A VIRAL LOAD DONE 1 TO 4 WEEKS BEFORE DELIVERY**

TABLE 5: HEI ARV PROPHYLAXIS IN COMPLICATED CASES

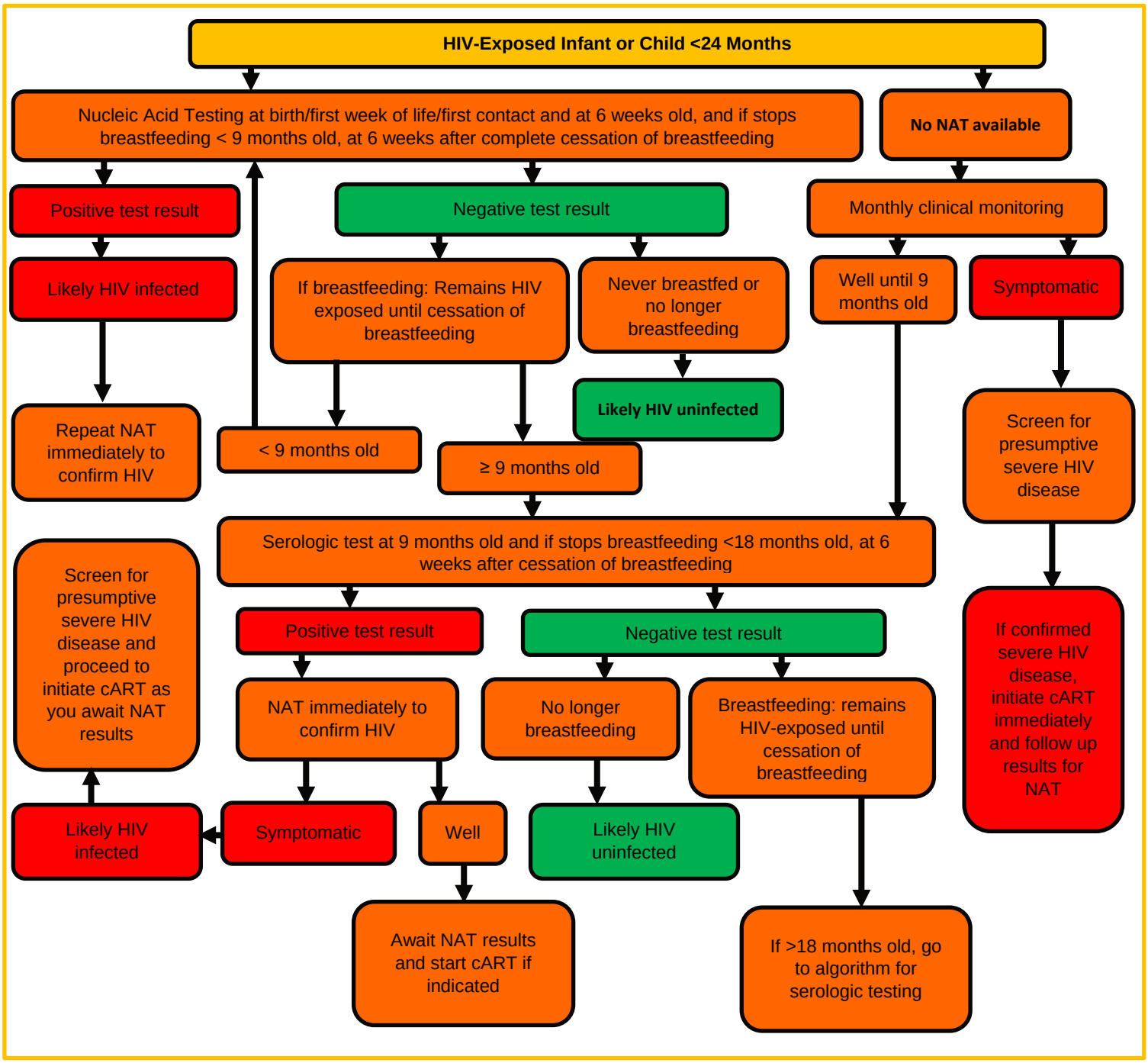
Case scenario	Management of the mother at delivery and in Postnatal Care (PNC)	Infant ARV prophylaxis and Nucleic acid test (NAT)
Woman with an HIV positive test in ANC who starts cART in ANC and has been on cART for >12 weeks. She has a home delivery. Infant does not receive AZT/3TC+NVP at birth, but presents >72 hours after birth	Continue cART	Do NAT: If positive, start cART. If negative, start AZT/3TC+NVP for 6 weeks and repeat NAT at 6 weeks of age. *If NAT results are delayed, start AZT/3TC+NVP immediately
Woman with unknown antenatal HIV status who has a home delivery and has an HIV positive test in postnatal clinic >72 hours after delivery Born to woman with established HIV infection who has received less than 12 weeks of cART at the time of delivery; or Born to woman with established HIV infection with viral load >1000 copies/mL in the four weeks before delivery, if viral load measurement available	Start (or switch to) cART	AZT/3TC+NVP for 12 weeks NAT testing
Woman with an HIV negative test in ANC and has an HIV positive test in L&D or during breastfeeding period*		

TABLE 6: SIMPLIFIED INFANT PROPHYLAXIS DOSING

Infant age	Dosing of NVP	Dosing of AZT/3TC
Birth to <6 weeks old		
Birth weight 2000g – 2499g**	10mg once daily (1mL of syrup once daily)	10mg/5mg twice daily (1mL of syrup twice daily)
Birth weight 2500g – 2999g	15mg once daily (1.5mL of syrup once daily)	15mg/7.5mg twice daily (1.5mL of syrup twice daily)
> 6 weeks to 12 weeks		
3000g – 5900g	20mg once daily (2mL of syrup once daily or half a 50mg tablet once daily)	Use treatment dose 60mg/30mg twice daily (6mL syrup twice daily or a 60mg/30mg tablet twice daily)

**For infants weighing <2000g and older than 35 weeks of gestational age, the suggested doses are: NVP 2mg/kg per dose once daily and AZT 4mg/kg per dose twice daily. Premature infants younger than 35 weeks of gestation age should be dosed using expert guidance

FIGURE 6: ALGORITHM FOR HIV TESTING (NAT) IN CHILDREN < 24 MONTHS OLD



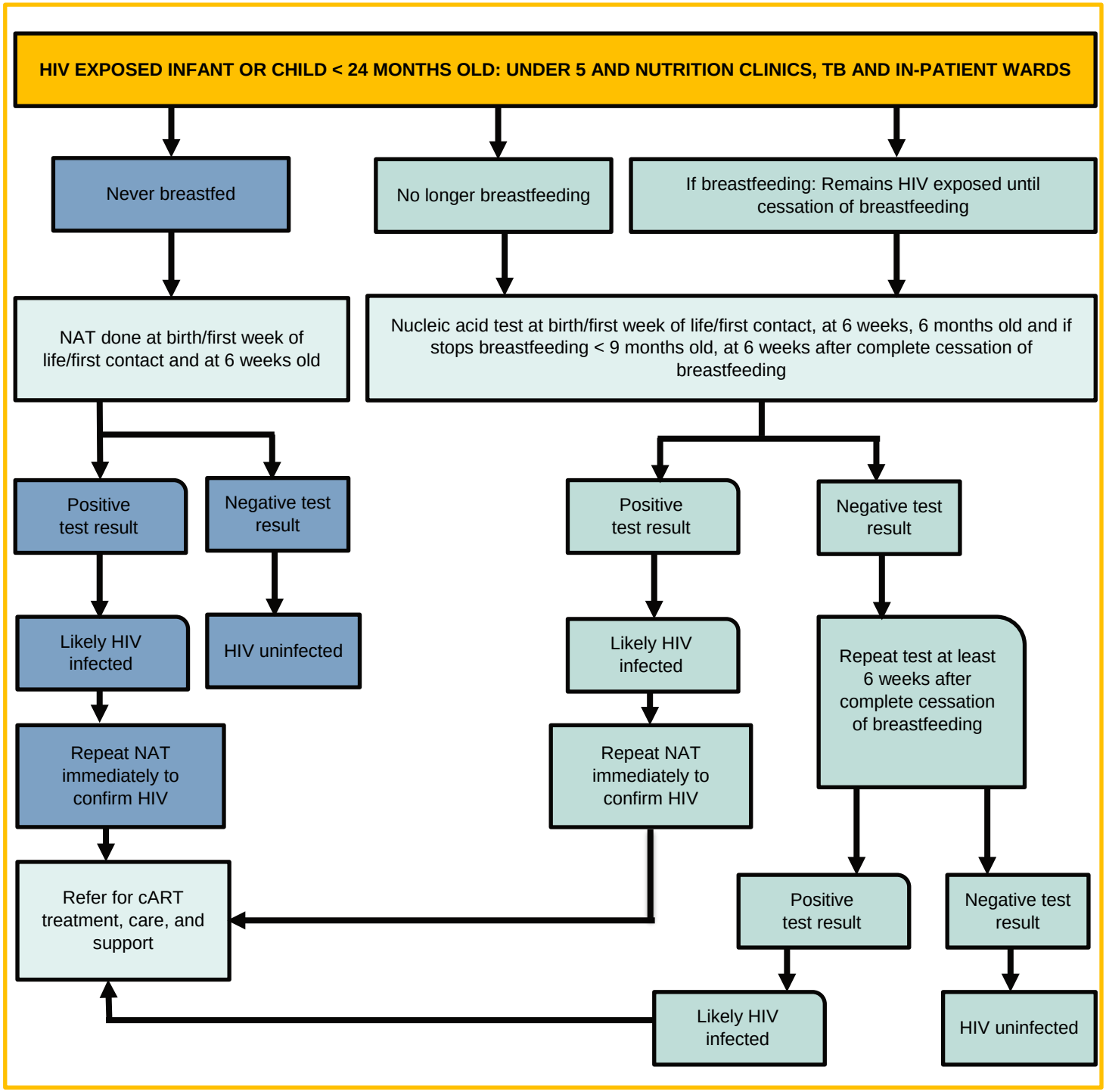
*Presumptive clinical diagnosis of HIV infection is done in infants and children <18 months old where there is no access to Nucleic acid testing (NAT), or reporting of results is delayed, but the child has symptoms suggestive of HIV infection. The criteria for making a presumptive diagnosis of HIV infection are:

HIV serologic test positive in infant or child **AND**

Symptomatic with 2 or more of the following: oral thrush, severe pneumonia, severe sepsis, or has any Stage 4 condition

NAT available means unable to collect sample or the test cannot be run at the testing lab due to various logistical issues

FIGURE 7: TESTING ALGORITHM OF HIV-EXPOSED INFANTS



Testing should be done alongside immunization visits

TABLE 7: ARV PRESCRIBERS AND CORRESPONDING REGIMENS FOR cART INITIATION

Cadre with specific training	Initiation of cART
Nurse/Midwife (registered, enrolled) certified with Integrated HIV Care Training*	1st line
Nurse Prescribers with Integrated HIV Care Training*	1st line, 2nd line**
Clinical Officers with Integrated HIV Care Training*	1st line, 2nd line**
Medical Licentiates with Integrated HIV Care Training*	1st line, 2nd line
Medical Officers with Integrated HIV Care Training*	1st line, 2nd line
Medical Specialists with relevant training and experience†	1st line, 2nd line, 3rd line

*Providers with Integrated HIV Care Training should satisfy requirements of competency-based training in the use of cART for treatment and prevention of HIV

**Initiation on second-line should only be done in consultation with a medical officer with appropriate training

†Relevant training and experience refers to management of advanced and complicated HIV, including second-line treatment failure

To improve cART initiation and adherence, counseling must be done so that the individual (or caregiver) understands its benefits. The benefits of starting cART earlier include:

- Reduced rates of HIV-related morbidity and mortality
- Reduced MTCT (in pregnant and breastfeeding women)
- Potential reductions in the incidence and severity of chronic conditions (e.g., renal disease, liver disease, certain cancers, and neurocognitive disorders)
- Reduction in infectious complications (e.g., TB)
- Reduced sexual transmission
- High levels of adherence to cART are needed to attain these objectives.

FIGURE 8: FLOW DIAGRAM FOR HIV CARE AND TREATMENT FROM HIV TESTING TO CART INITIATION

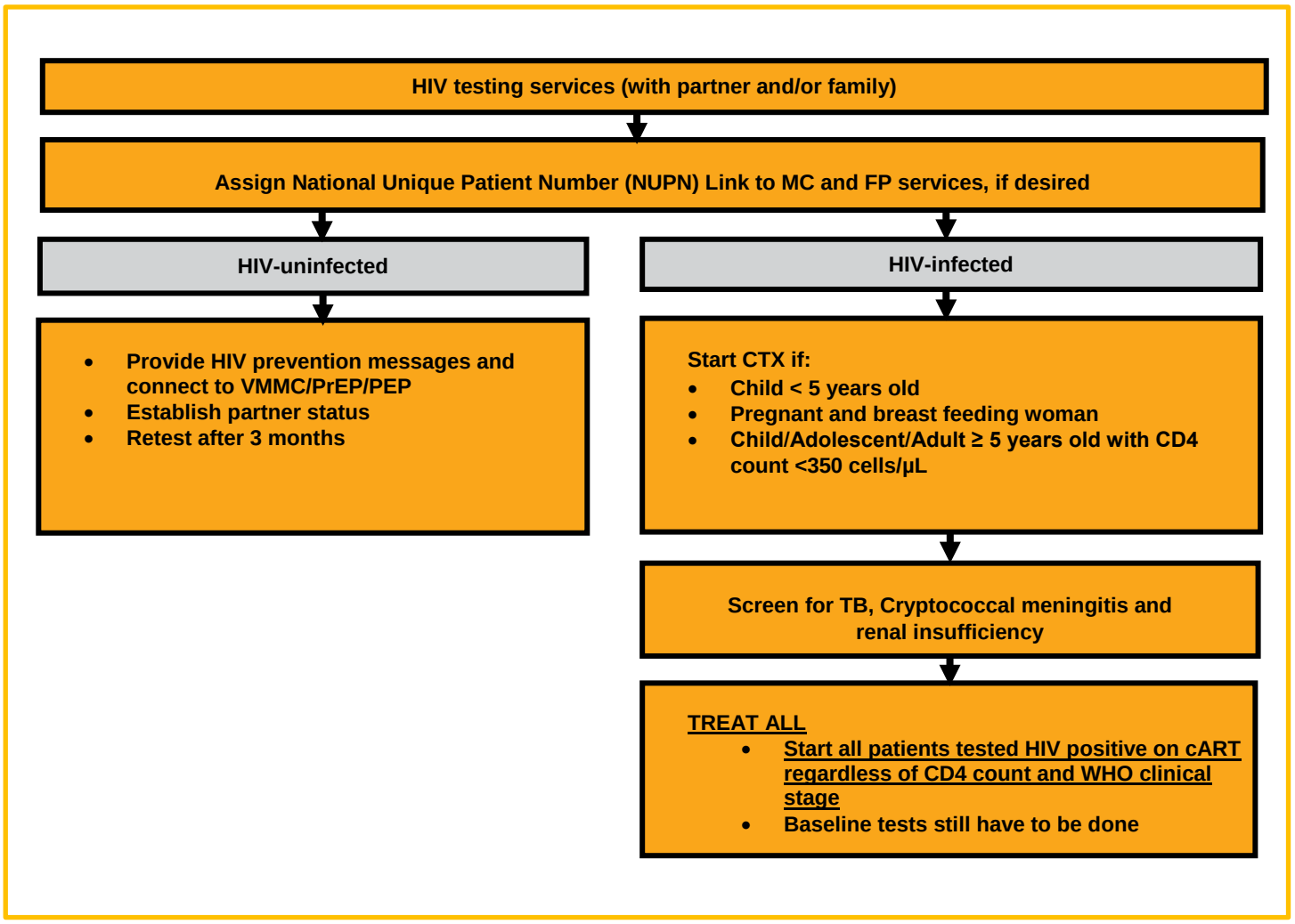


TABLE 8: WHO CLINICAL STAGING OF HIV DISEASE BY SPECIFIC POPULATIONS

Children (0 to <10 years old) Adolescents (10 to 15 years old)	Adolescents (15 to 19 years old) Pregnant & Breastfeeding Women Adults
Clinical Stage 1	
• Asymptomatic • Persistent generalized lymphadenopathy	• Asymptomatic • Persistent generalized lymphadenopathy
Clinical Stage 2	
• Unexplained persistent hepatosplenomegaly • Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) • Herpes zoster • Lineal gingival erythema • Recurrent oral ulceration • Papular pruritic eruption • Fungal nail infections • Extensive wart virus infection • Extensive molluscum contagiosum • Unexplained persistent parotid enlargement	• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) • Herpes zoster, Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruption • Fungal nail infections • Seborrhoeic dermatitis
Clinical Stage 3	
• Unexplained moderate malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5°C, intermittent or constant, for >1 month) • Persistent oral candidiasis (after 6 weeks old) • Oral hairy leukoplakia • Lymph node tuberculosis • Pulmonary tuberculosis • Severe recurrent bacterial pneumonia • Acute necrotizing ulcerative gingivitis or periodontitis, Unexplained anaemia (<8g/dL), neutropaenia (<0.5 x 10^9/L) or chronic thrombocytopaenia (<50 x 10^9/L) • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease, including bronchiectasis	• Unexplained severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhoea for longer than 1 month Unexplained persistent fever (intermittent or constant for >1 month) • Persistent oral candidiasis • Oral hairy leukoplakia • Pulmonary tuberculosis • Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis • Unexplained anaemia (<8g/dL), neutropaenia (<0.5 x 10^9/L) and/or chronic thrombocytopaenia (<50 x 10^9/L)

Children (0 to <10 years old)	Adolescents (15 to 19 years old)
	Pregnant & Breastfeeding Women
Adolescents (10 to 15 years old)	Adults
Clinical Stage 4	
• 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 (or labial or cutaneous of more than 1 month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs with onset at > 1 month old) • Central nervous system toxoplasmosis (after the neonatal period) • HIV encephalopathy • Extrapulmonary cryptococcosis, including meningitis • Disseminated non-tuberculous mycobacterial infection • Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis (with diarrhoea) • Chronic isosporiasis • Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) • Cerebral or B-cell non-Hodgkin lymphoma • HIV-associated nephropathy or cardiomyopathy	• HIV wasting syndrome • Pneumocystis (jirovecii) pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (or labial, genital or anorectal of more than 1 month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis HIV encephalopathy • Extrapulmonary cryptococcosis, including meningitis • Disseminated 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 septicaemia (including non-typhoidal Salmonella) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis

TABLE 9: ELIGIBILITY CRITERIA FOR CART INITIATION IN CHILDREN, ADOLESCENTS, PREGNANT AND BREASTFEEDING WOMEN, AND ADULTS

Specific populations	Description
Pregnant & Breastfeeding Women	Treat irrespective of WHO clinical stage or CD4 count
Children (0 to <10 years old)	
Adolescents (10 to ≤19 years old)	
Adults	

Under these new guidelines: Treat ALL, the assessment through WHO Staging (Table 8) guides the evaluation and management of HIV; however initiating on ART does not require a CD4

TABLE 10: PRE-INITIATION TASKS

Timeline/Specific populations		Clinical tasks	Laboratory tests*
Visit 1 Enrollment/ **Initiate cART based on patient readiness**	Children	Complete history & examination Screen for TB and other opportunistic infections (OIs) □ Adherence counseling and PHDP† messages, including the caregiver: sessions 1 & 2 □ WHO clinical assessment □ Initiate CTX for child >6 weeks old □ HPV vaccine for girl <10 years old	□ Creatinine (calculate CrCl) ** □ ALT □ Hb/FBC** □ CD4 ** □ HBsAg (if not vaccinated) □ Pregnancy test (Adolescent or woman of reproductive age) □ Syphilis test (adolescent or adult) □ Cholesterol, and triglycerides (especially if starting PI) □ HPV test or visual inspection with acetic acid (VIA) in sexually active adolescent or woman
	Adolescents Adults	□ Complete history & examination □ Screen for TB and other OIs □ WHO clinical assessment □ Initiate CTX for ALL adolescents □ Initiate CTX for adults if eligible (CD4 <350 cells/μL, Pregnancy and breastfeeding) □ Adherence counseling and PHDP† messages □ Urinalysis	
Visit 2 1-2 weeks later **Initiate cART if not initiated at visit 1**	Children Adolescents Adults	□ Targeted history and examination □ Screen for TB, Cryptococcus, and PCP □ Review CTX adherence (if already started) □ Initiate CTX (if eligible and not initiated at enrollment) □ Review laboratory test results □ **Initiate cART if not initiated at visit 1** □ Adherence counseling and PHDP† messages, including the caregiver	□ Urinalysis □ Sputum AFB smear/GeneXpert MTB RIF in individuals with a positive Screening □ Serum CRAG for adolescents and adults with CD4 count < 100 cells/μL
Visit 3 2-4 weeks from enrollment **Initiate cART if not initiated at visits 1 and 2**	Children Adolescents Adults	□ Targeted history and examination □ Screen for TB and other OIs □ And review CTX adherence □ **Initiate cART if not yet started in the last two visits** □ Adherence counseling and PHDP† messages	□ Urinalysis □ Sputum AFB □ Serum CRAG for adolescents and adults with CD4 count < 100 cells/μL

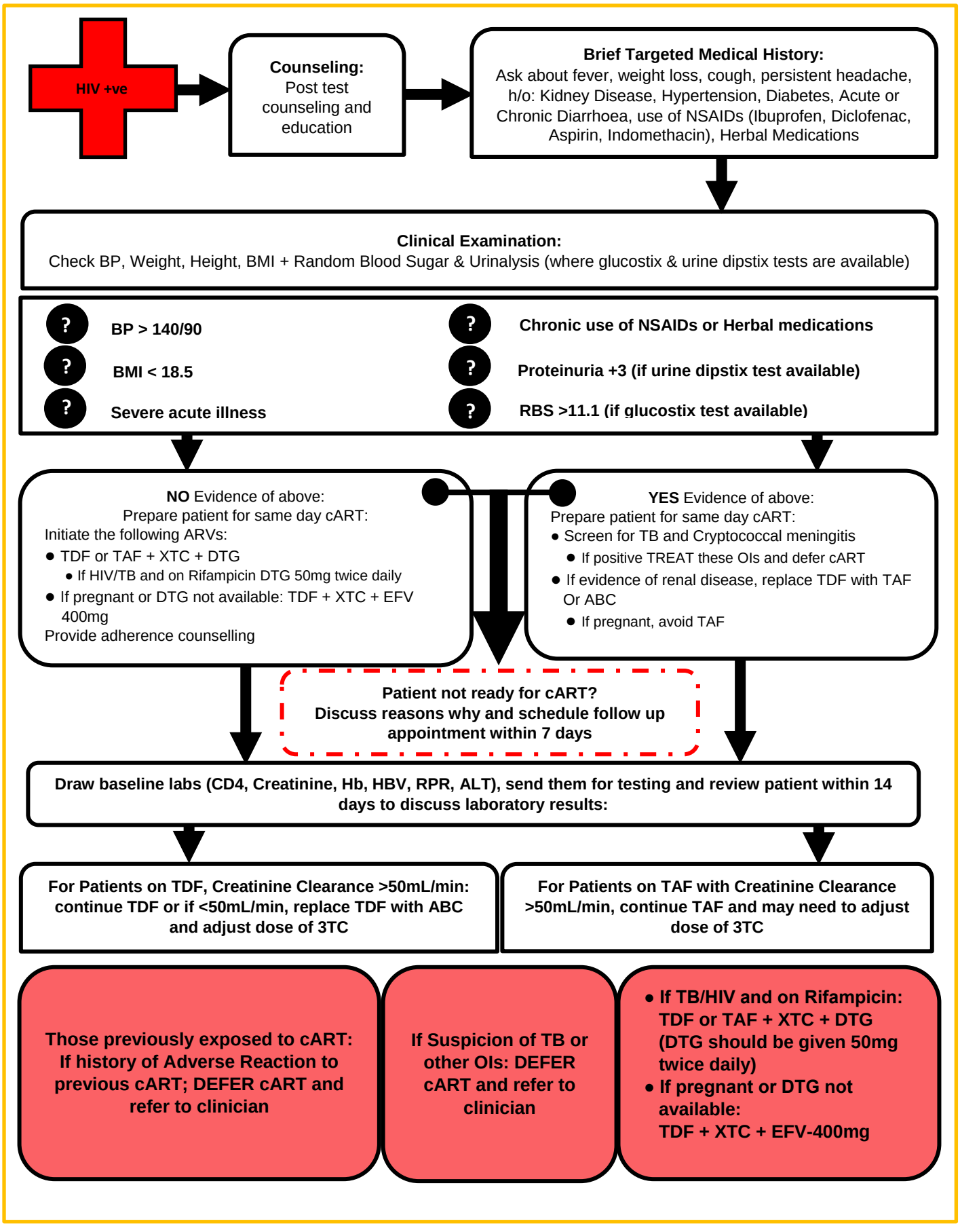
† Positive Health Dignity and Prevention (PHDP) includes: risk reduction, ART adherence, correct condom use, family planning, STI screening, and partner HIV testing.

*If health facility is unable to perform a required laboratory test, refer sample or patient to higher level facility.

** Creatinine should be done in all patients initiating TDF based cART and Hb for all children initiating AZT based cART, according to the guidelines. CD4 should be done in all patients, but should not be used to determine eligibility.

TAT = Toxoplasmosis Antigen Test

FIGURE 9: SAME DAY CART INITIATION ALGORITHM IN ADULTS



First Line cART

Providing optimized, fixed-dose cART regimens in all populations have consistently demonstrated that there are better clinical and laboratory outcomes if HIV treatment is initiated early. Reduce the time between HIV diagnosis and cART initiation. This is based on an assessment of the person's readiness and must be done within 2 weeks.

Table 11: Preferred First-Line cART and Alternative Regimens by Specific Populations

Specific Populations	Description	Preferred 1st line cART	Alternative regimen
Pregnant & Breastfeeding Women [b]	ARV naïve or Sure of tail coverage	TDF + XTC + EFV_{400} [a]	TDF + XTC + ATV-r (or LPV-r) or ABC + 3TC + EFV
	Previous sdNVP exposure; or NVP monotherapy exposure (NVP without 7 days of AZT + 3TC cover); or unsure of tail coverage	TDF + XTC + LPV-r	ABC + XTC + LPV-r or ABC + XTC + ATV-r
Children (0-2 weeks)	All	AZT + 3TC + NVP	Consult or refer to expert opinion
Children (2 weeks to < 5 years old)	All	ABC + 3TC + LPV-r	AZT + 3TC + LPV-r
	HIV and TB co-infection	AZT + ABC + 3TC *(if < 3 months)* ABC + 3TC + EFV	After completion of ATT, substitute to preferred 1st line with LPV-r
Children (5 to <10 years old)	ARV naïve	ABC + 3TC + EFV	AZT + 3TC + EFV or ABC + 3TC + NVP
	History of maternal sdNVP; maternal or infant NVP monotherapy; mother unsure of tail coverage [b]	ABC + 3TC + LPV-r	AZT + 3TC + LPV-r or AZT + 3TC + ATV-r
Adolescents (10 to <19 years old) weighing ≥35kg	NO history of maternal sdNVP; maternal or infant NVP monotherapy; mother sure of tail coverage	TDF or TAF [c] + XTC[d] + DTG [e]	TDF or TAF [c] + XTC[d] + EFV ABC + 3TC + EFV (weight-based dosing)
	History of maternal sdNVP, unsure of tail coverage; maternal or infant NVP monotherapy	TDF or TAF [c] + XTC[d] + DTG[e]	TDF or TAF [c] + XTC[d] + EFV ABC + 3TC + EFV (weight-based dosing)
Adults	All	TDF or TAF [c] + XTC[d] + DTG [e]	TDF or TAF [c] + XTC [d] + EFV_{400} or ABC + 3TC + EFV

[a] EFV_{400} is lower dose EFV of 400-mg/day
[b] If NVP exposure, initiate on LPV-r based therapy
[c] TAF is Tenofovir alafenamide. Avoid in pregnancy and HIV/TB patients on Rifampicin
[d] Can either be 3TC or FTC
[e] DTG (Dolutegravir) to be given to cART naïve adolescents and adults. Avoid in pregnancy. For HIV/TB patients on Rifampicin, increase the frequency of DTG to 50mg twice daily instead of the usual 50mg once daily only if single tablet *is available*

NEWER ANTIRETROVIRAL AGENTS AND THEIR USE

1. Dolutegravir (DTG)

a. Dolutegravir (DTG) is a newer Integrase Inhibitor with a higher genetic barrier to resistance than Raltegravir(RAL) and Elvitegravir (EVG) and NNRTIs
b. DTG is associated with the following mutations: F121Y, E138A/K, G140S/A, **Q148 H/K/R**, N155H, R263K.
c. Cross-resistance studies with RAL and EVG-resistant viruses indicate that G140S and **Q148 H/K/R in combination with** L74I/M, E92Q, T97A, E138A/K, G140A, or **N155H** are associated with 5-fold to 20-fold reduced DTG susceptibility and reduced virologic suppression in patients.
d. It is dosed as 50mg dosed as once daily EXCEPT as 50mg twice daily in patients on Rifampicin or those with integrase mutations
e. It has no food requirements and has few drug interactions
f. It has drug interactions with UDP glucuronyl transferase (UDP) inducers like Rifampicin, which leads to decreased plasma DTG levels
g. It also has decreased absorption with aluminum, calcium or magnesium containing anti-acids
h. There is also reported increase in serum creatinine with no true effect on the glomerular filtration rate (GFR)
i. There is no safety and efficacy data on the use of DTG in pregnant women and adolescents younger than 12 years of age.

Practical hints on use of DTG

- It should be used in the following populations:
  - Adults and adolescents with HIV-1 or HIV-2 or HIV-1/HIV-2 mixed infection who are being initiated on cART as part of combination ART as
    - TDF or TAF + XTC + DTG
  - Adults and adolescents with HIV-1 who have an undetected viral load while on NNRTI based first line as
    - TDF + XTC + EFV to TDF or TAF + XTC + DTG
    - TDF + XTC + NVP to TDF or TAF + XTC + DTG
    - ABC + 3TC + EFV to ABC or TAF + XTC + DTG
    - ABC + 3TC + NVP to ABC or TAF + XTC + DTG
  - Adults and adolescents with HIV-2 or HIV-1/HIV-2 mixed infection who have an undetected viral load while on PI based first-line as
    - TDF + XTC + LPV-r to TDF or TAF + XTC + DTG
    - ABC + 3TC + LPV-r to ABC or TAF + XTC + DTG
- In HIV/TB infected populations on Rifampicin, increase the frequency of DTG to 50mg twice daily instead of the usual 50mg once daily. However, where the single 50mg tablet is not available, give:
  - TDF + XTC + EFV-400mg. This switch should be done if viral load is <20 copies/mL, if it is >20 copies/mL, give TDF + XTC + LPV-r
- It should not be used in HIV infected individuals who are pregnant
- DTG significantly increases Metformin plasma levels, which can be partially explained by Organic Cation Transporter-2 inhibition. It is recommended that dose adjustments of Metformin be considered to maintain optimal glycaemic control when patients are starting/stopping DTG while taking Metformin
  - In patients taking DTG who are starting Metformin, begin with low Metformin dose and titrate up carefully. Recommended dose limit of Metformin 1000 mg daily. If patient is already on Metformin and initiating DTG, monitor glucose, haemoglobin a1c, and Metformin adverse effects and adjust dose as necessary.

2. Tenofovir alafenamide (TAF)

Tenofovir alafenamide is a phosphonoamidate prodrug of the nucleotide analog Tenofovir which belongs to a class of Nucleotide reverse transcriptase inhibitors. It is predominantly metabolized intracellularly to Tenofovir which undergoes subsequent phosphorylations to yield the active Tenofovir diphosphate (TFV-DP) metabolite which inhibits the activity of HIV reverse transcriptase by competing with natural substrates and causing DNA chain termination after being incorporated into viral DNA

a. TAF is dosed as 25mg once daily (when used without pharmaco-enhancers)
b. TAF has also demonstrated **IN VITRO** and **IN VIVO** activity against HBV
c. The median terminal half-life of TAF is 0.51 hours and the active metabolite, TFV-DP, has an intracellular half-life of 150 to 180 hours
d. TAF is intracellularly metabolized in hepatocytes, peripheral blood mononuclear cells (PBMCs) and macrophages and less than 1% of the dose is excreted in the urine and 31.7% excreted in feces
e. TAF has been associated with K65R and the K70E substitutions which lead to reduced susceptibility to Abacavir, Didanosine, Emtricitabine, Lamivudine, and TDF. HIV-1 containing multiple thymidine analog mutations (TAMs) (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R) lead to resistance to TAF. In addition, multi-nucleoside resistant virus with a T69S doubles insertion mutation or with a Q151M mutation complex including K65R exhibit **IN VITRO** resistance to TAF
f. Adverse events include diarrhea, fatigue, nausea, and rash
g. TAF is associated with significantly less increase in proximal tubular proteinuria and less reduction in estimated glomerular filtration rate (eGFR) when compared to TDF
h. TAF is associated with significantly less change in spine and hip bone mineral density (BMD) compared to TDF
i. There is no safety and efficacy data on the use of TAF in pregnant women and people with HIV/TB co-infection

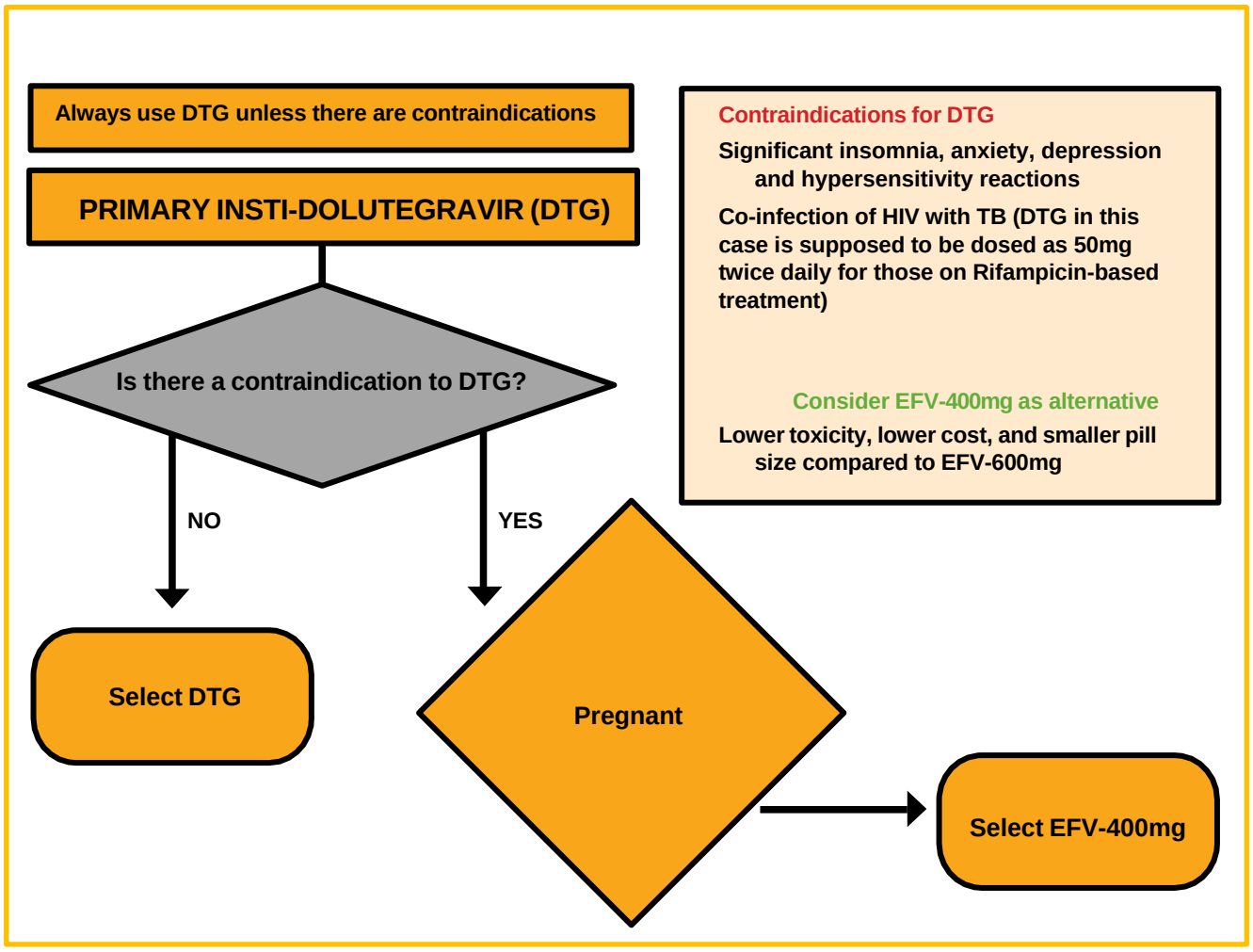
Practical hints on use of TAF

- It should be used in the following populations:
  - Adults and adolescents with HIV-1 or HIV-2 or HIV-1/HIV-2 mixed infection who are being initiated on cART as part of combination ART as
    - TAF + XTC + DTG
  - Adults and adolescents with HIV-1 who have an undetected viral load while on NNRTI based first-line as
    - TDF + XTC + EFV to TAF + XTC + DTG
    - TDF + XTC + NVP to TAF + XTC + DTG
    - ABC + 3TC + EFV to TAF + XTC + DTG
    - ABC + 3TC + NVP to TAF + XTC + DTG
  - Adults and adolescents with HIV-2 or HIV-1/HIV-2 mixed infection who have an undetected viral load while on PI based first-line as
    - TDF + XTC + LPV-r to TAF + XTC + DTG
    - ABC + 3TC + LPV-r to TAF + XTC + DTG
- It should NOT be used in HIV/TB infected populations
  - It is therefore recommended that such patients are on TDF or ABC containing regimen instead of TAF containing regimen
- It should not be used in HIV infected individuals who are pregnant
  - It is therefore recommended that such patients are on TDF or ABC containing regimen instead of TAF containing regimen

Practical Hints for EFV initiation

- EFV-400mg is the preferred NNRTI for first-line cART initiation in Pregnant and Breastfeeding Women
  - Consider using EFV at all times unless there are contraindications to its use, see Figure 10
- EFV- 600mg is associated with central nervous system (CNS) side effects (e.g. dizziness, drowsiness, insomnia, abnormal dreams, and impaired concentration).
  - In systematic reviews, there is evidence showing that EFV-400mg is comparable to EFV-600mg in terms of viral suppression, but better in terms of CD4 cell count recovery and protective in terms of treatment discontinuation because of adverse events. When compared with the standard dose of EFV, EFV-400mg is also associated with lower toxicity, lower cost, and smaller pill size. It is also comparable to other treatment regimens with respect to mortality or AIDS-defining illnesses and emergent serious adverse events.
- EFV- 400mg is recommended as part of the preferred first- line regimen
- If CNS effects persist beyond 6-8 weeks on EFV-400mg substitute to PI-based regimen
- Avoid fatty meals 4 hours before or after taking EFV. Recommend taking EFV before bedtime
- **EFV should not be used to treat patients with HIV-1/HIV-2 co-infections or HIV-2 mono-infection. See section on HIV-2 Treatment**

FIGURE 10: ALGORITHM FOR CHOOSING DTG OR EFV-400MG IN PATIENTS INITIATING CART



HIV-2 Treatment

Clinicians should:

- Use the preferred standard first-line regimen TDF or TAF + XTC + DTG
    - If unable to tolerate DTG, substitute with a Lopinavir-ritonavir when prescribing cART for HIV-2 mono-infected or HIV-1/ HIV-2 co-infected individuals
- Not prescribe NNRTIs (NVP, EFV or RPV) or the PI Atazanavir-ritonavir as part of a cART regimen against HIV-2 mono-infection
- Consult with a provider with the ATCs in the management of HIV-2 where there doubts before initiating cART in HIV-2-infected patients
- Educate patients with confirmed HIV-2 infection about the types of drugs that can be used to treat it

No randomized clinical trials have been conducted to determine when to initiate cART in the setting of HIV-2 infection, and the best choices of therapy for HIV-2 infection remain under study. Because the optimal treatment strategy for HIV-2 infection has not been defined, the recommendations provided in this section are based on this committee's expert opinion with supporting evidence highlighted in Table 12 below.

Although HIV-2 is generally less aggressive, and progression to AIDS is less frequent, HIV-2 responds less predictably to cART when progression occurs, and response is more difficult to monitor. The standard methods and interpretation protocols that are used to monitor cART for HIV-1-infected patients may not apply for HIV-2-infected patients. Some cART regimens that are appropriate for HIV-1 infection may not be as effective for HIV-2. The following factors should be considered:

- The majority of HIV-2-infected patients are long-term non-progresses
- HIV-2 may confer more rapid resistance to cART agents because of wild-type genetic sequence that results in a significant increase in resistance to cART agents compared with HIV-1
- Pathways for the development of drug mutations may differ between HIV-1 and HIV-2

Table 12: Preferred First-Line cART and Alternative Regimens for HIV-2

Specific Populations	Description	Preferred 1st line cART	Alternative regimen
HIV-1 / HIV-2 co-infected	First-line	TDF or TAF* + XTC + DTG**	TDF or TAF + XTC + LPV – r ** or ABC + 3TC + LPV-r
HIV-2 mono- infected			

* TAF should also be avoided in pregnancy and in HIV/TB patients on Rifampicin

**DTG is active against HIV 1 and 2. However, it should be avoided in pregnancy and in HIV/TB patients on Rifampicin

** *LVP-r is the only PI that actively works against HIV -2

Table 13: Efficacy of Antiretroviral Therapy against HIV-2 Infection

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
• Although most in vitro studies have shown that similar concentrations of NRTIs are needed to block both HIV-1 and HIV-2 replication, data suggest that some NRTIs may not be as effective against HIV-2 o For example, HIV-1 more readily incorporates Zidovudine and is more susceptible to Zidovudine than HIV-2, and there is a lower barrier to resistance with HIV-2 than with HIV-1. • Genotypic analysis of HIV-2-infected patients on cART has shown that many of the same amino acid substitutions that are associated with NRTI resistance in HIV-1 may be implicated in HIV-2. Some resistance mutations (*K65R, Q151M, and M184V*) in combination can confer class-wide NRTI resistance and cause rapid virologic failure.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
• NNRTIs block HIV-1 reverse transcription through a specific binding site that is not present in HIV-2; this class of drugs will not be effective against HIV-2. • HIV-2 appears to be intrinsically resistant to NNRTIs; the *Y188L* polymorphism appears naturally in all HIV-2 isolates. Reversion to *Y188* restores the reverse transcriptase sensitivity to some NNRTIs, including Efavirenz • In general, NNRTIs inhibit HIV-2 at effective concentrations that are at least 50-fold higher than those that inhibit HIV-1, making the use of these drugs for HIV-2 infection problematic. • Etravirine appears to have limited activity against HIV-2, but this may not be clinically relevant because the mean 50% effective concentration in MT4 cells is 2500-fold higher than that observed for HIV-1.
Protease Inhibitors (PIs)
• HIV-2 expresses natural polymorphisms in the protease that may be implicated in emergent drug resistance and accelerate time to development of PI resistance. • One study noted that the pathways for HIV-2 protease drug resistance may differ from those for HIV-1 • Saquinavir, Lopinavir, and Darunavir have shown comparable activity against HIV-1 and HIV-2. • Atazanavir has lower and variable activity against HIV-2 in comparison with HIV-1. It should not be prescribed for HIV-2 and in HIV/TB patients on Rifampicin-based treatment. • Lopinavir dose should be doubled for HIV/TB patients on Rifampicin-based treatment
Integrase Strand Transfer Inhibitors (INSTIs)
• Dolutegravir is safe for use in HIV-2 • The integrase inhibitors Raltegravir and Elvitegravir have demonstrated activity in vitro. Clinical response to Raltegravir was reported in a patient with highly treatment-experienced HIV-2 infection but the emergence of mutations was reported in another patient.
CCR5 co-receptor antagonists
• The activity of Maraviroc has been limited to patients with CCR5-tropic viruses. • Primary HIV-2 isolates can utilize a broad range of co-receptors, including CXCR4, CCR5, CCT-5, GPR15, and CXCR6. This limits the therapeutic utility of Maraviroc in HIV-2 infection.
Fusion inhibitors
• HIV-2 is intrinsically resistant to the fusion inhibitor Enfuvirtide.

MONITORING HIV INFECTED POPULATIONS ON CART

CLINICAL AND LABORATORY MONITORING

Monitoring consists of two components: clinical and laboratory

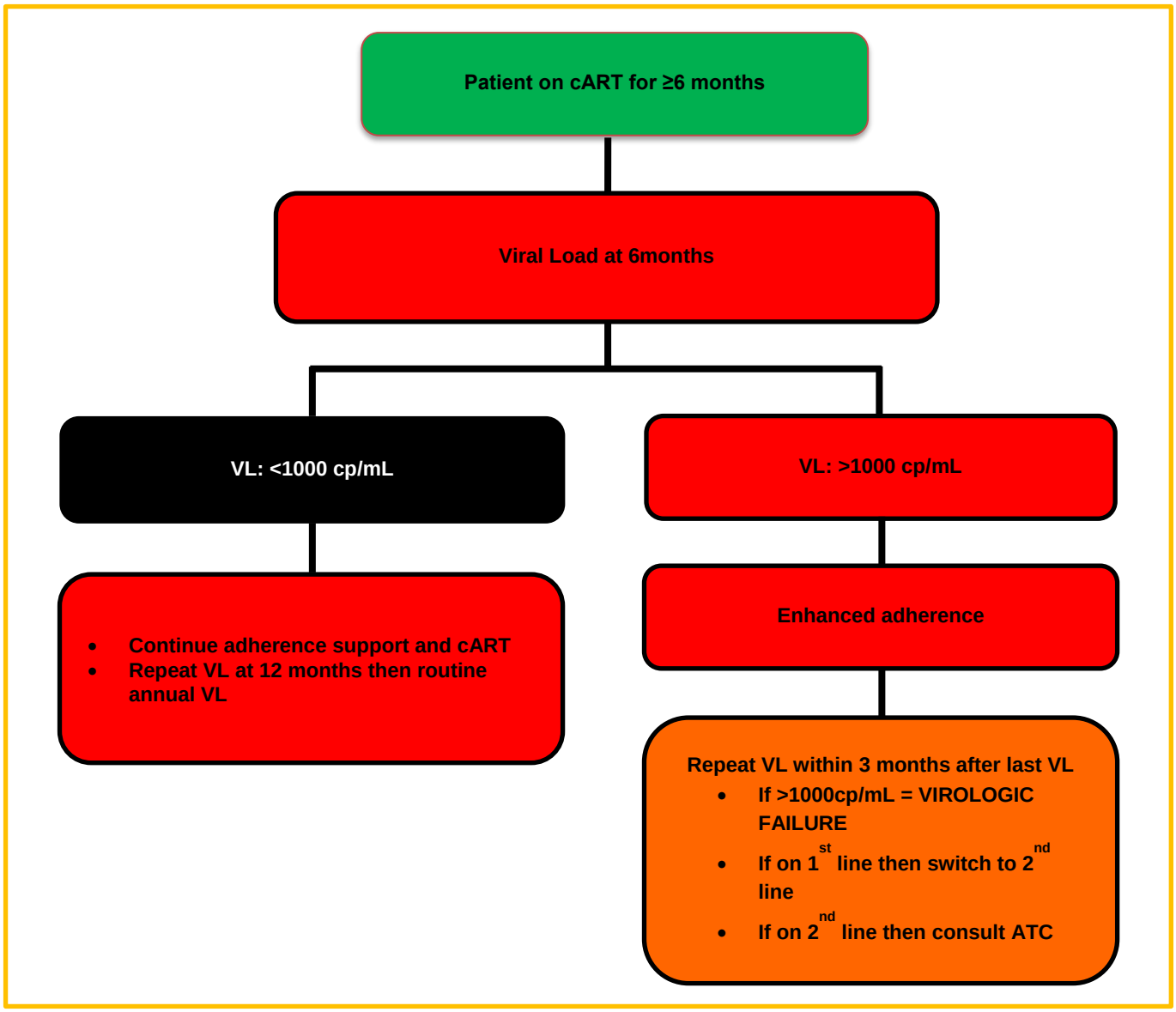
- Clinical monitoring includes history and examination, as well as evaluation of adherence, side effects, and relevant drug toxicities.
- Laboratory tests need to be conducted routinely and as needed (Table 14). It includes CD4 count, viral load, and toxicity monitoring.

The purpose of monitoring includes:

- Evaluation of treatment response and diagnose treatment failure early
- Evaluation of adherence
- Screening for Pulmonary tuberculosis
- Detection of toxicity to ARV drugs

Viral load is recommended as the preferred monitoring approach to determine the performance of cART in an individual. If viral load is not routinely available, CD4 count and clinical monitoring should be used.

FIGURE 11: VIRAL LOAD MONITORING IN PATIENTS ON CART



* Priority should be given to samples for Children when there are limitations to performing Routine Viral Load Testing
* Children may require more frequent viral load monitoring

TABLE 14: CLINICAL AND LABORATORY MONITORING – GENERAL POPULATION

Timeline	Clinical tasks	Laboratory tests
Enrollment and cART initiation	• History and examination • Screen for TB, Cryptococcus • Adherence counseling • PHDP† messages • Initiate cART after adherence counselling • If no signs and symptoms of active TB disease, initiate IPT (i.e. after ruling out TB)	• Serum creatinine • ALT • Hb or FBC • Blood glucose • CD4 count • HBsAg • Syphilis test • Urinalysis for protein and glucose, RBCs • Cholesterol, and triglycerides (especially if starting PI)
Week 2 post-initiation	• Targeted history & examination • Screen for TB, Cryptococcus • Review adherence, side effects, toxicity • Review laboratory tests • Adherence counseling	• Serum creatinine (if on TDF) • Urinalysis (if on TDF)
Week 4 post-initiation	• Targeted history & examination • Screen for TB, Cryptococcus • Review adherence, side effects, toxicity • Adherence counseling	• Serum creatinine (if on TDF) • Urinalysis (if on TDF)
Week 12 post-initiation	• Review adherence, side effects, toxicity* • Adherence counseling • PHDP† messages Review laboratory tests • Refill cART with enough supply to next visit (maximum: 3 months of supply	• Serum creatinine (if on TDF) • Urinalysis (if on TDF)
6 months post-initiation	• Review adherence, side effects, toxicity* • Adherence counseling • PHDP† messages • Review laboratory tests • Refill cART with enough supply to next visit (maximum: 3 months of supply unless transferred to appropriate DSD models)	• Viral load • CD4 cell count * • Serum creatinine (if on TDF) • Urinalysis (if on TDF)
12 months post-initiation and every 12 months	• Review adherence, side effects, toxicity* • Adherence counseling • PHDP† messages • Review laboratory tests • Refill cART with enough supply to next visit (maximum: 3 months of supply unless transferred to appropriate DSD models)	• Viral load • CD4 cell count * • Serum creatinine (if on TDF) • Urinalysis (if on TDF)

TABLE 15: CLINICAL AND LABORATORY MONITORING FOR HIV-INFECTED PREGNANT AND BREASTFEEDING WOMEN

Timeline	Clinical tasks		Laboratory tests	
Day 0: Enrollment & cART initiation	›	History and examination	›	Serum creatinine
	›	If pregnant, focused ANC (FANC)	›	ALT
	›	Screen for TB, Cryptococcus	›	Hb or FBC Blood
	›	Adherence counseling	›	CD4 count
	›	PHDP† messages	›	HBsAg
	›	Initiate cART after adherence counselling	›	Syphilis test
	›	If no signs and symptoms of active TB disease, initiate IPT (i.e. after ruling out TB)	›	Viral load testing at baseline for known HIV positives
			›	Urinalysis for protein and glucose, RBCs
			›	cholesterol, and triglycerides (especially if starting PI)
Week 2 post-initiation	›	Targeted history & examination	›	Serum creatinine
			›	Urinalysis
Week 4 post-initiation	›	Screen for TB, Cryptococcus, and other OIs	›	As needed
Subsequent visits to occur per: › FANC if pregnant › HEI schedule if postnatal and breastfeeding › Adult cART schedule if postnatal and not breastfeeding	›	If pregnant, FANC	HIV viral load to be done every 6 months during pregnancy and breastfeeding period › Serum creatinine and urinalysis at every FANC visit Laboratory testing to occur per: FANC while pregnant except for viral load › VL 1 – 4 weeks before labour & delivery	
	›	Review adherence, side effects, toxicity*		
	›	Adherence counseling		
	›	PHDP† messages		
		Review laboratory tests		
	›	Refill cART with enough supply to next visit (maximum: 3 months of supply		
First postnatal visit	›	CD4 cell count to determine need for continuation of Co-trimoxazole		
24 months after delivery	›	cART dispensed in MNCH until transferred		
	›	Transfer to ART clinic for continuum of HIV care and treatment		
	›	Earlier transfer or referral may be done for logistical reasons or complicated cases		

† Positive Health Dignity and Prevention (PHDP) includes: risk reduction, cART adherence, correct condom use, family planning, STI screening, and partner HIV testing

* See Appendix 3 regarding WHO toxicity estimate

MONITORING DRUG SIDE EFFECTS AND TOXICITIES

Changing an ARV drug should be done only after careful review of adherence. The indication for changing needs to be addressed. A specific ARV drug may be changed (substitution) because of:

- Toxicity, such as anaemia, peripheral neuropathy, lipodystrophy, liver or renal abnormalities
- Intolerance or unresolved and prolonged side effects
- Poor adherence: change indicated only to simplify dosing schedule and to improve adherence
- Occurrence of active TB (refer to section on TB-HIV co-infection)
- Failure (clinical, immunologic, or virologic)

When patients are substituted to alternative regimen (see Table 16), the goals are to achieve HIV viral suppression, avoid adverse events, and optimize adherence.

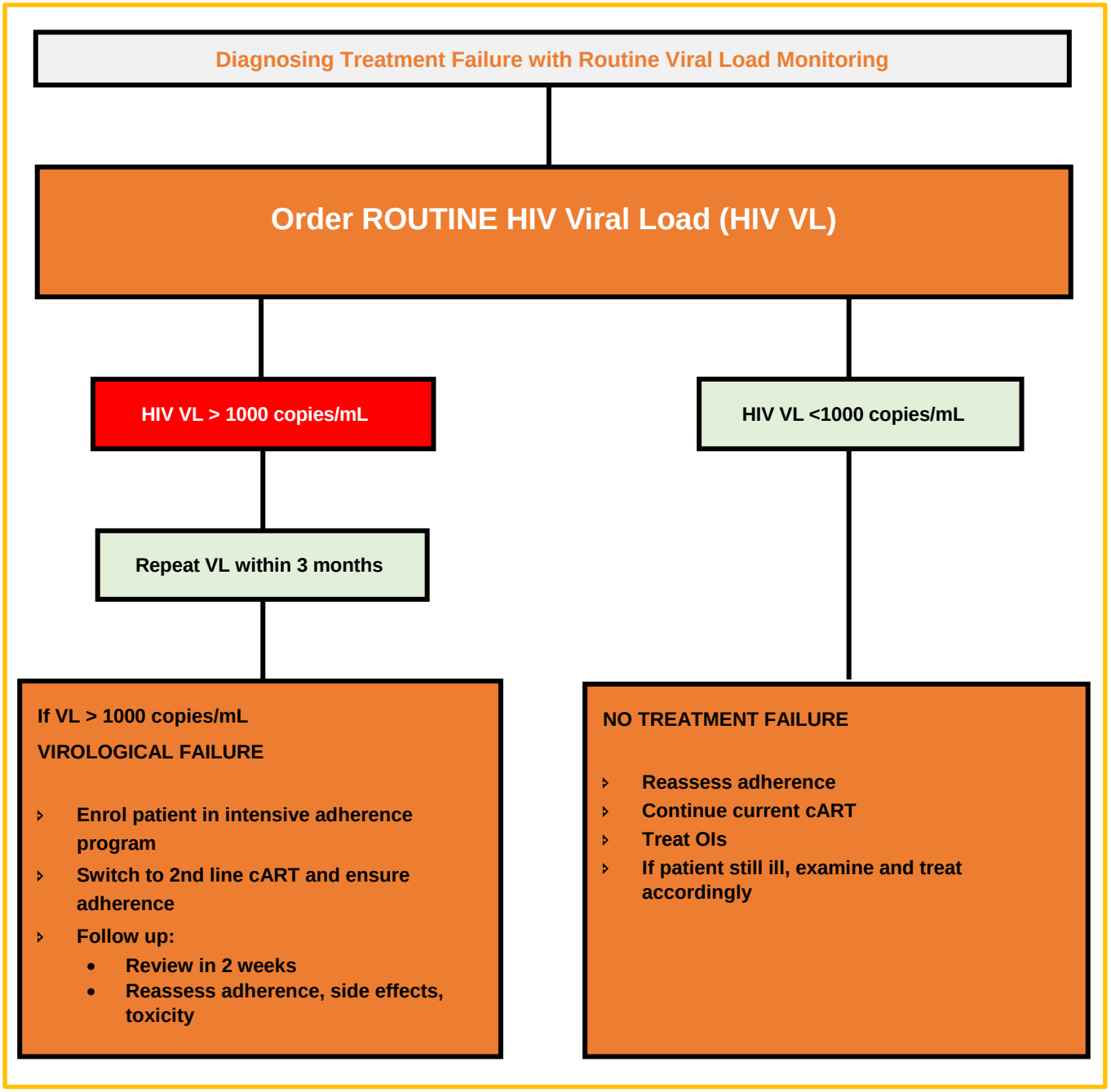
TABLE 16: COMMON CART TOXICITIES AND RECOMMENDED SUBSTITUTES (FOR ALL POPULATIONS)

ARV drug	Common associated toxicity	Recommended ARV substitute
ABC	Hypersensitivity reaction	TDF (if normal creatinine clearance) AZT (if child <10 years old)
ATV-r	Hyperbilirubinaemia, icterus*	LPV-r
AZT**	Severe anaemia or neutropenia, severe gastrointestinal intolerance, lactic acidosis	TDF or ABC (if on 1st line cART regimen; rule out failure before substitution) d4T (if on 2nd line cART regimen for anaemia)
DTG	Insomnia, anxiety, depression and hypersensitivity reactions	ATV-r or LPV-r
EFV	Severe or persistent CNS side effects	ATV-r or LPV-r
LPV-r	Persistent diarrhoea, hyperlipidaemia	ATV-r
NVP (or EFV)	Rash, Stevens Johnson Syndrome, hepatitis	ATV-r or LPV-r
RAL	Rash and hypersensitivity reaction	ATV-r or LPV-r
TAF	Gastrointestinal symptoms, headache	Rarely causes significant side toxicities, if occurs consult expert advice
TDF	Renal toxicity (renal tubular dysfunction)	ABC or TAF

*Hyperbilirubinaemia and icterus do not reflect hepatic disease and are not contraindications to continued therapy. Only substitute ATV-r if the condition is intolerable to the patient.

**AZT should no longer be used in 1st line cART. Patients on AZT-based 1st line cART and are not failing treatment should be substituted to TDF- or ABC-based 1st line cART.

Figure 12: Algorithm for Diagnosing Treatment Failure with Routine Viral Load Monitoring



SWITCHING cART REGIMENS

When patients are switched to second-line cART regimens, the goals are to achieve HIV viral suppression resulting in reconstitution of the clinical and immunologic status, avoid adverse events, and optimize adherence. LPV-r is the primary recommended second-line PI (see Figure 13).

TABLE 17: RECOMMENDED SECOND-LINE cART REGIMENS BY SPECIFIC POPULATIONS

Specific populations	Initial 1st line category	Failing 1st line cART	2nd line cART
Children <5 years old	LPV-r-based first-line regimen	ABC + 3TC + LPV-r	AZT + 3TC + RAL
Children 5-10 years old		AZT + 3TC + LPV-r	ABC + 3TC + RAL
Adolescents and Adults	DTG and NNRTI -based first line regimen	TDF + XTC + DTG*	AZT + 3TC + LPV-r or ATV-r
		ABC + 3TC + EFV**	
		TDF + XTC + EFV*	
		TAF + XTC + DTG*	
		TDF + XTC + NVP**	
		ABC + 3TC + NVP**	
Pregnant & Breastfeeding Women	NNRTI-based first-line regimen	TDF + 3TC + EFV	AZT + XTC + LPV-r or ATV-r

* Represents newer regimens
* *Represents older regimens

TABLE 18: SUMMARY OF PREFERRED SECOND-LINE cART REGIMENS FOR ADULTS AND ADOLESCENTS

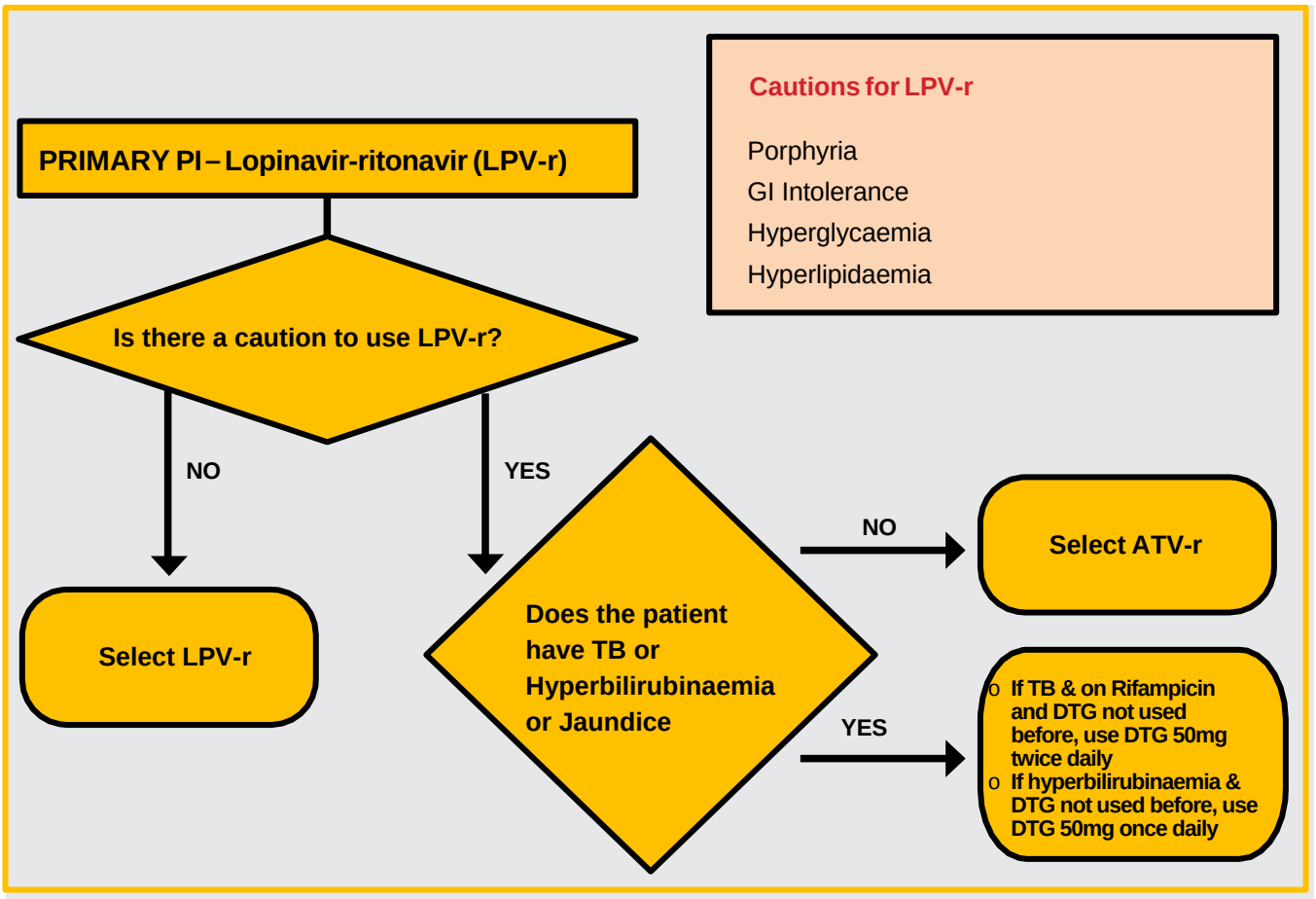
Specific populations		Preferred 2nd line cART	
Adults and adolescents		If AZT was used in first-line cART	TDF + XTC + LPV-r or ATV-r
		If TDF or TAF was used in first-line cART	AZT + 3TC + LPV-r or ATV-r
Pregnant or breastfeeding women		Same regimens as recommended for adults and adolescents as long as no previous NVP exposure without tail coverage	
HIV & TB Co-infection	On Rifampicin based TB treatment	If AZT +3TC + EFV or NVP was used in first-line cART	TDF or TAF + XTC+ DTG (50mg twice daily) *If DTG not available:* *Double dose LPV-r (LPV-r-800mg/200mg twice daily)*
		If TDF or ABC + XTC + EFV or NVP was used in first-line cART	AZT + 3TC + DTG (50mg twice daily) *If DTG not available:* *Double dose LPV-r (LPV-r-800mg/200mg twice daily*
	On Rifabutin based TB treatment	If Rifabutin available use same PI regimens as recommended for adults and adolescents	
HIV and HBV co-infection		AZT + TDF + XTC* + (LPV-r or ATV-r) * TDF+XTC should always be part of the combination in HBV/HIV co-infections	

TABLE 19: RECOMMENDED SECOND-LINE CART REGIMENS FOR HIV-2

Specific populations	Initial 1st line category	Failing 1st line cART	2nd line cART
HIV-1 / HIV-2 Co-infected	DTG -based first-line regimen	TDF + XTC + DTG	AZT + 3TC + LPV-r[a]
HIV-2 mono-infected		ABC + 3TC + DTG	AZT + 3TC + LPV-r[a]

[a] DO NOT substitute with Atazanavir in HIV-1/HIV-2 con-infection or HIV-2 mono-infection. Atazanavir is not active against HIV-2

FIGURE 13: ALGORITHM FOR CHOOSING A PI IN SECOND-LINE



CLINICAL GUIDANCE ON USE OF ATV-R

Administration

- ATV-r is given once a day (300/100mg)
- Do not split or crush ATV-r tablets
- ATV-r should be used in children above 6 years and those weighing >25kg or more and adults

Patient Sensitization

- ATV-r is safe for use in pregnancy
- Ensure patients on ATV-r drink plenty of fluids to reduce the risk of kidney stones
- A common side effect associated with ATV-r is jaundice, which is benign and in most cases, should resolve in a few weeks.
- Jaundice from unconjugated hyperbilirubinaemia is largely a cosmetic issue and not related to hepatitis or liver damage
- A liver function test, if available, should be conducted to help rule out other causes of jaundice
- If patient has symptomatic or profound jaundice, consult the UTH Advanced Treatment Centre

Contraindications

- **Do not use ATV-r** with Rifampicin-containing TB treatment. If patient is on ATV-r with no exposure to DTG in first line and they develop TB replace ATV-r with DTG 50mg twice daily (see Figure 13).
- Do not use ATV-r with proton pump inhibitors (Omeprazole, Pantoprazole, Lansoprazole).
- Substitute PPIs (Omeprazole) with H2 receptor blockers (e.g. Cimetidine). It should be taken 2-3 hours apart with ATV-r
- Do not start patients with pre-existing jaundice or suspected hepatitis on ATV-r

MANAGEMENT OF PATIENTS PREVIOUSLY ON cART (INCLUDING DEFAULTERS)

Individuals who interrupt cART for any reason are at increased risk of resistance and treatment failure. Management in cART re-initiation is based on several factors, and a complete history to establish why the treatment was stopped is critical. For HIV- infected children, the caregivers must be questioned.

- If treatment failure or toxicity is not suspected as the reason for stopping cART, and previous good adherence is reported, reinitiate original cART in consultation with next level.
- If previous adherence is poor and there is treatment failure, these individuals (and caregivers of children) MUST be enrolled in intensive adherence counseling sessions until there is agreement among the patient, provider, and adherence counsellor that the patient is ready to commence second line cART. Use of treatment supporters for such patients is strongly recommended.
- If severe toxicity is the reason for stopping cART, refer to the next level and initiate cART using the appropriate drug substitution and counsel regarding adherence.
- Viral load testing should be done 6 months after re-initiation of the original regimen to document HIV viral suppression.

When to stop cART

Patients may choose to postpone or stop therapy, and providers, on a case-by-case basis, may elect to defer or stop therapy on the basis of clinical and/or psychosocial factors.

The following are indications for stopping cART:

- Patient's inability to tolerate all available ARV medications
- Patient's request to stop after appropriate counselling
- Non-adherence despite repeated counselling: treatment should be stopped to avoid continued toxicity, continued evolution of drug resistance, and transmitting drug resistant HIV
- Unreliable caregiver
- For children, the caregiver is instrumental in ART adherence. Any factors that affect the capability for the caregiver to give medications consistently may be an indication to stop cART in an HIV-infected child.
- Serious drug toxicity or interactions
- Intervening illness or surgery that precludes oral intake
- ARV non-availability

How to stop cART

- Stop ALL the drugs when discontinuing therapy
- Discontinue EFV or NVP; continue the NRTI components (backbone) for 1-2 additional weeks
- Preventive measures, such as condom use and safer sex practices, should be strongly emphasized for all patients, especially those discontinuing treatment

Treatment Failure with No Further Treatment Options

Continue the failing cART regimen unless there are intolerable toxicities or drug interactions. Even with treatment failure, the regimen is likely to have some residual antiviral activity. Stopping therapy in the setting of virologic failure can be associated with rapid falls in CD4 counts and development of OIs.

When to Consult or Refer to the Next Level

The following criteria are indications to consult or refer to the next level:

- Suspected hepatotoxicity not responding to standard management (e.g. TB/HIV co-infection treatment, ALT/AST >5-fold of upper limit of normal)
- Second line treatment failure or inability to tolerate second-line therapy
- Complications on PI-based regimen
- Severe or life-threatening adverse reactions
- Inability to tolerate therapy despite change in regimen
- HIV-HBV co-infection with renal insufficiency

THIRD-LINE CART: SECOND-LINE TREATMENT FAILURE

Treatment failure is defined by a persistently detectable viral load >1,000 copies/mL. For adolescents and adults, failure is two consecutive viral load measurements within a three-month interval, with adherence support between measurements after at least six months of using triple combination ARV drugs. For children, viral load may still be detectable at 6-9 months after initiation and does not necessarily mean treatment failure. Viral blips or intermittent low-level viremia (20–1,000 copies/mL) can occur during effective treatment, but have not been associated with an increased risk of treatment failure unless low-level viremia is sustained. A repeat blip should be assessed further at the ATC. Additionally, clinical and epidemiological studies show that the risk of HIV transmission and disease progression is very low when the viral load is lower than 1,000 copies/mL

Provision of third-line cART occurs in very rare circumstances and is beyond the scope of most cART providers. All patients being considered for third-line cART should have:

- Confirmed second-line cART failure (defined by a persistently detectable viral load exceeding 1,000 copies/mL [i.e., two consecutive viral load measurements within a three-month interval with enhanced adherence support between measurements] after at least six months of using second-line cART)
- Genotype (resistance) testing
- Refer (see Figure 14) to an HIV Specialist at an Advanced Treatment Centre (ATC) with a complete cART treatment history (i.e., all previous ARV drugs that the patient has taken with duration of use)
- Before starting third line, establish the reason for treatment failure (e.g., poor adherence, suboptimal dosing, drug-drug interactions) and conduct intensive adherence counseling sessions until there is agreement between the patient, provider, and adherence counselor that the patient is ready to commence third-line cART
- Use of treatment supporters for such patients is STRONGLY recommended
- The most likely ARVs to be successful in patients who have followed National Guidelines are Dolutegravir or Raltegravir (Integrase inhibitor) or Darunavir with ritonavir (Protease inhibitor) plus optimal nucleoside background (e.g. TDF+XTC or AZT+3TC)

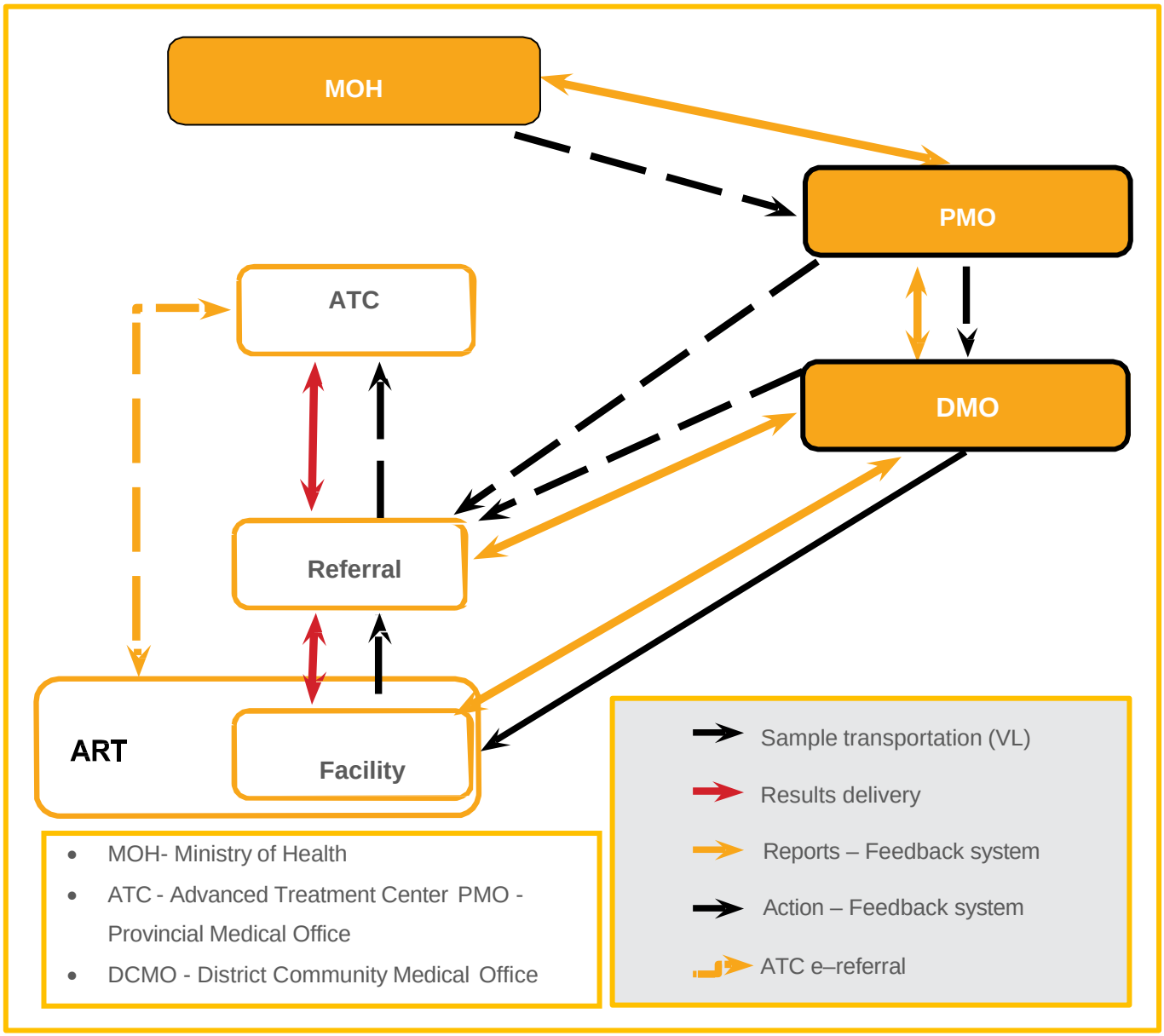
Other considerations with major constraints:

- Etravirine: especially if genotype is available at time of 1st line NNRTI failure, although in some patients NNRTI mutations persist even after non-exposure to NNRTIs in second line
- Maraviroc: needs special tropism test before initiation, which is currently not available in Zambia

Before switching therapy in suspected treatment failure, HCWs need to rule out:

- Poor adherence: change therapy only after enhanced adherence counseling has been conducted
- Immune Reconstitution Inflammatory Syndrome (IRIS): treat underlying condition and continue cART if tolerated
- Untreated OIs: treat underlying condition and continue cART if tolerated
- Pharmacokinetics (e.g. Rifampicin reduces NVP or LPV-r blood levels): switch NVP to EFV or double the dose of LPV-r or switch Rifampicin to Rifabutin
    - Current infections causing transient decrease in CD4 count: treat infection, and if possible, repeat CD4 one month after resolution of illness to confirm immunologic failure

FIGURE 14: INFORMATION PATHWAYS FOR PATIENTS NEEDING ATC SERVICES



NUTRITIONAL CARE

Nutrition in HIV-Infected Children

Routine assessment is essential to identify malnutrition and growth faltering early. The following should be done for HIV-infected infants and children:

- Assess nutritional status, diet, and symptoms at every visit
- Laboratory monitoring includes: total cholesterol, triglycerides, glucose, and Hb
- Assess WHO clinical stage, ask about history of recent diseases such as persistent diarrhoea or OIs (associated with increased nutritional need), determine energy needs, and provide additional energy
- Measure weight and height at each visit and plot against national growth curves
    - Normal growth
    - Underweight (weight-for-age <3rd %)
    - Stunted (height-for-age <3rd %)
    - Wasted (weight-for-height <3rd %)
- If normal child growth, inform on healthy eating and avoidance of obesity
- If poor child growth
    - Full dietary assessment is needed
    - Assessment of drug adherence if the child is on cART
    - Mothers or caregivers should be asked about food availability and food types offered to the child, as well as who feeds the child, how much, and how often children should be examined for signs of OIs or wasting
    - Provide appropriate clinical interventions (e.g., food support programmes)
- If severe malnutrition
    - Stabilize the acute phase of malnutrition, similar to HIV-uninfected children with severe malnutrition, and initiate cART soon after
    - Immediately initiate cART if unexplained malnutrition (e.g., not associated with untreated Opportunistic Infection [OI]) and does not respond to standard nutritional therapy
    - If unknown HIV status, test for HIV and consider cART initiation as needed
- If on cART, reassess frequently to adjust dose as needed. Recurrence of growth failure and severe malnutrition may indicate treatment failure, poor cART adherence, or OIs.

Nutrition supplementation

- Give high-dose vitamin A supplementation every 6 months for children 6 to <60 months old
- Give Zinc supplementation for acute diarrhoea
- Mothers should exclusively breastfeed HIV-infected infants and young children for 6 months minimum and may continue up to 2 years old

Infant and Young Child Feeding

As a public health approach, all mothers should be encouraged to practice exclusive breastfeeding (EBF) for 6 months (Table 20). EBF is defined as giving a baby only breast milk and no other liquids or solids, not even water unless medically indicated. Thereafter, mothers should introduce nutritionally adequate complementary feeding while continuing breastfeeding up to at least 24 months old. Replacement feeding should only be considered if acceptable, feasible, affordable, sustainable, and safe (AFASS).

TABLE 20: INFANT AND YOUNG CHILD FEEDING OPTIONS

Maternal HIV status	Infant HIV status	Recommended Feeding	Timing of Complementary feeding	Recommended Timing of Complete Cessation of Breastfeeding*
Positive on cART	Negative or unknown	Exclusive breastfeeding (EBF) for 6 months Replacement feeding	After 6 months	At 12 months if food security assured Up to 2 years if food security not assured
Positive	Positive	EBF for 6 months		Up to 2 years
Negative or unknown	N/A	EBF for 6 months		Up to 2 years

*HIV-infected women should stop breastfeeding (at any time) gradually within one month.

Nutrition in HIV Infected Adolescents, Breastfeeding Women and Adults

- Calculate the body mass index (BMI) = weight/height^2 to determine if the individual is underweight (<18.5kg/m^2), normal (18.5 to 24.9kg/m^2), overweight (25 to 29.9kg/m^2), or obese (≥30kg/m^2).
- If BMI <16kg/m^2 or anaemia (Hb <10g/dL) or has TB, refer for nutrition support programmes. Observe closely for treatment complications, such as re-feeding syndrome, undiagnosed OIs, and IRIS.
- If BMI >25kg/m^2, provide nutrition counseling, including dietary advice and need for physical exercise.
- **Table 19** lists some of the specific BMI-related ARV drug risks

TABLE 21: SPECIFIC BMI-RELATED ARV DRUG RISKS

BMI	ARV drug	Associated Risks	Recommended Actions
<1kg/m^2	TDF	Tubular renal dysfunction Fanconi syndrome	Manage these patients with caution. Consult next level if necessary.
>25kg/m^2	AZT	Lactic acidosis Severe hepatomegaly with steatosis	
	d4T	Lactic acidosis Severe hepatomegaly with steatosis Acute pancreatitis	

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME AND HIV

Immune reconstitution inflammatory syndrome (IRIS) is an exaggerated inflammatory reaction from a re-invigorated immune system presenting as unmasking of previously sub-clinical opportunistic infections OR clinical deterioration of pre-existing opportunistic infections OR development of autoimmune disease.

- Onset: usually within 2-12 weeks after starting cART
- Frequency: 10% among all patients on cART, up to 25% when cART initiated with CD4 <50 cells/µL
- Risk factors:
- Initiating cART close to diagnosis of an opportunistic infection
    - Initiating cART when CD4 is less than 50 cells/µL
    - Rapid initial fall in HIV-1 RNA level in response to cART in patients with low CD4 counts
    - Commonly seen with TB, cryptococcal disease, Kaposi's sarcoma, and Mycobacterium avium complex infection
    - Patients initiated on DTG and with low cd4 counts have a higher risk of having IRIS

Management of IRIS

- Have high index of suspicion with early complications
- cART should be continued
- If cART continuation is impossible, temporarily interrupt the cART and restart same regimen after OI or IRIS is addressed
- Diagnose and treat OI or inflammatory condition
- Corticosteroid treatment in moderate to severe cases: Prednisolone 0.5-1.0mg/kg/day for 5-10 days

Recommendations

Strengthening adherence support interventions at the community level

Provider-Related Strategies to Improve Adherence

- Establish trust and make sure the patient feels you are there to help manage and solve problems
  - Involve the patient in developing a plan for taking the drugs that is simple and works with the patient's daily activities
  - Educate about goals of therapy, side effects, what will happen if the patient does not take all the drugs
- Treat depression or substance abuse issues
- Treat and manage side-effects
- Monitor adherence at each visit
- Reinforce importance of adherence at each follow-up visit

Ensure patients identify treatment supporters with whom they are comfortable (e.g., family members, buddies) and encourage treatment supporters to attend counselling sessions and clinic visits

Main Populations to be targeted for reinforced adherence

- **Late** - classified as late up to 60 days of missing scheduled appointment
- **Lost to follow up (LTFU)** - more than 60 days after last scheduled pharmacy pick up (all tracking efforts have been exhausted) and patient cannot be traced
- **Defaulter** - when a person who has been located as late or lost to follow up chooses not to return to care
- **Unknown status** - tracking measures not exhausted to determine enrolment status

Structured treatment preparation before cART initiation (**Table 10** and **Figure** 8) should be conducted for all patients for successful HIV treatment and care. Take note that cART can be initiated during any of these sessions (all patients should be fast-tracked after looking at safety and also readiness):

- Session 1: Enrolment and Assessment, HIV education and cART initiation
- Session 2: cART support, preparation and cART initiation
- Session 3: cART education, preparation, and cART initiation

Adherence assessment should be done by all members of the health care team using:

- Clinical and laboratory parameters
- Patient reports
- Pill counts
- Pharmacy pick-ups
- Other tools of adherence

CO-MORBIDITIES

Recommendations

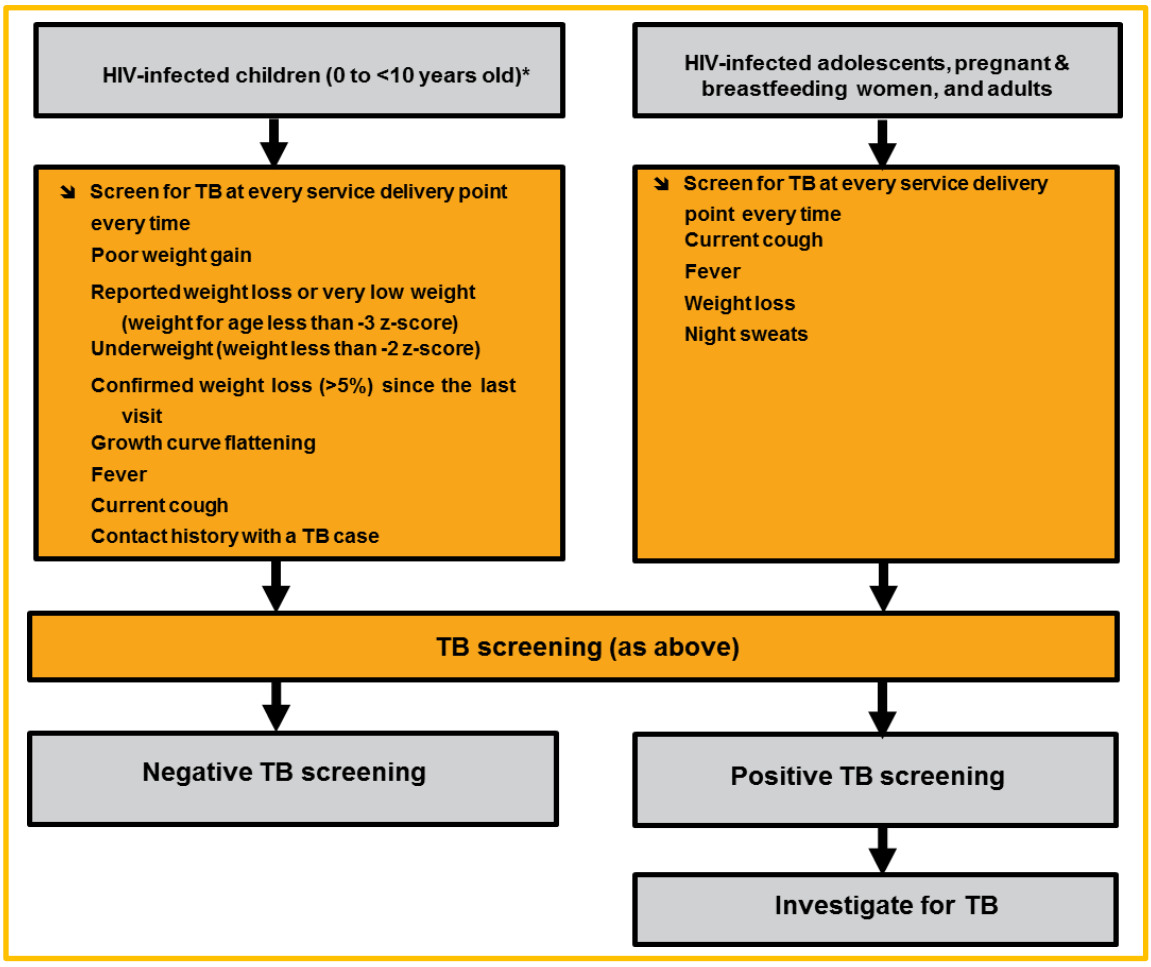
- cART should be started in all TB patients living with HIV regardless of CD4 count
- Xpert MTB/RIF is the preferred diagnostic test for HIV associated TB
- Assessment and management of Cardiovascular Diseases (CVDs) in all HIV patients

TUBERCULOSIS AND HIV

There is a high incidence of TB among HIV-infected persons. All HIV-infected individuals should be screened for TB and placed on TB treatment if found with TB. HIV-infected individuals with TB should begin anti-tuberculosis therapy (ATT) via directly observed therapy, short course (DOTS) as per National TB Guidelines. Persons who screen negative for TB should be given TB INH Preventive Therapy (TB-IPT).

Screening for Active Tuberculosis

FIGURE 15: TB SCREENING ALGORITHM



Diagnostic Tools and Tests for TB

Tools and tests used for TB diagnosis provide either a definitive diagnosis (bacteriological confirmation of TB) or supportive information to aid diagnosis of tuberculosis.

Key Messages

- Xpert MTB/RIF is recommended as the initial diagnostic test in all presumptive TB patients
- Smear microscopy may continue being the initial test in settings where Xpert MTB/RIF is not yet available
- Smear microscopy --- and NOT Xpert MTB/RIF --- should be used for treatment monitoring
- All TB retreatment patients tested RIF negative on Xpert MTB/RIF should have FL LPA, Culture and DST
- All DR-TB and RIF positive on Xpert MTB/RIF patients should be tested with SL LPA, Culture and DST
- A negative laboratory test (i.e. smear, Xpert MTB/RIF, LPA and/or culture) in the setting of a TB-compatible clinical presentation does NOT definitively rule out TB. Such patients should be clinically evaluated for TB.
- Patients with strong clinical evidence of TB (especially PLHIV, Children, EPTB) should start TB treatment even if bacteriological tests are negative or not available (clinically diagnosed TB)

Bacteriological Tests for TB Diagnoses

Xpert MTB/RIF

Xpert MTB/RIF test * is a fully automated real time PCR based (molecular) test, disposable, cartridge-based nucleic acid amplification test.

- Highly sensitive and specific, more sensitive than smear microscopy.
- Rapid and simultaneous detection of tuberculosis and Rifampicin resistance (a reliable proxy for MDR-TB).
- Results are available within 2 hours.
- Xpert MTB/RIF should not be used for follow up (use smear microscopy instead)
- Collect one spot specimen (3-5 mL).
- Submit the specimen as soon as possible for testing. Samples must be stored at 2-8°C for maximum of 5 days or at room temperature for a maximum of 3 days if testing cannot be done on the same day.
- Xpert MTB/RIF is recommended as the first diagnostic test in all adults and children with signs and symptoms of TB where available (Algorithm 1).
- If not available, the samples from Priority* patients should be referred to facilities with GeneXpert machines (PLHIV, Children, EPTB, risk of DR-TB, HCW, miners, prisoners).

Limitations:

- Does not detect resistance to Isoniazid or other first- or second-line anti-tuberculosis medications
- Cannot be used for treatment monitoring (may remain positive even after treatment kills the bacteria because it detects TB DNA and not live bacteria).

XPERT MTB RIF MACHINE

Xpert MTB RIF Cartridge

Reporting Xpert MTB RIF Results

Reporting Xpert positive results must also include the results from Rifampicin resistance testing
- MTB detected, RR+ve (MTB detected with Rifampicin resistance detected)
- MTB Detected, RR-ve (MTB detected with no Rifampicin resistance detected)
- MTB detected, RRI (MTB detected Rifampicin resistance indeterminate)

Xpert Negative results must be reported:
- MTB not detected

In rare cases, where the only result that is available for Xpert MTB RIF is error, invalid or no result- this result should be captured as below and a repeat sample collected for testing:
- Err, Inv, No result

**Operational problems associated with this test include: the shelf-life of the cartridges is only 18 months, a very stable electricity supply is required, the machine needs to be calibrated annually, and the temperature ceiling is critical*

Smear Microscopy

Smear microscopy is the first diagnostic test in facilities where Xpert MTB/RIF is not available. Smear microscopy is recommended to monitor treatment response (follow up). Results should be reported according to Tables 22-23.

Limitations:

It is often negative in PLHIV, children and EPTB samples and cannot detect rifampin resistance.

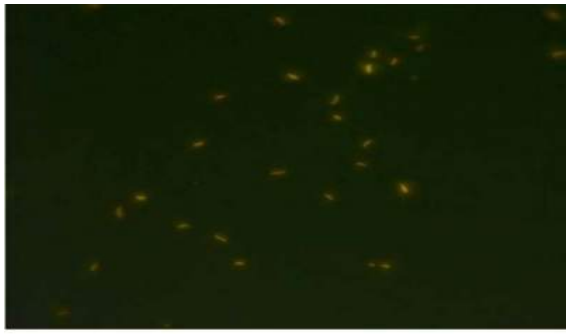
- Two spot specimens should be collected for smear microscopy at the time of request (at least 15 to 30 minutes apart).
- Should be used for treatment monitoring.
- LED microscopy has a sensitivity gain of 10% over ZN and should be used in place of ZN.
- The results of positive sputum examination should be recorded in red ink in the register for easy identification.
- Sputum results must be reported within 24 hours.

Key Message

Sputum smear microscopy should only be used for diagnosis where Xpert MTB RIF is not accessible and in such an instance, ensure sample is sent for Xpert at the nearest centre

LED MICROSCOPE

ACID FAST BACILLI



The following WHO recommended method of reporting of smear microscopy results should be used.

TABLE 22: REPORTING FOR FLUORESCENCE MICROSCOPY (FM) RESULTS

200x	400x	Result Reported
No AFB in one length	No AFB in one length	No AFB Seen
1– 4 AFB in one length	1 – 2 AFB in one length	Report actual number *
5 – 49 AFB in one length	3 – 24 AFB in one length	Scanty Positive
3 – 24 in one field	1 – 6 AFB in one field	1+
25 – 250 AFB in one field	7 – 60 AFB in one field	2+
>250 AFB in one field	>60 AFB in one field	3+

**Confirmation required by another technician or prepare another smear, stain and read. Report as positive (actual number only if the result is confirmed by a second reader of a repeat smear)*

TABLE 23: REPORTING OF ZIEHL–NEELSEN (ZN) RESULTS

Number of bacilli seen in smear	Results	Result Reported
No AFB in 100 fields	Negative	No AFB Seen
1 – 9 AFB in 100 fields	Positive	Record exact number of bacilli
10 – 99 AFB in 100 fields	Positive	1+
1 – 10 AFB per fields, check 50 fields	Positive	2+
>10 AFB per field, check 2o fields	Positive	3+

Line Probe Assay (LPA)

LPA is based on polymerase chain reaction (PCR) and the DNA strip technology. LPA does not eliminate the need for conventional culture and phenotypic drug susceptibility testing. LPA is available in Zambia at referral Mycobacterial culture laboratories. Line Probe Assay can be performed directly using a processed sputum sample or indirectly using DNA isolated and amplified from a culture of *M. tuberculosis*.

First-line LPA is recommended for the rapid detection of resistance to rifampicin and isoniazid in sputum specimens and cultures of *Mycobacterium tuberculosis*. It is recommended on DR –TB suspected patients with MTB detected and RIF negative on Xpert.

Second-line drugs Line probe assay (SL LPA) is recommended for patients with confirmed Rifampicin resistance (RR-TB) or multi drug resistant tuberculosis (MDR-TB);

TABLE 24: INTERPRETATION OF RESULTS FOR LPA

Result	Interpretation
MTB complex detected	MTB was isolated from the specimen therefore the patient has bacteriologically confirmed TB
MTB complex not detected	MTB was not isolated from the specimen
Rifampicin and Isoniazid susceptible	Patient has drug susceptible TB
Rifampicin and Isoniazid resistant	Patient has multi drug resistant TB (MDR-TB)
Rifampicin resistant and Isoniazid susceptible*	Patient has Rifampicin resistance (RR-TB)
Rifampicin susceptible and Isoniazid resistant	Patient has Isoniazid resistance

Mycobacterial Culture

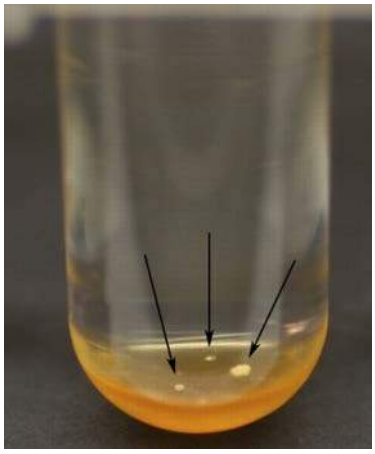
Culture is the gold standard for TB Diagnosis.

- Highly sensitive and specific method.
- There are two culture methods available, namely solid and liquid. If liquid culture is used, sensitivity gain is +10% compared with Löwenstein-Jensen solid culture.
- Refrigerate culture specimens at 2-8°C until ready for transport to the laboratory.
- If a refrigerator is not available, specimens must be held in coolers with ice packs.
- Specimens must be delivered as soon as possible, but no later than 48 hours from time of collection.

Limitations:

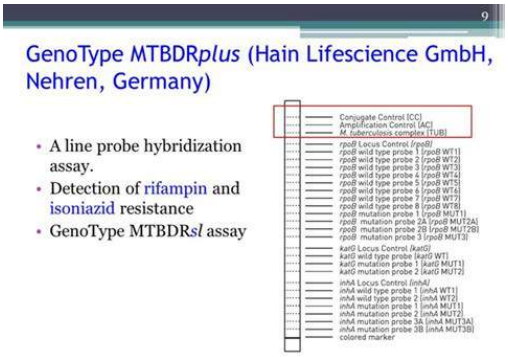
- Long turnaround time of the results (Liquid 21 days, Solid 48 days to inform a negative result)
- Expensive

Positive Liquid Culture



Positive LJ Culture

Genotype Results



Culture is recommended for:

- All previously treated TB patients (loss to follow up, retreatment, failure)
- Smear-positive after 2 months of first line treatment
- Drug resistant TB contacts
- RR TB patients by Xpert MTB/RIF
- Patients who develop active PTB during or after IPT
- Health care worker, miners, prisoners
- Extra-pulmonary specimens
- Specimens from Children
- Diagnostic uncertainty

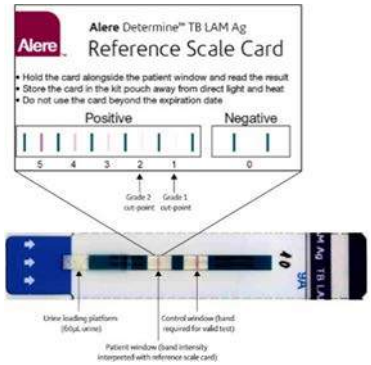
TABLE 25: INTERPRETATION OF RESULTS FOR CULTURE

Result	Meaning
Mycobacterium tuberculosis isolated	Positive
Mycobacterium tuberculosis not isolated	Negative
Contaminated	Specimen not properly handled (repeat specimen collection)
Not Done	The test was not performed due to many reasons such leaked specimen, mismatch information on the sample and request form and insufficient specimen etc.
Mycobacteria's other than Mycobacterium tuberculosis isolated (MOTT)	Non Tuberculous Mycobacterium (NTM) which may or may not be clinically significant

Notes: A practical description of all the procedures for sputum smear microscopy, culture and DST and Xpert MTB/RIF are detailed in the relevant TB laboratory Manuals.

Phenotypic Drug Susceptibility Test (DST)

Phenotypic, culture methods are based on assessment of the ability of *M. tuberculosis* to grow in culture media (solid or liquid) containing a critical concentration of specific anti-TB agents (which indicates resistance) or, conversely, its inability to grow in the same media (which indicates susceptibility).

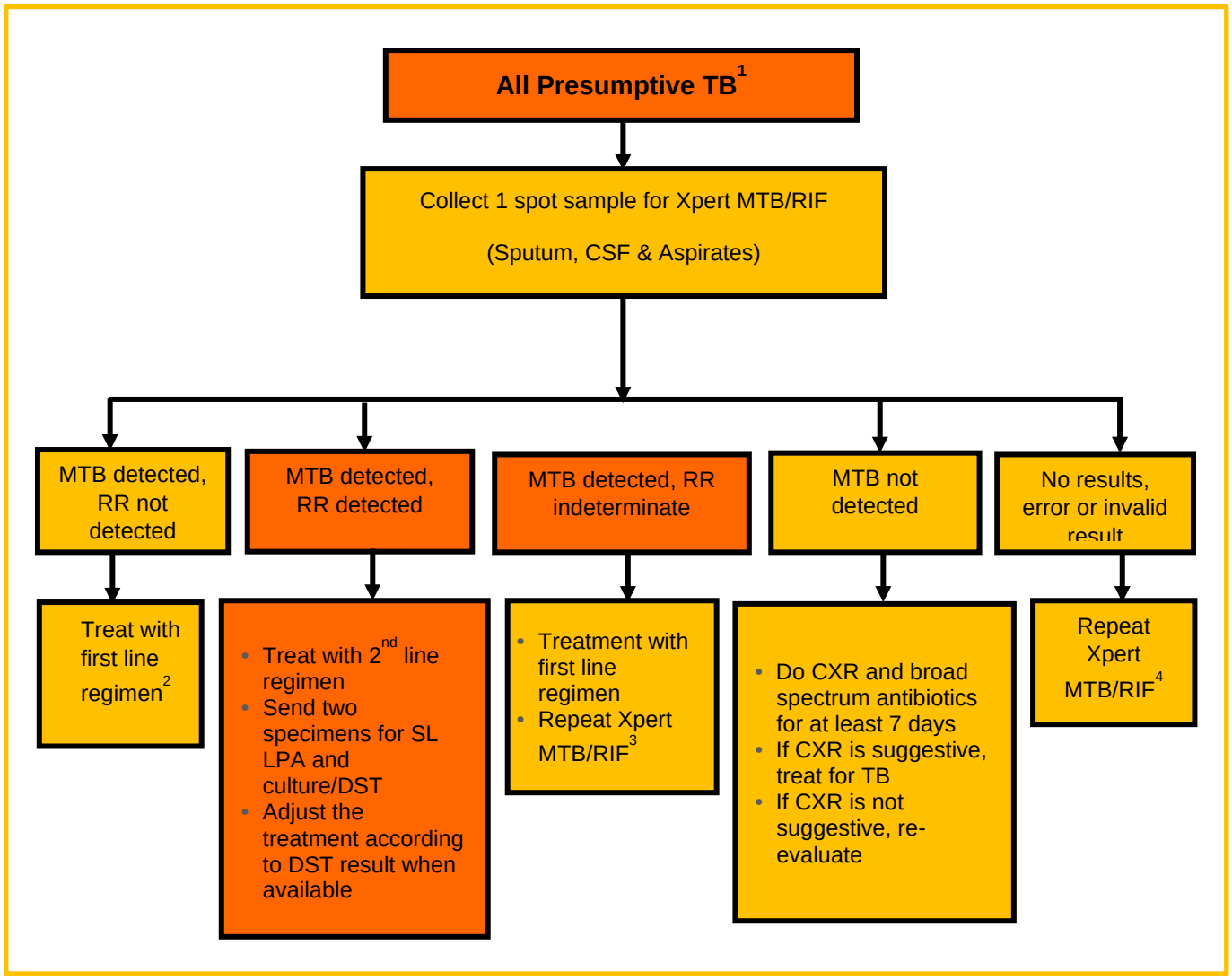


- Phenotypic DST for first-line agents (Isoniazid, Rifampicin Ethambutol and Streptomycin), and selected second-line anti-TB drugs (Kanamycin, Amikacin, Ofloxacin, Levofloxacin) is generally reliable and reproducible.
- Other anti-TB agents such as the later generation fluoroquinolones (Moxifloxacin and Gatifloxacin), Capreomycin, Thioamides, Cycloserine and Pyrazinamide are becoming increasingly important in the treatment of DR-TB and there is a need for their critical concentrations to be re-evaluated
- DST methods for new and repurposed drugs for the treatment of MDR-TB such as Bedaquiline, Delamanid, Linezolid, Clofazimine need validation.

Lateral Flow Urine Lipoarabinomannan (LF-LAM)

- Tests based on the detection of LAM antigen in urine. LAM antigen is released from metabolically active or degenerating bacteria.
- A positive results is diagnostic of active TB disease
- A negative results does not rule out TB
- Urine is easy to collect and the test can be performed at bed side, and lacks the infection control risks associated with sputum collection.
- Is recommended for HIV-positive persons with low CD4 (<100 cell/µL) counts and signs and symptoms of TB (pulmonary and/or extrapulmonary) OR who are seriously ill/ hospitalized regardless of CD4 count or without a known CD4 count.
- Can be used as an additional test in a critically ill patient with sputum negative

FIGURE 16: XPERT MTB RIF ALGORITHM



[1] For PLHIV who have CD4 counts ≤100 cells/µl or are seriously ill with one or more danger signs, a urine LF-LAM assay may also be used if available.

[2] Patients should be initiated on a first-line regimen. A sample may be sent for first-line LPA and culture/phenotypic DST if there is a risk of DR-TB:

- Previously treated TB patients: loss to follow up, retreatment, failure
- DR-TB contacts
- Smear positive at month 2 of first-line treatment
- Health care worker
- Miners
- Prisoners

If patient has high risk of DR TB as a contact of a DR TB patient and patient is failing first line treatment, start second-line treatment while waiting DST results

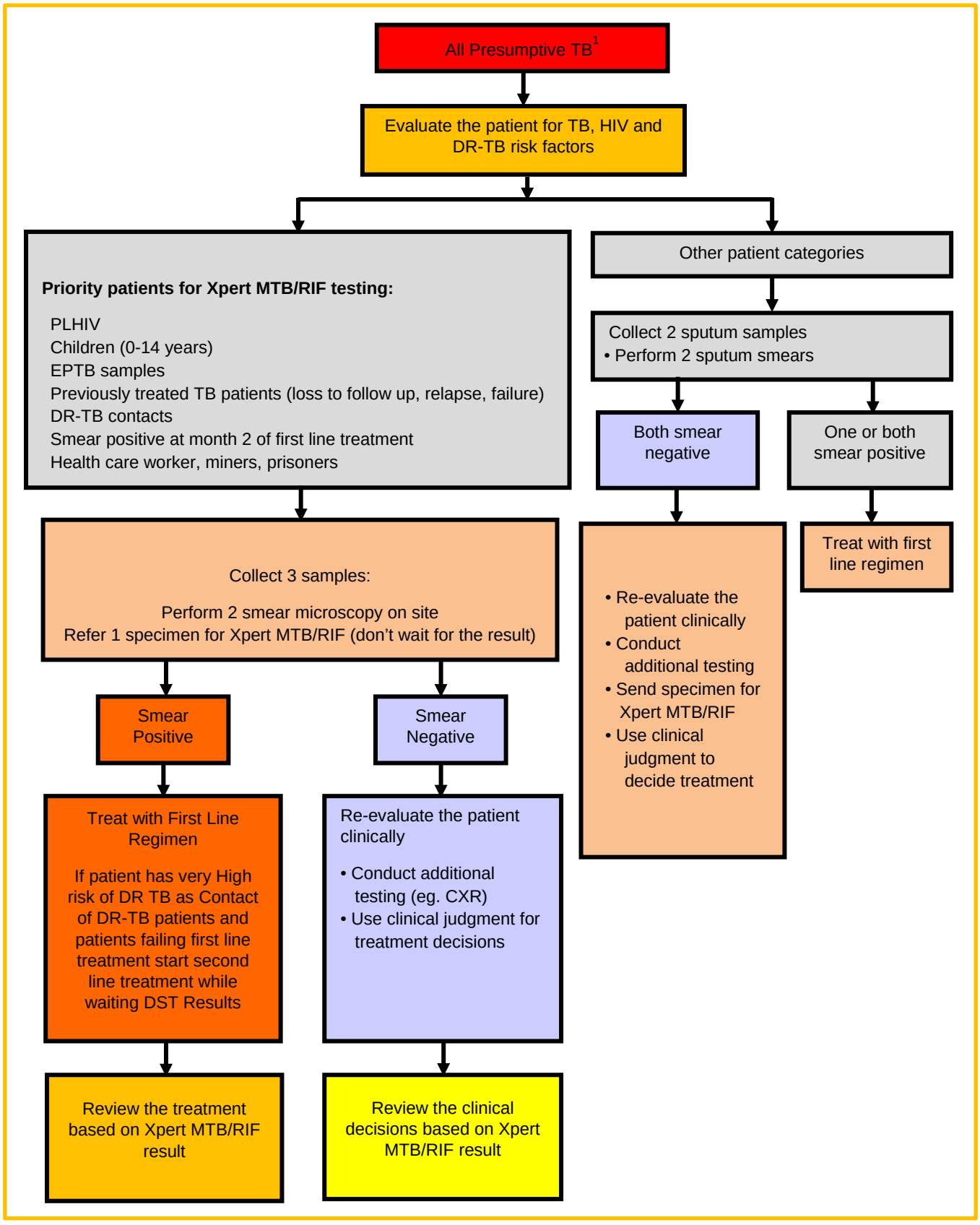
[3] Treat the patient according to result of the repeat test. If the second Xpert MTB/RIF is negative, continue the first line TB treatment and send specimen for FL LPA, culture and phenotypic DST
Note that FL-LPA is recommended for use with smear-positive sputum samples only.

[4] Treat the patient according to result of the repeat test.

Figure 17 is an interim algorithm in facilities where Xpert MTB/RIF is not yet available for all presumptive TB patients but is only available for priority populations, and smear microscopy is used for other patients.
HCW need to assess carefully the patients and ensure that all the priority patients (i.e. PLHIV, children, EPTB and patient with risk of DR-TB) collect and send samples to a facility where Xpert MTB/RIF is available.

HCW should decide the treatment of the patients without waiting for Xpert MTB/RIF results (as it can be delayed). Consider the possibility of clinically defined TB (i.e., no bacteriological confirmation).Use clinical judgement for treatment decisions. When the Xpert MTB/RIF result is available, treatment can be adjusted accordingly.

FIGURE 17: ALGORITHM OF SPUTUM SMEAR PLUS PRIORITY PATIENTS FOR XPERT MTB/RIF TESTING (FOR FACILITIES WITHOUT XPERT MTB/RIF ACC)



TUBERCULOSIS TREATMENT AND MANAGEMENT

Key Messages

- First Line treatment (previously Category I) remains the same: 2 RHEZ/4 RH
- TB meningitis and Osteoarticular/spine TB are treated for 12 months (2RHEZ/10 RH)
- Category II treatment (2SRHEZ/1RHEZ/5RHE) should no longer be prescribed
- All previously treated patients should have their samples sent for Xpert MTB/RIF, First Line LPA, Culture and phenotypic DST to guide the treatment. Start first line treatment while awaiting the results.
- All DR TB contacts with a diagnosis of TB should start second-line treatment while awaiting the DST Results
- Patients failing first line treatment should start second-line treatment while awaiting the DST results
- Patients diagnosed with TB and are HIV infected should initiate cART within 2-3 weeks once TB treatment is tolerated. In cases of TB Meningitis, TB therapy should be delayed until after 8 weeks on TB therapy

Aims and Principles of TB Treatment

Early case finding and adequate treatment of tuberculosis using DOTS is the cornerstone of TB control.

The aims of treatment are:

- To cure patients and restore their quality of life and productivity
- To prevent further transmission of TB in the community
- To prevent relapse
- To prevent death from active TB or its late effects and complications
- To prevent the development of drug resistance—including MDR-TB and XDR-TB

The Principles of TB Treatment are:

- TB treatment involves use of correct doses of multiple drugs to ensure effectiveness of therapy
- Never add a single drug to a failing regimen
- At no time should monotherapy (use of a single anti-TB drug) be employed as treatment for active TB
- TB drugs should be taken daily for a specified period depending on the severity of the disease

Essential Anti-TB Medicines

The recommended essential first-line anti-TB medicines are Rifampicin (R), Isoniazid (H), Ethambutol (E) and Pyrazinamide (Z). Fixed dose combination (FDC) is preferred over single drug formulation. The fixed dose combination are 4FDC (RHZE) and 2FDC (RH). Drug dosage is based on weight. Monitoring the patient's weight is essential for proper dosing.

Key Message

- TB medicines are available free of charge
- It is essential that all facilities treating TB patients stock single formulation drugs for use when necessary, especially in an event of side effects

Properties of Anti-Tuberculous Drugs

TABLE 26: PROPERTIES OF FIRST-LINE TB DRUGS

Drug	Drug Property	Target Bacilli	Site of Action
Rifampicin	Bactericidal within 1 hour. High potency. Most effective sterilizing drug	All populations including dormant bacilli	Intracellular and extracellular
Isoniazid	Bactericidal after 24 hours. High potency: kills>90% bacilli in the first few days of treatment	Rapid and intermediate growing bacilli	Intracellular and extracellular
Ethambutol	Bacteriostatic. Low potency. Minimizes the emergence of drug resistance	All bacterial populations	Intracellular and extracellular
Pyrazinamide	Bactericidal with a low potency. Achieves its sterilizing action within 2-3 months	Slow growing bacilli	Intracellular bacilli in macrophages

Standardized First Line Treatment

A standardized treatment regimen has been adopted comprising the 4FDCs (RHZE) and 2FDC (RH) for a period of 6-12 months depending on the severity and anatomical location of the disease

Intensive Phase

- Designed for the rapid killing of actively growing and semi-dormant bacilli.
- Achieves a shorter duration of infectiousness.
- The duration of the phase is two (2) months in new and retreatment cases.

Continuation Phase

- Eliminates bacilli that are still multiplying and reduces the risk of failure and relapse.
- The duration is for at least four (4) months in most cases and ten (10)* months if the patient has meningitis, Osteoarticular or spinal TB.

*It is recommended to extend treatment to 12 months for TB meningitis because of serious risk of disability and mortality and Osteoarticular /spinal TB because of difficulties of assessing response to treatment.

Recommended Regimens

TABLE 27: RECOMMENDED REGIMENS

TB disease category	Recommended Regimen	
Treatment Phase	Intensive Phase	Continuation Phase
All forms of TB (non-severe)	2RHZE	4RH
TB Meningitis, Osteoarticular and Spinal TB (severe forms)	2RHZE	10RH

Weight Bands for Dosing of Anti-Tuberculous Drugs

TABLE 28: WEIGHT BANDS FOR DOSING OF ANTI-TB DRUGS

Body Weight(Kg)	Intensive Phase (RHZE 150/75/400/275)	Continuation Phase (RH 150/75)
25-37	2	2
38-54	3	3
55-70	4	4
Above 71	5	5

Key Message

Dosing for all patients should be according to weight and adjusted according to close weight monitoring

TB Treatment of New and Previously Treated Patients

- Treat all new TB patients (bacteriologically confirmed, clinically diagnosed and extra-pulmonary TB) with first-line TB drugs with the exception of the new patients who are confirmed DR-TB patients.
- For patients with a known DR-TB contact, a second-line regimen based on the DST of the presumed index case should be started while awaiting for DST results
- In previously treated patients, send samples for Xpert MTB/RIF, first-line LPA, Culture and phenotypic DST. Start first-line treatment while waiting for the results.
- For patients failing first-line regimen, send samples for Xpert MTB/RIF, first-line LPA and culture. Start second-line regimen while waiting for the results. Adjust the therapy once DST results are available

Standard Indications of Steroids in the Treatment of Tuberculosis

- TB meningitis
- Constrictive TB pericarditis with suspected constrictive physiology
- TB IRIS
- Massive Pleural effusion
- Massive lymphadenopathy with pressure effects Severe hypersensitivity reactions to anti-TB drugs

Other Possible Indications for Steroids in the Treatment of Tuberculosis:

- Hypoadrenalism
- Renal tract TB (to prevent ureteric scarring)
- TB laryngitis with life threatening airway obstruction

Recommended Doses of Adjuvant Steroid Therapy

TABLE 29: RECOMMENDED DOSES OF ADJUVANT STEROID THERAPY (DRUG OF CHOICE IS PREDNISOLONE)

Indication	Prednisolone (Dosage)
TB Meningitis	1-2mg/kg (max 60mg) for 2 weeks then taper off by 10 mg in the daily dose each week over about 6 weeks
TB Pericarditis	1-2mg (max 60mg for 4 weeks then half for 4 weeks (max 30mg/day) then 15 mg/day x 2 weeks, then 5 mg/kg x 1 week, then off
TB Pleural effusion (severe) /or IRIS	0.5 to 1mg (max 30mg) for 1-2 weeks then taper off over several weeks

Note: Steroids doses must not be stopped abruptly, but must be tapered. If prednisolone is unavailable, equivalent doses of dexamethasone may be used as a substitute.

Key Message

Steroids are immunosuppressant and may theoretically increase the risk of developing opportunistic infections in TB/HIV patients. However, used as indicated above, the overall benefit of steroid use outweighs the potential risk.

TB Patients Monitoring and Follow-Up

- All TB patients must be seen at least once monthly by a health care provider for clinical review, assessment of side effects and dose adjustment according to weight.
- All patients should have 1 sputum specimen (morning) taken for AFB smear at 2, 5 and 6 months. If sputum smear is positive at 2 months, proceed to continuation phase and send sputum specimens for Xpert MTB/RIF, First line LPA, culture and phenotypic DST.
- Repeat smear microscopy at month 3. If sputum smear is still positive at month 3, send samples for Xpert MTB/RIF, First line LPA, culture and phenotypic DST (continue or adjust the treatment according to the results). Results should be available at these visits and must be recorded on the patient treatment card and registers.

Key Messages

1. If a patient is found to have a drug resistant strain of TB at any time during the therapy, treatment is declared as failed and patient referred for DR-TB treatment and re-register as such.

2. For previously treated TB patients, specimens for Xpert MTB/RIF, LPA, culture and phenotypic DST should be sent before starting treatment (DST should be performed for at least Rifampicin and Isoniazid, WHO 2017)

TABLE 30: SUMMARY OF SPUTUM MONITORING BY SMEAR IN FIRST-LINE TREATMENT

Treatment Phase	Months of Treatment	Sputum Smear Exam
Intensive Phase	**1**	
	2	If smear positive, send sample for LPA, culture and DST
Continuation Phase	**3**	If smear was positive at month 2, repeat smear at month 3. Send samples for culture, LPA and DST if still positive; ensure samples are received at the laboratory.
	4	
	5	If smear positive, obtain samples for LPA, Culture and DST. If there is concern for MDR-TB, send sample for Xpert MTB/RIF to assess for rifampin resistance.
	6	If smear negative, assign appropriate treatment outcome. If positive, obtain samples for LPA, Culture and DST.

TABLE 31: HIV-TB CO-INFECTION CASE SCENARIOS AND RECOMMENDED MANAGEMENT FOR SUSCEPTIBLE TB

Scenario	TB management	Recommended cART
Pregnant, on cART and develops TB	Start ATT immediately	Continue EFV-based cART Evaluate for failure and consider switching to 2nd line cART in consultation with next level
Pregnant, on ATT, and diagnosed with HIV	Continue ATT	Start cART immediately TDF + XTC + EFV-400mg If renal insufficiency, ABC + 3TC + EFV
Children 3 months to <3 years old with TB-HIV co-infection	Start ATT (RHEZ) immediately	ABC + 3TC + EFV
Newly diagnosed TB and HIV co-infection TB retreatment case and HIV co-infection	Start ATT immediately	Start cART as soon as ATT is tolerated (usually within 2-3 weeks) regardless of CD4 count or WHO Clinical Stage TDF + XTC + DTG (DTG 50mg twice daily if single DTG tablet is available). ***If not available***, give: TDF + XTC + EFV-400mg* If renal insufficiency, ABC + 3TC + DTG 50mg twice daily
On cART and develops TB	Start ATT immediately	If NVP-based regimen, switch NVP to DTG 50mg twice daily and continue cART. If on ATV-r, switch to LPV-r and double the dose If on LPV-r, double dose of LPV-r Evaluate for failure and consider switching to 2nd line cART in consultation with next level
On ATT and diagnosed with HIV	Continue ATT	Start cART as soon as ATT is tolerated (usually within 2-3 weeks*), regardless of CD4 count or WHO clinical stage TDF + XTC + DTG (DTG 50mg twice daily if single DTG tablet is available). ***If not available***, give: TDF + XTC + EFV-400mg If renal insufficiency, ABC + 3TC + EFV
On 2nd line cART with LPV-r and develops TB	Start ATT per guidelines immediately	Increase LPV-r from 2 tabs BD to 3 tabs BD for 2 weeks and then to 4 tabs BD for the remainder of TB treatment. If Rifabutin available (in place of Rifampicin), start at 150mg Monday/Wednesday/Friday.

- Patients on TB treatment should be initiated on TDF + XTC + DTG. Take note that DTG in this case should be given as 50mg twice daily**.**
- For treatment experienced patients on DTG who develops TB and DTG single tablet is *not available*: Switch to TDF+XTC+EFV-400mg if viral load <20 copies/mL, and TDF+XTC+LPV-r if viral load > 20 copies/mL
- **REMEMBER to switch back to DTG 50mg once daily after TB treatment!**
- Patients on cART on TAF who develop TB, should be switched to TDF
- HIV-positive TB patients with profound immunosuppression (e.g., CD4 counts less than 50 cells/µL) should receive cART within the first two weeks of initiating TB treatment.
- TB meningitis patients with a new HIV diagnosis should have ART initiation delayed until after the first 8 weeks of ATT are completed, regardless of CD4 count.

DRUG RESISTANT TB

Drug Resistant TB Patient Detection

The diagnosis and treatment of persons with drug resistant TB (DR-TB) starts with identification of a presumptive DR-TB patient.

Sputum samples from all presumptive TB patients should be sent for Xpert MTB/RIF rapid diagnostic testing, and a chest x-ray should be obtained for patients when the diagnosis of TB is uncertain.

Every effort should be undertaken to confirm the diagnosis of RR-TB/MDR-TB with Xpert MTB/RIF, especially for patients in the following risk categories:

- A close contact of a person diagnosed with DR-TB, especially if the person is not on treatment, is failing treatment, or has recently died from DR-TB disease;
- Someone who has a history of TB treatment failure (either DS-TB or DR-TB), lost to follow up from DS-TB or DR-TB treatment, or could be considered to have early relapse from a previously treated case of DS-TB or DR-TB (successfully treated less than two years previously);
- HIV co-infected patients with severe immunosuppression: bacteriologic confirmation may be difficult so a history of contacts and risk factors is important;
- Persons recently from facilities with high rates of DR-TB: the risk of nosocomial infection is high for health care workers, miners, prisoners, and patients admitted for prolonged periods, especially in the absence of appropriate infection control measures;
- DS-TB patients who remain smear positive ≥ 2 months on first line drug treatment, as this may indicate the presence of drug resistance.

Diagnosis of Drug Resistant Tuberculosis

a) Clinical Presentation

- The clinical features of DR-TB are not different from those of drug susceptible TB (both pulmonary and extra-pulmonary TB).
- DR-TB is by definition a bacteriological diagnosis. However, in patients where bacteriological confirmation is difficult, such as children, HIV positive patients, or those with extra-pulmonary TB, and who are also close contacts of known DR-TB patients, a clinical diagnosis of DR-TB can be made. Such cases should be discussed with the Clinical Expert Committee (CEC).

b) Bacteriologic Confirmation

Xpert MTB/RIF has been recommended as the primary diagnostic test in all adults and children with signs and symptoms of TB where available

- The diagnosis of DR-TB is done by Xpert MTB/RIF, line probe assay (first and second-line LPA), culture and phenotypic drug susceptibility testing (pDST).
- In facilities where Xpert MTB/RIF is not yet available, samples should be referred to the nearest facility where the test is available, especially for individuals with risk factors of DR-TB.

- Only as a last resort should patients be started on empiric DS-TB treatment based on clinical history and positive smear microscopy results alone (e.g. severely ill patients in whom treatment initiation should not be delayed pending Xpert MTB/RIF, LPA, or culture/DST results
- Patients who require TB re-treatment based on history should NOT get the category II regimen (the standard DS-TB regimen plus streptomycin). Instead, patients should get drug susceptibility testing with rapid molecular testing (Xpert MTB/RIF, FL and SL LPA) to inform the choice of treatment. WHO no longer recommends the use of the category II regimen.
- For all patients with Rifampicin resistance detected on Xpert MTB/RIF, samples should be sent for SL LPA, culture and phenotypic DST; for those eligible, the shorter DR-TB treatment regimen should be started while awaiting results from LPA and/or culture/DST.
- The turnaround time (specimen collection until receipt of results) for LPA and culture/DST results varies on when the test becomes positive and the type of media used (e.g. liquid or solid media for culture):
    - Line probe assay results should take between 3-14 days (turnaround time of LPA within the processing lab should be 48 hours);
    - Liquid culture (MGIT): positive results at 4-14 days, negative result by 42 days;
    - Solid culture (LJ): positive results at 28-56 days, negative result by 60 days;
    - Phenotypic DST results (from the date culture was positive): MGIT 14 days, LJ 30 days;
- Phenotypic DST (pDST) is reliable and reproducible for Rifampicin, Isoniazid, Kanamycin, Amikacin, Ofloxacin, Levofloxacin.
    - Moxifloxacin: there is a need for critical concentrations to be re-evaluated;
    - Ethambutol, Streptomycin, Capreomycin, Ethionamide/Protionamide, Cycloserine, Pyrazinamide, para – Amino Salicylic Acid: pDST is not reliable;
    - New and repurposed drugs Bedaquiline, Delaminid, Clofazimine, Linezolid: pDST needs validation and is not widely available outside of research settings.

Causes of DR-TB

- Transmission from a patient with drug resistant TB
- Poor adherence to treatment by patients
- Use of anti-TB drugs of unproven quality (sale of such medications over the counter and on the black-market).
- Incorrect management of individual cases by clinicians
- Sub-optimal dosage
- Poor drug absorption
- Prolonged shortages of anti-TB drugs

Groups at Risk of DR-TB

- Contacts of DR- TB patients
- Patients previously treated for TB (Treatment failures, relapses, treatment after loss to follow up)
- Patients who are smear positive after 2 months of first line TB treatment
- TB patients who are close contacts of DR-TB cases.

- Health care workers
- Prisoners from facilities with high rates of DR-TB

Management of Presumptive DR-TB Patients

If a patient is presumed to have DR-TB, the following should be done:

- Collect sputum specimens for Xpert MTB RIF, LPA, culture and phenotypic DST
- Do not admit patient to a general ward (especially in high HIV settings as HIV positive individuals can easily get infected).

If hospital admission is necessary, the patient should be admitted to a special ward, which has good ventilation. At home advise patient to sleep in a well-ventilated room that is separate from others (if possible). If DR-TB is confirmed by the laboratory the patient should be referred for treatment at a designated treatment facility under strict supervision.

Detection of DR-TB patients

Case detection for DR-TB is similar to that of TB in general. The basis for identification of DR-TB patient is bacteriological examination, which includes Xpert MTB/RIF, LPA, Culture and Phenotypic Drug Susceptibility Testing (DST) as well as previous history of treatment.

Standardized Shorter Regimen for RR and MDR patients

In order to improve the treatment outcomes, adherence and the quality life for RR/MDR TB patient, the NTLP has adopted the WHO recommended shorter regimen in patients without additional resistance or intolerance to key second-line drugs (SLD), i.e. Fluoroquinolones (FQ) and Second Line Injectable (SLI). For ineligible patients, individualized regimen is recommended that may include the new drugs - Bedaquiline (Bdq) and Delaminid (Dlm).

Eligibility criteria:

All patients with DR -TB are eligible to start DR-TB treatment without delay. The patient should be evaluated to assess the risk of resistance or intolerance to FQ and/or SLI and the eligibility criteria. If there is no risk of intolerance and/or resistance for FQ and/or SLI the patient will start with the shorter regimen. If there is risk of intolerance/resistance to FQ and/or SLI and/or bacterial confirmation of drug resistance or other risk factors for poor treatment outcome (such as severe TB disease), the patient shall start with an individualized treatment regimen.

Before starting treatment, **two sputum samples must** be sent for Second-line - Line Probe Assay (SL LPA) and for culture, as well as first-line and second-line drug susceptibility tests (phenotypic FL/SL DST). Once the results are available, the initial regimen may then be adjusted if necessary with clear lack of response (clinically, smear grading, culture).

Standard duration of the intensive phase is at least 4 months of Km (Am, Cm), Mfx (Gfx), Cfz, Z, E, HHD, Pto (Eto) given daily. If smear conversion is not achieved at month 4, the intensive phase shall be extended to a maximum of six months until sputum smear conversion. The Km (Am or Cm) will be given three times-weekly from the fourth month onwards; the continuation phase consists of Mfx (Gfx,) Cfz, E, Z for a fixed duration of five months. If the patient remains smear positive and/or is still culture positive at 6 months, the patient will be declared as a failure. Failure declaration and a switch to an individualized treatment will be considered earlier in patients.

Shorter Regimen

4-6 Km-Mfx-Cfz-Eto-Z-E- H^h / 5 Mfx-Cfz-E-Z
Add vitamin B6 100 mg

Standardized Longer Regimen for RR and MDR-TB patients

Intensive Phase for 8 months:

- Kanamycin (Km), Levofloxacin (Lfx), Ethionamide (Eto), Cycloserine (Cs), Pyrazinamide (Z)

Intensive Phase for 8 months

8 Km-Lfx-Eto-Cs_Z/12 Lfx-Eto-Cs-Z*

*Note: This regimen will no longer be prescribed

Continuation Phase for 12 months:

- Levofloxacin (Lfx), Ethionamide (Eto), Cycloserine (Cs), Pyrazinamide (Z)

Individualized regimen

For patients with resistance to second-line drugs (pre-XDR/XDR-TB), the treatment is individualized according to contact history, drug history, drug susceptibility results, adherence history, clinical course and adverse reactions to drugs used previously. The design of the individualized regimen will include new and repurposed drugs such as Bedaquiline (Bdq), Delaminid (Dlm), Linezolid (Lnz) and Clofazimine (Clf).

Key Message

It is strongly recommended that individualized regimen should be designed by the DR Clinical Expert Committee

FIGURE 18: RR/DR TB PATIENT TRIAGE FLOW CHART

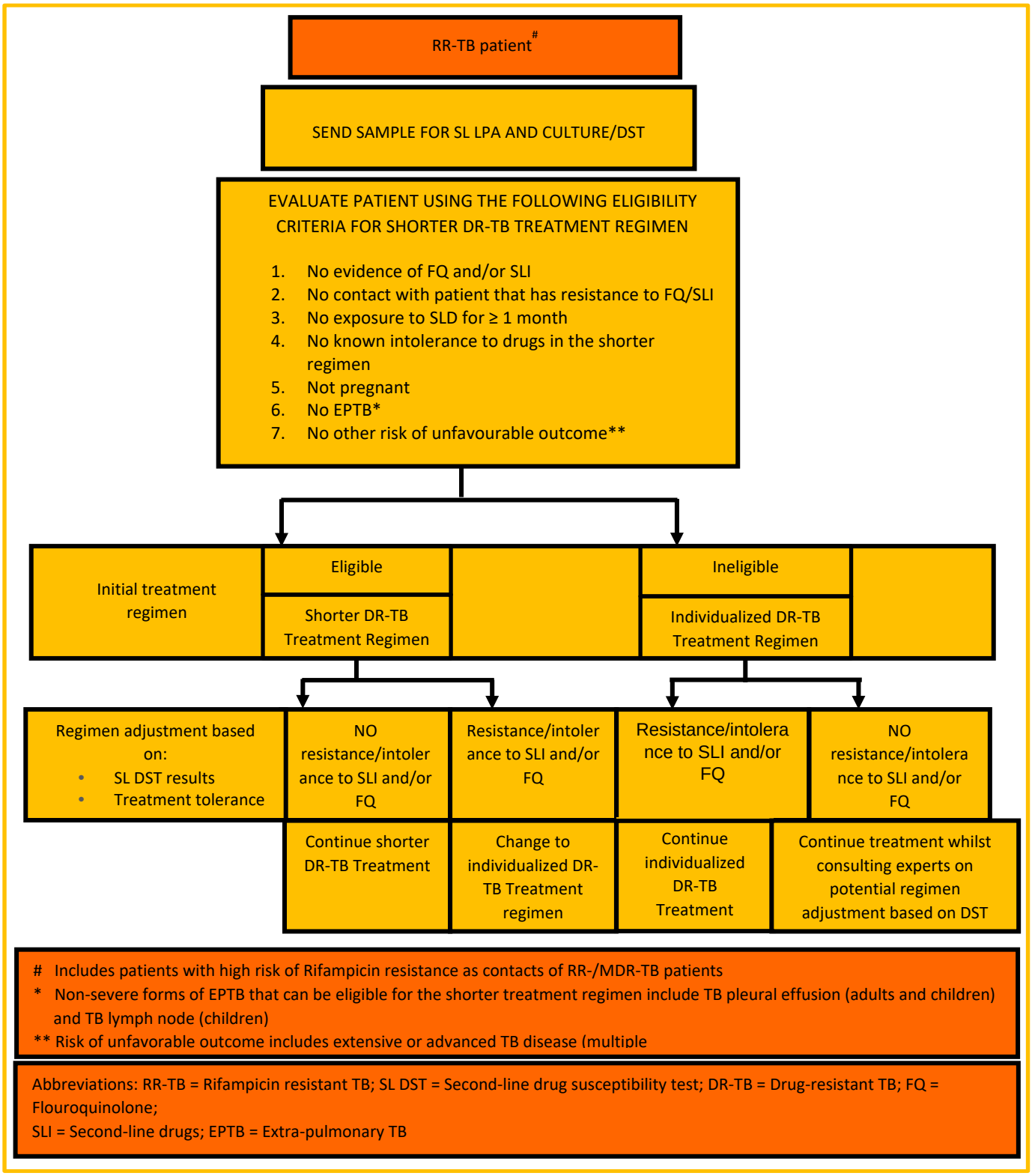


TABLE 32: WEIGHT-BASED DR-TB DRUGS IN ADULTS ≥30 KG

Drugs	Daily dose	30–35 kg	36–45kg	46–55 kg	56–70kg	>70 kg
Isoniazid- High dose (H^h)	10 mg/kg Maximum 600 mg/day	300 mg	400 mg	500 mg	600 mg	600 mg
Pyrazinamide (Z)	20–30mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg
Ethambutol (E)	15–25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg
Kanamycin/Capreomycin/ Amikacin (Km/Cm/Am)	15–20 mg/kg once daily	500 mg	625 mg	750 mg	825 mg	1000 mg
Levofloxacin (Lfx)	750–1000mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin (Mfx)	400 mg once daily	400 mg	600 mg	<50kg=600mg >50kg=800mg	800 mg	800 mg
Prothionamide (Pto)/ Ethionamide (Eto)	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine (Cs)/ Terizidone (Trd)	500–750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
p-aminosalicylic acid (PAS)	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8–12 g
Bedaquiline (Bdq)	400 mg once daily for 2 weeks then 200 mg 3 times per week					
Delamanid (Dlm)	100 mg twice daily (total daily dose = 200 mg)					
Clofazimine (Cfz)	100 mg twice daily for 2 first months, then reduce to 100 mg daily					
Linezolid (Lzd)	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg
Amoxicillin/clavulanate (Amx/clv) 7/1	80 mg/kg/day in 2 divided doses	2600 mg	2600 mg	2600 mg	2600 mg	2600 mg
Amoxicillin/clavulanate (Amx-clv) 8/1	80 mg/kg/day in 2 divided doses	3000 mg	3000 mg	3000 mg	3000 mg	3000 mg
Imipenem/Cilastatin (Imp/cln)	1000mg Imipenem/1000 mg Cilastatin twice daily					
Meropenem (Mpm)	1000mg three times daily (alternative dosing is 2000 mg twice daily)					

Treatment Monitoring For MDR-TB/RR-TB Patients on Therapy

Adverse effects may occur with MDR-TB drugs and are dose dependent. However adverse effects can occur at normal dose. Patients should be monitored for adverse effects at each contact with a health care provider.

- Patients should be monitored closely for signs of treatment failure and adverse drug reactions (compare baseline and follow up examinations).
- Treatment can be monitored through clinical history; physical examination; psychosocial assessment; chest radiography; audiometry, bacteriological test (smear and culture); laboratory monitoring (hematology-FBC, Creatinine, Potassium, LFT, TSH); Pregnancy test, hepatitis B,C and HIV test (if positive CD4 and VL every 6 months) should be included when doing the baseline investigations.
- Weight should be monitored monthly and drug dosages should be adjusted accordingly.
- For patient under individualized regimen, additional monitoring is required: ECG (Dlm, Bdq), Serum Albumin (Dlm), and for Linezolid: vision test chards, Serum Amylase/Lipase and monthly hematology-FBC.

For details on adverse effects monitoring and management, refer to the DR-TB manual

TABLE 33: DR-TB TREATMENT MONITORING SCHEDULE FOR CONVENTIONAL DR-TB REGIMEN

Parameters	Month of Treatment																				
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Clinical evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sputum-smear	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sputum-culture	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DST	X				P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
FBC/DC	X						X						X						X		X
LFTs	X			X			X			X			X			X			X		X
Na^{2+} , K^{2+}, u , Creatinine	X	X	X	X	X	X	X			X	I	I	I	I	I	I	I	I	I	I	I
TSH/free T-4	X			X			X			X			X			X			X		X
Pregnancy test	X																				
HIV test	X			X			X			X			X			X			X		
Audiometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CXR	X						O						O								O

KEY: X = Required, O = Optional, P = If culture is positive, I = If indicated

HEPATITIS B AND HIV

Screening and Management of Hepatitis B Virus (HBV) and HIV Co-Infection

- Patients with HIV-HBV co-infection experience twice the risk of mortality during cART compared to HIV-infected individuals who do not have HBV.
- Both XTC and TDF are active against HBV; however, using XTC as the only HBV-active antiretroviral drug will lead to HBV drug resistance and is not recommended. cART regimens that contain TDF as the only HBV-active antiretroviral are okay because HBV resistance with TDF alone is very very rare.
- Hepatitis B surface antigen (HBsAg) should be done at baseline and in patients with unknown HBV status
- For children who have been fully vaccinated (i.e., 3 doses), do not screen for HBV unless there is strong clinical suspicion
- Start TDF-containing cART regardless of CD4 count
- Patients failing 1st-line TDF + XTC treatment should continue the TDF in their 2nd-line therapy (i.e. TDF+AZT+3TC+LPV-r or ATV-r) to control their HBV infection
- For HBsAg positive patients with renal insufficiency (CrCl <50mL/min), consult or refer to next level
- For HBV-HIV co-infection in child <36 months old, consult or refer to next level

HEPATITIS B MONO-INFECTION

Screening and Management of Hepatitis B Virus (HBV)

- Hepatitis B surface antigen (HBsAg) should be used for screening and diagnosis of active HBV infection; a negative HIV test is required to classify a person as having HBV mono-infection.
- The ZAMPHIA study reported that 5.6% of adults were hepatitis B surface antigen positive; of these most were HIV-negative.
- Other hepatitis B tests (like surface antibody or core antibody) cannot be used to know if the person has active infection
- Many cases of active HBV infection will not require immediate antiviral therapy but instead can be observed and followed up every 6-12 months.
- APRI (AST-to-platelet ratio index) is the preferred non-invasive test (NIT) to assess for the presence of cirrhosis and can be calculated as follows:

$$\text{APRI} = \frac{\text{[AST Level / AST (Upper Limit of Normal)]}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

APRI Score Interpretation

AST aminotransferase to Platelet Ratio Index

- APRI score >2.0 in adults is highly suggestive of cirrhosis
- APRI score <1.0 can rule out the presence of cirrhosis
- APRI score 1.0-2.0 is a gray area

Eligibility Criteria for Antiviral Treatment

- The presence of cirrhosis is a treatment indication in all adults, adolescents, and children with chronic HBV infection regardless of ALT levels, HBeAg status, or HBV DNA levels
- Diagnosis of cirrhosis is based on APRI score >2.0 in adults
- Clinical signs of decompensated cirrhosis may include portal hypertension (ascites, variceal haemorrhage, and hepatic encephalopathy), coagulopathy, or liver insufficiency (jaundice). Other clinical features of advanced liver disease/cirrhosis may include hepatomegaly, splenomegaly, pruritis, fatigue, arthralgia, palmar erythema, and edema.
- Treatment is recommended for adults who do not have clinical evidence of cirrhosis (or based on APRI score >2 in adults) but do have one of the following:
    - Persistently elevated ALT levels and evidence of high-level HBV replication (HBV DNA >20 000 IU/mL), regardless of HBeAg status
    - When HBV DNA testing (and/or HBeAg testing) is not available, treat when ALT is persistently elevated. Persistent means at least two elevated ALT levels over 6-12 months and newer HBV guidelines now define ‘ALT elevation’ as ALT >19 U/L for women and ALT>30 U/L for men.
    - In HBV/HIV co-infected individuals, TDF based cART should be initiated regardless of CD4 count
- Remember in Zambia other common causes of ALT elevation are medications (such as ATT), liver infections (such as TB), and heavy alcohol consumption.
- In treatment-eligible patients, measurement of creatinine is recommended.

Non-Eligible Patients

Antiviral therapy is not recommended or deferred in the following situations:

- No clinical evidence of cirrhosis
- APRI score ≤2.0 in adults
- Persistently normal ALT levels (i.e., ALT ≤20 in women and ≤30 in men)
- Low levels of HBV DNA replication (HBV DNA <2000 IU/mL), regardless of HBeAg status

Continue monitoring in all persons with chronic HBV infection especially those who do not meet the above eligibility and non-eligibility criteria to determine if antiviral therapy may be indicated in the future to prevent progressive liver disease. Monitoring could be done every 3-6 months in those with ALT elevation and every 6-12 months in those with normal ALT.

First-line Regimen

- In all adults, adolescents and children aged 10 years or older the preferred drug is TDF + XTC
- In children aged 2 to <10 years, Entecavir is the preferred drug over Tenofovir
- The dosing should be as follows:
    - Tenofovir 300mg once daily
    - Tenofovir 300mg plus Lamivudine 300mg
    - Entecavir 0.5mg once daily (adult with compensated liver disease and lamivudine naive)
    - Entecavir 1mg once daily (adult with decompensated liver disease)
- Patients with CrCl <50 mL/min should be referred to a higher level for further management
- Counseling patients that HBV treatment is potentially lifelong is important to set their expectations

Monitoring of Therapy in HBV

- There are several goals of HBV antiviral therapy, as follows:
    - Suppression of HBV viral load (i.e., HBV DNA below assay detection)
    - Normalization of the ALT
    - Conversion from HBeAg-positive to negative
    - Conversion from HBsAg-positive to HBsAg-negative
- Repeat ALT every 6 months is recommended during treatment
- Every 1-2 years HBsAg can be repeated; however, conversion to HBsAg-negative occurs at a rate of <5% per year during chronic infection
- Repeat creatinine every 12 months is also recommended as TDF carries a small risk of renal toxicity
- Repeat an HIV antibody test every 12 months; if patient becomes HIV-positive during HBV treatment (i.e., HIV-HBV co-infection), cART should be initiated

When to Discontinue Therapy

- Discontinuation of HBV-active therapy can be associated with a fatal flare-up of hepatitis; therefore, counsel patients that after stopping they should return if they develop fever and jaundice or other signs of liver disease
- When there is evidence of conversion from HBeAg-positive to HBeAg-negative and after completion of at least one additional year of treatment AND the ALT is persistently normal
- When there is conversion to HBsAg loss and completion of at least one additional year of treatment and the ALT is persistently normal
- If HBV DNA testing is available, persistently undetectable HBV DNA in addition to the above criteria should also guide when to discontinue
- IMPORTANT NOTE: Relapse may occur after stopping therapy, especially in patients who were HBeAg-negative at the start of antiviral therapy. Therefore, after discontinuation, ongoing monitoring of ALT (every 6-12 months) is recommended. Restart therapy if there are signs of reactivation such as HBsAg or HBeAg become positive, ALT levels increase significantly, or HBV DNA becomes detectable again

General Measures to Reduce HBV Transmission

- HBsAg-positive persons should adopt correct and consistent condom use during sexual intercourse; not share razors, toothbrushes, or other personal care items; not donate blood, organs, or sperm; and follow standard universal precautions with open cuts or bleeding.
- HBV vaccination of household and sexual contacts to HBsAg-positive individuals. Household members and sexual partners of persons with Chronic Hepatitis B should be vaccinated if they are negative for HBsAg
- Alcohol reduction to reduce disease progression
- Infants should receive all vaccines recommended through the Extended Program on Immunizations.
- Infants born to HBsAg-positive mothers should have an extra “birth dose” of HBV vaccine as soon as possible after birth if possible, which provides protection against mother to baby transmission

Measures to Reduce HBV Transmission in Hospital Settings

- Health care workers should be tested for HBsAg and vaccinated if they are negative for HBsAg
- Hand hygiene: including surgical hand preparation, hand washing, and use of gloves
- Safe handling and disposal of sharps and waste
- Safe cleaning of equipment
- Testing of donated blood
- Improved access to safe blood
- Training of health personnel

CRYPTOCOCCAL DISEASE AND HIV INFECTION

Diagnosis of Cryptococcal Disease

- Prompt lumbar puncture with measurement of Cerebrospinal fluid (CSF) opening pressure and rapid CSF Cryptococcal antigen (CrAg) assay or rapid serum CrAg (either LA or LFA) is the preferred diagnostic approach

Prevention of Cryptococcal Disease

- The routine use of antifungal primary prophylaxis for Cryptococcal disease in HIV-infected adults, adolescents, and children with a CD4 count less than 100 cells/µL and who are CrAg negative or where CrAg status is unknown is not recommended before cART initiation, unless a prolonged delay in ART initiation is likely

Treatment Options

- Induction phase of treatment in HIV-infected adults, adolescents, and children with cryptococcal disease (meningeal and disseminated non-meningeal)
- The following two-week antifungal regimens are recommended in order of preference.
    - Amphotericin B + Fluconazole
    - Amphotericin B + Flucytosine

- For the consolidation phase treatment of HIV-infected adults, adolescents, and children with cryptococcal meningitis or disseminated non-meningeal disease, the following eight-week antifungal regimen is recommended:
    - Fluconazole 400–800mg/day after a two-week induction with Amphotericin B regimen (6–12mg/kg/day up to 400–800mg/day, if below 19 years)
    - Fluconazole 800mg/day after induction treatment with short-course amphotericin B or Fluconazole-based induction regimen (Fluconazole 12mg/kg/day up to 800mg/day, if below 19 years)

- For maintenance treatment of cryptococcal disease in HIV-infected adults, adolescents, and children, oral Fluconazole 200mg daily (6mg/kg/day up to 200mg/day, if below 19 years) is recommended

MENTAL HEALTH AND HIV INFECTION

All HIV patients should be assessed and managed for neuropsychiatric conditions (e.g., depression, anxiety, mania, alcohol and substance use, HIV-associated neurocognitive disorder, and delirium disorders) may have a substantial impact on HIV disease progression and cART adherence. For individuals with mental illness, refer to a mental health provider. If an individual with mental illness appears to worsen after EFV-400mg initiation, consider switching EFV-400mg to ATV-r or LPV-r.

Non–Communicable Diseases and HIV

Cardiovascular Disease (CVD) assessment and Management of Non-Communicable Diseases (NCDs)

HIV-infected persons are at increased risk of cardiovascular disease and other non-communicable diseases, including cancers. This is in part because of the chronic immune activation that persists even in HIV infection, even if on treatment. Assessment and management of cardiovascular risk should be provided for all individuals living with HIV according to standard protocols recommended for the general population using risk factors:

- Older than 40 years, obesity, diabetes mellitus, known hypertension, waist circumference of >90cm (women) and 110cm (men), family history of premature CVDs

Up to two thirds of premature deaths from the major NCDs are linked to four shared modifiable risk factors:

- Tobacco use, harmful use of alcohol, unhealthy diet, and physical inactivity.

These risk factors result in a series of metabolic and physiological changes that eventually lead to NCDs. Broader social, economic, and environmental determinants of health and inequities associated with globalization and urbanization, alongside population ageing, are the underlying drivers of the behavioural risk factors, and thus the NCD epidemic.

FIGURE 19: CAUSAL LINKS BETWEEN UNDERLYING DRIVERS FOR NCDS, BEHAVIORAL RISK FACTORS, METABOLIC/PHYSIOLOGIC RISK FACTORS AND NCDS

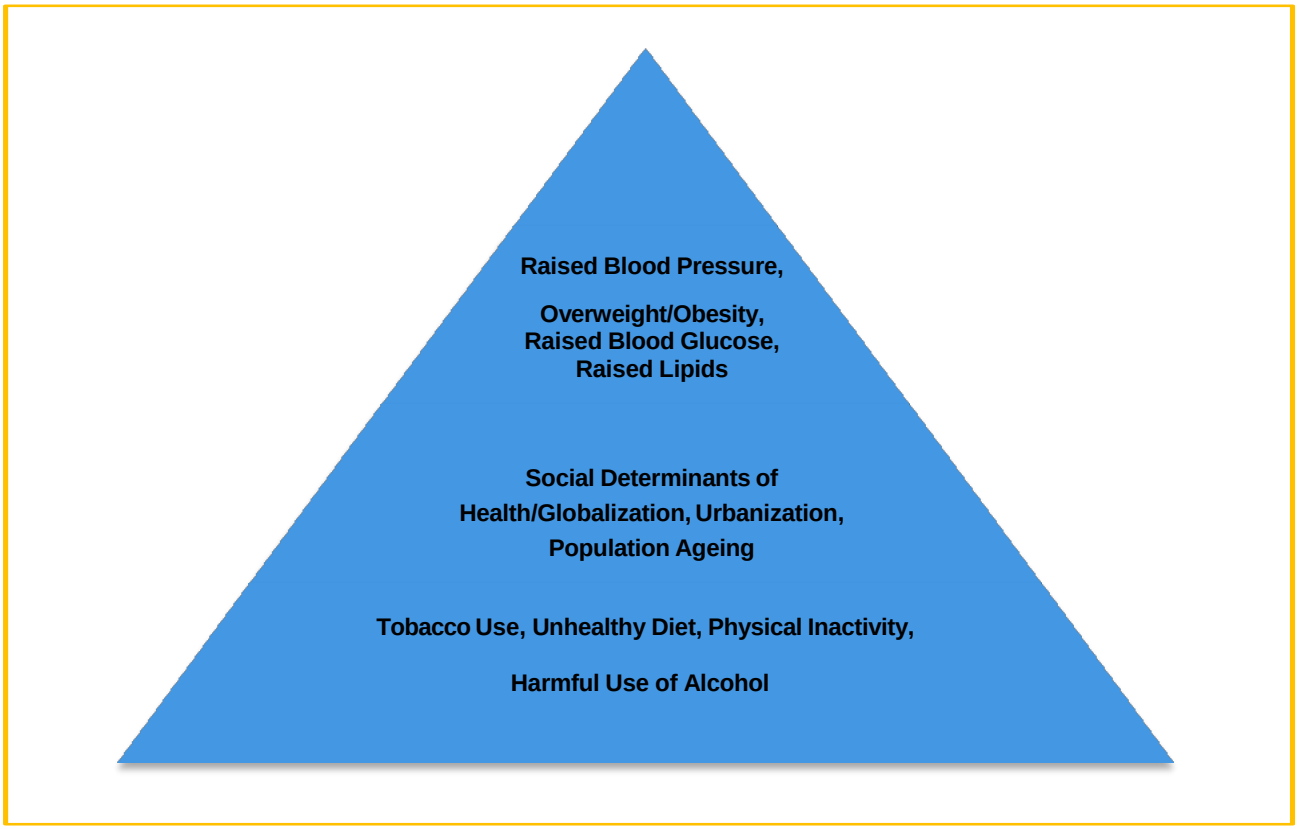


Table 34: Lifestyle Modifications to Prevent and Manage CVDs Among HIV-Infected Individuals

Smoking Cessation
• Smoking cessation has multiple short-term and long-term benefits, including: ✓ Skin does not age/wrinkle as quickly ✓ Improved fitness and quicker recovery from common infections ✓ Reduced risk of respiratory infections and chronic lung disease ✓ Reduced risk of high blood pressure, diabetes, kidney disease, heart disease, and stroke ✓ Improved infant outcomes (for pregnant women who smoke) ✓ Reduced risk of cancers: lung, bladder, breast, mouth, throat, esophagus ✓ Evidence of better response to ART (better viral suppression)
Dietary Changes and Weight Loss
✓ Weight loss to maintain a healthy BMI (nutritionists to be engaged in patient care) ✓ Reduce/abstain from alcohol ✓ Cut down sugar intake ✓ Cut down red meat intake ✓ Cut down consumption of fatty foods, fat for flavouring, and fried foods ✓ Increase intake of whole grains, vegetables, fruit, and beans (eating at least five servings of fruit and vegetables a day) ✓ Increase intake of fish ✓ Cut down salt intake to less than one teaspoon a day
Physical Activity
• Active lifestyle with moderate-intensity physical activity

Table 35: Dyslipidaemia Screening, Diagnosis, and Initial Management for HIV-Infected Individuals

Screening
• Fasting lipid profile should be evaluated at baseline for all PLHIV, then annually if baseline screening is normal
Diagnosis
• Dyslipidaemia is defined as high fasting total cholesterol (>5.2mmol/L), LDL (>3.4mmol/L) or triglycerides (>2.2mmol/L)
Management
• Lifestyle modifications for 3-6 months • If the patient is on an ARV known to cause or exacerbate dyslipidaemia (primarily LPV-r) then consider a single-drug substitution to a more lipid-friendly drug (such as from LPV-r to ATV-r) as the treatment of choice before adding a lipid-lowering drug. • If does not meet treatment target with lifestyle modifications, then add drugs: ✓ Atorvastatin: starting dose of 10mg OD (maximum dose 20mg if patient is on a PI/r and a maximum dose of 80mg once daily if not on a PI/r) ✓ Allow at least 3 months before repeating fasting lipids and titrating dose • Once targets achieved can monitor lipids every 6-12 months

TABLE 36: HYPERTENSION SCREENING, DIAGNOSIS, AND INITIAL MANAGEMENT FOR HIV-INFECTED INDIVIDUALS

Screening

- BP should be measured and recorded at every visit

Diagnosis

- Hypertension requiring intervention is defined as BP ≥140/90mmHg on at least two different occasions
  - ✓ It can also be diagnosed at the same visit if the BP is 180/110 or any BP associated with target organ damage

Management

If baseline BP is 140-159/90-99:

- Lifestyle modifications for at least 6 months, along with monthly BP monitoring
- If does not meet treatment target with lifestyle modifications, then add drugs:
  - ✓ Introduce 1 drug at a time, and allow 2-3 weeks to achieve maximal effect before titrating up dosage; titrate to maximum dosage before adding an additional drug
  - ✓ In PLHIV without kidney disease or diabetes, first-line antihypertensive therapy is a **thiazide diuretic** such as Hydrochlorothiazide starting at 12.5mg OD (maximum dose 25mg OD) **OR** a **calcium channel antagonist** such as Amlodipine starting at 2.5mg OD (maximum 10mg OD)
  - ✓ In PLHIV **with** kidney disease or diabetes the first antihypertensive should be an ACE-I or ARB such as Enalapril 2.5-10mg OD (maximum dose is 20mg BD); Losartan 50mg OD (maximum dose is 100mg OD)
  - ✓ If inadequate response once dose has been titrated, an additional agent may be required (e.g., Hydrochlorothiazide starting at 12.5mg OD [maximum dose 25mg OD])
  - ✓ If inadequate response to two agents, consider consultation with or referral to a clinician experienced in the management of refractory hypertension. Note: Calcium-channel blockers have known drug interactions with PIs and NNRTIs and should be used with caution
- If baseline BP ≥160/100mmHg: initiate lifestyle modifications and introduce anti-hypertensive medications concurrently
- Target BP measurements
  - ✓ Diabetic patients: <140/90
  - ✓ None Diabetic & Chronic Kidney Disease (CKD) patients: 140/90
  - ✓ None Diabetics & None CKD patients: <140/90 (<60 years); 150/90 (>60 years old)

TABLE 37: TYPE 2 DIABETES MELLITUS SCREENING, DIAGNOSIS, AND INITIAL MANAGEMENT FOR HIV-INFECTED INDIVIDUALS

Screening

- Blood glucose (fasting or random) should be evaluated at baseline for all PLHIV, then annually if baseline screening is normal; urine dipstick for protein and glucose can be used if blood glucose testing is not available

Diagnosis

- Diabetes Mellitus is defined as fasting blood sugar ≥7.0mmol/L, or random blood sugar ≥11.1mmol/L, or HbA1C >6.5%
- Abnormal results should be repeated to confirm the diagnosis

Management (treatment target is HbA1C ≤7.0% or FBS 4-7mmol/L)

- Monitor HbA1c (or FBS if HbA1c not available) every 3 months for patients with confirmed diagnosis of diabetes mellitus
- Lifestyle modifications (weight loss, nutritional support to manage portion sizes and calculate glycaemic index of various foods to help with control of blood sugar) for 3-6 months
- If does not meet treatment target with lifestyle modifications, then add drugs:
  - ✓ Metformin
  - ✓ Obtain baseline Creatinine; do NOT use Metformin if creatinine clearance <45mL/min
  - ✓ Start with low dose (500mg OD or BD) and titrate up every 1-2 weeks until reaches 1g BD (or maximum tolerated dose if less than 1g BD)
  - ✓ If does not meet treatment targets with Metformin for 3-6 months at maximum tolerated dose, then consider adding oral drugs from another class (such as glyburide) and/or specialist consultation. Some patients may require Insulin
- At every visit: A thorough history (to elicit features of hypoglycaemia, other cardiovascular disease risk factors, neuropathy, diabetic foot ulcers) and a physical exam (for BP, neuropathy, foot ulcers)
- Additional routine screening for patients with diabetes:
  - ✓ Annual ophthalmology examination for diabetic retinopathy
  - ✓ Annual urinalysis: start on an ACE-I/ARB if proteinuria develops (even if BP normal)

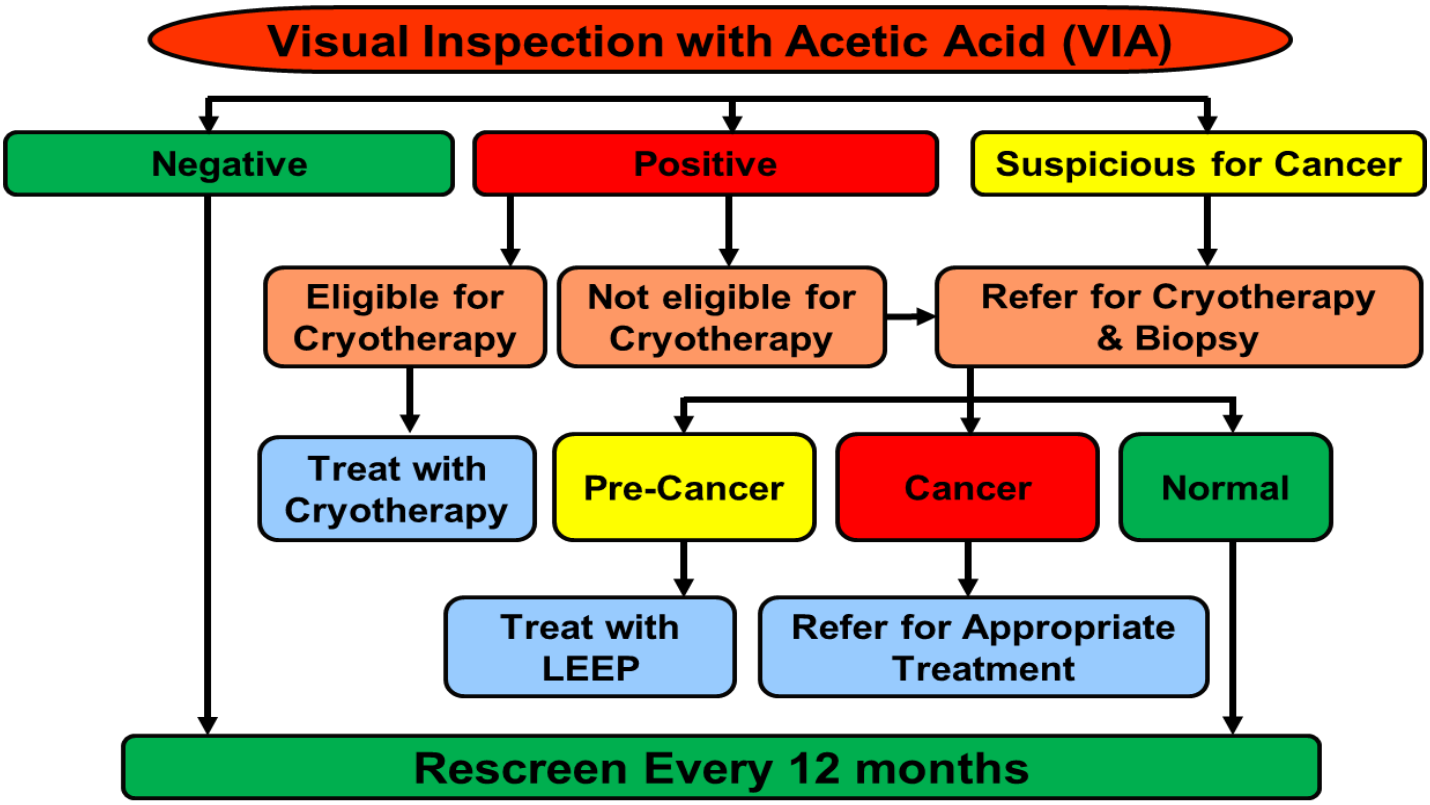
TABLE 38: CHRONIC KIDNEY DISEASE SCREENING, DIAGNOSIS, AND INITIAL MANAGEMENT FOR HIV-INFECTED INDIVIDUALS

Screening
• Urinalysis (for protein) and serum creatinine should be evaluated at baseline for all PLHIV
Diagnosis
• Impaired renal function is defined as creatinine clearance < 50mL/min, or dipstick proteinuria ≥ 1 • Abnormal results should be repeated to confirm diagnosis
Management
• Management depends on the cause of the renal impairment; additional investigations and/or specialist consultation may be required • Treat dehydration promptly and aggressively • If on TDF-containing regimen, substitute with another ARV, with the exception of patients with HBV/HIV co-infection who need TDF to be maintained on adjusted doses or switch to Entecavir (see section on Hepatitis B/HIV co-infected) • Avoid nephrotoxic drugs • Evaluate for and treat hypertension • All NRTIs except ABC require dose adjustments for renal impairment, depending on the severity. NNRTIs, PIs, and Integrase Strand Transfer Inhibitors (INSTIs) do not require dose adjustments for impaired renal function

CERVICAL CANCER AND HIV

Cervical cancer is preventable and is curable if diagnosed and treated early. All women regardless of age should be assessed for cervical cancer; women living with HIV have a higher risk of pre-cancer and invasive cancer. Cervical cancer screening leads to early detection with HPV test or visual inspection with acetic acid (VIA).

FIGURE 20: RECOMMENDED SCREENING FOR CERVICAL CANCER AMONG HIV INFECTED WOMEN



Terminal Illness/Cancer and HIV

- Palliative care aims to relieve suffering in all stages of disease and is not limited to end-of-life care. The goals of palliative care include:
    - To improve the quality of life
    - To increase comfort
    - To promote open communication for effective decision making
    - To promote dignity
    - To provide a support system to the person who is ill and those close to them

In HIV-infected individuals, palliative care focuses on symptom management and end-of-life care. Throughout all stages of HIV disease, including when on cART, individuals may experience various forms of pain and other discomfort. HCWs should identify and treat the underlying cause when possible, while controlling the pain. Effective management of side effects and possible overlapping cART-associated toxicities is important to support adherence

The care of the terminally ill child is a particular challenge in Zambia because there are few replicable models of planned terminal care, both institutional and community-based. At the end of life, there are typically more symptoms that must be addressed, and the child may need to take multiple drugs to control and treat a variety of symptoms and conditions.

Terminal care preparation for children and their families is a long-term process and requires continuity of care through providers and services. Families must be involved in decisions about the best place for care and the preferred place of death in the child with end-stage HIV disease

TABLE 39: RECOMMENDED TESTS FOR HIV SCREENING AND MONITORING FOR CO-INFECTIONS AND NCDS

Phase of HIV Management	Recommended	Desirable (*if feasible)
HIV Diagnosis	• HIV testing (serology for adults and children 18 months or older: NAT or children younger than 18 months • Screen for TB • CD4 cell count (assess CTX)	• HBV or HCV serology • Screening for STIs • Hb or FBC • Pregnancy test (woman of reproductive age) • HPV test or visual inspection with acetic acid (VIA) in sexually active adolescent or woman) • Syphilis test (adolescent or adult) • NCDs risk factors: cholesterol, glucose, and triglycerides
cART Initiation		• Hb • Pregnancy test (woman of reproductive age) • BP measurement • Serum creatinine (for starting TDF) • Baseline CD4
Receiving cART	• Viral load (at 6 months, 12 months after initiating cART and every 12 months thereafter)	• Pregnancy test, especially for women of childbearing age not receiving family planning or on treatment with TDF+XTC+EFV-400mg • Serum creatinine for TDF
Suspected Treatment Failure	• Serum creatinine for TDF • Pregnancy test, especially for women of childbearing age not receiving family planning or on treatment with TDF+XTC+EFV-400mg • And review CTX adherence • Initiate cART if eligible • Adherence counseling and positive health dignity and prevention (PHDP) messages	• HBV (HBsAg) serology (for HIV/HBV co-infected already using TDF and develop ART failure, TDF should be maintained regardless of selected second-line regimen)

*Reference 2016 WHO Guidelines

PROPHYLAXIS

TUBERCULOSIS ISONIAZID PREVENTIVE THERAPY (TB-IPT)

These guidelines focus on key interventions branded as the THREE I's (Intensive case finding, Isoniazid prophylaxis therapy, Infection control for TB) for HIV-TB activities that reduce TB-related morbidity and mortality in HIV-infected individuals. Another key intervention is the provision of cART.

Daily TB-IPT can prevent TB in people who are at a high risk for developing TB, including HIV-infected individuals.

- Screen all patients for TB at any opportunity that presents (see Figure 15)
- Screen all pregnant and breastfeeding women, regardless of HIV status, for TB at every contact as it is part of Focused ANC
- Screen all children for TB at every contact

- Give TB-IPT for 6 months to the following:
    - HIV-infected children <12 months old with TB contact and after ruling out active TB
    - Newly HIV-infected pregnant and breastfeeding women, children ≥12 months old, adolescents, and adults after ruling out active TB
    - After completing a full course of ATT, HIV-infected children should be given an additional IPT x 6 months
- Do not give IPT to a patient who has any signs suggestive of active TB. This patient needs full investigation for TB and combination TB treatment if confirmed to avoid TB drug resistance.

- Standard TB screening questions include:
    - Current cough: any duration, productive or non-productive
    - Unexplained weight loss (adults)
    - Failure to thrive and/or malnutrition (children)
    - Fever or night sweats

- Contraindications and/or when to Stop IPT:
    - Suspected or confirmed active TB (start ATT)
    - Jaundice and/or icterus (yellow eyes) or active hepatitis
    - Known or suspected hypersensitivity to INH or severe skin rash
    - Confusion/convulsions
    - Dizziness
    - Peripheral neuropathy i.e. Severe numbness/burning pain and muscular weakness of legs and/or arms
    - Concomitant medication: Phenytoin, Carbamazepine, Warfarin, Theophylline, Selective Serotonine Re-uptake Inhibitor antidepressants (e.g. Fluoxetine, Paroxetine) oral Ketoconazole or Itraconazole

- How to give IPT
    - Give IPT during pre-cART period and to HIV-infected children <12 months old with TB contact and after ruling out active TB
    - Review and assess for side effects at months 1, 3, and 6 after starting IPT
    - IPT initiation: Give INH and Pyridoxine for 1 month
    - Month 1: Give INH and Pyridoxine for 2 months
    - Month 3: Give INH and Pyridoxine for 3 months
    - Give concomitant Pyridoxine (vitamin B6) 1 tablet 25mg once daily to prevent side effects of Isoniazid in pregnant and breastfeeding women, adolescents, and adults.

TABLE 40: DOSAGE FOR ISONIAZID PREVENTATIVE THERAPY, CO-TRIMOXAZOLE PROPHYLAXIS, AND COMBINATION INH/CTX/VIT B6 DRUGS

Drug	Child tablet or oral suspension	Number of scoops or tablets by weight band					Adult tablet
		3 to < 6kg	6 to < 10kg	10 to < 14kg	14 to < 20kg	20 to < 25kg	≥ 25kg
Isoniazid (INH)	100mg	0.5	1	1.5	2	2.5	300mg (1 tablet)
Co-trimoxazole (CTX)	Suspension 200/40mg per mL	2.5 mL	5 mL	5 mL	10 mL	10 mL	–
	Tablet 100/80mg	1	2	2	4	4	–
	Tablet 400/80mg	NA*	½	½	1	1	400/80mg (2 tablets)
	Tablet 800/160mg	NA	NA	NA	½	½	800/160mg (1 tablet)
Pyridoxine (Vitamin B6	Tablet 25mg	NA	NA	NA	½	½	25mg (1 tablet)
INH/CTX/Vit B6	Tablet 300/960/25mg	NA	NA	NA	½	½	300/960/25mg (1 tablet)

*NA = Not Applicable

CO-TRIMOXAZOLE PREVENTIVE THERAPY (CPT)

CPT prevents Pneumocystis Jirovecii Pneumonia (PCP), toxoplasmosis, isosporiasis, malaria, and other HIV- and non-HIV related diseases and prolongs survival. CPT can be safely taken with cART and/or ATT and in pregnancy (Table 17 and Table 18). HIV-infected pregnant women on CPT should not be given Sulfadoxine-Pyrimethamine (SP; malaria prophylaxis in pregnancy)

TABLE 41: CRITERIA FOR INITIATING, DISCONTINUING, AND MONITORING CO-TRIMOXAZOLE PREVENTIVE THERAPY

Specific populations	Whom to Start	When to Start	When to Stop*
Pregnant & Breastfeeding Women	Pregnant women	Start as early as possible. Do not give SP. If SP taken, start CTX after 14 days.	Continue throughout pregnancy
	Breastfeeding women	Continue if CD4 count <350 cells/µL or WCS 2, 3 or 4	CD4 count ≥350 cells/µL for two consecutive values at least 6 months apart while on cART
Children (0 to <5 years old)	HIV-exposed (e.g. breastfed) child	At 6 weeks old or first contact	Confirmed HIV-uninfected after full cessation of breastfeeding
	HIV-infected child <24 months old	Start regardless of WCS or CD4%	At 5 years old and CD4 ≥25% and Stage I
	HIV-infected child ≥24 months to <5 years old	WCS 2, 3 and 4 or CD4 level <25%	
	Presumptive HIV diagnosis <18 months old	Start (or continue) regardless of WCS or CD4%	Stop if confirmed HIV negative; if infected, stop at 5 years old and CD4 level ≥25% and Stage I
	Child with a history of PCP	Start regardless of CD4 count or CD4%	At 5 years old and CD4 level ≥25% and Stage I If 5 to <10 years old, stop based on adult criteria
Children (5 to <10 years old)			
Adolescents	HIV-infected children ≥5 years old, adolescents, and adults	CD4 count <350 cells/µL or WCS 2, 3 or 4	CD4 count ≥350 cells/µL for two consecutive values at least 6 months apart while on cART
Adults			

Stop CTX if the person has Stevens-Johnson syndrome, severe liver disease, severe anaemia, severe pancytopaenia, or HIV negative status.

CPT contraindications: severe allergy to sulfa drugs; severe liver disease, severe renal disease, and glucose-6-phosphate dehydrogenase (G6PD) deficiency and in these conditions DO NOT re-challenge

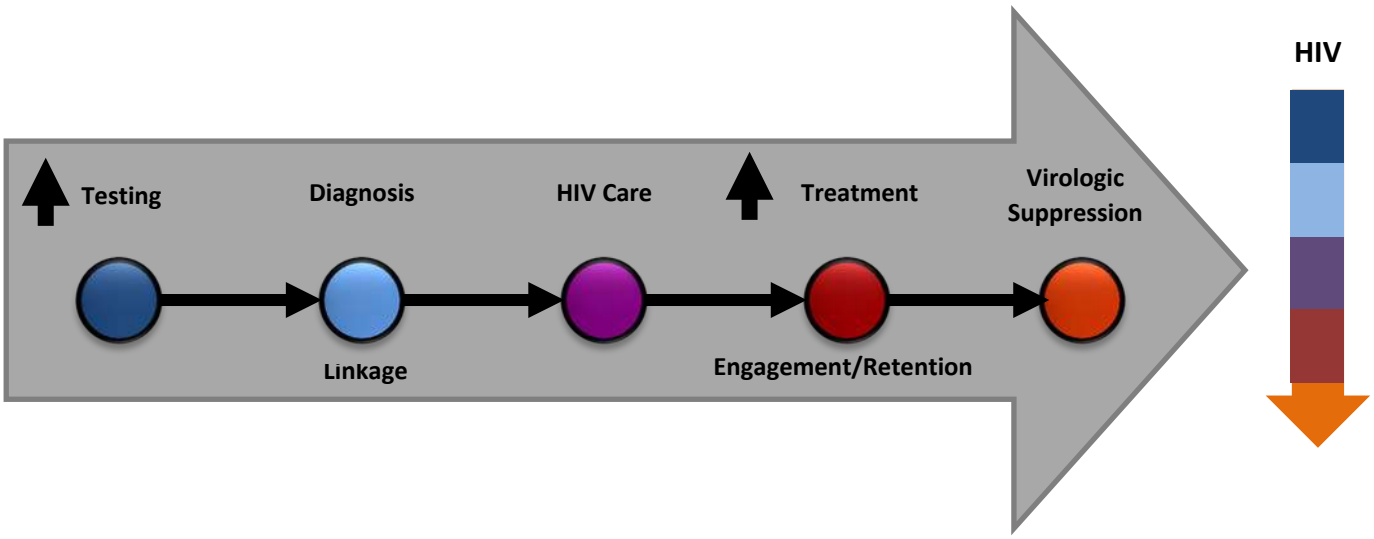
SERVICE DELIVERY

Recommendations

- Diversify interventions to ensure timely linkage to HIV Services
- Patient-centeredness to allow for delivery of care based on people's needs, preferences, clinical characteristics, and context
- Special considerations for Priority and Key Populations
- Task-shifting and investment in staff training and development
- Service delivery should be across the HIV continuum of care
- Establish effective systems for monitoring patients in care

Following diagnosis and throughout the spectrum of care, HIV services should be tailored to respond to specific challenges or barriers faced by patients and aim to offer high quality care, client satisfaction and improved health outcomes. In order to ensure timely linkage to care and follow up for all people living with HIV a package of differentiated interventions should be offered to clients.

FIGURE 21: HIV IMPLEMENTATION CASCADE FOR THE CONTINUUM OF CARE



The Ministry of Health (MoH) of the Republic of Zambia is committed to achieving the 90-90-90 targets and is aware that innovative strategies are needed in order to end the HIV epidemic. Critical to this is to ensure the provision of HIV treatment to all. Continuing to provide services in the same way for all clients will not allow for the achievement of reaching 90-90-90 targets. MOH is aware that the conventional human resources and physical infrastructure currently are not adequate to accommodate national scale up of ART. Differentiated service delivery (DSD) is a client-centered approach that simplifies and adapts HIV services across the cascade in order to reflect the preference and expectations of various groups of PLHIV while also reducing unnecessary burdens on the health system.

The MOH supports the promotion and provision of various differentiated service delivery models in order to lessen the burden of care for both patients and providers and to allow the health system to refocus resources on those patients in most need

PRINCIPLES OF DIFFERENTIATED CARE

The principals of DSD are aimed at supporting the achievement of 90-90-90 targets while also improving the quality of care clients receive.

1. Patient Centeredness

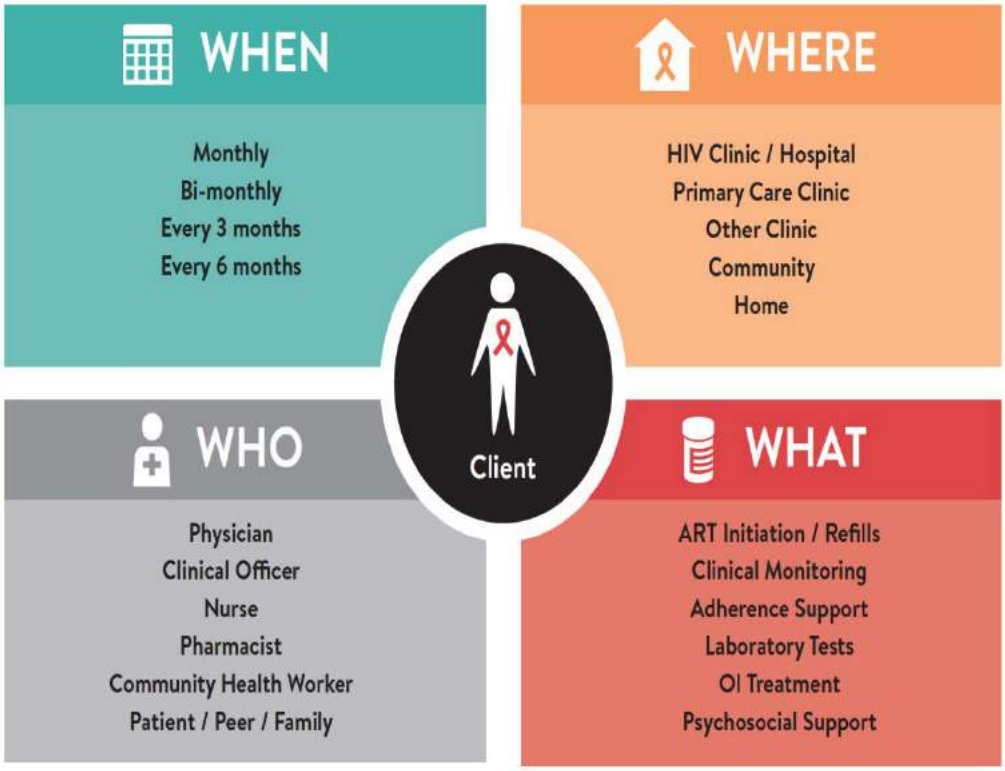
To allow for delivery of care based on people's needs, preferences and expectations with the aim of empowering clients to manage their disease with support from the health system.

2. Health System Efficiency

Ensure the health system is functioning with the highest efficiency. For this to be achieved, investment in human resources for health and infrastructure upgrade is required

BUILDING BLOCKS OF ART DIFFERENTIATED SERVICE DELIVERY MODELS

The building blocks are key components of a service delivery model and address the 'when, where, who, and what' of HIV services and should be used for whichever characteristic(s) (clinical, specific, populations, context) are being considered. At each step in the treatment cascade, DSD models should be designed and implemented as a direct response to specific challenges or barriers identified for clients and health care workers.



Patient Classification for Differentiated Services Delivery

DSD should be provided to all PLHIV across the HIV cascade and extended to other diseases. A growing number of people receiving ART are virally suppressed (stable) and do not require frequent visits to the Health Facility. Offering DSD models of care reduces the burden of frequent visits to the facility for stable clients and allows for resources to be redistributed to patients most in need.

Stable client is defined as follows;

- On cART for at least >6 months
- No adverse drug reactions
- No current illnesses or pregnancy
- Proven record of good adherence and evidence of treatment success
- Viral suppression below 1000 copies /mL within the last 12 months

Unstable client is defined as follows;

- On cART for < 6 months
- On cART for > 6 months but presenting with advanced HIV disease
- CD4 <200
- WHO stage 3 or 4 event
- All children younger than five years old with HIV are considered as having advanced HIV disease
- Not virally suppressed
- Advanced immunosuppression
- Adverse drug reactions
- Active opportunistic infection
- Non-adherent to cART
- Substance use
- Mental illness
- Any other uncontrolled chronic condition/comorbidity like NCDs

Categories of DSD

DSD models can be categorized into four models: (www.differentiatedcare.org)

1. Health care worker managed Group:
    - Clients receive their cART refills in a group and either a professional or a lay health care worker manages this group (e.g., Urban Adherence Groups/Clubs) Health care worker-managed groups meet within and/or outside of health care facilities.
2. Client Managed Groups
    - Clients receive their cART refills in a group but this group is managed and run by clients themselves (e.g. Community Adherence Groups (CAGs). Generally, client- managed groups meet outside of health care facilities.
3. Out of Facility Managed Individuals
    - cART refills and are provided to individuals outside of health care facilities (e.g., of Health Post Dispensation, Home delivery and Community based drug pick-ups)
4. In-Facility Managed Models
    - cART refill visits are separated from clinical consultations. When clients have a cART refill visit, they bypass any clinical staff or adherence support and proceed directly to receive their medication (e.g., appointment spacing and “fast-track”)

DSD for Unstable Clients

There is limited evidence on the building blocks and models for unstable clients however, these clients may also benefit from DSD model access in supporting viral suppression and improving retention. Therefore, DSD building blocks and models should be adapted to accommodate all PLHIV.

Principles of DSD for Specific Populations (children, adolescents, pregnant and breastfeeding women)

- Family based Approach
  Important when considering care for children and their parents. Service provision models for children and their parents/caregivers should be aligned as this can improve the entire family cascade.

- Integration of Services
  Integration of HIV care with other services is a WHO recommendation to strengthen the continuum of treatment care. Integration has been highlighted as key to providing benefits to mothers and their infants, and combining adolescent HIV services with comprehensive services.

- Leveraging and encouraging psychosocial support
  The importance of psychosocial support for all PLHIV, including support from communities and peers, is of particular significance to these special populations

Approach of DSD model to be offered at any given facility should consider:

- Clinical Characteristics of the client (stability, unstable, co-morbid/co infections)
- Client preference
- Model available at the facility

TABLE 42: CATEGORIZATION OF SERVICES OFFERED AT DELIVERY POINTS

<table>
<tr><td colspan="2">HIV/AIDS Management
• At facility level are “high risk,” i.e., Pregnant and breastfeeding women, HEI, discordant couples, newly diagnosed/initiated patients
• Community services to focus on “stable” patients</td></tr>
<tr><td>Community structures such as: Community Adherence Groups (CAGs), Treatment Clubs, Private sector, Faith based groups, Health shops, etc.</td><td>Facility: Health Centre, Level 1, Level 2, Level 3, and Level 4</td></tr>
<tr><td>Decentralization of Services</td><td>Diagnostic and Clinical Services</td></tr>
<tr><td>Retention in Care:</td><td>Health Centre:</td></tr>
<tr><td>• PMTCT sites should have functional community structure/groups affiliated with timely support and connection between health facility and community
• Interventions of mother-baby follow up through reminders for appointments, adherence support
• Community workers and message on identifying sick infants and sending to facilities
• Use of current interventions to follow up patients and infants (e.g., nutritional assessment and</td><td>• HIV testing at birth, 6 weeks, 6 months, 9 months, 12 months, 18 months, 24 months and across all populations (see Table 1)
• Triple prophylaxis depending on risk assessment
• Co-trimoxazole (CTX)
• Growth monitoring
• Immunization as per EPI schedule
• Clinical review and follow up
• Infant feeding counseling
• Ongoing HIV/AIDS counseling and screening.
• Uptake of newly diagnosed cases and commence ARVs
• Treatment of OIs as per Standard Treatment Guidelines
• Palliative care (pain relief and management of common illnesses)</td></tr>
<tr><td>Task Shifting and Sharing:</td><td>Level 1:</td></tr>
<tr><td rowspan="4">• Less frequent clinical visits (3-6 months) being recommended for people stable on cART.
• The use of Community cART models for pick-up of cART, while initiation and monitoring at peripheral health facilities with maintenance at community level
• Trained and supervised community health workers can dispense cART between regular clinical vests</td><td>All of the above and:
• Clinical review/examination
• FBC, CXR, HIV +/-CD4 count, U+E, Creatinine, urinalysis, treatment, and follow up management of OIs
• Infant feeding counselling If referred for further management
• Acceptance of referral back and joint management</td></tr>
<tr><td>Level 2:</td></tr>
<tr><td>All of the above and:
• Management of severe symptoms and investigations
• Urine protein creatinine ratio
• LFTs</td></tr>
<tr><td>Level 3:</td></tr>
<tr><td></td><td>• VL and genotype for treatment failures
• Metabolic complications management
• Research 3rd line management
• Triple prophylaxis depending on risk assessment
• Highly specialized research
• CTX prophylaxis
• Complicated cases:
▪ HIV plus co-morbidities</td></tr>
</table>

MANAGING THE HIV PROGRAM

Tracking and Keeping Patients in Care

Keeping patients in care is essential for achieving good outcomes and preventing resistance. Lost to follow up (LTFU), defaulting and late drug pick-ups may lead to treatment failure, emergence of resistance, and the possibility of transmitting resistant virus. Health facilities should aim to do the following to minimize LTFU:

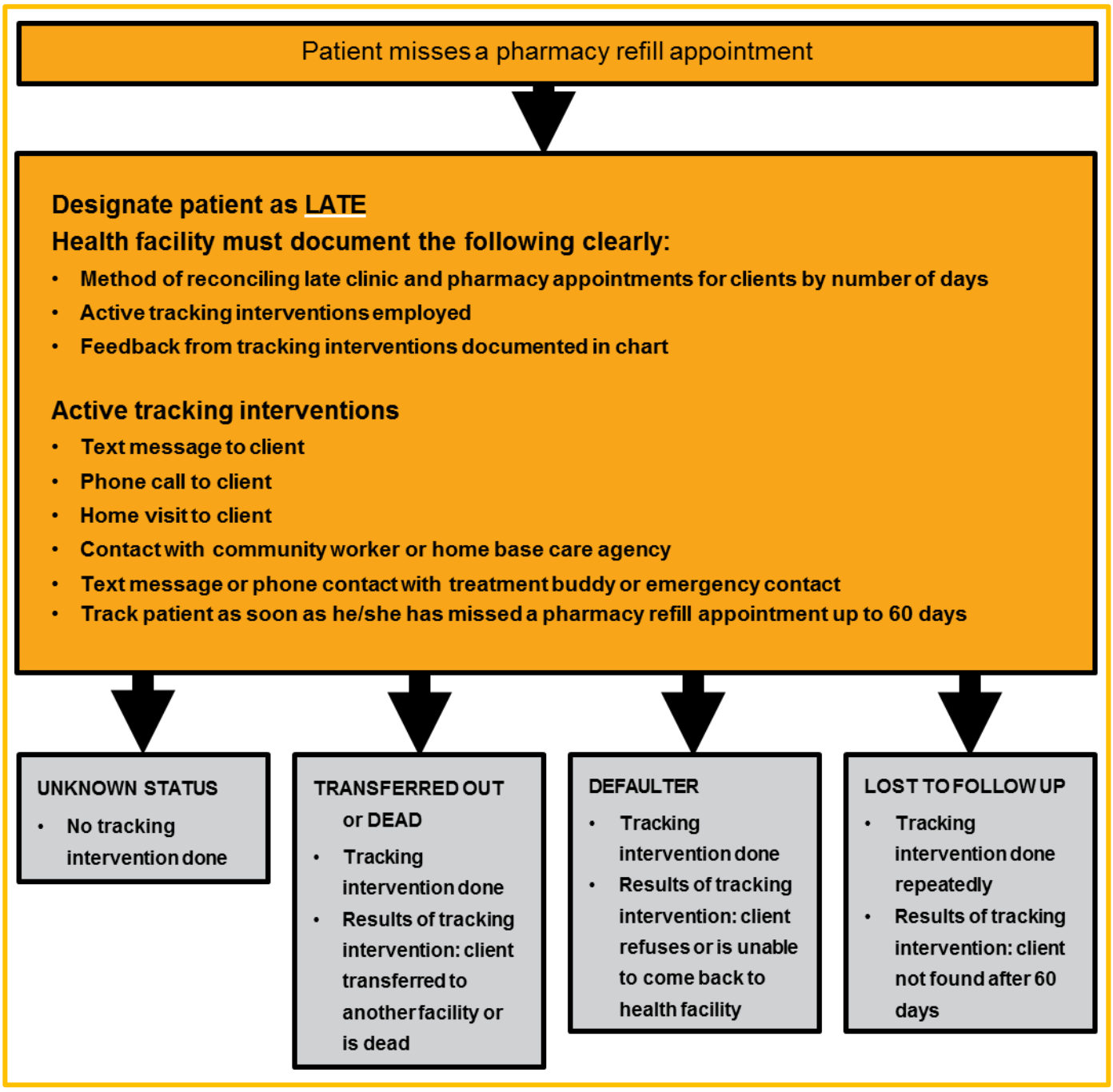
- Have a structured plan to track patients and prevent LTFU
- Monitor all missed clinic and pharmacy visits
- Create linkages with home-based care workers and volunteers
- Dedicate health facility staff to ensure patients who miss visits are contacted

Attrition

Attrition in an HIV programme can occur as the following: late, LTFU, defaulter, death, transferred out to another facility, or unknown status.

- Late: HIV-infected individual misses a pharmacy refill visit, from 1 to <60 days after the last scheduled pharmacy visit
    - For pregnant and breastfeeding women, late is defined as missing a scheduled pharmacy visit
    - Take immediate action (e.g., CHW follow up, text message or mobile health [mHealth] follow up) and document findings. Every effort must be made to re-engage these women in care
- LTFU: HIV-infected individual is missing for ≥60 days after missed pharmacy refill visit after all active tracking interventions (e.g., documented physical follow up to home, phone calls to client and emergency contacts, text message recall, treatment buddy) have been exhausted and HIV-infected individual cannot be traced
    - For pregnant and breastfeeding women, LTFU is defined as missing for ≥60 days after last scheduled pharmacy refill visit with inability to be traced after all active tracking mechanisms have been exhausted.
- Defaulter: HIV-infected individual has been located while late or LTFU, but chooses not to return to care.
- Unknown status: all active tracking interventions have not been exhaustively done to determine current status of HIV-infected individual (for ≥60 days), see Figure 22.

FIGURE 22: ALGORITHM FOR ACTIVE INTERVENTIONS WHEN HIV-INFECTED CLIENTS ARE LATE AND DETERMINING THEIR ATTRITION STATUS



Structured Plan for Tracking Patients

Ideally patients should be tracked as soon as possible after missed pharmacy pickup or clinic appointment. Each day that elapses after missed appointment could be a day without cART, and increasing the likelihood of resistance development and treatment failure. Scheduling patients for appointments and reviewing the list of patients expected on a given day is critical to tracking patients' missed appointments. If the facility does not schedule patients, then a clear log of pharmacy refills must be reviewed daily to identify patients that have missed pharmacy pickups and are potentially out of cART medications. Once a patient is identified as missing, a plan of action for tracking must be initiated.

Monitoring and Evaluation Tools

There are many government tools to assist sites in providing comprehensive, family-centred HIV care and treatment. The standard data collection and patient care tools include documents for children, adolescents, pregnant and breastfeeding women, and adults.

- Safe Motherhood Card (with SM number)
- cART file/clinical case record with cART number and SmartCard
- Antenatal Care register
- Safe Motherhood register
- L&D register
- Postnatal Care register
- Mother Baby Follow-up register
- Community Follow-up register
- Family Planning register
- Under five cards
- Under five registers
- Early Infant Diagnosis (EID) register/log book/EID lab requisition
- Laboratory register

Wherever feasible, data regarding the continuum of HIV care and treatment should be entered into electronic health record systems (e.g. SmartCare). In addition, all facilities should record birth defects using the forms obtainable from the Zambia Medicines Regulatory Authority (ZAMRA, formerly PRA) to feed into the national Birth Defects Registry.

Use of standard tools is required by all health facilities to ensure a functioning supply chain system to avoid stock outs.

The recommended standard tools include:

- Report and Requisition (R&R) form
- Daily Activity Register
- Interval Monthly Summary Report
- Stock Control Cards
- Laboratory Usage report
- Report for Essential Medicines and Medical Supplies

Quality Improvement

Quality Improvement (QI) is a process that aims to strengthen the quality of services provided at health facilities. The QI Technical Working Group (TWG) at MOH has identified five key QI indicators that will be tracked by all levels in the health sector. Of the five indicators, two are HIV-related:

- Percentage of exposed infants tested for HIV at 9 months old
- Percentage of all HIV positive clients retained on HIV care and treatment the last 12 months
    - Number of HIV testing sites scoring ≥80% in proficiency testing
    - Number of EID testing labs scoring ≥80% in proficiency testing
    - Number of viral load testing labs scoring ≥80% in proficiency testing
    - Number of labs enrolled in the CD4 External Quality Assurance (EQA) program scoring ≥80% in proficiency testing

Lifelong cART in pregnant and breastfeeding women also enhances maternal and child survival. For this reason, the following two QI indicators are also pertinent:

- Number of maternal deaths at the facility recorded in the last 1 month, 3 months (quarter), and 12 months
- Number of under-five children who died in the last 1 month, 3 months (quarter), and 12 months. (If possible, differentiate between early neonatal death, neonatal death, infant death, and under-five death)

Through structures that have been formed at all levels, the QI committees review these indicators regularly to identify performance gaps and root causes using the Performance Improvement Approach (PIA). This should be followed by implementation of appropriate interventions coupled with regular monitoring and evaluation to track progress.

These indicators will be reported through the Health Management Information System (HMIS), as well as tracked through the QI reporting structures from the health facility to the national level QI TWG. QI committees at any level should not be restricted to implement QI projects only related to the key indicators. Other areas of underperformance in health service delivery should be covered at the local level as identified with stakeholders, including clients and the community.

Mentoring and Supervision

Mentorship is a QI strategy that provides motivation to HCWs while building their knowledge and skills base.

In collaboration with cooperating partners, MoH developed national guidelines and a mentorship training package. The multi-disciplinary Clinical Care Teams (CCT) at national, provincial, and district level spearhead mentorship and supervision of health facility staff. CCTs comprise clinicians, nurses, nutritionists, pharmacy staff, and laboratory staff and hold regular meetings to review HMIS reports, performance assessment reports, and any other source of information to identify performance gaps in health service delivery, including HIV care and treatment and PMTCT. Appropriate mentors are assigned from the CCT to conduct targeted, needs-based mentorship for QI. Request for specialized mentorship from higher level CCTs is encouraged. The multi-disciplinary approach achieves the following:

- Comprehensive coverage of clinical and support systems, including logistical and health information management
- Coordination, continuity, and availability of a pool of highly experienced mentors in the relevant fields
- Strengthened institutionalized, decentralized system of mentorship

APPENDIX 1: DOSAGES OF ANTIRETROVIRALS FOR ADULTS AND ADOLESCENTS

a) DOSAGES OF ANTIRETROVIRALS FOR ADULTS AND ADOLESCENTS

Drug	Normal Dose	Renal Dose
Abacavir (ABC)	Adult: 300mg BID PO Paediatrics: 8mg/kg BID PO	No adjustment
Atazanavir–r	Adult: 300/100mg OD PO Paediatrics: paediatric dosing by weight bands. No data for children <6 years old.	No adjustment
Darunavir–r	Adult: 600/100mg BID PO Paediatrics: see paediatric dosing by weight bands. Do not use in children <3 years old.	No adjustment
Dolutegravir (DTG)	Adult: 50mg OD PO No sufficient data for use in adolesents younger than 12 years old	No adjustment
Efavirenz (EFV)	Pregnant and/or breastfeeding: 400mg OD PO 600mg OD PO	No adjustment
Emtricitabine (FTC)	Adult: 200mg OD PO Pediatrics: 0-3 months old: 3 mg/kg/day (solution) 3 months-15years old (>33kg): 6mg/kg/day (solution; max 240mg daily) or capsule: 200mg OD (capsule)	Adult: CrCl 30-49: 200mg every 48 hours CrCl 15-29: 200mg every 72 hours CrCl <15: 200mg every 96 hours (give after hemodialysis if on dialysis) Paediatrics: reduce dose or increase dosing interval following adult recommendations in consultation with experienced clinician in renal dosing
Etravirine (ETR)	Adult: 200mg BID PO Paediatrics: see paediatric dosing by weight bands. Not approved for children <6 years old (approval under way for 2 months to 6 year old). • 16kg-<20kg: 100mg twice daily • 20kg-<25kg: 125mg twice daily • 25kg-<30kg: 150mg twice daily	No adjustment

Lamivudine (3TC)	Adult: 150mg BID or 300mg OD PO Paediatrics: 2-4mg/kg BID PO	Adults: CrCl 30-49: 150mg OD PO CrCl 15-29: 150mg x1 then 100mg OD PO CrCl 5-14: 150mg x 1 then 50mg OD PO CrCl <5: 50mg x1 then 25mg OD (50- 75mg OD still acceptable) Paediatrics: reduce dose or increase dosing interval following adult recommendations in consultation with experienced clinician in renal dosing
Lopinavir–r	Adult: 400/100 BID PO Paediatrics: 10-13mg/kg BID PO for Lopinavir component	No dose adjustment, but use with caution in patients with CrCl <50
Nevirapine (NVP)	Adult: 200mg OD PO x 14 days then 200mg BID PO Paediatrics: 4-7mg/kg BID PO	No dose adjustment, but give dose after dialysis
Tenofovir Alafenamide (TAF)	Adult: 25mg OD PO Paediatrics: not approved for adolescents less than 12 years old	No adjustment
Tenofovir (TDF)	Adult: 300mg OD PO Paediatrics: 8mg/kg OD PO	Same for adult & paediatrics: NOTE: Generally avoid when CrCl <50 Only adjust dose when sure that the CKD is independent of the drug in consultation with experienced clinician in renal dosing. CrCl 30-49: 300mg (8mg/kg) every 48 hours CrCl 10-29: 300mg (8mg/kg) twice weekly CrCl <10: consider 300mg (8mg/kg) OD PO (inadequate data) Hemodialysis: 300mg (8mg/kg) once weekly. To be given after dialysis. CAPD: no data
Raltegravir (RAL)	Adult: 400mg BID PO (with Rifampicin 800mg BID PO)	No dose adjustment
Zidovudine (AZT)	Adult: 300mg BID PO Paediatrics: see paediatric dosing by weight bands.	CrCl 30-49: 300 BID PO CrCl 10-29: 300 BID PO CrCl <10: 300mg OD PO in consultation with experienced clinician in renal dosing

b) Simplified dosing of child-friendly fixed dose solid formulations for twice daily dosing for infants and children 4 weeks of age and older

Drug	Strength of tablet	Number of tablets by Weight band morning and evening										Strength of adult tablet (mg)	Number of tablets by Weight band	
		3.0-5.9 kg		6.0-9.9 kg		10.0-13.9 kg		14.0-19.9 kg		0.0-24.9 kg			25.0-34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
Zidovudine/Lamivudine AZT+3TC	Tablet (dispersible) 60mg/30mg	1	1	1.5	5	2	2	2.5	5	3	3	300mg/150mg	1	1
Zidovudine/Lamivudine/Nevirapine AZT+3TC+NVP	Tablet (dispersible) 60mg/30mg/50mg	1	1	1.5	5	2	2	2.5	5	3	3	300mg/150mg/200mg		
Abacavir/Lamivudine ABC+3TC	Tablet (dispersible) 60mg/30mg	1	1	1.5	5	2	2	2.5	5	3	3	600mg/300mg		
Abacavir/Lamivudine ABC+3TC	Tablet (dispersible) 120mg/60mg	0.5		0.5	1	1	1	1	1.5	1.5	1.5	600mg/300mg		

c) Simplified dosing of child-friendly fixed dose solid and oral liquid formulations for once daily dosing for infants and children 4 weeks of age and older

Drug	Strength of tablet (mg)	Number of tablets by Weight band morning and evening					Strength of adult tablet (mg)	Number of tablets by Weight band
		3.0-5.9 kg	6.0-9.9 kg	10.0-13.9 kg	14.0-19.9 kg	20.0-24.9 kg		25.0-34.9 kg
Efavirenz (EFV)	Tablet (scored) 200mg	-	-	PM	PM	1.5	200mg/150mg	2
Abacavir/Lamivudine ABC+3TC	Tablet (dispersible) 60mg/30mg	2	3	1	1.5	6	600mg/300mg	1
Abacavir/Lamivudine ABC+3TC	Tablet (dispersible) 120mg/60mg	1	1.5	2	2.5	3	300mg	1
Atazanavir (ATV)	Capsules 100mg Oral powder scoops 40mg/scoop	-	-	1	2	2	300mg	2 (100mg) or 1 (300mg)
	Tablet 150mg or 200mg	-	-	3	-	-	300mg	1 (200mg) or 1 (300mg)
		-	-	-	1(150mg)	1(200mg)		

d) Simplified dosing of Child-Friendly Fixed Dose Solid and Oral Liquid Formulations for Twice Daily Dosing for Infants and Children 4 Weeks of Age and Older

Drug	Strength of Tablet (mg) or oral liquid (mg/mL)	Number of Tablets or mL by Weight Band morning and evening										Strength of Adult Tablet (mg)	Number of Tablets by Weight Band	
		3.0-5.9 kg		6.0-9.9 kg		10.0-13.9 kg		14.0-19.9 kg		20.0-24.9			25.0-34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
Solid formulations														
Zidovudine (AZT)	Tablet (dispersible) 60mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg	1	1
Abacavir (ABC)	Tablet (dispersible) 60mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg	1	1
Nevirapine (NVP)	Tablet (dispersible) 50mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200mg	1	1
Lopinavir/ritonavir (LPV-r)	Tablet 100mg/25mg	-		-	-	2	1	2	2	2	2	100mg/25mg	3	3
	Pellets 40mg/10mg	2	2	3	3	4	4	5	5	6	6	100mg/25mg	3	3
Darunavir (DRV)	Tablet 75mg	-		-	-	3	3	5	5	5	5			
Raltegravir (RAL)	Chewable tablets 25mg	-		-	-	3	3	4	4	6	6	400mg	1	1
	Chewable tablets 100mg	-		-	-	-	-	1	1	1.5	1.5	400mg	1	1
	Granules (100mg/sachet)	0.25	0.25	0.5	0.5	-	-	-	-	-	-			
Liquid formulations														
Zidovudine (AZT)	10mg/mL	6mL	6mL	9mL	9mL	12mL	1L	-	-	-	-	-	-	-
Abacavir (ABC)	20mg/mL	3mL	3mL	4mL	4mL	6mL	mL	-	-	-	-	-	-	-
Lamivudine (3TC)	10mg/mL	3mL	3mL	4mL	4mL	2.5mL	6mL	-	-	-	-	-	-	-
Nevirapine (NVP)	10mg/mL	5mL	5mL	8mL	8mL	10mL	10mL	-	-	-	-		-	-
Lopinavir/ritonavir (LPV-r)	80/20mg/mL	1mL	1mL	1.5mL	1.5mL	2.0mL	2.0mL	2.5mL	2.5mL	3mL	3mL	-		
Darunavir (DRV)	100mg/mL	-		-	-	2.5mL	2.5mL	3.5mL	3.5mL	-	-			

e) Drug Dosing Of Liquid Formulations For Twice Daily Dosing Of Infants Younger Than 4 Weeks Of Age

Drug	Strength of oral liquid (mg/mL)	2-3 kg	3-4 kg	4-5 kg
Zidovudine (AZT)	10mg/mL	1mL	1.5mL	2mL
Nevirapine (NVP)	10mg/mL	1.5mL	2mL	3mL
Lamivudine (3TC)	10mg/mL	0.5mL	0.8mL	1mL
Lopinavir/ritonavir (LPV-r)	80/20mg/mL	0.6mL	0.8mL	1mL

f) Simplified Weight Band Dosing Schedule For LPV-R

Weight band (kg)	Number of LPV-r oral pellets 40mg/10mg capsules		LPV-r 80mg/20mg/mL oral liquid		Number of LPV-r 100mg/25mg tablets	
	AM	PM	AM	PM	AM	PM
3 – 4.9kg*	2	2	1mL	1mL	NR	NR
5 – 5.9kg	2	2	1mL	1mL	NR	NR
6 – 9.9kg	3	3	1.5mL	1.5mL	NR	NR
10 – 13.9kg	4	4	2mL	2mL	2	2
14 – 19.9kg	5	5	2.5mL	2.5mL	2	2
20 – 24.9kg	6	6	3mL	3mL	2	2
25 – 29.9kg	7	7	NR	NR	3	3
30 – 34.9kg	8	8	NR	NR	3	3

NR = NOT RECOMMENDED

*Adapted from Cipla package insert approved by USFDA and WHO 2013 dosages of recommended antiretroviral drugs

g) Dosing of EFV for HIV-infected children (≥3 month old)

Body Weight	Daily Dose	Number of Capsules or Tablets and Strength
3.5 to <5kg	100mg	2 x 50mg capsules
5 to <7.5kg	150mg	3 x 50mg capsules
7.5 to <15kg	200mg	1 x 200mg capsule
15 to <20kg	250mg	1 x 200mg capsule + 1 x 50mg capsule
20 to <25kg	300mg	1 x 200mg capsule + 2 x 50mg capsules
25 to <32.5kg	350mg	1 x 200mg capsule + 3 x 50mg capsules
32.5 to <40kg	400mg	2 x 200mg capsules
≥40kg	600mg	1 x 600mg capsule OR 3 x 200mg capsules

APPENDIX 2: KEY DRUG-DRUG INTERACTION FOR ARVS

	ABC	TDF	AZT	3TC	FTC	d4T		ATV	LPV	RTV		EFV	NVP		DTG	RAL
Antibiotics (incl. TB drugs)																
Rifampicin																
Rifabutin																
Bedaquiline																
Antimalarial drugs																
Amodiaquine																
Artemisinin																
Halofantrine																
Lumefantrine																
Antifungal																
Itraconazole																
Ketoconazole																
Antiretrovirals																
Efavirenz																
Etravirine																
Nevirapine																
Emtricitabine																
Zidovudine																
Lamivudine																
Stavudine																
Atazanavir																
Darunavir																
Lopinavir																
Abacavir																
Ritonavir																
Dolutegravir																
Gastrointestinal Agents																
Omeprazole																
Esomeprazole																
Lansoprazole																
Cardiovascular drugs																
Quinidine																
Simvastatin																
Amlodipine																
Enalapril																
Hydrochlorothiazide																
Anticonvulsants																
Carbamazepine																
Phenytoin																

Colour Codes for the Key Drug–Drug Interactions for Antiretroviral Drugs

	No clinically significant interaction or interaction unlikely based on knowledge of drug metabolism.
	Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration.
	Interaction likely: do not use or use with caution.
	No clear data, actual or theoretical, indicate whether an interaction will occur.

APPENDIX 3: WHO TOXICITY ESTIMATES

Grade (Severity)	Characteristics	Management
1 (mild)	Transient or mild discomfort, no limitation in activity, no medical intervention needed	Does not require change in therapy Symptomatic treatment may be given
2 (moderate)	Limitation in activity, some assistance may be needed, no or minimal medical intervention or therapy required	Consult Continue cART if possible If no improvement, consider substitution with a drug in the same ARV class, but with a different toxicity profile
3 (severe)	Marked limitation in activity, some assistance usually required, medical intervention required, possible hospitalization	Refer or consult Substitute the offending drug without stopping therapy
4 (life-threatening)	Extreme limitation in activity, significant assistance required, significant medical intervention or therapy required, hospitalization or hospice care	Discontinue all ARV drugs, manage the medical event until patient is stable and toxicity has resolved

APPENDIX 4: CO-TRIMOXAZOLE DESENSITIZATION PROTOCOL FOR ADOLESCENTS AND ADULTS

Time Point	Dose for desensitization
Day 1	80mg SMX/16mg TMP (2mL of oral suspension)
Day 2	160mg SMX/32mg TMP (4mL of oral suspension)
Day 3	240mg SMX/48mg TMP (6mL of oral suspension)
Day 4	320mg SMX/64mg TMP (8mL of oral suspension)
Day 5	1 single-strength SMX/TMP tablet (400mg SMX/80mg TMP)
Day 6 onward	2 single-strength SMX/TMP tablets or one double strength tablet (800mg SMX + 160mg TMP)

Oral suspension is 40mg TMP/200mg SMX per 5mL of syrup

APPENDIX 5: POSITIVE HEALTH DIGNITY & PREVENTION (PHDP)

To have a significant effect on slowing the spread of the epidemic, prevention efforts must also be directed towards HIV-infected individuals who can transmit the virus.

Deliver consistent, targeted prevention messages and strategies during routine visits

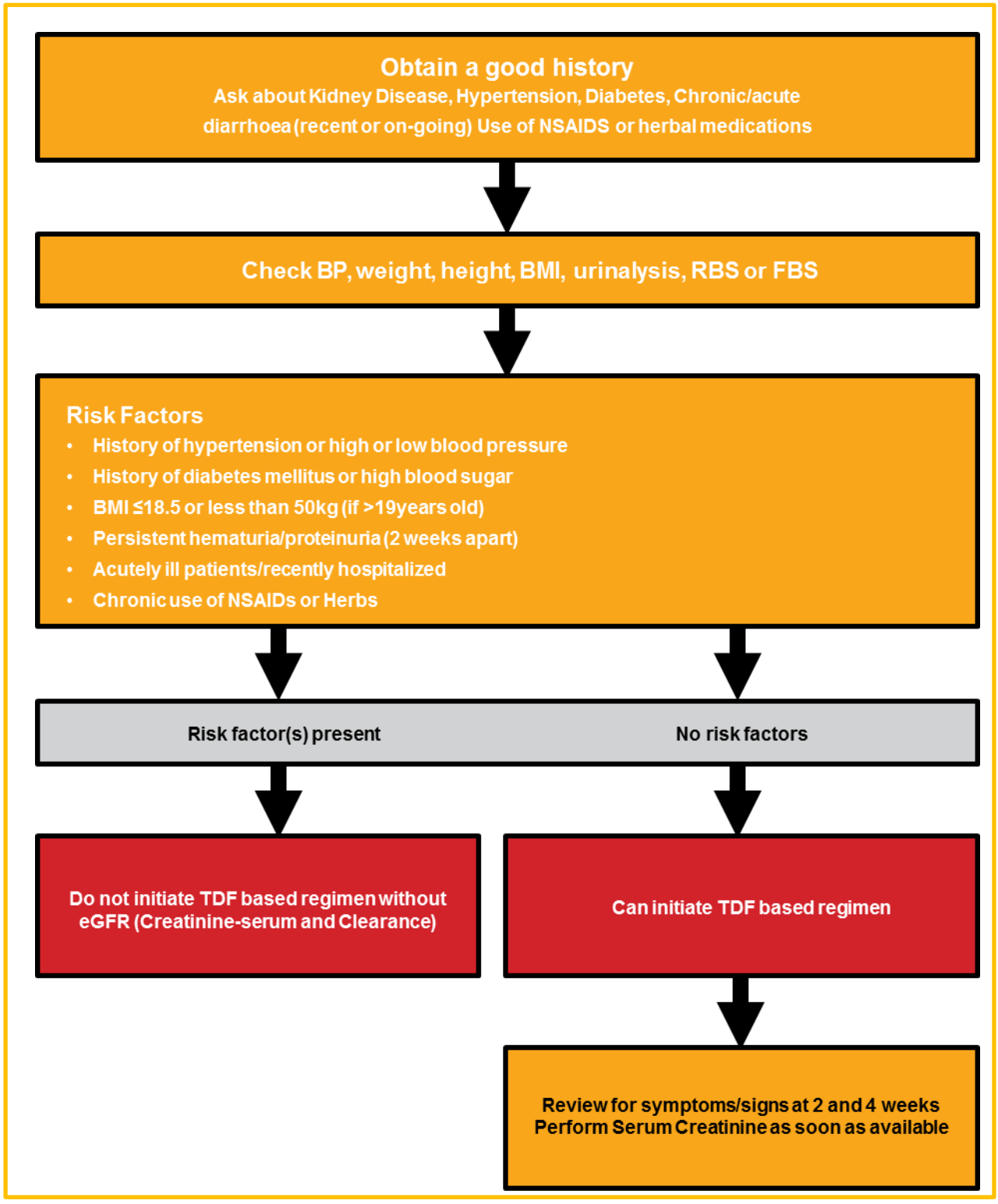
At every visit, assess for and counsel regarding:

- High risk sexual activity
- Partner's and children's HIV status
- Disclosure to partner/guardian/treatment supporter
- Signs and symptoms of STIs and cervical cancer
- Pregnancy status
- Adherence to cART and other medications
- Abuse of alcohol and other substances
- Positive living (nutrition, alcohol and smoking cessation)

Six (6) key steps for PHDP:

- Step 1: Give risk reduction messages to every patient at every visit
- Step 2: Assess adherence to ARVs
- Step 3: TB and STI screening and management
- Step 4: Family planning services and safer pregnancy counselling
- Step 5: Give patient condoms at every visit
- Step 6: Partner HIV testing

APPENDIX 6: RENAL INSUFFICIENCY SCREENING ALGORITHM (IN THE ABSENCE OF CREATININE TEST)



APPENDIX 7: FORMULAE FOR CALCULATING CREATININE CLEARANCE IN DIFFERENT PATIENT POPULATIONS

IN CHILDREN (10-18 YEARS) GLOMERULAR FILTRATION (SCHWARTZ)

Clinical Use: A simple estimate of Glomerular Filtration Rate in children derived from body length and serum Creatinine.

Formula:

$$\text{Creatinine Clearance} = \frac{(k \times \text{height})}{\text{Creatinine}}$$

ADULTS (≥19 YEARS)

- **For Men:**

$$\text{CrCl} = \frac{[(140-\text{age})(\text{weight in kg})]}{72 \text{ x serum Creatinine (mg/dL)}}$$

OR

$$\text{CrCl} = \frac{[(140-\text{age})(\text{weight in kg})]}{0.815 \text{ x serum Creatinine (µmol/L)}}$$

- **For Women**

$$\text{CrCl} = \frac{[(140-\text{age})(\text{weight in kg})(0.85)]}{72 \text{ x serum Creatinine (mg/dL)}}$$

OR

$$\text{CrCl} = \frac{[(140-\text{age})(\text{weight in kg})(0.85)]}{0.815 \text{ x serum Creatinine (µmol/L)}}$$

Units:

- Creatinine: [mg/dL] mg/dl=88.4µmol/L
- Height: [cm]
- Constant as follows: 0.55 for adolescent girls and 0.7 for adolescent boys
- For pregnant women use serum Creatinine (should be less than 125µmol/L to use TDF)

GLOSSARY

Combination antiretroviral therapy (cART): Use of antiretroviral regimens consisting of a combination of at least three or more drugs from at least 2 classes

Body Mass Index (BMI): A measure of body fat based on one's weight in relation to height

Co-trimoxazole Preventive Therapy (CPT): Use of Co-trimoxazole to prevent opportunistic infections in susceptible Persons Living With HIV/AIDS (PLWHA)

Creatinine Clearance (CrCl): An estimation of milliliters of blood filtered by the kidneys per minute

Directly Observed Therapy short course (DOTs): refers to the WHO-recommended strategy for TB control and involves direct observation of patients taking TB medications. This is done to ensure that the patient takes the right medicines, in the right doses, at the right intervals.

Focused Antenatal Care (FANC): A standard package of basic ANC services that all pregnant women should receive. FANC emphasizes the importance of developing a plan of care that meets each woman's individual needs.

HIV Testing Services (HTS): Refers to the full range of services provided with HIV testing, including counseling; linkage to appropriate HIV prevention, treatment, and care, and other clinical services; and coordination with laboratory services to ensure delivery of accurate results

Isoniazid Preventive Therapy (IPT): Use of Isoniazid for prophylaxis to susceptible patients to offer protection against Mycobacterium TB

Immune Reconstitution Inflammatory Syndrome (IRIS): An exaggerated inflammatory reaction from a re-invigorated immune system

National Unique Patient Number (NUPN): A unique client identification number used in SmartCare patient records system

Nucleic Acid Test (NAT): Virological testing technology used for early infant HIV diagnosis developed and validated for use at the point of care. This test detects both viral RNA and DNA

Polymerase Chain Reaction (PCR): A test done to detect HIV specific genetic material that indicates presence of HIV. In Zambia, through the use of Dry Blood Spot (DBS) specimen, this test diagnoses HIV infection in children below 18 months of age.

Positive Health Dignity and Prevention (PHDP): An HIV prevention strategy among PLWHA that focuses on: risk reduction, ART adherence, correct condom use, family planning, STI screening, and partner HIV testing

Pre-exposure Prophylaxis (PrEP): An HIV prevention strategy where those at high risk of acquiring HIV are covered on prophylactic ARVs before exposure to the HIV virus

Post-exposure Prophylaxis (PEP): Short term antiretroviral treatment to reduce the likelihood of HIV infection after potential exposure to the virus

Severe Liver Disease: Progressive destruction of the liver parenchyma over a period greater than 6 months leading to fibrosis and cirrhosis

Treatment as Prevention (TasP): Refers to use of antiretroviral therapy in PLWHA to decrease the risk of HIV transmission to others

Treat All: WHO recommendation that all clients testing HIV positive should be initiated on cART irrespective of their WHO Clinical staging, CD4 or Viral load levels

Visual Inspection with Acetic acid (VIA): A cervical cancer screening method done using Acetic acid