Guidelines for the clinical management of HIV infection in Myanmar

Sixth Edition

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List of abbreviations

3HP	once weekly rifapentine plus isoniazid
3TC	lamivudine
ABC	abacavir
AFB	acid fast bacilli
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral drug
ATV	atazanavir
AZT	azidothymidine or zidovudine
BD	twice daily
bPI	boosted protease inhibitor
CAB-LA	Cabotegravir – long acting
CD4 count	CD4+ T-lymphocyte count
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CSF	cerebrospinal fluid
CrAg	cryptococcal antigen
CVD	cardiovascular diseases
d4T	stavudine
DAA	direct acting antiviral agent for HCV
DBS	dried blood spot
DDI	didanosine
DRV	darunavir
DVR	dapirivine vaginal ring
DTG	dolutegravir
ED-PrEP	event driven pre-exposure prophylaxis
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EID	early infant diagnosis
ETV	etravirine
FDC	fixed-dose combination

FTC	emtricitabine
Hb	haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV DNA	HIV deoxyribonucleic acid
HIV RNA	HIV ribonucleic acid
HIVST	HIV self-test
HSV	herpes simplex virus
HTS	HIV testing services
INH	isoniazid
INSTI	integrase strand transfer inhibitor (integrase inhibitor)
IRIS	immune reconstitution inflammatory syndrome
IVD	in vitro diagnostics
LA	latex agglutination
LAM	lipoarabinomannan
LF	urine lateral flow (test for diagnosing TB)
LPV	lopinavir
LPV/r	ritonavir-boosted lopinavir
MTCT	mother-to-child transmission of HIV
MDR-TB	multi-drug resistance tuberculosis
NAP	National AIDS Programme
NAT	nucleic acid test
NCD	non-communicable disease
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NVP	nevirapine
OD	once a day
OI	opportunistic infection
OST	opioid substitution therapy
Us P 24 Ag	ultrasensitive P 24 antigen test
PJP	pneumocystis jerovercii pneumonia
PEN	Package of Essential NCD interventions

PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
PITC	provider-initiated HIV testing and counseling
PLHIV	people living with HIV
PMTCT	prevention of mother-to-child transmission of HIV
PPE	pruritic papular eruption
/r	low dose ritonavir to boost another PI
RAL	raltegravir
RCT	randomized control trial
RTV	ritonavir
RDT	rapid diagnosis test
STI	sexually transmitted infections
TAF	tenofovir alafenamide
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TG	transgender
TPT	tuberculosis preventive therapy
TST	tuberculin skin test
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
VL	viral load
VMMC	voluntary male medical circumcision
WHO	World Health Organization

Summary of key recommendations

Chapter	Recommendation
Diagnosis of HIV: HIV testing should be offered for: • adults, adolescents or children who present in clinical settings with signs and symptoms or medical conditions that could indicate HIV infection, including TB, viral hepatitis and sexually transmitted infections; • HIV-exposed children and symptomatic infants and children; • key populations and their partners; • all pregnant women; • anyone with a self-perceived risk or suspected exposure .	
Retesting prior to enrollment in care	
	Retest all clients diagnosed HIV-positive with a second specimen and preferably second operator using the same testing strategy and algorithm before initiating ART.
	Retesting people on ART is not recommended, as there are potential risks of incorrect result
HIV diagnosis in infants , children, adolescents and key populations	
Overview	HIV serological assays used for purpose of clinical diagnostic testing have a minimum sensitivity of 99% and specificity of 98% under quality assured laboratory conditions. In infants and children undergoing virological testing, the following nucleic acid test (NAT) assays are strongly recommended for use: HIV DNA on DBS; HIV RNA on plasma or DBS in case HIV DNA is not available. Point-of-care nucleic acid testing should be used to diagnose HIV among infants and children younger than 18 months of age. In infants with an initial positive virological test result, ART should be started without delay and, at the same time, a second specimen is collected to confirm the initial positive virological test result. Immediate initiation of ART saves lives and should not be delayed while waiting for the result of the confirmatory testing.

	HIV-exposed infants who are well should undergo HIV serological testing at around 9 months of age with a NAT. Children (18 months or older) with suspected HIV infection or HIV exposure should have HIV serological testing performed according to the standard diagnostic HIV serological testing algorithm used in adults.
2. Antiretroviral drugs for HIV prevention	
Oral pre-exposure prophylaxis for preventing the acquisition of HIV	
PrEP should be considered for people who are at substantial risk of acquiring HIV. Clients who fall under one of the following 4 categories are assumed to have substantial risk. I. Sexually active in a high HIV incidence/ prevalence population and any of the following in the last 6 months: Vaginal or anal sexual intercourse without condoms with more than one partner, OR • A sexual partner with one or more HIV risk factors, OR • A history of a sexually transmitted infection (STI) by lab testing or self-report or syndromic STI treatment, OR • Use of post-exposure prophylaxis (PEP) for sexual exposure II. People who inject drugs (PWID) III. The sexual partner of someone with HIV who is not on suppressive ART IV. Individual requesting PrEP	
Oral PrEP	
	Oral pre-exposure prophylaxis (PrEP) containing TDF - TDF + 3TC (or FTC) should be offered as an additional prevention choice as part of combination HIV prevention approaches:
Dapivirine vaginal ring (DVR)	
	The DVR may be offered as an additional prevention choice for women at substantial risk of HIV infection as part of combination prevention approaches
Long-acting injectable cabotegravir (CAB-LA)	

	Long-acting injectable cabotegravir (CAB-LA) may be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches Dose of 600 mg, intramuscularly, four weeks apart for the first two injections and every eight weeks thereafter.
Post-exposure prophylaxis	
	A regimen for post-exposure prophylaxis for HIV with two drugs is effective, but three drugs are preferred. Post-exposure prophylaxis ARV regimens for adults and adolescents: • Preferred backbone regimen: TDF + 3TC (or FTC) • Preferred third drug: DTG • Alternative third drug options: ATV/r, DRV/r, LPV/r and RAL Post-exposure prophylaxis ARV regimens for children ≤10 years: • Preferred backbone regimen: AZT + 3TC • Alternative regimens: ABC + 3TC or TDF + 3TC (or FTC). • Preferred third drug: DTG with approved DTG dosing (5 mg and 10 mg) • Age appropriate alternative third drug can be: ATV/r, DRV/r, LPV/r and RAL. A full 28-day prescription of antiretroviral drugs should be provided for HIV post-exposure prophylaxis following initial risk assessment. Enhanced adherence counselling is suggested for all individuals initiating HIV post-exposure prophylaxis.
4. Antiretroviral therapy	
When to start	
When to start ART in adults and adolescents	Initiate ART in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count. As a priority, initiate ART in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with a CD4 count ≤350 cells/mm^3
When to start ART in pregnant and breastfeeding women	Initiate ART in all pregnant and breastfeeding women living with HIV, regardless of WHO clinical stage and at any CD4 cell count and continue lifelong

When to start ART in children younger than 10 years of age	Initiate ART in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count.
Timing of ART for adults and children with TB	Initiate ART in all TB patients living with HIV regardless of CD4 count. TB treatment should be initiated first, followed by ART as soon as possible within the first 2 weeks of treatment, regardless of CD4 count except when signs of meningitis are present. ART should be started in any child with active TB disease as soon as possible and within 2 weeks following the initiation of anti-tuberculosis treatment regardless of the CD4 cell count and clinical stage.
Timing of ART for adults and children with cryptococcal meningitis	Immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred by 4–6 weeks from the initiation of antifungal treatment
Timing of ART for adults and children with disseminated histoplasmosis	ART should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven
What to start: first-line ART	
First-line ART for adults and adolescents	Recommended regimen: TDF + 3TC (or FTC) + DTG as a fixed-dose combination Alternative first line regimen: TAF + 3TC (or FTC) + DTG ABC + 3TC + DTG TDF + 3TC (or FTC) + EFV low dose (400mg) as a fixed-dose combination
First-line ART for pregnant and breastfeeding women	Preferred regimen: TDF + 3TC (or FTC) + DTG as a fixed-dose combination Alternative first line regimen: TAF + 3TC (or FTC) + DTG ABC + 3TC + DTG TDF + 3TC (or FTC) + EFV low dose (400mg) as a fixed-dose combination

First-line ART for infants and children older than 4 weeks and weighting at least 3 kg	Preferred regimen: ABC + 3TC + DTG with approved DTG dosing Alternative first line regimens: • ABC + 3TC + LPV/r • TAF + 3TC (or FTC) + DTG • AZT+3TC+LPV/r • ABC+3TC+EFV • AZT+3TC+EFV
First-line ART for neonates	Preferred first line regimen: AZT (or ABC) + 3TC + RAL is recommended as the preferred first-line regimen for neonates Alternative first line regimen: AZT (or ABC) + 3TC + NVP AZT (or ABC) +3TC+LPV/r
Monitoring the response to ART and diagnosing treatment failure	
Laboratory monitoring before and after initiating ART	Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure. Routine viral load monitoring should be carried out at 6 months of ART, at 12 months of ART and then every 12 months thereafter if the patient is stable on ART. Point-of-care viral load testing may be used to monitor treatment among people living with HIV receiving ART. In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed. (Note: WHO defines people stable on ART according to the following criteria: on ART for at least 1 year, no current illness or pregnancy, good understanding of lifelong adherence and evidence of treatment success) Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, two consecutive viral load measurements within a 2-3 month interval, with adherence support between measurements) after at least 6 months of starting a new ART regimen.
What ART regimen to switch to (second and third line)	
Second-line ART for adults and adolescents	Recommended second-line ART regimen: TDF (or ABC) + 3TC (or FTC) + DTG or AZT + 3TC + LPV/r (or ATV/r) or AZT +3TC + DTG DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone may be recommended as a preferred second-line

	regimen for people living with HIV for whom non-DTG-based regimens are failing. Boosted protease inhibitors in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone are recommended as a preferred second-line regimen for people living with HIV for whom DTG-based regimens are failing The following sequence of second-line NRTI options is recommended: After failure on an AZT + 3TC-based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens.
Second-line ART for children	After failure of a first-line LPV/r- or NNRTI-based regimen, children should be switched to a second-line regimen containing an optimized nucleoside reverse-transcriptase inhibitor (NRTI) backbone plus DTG. After failure of first line DTG based regimen, children should be switched to regimen containing boosted protease inhibitor. After failure of a first-line regimen containing AZT + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC). After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC.
Third-line ART	Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as INSTIs and second-generation NNRTIs and PIs. Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen.
5. Managing common co-infections and comorbidities	
Co-trimoxazole prophylaxis	Co-trimoxazole prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a CD4 count ≤350 cells/mm^3. Co-trimoxazole prophylaxis may be discontinued in adults (including pregnant women) with HIV who are clinically stable on ART, with evidence of immune recovery and viral suppression.

	Routine co-trimoxazole prophylaxis should be given to all HIV-infected patients with active TB disease regardless of CD4 cell count. Co-trimoxazole prophylaxis is recommended for infants, children, and adolescents with HIV, irrespective of clinical and immune conditions. Priority should be given to all children less than 5 years old regardless of CD4 count or WHO clinical stage and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4 and/or those with CD4 ≤ 350 cells/mm^3. Co-trimoxazole prophylaxis is recommended for HIV-exposed infants from 4-6 weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding. Co-trimoxazole prophylaxis in children and adolescents may be discontinued for children 5 years of age and older in those who are clinically stable, with evidence of immune recovery and/or viral suppression on ART.
Tuberculosis	All people living with HIV be screened for TB. Screening can be conducted with the WHO-recommended four-symptom screen, which includes screening for any one of cough, fever, weight loss and night sweats. Lymph node enlargement is also suggestive of TB and clinicians should consider further investigation with ultrasound and/or biopsy. Everyone with a positive screening test (i.e. everyone with presumptive TB) should have a recommended sputum TB molecular test using Gene Xpert. For children with signs and symptoms of pulmonary or extrapulmonary TB, recommended TB molecular tests (GeneXpert) should be performed on sputum, nasopharyngeal aspirate, gastric aspirate, stool, blood or urine, together with urine LF-LAM. LF-LAM should be used to assist in the diagnosis of active TB in adults inpatients living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary), who have a CD4 count < 100 cells/mm3 or people living with HIV who are seriously ill regardless of CD4 count or with unknown CD4 count. This recommendation also applies to adult outpatient living with HIV., who have a CD4 count < 200 cells/mm3who with same criteria of inpatients, and hence, LF-LAM could be performed for seriously ill HIV-positive adult patients with danger signs, regardless of CD4 count, in both in-hospital and outpatient settings. This recommendation also applies to children living with HIV, with sign and symptoms of TB (pulmonary and/or extrapulmonary).

	LF-LAM should not be used as a screening test for active TB.
Tuberculosis Preventive Therapy (TPT)	All PLHIV aged 1 years or older (i.e. adults and adolescents) should take TPT as part of a comprehensive package of HIV care in addition to their antiretroviral treatment (ART). This is regardless of their CD4 cell count. While regular ART reduces the overall risk of developing TB, this risk remains higher than in HIV-negative people, especially where background rates of TB are higher. Combined use of TB preventive treatment and ART significantly reduces the risk of TB. Weekly rifapentine plus isoniazid for 3 months (3HP) regimen is recommended for use in children aged 2 years or older, adolescents and adults. 3HP can be administered to people receiving DTG- or EFV-based without dose-adjustment. 3HP should not be administered to people receiving protease inhibitors or nevirapine. Isoniazid given daily for 6 to 9 months is recommended for pregnant women and children younger than 2 years.
Multidrug-resistant TB and HIV	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs irrespective of CD4 cell count, as early as possible (within the first 2 weeks) following initiation of anti-tuberculosis treatment.
Cryptococcal disease	Adults and adolescents with advanced HIV disease, particularly, CD4 cell count < 100 cells/mm^3, should receive serum cryptococcal antigen screening, followed by cryptococcal antigen testing in cerebrospinal fluid (CSF) if the serum cryptococcal antigen test is positive. Cryptococcal antigen screening among children younger than 10 years without symptoms of cryptococcal disease is not generally recommended, since children have a low prevalence of cryptococcal disease. However, if a child has signs and symptoms of cryptococcal meningitis, then diagnostic testing using serum cryptococcal antigen should be offered. If serum cryptococcal antigen is positive, then diagnostic testing using CSF cryptococcal antigen should be offered if lumbar puncture is available. Prompt lumbar puncture with measurement of CSF opening pressure by using spinal manometer and rapid CSF cryptococcal antigen (CrAg) assay (either lateral flow assay or latex agglutination assay) is the preferred diagnostic approach. Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease is recommended before

	initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 count <100 cells/mm^3. Fluconazole 800 mg/day for two weeks, then 400 mg/day for eight weeks and continued maintenance with fluconazole 200 mg/day. Maintenance treatment should continue until person is stable on ART with CD4 cell count >200 cells/mm^3. All people living with HIV with a positive cryptococcal antigen result on screening should be carefully evaluated for meningitis before pre-emptive therapy. When cryptococcal antigen screening is not available, fluconazole primary prophylaxis can be considered for adults and adolescents living with HIV who have a CD4 count <100 cells/mm^3. The preferred induction regimen for adults, adolescents and children is a single high dose (10 mg/kg) of liposomal amphotericin B (AmB) with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1200 mg/daily for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). Maintenance treatment should continue until person is stable on ART with CD4 cell count >200 cells/mm^3. Immediate ART initiation is not recommended in HIV-infected patients with cryptococcal meningitis due to the high risk of IRIS, which may be life-threatening. ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy, and within 4-6 weeks of induction and consolidation treatment with Amphotericin containing regimen.
Histoplasmosis	Among people living with HIV, disseminated histoplasmosis should be diagnosed by detecting circulating Histoplasma antigens. Lateral flow assay–based rapid diagnostic tests for Histoplasma antigen provide additional opportunities to rapidly diagnose histoplasmosis at the point of care <u>Induction therapy</u> Treating severe or moderately severe histoplasmosis among people living with HIV: a single induction dose of liposomal AmB, 10.0mg/Kg, is preferred, whereas liposomal AmB, 3.0 mg/kg, for two weeks can also be considered. In settings where liposomal amphotericin B is unavailable, deoxycholate AmB, 0.7– 1.0 mg/kg, is recommended for two weeks. As a good practice for people with renal failure, or at risk of renal injury, measures to prevent or treat toxicity are recommended. Induction therapy should be given for two weeks. Since deoxycholate amphotericin B may be associated with renal toxicity, therapy may need to be shorter than two weeks based on the clinical assessment of how the person responds to treatment. Involvement of the central nervous system may require extending induction therapy or increasing dosage.

	Treating mild to moderate histoplasmosis among people living with HIV: itraconazole 200 mg three times daily for three days and then 200 mg twice daily is recommended. Maintenance therapy Itraconazole 200 mg twice daily for 12 months is recommended (conditional recommendation; very-low-certainty evidence). Less than 12 months of therapy can be considered when the person is clinically stable, receiving antiretroviral therapy, has suppressed viral load, and the immune status has improved. Antiretroviral therapy should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven
Talaromycosis	Typical skin lesions, fever, and weight loss syndromes were observed in the majority of clinical HIV-positive persons. Anemia and diarrhea were also common in approximately half of the infected populations, as were hepatomegaly, lymphadenopathy, splenomegaly, and cough. The gold standard for clinical *T. marneffei* infection diagnosis is microscopic proof of the presence of the pathogen in tissues, the effective isolation of the fungus from patient specimens, or both. Amphotericin B is the first-line antifungal medicine used for severe talaromycosis, followed by weeks to months of azoles such as itraconazole and voriconazole and posaconazole. For HIV infected persons, international recommendations include intravenous deoxycholate Amphotericin B at 0.6 to 0.7 mg/kg of body weight or, where available, 3 to 5 mg/kg of liposomal Amphotericin B daily for 2 weeks.
Cervical cancer	All HIV+ women should be screened for cervical cancer using HPV DNA detection in a screen, triage and treat approach starting at the age of 25 years with regular screening every 3 to 5 years. Until HPV DNA testing becomes operational, quality-assured cytology or visual inspection of the cervix with acetic acid (VIA) should be continued as the primary screening test. Implementing screening for cervical cancer is also important as a means to improve the overall sexual health of HIV+ women. Prioritize routine HPV-vaccination for HIV+ girls and women at age 9-11 years. A three-dose schedule (0, 1–2 and 6 months) should be used for all vaccinations initiated at 15 years and older, including those younger than 15 years known to be

	immunocompromised and/or living with HIV (regardless of whether they are receiving ART.
Assessment and management of non-communicable diseases	Assessment of risk factors and screening for hypertension and diabetes including CVD risk assessment are recommended for all PLHIV above 40 years of age
Assessment and management of depression in people living with HIV	Assessment and management of depression should be included in the package of HIV care services for all individuals living with HIV.

Introduction

HIV is now a treatable condition and the majority of people who have HIV remain fit and well on treatment. Despite this, a significant number of people are unaware of their HIV status and remain at risk to their own health and unknowingly passing their virus to others. Late diagnosis is the most important factor associated with HIV related morbidity and mortality. Patients should therefore be offered and encouraged to accept HIV testing in a wider range of settings.

In 2022, HIV programme review recommended to update the national HIV clinical management guidelines according to the latest global guidance and recommendations. Under the leadership of the National AIDS Programme, the core writing group was formed and drafted the Guidelines on the clinical management of HIV infection in Myanmar: Sixth Edition. These guidelines aim to guide all health care providers in Myanmar, accommodating the situation of different settings in the context of progressive decentralization of HIV services. Notable changes from the previous edition include:

- diagnosis of HIV
- preferred ARV regimen and optimization
- PrEP and PEP updates
- updates on co-infections and comorbidities management

It should be noted that these guidelines are meant for the operational level and are adapted and adopted in line with existing Myanmar context.

1. Diagnosis of HIV infection

1.1. HIV testing services (HTS)

The overarching goals of HIV testing services are to:

- identify people with HIV through the provision of quality services for individuals, couples and families
- link individuals and their families to appropriate HIV treatment, care and support, as well as HIV prevention services, based upon their serostatus
- support the scale-up of high impact interventions in Myanmar to reduce HIV transmission, morbidity and mortality, including early access to antiretroviral therapy (ART), prevention of mother-to-child transmission (PMTCT), post-exposure prophylaxis (PEP), Pre-exposure Prophylaxis (PrEP) and other interventions as approved by the National AIDS Programme and the Ministry of Health.

The 5 Cs are principles that apply to all HIV Testing Services and in all circumstances:

- Consent: People receiving HTS must give informed consent to be tested and counselled. (Verbal consent is sufficient; written consent is not required.) They should be informed of the process for HIV testing and counselling and of their right to decline testing.
- Confidentiality: HTS must be confidential, meaning that what the HTS provider and the client discuss will not be disclosed to anyone else without the expressed consent of the person being tested. Although confidentiality should be respected, it should not be allowed to reinforce secrecy, stigma or shame. Counsellors should discuss, among other issues, whom else the person may wish to inform of their sero-status and how they would like this to be done. Shared confidentiality with a partner or family members – trusted others – and health-care providers is often highly beneficial.
- Counselling: Pre-test information can be provided in a group setting if appropriate, but all persons should have the opportunity to ask questions in a private setting if they request. All HTS must be accompanied by appropriate and high-quality post-test counselling, based on HIV test results. Quality assurance (QA) mechanisms as well as supportive supervision and mentoring systems should be in place to ensure the provision of high-quality counselling.

- Correct: Providers of HTS should strive to provide high-quality testing services, and Quality assurance mechanisms should ensure that people receive a correct diagnosis. Quality assurance may include both internal and external measures and should include support from the national reference laboratory. All people who receive a positive HIV diagnosis should be retested to verify their diagnosis before initiation on ART or engagement in HIV care.

- Connection: Linkage to prevention, care and treatment services should include the provision of effective and appropriate follow-up as indicated, including long-term prevention and treatment support.

HIV testing services, with linkage to prevention, treatment and care, should be offered for adolescents from key populations in all settings.

Adolescents with HIV should be counselled about the potential benefits and risks of disclosure of their HIV status and empowered and supported to determine if, when, how and to whom to disclose.

HIV testing services should be routinely offered to all key populations in the community, in closed settings such as prisons and in facility-based settings.

Pre-test services

All clients who request/receive HIV testing should be given information on the following:

- the benefits of HIV testing
- the meaning of a first reactive rapid test and the importance of immediate referral for confirmation testing where screening testing is implemented
- the meaning of a confirmed HIV-positive and an HIV-negative diagnosis
- the meaning of an inconclusive result and the importance of retesting after 14 days
- the services available in the case of an HIV-positive diagnosis, including where ART is provided
- a brief description of prevention options
- encouragement of partner testing in particular for all persons who test positive
- the fact that the test result and any information shared by the client is confidential
- the fact that the client has the right to refuse to be tested and that declining testing will not affect the client's access to services or general medical care
- potential risks to the client in settings where there are legal implications for those who test positive and/or those whose sexual or other behaviour is stigmatized
- an opportunity to ask the provider additional questions.

Post-test services

For persons who test negative, the following information should be provided:

- an explanation of the test result

- for people with ongoing HIV risk should have education on methods to prevent HIV acquisition and promotion of condom use. Note that key population clients should be provided with male and female condoms, lubricant and guidance on their use where possible.
- emphasis on the importance of knowing the status of sexual partner(s) and information about the availability of partner and couples testing services
- referral and linkage to relevant HIV prevention services should be prioritised for people at ongoing HIV risk, particularly people from key populations, including harm reduction and other interventions such as pre-exposure prophylaxis (PrEP). PrEP has been shown to be highly effective in preventing new HIV infections among persons at risk. The National AIDS Programme is assessing the potential of PrEP in Myanmar.
- Note that for most people who test HIV-negative, additional retesting to rule out being in the window period is not necessary. However a recommendation for retesting for HIV-negative persons, based on the client's risk of exposure should be made for the following two scenarios
    - a person with recent and specific risk that occurred in the last 6 weeks should return for re-testing in 4 to 6 weeks
    - an HIV-negative person with on-going risk of exposure such as key populations and persons in sero-discordant relationship (s) may benefit from testing every 6 months

Persons who do not report recent or on-going risk should be advised to return for testing only if their personal situation changes and if they are potentially exposed to HIV infection.

In case test results are inconclusive, persons should be encouraged to return in 14 days for retesting.

A person with a reactive HIV test result on a first rapid test diagnosed in a screening testing service needs to be linked immediately to the nearest HIV confirmation site.

The information and counselling that health workers or others provide to those with a confirmed HIV diagnosis should include that listed below. Providing all of this information in one session may be very challenging, and a follow-up counselling session may be required.

- Explain the testing results and diagnosis (status).
- Give the client time to consider the results and help the client cope with emotions arising from the diagnosis of HIV-infection.
- Discuss immediate concerns and help the client decide who in her or his social network may be available to provide immediate support.
- Assess the risk of intimate partner violence and discuss possible steps to ensure the physical safety of clients, particularly women, who are diagnosed HIV-positive.
- Assess the risk of suicide, depression, and other mental health consequences of a diagnosis of HIV-infection.

- Provide clear information on ART and its benefits for maintaining health and reducing the risk of HIV transmission, as well as where and how to obtain ART.
- Explain that the Care and Treatment site will retest repeat HIV testing once more for verification prior to enrolment.
- Arrange a specific date and time for active referral. The health worker or person doing the test should make an appointment for the client and if at all possible, accompany the client or patient to the appointment and assist the client to enroll in clinical care and treatment. Discuss barriers to linkage to care, same-day enrolment and ART eligibility assessment. Arrange for follow-up of clients who are unable to enroll in HIV care on the day of diagnosis.
- Provide information on how to prevent transmission of HIV, including information of the reduced transmission risks when virally suppressed on ART
- Provide male or female condoms and lubricants and guidance on their use. Consistent use of condoms is particularly important for people with HIV infection to prevent HIV transmission to sexual partners until they are virally suppressed on ART.
- Discuss possible disclosure of the result and the risks and benefits of disclosure, particularly among couples and partners. Offer couples counselling to support mutual disclosure.
- Encourage and offer HIV testing for sexual partners, children and other family members of the client. This can be done individually, through couples testing, index case testing or partner notification.
- Provide information about PrEP for HIV-negative partners at sites where services may become available in the future, to protect the HIV-negative partner in a sero-discordant relationship until the HIV-positive partner has successfully enrolled in ART and achieved viral suppression.
- Provide additional referrals for prevention, counselling, support and other services as appropriate (for example, TB screening and treatment and TPT for people screened negative for TB, HBV and HCV testing prophylaxis for opportunistic infections, STI screening and treatment, contraception, antenatal care, opioid substitution therapy and access to sterile needles and syringes).
- Encourage and provide time for the client to ask additional questions.

Special considerations for specific populations and for specific procedures are described in the HTS Guidelines.

Priority population for HIV testing services

HIV testing should be offered for:

- adults, adolescents or children who present in clinical settings with signs and symptoms or medical conditions that could indicate HIV infection, including TB, viral hepatitis and sexually transmitted infections;
- HIV-exposed children and symptomatic infants and children;
- key populations and their partners; and
- all pregnant women.

HIV testing services should be routinely offered to all key populations in the community, in closed settings such as prisons and in facility-based settings. HIV testing services, with linkage to prevention, treatment and care, should be offered for adolescents from key populations in all settings. Adolescents with HIV should be counselled about the potential benefits and risks of disclosure of their HIV status and empowered and supported to determine if, when, how and to whom to disclose.

Differentiated approaches for HIV testing services

Facility-based HIV testing: HIV testing services are provided at in a health facility or laboratory setting. It can be provided at stand-alone HIV testing services sites (often referred to as voluntary counseling and testing sites) or routinely offered at clinical sites (often referred to as provider-initiated testing and counseling).

Community-based HIV testing services for key populations linked to prevention, treatment and care services are recommended, in addition to routine facility-based HIV testing services, in all settings. This will be the screening test carried out by basic health staff or trained peers/volunteers. Individuals with a reactive test result must receive further testing for confirmation.

HIV self-testing (HIVST) should be offered as an approach to HIV testing. Providing HIV self-testing service delivery and support options is desirable. HIV self-testing does not provide a definitive HIV-positive diagnosis. Individuals with a reactive test result must receive further testing from a trained tester using the national testing algorithm.

HIV partner services

Partner services offer voluntary HIV testing services to the sexual and/or drug-injecting partners of people living with HIV. This is an effective way of identifying additional people living with HIV. Partners who are diagnosed with HIV can be linked to treatment services, and those who are HIV-negative and at ongoing risk of acquiring HIV can be linked to effective HIV prevention. Partner services include partner notification, contact tracing, index testing and family-based index case testing for reaching the partners of people living with HIV. Provider-assisted referral should be offered to people with HIV as part of HIV care.

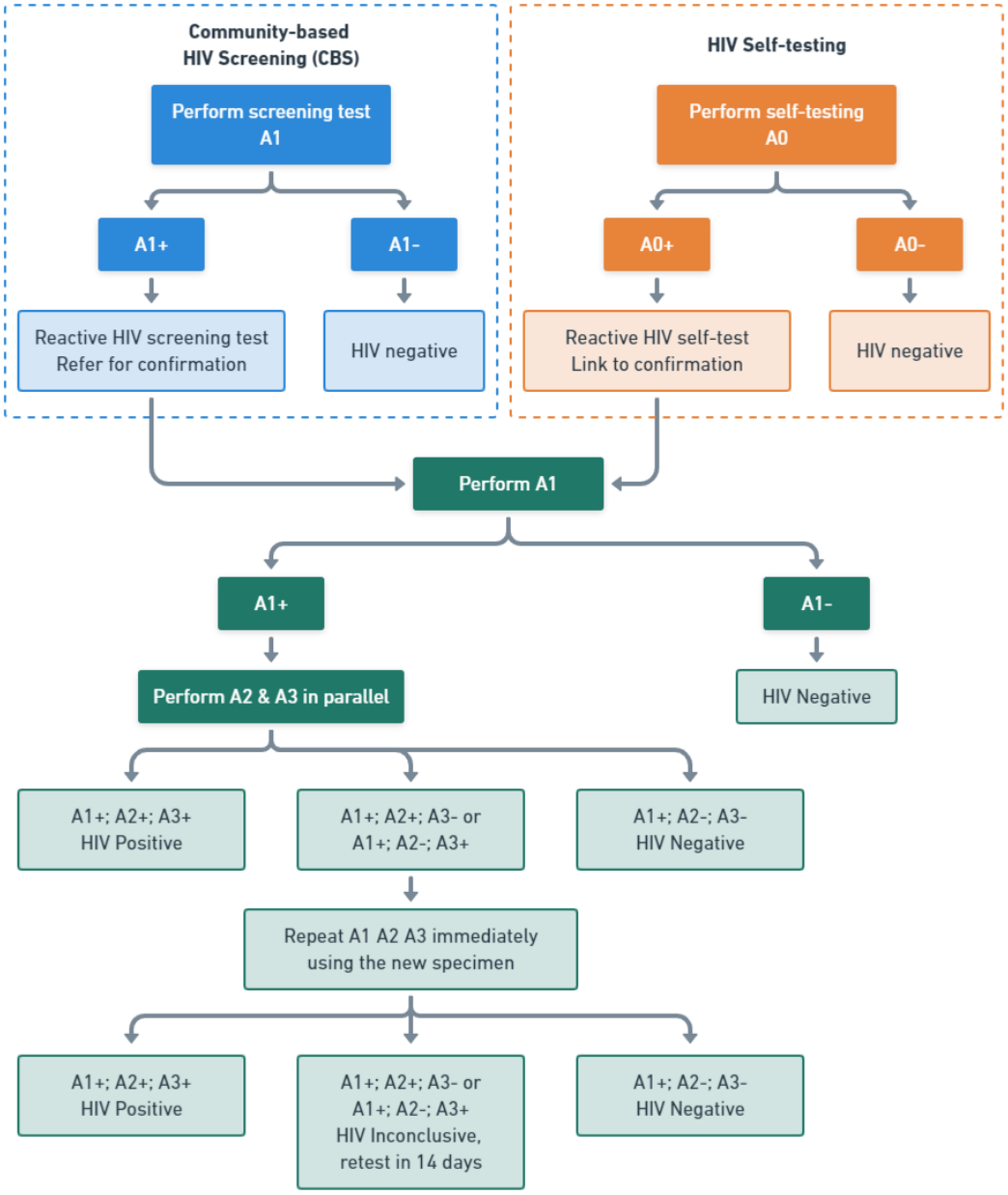
1.2. Laboratory diagnosis of HIV infection

HIV testing may take place at any level of the health-care system, and a diagnosis can be established for many individuals on the same day. Some people will access HIV testing in their community or at the primary care level; others will be tested in hospitals or special testing sites. Rapid diagnostic tests (RDTs) are a critical tool for scaling up HIV testing. They can be performed by trained community workers, health-care workers and laboratory professionals in various settings.

HIV diagnosis in those 18 months of age and older

The testing algorithm for HIV screening (Figure 1) is recommended in settings (e.g. community outreach, community based sites, health facilities, and general practitioners) where the provider and/or the site does not meet the minimum standards needed for confirmation testing but has been certified to provide screening testing. A trained community worker or health care worker will conduct only a single RTD.

Figure 1. Testing algorithm for HIV screening and diagnosis



The assay (labelled A1 in Figure 1 above) must be a RDT that is **highly** sensitive.

Individuals who test HIV reactive should be referred immediately to the nearest site approved for confirmatory testing to confirm their HIV status as per the national HIV testing algorithm. Approved sites for testing to confirm HIV status can be a community site, or health facility, or a certified laboratory, or a health facility which provides ART. The provider who performed the first assay **must take an active role to ensure that all persons who screen reactive actually receive testing to confirm their HIV status.**

All specimens are first tested with a highly sensitive assay (A1), and specimens that are non-reactive (A1−) are considered HIV-negative and reported as such. These RDTs are the most sensitive assays currently available in Myanmar and take into account diagnostic sensitivity, and seroconversion sensitivity.

Any person with a reactive result on the first-line assay (A1+) should be retested using a separate and distinct second and third assay (A2 and A3) comprised of a different antigen preparation to avoid false cross-reactivity with A1. A2 and A3 which are required for HIV-positive diagnosis will be run in parallel. Assays A2 and A3 must have a higher specificity than A1.

For specimens that are reactive on the first, second and third assays (**A1+ A2+A3+**), the diagnosis is reported as **confirmed HIV-positive** and the individual needs to be referred for prompt enrollment in ART. Note, retesting to verify the HIV diagnosis should be performed prior to ART initiation.

If the results of the second and third assays are non-reactive (**A1+ A2- A3−**), the diagnosis is reported as **confirmed HIV-negative**. If the A1 assay is 4th generation, this should be considered HIV-inconclusive and the individual should be retested in 14 days.

For specimens that are reactive on the first-line assay but non-reactive on the second-line or third-line assay (A1+ A2− A3+ or A1+A2+A3-) testing should be repeated using a new specimen with the same three assays.

Any specimens that remain reactive on retesting with the first assay but are non-reactive on the second or third assay (**A1+ A2− A3+ or A1+A2+A3-**) **should be reported HIV-inconclusive and re-testing in 14 days be recommended.**

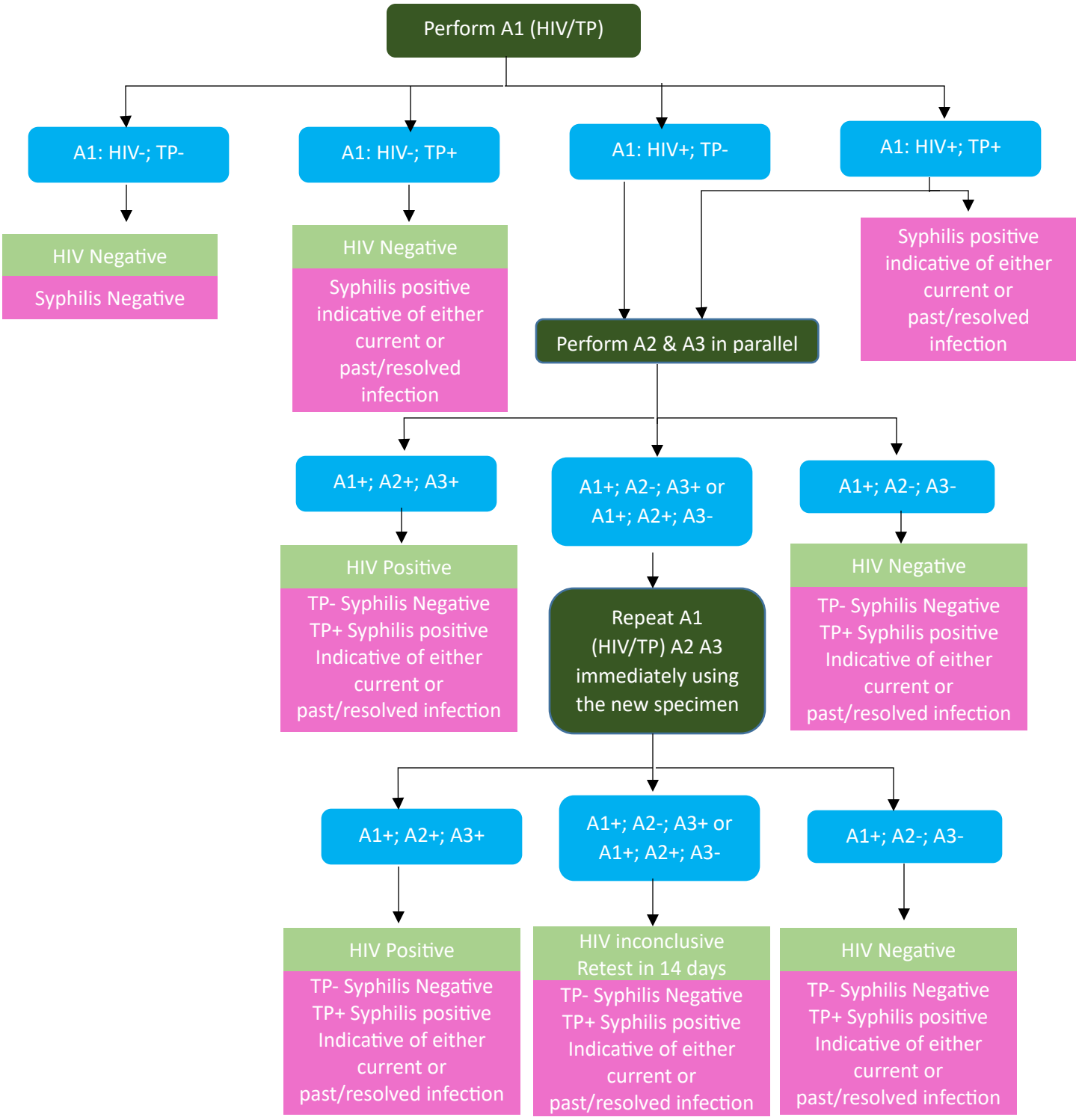
Recommended rapid test kits for 3-assay HIV Testing Strategy are:

A1 = Alere Determine HIV-1/2 (manufactured by Alere Medical Co., Ltd., Japan) (D) ICT (sensitivity 100% and specificity 99.75%); If not available, WHO pre-qualified RDT with 100% sensitivity and specificity similar to Determine.

A2 = Uni-Gold HIV (manufactured by Trinity Biotech Manufacturing Ltd., Ireland) (UG) ICT (sensitivity 100% and specificity 100%) If not available, WHO pre-qualified RDT with 100% specificity similar to Uni-Gold .

A3 = HIV 1/2 STAT-PAK (manufactured by Chembio Diagnostic Systems Ltd., USA) (SP) ICT (sensitivity 99% and specificity 100%) If not available, WHO pre-qualified RDT with 100% specificity similar to STAT-PAK .

Figure. 2 Testing strategy for dual detection of HIV and syphilis infection in antenatal care settings



- A1:Assay 1, A2: Assay 2, A3: Assay 3, TP: Treponema pallidum (syphilis).
- A1 (Assay 1) is a dual HIV/syphilis rapid diagnostic test (RDT).
- A2 and A3 (Assay 2 and Assay 3) are HIV RDTs or enzyme immunoassay (EIAs).
- *When resolving discrepant results, all reactive TP (syphilis) results, including A1:TP+ or Repeat A1: TP+, should be immediately referred for confirmation and further treatment according to national guidelines.
- When resolving discrepant results, if A1 and Repeat A1 are both TP (syphilis) nonreactive results, report syphilis-negative.
- Pregnant women already on ART should not retested.
- Serological tests for syphilis can remain positive even after successful treatment.

HIV diagnosis in infant and children

Because of high mortality in the first year of life among untreated HIV-infected infant, early HIV testing, prompt return of results and rapid initiation of treatment are essential. Regarding early infant diagnosis (EID), it is recommended that:

- If resources are available, addition of nucleic acid testing (NAT) at birth to existing early infant diagnosis (EID) testing approaches can be considered to identify HIV infection in HIV-exposed infants.
- All HIV exposed infant should have HIV virological testing at 4-6 weeks of age or at the earliest opportunity thereafter.
- In infants and children undergoing virological testing, the following NAT assays are strongly recommended for use: HIV DNA on DBS; HIV RNA on plasma or DBS.

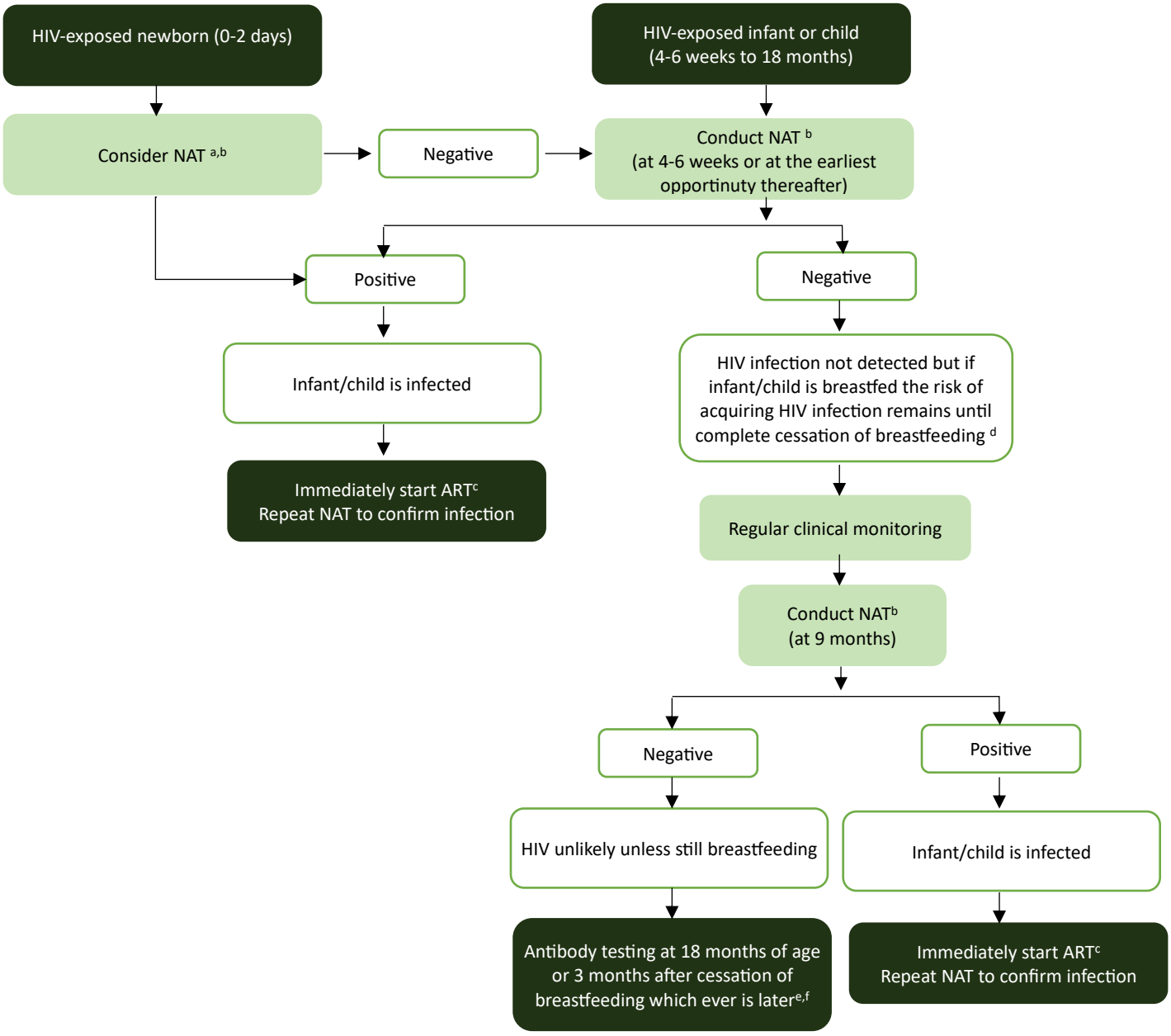
HIV virological assays used for the purpose of clinical diagnostic testing (usually during 4-6 weeks) have a sensitivity of at least 95% and ideally greater than 98%, and specificity of 98% or more under quality assured, standardized and validated laboratory conditions.

For children of 18 months of age or older, who are not on breastfeeding anymore, or who have stopped breastfeeding at least 3 months earlier), can be diagnosed with standard HIV serological tests. HIV testing algorithm for infants born to HIV infected mother is shown in Figure 3.

In infants with an initial positive virological test result, ART should be started without delay and, at the same time, a second specimen is collected to confirm the initial positive virological test result. ART should not be delayed while waiting for the result of the confirmatory testing.

Test results from virological testing in infants should be returned to the clinic and mother/caregiver as soon as possible, preferably within four weeks of specimen collection.

Figure 3. Algorithm for infant diagnosis



Important Notes:

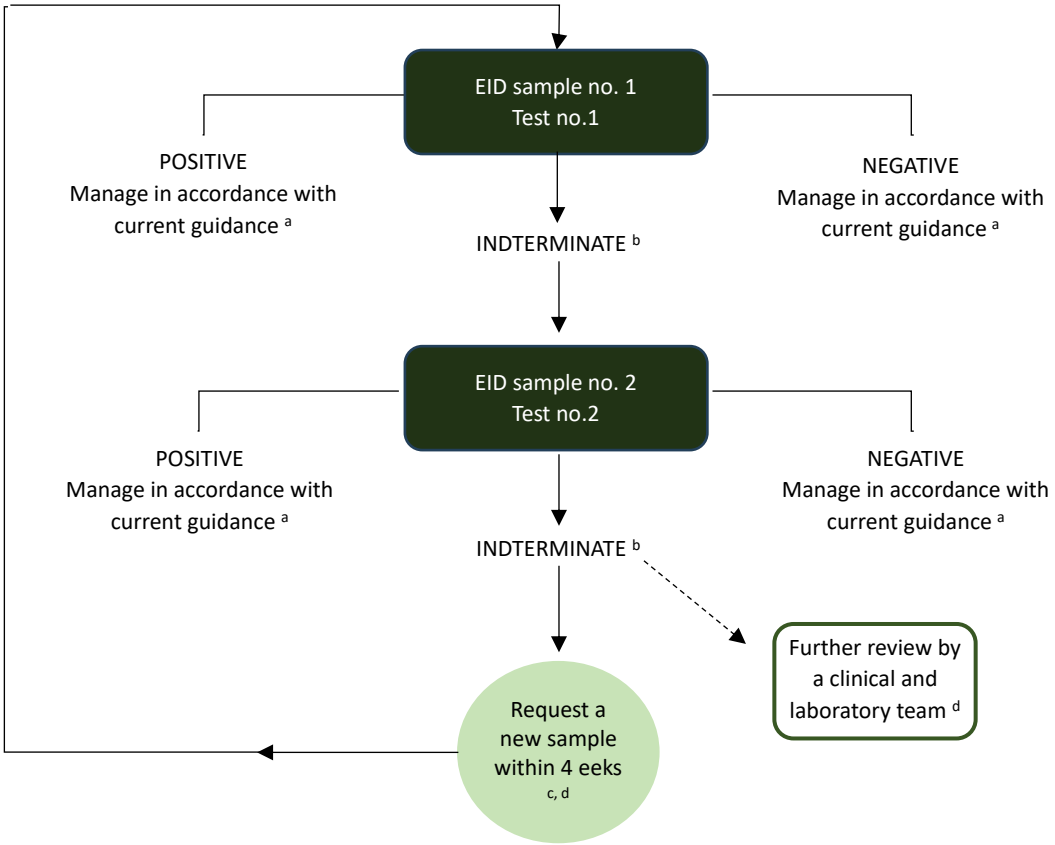
[a] Addition of NAT at birth to the existing testing algorithm can be considered.

[b] Point-of-care NAT can be used to diagnose HIV infection as well as to confirm positive results.

[c] Start ART without delay. At the same time, retest to confirm infection. As maternal treatment is scaled up and MTCT transmission rates decrease, false-positive results are expected to increase: retesting after a first positive NAT is hence important to avoid unnecessary treatment, particularly in settings with lower transmission rates. If the second test is negative, a third NAT should be performed before interrupting ART.

[d] For children who were never breastfed, additional testing following a negative NAT at 4–6 weeks is included in this algorithm to account for potential false-negative NAT results.
[e] The risk of HIV transmission remains as long as breastfeeding continues. If the 9-month test is conducted earlier than 3 months after cessation of breastfeeding, infection acquired in the last days of breastfeeding may be missed. Retesting at 18 months or 3 months after cessation of breastfeeding (whichever is later) should be carried out for final assessment of HIV status.
[f] If breastfeeding extends beyond 18 months, the final diagnosis of HIV status can only be assessed at the end of breastfeeding. If breastfeeding ends before 18 months, the final diagnosis of HIV status with antibody testing can only be assessed at 18 months. Antibody testing should be undertaken at least 3 months after cessation of breastfeeding (to allow for development of HIV antibodies). For infants younger than 18 months of age NAT should be performed to confirm infection. If the infant is older than 18 months, negative antibody testing confirms that the infant is uninfected; positive antibody testing confirms infant is infected.

Figure 4: Managing indeterminate test results: standard operating procedure



[a]Please refer to Section 4.4.
[b]Do not report as positive or initiate ART but maintain prophylaxis in accordance with current guidance.
[c]Repeat samples should be given priority in the laboratory.
[d]A team of laboratories, clinicians, paediatricians, complex case experts (if possible) and caregivers should review repeated indeterminate results in two separate samples together with clinical information. Infants should be actively tracked to ensure follow-up and retention.

Retesting

Retesting refers to using the same algorithm on a second specimen from the same individual. The followings are recommended.

- Retesting for the window period only for people who report specific recent risk
- Retesting for HIV negative people with ongoing risk (key populations and people in sero-discordant relationship) may benefit from testing every 6 months
- Retesting for HIV positive person prior to ART initiation (Verification)
- Retesting for person with inconclusive HIV test result after 14 days or 2 weeks

It should be noted that retesting people on ART is not recommended.

2. Antiretroviral drugs for HIV prevention

2.1. Oral pre-exposure prophylaxis (PrEP)

Oral PrEP is the use of antiretroviral (ARV) drugs before HIV exposure by people who are not infected with HIV in order to block the acquisition of HIV.

Oral pre-exposure prophylaxis (PrEP) containing TDF should be offered as an additional prevention choice for the following groups of people as part of combination HIV prevention approaches:

- Men who have sex with men
- Transgender women
- Heterosexual men and women who have sexual partners with untreated HIV infection or with high risk behavior and unknown HIV status

- Hepatitis B virus (HBV) infection is not a contraindication for ED-PrEP.
- Individuals eligible for oral ED-PrEP can start oral PrEP by taking two doses 2–24 hours prior to potential exposure, regardless of whether they intend to use an oral daily or ED-PrEP dosing regimen, and continue to take one dose per day until two days after the day of the last potential sexual exposure.
- All other individuals should start daily oral PrEP by taking one dose per day for seven days prior to potential exposure to HIV and can stop taking daily PrEP seven days after the last potential exposure.
- Oral event-driven PrEP (ED-PrEP) can be used to prevent sexual acquisition of HIV by cisgender men and trans and gender diverse people assigned male at birth who are not taking exogenous estradiol-based hormones.
- **HIV testing is required before PrEP is offered and 3 monthly interval while PrEP is taken.**
- Individuals at substantial risk of HIV infection may also be at a higher risk for HBV and hepatitis C virus (HCV) infection. PrEP services provide an important opportunity to screen for HBV and HCV infection and provide linkages to care.
- Testing PrEP users for HBV surface antigen (HBsAg) once, at or within one to three months of PrEP initiation, is strongly encouraged where feasible, particularly in highly endemic countries.
- HCV antibody testing is strongly encouraged at or within one to three months of PrEP initiation and every 12 months thereafter where PrEP services are provided to populations at high risk of HCV infection.

- TDF-based daily or event-driven oral PrEP and the dapivirine vaginal ring (DVR) can be safely offered to people with HBV or HCV infection.
- Lack of HBV and HCV testing should not be a barrier to PrEP initiation or use. PrEP can be initiated before HBV and HCV test results are available. HBV or HCV testing are not a requirement for PrEP use (see this section for specific considerations for long-acting injectable cabotegravir (CAB-LA).
- **Hepatitis B screening and serum Creatinine testing is preferred before starting PrEP.**
- **PrEP is highly effective only when adherence is good.**
- **PrEP users should be advised that PrEP reaches protection after 7 doses.**
- **PrEP can be discontinued if a person taking PrEP is no longer at risk and when this situation is likely to be sustained.**
- Measuring kidney function is optional for those aged under 30 years without kidney-related comorbidities. Individuals aged 30 years and older without comorbidities may be screened once, at or within one to three months of oral PrEP initiation. Depending on available resources, this can be considered optional for those aged 30–49 years, particularly those aged 30–39, given the low risk of kidney impairment.
- More frequent screening (every 6–12 months) is suggested for individuals with comorbidities, those aged 50 years and older, and those with a previous kidney function test result suggesting at least a mild reduction in function (eGFR < 90mL/min per 1.73 m^2)
- Waiting for kidney function test results should not delay initiation or continuation of oral PrEP
- Differentiated service delivery models have the potential to remove barriers to accessing PrEP and increase uptake, persistence and effective use.
- HIV self-test (HIVST) can complement existing HIV testing strategies for PrEP to support differentiated service delivery approaches for oral PrEP and the DVR to reduce clinic visits, and it may increase PrEP use and frequency of HIV testing.

Individuals eligible for oral event-driven (ED)-PrEP can start oral PrEP by taking two doses 2–24 hours prior to potential exposure, regardless of whether they intend to use an oral daily or ED-PrEP dosing regimen, and continue to take one dose per day until two days after the day of the last potential sexual exposure.

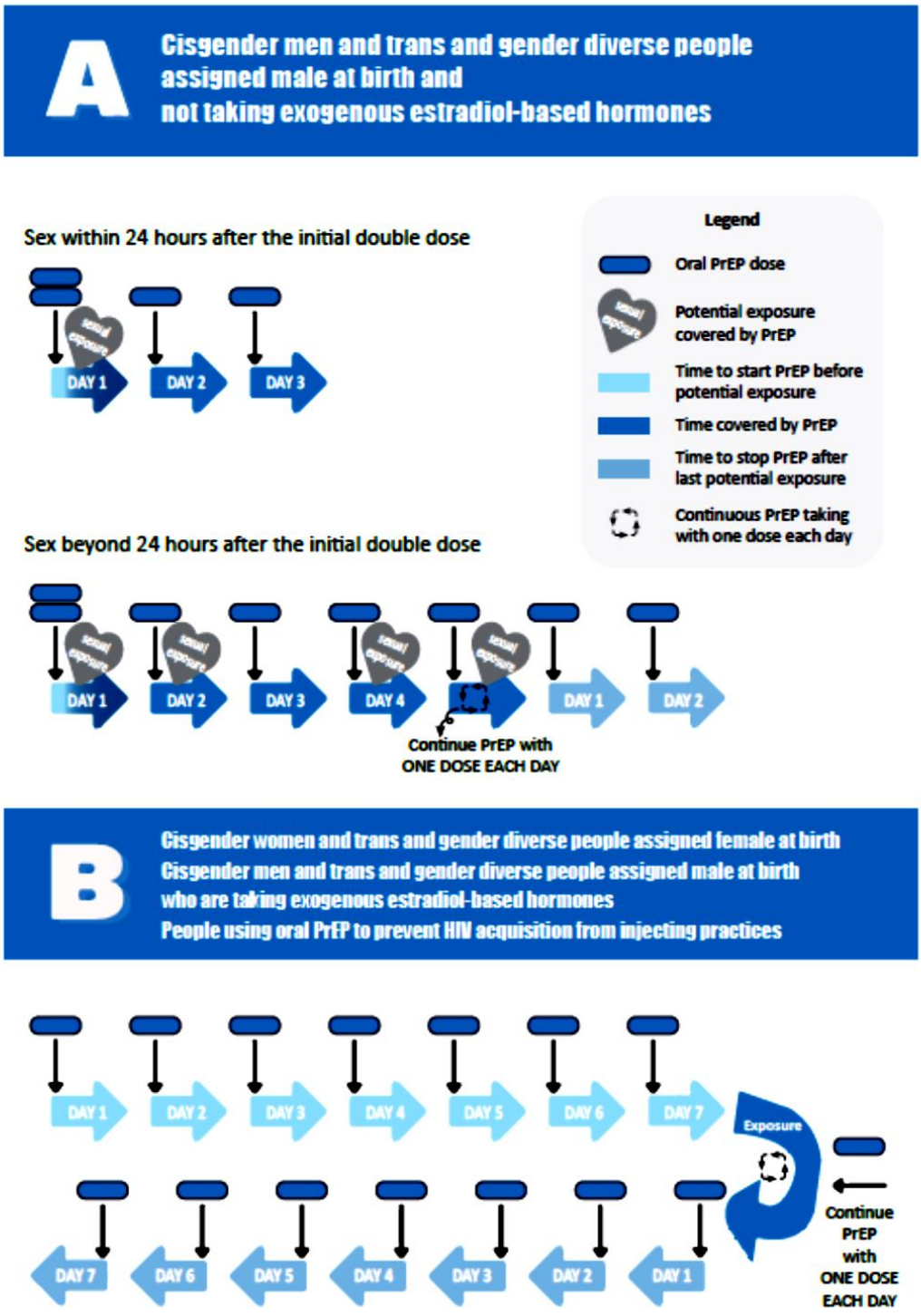
All other individuals should start daily oral PrEP by taking one dose per day for seven days prior to potential exposure to HIV and can stop taking daily PrEP seven days after the last potential exposure.

Table 1. How to safely start, use and stop TDF-based oral PrEP

	Population	Starting oral PrEP	Using oral PrEP	Stopping oral PrEP
A	Cisgender men and trans and gender diverse people assigned male at birth* who: • have sexual exposure AND • are not taking exogenous estradiol-based hormones	Take a double dose 2–24 hours before potential sexual exposure (ideally closer to 24 hours before potential exposure)	Take one dose per day	Take one dose per day until two days after the day of the last potential sexual exposure
B	Cisgender women and trans and gender diverse people assigned female at birth Cisgender men and trans and gender diverse people assigned male at birth who are taking exogenous estradiol-based hormones People using oral PrEP to prevent HIV acquisition from injecting practices	Take one dose daily for seven days before potential exposure	Take one dose per day	Take one dose daily for seven days after last potential exposure

* "Trans and gender diverse people" is an umbrella term for those whose gender identity, roles and expression does not conform to the norms and expectations traditionally associated with the sex assigned to them at birth; it includes people who are transsexual, transgender, or otherwise gender nonconforming or gender incongruent. Transgender people may self-identify as transgender, female, male, transwoman or transman, trans-sexual or one of many other gender nonconforming identities.

Figure 5: How to safely start, use and stop TDF based oral PrEP



2.2. Dapivirine vaginal ring (DVR)

The DVR may be offered as an additional prevention choice for women at substantial risk of HIV infection as part of combination prevention approaches.

It is made of silicone and contains dapivirine (NNRTI), which is released from the ring into the vagina slowly over one month. The ring should be continuously worn in the vagina for one month and then should be replaced by a new ring.

Use of the DVR does not affect the risk of virological and clinical relapse of HBV. However, in HBV-endemic areas, PrEP services, including for the DVR, provide an opportunity to screen for HBV and provide linkage to care. This would also contribute to efforts to prevent vertical transmission of HBV during pregnancy.

2.3. Long-acting injectable cabotegravir (CAB-LA)

CAB-LA may be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches.

Long-acting injectable cabotegravir (CAB-LA) is an integrase strand-transfer inhibitor (INSTI). A dose of 600 mg, intramuscularly, four weeks apart for the first two injections and every eight weeks thereafter is recommended.

Clinical trial data on or implementation experience with CAB-LA for people with HBV or HCV infection are limited. CAB-LA may be inappropriate for those with advanced liver disease and acute viral hepatitis, and those requiring treatment for HBV. For CAB-LA implementation, testing for HBV and HCV and further assessment for those with reactive test results is strongly encouraged.

2.4. Post-exposure prophylaxis (PEP)

Post-exposure Prophylaxis (PEP) is a short-term antiretroviral treatment to reduce the likelihood of HIV infection after all potential exposures. PEP should be provided for both occupational (e.g. within health sector) and non-occupational (e.g. condom break with high risk sexual partner) exposures.

Preferred recommendations for adults, adolescents and children are:

- Alignment with recommendations on ART regimens for different age groups
- Emphasis on simplification to support completion rates
- Full course prescription (28 days)
- Adherence support

When considering the eligibility for PEP, the best practice guidance is as follows.

1. PEP should be offered, and initiated as early as possible, to all persons with a HIV exposure, and preferably within 72 hours.

2. Assessing the eligibility for PEP should be based on the HIV status of the source whenever possible and may include consideration of background prevalence and local epidemiological patterns.

3. Exposures that may warrant PEP include:

- exposure to bodily fluids (e.g. blood, semen, cervico-vaginal secretions, breast milk, amniotic fluids, cerebrospinal fluids, etc.)
- through mucous membranes such as sexual exposure and splashes to eyes, nose or oral cavity
- through parenteral/percutaneous exposures

4. Exclusions for PEP would include:

- when the exposed individual is already HIV positive
- when the source is HIV negative
- exposure to the bodily fluids that do not pose significant risk, i.e. tears, non-bloodstained saliva, urine and sweat

PEP provision and monitoring

- A regimen for PEP for HIV with two ARV drugs is effective, but three drugs are preferred.

	Backbone regimen		**3rd drug**	
	Preferred	**Alternative**	**Preferred**	**Alternative**
Adults and adolescents	TDF + 3TC		DTG	ATV/r, DRV/r, LPV/r and RAL
Children <10 years	AZT + 3TC	ABC + 3TC or TDF + 3TC (or FTC).	DTG (5 mg and 10 mg)	ATV/r, DRV/r, LPV/r and RAL

- Timing of HIV testing in PEP: Baseline testing at day 0 (at the day of exposure) and follow-up testing is to be done at 3 and 6 month if day 0 is negative. If health care worker is infected with Hepatitis C, window period may be prolonged. So follow up period may be prolonged up to one year.
- Enhanced adherence counselling is recommended for individuals initiating HIV PEP.

2.5. Combination HIV prevention

The combination HIV prevention programmes use a mix of biomedical, behavioral and structural interventions to meet the current HIV prevention needs of particular individuals and communities so as to have the greatest possible impact on reducing new infections. They should be thoughtfully planned and managed to operate synergistically and consistently on multiple levels.

ARV drugs play a key role in HIV prevention. People taking ART who achieve optimal viral suppression are extremely unlikely to pass HIV to sexual partners. ARV drug taken by people without HIV as PrEP or PEP are highly effective in preventing HIV acquisition.

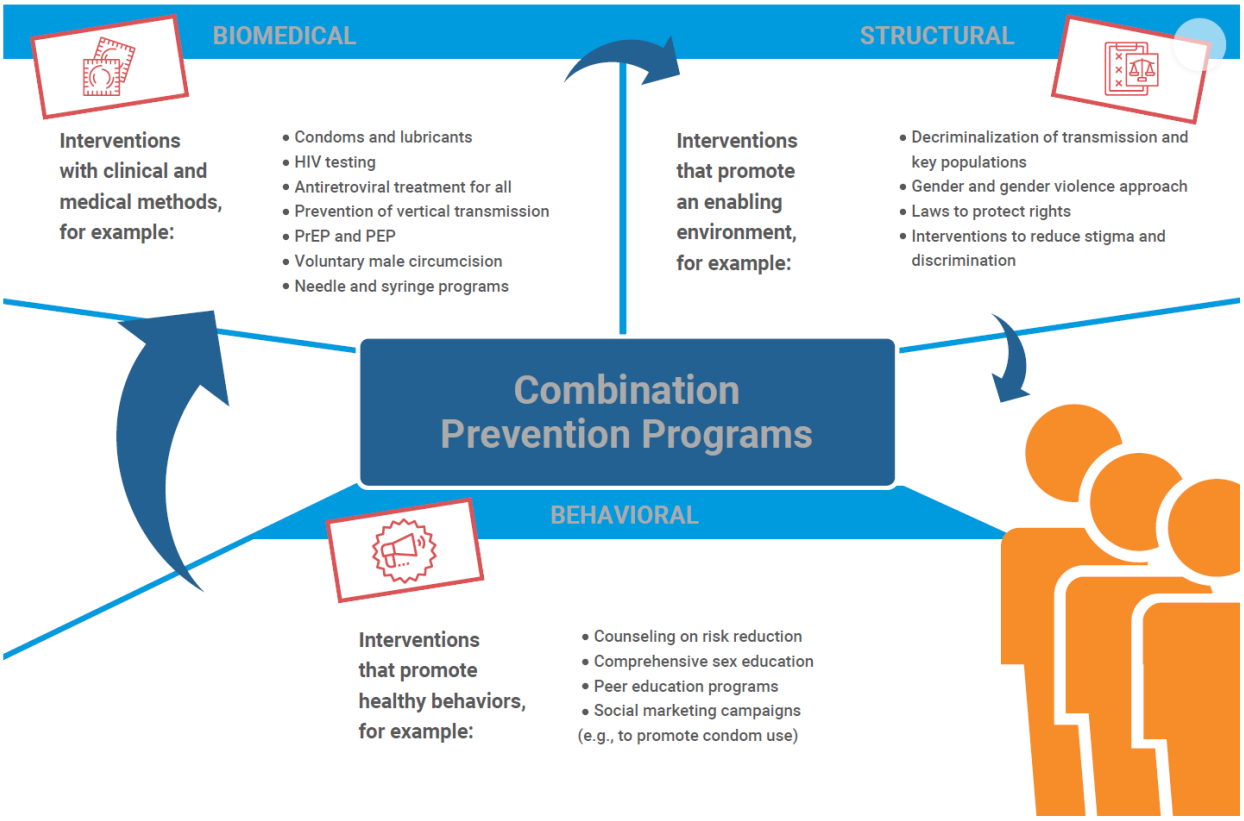
Other **biomedical interventions** that reduce HIV risk include the following:

- Male and female condoms and condom compatible lubricant: male condoms are estimated to reduce heterosexual transmission by at least 80% and to offer 64% protection in anal sex among MSM, if used consistently and correctly.
- Needle and syringe programmes: reduction in HIV transmission through injecting drug use
- Opioid substitution therapy (OST): the most effective form of treatment for opioid dependence and reduce HIV risk behavior and transmission through injecting drug use.
- Voluntary medical male circumcision (VMMC): Three randomized control trials (RCT) in Africa demonstrated an approximately 60% reduction in the risk of female to male sexual transmission. It is implemented in Africa.

Behavioral interventions can reduce the frequency of potential transmission events, including the following:

  - Targeted information and education: use various communication approaches
  - Structural and supportive interventions: address the social, legal and political and environmental enablers that contribute to HIV transmission, including legal and policy reforms, measures to reduce stigma and discrimination.

Figure 6. Combination Prevention Programs



3. Pre-ART care

3.1. Natural history of HIV infection

The typical course of HIV infection can be described in three phases:

1. **Primary infection** (1 to 3 months): After infection, there is in general a first peak in HIV RNA copies and a steep decline in CD4 cells in the blood. These changes can be explained by the fact that during the early days, HIV can replicate without being controlled by the immune system. When the body's anti-HIV immune response begins (antibody responses begin to develop 4 to 8 weeks after infection), symptoms of seroconversion may develop and viral load falls.
2. **Clinical latency** (on average 8-10 years, without antiretroviral treatment, in developed countries): After the acute infection phase, CD4 cell concentration in the peripheral blood increases again, although not as high as before infection. HIV RNA copy number in the plasma declines again, and the stabilized plasma concentration after the peak of the primary infection is called the viral set-point.
3. **Acquired immune deficiency syndrome (AIDS)** (on average 2-3 years, without antiretroviral treatment, in developed countries): The third phase is characterized by a rapid increase in HIV RNA copies and a decline in CD4 cell counts in peripheral blood.

   The Fig 7 and 8 show the structure of HIV virus and the typical course of untreated HIV infection.

Figure 7. Human immunodeficiency virus (HIV)

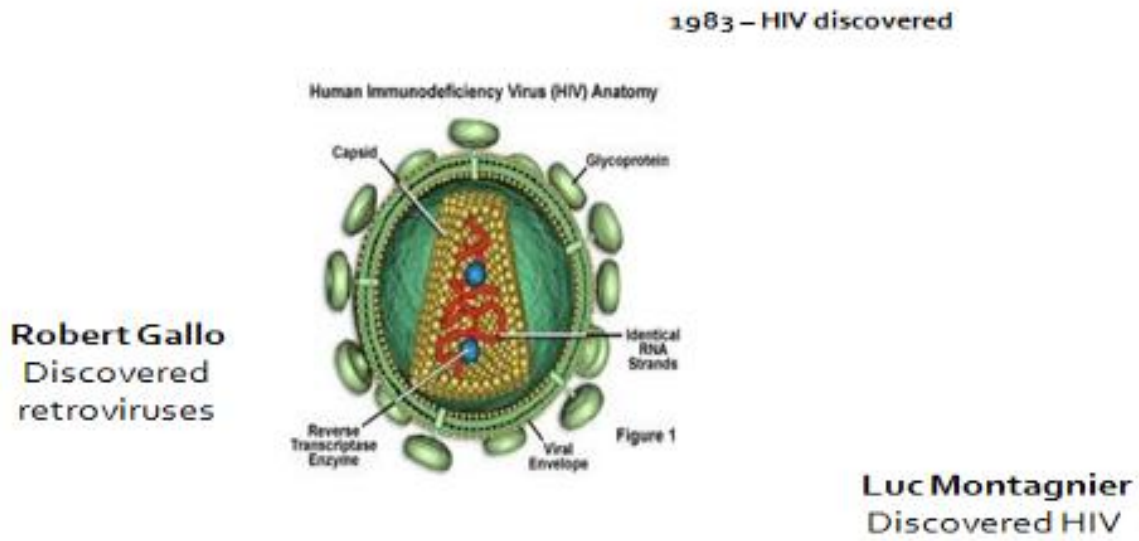
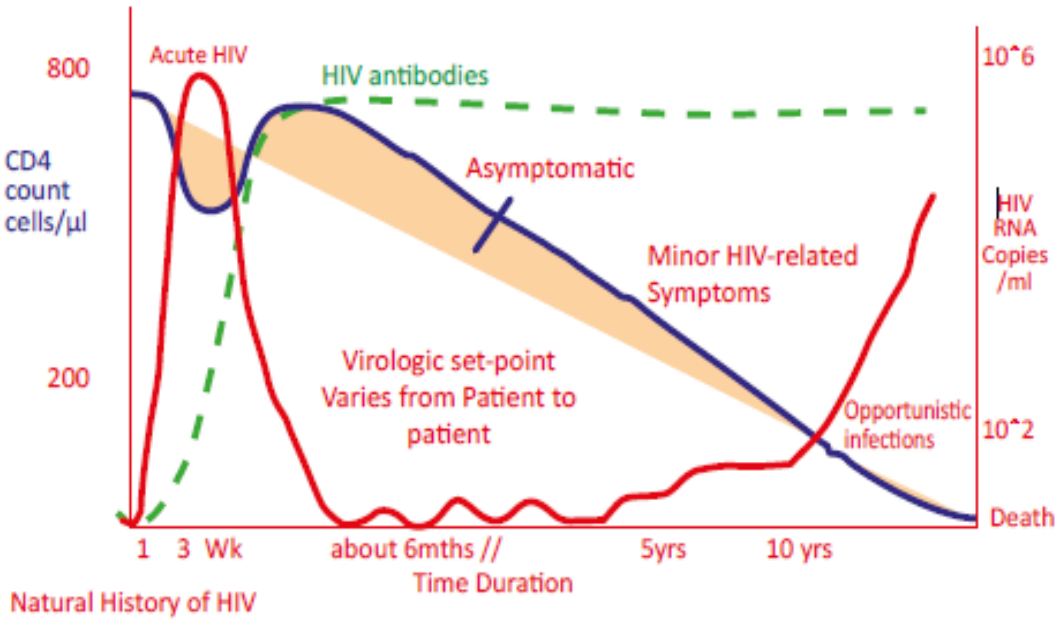
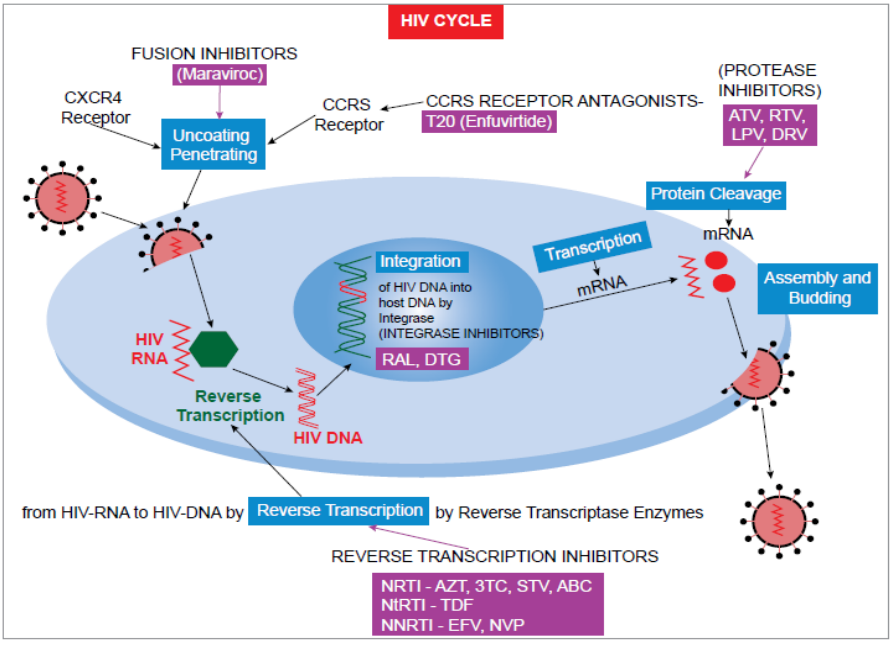


Figure 8. Typical course of untreated HIV infection



HIV uses the machinery of the CD4 cells to multiply and spread throughout the body. This process, which is carried out in seven steps or stages, is called HIV life cycle. The seven stages of HIV life cycles are: (1) binding, (2) fusion, (3) reverse transcription, (4) integration, (5) replication. (6) assembly, and (7) budding. HIV medicines protect the immune system by blocking HIV at different stages of the HIV life cycle. The Fig 9 demonstrates the life cycle of HIV infection and site of action of ARV drugs.

Figure 9. Diagram of HIV life cycle and site of action of ARV drugs



With the advent of modern and less toxic antiretroviral drugs, provided that virologic suppression is attained, people who have HIV have now longer and healthier lives with virtually zero risk of transmission to a serodiscordant partner. However, despite immune recovery and virologic control following antiretroviral therapy initiation, people who have HIV remain at excess mortality risk when compared to the general population. In fact, people who have HIV have a significantly increased risk of a variety of non-AIDS comorbid conditions, such as cancer, cardiovascular disease, chronic pulmonary obstructive disease, neurocognitive impairment, renal and liver failure. The factors leading to an increased risk of non-AIDS comorbid conditions remain poorly understood. High prevalence of traditional risk factors (e.g., smoking, dyslipidemia, pro-oncogenic virus co-infections), persisting immunodeficiency, ongoing viral replication below detectable levels, activated inflammation and coagulation, microbial translocation, microbial dysbiosis, and antiretroviral therapy toxicity have all been postulated to play a role. Clinicians should be aware of this increased risk to diagnose and treat non-AIDS comorbid conditions among people who have HIV.

3.2. WHO clinical staging of HIV disease in adults, adolescents and children

Adults and adolescents	Children
Clinical stage 1	
• Asymptomatic • Persistent generalized lymphadenopathy	• Asymptomatic • Persistent generalized lymphadenopathy
Clinical stage 2	
• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Seborrhoeic dermatitis • Fugal nail infections	• 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 infection • Extensive wart virus infection • Extensive molluscum contagiosum • Unexplained persistent parotid enlargement
Clinical stage 3	
• Unexplained severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhoea for >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 (<8 g/dl), neutropaenia (<0.5 x 10^9/l) and/ or chronic thrombocytopaenia (<50 x 10^9/l)	• Unexplained moderate malnutrition[a] 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 first 6 weeks of life) • Oral hairy leukoplakia • Lymph node TB • Pulmonary TB • Severe recurrent bacterial pneumonia • Acute necrotizing ulcerative gingivitis or periodontitis • Unexplained anaemia (<8.0 g/dl), neutropaenia (<0.5 10^9/l) or chronic thrombocytopaenia (<50 10^9/l) • Symptomatic lymphoid interstitial pneumonitis

	• Chronic HIV-associated lung disease, including bronchiectasis
Clinical stage 4	
• HIV wasting syndrome • *Pneumocystis jirovecii* pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary TB • 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 • Penicilliosis (Talaromycosis) • Disseminated mycosis(extrapulmonary histoplasmosis, coccidioidomycosis) • Lymphoma (cerebral or B-cell non- Hodgkin) • Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy • Recurrent septicaemia (including nontyphoidal Salmonella) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis	• Unexplained severe wasting, stunting or severe malnutrition[b] not responding to standard therapy • *Pneumocystis jirovecii* pneumonia • Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) • Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary TB • Kaposi sarcoma • Cytomegalovirus infection; retinitis or infection of other organs with onset at age older than 1 month • 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 cardiomyopathy or nephropathy

[a]For children younger than 5 years, moderate malnutrition is defined as weight-for-height <–2 z-score or mid-upper arm circumference ≥115 mm to <125 mm.

[b]For children younger than 5 years of age, severe wasting is defined as weight-for-height <–3 z-score; stunting is defined as length-for-age/height-for-age <–2 z-score; and severe acute malnutrition is either weight for height <–3 z-score or mid-upper arm circumference <115 mm or the presence of oedema.

3.3. TB screening and diagnosis

All people living with HIV should be properly screened for TB. Check whether there is any of the following TB symptoms or not.

- Current cough
- Fever
- Weight loss
- Night sweat

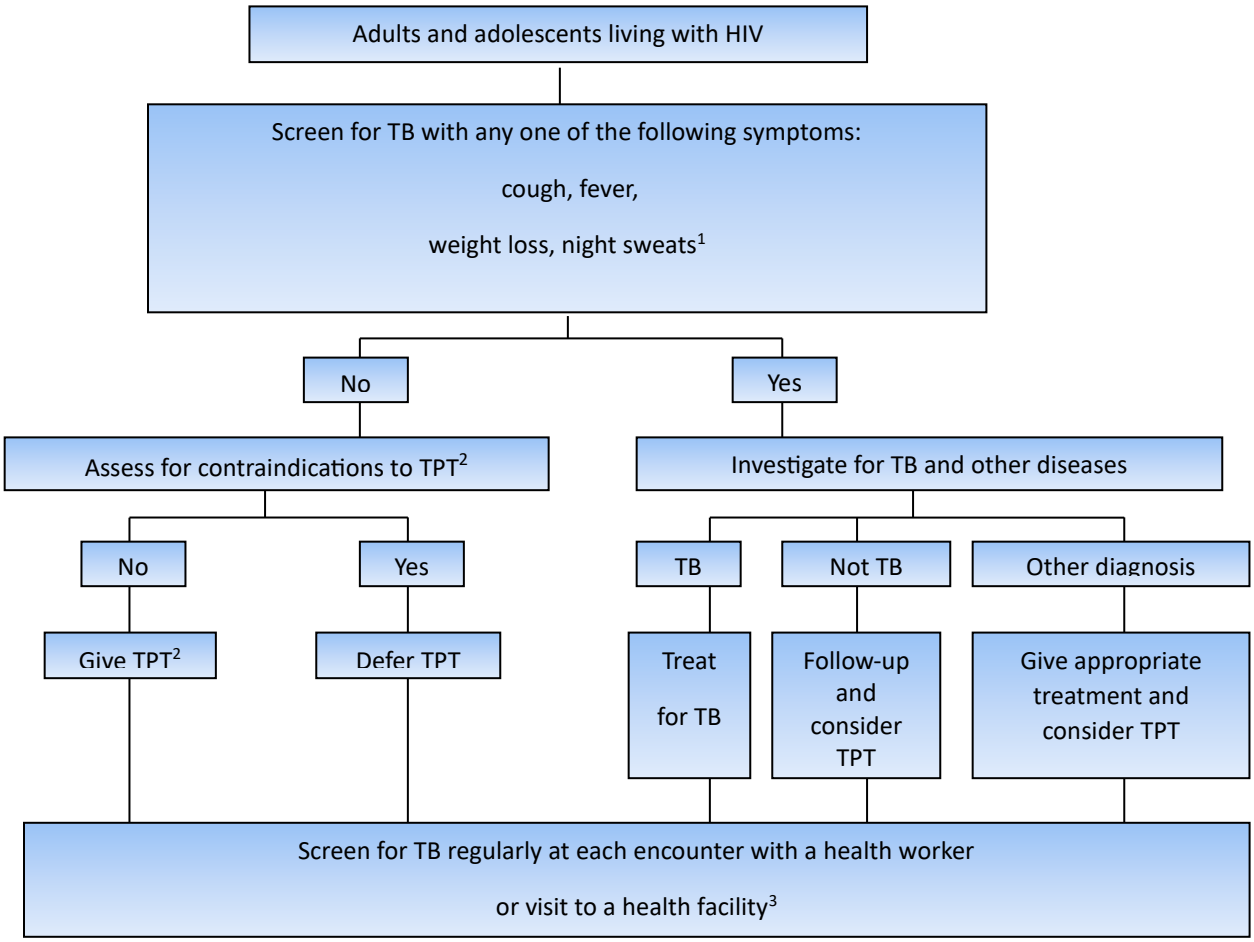
Clinicians should check lymph nodes during the physical examination, as lymph adenomegaly is a common presentation of TB and other opportunistic conditions.

Algorithm for TB screening and diagnosis of pulmonary TB/MDRTB in adults and adolescent living with HIV is shown in Fig 10 and Fig 11. Refer to the Guidelines for programmatic management of HIV/TB in Myanmar 2020 for more detail.

In children living with HIV, the symptom-based algorithm consists of poor weight gain, fever or current cough or contact history with a TB case (Fig 13). Poor weight gain in children is defined as reported weight loss or confirmed weight loss (>5%) since the last visit or growth curve flattening or very low weight (weight for age ≤3 z score) or underweight (weight for age ≤2 z score).

Children, adolescents and adults living with HIV should be screened at the time of initial presentation for HIV care and at every visit to a health facility or contact with a health-care worker afterwards.

Figure 10: Algorithm for TB screening in adults and adolescents living with HIV



[1] Lymph nodes enlargement is also suggestive of TB; clinicians should consider further investigation with ultrasound and/or biopsy

[2] Contraindications include: active acute or chronic hepatitis, regular and heavy alcohol consumption, symptoms of peripheral neuropathy.

[3] TPT can be given regardless of prior TB treatment history, TPT can be considered again if the patient has risk of developing TB, for example, close contact with TB cases.

Figure 11: Diagnosis of pulmonary TB/MDR-TB in HIV-positive patients

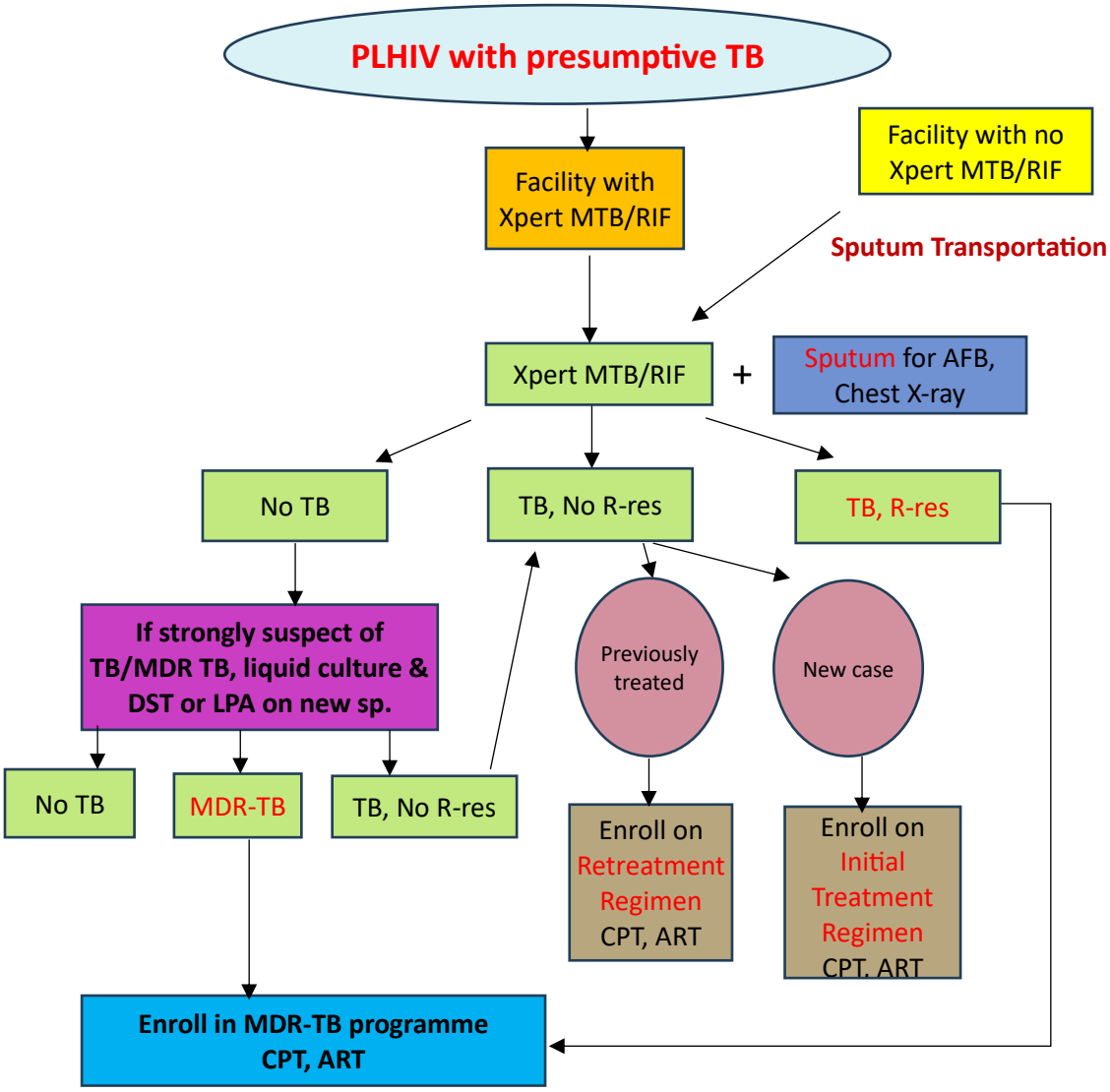
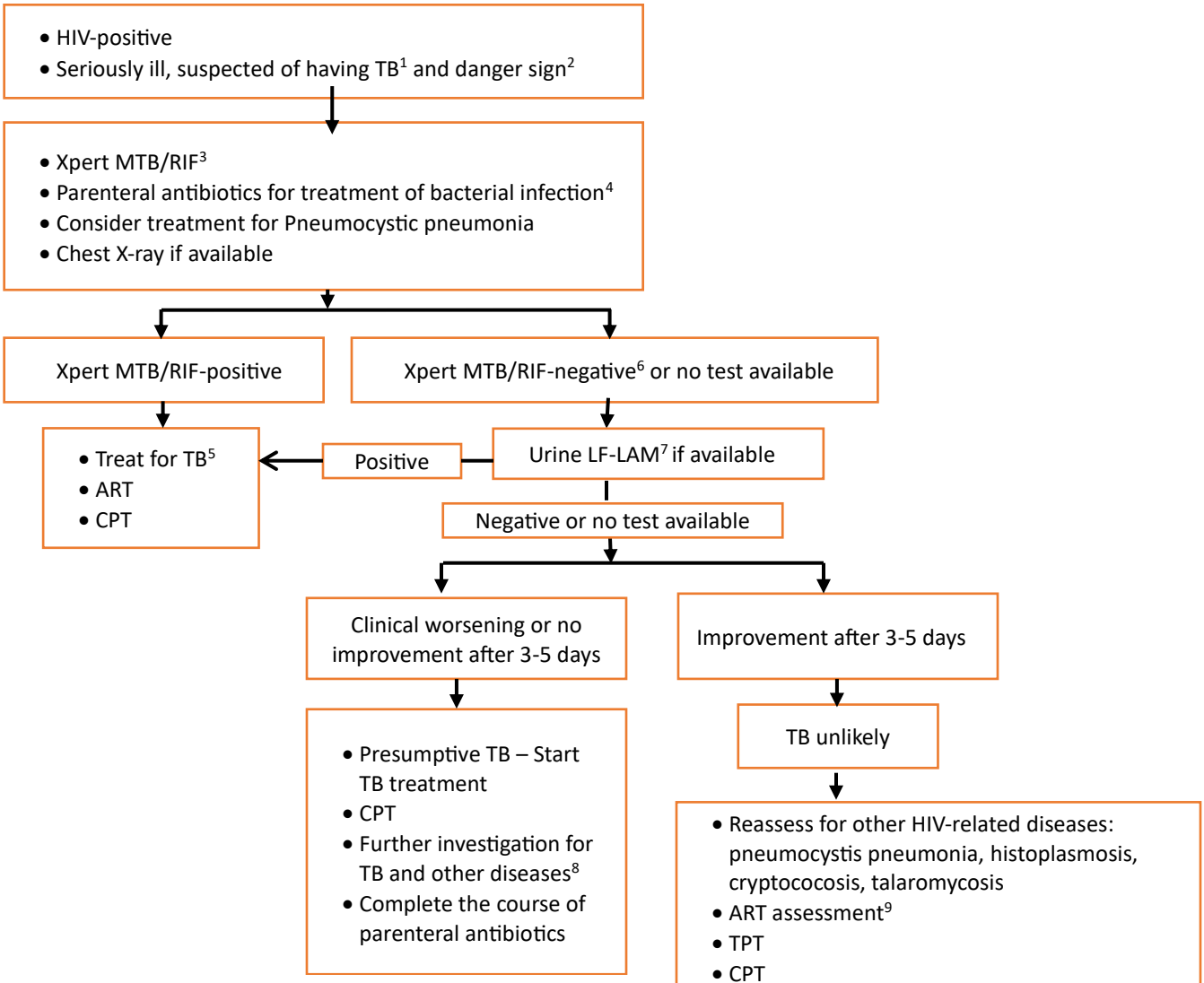
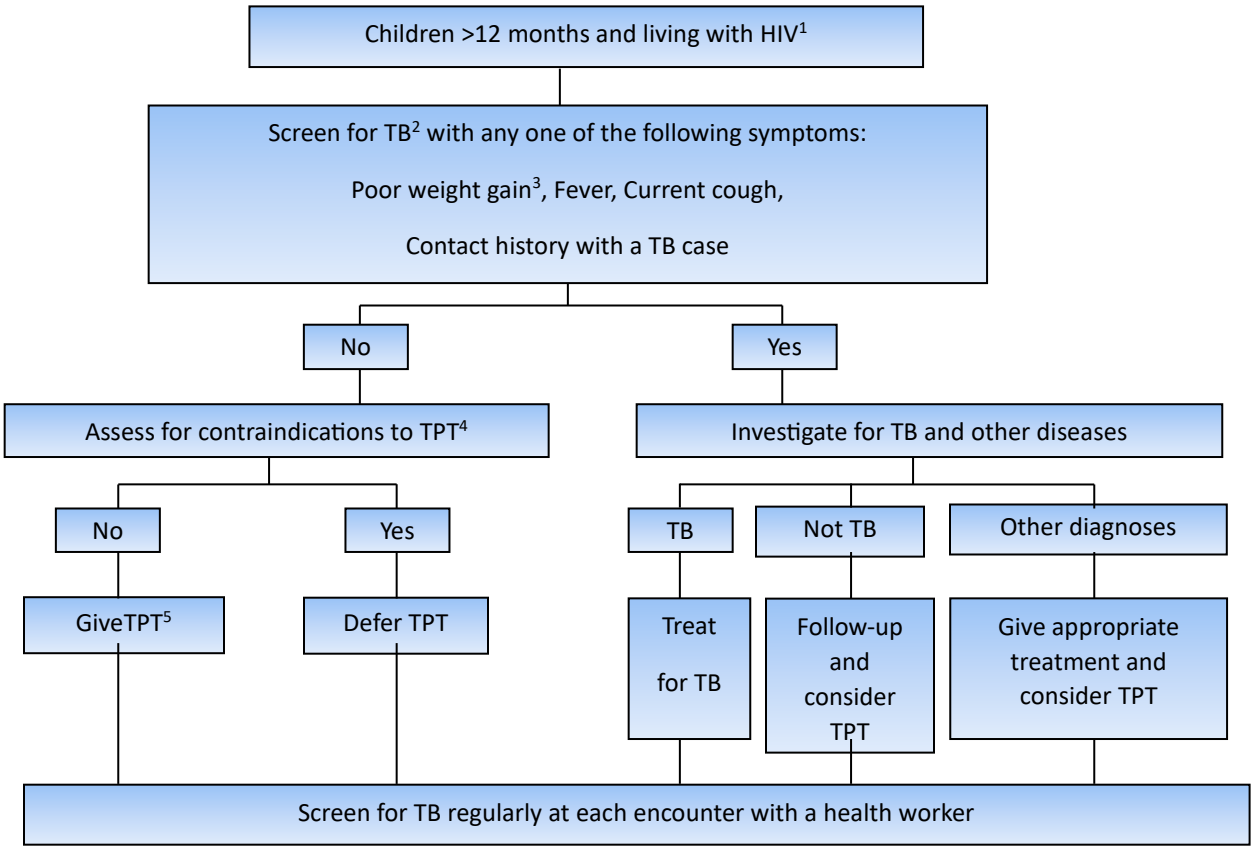


Figure 12: Algorithm for managing people living with HIV and suspected of having TB (seriously ill)



[1]Suspicion of TB is defined by the presence of any one of the following symptoms.
– For adults and adults and adolescents living with HIV: current cough, fever, weight loss or night sweat
– For children living with HIV: poor weight gain, fever, current cough or history of contact with a TB case.
[2]Danger signs include any one of the following: respiratory rate >30 per minute, temperature >39°C, heart rate >120 beats per minute and unable to walk unaided.
[3]For people suspected of having extrapulmonary TB, extrapulmonary specimens should be obtained for Xpert MTB/RIF (cerebrospinal fluid, lymph nodes and other tissues: Xpert MTB/RIF has low sensitivity for pleural fluid and data are limited for stool, urine or blood).
If Xpert MTB/RIF is not available, conduct AFB microscopy. AFB-positive is defined as at least one positive smear and AFB-negative as two or more negative smears. Refer the specimen for TB culture where feasible.
[4]Antibiotics with broad-spectrum antibacterial activity (except fluoroquinolones) should be used.
[5]If Xpert MTB/RIF shows rifampicin resistance, treatment for multidrug-reistant TB should be initiated. If the person is considered at low risk for rifampicin resistance, a second Xpert MTB/RIF test should be performed on a fresh specimen. Collect and refer a sample for culture and additional drug sensitivity testing.
[6]If Xpert MTB/RIF shows negative results, the test can be repeated using a fresh specimen.
[7]If Xpert MTB/RIF shows negative results or the test is not available or specimen cannot be collected, the urine lateral flow lipoarabinomannan (LF-LAM) assay may be used to assist in diagnosing active TB among seriously ill adults and children living with HIV, regardless of CD4 count.
[8]Further investigations for TB include chest X-ray, clinical assessment, a repeat Xpert MTB/RIF using a fresh specimen an culture. If extrapulmonary TB is suspected, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed.
9ART should be recommended for all adults, regardless of CD4 cell count or clinical stage.

Figure 13: Algorithm for TB screening in children living with HIV older than one year old



[1] All children (including infants less than one year of age) should be provided with IPT if they have a history of household contact with a TB case.

[2] Lymph nodes enlargement is also suggestive of TB; clinicians should consider further investigation with ultrasound and/or biopsy

[3] Poor weight gain is defined as reported weight loss or confirmed weight loss (>5%) since the last visit or growth curve flattening or very low weight (weight for age ≤3 z score) or underweight (weight for age ≤2 z score).

[4] Contraindications include active acute or chronic hepatitis, symptoms of peripheral neuropathy.

[5] In general, TPT is not indicated for the HIV infected children who had completed prior TPT. However, TPT may be considered as individual case, for those at high risk of becoming re-infected and progressing to TB disease.

3.4. Cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis is an important part of the management of people living with HIV. It is recommended for adult including pregnant women with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with CD4 count of < 350/mm^3. One double-strength tablet daily of Cotrimoxazole daily is recommended (sulfamethaxazole 800 mg/ trimethoprim160 mg= 960 mg).

Skin reaction is the most common side effect with Cotrimoxazole. Other side effects, which are less frequent, are bone marrow toxicity and hepatotoxicity. Side effects can be monitored clinically. However these drug-related adverse effects are not common and typically occur within the first few week of starting prophylaxis. Clinical monitoring is usually sufficient. The safety of Cotrimoxazole in long-term use has been established.

Dapsone 100 mg a day may be used if there is hypersensitivity to Cotrimoxazole, but Dapsone is less effective than Cotrimoxazole. If there is hypersensitivity to both Cotrimoxazole and Dapsone, it may be possible to carry out Cotrimoxazole desensitization under careful supervision. Both Cotrimoxazole and Dapsone can cause intravascular haemolysis in patients with G6PD deficiency and should not be prescribed if the patient is known to be enzyme deficient.

Table 2. Criteria for initiating and discontinuing co-trimoxazole prophylaxis

Population	Recommendations	
	Criteria for initiating cotrimoxazole prophylaxis	Criteria for discontinuing cotrimoxazole prophylaxis
Adults (including pregnant women) living with HIV	• Initiate for everyone with severe or advanced HIV disease (WHO clinical stage 3 or 4) or CD4 cell count ≤350 cells/mm^3[a] • Initiate for everyone regardless of WHO clinical stage or CD4 cell count	• Stop for those who are clinically stableb, with evidence of immune recovery and/or suppression of viral loads on ART[c,d]
Children and adolescents living with HIV	• Initiate for everyone regardless of WHO clinical stage or CD4 cell count • As a priority: – Initiate for everyone younger than five years regardless of WHO clinical stage or CD4 cell count – Initiate for everyone five years and older with severe or advanced HIV disease (WHO clinical stage 3 or 4) or CD4 cell count ≤350 cells/mm^3	• In settings with low prevalence of both malaria and severe bacterial infections: may be discontinued for those older than five years who are clinically stable, with evidence of immune recovery[e] and/or suppression of viral loads on ART
HIV-exposed infants	Initiate for everyone starting at 4–6 weeks after birth	Until the risk of HIV transmission ends and HIV infection is excluded with age appropriate test[f]
People living with HIV and TB[g]	Initiate for everyone with active TB regardless of CD4 cell count	Until the criteria for discontinuation for adults or children are met

[a]This group is also given priority for initiating.
[b]Clinically stable adults are defined as individuals receiving ART for at least one year without any new WHO clinical stage 2, 3, or 4 events.
[c]CD4 cell count >350 cells/mm3, with suppression of viral loads, is considered immune recovery (some countries may adopt a threshold of CD4 cell count >500 cells/mm3).
[d]WHO recognizes that in settings with low prevalence of malaria and severe bacterial infection in which co-trimoxazole is used primarily as prophylaxis for some AIDS-associated opportunistic infections (*Pneumocystis jirovecii* pneumonia and toxoplasmosis), guidelines exist for adults living with HIV discontinuing co-trimoxazole when there is evidence of suppressed viral loads and immune recovery at CD4 cell count >200 cells/mm3 and they have been receiving ART for at least one year.
[e]Parameter for immune recovery among children older than five years: CD4 cell count >350 cells/mm3, with suppressed viral loads.

[f]In settings with low vertical transmission rates, high HIV infant diagnosis coverage and strong retention in the testing-to-treatment cascade, country programmes may consider stopping providing routine co-trimoxazole as soon as HIV infection is ruled out by age-appropriate HIV testing.
[g]Recommendation maintained from WHO policy on collaborative TB/HIV policy activities: guidelines for national programmes and other stakeholders.

3.5. Laboratory assessment before starting ART

The following table demonstrates the recommended and desirable laboratory investigation before starting ART.

Table 3. Laboratory assessment and screening before starting ART

Recommended	Desirable
• HIV verification test (Retesting) • CD4 count[a] • TB symptom screening[c]	Haemoglobin test[b] Serum creatinine and estimated glomerular filtration rate (eGFR) Screening of STIs HBV serology HCV serology Assessment for major NCD[d]

[a]CD4 count is recommended for identifying advanced HIV disease and subsequent offer of the package of care for advanced HIV disease to prevent OIs. CD4 count should not be used to determine ART eligibility.

[b]Haemoglobin, serum creatinine and estimated glomerular filtration rate (eGFR) should be prioritized when these laboratory testing services are accessible.

[c] TB screening should be conducted with 4 symptoms screening and lymph node examination in case of lymph node enlargement

[d] Assessment of risk factors and screening for hypertension and diabetes including CVD risk assessment are recommended for all PLHIV above 40 years of age

3.6. Adherence- important measure when starting ART

Patient should understand that

- ART is suppressive therapy
- ART is life-long
- near perfect adherence is necessary to prevent ART resistance

- there are possibilities of side effects

Assessment of patient readiness should be carried out before starting ART (ART should never be prescribed casually at the first visit).

Treatment adherence counselling

- Establish trusting relationship
- Provide necessary information and advice
- Identify and encourage peer/family/friends/community/support groups' participation
- Try to fit in ART into patients' lifestyle and daily events
- Discuss cost if patient/family/friends have to pay
- Discuss need for regular follow up; patient's address, how he will attend clinic, who will help, cost of travel
- Assess readiness and commitment of patients for ART
    - past ability to attend clinic regularly
    - past ability to take drugs regularly, e.g. co-trimoxazole prophylaxis
    - past ability to complete full course of TB treatment if relevant
    - adequate understanding of what is involved
- Treatment adherence, at least 95% to the recommended regimens, should be emphasized. This means that missing more than 1 dose per month for 1 OD regimens or more than 3 doses per month for 1 BD regimen is associated with risk of developing drug resistance.
- If regular doses are missed or late, reinforce adherence counselling. May need to enlist help from peers, family etc.
- Timing of drug intake is crucial. E.g. BD drugs are taken every 12 hours +/- one hour. Missed doses can be taken up to 6 hours in a BD regimen. If > 6 hours late, skip dose and take next normal dose. If the patient is on OD dose, drug is taken every 24 hours. Missed dose can be taken up to 12 hours in OD regimen. If >12 hours late, skip dose and take next normal dose.
- Drug side effects have to be understood and explained in advance
- Do not acquire drugs only when the supply runs out. Always keep some spare pills for emergencies.
- People on ART still need to use condoms.
- Herbal products may interact with ART.
- Regular clinic attendance for monitoring of efficacy and adherence is essential.

Treatment regimen should be simplified by reducing the number of pills, reducing the number of dosing and minimizing side effects. Fixed dose combinations are very useful. At every clinic visit, check the following:

- Number of doses missed in last 3 days
- Number of doses missed since last visit
- If correct doses are taken at correct time
- Reason for poor adherence
- Reinforce adherence

Use fixed dose combination (FDC) pills if possible. Use of FDCs reduces pill burden and improves adherence. In children, there are also fixed dose combinations that are available as dispersible tablets. The details of the pediatric regimens based on weight bands and the dispensing guidance is enclosed in Annexes.

4. Antiretroviral therapy (ART)

Goals of ART

-Improvement of quality of life and prolongation of life

-Reduction of HIV related morbidity and mortality

-Greatest possible reduction in viral load (< 50 copies/ml) for as long as possible to stop or delay disease progression

-Restoration and preservation of immune function

-Minimization of drug side effects

-Reduction of HIV transmission

4.1. Classification and dosages of antiretroviral drugs

Table 4. Classification and dosage of ARV drugs

Generic name	Adult Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Zidovudine (AZT)	250-300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir disoproxil fumarate (TDF)	300 mg once daily
Tenofovir alafenamide (TAF)	10 or 25 mg once daily
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	400-600 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily
Protease inhibitors (PIs)	
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg daily
Darunavir + ritonavir (DRV/r)	800 mg + 100 mg daily [a] or 600 mg + 100 mg twice daily [b]
Lopinavir + ritonavir (LPV/r)	400 mg/100 mg twice daily
	Consideration for individuals receiving TB therapy

	In the presence of rifabutin, no dose adjustment required. In the presence of rifampicin, adjusted dose of LPV/r: (LPV 800 mg + RTV 200 mg twice daily or LPV 400 mg +RTV 400 mg twice daily)
Integrase strand transfer inhibitors (INSTIs)	
Dolutegravir (DTG)	50 mg once daily
Raltegravir (RAL)	400 mg twice daily

[a] For individuals with no previous use of protease inhibitors.

[b] For individuals with previous use of protease inhibitors.

4.2. What to expect in the first months of ART

Although ART is a lifelong commitment, the first months of therapy are crucial. Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART, but opportunistic infections (OIs) and/or immune reconstitution inflammatory syndrome (IRIS) may develop, as well as early adverse drug reactions, such as drug hypersensitivity, especially in the first three months of treatment. ART significantly decreases mortality overall, but death rates are also highest in the first three months of ART. These complications are most common when the people starting ART already have advanced HIV disease with severe immunodeficiency and existing co-infections and/or comorbidities, severely low haemoglobin, low body mass index and very low CD4 cell counts or are severely malnourished. Poor adherence in this period is also associated with the risk of early treatment failure and rapid development of drug resistance.

4.3. When to start ART

Table 5. Summary of recommendations on when to start ART in adults, adolescents, children and infants.

Adults (including pregnant women) and adolescents	**Initiate ART regardless of WHO clinical stage and at any CD4 count.** **As a priority**, initiate those: • severe HIV clinical disease (WHO clinical stage 3 or 4) • CD4 count ≤350 cells/mm^3
Children and infants	**Initiate ART regardless of WHO clinical stage or at any CD4 count.**

4.3.1. Starting ART in adults and adolescents

Early treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level. Hence, it is recommended in Myanmar to initiate ART to:

All HIV positive patients regardless of WHO clinical stage and at any CD4 count. However, priority should be given to those with:

-severe HIV clinical diseases (WHO clinical stage 3 or 4)

- CD4 count ≤350 cells/mm^3

Rapid initiation is recommended, which is within seven days. Even same day initiation is recommended for those who have undergone adequate preparedness including counselling. Within weeks after treatment initiation, clinical and immune improvement and viral suppression can be expected. Starting ART earlier also results in reduction of sexual transmission as well as MTCT of HIV. There is also reduction in TB as well as invasive bacterial infections when ART is started earlier rather than later. For these reasons, timely access to HIV testing services and strong and streamlined linkages to HIV treatment are very important.

4.3.2. Starting ART in pregnant and breastfeeding women

Providing ART to all pregnant and breastfeeding women living with HIV serve three synergistic purposes: (i) improving the mother's health (ii) preventing mother-to-child transmission of HIV (iii) preventing the transmission of HIV from mother to a sexual partner. Therefore, it is recommended in Myanmar:

to initiate ART in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 count and continue lifelong.

Based on increasing evidence to support earlier initiation among all adults, together with widespread uptake of option B+ and emerging program data on its success in practice at global level, global recommendation moved away from "options" for PMTCT. Globally, it is now recommended that all pregnant and breastfeeding women living with HIV should initiate ART and remain on lifelong treatment, regardless of clinical stage or CD4 count. **In Myanmar, it is recommended to give lifelong ART to all pregnant and breastfeeding women living with HIV.**

4.3.3. Starting ART in children and infants

Infant and young children living with `HIV have an exceptionally high risk of poor outcomes, with up to 52% of children born with HIV dying before the age of 2 years in the absence of any intervention. By five years of age, the risk of mortality and disease progression in the absence of treatment falls to rates similar to those of young adults. Therefore, it is recommended that

ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 count.

Improved access to early infant diagnosis has increased the identification of infant living with HIV, but rate of ART initiation among infants living with HIV remain suboptimal globally. Overall, most children who are eligible for ART are still not being treated, and ART coverage among children lags significantly behind that among adults globally in 2014. Diagnosing and retaining children exposed to and living with HIV in care present unique challenges because of their dependence on a caregiver.

This approach is expected to have significant programmatic advantages, especially in settings with limited access to immunological testing, a high burden of HIV disease and low ART coverage among children.

As ART is expanded to all children regardless of clinical and immune status, priority for treatment should be given to certain groups of children in case of limited resources. These include children younger than 2 years or children with WHO stage 3 or 4 disease or CD4 percentage below 25% or CD4 count at or below 750 cell/mm^3 (if younger than 5 years) and CD4 count at or below 350 cell/mm^3 (if older than 5 years). This is because of their higher risk of death and rapid disease progression.

4.3.4. Starting ART in co-infections

HIV/TB co-infection

TB is one of the most common public health problems even before the HIV era and with the HIV pandemic, the prevalence of TB has increased worldwide. Immunosuppression predisposes to acquisition of new infection as well as reactivation of latent TB. Active TB is also known to hasten further immune deterioration. ART has been reported to reduce TB rates at the individual level and to reduce TB recurrence rates. TB transmission rates and mortality rates at the population level can be also reduced if there is a high coverage of ART in patients with TB. The risk for TB

increases within one or two years after acquisition of HIV and remains significantly higher in case of CD4 cell counts < 500 cells /mm^3.

ART recommendations for HIV TB co-infection

ART should be started in all TB patients living with HIV, regardless of CD4 count.

TB treatment should be initiated first, followed by ART as soon as possible within the first 2 weeks of treatment except in cases of tuberculous meningitis where ART should be postponed for 4-6 weeks.

HIV/Histoplasmosis

ART should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven.

HIV/ Cryptococcal meningitis

Immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred by 4–6 weeks from the initiation of antifungal treatment.

4.4. What to start: first-line ART

Table 6. First-line ART regimen for adults, pregnant or breastfeeding women, adolescents and children[a]

First-line ART	Preferred first-line regimens	Alternative first-line regimens
Adults and adolescents	TDF [a] + 3TC (or FTC) + DTG [b] as fixed dose combination	TAF[c] + 3TC (or FTC) + DTG ABC + 3TC + DTG TDF + 3TC (or FTC) + EFV low dose (400mg) as a fixed-dose combination

Pregnant or breastfeeding women	TDF + 3TC (or FTC) + DTG [d] as fixed dose combination	TAF[c] + 3TC (or FTC) + DTG ABC + 3TC + DTG TDF + 3TC (or FTC) + EFV low dose (400mg) as a fixed-dose combination
Infants and children older than 4 weeks and weighting at least 3 kg	ABC + 3TC +DTG [e]	ABC + 3TC + LPV/r TAF + 3TC (or FTC) + DTG AZT+3TC+LPV/r ABC+3TC+EFV AZT+3TC+EFV
Infants younger than 4 weeks and weighting less than 3 kg	AZT (or ABC) + 3TC + RAL [f]	AZT (or ABC) + 3TC + NVP AZT (or ABC) +3TC+LPV/r

[a] TDF should be avoided for HIV+ MDR-TB cases who receive standard MDR-TB regimen including Amikacin.

[b] Doubling the dolutegravir dose from 50 mg daily to twice daily is recommended for patients with TB who receive rifampicin.

[c] TAF will be considered for special circumstances such as people with established osteoporosis and/or impaired kidney function.

[d] There are compelling safety and efficacy data to support the use of DTG as first line therapy in pregnant women, people living with HIV/TB coinfection and adolescents younger than 12 years of age.

[e] DTG should be used with approved dosing (5 and 10 mg) in infants and children older than 4 weeks and weighting at least 3 kg. Doubling the dolutegravir dose is recommended for infants and children with TB who receive rifampicin.

[f] RAL should be prioritized over NVP because the current prevalence of transmitted drug resistance to NNRTI is unknown among HIV positive infants in Myanmar. Neonates starting ART with RAL based regimen should transition to DTG as soon as possible.

4.4.1. First-line ART regimens for adults and adolescents (What to start)

Table 7. Summary of first-line ART regimens in adults and adolescents

Preferred regimen	TDF + 3TC (or FTC) + DTG
Alternative regimens	TAF + 3TC (or FTC) + DTG ABC + 3TC + DTG TDF + 3TC (or FTC) + EFV low dose (400mg)

Remark: The abovementioned table includes recommended first-line ART regimens (both preferred and alternative) for initiation of ART.

TDF + 3TC (or FTC) + DTG as fixed dose combination

This is the preferred first line combination. The advantage is that the 3 drugs are available as one pill once daily combination which is very simple to use.

There are compelling safety and efficacy data to support the use of DTG as first line therapy in people living with HIV/TB coinfection, adolescents younger than 12 years of age and pregnant women. Two NRTIs + INSTI is a generally more effective regimen (with higher viral suppression, CD4 cell recovery rate and lower risk of treatment discontinuation) than two NRTIs + EFV or two NRTIs + boosted PIs. DTG has other clinical and programmatic advantages when compared with EFV and boosted PIs, including lower potential for drug interactions, a shorter median time to viral suppression and a higher genetic resistance barrier. The safety and efficacy of DTG during pregnancy, among infants and children older than 4 weeks and weighting at least 3 kg (with the approved pediatric dosing of 5 and 10mg) and among TB/HIV co-infected patient using rifampicin (with double DTG dose) have been well established.

Creatinine clearance should be more than 30 ml/min to use DTG. Calcium and iron supplements can significantly reduce DTG drug levels. DTG should be administered at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: Fe-, Ca-, Mg-, Zn-, multivitamin supplements; mineral supplements, cations containing laxatives and Al-, Ca- or Mg- containing antacids. DTG should not be co-administered with certain anti-epileptic drugs (carbamazepine, phenobarbital and phenytoin) and with the antiarrythmic dofetilide. The dose of DTG should be doubled when co-administered with rifampicin.

TDF has been reported to have a potential for nephrotoxicity (proximal tubular damage, acute and chronic renal failure) but the incidence is quite low (1- 2%); predisposing factors include advanced age, low body weight, higher initial serum creatinine levels, comorbidities (diabetes, hypertension), other nephrotoxic medicines, concomitant PI use and advanced HIV infection. Creatinine measurements may be needed, or more simply proteinuria or glycosuria (due to tubular dysfunction without diabetes) can be checked every 6 months in those at risk. Creatinine clearance is more sensitive than serum creatinine and can be calculated (CKD-EPI formula).

When Cr measurements are not available, urine dipstick to check protein and glucose concentration can also be useful to monitor TDF-associated nephrotoxicity.

TDF + 3TC (or FTC) + EFV low dose (400mg) as a fixed-dose combination

This first line regimen also has the advantage of a fixed drug combination in one pill. It can be used in cases of intolerance to DTG-based regimens. EFV 400 mg has comparable efficacy and improved safety compared with EFV at the standard dose EFV 600mg. EFV 400 mg/day has greater viral suppression with less treatment discontinuation.

TAF + 3TC (or FTC) + DTG

This is another first-line ART alternative regimen that is recommended under Myanmar national guidelines. It is intended to use in special circumstances for the patients who cannot tolerate or have contraindications to TDF. TAF is considered a favourable option for special circumstances when bone and renal toxicity are a particular concern (such as the presence of osteoporosis or mild chronic renal disease and concomitant use of nephrotoxic drugs) for adults. If TAF is more available in the future, it can be preferably used in patients with high risk of renal problem such as those older than 50 years, with diabetes or hypertension. According to the evidence, people taking TAF may experience a rise in cholesterol levels and body weight gain. Another limitation with TAF is its interaction with rifampicin and other common anti-TB drugs, and the correct dose to administer during TB co-treatment has not been established. There is also limited information on safety and efficacy in important subpopulations, including pregnant women. For children and adolescents, safety and pharmacokinetic data limited only for weight bands above 25 kg.

ABC + 3TC + DTG

This is another first-line ART alternative regimen that is recommended under Myanmar national guidelines. It is intended to use in special circumstances for the patients who cannot tolerate TDF or AZT.

4.4.2. Prevention of mother to child transmission of HIV (PMTCT)

These guidelines provide recommendations for universal treatment at any CD4 count and any stage of disease, harmonized across all populations including pregnant and breastfeeding women. The preferred regimen is harmonized for all adults and adolescents, whether pregnant or not.

PMTCT programme must incorporate a spectrum of activities, including HIV prevention for HIV negative women, access to family planning to prevent unintended pregnancy, widespread testing of pregnant women early in antenatal care and support to women living with HIV to remain adherent to ART and retained in the care throughout pregnancy and breastfeeding and for life.

In addition to receiving ART, pregnant women living with HIV should be offered the recommended package of pregnancy care, and other interventions such as screening for STIs, nutritional support, infant feeding counselling and family planning guidance.

New born prophylaxis remains an important aspect of PMTCT and the guidance is provided under the section of infant prophylaxis.

For mother

Initiate ART to all pregnant and breastfeeding women regardless of WHO clinical stage or CD4 count.

The preferred first-line ART regimen is TDF + 3TC (FTC) + DTG.

For infants

AZT (twice daily) and NVP (once daily) for 6 weeks regardless of breast-fed or formula-fed

Table 8. Simplified infant prophylaxis dosing

Infant age	Dosing of NVP	Dosing of AZT
Birth to 6 weeks		
Birth weight 2000-2499 g	10 mg once daily (1 ml of syrup once daily)	10 mg twice daily (1 ml of syrup twice daily)
Birth weight ≥ 2500 g	15 mg once daily (1.5 ml of syrup once daily)	15 mg twice daily (1.5 ml of syrup twice daily)

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

Infant feeding

Infant feeding recommended for HIV-infected women is to choose between formula feeding or exclusive breastfeeding. Breastfeeding is a preferred option: exclusive breastfeeding for first 6 months, introducing complementary food thereafter, and continuing breastfeeding for 12 months, weaning gradually within 1 month.

Formula feeding without any breastfeeding can be chosen only if all the following conditions are met:

a. Safe water and sanitation are assured at the household level and in the community; and

b. The mother, or other caregiver can reliably provide sufficient formula milk to support normal growth and development of the infant; and

c. The mother or caregiver can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhoea and malnutrition; and

d. The mother or caregiver can, in the first six months, exclusively give infant formula milk; and

e. The family is supportive of this practice; and

f. The mother or caregiver can access health care that offers comprehensive child health services.

4.4.3. First-line ART regimens for children

Table 9. First-line ART for infants and children older than 4 weeks and weighting at least 3 kg

Preferred	**ABC + 3TC +DTG with approved DTG dosing (5mg or 10mg)**
Alternative	ABC + 3TC + LPV/r TAF [a] + 3TC (or FTC) + DTG AZT+3TC+LPV/r ABC+3TC+EFV AZT+3TC+EFV

[a] The evidence base for TAF for children and adolescents is limited to safety and pharmacokinetic data using adult dosing in weight bands above 25 kg. Limited data are available for children 14 to < 25 Kg and older than two years using a low dose of FTC + TAF 120/15 mg with a boosted third agent. TAF is considered a favourable option for special circumstances when bone and renal toxicity are a particular concern (such as the presence of osteoporosis or mild chronic renal disease and concomitant use of nephrotoxic drugs) for adults

In general, the choice of regimen in this age group should be guided by:

- the importance of using potent first-line regimens;
- the convenience of once-daily dosing and the use of FDCs whenever possible;
- the provision of treatment recommendations for older children that are aligned with those for adolescents and adults.

Table 10. Dosing of optimal paediatric ARVs

Formulation	3-5.9 kg		6-9.9 kg		10-13.9 kg		14-19.9 kg		20-24.9 kg		25-29.9 kg		≥ 30 kg	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC/3TC 120/60 mg scored dispersible tablet	1		1.5		2		2.5		3		1 adult tab (600/300 mg)		1 adult tab (600/300 mg)	
LPV/r 40/10 mg pellets (capsules)	2	2	3	3	4	4	5	5	6	6	-		-	
LPV/r 40/10 mg granules (sachets)	2	2	3	3	4	4	5	5	6	6	-		-	
LPV/r 100/25 mg tablets	-	-	-	-	2	1	2	2	2	2	3	3	3	3
4-in-1 ABC/3TC/LPV/r 30/15/40/10 mg (capsules)	2	2	3	3	4	4	5	5	6	6	-	-	-	-
DTG 5 mg dispersible tablets	1		3		4		5		-		-		-	
DTG 10 mg scored dispersible tablets	0.5		1.5		2		2.5		-		-		-	
DTG 50 mg tablet	-		-		-		-		1		1		1	
TDF/3TC (or FTC)/DTG 300/300 (or 200)/50 mg tablet	-		-		-		-		-		-		1	

4.4.4. First-line ART regimens for infants

Table 11. Frist line ART regimens for infants from birth to age 4 weeks who weigh less than 3 kg

Preferred regimen	AZT (or ABC) + 3TC + RAL[a]
Alternative regimen	AZT (or ABC) + 3TC + NVP [b] AZT (or ABC) + 3TC + LPV/r [c]

[a] RAL is preferred over NVP due to its ability to quickly reduce viral load. Furthermore, the current prevalence of transmitted drug resistance to NNRTI is unknown among people who have HIV in Myanmar and RAL is preferred to NVP among neonates.

[b] NVP should not be used if the mother was exposed to single dose NVP for PMTCT

[c] LPV/r syrup or granules can be used if starting after two weeks of age

4.4.5. TB co-infection in infants and children with HIV

Table 12. Guidance for adjusting ART when rifampicin-based TB treatment starts

	ART regimen	What to do when TB treatment is started
Neonates	RAL-based[a]	Dose adjustment needed: see the annexes for ARV dosing
	NVP-based	Change of regimen needed: NVP to be replaced as soon as possible with DTG or LPV/r (with appropriate dose adjustment)
Children	DTG-based regimen[a]	Dose adjustment needed: see the annexes for ARV dosing
	LPV/r-based regimen	Transition to DTG-based regimen (with appropriate dose adjustment) is preferable, and if not possible, LPV/r dose adjustment is needed: see the annexes for ARV dosing
	RAL-based regimen	Transition to DTG-based regimen (with appropriate dose adjustment) is preferable, and if not possible, RAL dose adjustment is needed: see the annexes for ARV dosing
	TAF-containing regimen	Change of regimen needed: TAF to be replaced by ABC or TDF
	ATV/r-based regimen	Change of regimen needed: replace ATV/r with DTG if DTG naive, with LPV/r if DTG experienced
	DRV/r-based regimen	Change of regimen needed: replace DRV/r with DTG if DTG naive, with LPV/r if DTG experienced

[a]Preferred for ART initiation while receiving TB treatment.

4.5. Monitoring ARV toxicities and response to treatment

4.5.1. ARV toxicities

Table 13. Types of toxicities associated with first-, second- and third-line ARV drugs

The following table summarizes the major toxicities of the commonly used drugs, risk factors for these toxicities and suggests the management:

ARV drug	Major type of toxicity	Risk factors	Suggested management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 gene	Do not use ABC in the presence of HLA-B*5701 gene. Substitute with AZT or TDF.

ATV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome	Use with caution in people with pre-existing conduction disease or who are on concomitant drugs that may prolong the PR or QRS intervals.
	Indirect hyperbilirubinaemia (clinical jaundice)	Presence of uridine diphosphate (UDP)-glucuronosyltransferase 1-1 enzyme (UGT1A1*28 gene)	This phenomenon is clinically benign but potentially stigmatizing. Substitute only if adherence is compromised.
	Nephrolithiasis	History of nephrolithiasis	Substitute with LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider substituting with integrase inhibitors.
AZT	Severe anaemia, neutropaenia	CD4 cell count of ≤200 cells/ mm^3	Substitute with TDF or ABC. Consider use of low-dose zidovudine
	Lactic acidosis or severe hepatomegaly with steatosis Lipoatrophy Lipodystrophy Myopathy	BMI >25 (or body weight >75 kg) Prolonged exposure to NRTIs	Substitute with TDF or ABC.
DTG	Hepatotoxicity Hypersensitivity reactions	Hepatitis B or C coinfection Liver disease	If DTG is used in first-line ART, and there are hypersensitivity reactions, substitute with another therapeutic class (EFV or boosted PIs).
	Insomnia Weight gain	Older than 60 years Low CD4 or high viral load Female Concomitant use of TAF	Consider morning dose or substitute EFV, boosted PI or RAL Adequate counselling on lifestyle and dietary changes Monitor body weight and promote anti-obesity measures (such as diet and physical exercise); routine blood pressure to assess for hypertension; glucose and lipid monitoring; and monitoring

			weight and associated complications. If significant increase despite measures, consider substituting EFV or boosted PI
DRV/r	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	Substitute with ATV/r or LPV/r. When it is used in third-line ART, limited options are available. For hypersensitivity reactions, substitute with another therapeutic class.
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	
EFV	Persistent central nervous system toxicity (such as dizziness, insomnia, abnormal dreams) or mental symptoms (anxiety, depression, mental confusion)	Depression or other mental disorder (previous or at baseline) Daytime dosing	For CNS symptoms, dose at night-time. Consider using EFV at a lower dose (400 mg/ day) or substitute with integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms.
	Convulsions	History of seizure	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
	Severe skin and hypersensitivity reactions	Risk factor(s) unknown	
	Gynaecomastia	Risk factor(s) unknown	Substitute with another therapeutic class (integrase inhibitors or boosted PIs).
ETV	Severe skin and hypersensitivity reactions	Risk factor(s) unknown	Substitute with another therapeutic class (integrase inhibitors or boosted PIs).
LPV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome Hypokalaemia	Use with caution in people with pre-existing conduction disease or those on concomitant drugs that may prolong the PR or QRS intervals

	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If LPV/r is used in first-line ART for children, substitute with NVP or RAL for children younger than 3 years and EFV for children 3 years and older. ATV can be used for children older than 6 years. If LPV/r is used in second-line ART for adults, and the person has treatment failure with NNRTI in first-line ART, consider integrase inhibitors.
	Pancreatitis	Advanced HIV disease, alcohol	Substitute with another therapeutic class (integrase inhibitors).
	Dyslipidaemia	Cardiovascular risk factors such as obesity and diabetes	Substitute with another therapeutic class (integrase inhibitors).
	Diarrhoea		Substitute with ATV/r, DRV/r or integrase inhibitors.
NVP	Hepatotoxicity Severe skin rash and hypersensitivity reaction, including Stevens-Johnson syndrome	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs High baseline CD4 cell count (CD4 count >250 cells/mm^3 in women or >400 cells/mm^3 in men)	If hepatotoxicity is mild, consider substitution with EFV, including in children 3 years and older. For severe hepatotoxicity and hypersensitivity, and in children under the age of 3 years, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis, including statins	Substitute with another therapeutic class (etravirine, boosted PIs).
	Hepatitis and hepatic failure Severe skin rash and hypersensitivity reaction	Risk factors unknown	
TDF	Chronic kidney disease Acute kidney injury and Fanconi syndrome	Underlying renal disease Older than 50 years of age	Substitute with TAF or ABC or AZT.

		BMI <18.5 or low body weight (<50 kg) notably among women Untreated diabetes Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	Do not initiate TDF at eGFR <50 mL/min, uncontrolled hypertension, untreated diabetes, or presence of renal failure. More frequent creatinine screening (every 6–12 months) is suggested for individuals with comorbidities, those aged 50 years and older, and those with a previous kidney function test result suggesting at least a mild reduction in function (eGFR < 90 mL/min)
	Decreases in bone mineral density	History of osteomalacia (in adults) and rickets (in children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss Vitamin D deficiency	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity Liver disease	
TAF	Dyslipidaemia Body weight gain	Female sex Concomitant use of DTG	Monitor body weight and promote anti-obesity measures (such as diet, physical exercise). If significant increase despite measures, consider substituting EFV or boosted PI

Monitor TDF Toxicity

TDF nephrotoxicity is characterized by proximal tubular cell dysfunction that may be associated with acute kidney injury or chronic kidney disease.

According to a systematic review, no studies have properly compared monitoring strategies for people receiving TDF, such as routine toxicity monitoring versus care with no monitoring or incidental monitoring in case of perceived clinical need. One clinical trial (the DART trial) comparing laboratory with clinical monitoring showed that individuals receiving TDF have an increased risk of reduced estimated glomerular filtration rate but no increased risk of renal failure over a median five years of follow-up (low-quality evidence). A few observational cohort studies reported that using TDF was associated with an increased risk of chronic kidney disease. However, the exposure time to TDF in all these studies was considered too short to indicate a long-term increased risk for renal failure, the occurrence of bone fractures or changes in fat distribution.

The best parameter for TDF-related renal toxicity monitoring needs to be evaluated; meanwhile, laboratory monitoring using a creatinine test is not mandatory to initiate treatment with TDF. However, it is advisable for high-risk people (those who are older or have underlying renal disease, long-term diabetes or uncontrolled hypertension concomitant with boosted PIs or nephrotoxic drugs) to detect and limit further progression of renal impairment. High frequency of glycosuria has also been found in people without diabetes biopsied for TDF nephrotoxicity with increased serum creatinine compared with TDF-treated people with a normal glomerular filtration rate, suggesting that dipstick glycosuria may be a cost-effective screening test for serious TDF-induced kidney injury.

TDF-related decreases in bone mineral density have been observed in children, although it is unclear how reducing bone mineral density might impact future growth patterns or the risk of bone fracture. In addition, an accurate and feasible method to measure bone mineral density still needs to be identified, and significant uncertainty remains around how best to monitor TDF-related bone toxicity among children. Dual-energy X-ray absorptiometry testing is not possible in most settings, but careful growth monitoring is recommended while children are receiving treatment with TDF.

Clinical considerations for TDF toxicity

- Laboratory monitoring is not mandatory to initiate treatment with TDF.
- Routine blood pressure monitoring may be used to assess for hypertension.
- Urine dipsticks may be used to detect glycosuria or severe TDF nephrotoxicity in individuals without diabetes using TDF-containing regimens.
- If the creatinine test is routinely available, use the estimated glomerular filtration rate at baseline before initiating TDF regimens.
- Do not initiate TDF when the estimated glomerular filtration rate is <50 ml/min, or in long-term diabetes, uncontrolled hypertension and renal failure.
- Monitor growth in children using TDF.

[a] The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or Cockcroft-Gault formula are commonly used to determine eGFR and considered a more accurate measure of GFR than Cockcroft-Gault estimated creatinine clear. An online calculator is available at https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/historical.

TAF Toxicity

The most common adverse effects are nausea, diarrhea and headache. Greater weight gain has been reported with the use of TAF than with tenofovir disoproxil fumarate (TDF) in adults and children. Less common but more severe side effects are lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of other nucleoside reverse transcriptase inhibitors (NRTIs). TAF causes bone toxicity less frequently

than TDF. TAF is less frequently associated with glomerular and renal tubular damage than TDF. TAF may require less intense renal safety monitoring than TDF, but more experience with the drug in broad clinical practice will be needed before a specific recommendation can be made. Observational data are limited, and no randomized controlled trials have examined TAF-associated weight gain in children. In adults, greater weight gain has been reported with the use of TAF than with the use of TDF.

Weight gain

There have been randomized data indicating more weight gain, as measured by changes in body mass index, absolute weight and emergence of obesity, among people receiving DTG. It is important to monitor weight gain among people on dolutegravir-based antiretroviral therapy in Myanmar because of the clear link between obesity, metabolic syndrome and type 2 diabetes. Studies have shown significantly higher weight gain after initiating a DTG + TAF + 3TC or FTC regimen than DTG associated with other ART drug backbones. Initiating DTG-based treatment also led to higher weight increases relative to NNRTI- and elvitegravir/cobicistat-based regimens but was comparable to RAL and bictegravir-based regimens. In reports from clinical trials comparing initiation of DTG- to EFV-based treatment among adults living with HIV, the weight gain observed with DTG was an increase of about 2 kg over 96 weeks and 3 kg at 144 weeks relative to EFV. Greater weight gain with DTG when combined with TAF + 3TC or FTC relative to TDF, ABC and AZT + 3TC or FTC–based ARV drug backbones were more consistent between studies, since TAF led to higher weight gain relative to all comparison drugs. The relative weight gains observed with use of TAF-based drug backbone versus TDF and AZT-based drug backbones increased consistently over time, reaching differences of 4 kg and 5 kg at 144 weeks relative to TDF and AZT-based drug backbones, respectively. Both low CD4 and high HIV RNA were highly prognostic of higher weight gain, while the effects of sex on weight gain appear to be ethnicity dependent, with higher rates among African women compared with men. The following are useful to consider:

- adequate counselling on lifestyle and dietary changes for everyone gaining weight;
- using routine blood pressure to assess for hypertension, with special attention to the risk of hypertension during pregnancy;
- monitoring and treating metabolic parameters – glucose and lipid monitoring when routinely available; and
- monitoring weight and associated complications as part of routine or active toxicity monitoring

4.5.2. Drug interactions

Antituberculosis drugs

Rifampicin is known to significantly lower plasma concentrations of DTG, and increasing the dose to a twice-daily schedule is necessary which should be continued until 2 weeks after the last dose of Rifampicin. New drugs to treat drug resistant TB have little potential for clinically relevant interactions with DTG.

A key contraindicated drug combination is rifampicin with PIs. When people with HIV-related TB are receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r can be used for the duration of TB treatment by doubling the standard dose of LPV/r or increasing the boosting dose of RTV. For patients who are co-infected with HIV and extensively drug-resistant or multidrug-resistant (XDR/MDR) TB, there is limited information on the drug interactions of ARV drugs with new drugs such as bedaquiline and delamanid.
TDF should be avoided for HIV+ MDR-TB cases who receive standard MDR-TB regimen including Amikacin.
The University of Liverpool has a comprehensive, up-to-date, evidence-based drug-drug interaction resource for people who have HIV, freely available to clinicians at https://www.hiv-druginteractions.org/checker.

Drugs for Hepatitis C

Potential drug interactions should be considered when using ARV drugs and DAAs for HCV co-infected persons. Daclatasvir is associated with significant drug interactions with many NNRTIs and PIs, and its concomitant use requires caution, dose adjustments or consideration of alternative DAAs. If Daclatasvir is used in a patient receiving EFV, the dose of Daclatasvir needs to be increased from 60 mg/day to 90mg/day. Sofosbuvir has few interactions with ARV drugs and can be co-administered with ARV drugs recommended in the current National guidelines without dose adjustments. Velpatasvir has significant interactions with NVP and EFV. So they cannot be co-administered. If Velpatasvir is used, DTG or a PI based regimen needs to be given.

Table 14 describes DDI between commonly used ARV's and anti-HCV medications and dose adjustments.

Table 14. DDI between commonly used ARV's and anti-HCV medications

ARV \ Anti-HCV	Sofosbuvir	Daclatasvir	Ledipasvir/Sofosbuvir	Velpatasvir/Sofosbuvir
NVP	✓	✓ ↑ DCV dose to 90 mg/day	X	X
EFV	✓	✓ ↑ DCV dose to 90 mg/day	X	X
ETV	✓	✓ ↑ DCV dose to 90 mg/day	X	X
RPV	✓	✓	✓	✓
ATV/r	✓	↓ DCV dose to 30 mg/day	If a PI/r is used with TDF, ↑ TDF concentrations are expected. Monitor renal function.	
LPV/r	✓	✓		
DRV/r	✓	✓		
DTG	✓	✓	✓	✓
RAL	✓	✓	✓	✓

✓ = ARV that can be used concomitantly.
X = ARV not recommended.

Antifungal agents

Itraconazole, fluconazole and ketoconazole are often used to treat fungal infections. Studies have shown that NVP may decrease the concentrations of these antifungal agents to sub-therapeutic levels. Alternative antifungal agents (such as flucytosine) could be used to ensure adequate treatment of fungal infections among people with HIV.

Opioid substitution therapy

The WHO recommends methadone and buprenorphine for treating opioid dependence. Co-administering EFV decreases methadone concentrations. This could subsequently cause withdrawal symptoms and increase the risk of

relapse to opioid use. People taking methadone and NNRTIs should be monitored closely, and those experiencing opioid withdrawal may need to adjust their methadone dose.

Hormonal contraceptives

ARV drugs have the potential to either decrease or increase the levels of steroid hormones in hormonal contraceptives. There may be drug interactions between some NNRTIs and RTV-boosted PIs with hormonal contraceptives, which can reduce the effectiveness of both the hormonal contraceptive and the ARV drug.

Statins

WHO recommends statins for people with a 10-year cardiovascular risk exceeding 30%. Boosted PIs may lead to increased concentrations of lovastatin and simvastatin, which may increase the risk of serious adverse events such as myopathy, including rhabdomyolysis. Alternative cholesterol-lowering agents should be used to prevent severe toxicity in people with HIV.

Table 15. Key ARV drug interactions and suggested management

ARV drug	Key interactions	Suggested management
TAF	Rifampicin	TAF 25 mg once daily may still provide sufficient concentrations of intracellular tenofovir diphosphate
TDF	Ledipasvir- or velpatasvir-containing regimens	Monitor for TDF-associated adverse effects, including renal dysfunction, particularly when TDF is co-prescribed with boosted HIV PIs
	Lithium	TDF: monitor renal function closely
Boosted PI (ATV/r, DRV/r, LPV/r)	Rifampicin	Replace rifampicin with rifabutin Adjust the dose of LPV/r or substitute three NRTIs (for children)
	1HP or 3HP	Avoid the combination Consider alternative ARV drugs such as EFV + DTG Consider a non-rifamycin-based approach, such as daily isoniazid
	Bedaquiline or delamanid	Use with caution as there is a risk of QT prolongation
	Lumefantrine	Potential for increased lumefantrine exposure Risk of QT prolongation with ATV/r and LPV/r
	Methadone and buprenorphine	Adjust methadone and buprenorphine doses as appropriate
	Quetiapine	If co-administration is unavoidable, use quetiapine at one sixth the normal dose
	Pimozide	Avoid this combination because of the risk of serious arrhythmia; use alternative ARV drugs or antipsychotic drugs
	Lithium, haloperidol, fluphenazine	Use with caution since there is a risk of QT prolongation with ATV/r and LPV/r
	Amlodipine	Consider reducing the dose of amlodipine by 50%

	Antidiabetic drugs (such as glibenclamide and gliclazide)	Adjust the antidiabetic drug dose as appropriate
	Statins	Simvastatin: contraindicated because of the risk of rhabdomyolysis; use alternative dyslipidaemia agent Atorvastatin: dose adjustment required; total daily dose should be limited to 10 mg with ATV/r, 40 mg with DRV/r and 20 mg with LPV/r
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Fluticasone or budesonide	Risk of Cushing's syndrome; use alternative corticosteroid (such as beclomethasone)
	Acid-reducing agents	ATV/r: use at least 2 hours before or 1 hour after antacids; contraindicated with proton pump inhibitors
DTG	Carbamazepine, phenobarbital and phenytoin	Use an alternative anticonvulsant agent (such as valproic acid or gabapentin)
	Rifampicin	Increase DTG to 50 mg twice daily; avoid in the presence of integrase class resistance. Continue with twice daily dosing of DTG in children for 2 weeks after use of rifampicin has ended
	Rifapentine in TB preventive treatment regimens (1HP or 3HP)	No evidence that change of dose of rifapentine or DTG is needed to achieve adequate exposures of DTG
	Metformin	Avoid high-dose metformin with DTG; adjust the metformin dose as appropriate
	Polyvalent cation products containing Mg, Al, Fe, Ca and Zn	Use DTG at least two hours before or at least six hours after supplements containing polyvalent cations, including but not limited to the following products: Fe-, Ca-, Mg- or Zn-multivitamin supplements; mineral supplements, cation-containing laxatives and Al-, Ca- or Mg- containing antacids. Monitor for antiviral efficacy
RAL	Carbamazepine, phenobarbital and phenytoin	Use alternative anticonvulsant agent (such as valproic acid or gabapentin).
	Rifampicin	Increase RAL to 800 mg twice daily (RAL 400 mg twice daily can be used with 3HP). Continue with twice daily dosing of RAL in children for 2 weeks after use of rifampicin has ended
	Rifapentine in TPT regimens (1HP or 3HP)	No evidence that change of dose of rifapentine or RAL is needed to achieve adequate exposures of RAL
	Antacids	Al- or Mg-containing antacids – not recommended Ca-containing antacids – not recommended with RAL once daily; no dose adjustment with RAL twice daily
	Ca-, Fe- and Mg-containing supplements or multivitamins	RAL twice daily: separate intake by at least four hours RAL once daily: not recommended
EFV	Bedaquiline	Avoid the combination
	Amodiaquine, DHA/piperaquine	Use an alternative antimalarial agent or substitute EFV for DTG
	Artemisinins or lumefantrine	Use an alternative antimalarial agent or substitute EFV for DTG

		Risk of QT prolongation with ATV/r and LPV/r
	Methadone	Adjust the methadone dose as appropriate
	Quetiapine	Adjust the quetiapine dose as appropriate
	Hormonal contraceptives	Use alternative or additional contraceptive method
	Amlodipine	Adjust the amlodipine dose as appropriate
	Simvastatin and atorvastatin	Adjust the statin dose as appropriate
	Low-dose dexamethasone (COVID-19)	Double dose of dexamethasone
NVP	Rifampicin	Replace NVP with EFV
	HCV NS3/4A protease inhibitors	Use alternative HCV direct-acting antiviral drug regimen
	Quetiapine	Adjust the quetiapine dose as appropriate
	Amlodipine	Adjust the amlodipine dose as appropriate
	Simvastatin	Adjust the simvastatin dose as appropriate
	1HP or 3HP	Avoid the combination. Consider a non-rifamycin-based approach, such as daily isoniazid or an alternative ARV drug such as EFV + DTG
	Low-dose dexamethasone (COVID-19)	Double dose of dexamethasone

4.5.3. Monitoring response to ART

Clinical assessment and laboratory tests play a key role in assessing individuals before ART is initiated and then monitoring their treatment response and possible toxicity of ARV drugs. The following table summarizes recommended laboratory tests for HIV screening and monitoring, as well as approaches to screen for co-infections and non-communicable diseases.

For a person on ART, the following frequency of investigation is recommended as a general guidance:

Table 16. Recommended laboratory monitoring of ART.

Phase of HIV management	Recommended	Desirable
Receiving ART	-HIV viral load (at 6 months and 12 months after initiating ART and every 12 months thereafter).	Serum creatinine and eGFR for TDF[a] Pregnancy test, especially for women of childbearing age not receiving family planning and on treatment with DTG or low-dose EFV

	If routine viral load is not available, targeted viral load testing is recommended.	For patients with CD4<350, CD4 cell count every 6 months to decide discontinuation of cotrimoxazole prophylaxis
Suspected treatment failure		HBV (HBsAg) serology [b,c] (before switching ART regimen if this testing was not done or if the result was negative at baseline and the patient was not vaccinated thereafter)

[a]Consider assessing for the presence of chronic conditions that can influence ART management, such as hypertension and other cardiovascular diseases, diabetes and TB according to the WHO Package of Essential NCD interventions (PEN), mental health Gap Action Programme (mhGAP) or national standard protocols (see section 5.3 "Prevention, screening and management of other comorbidities and chronic care for people living with HIV"). Monitoring may include a range of tests, including serum creatinine and estimated glomerular filtration rate (eGFR), serum phosphate and urine dipsticks for proteinuria and glycosuria. See formula for eGFR in the footnote to section 4.6.3.

[b]If feasible, HBsAg testing should be performed at baseline to identify people with HIV and HBV coinfection and who should therefore initiate TDF-containing ART.

[c]For HIV/HBV coinfected individuals who are already using TDF-containing regimens and develop ART failure, this NRTI should be maintained regardless of the selected second-line regimen.

*Haemoglobin, serum creatinine and estimated glomerular filtration rate (eGFR), ALT, AST, Cryptococcus antigen and pregnancy test should be prioritized as baseline assessment for ART initiation when these laboratory services are available.

4.6. When to switch to second line

When the first line ART regimen fails it becomes necessary to switch to second line ART. Utmost attempts must be made to optimize adherence and prevent resistance to first line regimens.

Table 17. WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens

Failure	Definition	Comments
Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)[a] after 6 months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with the exception of TB) after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure[a]
Immunological failure	**Adults and adolescents** CD4 count at or below 250 cells/mm^3 following clinical failure[b] or Persistent CD4 levels below 100 cells/mm^3 **Children** Younger than 5 years Persistent CD4 levels below 200 cells/mm^3 Older than 5 years Persistent CD4 levels below 100 cells/mm^3	Without concomitant or recent infection to cause a transient decline in the CD4 cell count Current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure
Virological failure	Viral load above 1000 copies/mL based on two consecutive viral load measurements within 2-3 months, with adherence support following the first viral load test	An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed

[a] See the list of clinical conditions associated with advanced or severe HIV disease in WHO clinical staging table

[b] Previous guidelines defined immunological failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation.

Virological failure (increase in HIV viral load) usually occurs before immunological failure (fall in CD4 count) and clinical failure (new or recurrent opportunistic infections). Clinical monitoring alone results in increases in mortality

and disease progression. Clinical monitoring may result in late switches to second line ART so that more drug resistant HIV clones have developed. An immunological criterion (CD4 count) is not a good predictor of virological failure. Some individuals with immunological failure still have virological suppression and risk being unnecessarily switched to second line.

When early switching is done when virological failure occurs some of the first line ARV drugs will still be effective thus maximizing the effect of second line ART regimens which are expensive and not universally available (some first line ARVs are still employed together with a new class in second line ART). Late switching, after a protracted period following clinical failure will render the second line ART regimen to be less effective as the viral load gets higher and more drug resistant clones to remaining NRTIs develop.

Routine versus targeted viral load monitoring to detect viral failure

Viral load should be monitored routinely at 6 months, at 12 months, and then every 12 months thereafter if the patient is stable on ART to detect treatment failure earlier and more accurately.

In settings with limited access to viral load testing, a targeted viral load strategy to confirm suspected treatment failure based on immunological or clinical criteria should be used to avoid unnecessary switching to second-line ART regimens. However, targeted viral monitoring has the potential to delay switching to second-line ART and may subsequently increase the risk of disease progression, selection of ARV drug resistance and HIV transmission.

4.6.1. Plasma HIV viral load

Plasma HIV viral load is measured using PCR (polymerase chain reaction) technology. The result is expressed as copies/ml. In HIV symptomatic or in late cases VL may be as high as 100,000- 1,000,000 copies/ml or more. Plasma viral load can be used to monitor therapeutic success of ART. It is the most important indicator of response to ART.

The ideal aim of ART is to reach sustained undetectable plasma VL. For most individuals who do not have resistant HIV and have good adherence to ART viral suppression is generally obtained in 12 – 24 weeks. In patients with a suboptimal response to ART other causes should be excluded which include adherence, drug interactions or malabsorption. The probability of HIV transmission is directly correlated with VL. Effective ART with sustained viral suppression almost eliminates or substantially reduces HIV transmission with nearly any type. There is little likelihood of developing resistance or disease progression at this VL level.

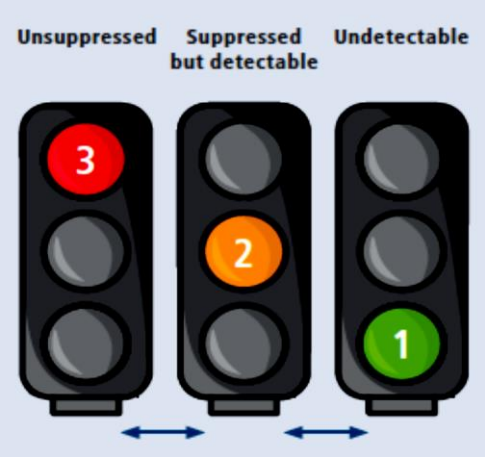
Thus effective ART resulting in undetectable VL is very important not only in preventing sexual transmission and mother-to-child transmission, but also in reducing HIV transmission in the community when a wide ART coverage can be obtained. The cost of a single HIV viral load test is less than the cost of a month's supply of second line ART

but requires expensive equipment and expertise to perform. However, lack of VL facilities does not preclude effective ART.

The optimal threshold for defining viral failure and for switching ART regimens has not been established. WHO recommends a threshold of 1000 copies/ml based on the fact that the risk of HIV transmission and disease progression is very low when viral load is lower than 1000 copies/ml, and that below this threshold, viral blips or intermittent low-level viraemia (≤1000 copies/ml) can occur during effective treatment but have not been associated with an increased risk of treatment failure.

Three categories of viral load levels

There are three key categories of viral load suppression: unsuppressed, suppressed, and undetectable. The viral loads of people living with HIV can fluctuate between these categories depending on their access and adherence to antiretroviral therapy.



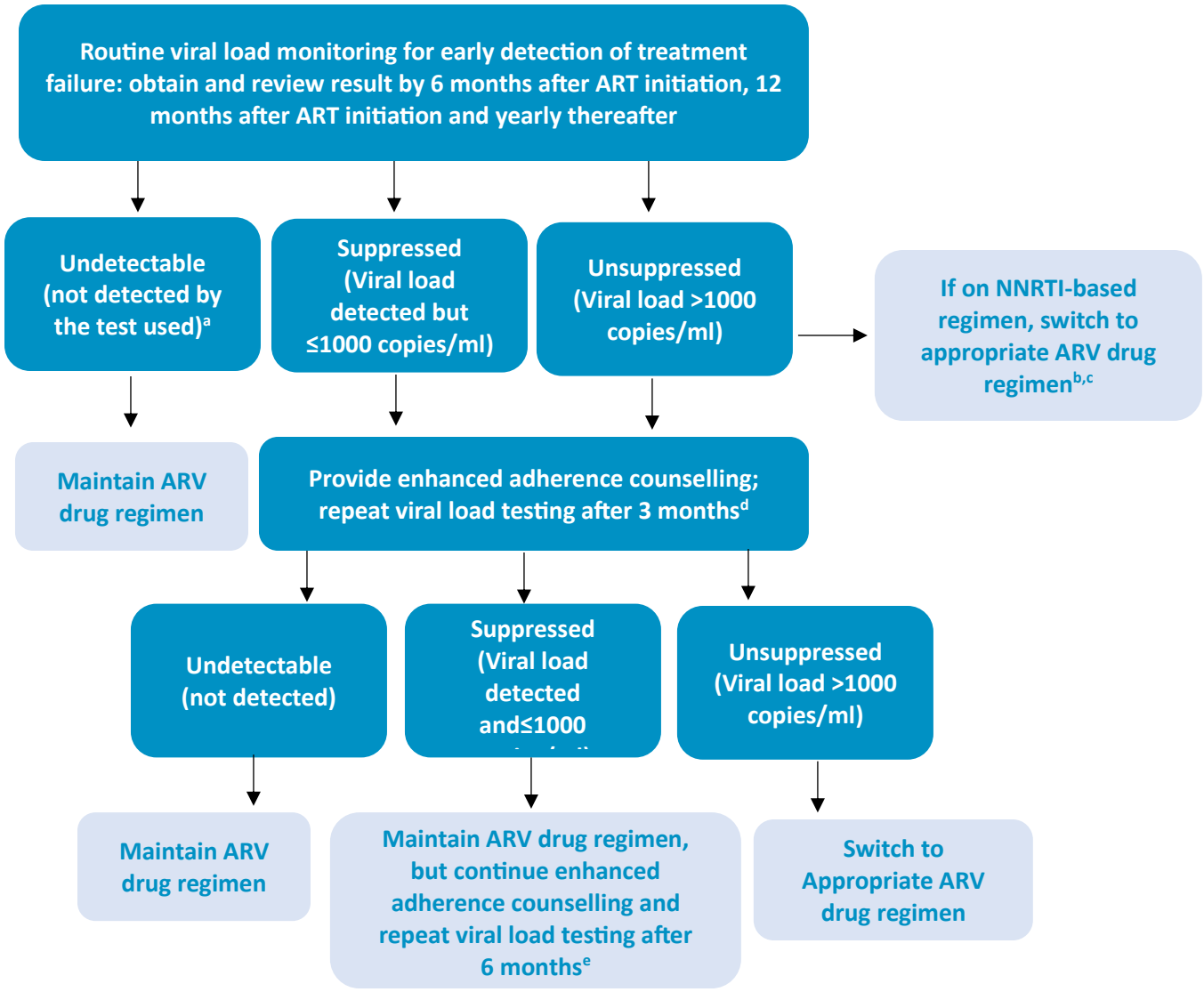
1 **Undetectable (not detected*)**: no measurable virus. Zero risk of transmission to sexual partner(s); minimal risk of mother to child transmission.

2 **Suppressed (detected but ≤1000 copies/mL):** some virus replicating and present: could be due to missing doses, recent treatment initiation or drug resistance. Almost zero or negligible risk of transmission to sexual partner(s).

3 **Unsuppressed (>1000 copies/mL):** significant virus replicating and present: could be due to missing doses, recent treatment initiation or drug resistance. Increased risk of falling ill and/ or passing virus on to sexual partner(s) or children.

The ultimate goal for all people living with HIV is to reach and sustain undetectable viral loads. Taking antiretroviral therapy as prescribed will support this goal, prevent transmission to their sexual partner(s) and/or children, and improve their own clinical well-being.

Figure 14. Treatment monitoring algorithm



Adherence counselling should be provided at all visits to ensure that viral suppression is maintained or given priority throughout care

[a] Not detected by the test or sample type used.
[b] Switch after a single elevated viral load should be considered.
[c] A second viral load may be considered before regimen switch if DTG-based regimens are unavailable and the results of a viral load test can be returned and acted on rapidly.
[d] Conduct same-day testing using point-of-care viral load testing for a repeat viral load test, where available, to expedite the return of results. If not available, viral load specimens and results for a repeat viral load test should be given priority across the laboratory referral process (including specimen collection, testing and return of results).
[e] Consider switching ART for those receiving NNRTI-based regimens based on clinical considerations and address any adherence concerns.

4.6.2. Second line ART regimens

Table 18. Preferred second line ART regimen for adults, adolescents, children and infants

Population	Failing first-line regimen	second-line regimen
Adults and adolescents	TDF (or ABC) + 3TC (or FTC) + DTG	AZT+ 3TC + LPV/r (or ATV/r)
	TDF (or ABC) + 3TC (or FTC) + EFV (or NVP)	AZT +3TC + DTG
	AZT + 3TC +EFV (or NVP)	TDF (or ABC) + 3TC (or FTC) + DTG
Children and infants	ABC + 3TC + DTG	AZT+ 3TC + LPV/r (or ATV/r)
	ABC (or AZT) +3TC + LPV/r	AZT (or ABC) + 3TC + DTG
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG
	AZT + 3TC + NVP	ABC + 3TC + DTG

Adults, adolescent and children failing a NNRTI-based first line regimen should be switched to a DTG-based second line regimen. In children and infants failing a bPI-based first-line regimen, switching to a DTG-based second line regimen is recommended. If LPV/r cannot be used, Atazanavir/r is the alternate bPI for adults and children over 6 years of age. Adults, adolescent and children failing a DTG-containing first-line regimen should be switched to a boosted protease inhibitor (bPI)-based second line regimen.

As to the NRTI-backbone, adults and adolescents failing an AZT-containing first line regimen should be switched to TDF. Children and infants failing an AZT-containing first line regimen should be switched to ABC.

Adolescents and adults failing a TDF-containing first line regimen should be switched to AZT and monitored for anaemia. If anaemia develops after the switch to AZT, prescribing clinicians should switch anaemic persons back to

TDF-containing regimens. ABC should only considered when there is renal impairment. Among those co-infected with HBV failing a TDF-containing regimen, TDF should be kept in second line regimens.

4.7. Third line ART regimens

Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as INSTIs and second-generation NNRTIs and PIs.

Patients on a failing second-line regimen with no new options should continue with a tolerated regimen.

If possible, the choice of third line ART regimens should be guided by drug resistance testing. Drug resistance testing should be prioritized for persons with full adherence and confirmed virologic failure (namely, two viral load measurement above 1,000 copies/mL three months apart) with previous exposure to multiple antiretroviral drugs, in particular protease inhibitors

In the absence of drug resistance testing, an in-depth review of the medical history should be done. This should include a detailed account of drugs and regimens used as first- and second-line therapies together with the reasons for previous switches, including confirmed or likely viral failure or toxicity.

Boosted Darunavir (DRV/r) has potent anti-HIV activity and has excellent activity against HIV strains that are resistant to other PIs. Etravirine (ETV) is a second generation NNRTI which is active against most but not all EFV or NVP resistant virus.

Dolutegravir (DTG) can be successfully used in 3rd line regimens in combination with optimized NRTI backbone and DRV/r. There is also growing evidence that DTG in double dose can control viral replication even people with detected resistance to INSTIs.

Overall, third-line regimens are much expensive and have a much higher pill burden than first- or second-line regimens. For these reasons it is of utmost importance to make the first-line and second ART regimens work by all means (adherence, viral loads). The first chance is the best chance.

Table 19. Summary of sequencing options for first-line, second-line and third-line ART regimens for adults, adolescents and children

Population	First-line regimen	Second-line regimen	Third-line regimen
Adults and adolescents	TDF + 3TC (or FTC) + DTG	AZT+ 3TC + LPV/r (or ATV/r)	DRV/r + 1-2NRTI + DTG double dose
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT +3TC + DTG	DRV/r or ATV/r or LPV/r + 2NRTI + DTG double dose
	AZT + 3TC +EFV (or NVP)	TDF + 3TC (or FTC) + DTG	
Children and infants	ABC + 3TC + DTG	AZT+ 3TC + LPV/r (or ATV/r)	DRV/r + 1-2 NRTI + DTG double dose
	ABC (or AZT) +3TC + LPV/r	AZT (or ABC) + 3TC + DTG	
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG	DRV/r or ATV/r or LPV/r + 2 NRTI + DTG double dose
	AZT + 3TC + NVP	ABC + 3TC + DTG	

4.8. Principles for optimization of ART regimens

WHO supports the implementation of optimized ART regimens in resource constrained countries. It is cheaper and more logistically efficient to purchase, distribute and prescribe fewer ART regimens with fixed dose combinations to people with HIV across Myanmar. Prescribing clinicians are encouraged to carefully consider whether a switch of first- and second-line ART to more optimised regimens would be appropriate. This careful consideration is relevant not only for programmatic reasons, but also for the individual benefit of a person on stable ART. Special attention should be given to people receiving toxic NRTI backbones containing AZT- or ABC- and to those receiving non-DTG-based regimens.

Many resource constrained countries have adopted a policy of actively switching people with HIV on first- and second-line regimens to TLD without viral load monitoring with great success.

There are now compelling randomized data to support DTG use in young children weighting at least 3 Kg, adolescents, adults, pregnant women and people living with HIV/TB coinfection, adolescents younger than 12 years of age and pregnant women. With the approved pediatric dosing of 5 and 10mg, ART optimization with DTG-based regimens can be implemented among children as successfully as in adults. Below are suggested considerations for prescribing clinicians regarding switches from first- and second-line ART to optimize ART regimens in adolescents, adults and children in Myanmar.

Table 20: Considerations for optimization of ART regimens in adults and adolescents

Scenario	Preferred approach	Comments
Viral load suppressed (<1000 copies/mL)	Substitution to a TLD regimen may be considered in accordance with national recommendations	Substitution should be considered in the context of drug supply and patient choice. Substitution may confer new side-effects and interfere with adherence. However, DTG regimens may be more durable in the long term.
Clinically and immunologically established on ART and viral load unknown	Give priority to viral load testing if possible or consider other programmatic or clinical indications for decision making, and substitution to a TLD regimen may be considered	
Established on suboptimal first line ARV regimens e.g. AZT+3TC+EFV	Switch to TLD	

If the patient has renal impairment or osteoporosis or bone disease, stay on AZT or switch to ABC or TAF

4.8.2 Optimization of ART regimens in infants and children:

DTG-based ART can successfully be scaled up for HIV+ children older than 4 weeks and weighting more than 3 kg with availability of dispersible tablets 5 and 10mg. Prescribing paediatricians should consider switching HIV+ children receiving EFV, NVP, and LPV/r-based ART to dolutegravir using the 5 and 10 mg formulations. RAL-based ART should be prioritised for neonates and children weighting less than 3 kg given the lack of current data on pre-treatment resistance levels to NVP in Myanmar.

Clinicians should not delay the transition to more optimal regimens for children while waiting for new products to be approved, since the timelines for procurement and distribution of new products are approximate and may change due to global or local challenges. Instead, they should focus on rapidly implementing optimal regimens according to WHO guidelines and accelerate transitions to DTG-based therapies, including using TDF + 3TC + DTG for adolescents weighing more than 30 kg, 50-mg adult DTG tablets for those weighing 20–30 kg and planning for transition to the 10-mg scored dispersible DTG tablet for children weighing less than 20 kg when it becomes available in Myanmar.

The Table below summarizes recommendations for transition to optimal regimens for children who are on stable ART.

Table 21: Considerations for optimization of ART regimens in children

Current regimen	Weight	Optimal regimen for transition	Consideration
AZT+3TC+NVP **AZT+3TC+EFV**	**<30 kg**	**ABC + 3TC plus DTG**	**As long as above 3 kg and four weeks old**
ABC+3TC+NVP **ABC+3TC+EFV** **ABC+3TC+LPV/r** **AZT+3TC+LPV/r**	**>30 kg**	**TLD**	**-**

Transition to optimal ARV drug regimen will be considered for children who are established on ART. (WHO criteria for determining whether a person has been successfully established on ART:

- receiving ART for at least six months;
- no current illness, which does not include well-controlled chronic health conditions;
- good understanding of lifelong adherence: adequate adherence counselling provided; and

- evidence of treatment success: at least one suppressed viral load result within the past six months (if viral load is not available: CD4 count >200 cells/mm3 (CD4 count >350 cells/mm3 for children 3-5 years old) or weight gain, absence of symptoms and concurrent infections)

Note: Viral Load monitoring is recommended but not mandatory before transitioning to an optimized ART. Hence, to assure the child is successfully established on ART, it is suggested to review viral load result within one year and prioritize to check viral load for who haven't been monitor viral load status more than a year.

5. Managing common infections and comorbidities

Various co-infections, comorbidities and other concomitant health conditions are common among people living with HIV and have implications for their treatment and care, including the timing and choice of ARV drugs. This section provides a brief overview of the most common and important conditions. It summarizes selected key recommendations from existing WHO guidelines and related materials, focusing on the screening, prophylaxis and timing of ART for these conditions.

Most people with HIV die of opportunistic infections. Prevention, diagnosis and treatment of OIs are an important part of the management of HIV, since most people still present with OIs in resource limited countries. Major OIs need to be diagnosed and treatment started before starting ART. Giving ART without diagnosing and treating major OIs in late disease will lead to disaster. However, in advanced stages of immunosuppression typical signs and symptoms of infections will be absent or masked. It is important to be vigilant in treating late HIV. Unusual infections that do not occur in immunocompetent persons will also occur. Specific HIV associated OIs occur at specific levels of immunosuppression according to their degree of pathogenicity. Knowledge of CD4 count helps in the differential diagnosis of OIs. Other HIV associated conditions also relate to the CD4 count.

5.1. Prevention, screening and management of common co-infections

While many opportunistic infections may occur the following are the major opportunistic infections seen in this country and physicians treating HIV patients should be familiar with the diagnosis and treatment of these conditions since they can be associated with significant morbidity and mortality.

1. *Mycobacterium tuberculosis*
2. *Pneumocystis jirovecii* pneumonia
3. Toxoplasmosis
4. Cryptococcosis
5. Penicilliosis (Talaromycosis)
6. Histoplasmosis

5.1.1. Tuberculosis

Tuberculosis is the most common major opportunistic infection in HIV patients in developing countries and is the foremost cause of death in such patients. Immunosuppression due to HIV not only causes TB reactivation but also contributes to new infection. The timely initiation of ART and implementation of the Intensified TB case finding, tuberculosis preventive treatment (TPT), and infection control are critical to prevent TB and mortality from HIV-associated TB.

The CD4 T-lymphocyte that is activated due to infection from M. tuberculosis produces more HIV than a quiescent cell so that there is a higher viral load which in turn increases the rate of disease progression and also increases HIV infectiousness. HIV drives the TB epidemic. More TB infection in the population in turn predisposes more HIV positive people to develop tuberculosis as a major opportunistic infection.

TB in HIV can be found at all levels of CD4 counts in HIV patients. The clinical and pathological picture of tuberculosis depends on the level of immunosuppression i.e. the CD4 count. In patients with CD4 count >200/mm^3, the usual picture of pulmonary tuberculosis with apical infiltrations, cavitation and fibrosis is found. With advancing degrees of immunosuppression i.e. with falling CD4 count, pulmonary TB changes in clinical pattern. There are less apical infiltrations or cavitation. There can be infiltrations in the middle or lower lobes, the chest X-ray appearance may become atypical or non-specific. Sputum smears are less likely to be AFB positive as immunosuppression advances. In the chest X-ray the hilar and mediastinal glands become enlarged. In advanced immunosuppression there is extrapulmonary spread of tuberculosis. Pleural effusions and pericardial effusions, military TB, TB meningitis, TB of bone especially vertebra with psoas abscess may occur.

Widespread lymphadenopathy due to TB is a common presentation in HIV late stages. The cervical, axillary, hilar and mediastinal glands are involved. Intra-abdominal lymph nodes become enlarged which may occur in isolation or occur together with lymphadenopathy elsewhere. Ultrasound examination of the abdomen is a very useful investigation in patients with HIV to diagnose intra-abdominal lymphadenopathy due to tuberculosis. Ultrasound examination is easily available in many places in the country and is relatively inexpensive.

Whereas without immunosuppression, the typical histological features of tuberculosis with caseous necrosis, epithelioid cells, and Langhan's giant cells can be found on biopsy, with very low CD4 counts the histological examination will not reveal these classical appearances this is non-reactive tuberculosis. On the other hand, the tissue can be stained with acid-fast stain which will demonstrate the acid-fast bacilli without granuloma formation.

When lymphadenopathy in a patient with HIV who has the clinical features of fever, night sweats and weight loss is seen tuberculosis should be suspected.

Diagnosis of TB

Early identification of TB among people living with HIV through careful assessment of symptoms and signs, diagnosis using proper investigation (i.e. Chest X-ray, Xpert MTB/RIF, USG abdomen etc.) and prompt initiation of anti-TB treatment is important to improve survival and quality of life as well as reduce transmission of TB in the clinic and the community. All people living with HIV should be regularly screened for TB using a clinical symptoms based algorithm. Those who report any one of the symptoms may have active TB and should be evaluated for TB and other diseases.

WHO recommends to use Xpert MTB/RIF test as the initial diagnostic test in adults and children suspected of having HIV-associated TB or Multi-drug resistant TB (MDRTB). Those tested positive for Rifampicin resistance should be referred to MDR TB treatment centers.

LF-LAM should be used to assist in the diagnosis of active TB in adults inpatients living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary), who have a CD4 count ≤ 100 cells/mm^3 or people living with HIV who are seriously ill regardless of CD4 count or with unknown CD4 count.

This recommendation also applies to adult outpatient living with HIV who have a CD4 count ≤ 200 cells/mm^3 LF-LAM could be performed for seriously ill HIV-positive adult patients with danger signs, regardless of CD4 count, in both in-hospital and outpatient settings.

This recommendation also applies to children living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary).

LF-LAM should not be used as a screening test for active TB.

However, in very ill cases, diagnosis will have to depend mainly on clinical features and treatment (full treatment) may have to be started after excluding other differential diagnosis.

Tuberculosis in HIV patients is treated just like TB in immune-competent persons – standard 4 drugs (HRZE) for 2 months followed by 2 drugs (HR) for another 4 months. The continuation phase with HR is extended to 7-10 months in case of tuberculous meningitis, military TB and spinal TB with neurological involvement. The response to treatment is usually very good; in most cases, fever subsides and there is some clinical improvement usually in two weeks.

However, there are some problems associated with the use of anti-TB drugs in HIV patients. Rifampicin will induce the enzymes that metabolize NVP as well as PIs so that the drug levels of these agents decrease with the potential

to develop drug resistance by HIV. Because of drug to drug interactions, people co-infected receiving DTG-based ART and rifampicin-based TB treatment should be treated with a double dose of dolutegravir until 2 weeks after the completion of rifampicin-based TB treatment.

Adverse effects of anti-TB drugs are also seen more frequently in patients who have HIV. In advanced immunosuppression starting ART before giving TB treatment or starting ART very soon after TB treatment will lead to exacerbation of the signs and symptoms of tuberculosis due to effects of the recovering immune system which had failed to react to the tubercle bacilli. This is known as immune reactivation inflammatory syndrome (IRIS). Starting ART very soon will lead to severe reactions whereas delaying ART will predispose to further immune deterioration. It is important to note that the incidence of IRIS is relatively rare with newer ART regimens. ART should be started as soon as possible within two weeks of initiating TB treatment. In case of TB meningitis, ART initiation should be delayed at least four weeks (and initiated within eight weeks) after treatment for TB meningitis is initiated.

(For more detailed discussion on this important topic of TB HIV, refer to the guidelines on clinical management of TB/HIV co-infection, (including IP, use of Gene Xpert machines and MDR TB) by NTP)

MDR-TB in HIV

Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment. MDR-TB in HIV patients carries a poor prognosis. Treatment is difficult and costly. History of inadequate treatment or treatment interruptions for tuberculosis is the strongest risk factor for MDR-TB.

Infection control

Recommendations

Administrative (facility-level infection control committee and protocols)

A triage system should be in place to identify people suspected of having TB and minimize diagnostic delays. Separate people with suspected or confirmed TB. Ensure cough etiquette and respiratory hygiene. Minimize the time spent in health care facilities.

Health workers and caregivers

Inform and encourage health workers with TB symptoms to undergo TB diagnostic investigation and HIV testing. Provide a package of care for HIV positive workers (ART and TPT) and preferably relocate to a lower risk area.

Use of particulate respirators

Protective equipment (e.g. N95 mask) should be provided for health workers caring for patients with infectious TB.

Environmental

Ensure proper and adequate ventilation. Upper-room ultraviolet germicidal irradiation can be used.

Tuberculosis preventive therapy (TPT)

Tuberculosis (TB) preventive treatment (or TPT) consists of a course of one or more anti-tuberculosis medicines given with the intention of preventing the development of TB disease. TPT is considered one of the most critical public health measures to protect both individuals and the community from TB. PLHIV are at risk of developing active TB. All PLHIV aged 10 years or older (i.e. adults and adolescents) should take TPT as part of a comprehensive package of HIV care in addition to their antiretroviral treatment (ART). This is regardless of their CD4 cell count. While regular ART reduces the overall risk of developing TB, this risk remains higher than in HIV-negative people, especially where background rates of TB are higher. Combined use of TB preventive treatment and ART significantly reduces the risk of TB.

PLHIV aged 10 years or older (i.e. adults and adolescents) who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB. Those who do not have any of these symptoms are unlikely to have active TB and should be offered TPT, regardless of their ART status. Chest radiography (chest X-ray), if available, may be offered to PLHIV who are receiving ART and TPT given to those with normal findings. However, chest radiography should not be considered a mandatory requirement or be a barrier to initiating TPT in PLHIV.

Either a tuberculin skin test (TST) or interferon gamma release assays (IGRA) can be used to test for TB infection. The choice will depend on test availability, previous BCG vaccination, cost and the health infrastructure. Each of the two tests has its advantages and disadvantages, but there are no solid grounds to prefer one test over the other when it comes to predicting whether infection will progress to active TB disease in an individual. Neither the TST nor IGRA can be used to diagnose active TB disease nor for the diagnostic workup of adults suspected of having active TB. Testing with TST or IGRA is desirable to avoid giving TPT to people who are not infected but is not a requirement for initiating preventive treatment in PLHIV or household contacts aged < 5years. Repeating TPT can be considered when the risk of recurrent TB is considered high by the attending clinician.

Testing for LTBI is not a prerequisite for TB preventive treatment in PLHIV but its use is encouraged because people who are TST positive have a greater protective benefit from TPT. PLHIV with a negative TST should not receive TPT.

Once weekly rifapentine plus isoniazid (3HP)

Once-weekly rifapentine plus isoniazid for 3 months (3HP) regimen is recommended for use in children older than two years, adolescents and adults living with HIV in Myanmar. 3HP can be administered to people receiving DTG- or EFV-based without dose-adjustment. 3HP should not be administered to people receiving protease inhibitors or nevirapine.

Children aged at least 2 years, adolescents and adults living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered TPT. Testing for LTBI is not a prerequisite for TPT in PLHIV but its use is encouraged because people who are TST positive have a greater protective benefit from TPT. PLHIV with a negative TST should not receive TPT.

At the discretion of the attending clinician, daily rifapentine plus isoniazid for 1 month (1HP) can also be used as an alternative TPT regimens in Myanmar. Total daily pill burden for who people with HIV receiving ART and prophylaxis for opportunistic diseases is higher with 1HP than with 3HP. 1HP should thus be reserved for special circumstances.

Table 22: Dosage chart for TB preventive treatment – 3HP

Regimen	Dose by age and weight band					
Three months of rifapentine plus high dose isoniazid weekly (12 doses) 3HP	Age 2-14 years[c]					
	Medicine, formulation	10-15 kg	16-23 kg	24-30 kg	31-34 kg	>34 kg
	Isoniazid 100 mg[a]	3	5	6	7	7
	Rifapentine 150 mg	2	3	4	5	5
	Isoniazid + Rifapentine FDC (150 mg/150 mg)[b]	2	3	4	5	5
	Age > 14 years[c]					
	Medicine, formulation	30-35 kg	36-45 kg	46-55 kg	56-70 kg	>70 kg
	Isoniazid 300 mg	3	3	3	3	3
	Rifapentine 150 mg	6	6	6	6	6
	Isoniazid + Rifapentine FDC (300 mg/300 mg)[b]	3	3	3	3	3

[a] 300 mg formulation can be used to reduce the pill burden.
[b] Expected to become available in a near future.
[c] Dosage may differ among adults and children in overlapping weight-bands.

Isoniazid given daily for 6 months is recommended for children younger than two years and pregnant women living with HIV. IPT is effective in reducing the overall risk of developing TB in HIV positive persons by 33% up to 64%, the

higher rate of effectiveness being seen in those who are tuberculin skin test (TST) positive. Isoniazid is given at a dose of 300 mg/ day regardless of prior TB treatment history. Isoniazid is the medicine that has been used most frequently during pregnancy and, while more research is needed, there is no strong evidence to suggest that it is dangerous to the mother or baby. For patients with prior IPT history more than two years ago, IPT can be considered again if the patient has risk of developing TB, for example, close contact with TB cases. Contraindications to IPT include active hepatitis (acute or chronic), alcoholism, and peripheral neuropathy.

Children living with HIV younger than two years of age who do not have poor weight gain, fever or current cough and have no contact with a TB case are unlikely to have active TB disease and should receive IPT for 6 months at the dosage of 10mg/kg/day. In general, IPT is not indicated for the HIV infected children who had completed prior IPT. In children with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB using investigations such as chest X-ray should receive 6 months of IPT if the evaluation shows no TB disease.

The recommended duration of IPT in Myanmar is 6 months for children younger than two years and pregnant women living with HIV.

Table 23. Isoniazid dosage according to body weight

Weight range (kg)	Number of 100mg tablets of INH to be administered per dose (total dose 10mg/kg/ day)	Dose given (mg)
<5	½ tablet	50
5- 9.9	1 tablet	100
10 – 13.9	1 ½ tablet	150
14-19.9	2 tablets	200
20-24.9	2 ½ tablets	250
≥25	3 tablets	300

5.1.2. *Pneumocystis jirovecii* pneumonia

Pneumocystis jirovecii (previously known as *Pneumocystis carinii*) is a fungus that causes pneumonia in patients with CD4 count<200/mm^3. There is subacute onset and progression of exertional dyspnoea, non-productive cough and fever over days or weeks. In advanced cases, cyanosis is seen with the slightest exertion. Chest X-ray shows bilateral symmetrical interstitial shadows fanning out from the hilum and sparing the apices (differential diagnosis is acute pulmonary oedema) but in spite of the marked radiological appearance, auscultation of the lungs is remarkably free

of physical signs except for the tachypnoea. Definitive diagnosis requires staining the sputum; the best specimen is induced sputum, with Giemsa stain or cresyl violet or Wright stains for the presence of cysts and trophozoites. The cysts are better stained with silver methanamine nitrate stain. Immunoflourescent stains or PCR can be also used. These would not usually be available and a presumptive diagnosis is usually made from the clinical and radiological picture. Treatment should be started immediately with Cotrimoxazole double strength 2 tablets TDS for 3 weeks. Alternative is pentamidine iv infusion which is not usually available or with primaquine 15-30 mg base/day plus clindamycin 600 mg 8 hourly IV or oral for 21 days. Severe cases require prednisolone 40 – 60 mg per day for 5 days which is gradually tapered until day 21. In severe cases in which oral administration is complicated, Cotrimoxazole can be given intravenously (15-20 mg TMP/kg/day) divided q6-8hr. Prompt treatment is essential as the diagnosis is often late in resource limited settings and mortality can be high. Cotrimoxazole prophylaxis is given to all patients in WHO stage 3 or 4 or in those with any WHO stage and CD4 < 350 cells/mm^3 to prevent PCP. CPT is continued until the patient is clinically stable on ART at least one year and CD4 >350 cell/mm^3.

5.1.3. Toxoplasmosis

Toxoplasma gondii is a protozoan; primary infection is from eating undercooked meat which contains tissue cysts or ingestion of oocysts excreted in cats' feces. This commonly causes asymptomatic infection in immunocompetent hosts. In HIV patients with CD4 count <100/mm3 it usually causes cerebral abscesses due to reactivation of latent cyst in the brain. The usual clinical presentation is with fever, headache, confusion and/or focal neurological deficits. Toxoplasma IgG, IgM antibodies are not of help in diagnosis. Toxoplasma IgG antibodies are present in >50% of the population without any symptoms. The presumptive diagnosis is based on CNS imaging – CT or MRI. Typical features are 2 or more ring enhancing lesions with intravenous contrast. Most patients respond very well to treatment with clinical and radiological improvement in 2 weeks or less which is diagnostic. Failure to respond should prompt the consideration of alternative diagnosis especially tuberculoma, brain abscess or primary CNS lymphoma. In resource limited situations, CNS imaging is unavailable and in such situations treatment can be tried on clinical suspicion especially with the onset of focal neurological signs and look for clinical response to treatment.

Initial treatment is with Pyrimethamine 200 mg oral for one day then 50-75 mg per day plus Sulphadiazine 1000-1500 mg 6 hourly per day plus Leucovorin 10-25 mg oral/day for 6 weeks. Co-trimoxazole 960 mg OD will be followed as secondary prophylaxis. The higher dose is for those weighing >60kg; Leucovorin (folinic acid, not folic acid) is necessary to prevent bone marrow suppression due to Pyrimethamine.

The alternatives are Pyrimethamine plus Clindamycin 600 mg every 6 hours or Atovaquone 1500 mg BD with food.

5.1.4. Cryptococcosis in HIV

Cryptococcus neoformans, a yeast usually present in soil, bird droppings and moldy air, usually enters the body through inhalation. There may be fungal pneumonitis but it is usually subclinical. The usual diagnosis is subacute meningitis with fever and headache. The headache becomes more and more severe and becomes unrelentless and unresponsive to analgesics if the condition is not diagnosed. The headache is described as splitting and excruciating and is a very prominent symptom unlike any other headache. Features of increased intracranial pressure then develop. Cryptococcal meningitis usually occurs at CD4 count < 100/mm^3, usually at CD4 < 50/mm^3. Signs of meningeal irritation may be absent because of severe immunosuppression. Serum cryptococcal antigen is positive in >95% of cases, the diagnosis can be easily made from CSF stained with India ink which will show yeast cells with characteristic thick walls. Cryptococcal meningitis in HIV is associated with a high mortality and failure to manage elevated intracranial pressure is the most common cause.

Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 count <100 cells/mm3. Fluconazole 800 mg/day for two weeks, then 400 mg/day for eight weeks and continued maintenance with fluconazole 200 mg/day. Maintenance treatment should continue until person is stable on ART with CD4 cell count >200 cells/mm3.

When cryptococcal antigen screening is not available, fluconazole primary prophylaxis can be considered for adults and adolescents living with HIV who have a CD4 count <100 cells/mm3.

In HIV-infected adults receiving amphotericin B–containing regimens for treatment of cryptococcal disease, a minimum package of toxicity prevention, monitoring and management is recommended to minimize the serious amphotericin B–related toxicities of hypokalaemia and nephrotoxicity.

Immediate ART initiation is not recommended in HIV-infected patients with cryptococcal meningitis due to the high risk of IRIS, which may be life-threatening.

ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy, and within 4-6weeks of induction and consolidation treatment with Amphotericin containing regimen.

Prevention and Screening

Screening for cryptococcal antigen is the optimal approach for guiding resources in a public health approach and is the preferred approach for identifying infection when managing people presenting with advanced HIV disease.

Recommendations: Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 cell count < 100 cells/ mm3 and may be considered at a higher CD4 cell count threshold of < 200 cells/ mm3.

All people living with HIV with a positive cryptococcal antigen result on screening should be carefully evaluated for signs and symptoms of meningitis and undergo a lumbar puncture if feasible with CSF examination and CSF cryptococcal antigen assay (or India ink if cryptococcal antigen testing is unavailable) to exclude active cryptococcal disease.

Screening and primary prophylaxis are not recommended for children younger than 10 years without symptoms of cryptococcal disease is not generally recommended, since children have a low prevalence of cryptococcal disease. However, if a child has signs and symptoms of cryptococcal meningitis, then diagnostic testing using serum cryptococcal antigen should be offered. If serum cryptococcal antigen is positive, then diagnostic testing using CSF cryptococcal antigen should be offered if lumbar puncture is available.

Diagnosis of cryptococcal meningitis:

For adults, adolescents and children living with HIV suspected of having a first episode of cryptococcal meningitis, prompt lumbar puncture with measurement of cerebrospinal fluid (CSF) opening pressure and rapid cryptococcal antigen assay is recommended as the preferred diagnostic approach.

A. In settings with ready access to and no contraindication for lumbar puncture:

i. If both access to a cryptococcal antigen assay (either lateral flow assay or latex agglutination assay) and rapid results (less than 24 hours) are available: lumbar puncture with rapid CSF cryptococcal antigen assay is the preferred diagnostic approach.

ii. If access to a cryptococcal antigen assay is not available and/or rapid results are not available: lumbar puncture with CSF India ink test examination is the preferred diagnostic approach.

B. In settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated:

i. If both access to a cryptococcal antigen assay and rapid results (less than 24 hours) are available: rapid serum, plasma or whole-blood cryptococcal antigen assays are the preferred diagnostic approaches.

ii. If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured: prompt referral for further investigation and treatment as appropriate.

Table 24: Diagnosis of cryptococcosis

Summary of diagnostic approach	Lumbar puncture available	No lumbar puncture available or contraindicated
Rapid cryptococcal antigen test available	**CSF cryptococcal antigen (preferably lateral flow assay)**	**Serum, plasma or whole blood cryptococcal antigen (preferably lateral flow assay or latex agglutination assay), treat immediately and refer for further investigation**
No rapid cryptococcal antigen test available	**CSF India ink**	**Prompt referral for further investigation**

Treatment of Cryptococcal meningitis:

Induction:

The preferred induction regimen for adults, adolescents and children is a single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1200 mg/daily for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).

One of the following treatments can be used as alternative if liposomal amphotericin B and/or flucytosine are not available:

- Two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily
- a short-course (one-week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day), followed by 1 week of fluconazole (1200 mg/day for adults, 12 mg/kg/day for children and adolescents, up to a maximum dose of 800mg daily)
- Two weeks of fluconazole (1200 mg daily, 12 mg/kg/day for children and adolescents) + flucytosine (100 mg/kg/day, divided into four doses per day

Consolidation:

Fluconazole (400–800 mg daily, 6–12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily) is recommended for the consolidation phase for 8 weeks following the induction phase.

Maintenance (or secondary prophylaxis):

Fluconazole (200 mg daily, 6 mg/kg/day for adolescents and children) is recommended for the maintenance phase

Note: a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management can be provided to minimize treatment toxicity during induction phase with Amphotericin B containing regimens.

Using adjunctive systemic corticosteroids in treating cryptococcal meningitis:

Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended in treating HIV associated cryptococcal meningitis among adults, adolescents and children.

Table 25: Treatment of cryptococcal meningitis

Regimen	**Induction (2 weeks)**		**Consolidation (8 weeks)**	**Maintenance (1 year)**
	Week 1	Week 2		
Preferred regimen	a single high dose (10 mg/kg) of liposomal Amphotericin B + PO Flucytosine (100 mg/kg per day divided into four doses per day) + PO Fluconazole (Adult:1200 mg daily; Children/adol: 12 mg/kg/day up to 800mg daily)		PO Fluconazole (Adult: 800 mg daily; Children/Adol: 6-12 mg/kg/day up to 800mg daily)	PO Fluconazole (Adult: 200 mg daily; Children/Adol:6 mg/kg/day)

Alternative regimens	If liposomal amphotericin is not available:	IV Amphotericin B (1 mg/kg/day) + PO Flucytosine (100 mg/kg/day, divided into four doses)	PO Fluconazole (Adult:1200 mg daily; Children/adol: 12 mg/kg/day up to 800mg daily)		
	If no amphotericin formulation is available:	PO Fluconazole (Adult:1200 mg daily; Children/adol: 12 mg/kg/day up to 800mg daily) + PO Flucytosine (100 mg/kg/day, divided into four doses)			
	If flucytosine is not available:	IV Liposomal Amphotericin B (3-4 mg/kg/day) + PO Fluconazole (Adult:1200 mg daily; Children/adol: 12 mg/kg/day up to 800mg daily)			
	If liposomal amphotericin B and flucytosine are not available:	IV Amphotericin B deoxycholate (1 mg/kg/day) +			

		PO Fluconazole (Adult:1200 mg daily; Children/adol: 12 mg/kg/day up to 800mg daily)		

Preventing, Monitoring and managing amphotericin B toxicity:

Safe administration of amphotericin B should be given priority and may require referral to a centre with access to a minimum package of preventing, monitoring and managing toxicity. A minimum package of preventing, monitoring and managing toxicity should be provided to minimize the serious types of amphotericin B–related toxicity, especially hypokalaemia, nephrotoxicity and anaemia

Table 26: Preventing, Monitoring and managing amphotericin B toxicity

Pre-emptive hydration and electrolyte supplementation	
Adults and adolescents	One litre of normal saline solution with 20 mEq of potassium chloride (KCl) over two hours before each controlled infusion of amphotericin B and one to two 8-mEq KCl tablets orally twice daily. An additional 8-mEq KCl tablet twice daily may be added during the second week. If available, magnesium supplementation should also be provided (two 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily, or magnesium chloride 4 mEq twice daily).
Monitoring (adults, adolescents and children)	
Serum potassium	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Serum creatinine	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Haemoglobin	Baseline and weekly
Hypokalaemia	If hypokalaemia is significant (K <3.3 mol/l), increase potassium supplementation to 40 mEq KCl by intravenous infusion and/or one to two 8-mEq KCl tablets orally three times daily. Monitor potassium daily.
Elevated creatinine	If creatinine increase s by ≥2 fold from the baseline value, increase pre-hydration to 1 Litre every 8 hours and consider temporarily omitting a dose of amphotericin B. Once creatinine improves, restart amphotericin B at 0.7 mg/kg/day and consider alternate-day amphotericin B. If creatinine continues to rise, consider discontinuing amphotericin B and continuing with fluconazole at 1200 mg/day, especially if seven doses of

	amphotericin have been received. Consider fluconazole dose adjustment if significant renal impairment. Monitor creatinine daily.
Severe Anaemia	Transfusion should be undertaken if possible for severe amphotericin B–related anaemia (anaemia may also be a reason to discontinue amphotericin B prematurely in the second week of a planned two-week induction course of amphotericin B with fluconazole)
Note: • Potassium replacement should not be given to people with pre-existing renal impairment or hyperkalaemia. • Careful attention should be given to monitoring of intake and output of fluid and daily weight, especially among children. • Flucytosine – because of concerns about bone marrow suppression, regular monitoring of full blood counts should be considered. • The incidence of renal dysfunction and electrolyte disturbance is much less with liposomal amphotericin preparations, but renal function and electrolytes still need to be monitored.	

Monitoring for and managing raised intracranial pressure

Monitoring for raised intracranial pressure

Adults, adolescents and children living with HIV with suspected cryptococcal meningitis should have an initial lumbar puncture and an early repeat lumbar puncture with measurement of CSF opening pressure to assess for raised intracranial pressure regardless of the presence of symptoms or signs of raised intracranial pressure.

Common symptoms and signs of raised intracranial pressure:

Symptoms

- Headache
- Nausea with or without vomiting
- Changes in vision or hearing (such as double vision, blindness or deafness) Signs
- Change in mental status (ranging from confusion to lethargy to coma)
- Papilloedema
- Seizures
- Cranial nerve palsies (such as eye movement problems, particularly cranial nerve VI)
- Other focal neurological deficits

Managing raised intracranial pressure

- Therapeutic lumbar puncture: relieve pressure by draining a volume sufficient to reduce the CSF pressure to <20 cm H2O or halving the baseline pressure if extremely high
- The persistence or recurrence of symptoms or signs of raised intracranial pressure should determine the frequency of repeat therapeutic lumbar puncture. For people with persistent symptoms of raised intracranial pressure, repeat daily therapeutic lumbar puncture (with measurement of CSF opening pressure where available) and CSF drainage, if required, are recommended until the symptoms resolve or the opening pressure is normal for at least two days.

There is no data on the maximum volume of CSF that can be safely drained at one lumbar puncture. CSF opening pressure can be re-checked after every 10 ml removed. Usually 20–25 ml is enough to reduce the opening pressure sufficiently.

Monitoring treatment response

Regular and careful monitoring of clinical symptoms and signs is the most important and most feasible strategy to evaluate response to antifungal treatment.

Clinical response (including resolution or recurrence of fever, headache and symptoms or signs of raised intracranial pressure) should be assessed daily during the initial two weeks of induction therapy.

Persistent or recurrent symptoms

Many people with cryptococcal meningitis experience persistent (failing to resolve after two weeks of antifungal treatment) or recurrent symptoms (reappearing after initial resolution following treatment for an episode of cryptococcal meningitis). Among people receiving optimal induction therapy, the most common causes of recurrence of symptoms are raised intracranial pressure, nonadherence to fluconazole and immune reconstitution inflammatory syndrome.

Main causes of persistent and recurrent symptoms among people with cryptococcal meningitis

Persistent symptoms

- Raised intracranial pressure
- Treatment failure caused by suboptimal induction treatment
- Inadequate drug regimen, dose or duration
- Fluconazole drug resistance (rare)
- Other concomitant illness (such as viral, bacterial, or tuberculous meningitis)

Recurrent symptoms

- Raised intracranial pressure
- Treatment failure due to suboptimal induction, consolidation or maintenance treatment
- Inadequate drug regimen, dose or duration
- Failure to prescribe or to adhere to fluconazole consolidation or maintenance treatment
- Fluconazole drug resistance (rare)
- Cryptococcal immune reconstitution inflammatory syndrome (IRIS) following ART initiation
- Other concomitant illness (such as viral, bacterial or tuberculous meningitis)

Diagnostic approach to persistent or recurrent symptoms

- Review the patient history for evidence suggesting underlying treatment failure from (1) inadequate drug regimen, dose and duration, (2) poor adherence to fluconazole consolidation and maintenance treatment or (3) underlying fluconazole drug resistance among people with previous prolonged fluconazole therapy.
- Perform a lumbar puncture with measurement of the opening pressure to establish the presence or absence of raised intracranial pressure and CSF examination with other relevant investigations to exclude concomitant illnesses. Other diseases that can present with symptoms and signs similar to cryptococcal meningitis (such as viral, bacterial or tuberculous meningitis) should also be considered. Where possible, fluconazole susceptibility testing should be performed at a national reference laboratory when clinically suspected (culture-positive relapse despite fluconazole adherence).
- Consider paradoxical cryptococcal immune reconstitution inflammatory syndrome after excluding other causes of recurrent symptoms among people who have started ART.
- Send or resend CSF for prolonged fungal culture (two weeks of incubation).

Managing relapse

For people who present with cryptococcal meningitis relapse, the following steps are advised:

- Start or restart induction treatment according to the recommendations for induction treatment.
- Manage raised intracranial pressure with therapeutic lumbar puncture
- Reinforce adherence.
- If ART has not already been started, initiating ART after 4–6 weeks of optimal antifungal therapy is recommended.

Managing cryptococcal immune reconstitution inflammatory syndrome

Paradoxical cryptococcal immune reconstitution inflammatory syndrome occurs among 10–50% of people with cryptococcal disease initiating ART and is associated with high mortality. The median time to onset in reported cohort studies ranges from 1 to 10 months but typically is 3–12 weeks after initiating ART. Raised intracranial pressure is a common feature of cryptococcal immune reconstitution inflammatory syndrome and an important contributor to high mortality. Multiple repeat lumbar punctures may be necessary. Optimizing antifungal therapy and reinduction with an amphotericin-based regimen is important if sub-optimal antifungal treatment is considered to contribute to developing immune reconstitution inflammatory syndrome.

The following steps are advised for managing cryptococcal immune reconstitution inflammatory syndrome:

1. Continue ART.
2. Promptly manage raised intracranial pressure.
3. Optimize antifungal therapy and consider restarting induction therapy according to the recommendations for treatment.
4. Short-course oral steroid therapy, although not recommended for routine use in treating cryptococcal meningitis, may be considered if there is continued deterioration and/or the development of life-threatening complications (such as intracranial space-occupying lesions with mass effect or extracranial disease impinging on vital structures) despite the above measures.

Discontinuing fluconazole maintenance treatment (secondary prophylaxis)

Among adults, adolescents and children older than five years living with HIV who have successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuing antifungal maintenance treatment is advised based on the following criteria:

If HIV viral load monitoring is available:

The person is stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count ≥100 cells/mm3 and a fully suppressed viral load.

If HIV viral load monitoring is not available:

The person is stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count ≥200 cells/mm3.

For children living with HIV who are 2–5 years old and have successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuing antifungal treatment maintenance is recommended if the child is stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count percentage greater than 25% or an absolute count >750 cells/mm3.

Maintenance treatment for cryptococcal disease should not be discontinued for children younger than two years.

Secondary prophylaxis for cryptococcal disease should be restarted if the CD4 count drops to < 100 cells/ mm3 or less for adults, adolescents and children older than five years living with HIV (or CD4 cell count < 25% or ≤ 750 cells/ mm3 for children 2–5 years old) or if a WHO stage 4 clinical event occurs, regardless of age.

Timing of ART Initiation

Immediate ART initiation is not recommended among adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred 4–6 weeks from the initiation of antifungal treatment.

5.1.5. *Talaromyces marneffei* infection in HIV

Systemic infection with *Talaromyces marneffei* (previously known as *Penicillium marneffei* or penicilliosis) is a common OI in South-East Asia including Myanmar. Patients can present with fever, lymphadenopathy, hepatosplenomegaly and anaemia, but the most prominent feature is the skin lesion. Skin lesions usually start on the face and upper body and become generalized throughout the body. It is seen usually when the CD4 count is <100/mm^3. The lesions are papules with central umbilication.

The gold standard for clinical *T. marneffei* infection diagnosis is microscopic proof of the presence of the pathogen in tissues, the effective isolation of the fungus from patient specimens, or both. Diagnosis can be established by taking a smear by scraping the skin lesions which is then stained with Giemsa's stain. The fungus is dimorphic but exists in the yeast form in the human body. It is seen as oval yeast cells with a characteristic central septation.

The differential diagnosis is disseminated histoplasmosis and disseminated cryptococcosis which can also present with similar skin lesions and which are also treated similarly with antifungal agents. Skin lesions may resemble molluscum contagiosum (pox virus) but this causes skin lesions only without systemic involvement. Anemia and diarrhea are common in approximately half of patients with talaromycosis, as are hepatomegaly, lymphadenopathy, splenomegaly, and cough.

Untreated systemic talaromycosis can lead to death. Amphotericin B is the first-line antifungal medicine used for severe talaromycosis, followed by azoles such as itraconazole.

Severe infections have to be treated with intravenous amphotericin B deoxycholate at 0.6 to 0.7 mg/kg of body weight or, where available, 3 to 5 mg/kg of liposomal amphotericin B daily for 2 weeks followed by Itraconazole 200 mg BD for 10 weeks followed by secondary prophylaxis of 100 mg OD until ART increases the CD4 count to >100/mm^3. Relapse is common without secondary prophylaxis.

Less severe cases can be treated with oral Itraconazole alone which is preferred to Fluconazole.

5.1.6. Histoplasmosis

This form occurs mostly in hosts who are immunocompromised. Major risk factors include exposure to the fungus, AIDS with CD4 count of less than 150 cells/ mm3 and use of systemic corticosteroids. After initial exposure, *H. capsulatum* may remain dormant, and reactivation may occur years after initial exposure. Symptoms vary depending on duration of illness.

The usual presentation with disseminated disease is multi-organ disease with constitutional symptoms, fever, worsening cough, weight loss, malaise, and dyspnea. Gastrointestinal involvement may produce diarrhea and abdominal pain. Cardiac involvement resulting in valvular disease, cardiac insufficiency, or vegetations may produce dyspnea, peripheral edema, angina, and fever. CNS involvement may produce headache, visual and gait disturbances, confusion, seizures, altered consciousness, and neck stiffness or pain. Mucous membrane lesions are common in disseminated histoplasmosis.

Among people living with HIV, disseminated histoplasmosis should be diagnosed by detecting circulating Histoplasma antigens. Lateral flow assay–based rapid diagnostic tests for Histoplasma antigen provide additional opportunities to rapidly diagnose histoplasmosis at the point of care.

Induction therapy

Treating severe or moderately severe histoplasmosis among people living with HIV: liposomal amphotericin B, 3.0 mg/kg, for two weeks is recommended.

One day induction therapy with a single dose of 10 mg/kg of liposomal amphotericin B (the same dose used for cryptococcal meningitis) has recently been studied in AIDS-related histoplasmosis. One day induction with high dose liposomal amphotericin was found to be safe, cost-effective and associated with fever adverse events than other recommended. Although these encouraging results are yet to validated, clinicians should consider induction with a single high dose liposomal amphotericin for patients with disseminated histoplasmosis.

In settings where liposomal amphotericin B is unavailable, deoxycholate amphotericin B, 0.7– 1.0 mg/kg, is recommended for two weeks. As a good practice for people with renal failure, or at risk of renal injury, measures to prevent or treat toxicity are recommended. Induction therapy should be given for two weeks. Since deoxycholate amphotericin B may be associated with renal toxicity, therapy may need to be shorter than two weeks based on the clinical assessment of how the person responds to treatment. Involvement of the central nervous system may require extending induction therapy or increasing dosage. Response is seen within 1 week. 50% will have blood culture negative about 2-4 weeks after starting treatment.

Treating mild to moderate histoplasmosis among people living with HIV: itraconazole 200 mg three times daily for three days and then 200 mg twice daily is recommended.

Maintenance therapy

Itraconazole 200 mg twice daily for 12 months is recommended. Less than 12 months of therapy can be considered when the person is clinically stable, receiving antiretroviral therapy, has suppressed viral load, and the immune status has improved.

Antiretroviral therapy should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven.

5.1.7. Other conditions and opportunistic infections in HIV

Progressive Generalized Lymphadenopathy (PGL)

This may develop in 30-50% of patients with HIV. PGL involves more than two extra-inguinal lymph node areas, usually in the posterior triangle of neck and epitrochlear regions, measuring more than 1 cm in diameter. The nodes are not tender and are symmetrical. PGL does not involve the mediastinal or intra-abdominal lymph nodes and is not associated with fever or systemic symptoms. PGL is due to reactive hyperplasia in lymph nodes and regresses slowly as immunosuppression advances. The diagnosis is clinical. PGL has no prognostic significance. PGL should not be confused with tuberculous lymphadenopathy associated with HIV.

- PGL - seen in early stages, disappears as immunosuppression advances
- Tuberculosis – most commonly in late HIV with symptoms of fever, weight loss etc.
- Lymphomas – especially high-grade b-cell lymphoma, rapidly progressive and less common as cause of lymphadenopathy
- Bacterial infections – localized usually
- Fungal infections
- Kaposi's sarcoma – very uncommon in Myanmar

Herpes zoster

It is one of the early manifestations of immunosuppression; even though there is a risk at all strata of CD4 count it is usually seen when the CD4 count falls to $\leq$350/mm^3. Sometimes it can be multidermatomal. Diagnosis is clinical from the appearance of painful vesicular eruptions along the distribution of a dermatomal nerve. Herpes zoster involving the cornea can cause blindness and when the nasociliary branch of the 1st division of the fifth cranial nerve is involved, treatment should be prompt since there is a risk of corneal involvement. Early treatment with acyclovir 800 mg 5 times a day for 7 – 10 days is given. Analgesics may be required both for the acute pain and post-herpetic neuralgia. Herpes zoster may be seen as IRIS. Since zoster occurs before other opportunistic infections, a scar caused by herpes zoster should alert one to the diagnosis of HIV if another OI is suspected e.g. tuberculosis.

Seborrhoeic dermatitis

This presents as an erythematous scaly rash on the face especially on the eyebrows and along the sides of the nose, but is also present on the scalp, presternal and occasionally pubic areas. The yeast *Pityrosporum* can be recovered from the lesions. Ketoconazole 2% cream plus hydrocortisone 2% cream can be applied twice a day. Ketoconazole or Selenium sulphide shampoos can be also used.

Pruritic papular eruptions (PPE)

PPE is a very common condition seen when the CD4 count is < 200/mm^3. It is a cutaneous marker for immunosuppression and is very common in developing countries. It is a very intensely pruritic papular eruption in the exposed parts of the extremities and is thought to be due to an intense allergic reaction to insect bites (mosquitoes, bugs). Scratching produces hyperpigmentation and hyperkeratosis. Treatment is with anti-pruritic drugs. Local application of calamine lotion can be applied but in severe cases, steroid creams may be used to interrupt the vicious cycle of pruritus and scratching. Local steroids should not be used for prolonged periods since they may be absorbed. PPE can be a tell-tale sign in patients with HIV.

Scabies

Caused by the mite *Sarcoptes scabiei* (mite), it is not a sign of HIV infection but may be seen since it is a very common condition and should not be mistaken with PPE. There are intensely pruritic small red papules with burrow tracts, where the skin is thin so that they are characteristically found in the webs of the fingers and toes and in the genitalia region, axillae and breasts. They can also spread to other parts of the body if the infestation persists. The pruritus is characteristically more severe at night when the mite comes out and burrows under the skin to lay more eggs.

Scabies is not a sign of immunosuppression but scabies crostosus (crusted scabies or Norwegian scabies) is. In this condition because of severe immunosuppression, there is absent or minimal inflammatory response and hundreds of thousands of mites cause infestation of the skin with exudation of serum which becomes crusted.

Scabies is treated with permethrin 5% cream, lindane 1% or benzyl benzoate 25% emulsion. Repeated applications are necessary and household members should also be treated as it is infectious. Norwegian scabies is highly infectious and strict barrier precautions are necessary. In addition to the mentioned medications, keratolytic agents e.g. salicylic acid gel or urea creams are sometimes required.

Candidiasis

Thrush or oral candidiasis is the most commonly seen as white painless plaques on the buccal or pharyngeal mucosa that can be easily scraped off. In HIV patients it usually occurs when CD4 is < 250/mm^3 but it is also seen in non-HIV patients with the use of antibiotics, oral steroids, and in diabetes, malnutrition and cancer. Candidiasis can extend into the oesophagus usually as CD4 count further falls, causing painful dysphagia but candida esophagitis can also occur in the absence of oral candidiasis. In the less common erythematous or atrophic form, the tongue and oral mucosa becomes very red. Treatment is with nystatin 500,000 units solution gargled 4 times a day. Fluconazole orally 100 mg/day for 1 – 2 weeks is also quickly effective. Oral ketoconazole or Itraconazole are alternatives. With repeated use azole resistance may develop.

Oral leukoplakia

This is seen on the lateral surface of the tongue as vertical striations, believed to be due to Eb virus infection. It usually requires no treatment but oral acyclovir 400 mg 5 times daily may be used for florid cases.

Aphthous ulcers

Aphthous ulcers in the tongue or oral mucosa are commonly seen in HIV infection but may be also caused by HSV or CMV; sometimes they are drug induced. Minor ulcers < 1 cm usually heal by themselves but a large ulcer > 1 cm can be deep, painful, prolonged and interferes with eating. Triamcinolone paste can be used to relieve the pain; a tapering dose of prednisolone may be tried. Response to ART is very good.

Bacterial infections

Bacterial infections are common in people with HIV. Bacterial pneumonias may occur. Maxillary sinusitis is a known complication of HIV disease. Antibiotics are required.

Diarrhoea

Diarrhoea, intermittent or prolonged is a common complication. It is caused by common bacteria such as shigella, salmonella, *E.coli* and responds to antibiotics. It is also caused by protozoa like amoeba or giardia and responds very well to metronidazole.

TB intestine is one of the causes of chronic diarrhoea. It is chronic, and does not respond to antibiotics, usually used for diarrhoea, stool amount is not copious and there may be associated abdominal pain. Presumptive diagnosis may be made from barium follow- through examination – there is coarsening of villi, flocculation of barium with strictures and dilatation of the small bowel, most noticeable in the ileum. Biopsy may be obtained by colonoscopy from the ileocecal junction but usually this will not be possible. The condition responds very well to anti-TB treatment.

Late in the course of disease prolonged watery diarrhoea not responsive to antibiotics is usually caused by *Cryptosporidium parvum*, a coccidian parasite, which is commonly present in the water and does not cause disease in normal persons. It can be diagnosed by the demonstration of oocysts in the stool stained with modified acid fast stain. Cryptosporidiosis can be treated with nitazoxamide 1 gm BD for 60 days which can be tried but the diarrhoea responds best to ART.

Cytomegalovirus (CMV)

CMV can cause pneumonitis, oesophagitis, enteritis, cholecystis and encephalitis in patients with HIV but an important complication is CMV retinitis which is usually seen in patients with CD4 count < 50/mm^3. There remains a significant burden of HIV-related cytomegalovirus retinitis in adults living in middle and low-income countries. It may be asymptomatic when the periphery of the retina is involved but it is an important cause of blindness when it spreads to the macula area. Diagnosis is mainly clinical with ophthalmoscopy which shows perivascular yellow-white retinal infiltrates with intra-retinal haemorrhages ("scrambled eggs and tomato ketchup" appearance). Valganciclovir, an oral medication, (900 mg BD for 21 days followed by maintenance 900mg OD daily) provides equivalent systematic treatment to intravenous ganciclovir, the gold standard the treatment of CMV retinitis.

Thrombocytopenic purpura

Thrombocytopenic purpura is one of the complications seen in HIV. It has been ascribed to immune complexes on platelets as well as to the effect of HIV on megakaryocytes. In cases with very low counts, IV IG as well as steroids have been tried; the conditions respond to ART.

HIV and malaria

In malaria endemic areas it has been observed that HIV increases the risk of malaria infection especially in patients with advanced HIV disease. It has been also observed that Cotrimoxazole prophylaxis of HIV infected with CD4 count $\leq$ 350/mm^3 can reduce the prevalence of malaria in the population. There is no evidence however that malaria has a significant effect on clinical progression of HIV.

HIV associated dementia or AIDS dementia complex

Dementia is a complication due to chronic encephalitis due to HIV. Cognitive, motor and behavioral dysfunctions are seen. Its incidence has fallen due to the early introduction of ART.

Wasting syndrome

In HIV wasting syndrome there is unintended loss of weight for >10% associated with fever and chronic diarrhoea lasting more than 30 days in the absence of an underlying cause other than HIV. It is an indication to start ART. Androgenic steroids and nutritional supplements can be used. Other more common causes of marked weight loss in HIV disease are due to OIs especially tuberculosis.

HIV related tumours or opportunistic tumours in HIV

Kaposi's sarcoma was one of the common AIDS defining conditions in western countries as well as in Africa but is very rare in south-east Asia. It is due to human herpes 8 virus (Kaposi sarcoma herpes virus) which causes vascular proliferation and tumour growth mainly in the skin causing coppery papular or nodular lesions but which also spreads to the lymph nodes and viscera. It has been treated with cytotoxic drugs but responds also to ART.

Lymphomas occur with an increased frequency of more than 100 times in people with HIV than in the general population, but overall it is found in less than 10% of cases of HIV disease. It is usually a manifestation of late disease but it is also related to increasing duration of HIV infection. Typical cases are high grade b-cell non-Hodgkin lymphomas. Lymph nodes that are more than 2 cm or progressively enlarging should be biopsied to get the diagnosis. It is difficult to manage especially because of the overlapping toxicities of chemotherapy and ART but improvements in prognosis have been seen. Lymphomas are best treated in a specialized centre.

Primary brain lymphoma is seen particularly in advanced HIV disease and carries a poor prognosis. Presentation is with focal or non-focal signs or with signs of increased intracranial pressure. CD4 count is usually < 50/mm^3. Diagnosis requires neuroimaging.

Cervical Cancer - Infection with the human papilloma virus (HPV) causing intraepithelial dysplasia of the cervix is more common in women infected with HIV and can lead to cervical intraepithelial neoplasia, eventually causing invasive cancer of the cervix.

5.2. Managing advanced HIV disease

Advanced HIV disease is defined as people living with HIV with CD4 cell count < 200 cells/ mm3 or a WHO stage 3 or 4 condition. Majority of patients with HIV in resource limited countries will still present with late HIV disease with CD4 counts < 100/mm^3 or <50/mm^3. They will usually have fever > 1 month, diarrhoea off and on >1 month, weight loss > 10%, oral thrush, anaemia with or without lymphadenopathy. There are many causes of fever. Common conditions like pneumonia, typhoid, malaria, urinary tract infections and sepsis have to be excluded. Empirical antibiotics (not quinolones which are active in TB) can be tried. Then, other organisms like *Mycobacterium*

tuberculosis, *Cryptococcus neoformans*, *Pneumocystis jirovecii*, *Toxoplasma gondii* and *Salmonella sp.* bacteraemia will have to be considered. The most common cause is usually tuberculosis. Lymphadenopathy in the neck, axilla, mediastinum and intra-abdominal region associated with fever, weight loss and systemic symptoms is most commonly due to TB. The chest X-ray appearance may or may not be suggestive of TB.

Diarrhoea usually responds to the measures already mentioned. For weight loss, nutritional supplements are given but with response to treatment of OIs followed by ART, weight gain is usually obtained and sometimes this is several kgs. Weight gain is a good indicator of response to treatment. Anaemia is present in most cases of advanced HIV disease. While it may be contributed by nutritional deficiencies which results from oral candidiasis, diarrhoea or poor appetite, it is also due to anaemia of chronic disease. With response to treatment of OIs and ART, the anaemia also improves most of the time. Severe anaemia excludes the use of AZT which itself could also cause significant lowering of haemoglobin.

People living with HIV who are seriously ill need access to screening and diagnostic tests for certain opportunistic infections. Some tests are initial screening tests that should be offered to everyone with advanced HIV disease (criteria for screening are set out below), and some are diagnostic tests that should only be offered to people if there is clinical indication (signs and symptoms of the relevant disease), in a prespecified subgroup, or following a positive screening test. The screening tests mentioned below can be used both for screening and as a diagnostic test depending on the population investigated and clinical presentation. Consideration should be given to making these tests available at all levels of the health system where people might benefit from them. It is important to make these tests available at places where seriously ill people might be evaluated or triaged (such as hospital emergency departments) that are not typically considered part of HIV services and ensuring availability on evenings and weekends.

Cryptococcal disease: cryptococcal antigen

Adults and adolescents with advanced HIV disease should receive serum cryptococcal antigen screening, followed by cryptococcal antigen testing in cerebrospinal fluid (CSF) if the serum cryptococcal antigen test is positive. The 2022 WHO guidelines on diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV outline screening and diagnostic algorithms depending on availability of diagnostic tests and lumbar puncture.

Cryptococcal antigen screening among children younger than 10 years without symptoms of cryptococcal disease is not generally recommended, since children have a low prevalence of cryptococcal disease. However, if a child has signs and symptoms of cryptococcal meningitis, then diagnostic testing using serum cryptococcal antigen should be offered. If serum cryptococcal antigen is positive, then diagnostic testing using CSF cryptococcal antigen should be offered if lumbar puncture is available.

TB disease

WHO recommends that all people living with HIV be screened for TB and offers several methods. Screening can be conducted with the WHO-recommended four-symptom screen, which includes screening for any one of cough, fever, weight loss and night sweats. Screening can also be conducted with chest X-ray (with or without computer-aided detection) or sputum recommended molecular diagnostic test for TB. The choice of screening strategy depends on the characteristics of the population being screened and the resources available for screening and further diagnostic testing. Everyone with a positive screening test (i.e. everyone with presumptive TB) should have a recommended sputum TB molecular test. Adults and adolescents admitted to medical wards where the TB prevalence is estimated to be >10% should be tested with a recommended sputum TB molecular test, regardless of symptoms.

Testing using urine LF-LAM should be performed irrespective of TB symptoms in adults, adolescents and children who are seriously ill, or have clinical Stage 3 or 4 disease or with CD4 count < 100 cells/mm3 among outpatients. For programmatic reasons, some national guidelines include testing all people with Advanced HIV disease with urine LF-LAM, irrespective of setting. Extrapulmonary or disseminated TB with or without pulmonary TB occurs commonly among people with advanced HIV disease, and testing non-sputum samples with a recommended TB molecular test and testing using urine LF-LAM is important. Depending on the clinical scenario, other samples for molecular testing include: CSF (for TB meningitis), lymph node aspirates or biopsy (for TB lymphadenitis), urine (for genitourinary TB), blood (for disseminated TB) and lymph node, pleural, peritoneal, pericardial and synovial fluids for respective clinical indications. For children with signs and symptoms of pulmonary or extrapulmonary TB, recommended TB molecular tests should be performed on sputum, nasopharyngeal aspirate, gastric aspirate, stool, blood or urine.

Other disease-specific tests

If histoplasmosis is clinically suspected, WHO recommends diagnostic testing using antigen detection assays. Histoplasmosis is reported in certain countries of Asia, including Myanmar.

In areas of geographical risk for malaria, early diagnosis is recommended, using microscopy or a rapid diagnostic test. Depending on clinical symptoms, local epidemiology and laboratory capacity, specific tests could be offered for

other invasive fungal infections such as talaromycosis, and other diseases such as visceral leishmaniasis (i.e. migrants coming from visceral leishmaniasis endemic regions to Myanmar).

If a person is referred to hospital or a centre with diagnostic laboratory on site, or if additional rapid tests are available, it might be appropriate to take the opportunity to offer screening for chronic conditions or other relevant diseases – such as sexual health screening or screening for syphilis and chronic viral hepatitis B and C.

Table **27**: Summary of recommended disease-specific tests for screening and diagnosis of opportunistic infections in advanced HIV disease

Offer as screening tests		
Test	Use	Clinical considerations
Serum cryptococcal antigen test	Adults and adolescents with CD4 count <100 cells/mm3 [a] Adults, adolescents and children with signs and symptoms of cryptococcal meningitis	If serum cryptococcal antigen is positive, proceed to lumbar puncture and CSF cryptococcal antigen testing where available
TB screening procedures or tests	Adults, adolescents and children living with HIV should be screened for TB at every health-care visit. Screening can be performed using any of the following individually or in combination: • four symptom screen followed by • chest X-ray with or without computer-aided detection • recommended sputum TB molecular tests [b]	All screened positive individuals should have a diagnostic test (see below). If an individual is screened positive with a TB molecular test, see the TB screening guidelines for further guidance.

[a]WHO does not recommend systematic serum cryptococcal antigen screening for children due to low prevalence of cryptococcal disease. Serum cryptococcal antigen should be used only if cryptococcal disease is clinically suspected.
[b]Sputum TB molecular tests should be used for all people living with HIV admitted to hospital where TB prevalence >10%

Offer as diagnostic tests to people with signs and symptoms or following a positive screening test or prespecified subpopulations		
Test	Use	Clinical consideration
Urine LF-LAM test for TB	Adults, adolescents and children with signs and symptoms of TB (pulmonary and/or extrapulmonary) Adults, adolescents and children who are seriously ill or who have clinical stage 3 or 4 disease. Asymptomatic adults, adolescents and children in inpatient settings with CD4 <200 cells/mm3 and in outpatient settings of CD4 <100 cells/mm3	A negative urine LAM test does not rule out TB If LAM is positive, TB treatment should be started. Further sputum or extrapulmonary TB tests should be requested in addition, since urine LAM cannot detect drug resistance
TB molecular test	Screen-positive individuals: presumptive pulmonary TB Adults and adolescents: sputum or other respiratory samples Children: sputum, nasopharyngeal aspirate, gastric aspirate or stool Presumptive extrapulmonary TB: All individuals: Blood, urine, CSF, lymph node aspirates, lymph node biopsy, pleural, peritoneal, pericardial, synovial fluids as indicted by symptoms and likely site of TB.	Non-sputum and child samples vary in mycobacterial load and may be negative in some people who truly have TB
CSF cryptococcal antigen test	Adults, adolescents and children with signs and symptoms of cryptococcal meningitis Adults and adolescents and children who have a positive serum cryptococcal antigen	If lumbar puncture is available and no contraindication to lumbar puncture For alternative diagnostic and treatment algorithms where lumbar puncture is not available, see the cryptococcal disease guidelines
Histoplasma antigen test	Adults, adolescents and children with suspected histoplasmosis	Histoplasmosis is highly endemic in certain regions
Malaria rapid diagnostic test	All adults, adolescents and children with suspected malaria, including all people in malaria endemic area with fever	For children younger than five years, practical algorithms from Integrated Management of Childhood illness should be used
COVID-19 testing	Adults, adolescents and children for whom COVID-19 is clinically suspected	This is a rapidly changing area.

The package of care for people with advanced HIV disease includes prophylaxis and pre-emptive treatment. Prophylaxis and pre-emptive treatment should be started as soon as possible and before hospital discharge (for inpatients), if possible.

Table 28: prophylaxis and pre-emptive treatment for advanced HIV disease.

	Population	Drug Regimen	Clinical consideration
TB preventive therapy	Adults, adolescents and children who are unlikely to have active TB disease	A variety of different TB preventive therapy regimens are recommended; see the TB prevention guidelines	Consider giving pyridoxine alongside TB preventive therapy to reduce the risk of peripheral neuropathy
Cryptococcosis pre-emptive treatment	Adults and adolescents with serum cryptococcal antigen test positive but CSF cryptococcal antigen negative (Where cryptococcal antigen screening is not available, can be considered for adults and adolescents with CD4 cell count < 100mm^3.)	Fluconazole 800 mg/day for two weeks, then 400 mg/day for eight weeks and continued maintenance with fluconazole 200 mg/day	Maintenance treatment should continue until person is stable on ART with CD4 cell count >200 cells/mm^3
Co-trimoxazole prophylaxis	Adults and adolescents with CD4 cell count <350 cells/mm^3, consider for all in areas where malaria and/or severe bacterial infections are highly prevalent All children.	Adult dose is 960 mg of cotrimoxazole once per day; doses for infant and children as per table 35 in annex	Prophylaxis against bacterial infections, malaria and *P. jirovecii* pneumonia

Immune Reconstitution Inflammatory Syndrome (IRIS)

After starting ART especially in late HIV disease, some patients experience clinical deterioration. This is because the body's immune system has recovered and starts to react to infections or antigens to which it was not reacting before. Regulatory T cells may not expand at the same rate as the antigen-specific effector cells, resulting in dysregulated immune activation and a "cytokine storm".

The reaction can be sometimes very severe and can cause significant morbidity and mortality if it is not recognized. The reaction is towards viable or dead microbial antigens and sometimes host antigens. The antigenic load of the OI is also important. IRIS is most commonly seen with TB, cryptococcal meningitis, CMV (which could cause blindness after starting ART), hepatitis B, hepatitis C, herpes zoster and other conditions.
In resource poor countries, *Mycobacterium tuberculosis* and *Cryptococcus neoformans* are the most significant pathogens causing IRIS, because the former causes substantial morbidity and the latter causes substantial mortality.

IRIS has been described in one fifth of cases after starting ART in late cases. This underscores the importance of diagnosing and treating HIV earlier. TB IRIS is associated with fever, enlargement of lymph nodes sometimes with liquefactive necrosis, worsening pulmonary infiltrates, pleural or pericardial effusion, expanding CNS tuberculomas or appearance of TB meningitis. In managing IRIS, treatment for OI as well as ART is continued.
IRIS may be associated with paradoxical exacerbation of the OI that is being diagnosed and treated usually within 3 months of ART initiation, re-initiation, or regimen change because of treatment failure. IRIS may also unmask an OI which was not recognized because it remained silent with advanced immunosuppression. Autoimmune diseases sometimes appear after starting ART and this is known as autoimmune IRIS (thyrotoxicosis, SLE, sarcoidosis and other autoimmune disorders have been described after starting ART). IRIS usually starts within 2 to 3 months of starting ART but it may also be delayed for many months. Risk factors for IRIS include:

- Very low CD4 count at start of ART
- Very high VL and very rapid fall in VL after ART
- Short interval between OI treatment and ART

For this reason a brief delay is advisable in starting ART after the treatment of OI is started to control the OI. This delay may be 2 to 8 weeks in tuberculosis depending on the situation. In late disease with very low CD4 counts usually < 50/mm^3 delaying ART too long could be dangerous because of the risk of disease progression and this has to be balanced against the risk of IRIS.
HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm^3) should receive ART within the first two weeks of initiating TB treatment. Caution is needed in people living with HIV with TB meningitis, as immediate ART is significantly associated with more severe adverse events.

Immediate ART initiation is not recommended in HIV-infected patients with cryptococcal meningitis due to the high risk of IRIS that may be life threatening IRIS. ART should not be started within first 1-2 weeks of Amphotericin initiation. It can be started within 4-6 weeks of induction and consolidation treatment with amphotericin B–containing regimens until there is evidence of a sustained clinical response to antifungal therapy.

When the underlying condition has no specific treatment however ART can be started immediately. Cryptosporidiosis, HIV associated dementia and progressive multifocal leukoencephalopathy are examples where ART is indicated immediately. The excessive inflammatory response is controlled with NSAIDs or steroids if necessary which are gradually tapered according to symptoms. It may be necessary to stop ART only very rarely in life-threatening IRIS. Differential diagnosis of IRIS includes –

-Treatment failure of the OI (e.g. MDR TB)

-Adverse drug reaction

-A new OI (which is unmasking IRIS)

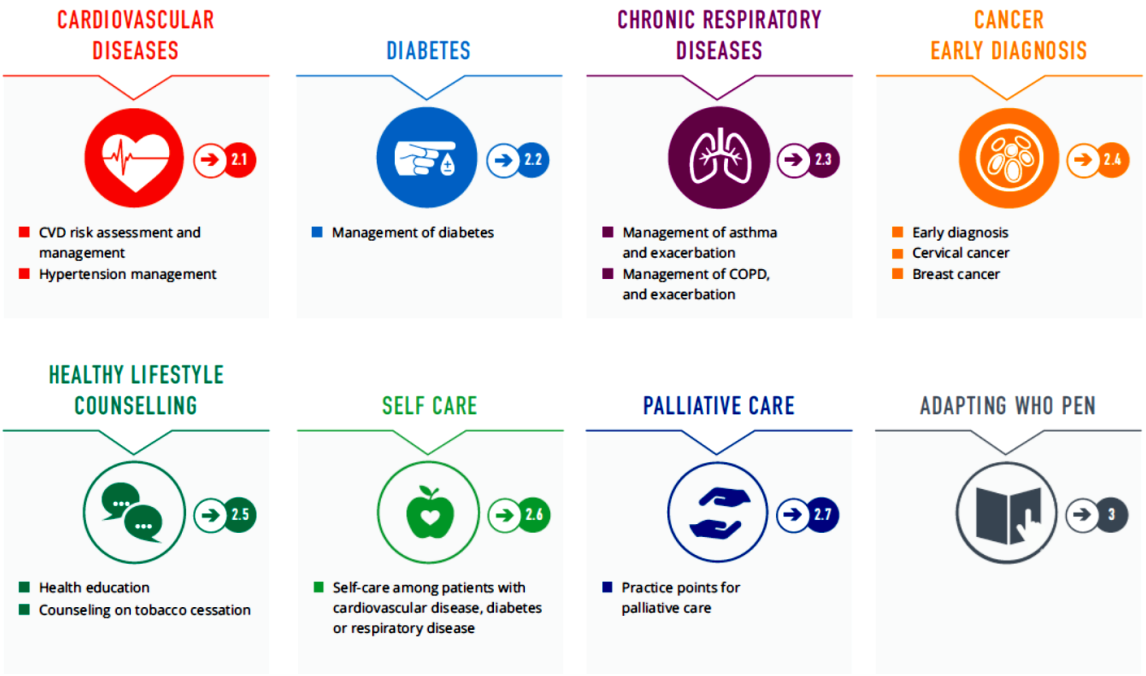
5.3. Prevention, screening and management of other comorbidities

5.3.1. Assessment and management of non-communicable diseases

People living with HIV are at risk of developing a range of non-communicable diseases (NCDs) compared to general population, including cardiovascular disease (CVD), hypertension, diabetes, chronic obstructive pulmonary disease (COPD), kidney diseases and cancers. The intersection of HIV and NCDs is strongly influenced by increasing survival due to effective ART, lifestyle factors, long-term complication of ART and other disease conditions associated with ageing.

Integrating interventions, such as nutrition assessment, dietary counselling and support, smoking cessation, exercise promotion, blood pressure monitoring and –where possible- cholesterol management as part of HIV care can help to reduce the risks of NCDs among people with HIV and improve HIV treatment outcomes. WHO has defined a package of essential NCD interventions (WHO PEN) and more information and additional guidance on management of NCDs is available on WHO PEN.

Strategies for the preventions and risk reduction of cardiovascular diseases by addressing modifiable factors such as high blood pressure, smoking, obesity, unhealthy diet and lack of physical activities should be applied to all people living with HIV/AIDS.



5.3.2. Assessment and management of depression

Systematic reviews showed that depression is one of the most prevalent mental health comorbidities in people living with HIV. A systematic review conducted in 2015 reported that depression prevalence rates as high as 80% among people with HIV. It is less likely to achieve optimal treatment adherence among people living with HIV who have depression. Health care providers often overlook and unrecognized depression.

Assessment and management of depression should be included in the package of HIV care services for all individuals living with HIV.

5.3.3. Drug use and drug use disorders

People living with HIV who use drugs may experience a range of disorders related to drug use, including drug dependence, intoxication, withdrawal and overdose. Injecting drug use is associated infections including viral

hepatitis, TB, septicaemia and bacterial endocarditis in addition to HIV. WHO, UNODC and UNAIDS recommend a comprehensive package of nine interventions for HIV prevention, treatment and care for people who inject drugs as followed.

- Needles and syringe programmes
- Opioid agonist maintenance therapy (OAMT)
- HIV testing and counselling
- ART
- Preventing and treating STIs
- Condom programmes
- Targeted behavioral change communication
- Preventing and treating viral hepatitis
- preventing, diagnosis and treating TB

5.3.4. Hepatitis B and C infection

Viral hepatitis is an increasing cause of morbidity and mortality among people living with HIV in some regions of the world, including among people on ART. A comprehensive approach includes prevention, HBV and HCV testing, hepatitis B vaccination and treatment and care for people with HIV who are coinfected with hepatitis B and/or hepatitis C.

HIV coinfection has a profound impact on the course of HBV infection, including more rapid progression to cirrhosis and hepatocellular carcinoma, higher liver related mortality and decreased treatment response. The risks of HBV infection may be higher in HIV infected adults. All people newly diagnosed with HIV should therefore be screened for hepatitis B surface antigen (HBsAg).

The recommended NRTI drugs for ART- TDF with 3TC or FTC – are active against HBV. Treatment of HIV-HBV coinfection without the use of TDF in the regimen may lead to flares of hepatitis due to ART-associated immune reconstitution. Treatment discontinuation especially of TDF, has been associated with HBV reactivation. If ARV drugs need to be changed because of HIV drug resistance or toxicity, then TDF with 3TC or FTC should be continued together with the new ARV drugs.

Hepatitis C virus related liver disease progresses more rapidly in people coinfected with HIV. Therefore, treatment of HCV infection is a priority for people with HIV/HCV coinfection. Among the coinfected patients, treatment

response rates are lower and the risk of potential toxicities is higher. In general, clinical stabilization of HIV disease with ART is advisable prior to starting treatment for HCV. The decision to start ART among HCV coinfected HIV patients should be the same as non-coinfected people.

Among the co-infected patients, treatment response rates might be lower and the risk of potential toxicities is higher. In general, clinical stabilization of HIV disease with ART is advisable prior to starting treatment for HCV. In a person taking an EFV based regimen, if a combination of Sofosbuvir and Daclastavir are used, EFV can lower the plasma level of Daclastavir. The dose of Daclastavir needs to be increased to 90mg/day. There is no need for Sofosbuvir dose adjustment. In persons taking an EFV based regimen, if a combination of Sofosbuvir and Velpatasvir are to be used, the EFV needs to be switched to either DTG or PI, before starting HCV treatment. In order to avoid switching only one drug in a failing regimen, the HIV viral load needs to be checked first.

If the viral load is undetectable, EFV can be substituted with DTG or PI. If viral load is high, the patient should be considered as having ARV treatment failure. The whole regimen will need to be changed. After completion of the concomitant treatment, switching back to the previous ARVs can be considered in patients with no treatment failure. But it should wait for two weeks before switching back to previous ARV combination, to avoid DDIs because of long half-life of some drugs.

5.3.5. Sexually transmitted infections (STIs)

The epidemiological synergy between HIV and STIs is well established, and they frequently coexist. Most STIs are asymptomatic especially among women. Even asymptomatic STIs can cause complications, be transmitted to sexual partners and enhance HIV transmission. It is necessary to appropriately screen, diagnose and treat STIs, especially among the most vulnerable populations and people living with HIV. STI services should be an important part of comprehensive HIV care among adults and adolescents.

5.3.6. Cervical Cancer

Cervical cancer is a preventable disease and is curable if diagnosed and treated early. Women living with HIV have a higher risk of pre-cancer and invasive cervical cancer. Cervical cancer screening leads to early detection of precancerous and cancerous cervical lesions that will prevent serious morbidity and mortality. Invasive cervical cancer is also considered a WHO Clinical Stage 4 AIDS defining illness.

All HIV+ women should be screened for cervical cancer using HPV DNA detection in a screen, triage and treat approach starting at the age of 25 years with regular screening every 3 to 5 years. Until HPV DNA testing becomes operational, quality-assured cytology should be continued as the primary screening test. Where HPV DNA testing is not yet operational, WHO suggests a regular screening interval of every 3 years when using visual inspection of the cervix with acetic acid (VIA) or cytology as the primary screening test among both the general population of women and women living with HIV.

WHO suggests that women living with HIV who have screened positive on an HPV DNA primary screening test and then negative on a triage test, are retested with HPV DNA testing at 12 months and, if negative, move to the recommended regular screening interval.

After the age of 50 years, WHO suggests screening is stopped after two consecutive negative screening results consistent with the recommended regular screening intervals among both the general population of women and women living with HIV.

Implementing screening for cervical cancer is also important as a means to improve the overall sexual health of HIV+ women.

Routine HPV-vaccination for HIV+ girls and women at age 9-11 years or through age 26 years (if not vaccinated younger). A three-dose schedule (0, 1–2 and 6 months) should be used for all girls and women living with HIV regardless of whether they are receiving ART.

5.3.7. Nutritional care and support

Low energy intake combined with increased energy demands due to HIV infection and related infections may lead to HIV related weight loss and wasting. Nutritional assessment, counselling and support should be an integral component of HIV care. Malnourish HIV patients may require in addition to ART. Weight loss or failure to regain or maintain a healthy weight at any stage of HIV infection and/or on ART should trigger further assessment.

In children living with HIV, nutritional assessment is essential to identify malnutrition and growth faltering early. Infants and children should undergo initial nutritional assessment and then be weighted and have height measured at each visit, and monitored with the reference to WHO or national growth curves. Growth monitoring should be integrated into the assessment of ART response.

5.3.8. Vaccines for people living with HIV

Immunizations are an important component of the HIV care package in many international guidelines, and people living with HIV should be assessed for eligibility for vaccination at all stages of care .

- Vaccines usually have better safety and efficacy among people living with HIV who are receiving ART and those without significant immunosuppression.
- People with more severe immunosuppression may be at higher risk of complications from some live attenuated vaccines.
- Inactivated vaccines, although safe, can be less effective among these people and may require supplemental doses or revaccination after ART-induced immune reconstitution.
- In general, HIV-exposed infants, children and adolescents with HIV should receive all vaccines under routine vaccination according to recommended national immunization schedules.

HIV-specific guidance for selected vaccines from WHO vaccine position papers

BCG: If people living with HIV, including children, are receiving ART, are clinically well and immunologically stable (CD4% >25% for children five years old), they should be vaccinated with BCG. Neonates born to women of unknown HIV status should be vaccinated since the benefits of BCG vaccination outweigh the risks. Neonates of unknown HIV status born to women living with HIV should be vaccinated if no clinical evidence suggests HIV infection, regardless of whether the mother is receiving ART. For neonates living with HIV confirmed by early virological testing, BCG vaccination should be delayed until ART has been started and the infant is confirmed to be immunologically stable (CD4 >25%).

HBV: In a 2014 systematic review addressing the immune responses among people living with HIV to HBV vaccine with standard versus high dosage, six studies among adults found higher peak anti-HBs antibody titres after the higher dosage compared with the standard dosage vaccines but no clear difference in the proportion of adults with protective antibodies up to five years after vaccination.

DTP-containing vaccines (diphtheria, tetanus and pertussis): Tetanus toxoid–containing vaccines are suitable for immunocompromised people, including people living with HIV, but the immune response may be lower than for fully immunocompetent people. All children living with HIV should be vaccinated against tetanus following the vaccine recommendations for the general population.

Measles: Measles vaccination should be routinely administered to potentially susceptible, asymptomatic children and adults living with HIV. Vaccination may even be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to conventional definitions. In areas with a high incidence of both HIV infection and measles, an initial dose of measles containing vaccine may be offered as early as age six months. The two routine doses of measles-containing vaccine should then be administered to these children according to the national immunization schedule. A supplementary dose of measles-containing vaccine should be given to infants from six months of age known to be HIV-infected or exposed.

HPV: HPV vaccines should be introduced as part of a coordinated strategy to prevent cervical cancer. Recommended target population for the prevention of cervical cancer: girls aged 9–14 years, before becoming sexually active.

A three-dose schedule (0, 1–2 and 6 months) should be used for all vaccinations initiated among those older than 15 years of age, including those younger than 15 years known to be immunocompromised and/or living with HIV

(regardless of whether they are receiving ART). Screening for HPV infection or HIV infection before HPV vaccination is not necessary.

Cholera: Appropriate case management, water, sanitation and hygiene interventions, surveillance and community mobilization remain the cornerstones of cholera control. Vaccination should be implemented in relevant settings as part of comprehensive cholera control strategies or while other activities are being developed. During humanitarian emergencies with a risk of cholera, but without a current cholera outbreak, vaccination with oral cholera vaccines should be considered as an additional preparedness measure for outbreak prevention, depending on the local infrastructure (capacity to organize a vaccination campaign). Pregnant and lactating women and people living with HIV should be included in oral cholera vaccine campaigns since there is a high potential benefit and minimal risks.

Dengue: No data are available on the safety of the first licensed dengue vaccine, CYDTDV, for individuals with immunodeficiency or HIV infection. The manufacturer stipulates that vaccination is contraindicated for individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.

Pneumococcal conjugate vaccines: Infants living with HIV and preterm neonates who have received their three primary vaccine doses before 12 months of age may benefit from a booster dose in the second year of life.

Rubella: Rubella-containing vaccines should not be given to anyone who has severe immunodeficiency, including individuals with symptomatic HIV infection and AIDS.

Typhoid: There are currently no data on typhoid-containing vaccine for immunocompromised people and people living with HIV. Although the typhoid Vi-polysaccharide vaccine is safe for people living with HIV, the induction of protective antibodies is directly correlated to CD4 cell count. Oral typhoid vaccine Ty21a can be administered to immunologically stable people living with HIV (CD4 >25% for children younger than five years, CD4 cell count ≥200 cells/mm3 if five years and older). Ty21a is not recommended for individuals with a known depression of cell-mediated immunity, although adverse effects have not been reported. There is no risk for immunocompromised household contacts of the people vaccinated with Ty21a.

COVID-19 vaccination

Many of the COVID-19 vaccine studies have included a few people living with HIV in their trials. Despite limited data, the available information suggests that current WHO-recommended COVID-19 vaccines are safe for people living with HIV. No interactions have been reported between COVID-19 vaccines and ARV drugs, which people living with HIV should continue to take after vaccination to maintain health.

Precautions for HIV exposed babies for certain vaccination are advised as below:

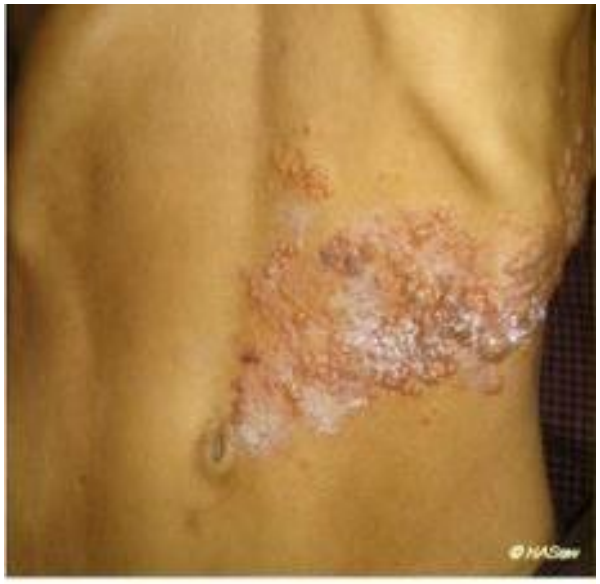
Table 29. Vaccination for HIV exposed babies

Age	Vaccine	Remark
At birth	BCG (Birth dose)	General condition well including PREM and LBW
	Hepatitis B (Birth dose)	Vaccinate as soon as after birth within 24 hours. If not, within 7 days of birth

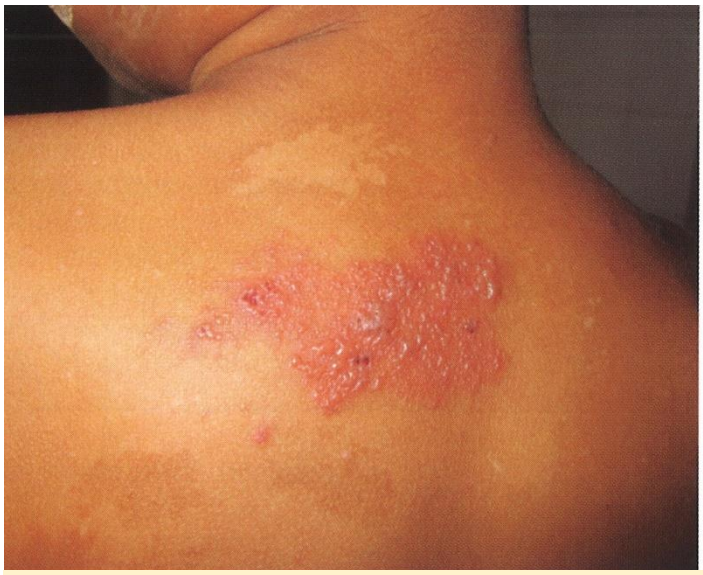
4 weeks	BCG if there was no birth dose	-Vaccinate if HIV unknown and no clinical evidence suggestive of HIV or DNA-PCR negative - If HIV DNA-PCR positive, Vaccinate BCG only after ART initiation and CD4>25%
2 months	BCG if there was no birth dose	Vaccinate if DNA-PCR negative If HIV DNA-PCR positive, Vaccinate BCG only after ART initiation and CD4>25%
	OPV1	
	Rota1	
	PCV1	
	Penta 1	
4 months	OPV2	
	Rota2	
	IPV	
	PCV2	
	Penta2	
6 months	OPV3	
	PCV3	
	Penta3	
	M0	If there no symptoms of HIV and the baby is in good health
9 months	MR1	If there no symptoms of HIV and the baby is in good health
	JE	- live vaccine if HIV status is negative - Inactivated vero cell derived vaccine should be used preferentially over live attenuated vaccine or live recombinant vaccine in immunocompromised infants and children
18 months	MR2	If there no symptoms of HIV and the baby is in good health
	Penta4	

9 years	HPV	

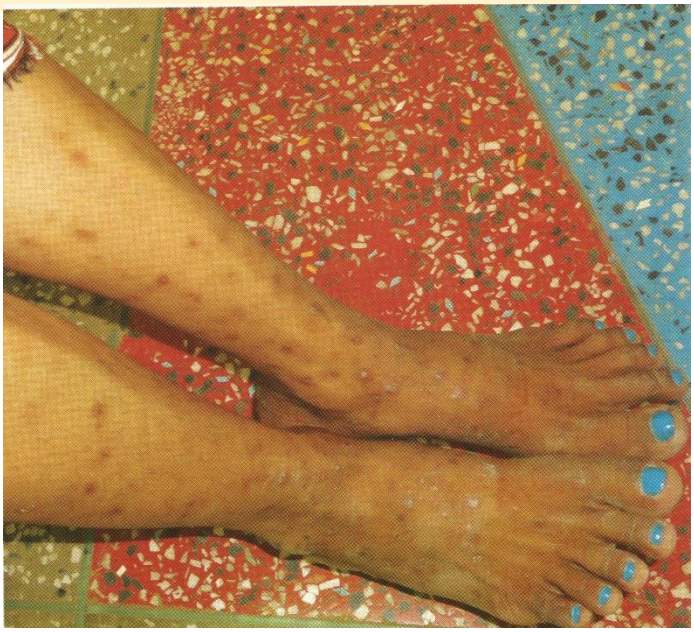
6. Atlas of HIV related conditions and opportunistic infections

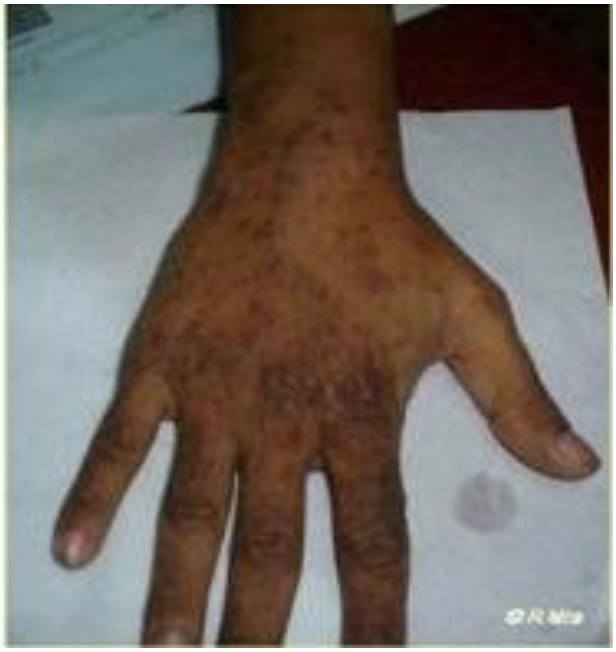


Herpes zoster is usually an early manifestation of immunosuppression and usually occurs at around CD4 300/mm3. It is seen as a painful vesicular eruption along a dermatone. It may be recurrent and is sometime multidermatomal.

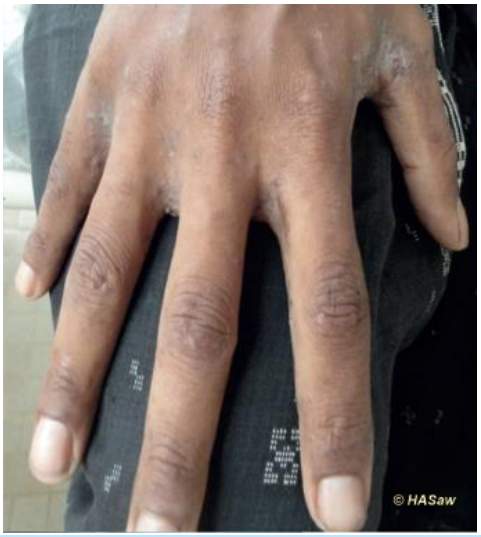


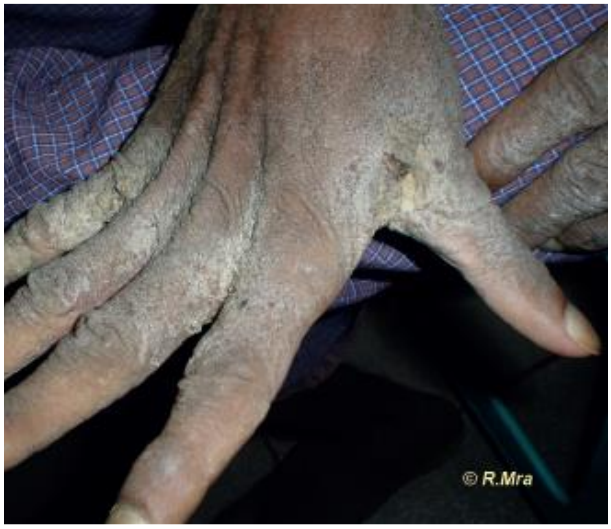
Eruption of Herpes Zoster 4 weeks after ART initiation. ART was continued and acyclovir was given for one week. the eruption was healed with no other complication.





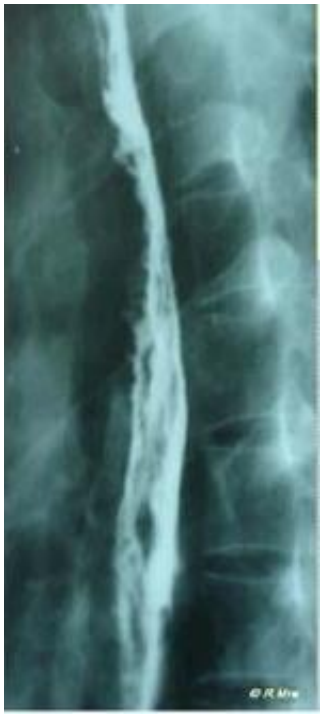
Pruritic papular eruptions are seen in the exposed parts of the limbs. Scratching produces infection and scarring. Pruritic papular eruption is thought to be due to allergic rection to insect bites. PPE is not scabies.



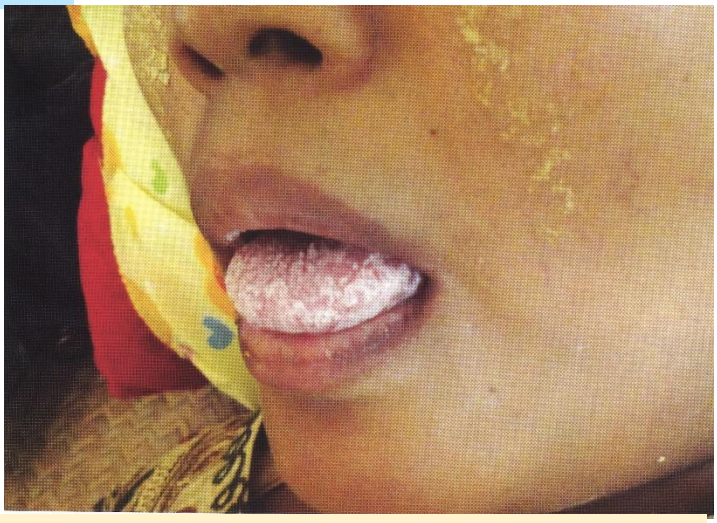


Scabies is caused by Sarcoptes scabiei mites burrow into the skin and is usually first seen in areas where the skin is thin e.g. webs of fingers and toes, genitalia and axillae. Scabies is intensely pruritic and the pruritis is worse at night. Scabies is not a sign of immunosuppression and is usually due to poor personal hygiene.

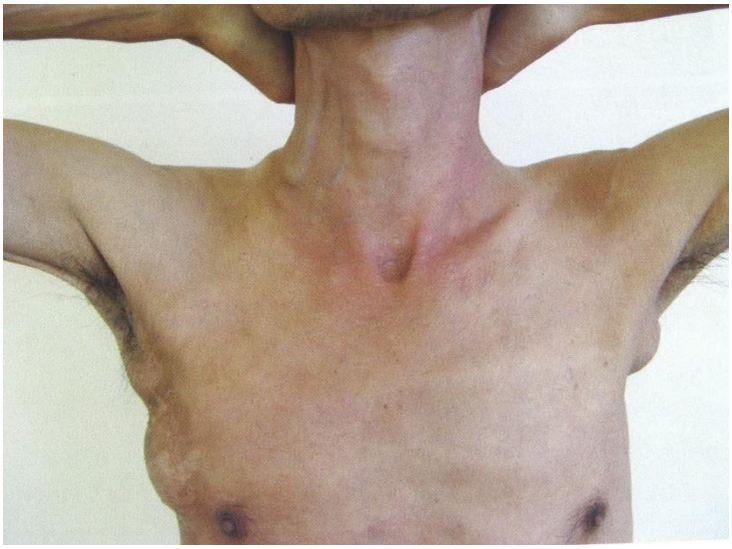
When there is advanced immunosuppression, there is hyperinfestation with the mites which do not cause an inflammatory reaction and pruritis and there is serum exudation causing encrustation. This is known as "crusted scabies" or Norwegian scabies. The condition indicates immunosuppression.

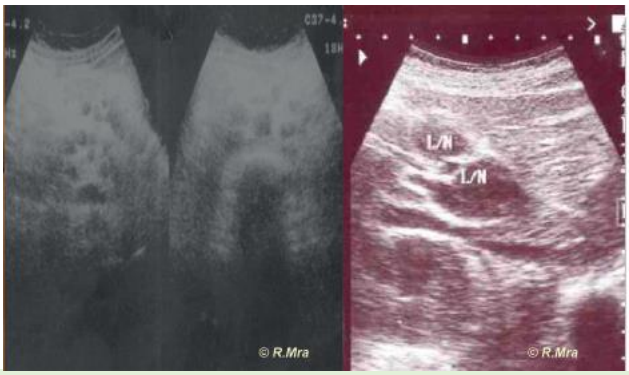


Barium swallow showing **oesophageal thrush** with mucosal ulcerations.



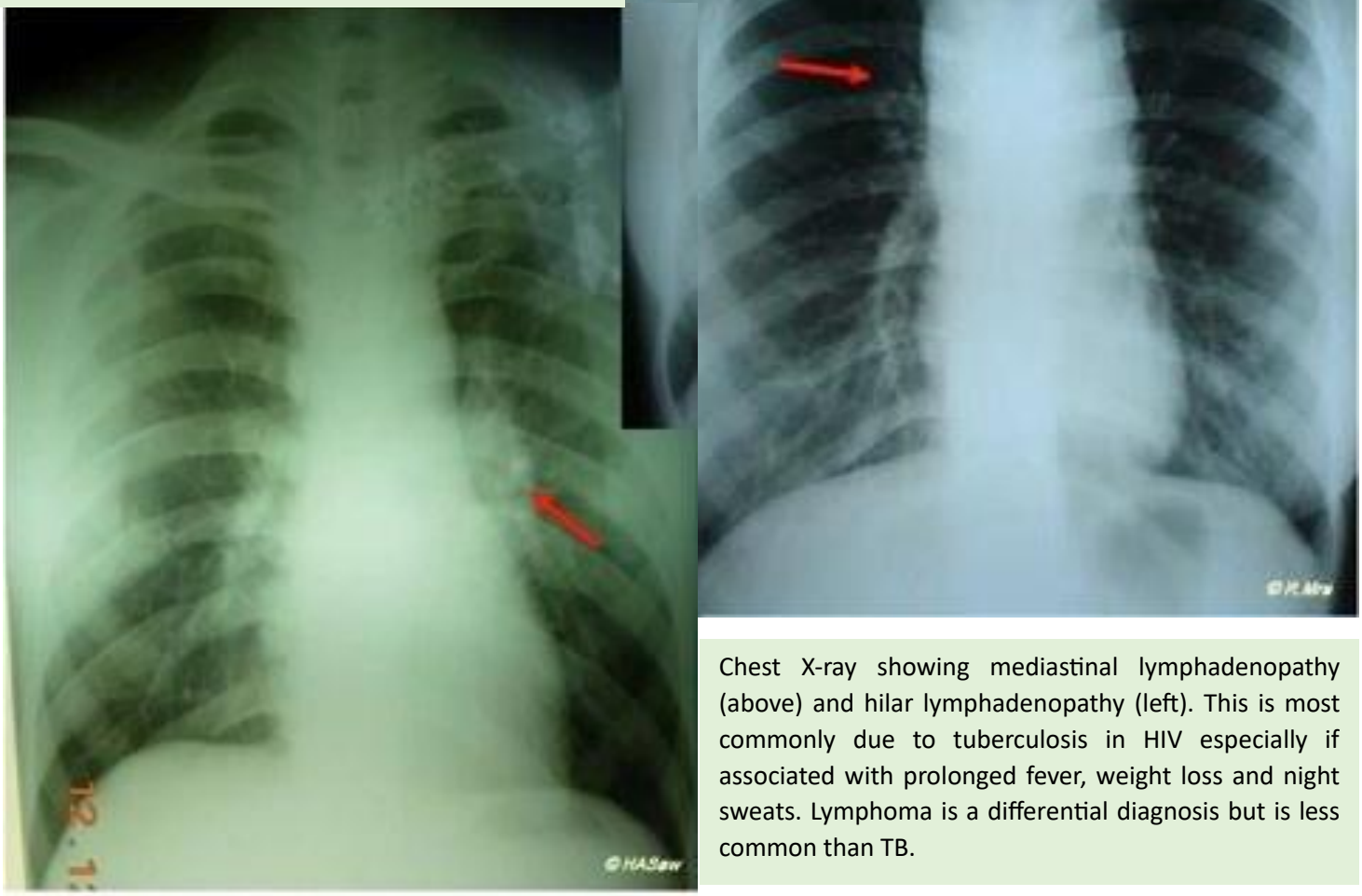
Oral thrush is due to Candida albicans in most cases and is usually seen as white plaques which can be easily scaped off and sometimes as erythematous raw red areas. There is soreness of the tongue and mouth. With advanced immunosuppression candidiasis extends into the oesophagus causing ulcerations and dysphagia.



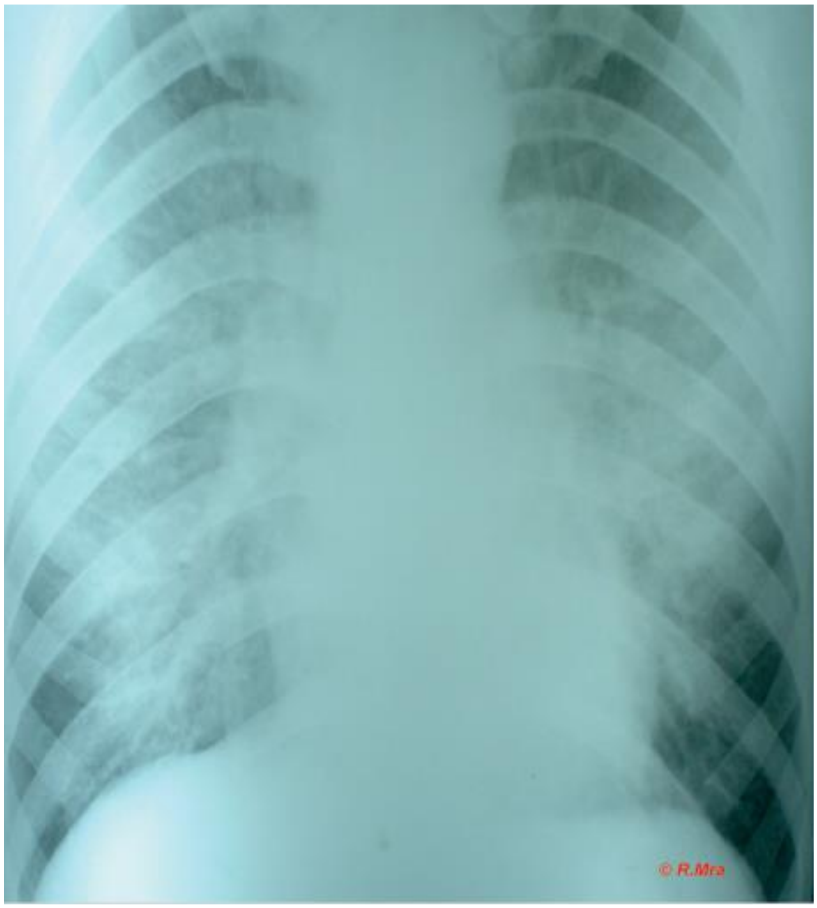


Intra-abdominal lymphadenopathy seen as hypoechoic areas on abdominal ultrasound examination. This is most commonly due to tuberculosis with advanced immunosuppression.

Extrapulmonary TB is common in HIV. Clinically suspicion of extrapulmonary TB is raised by fever, weight loss, bilateral, unilateral nodes increasing in size, matted nodes, fluctuant nodes.

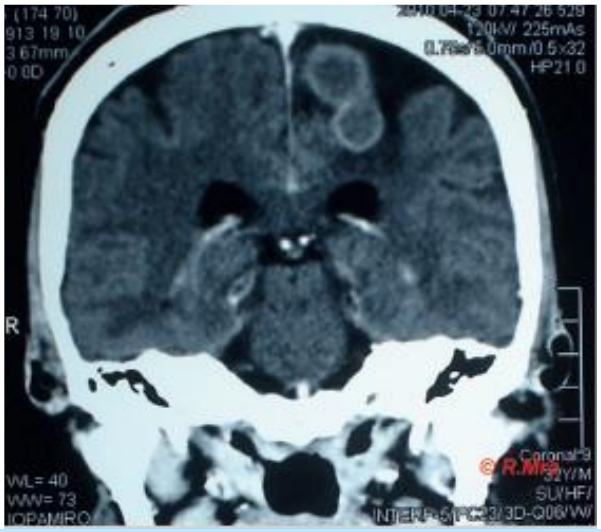


Chest X-ray showing mediastinal lymphadenopathy (above) and hilar lymphadenopathy (left). This is most commonly due to tuberculosis in HIV especially if associated with prolonged fever, weight loss and night sweats. Lymphoma is a differential diagnosis but is less common than TB.

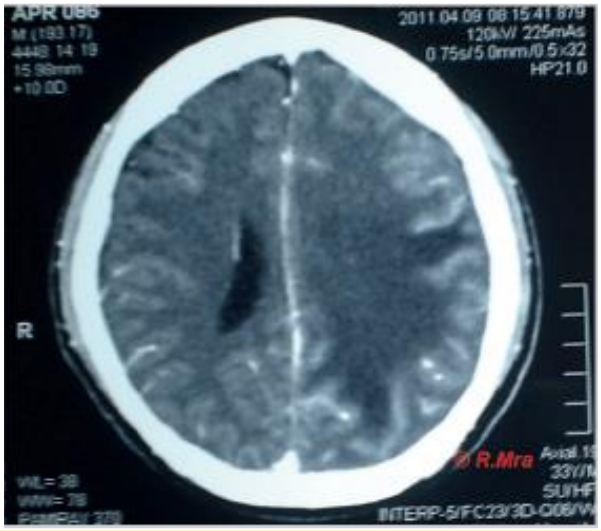


The patient presented with a low grade fever, dry cough and shortness of breath which had become progressively more severe over the past 3 weeks. The dyspnoea became worse after the slightest movement and cyanosis developed on exertion. There were very few lung signs. An urgent chest X-ray showed diffuse pulmonary infiltrates fanning out from the hilar region and sparing the apices and lower regions. The clinical and radiological picture are typical of pyeumocystis pneumonia (due to *Pneumocystis jerovecii*).

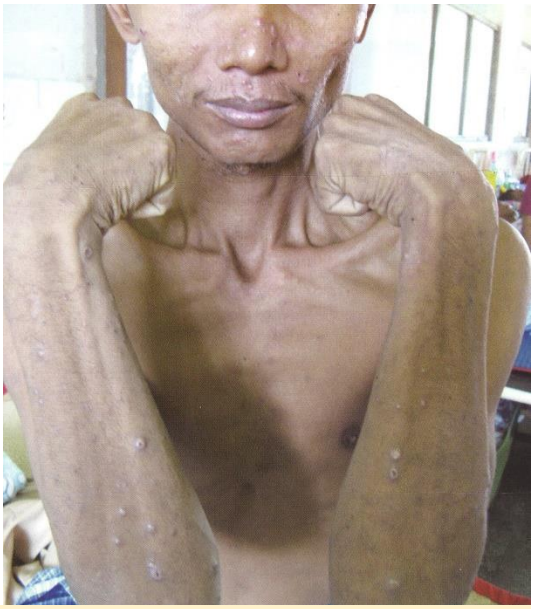
This is a late case. The patient responded to prompt treatment with high dose co-trimoxazole (steroids were also given initially and tailed off).



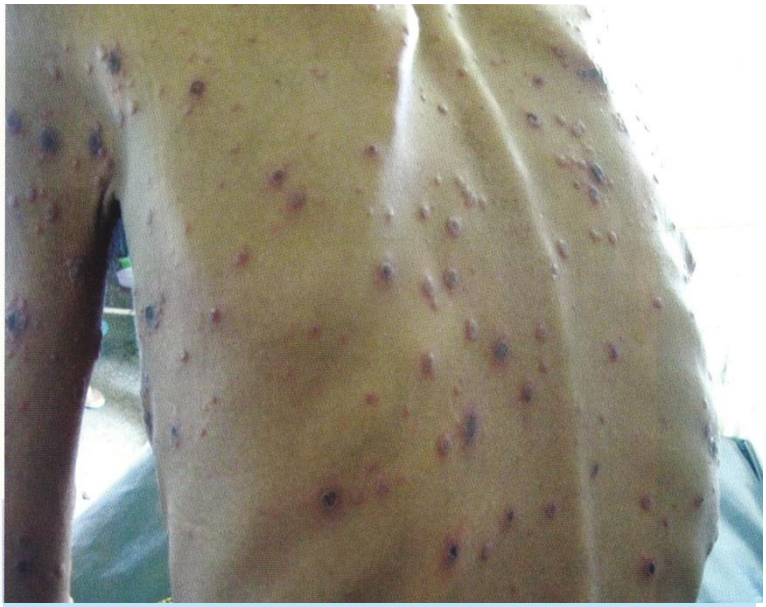
CT brain of cerebral toxoplasmosis case. In this picture massive cerebral oedema is seen in the left side of the brain. A small abscess can produce marked cerebral oedema and the small abscess can be missed if the CT slice interval is not small enough. MRI or high-resolution CT is the imaging technique of choice. In resource limited setting treatment for cerebral toxoplasmosis is started on clinical grounds alone; one should look for a response to treatment for the clinical diagnosis.



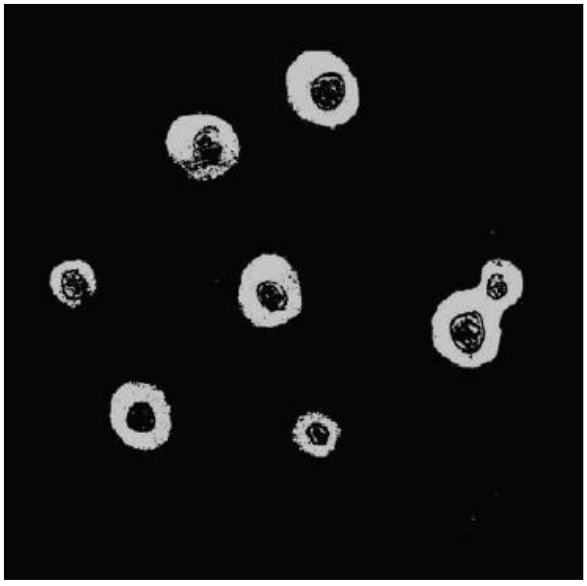
CT brain- cerebral toxoplasmosis with multiple abscesses with ring enhancement after contrast injection. The patient presented with right-sided hemiplegia and fits. Differential diagnoses included other causes of brain abscesses-pyogenic, tuberculous, fungal or secondaries. In cerebral toxoplasmosis there is a good clinical and radiological response in about 2 weeks with sulphadiazine and pyrimethamine therapy. This patient made a complete recovery and is now well on ART.



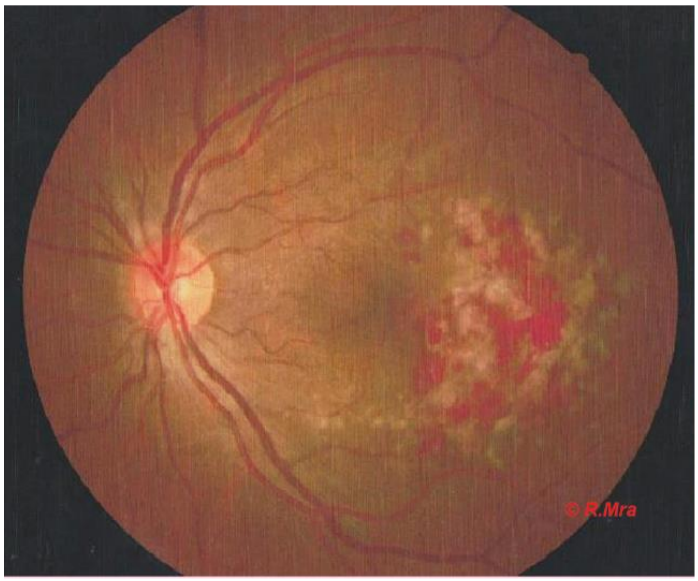
Maculopapular lesions with central umbilications on face and extremities in patient with **penicilliosis**



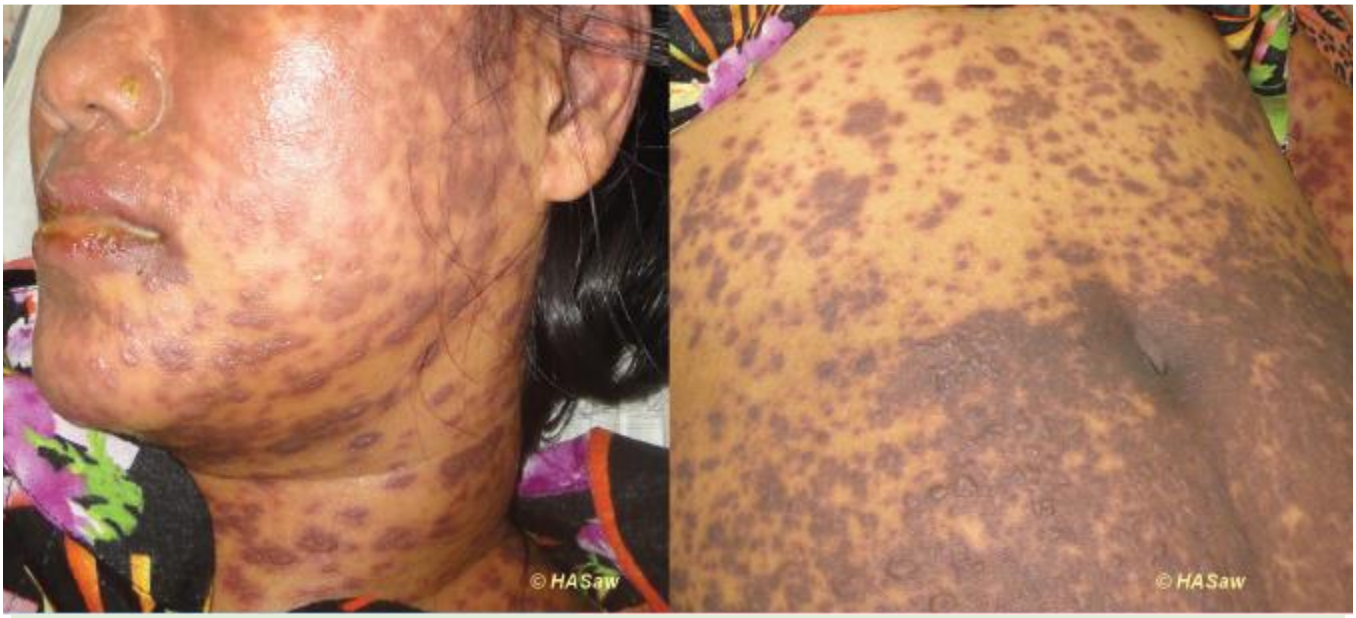
Skin lesion on the back of patient diagnosed with **Histoplasmosis**. Cutaneous lesions are present in 10% of patients. Erythematous maculopapular lesions, ulcerations, purpura, and/or manifestations of endocarditis may be present. Oropharyngeal lesions may also be present.



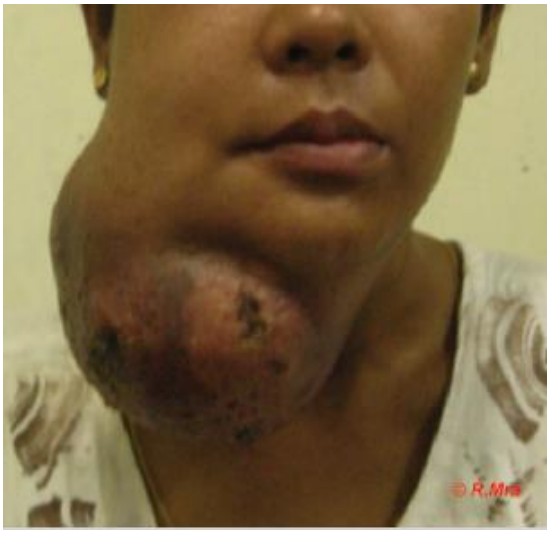
India ink preparation of CSF showing yeast cells of Cryptococcus neoformans with unstained thick capsules and budding (sketch)



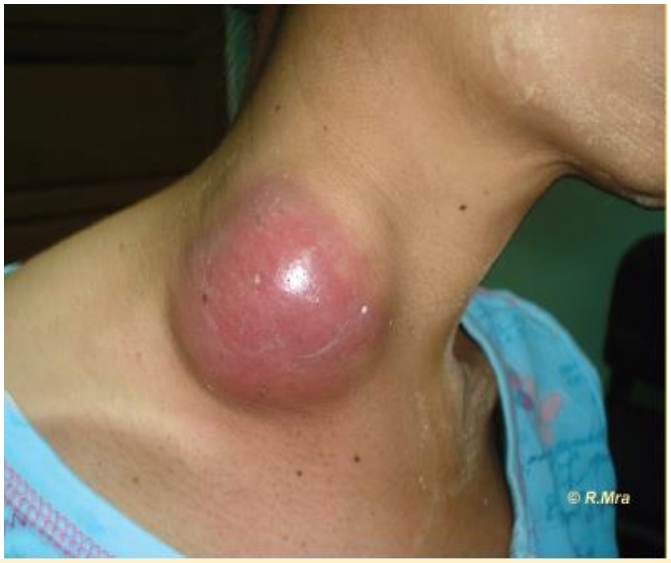
CMV retinitis showing haemorrhagic necrosis of the retina with exudates (scrambled eggs and tomato catchup appearance). Involvement of the macula area causes blindness.



Stevens-Johnson syndrome due to nevirapine involving the whole body as well as mucous membrane. This is a recognized complication of NVP and can occur at all levels of immunosuppression but particularly in women with CD4 count > 250/mm3. Stevens-Johnson syndrome can be also a rare complication of other drugs e.g rifampicin, co-trimoxazole.



HIV associated lymphoma is a high-grade B cell non-Hodgkin lymphoma.



Immune reconstitution Inflammatory syndrome or IRIS. This patient had a CD4 count of 50/mm3. There was a small lymph node at the root of the neck. TB treatment was started for pulmonary tuberculosis and ART started 2 weeks later. After one month symptoms worsened and the cervical lymph node had become enlarged, painful and then gradually became fluctuant. It was aspirated (should not be incised) and the pus showed the presence of many AFB. With continued TB treatment and ART the patient gradually improved. It took many weeks for the lymph node to regress and heal. This is an example of the immune reconstitution inflammatory syndrome.

7. Annexes

Table 30. Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing for infants and children four weeks and older [a]

Drug	Strength of paediatric tablets	Number of tablets by weight band morning and evening										Strength of adult tablet	Number of tablets by weight band	
		3-<6 kg		6-<10 kg		10-<14 kg		14-<20 kg		20-<25 kg			25-<35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
AZT/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg/150 mg	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg[b]	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600 mg/300 mg	0.5	0.5
	Tablet (dispersible) 120 mg/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600 mg/300 mg	0.5	0.5

[a] For infants younger than four weeks old, see Table A1.4 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolize medications. For infants who are at least four weeks old but weigh less than 3 kg, the immaturity of renal and hepatic pathways of elimination are less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birth-weight infants.

[b] This formulation will be phased out of use over time, and programmes should transition to using the 120 mg/60 mg dispersible scored tablets.

Table 31. Simplified dosing of child-friendly solid formulations for once-daily dosing for infants and children four weeks and older [a]

Drug	Strength of paediatric tablet	Number of tablets or capsules by weight band once daily					Strength of adult tablet	Number of tablets or capsules by weight band once daily
		3-<6 kg	6-<10 kg	10-<14 kg	14-<20 kg	20-<25 kg		25–<35 kg
EFV[b]	Tablet (scored) 200 mg	–	–	1	1.5	1.5	-	2
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	2	3	4	5	6	600 mg/300 mg	1
	Tablet (dispersible) 120 mg/60 mg	1	1.5	2	2.5	3		
TAF/FTC[c]	Tablet 25 mg/ 200 mg	–	–	–	–	–	25 mg/200 mg	1
ATV[d]	Capsules 100 mg	–	–	2	2	2	300 mg	1[e]
	Capsules 200 mg	–	–	1	1	1		
DRV[f]	Tablet 600 mg	–	–	–	1	1	600 mg	1
	Tablet 150 mg	–	–	–	4	4		
RTV[g]	Tablet 25 mg	–	–	–	4	4	100 mg	1
	Tablet 50 mg	–	–	–	2	2		
DTG[h]	Film-coated tablet 50 mg	–	–	–	–	1	50 mg	1
	Dispersible tablet 5 mg	1	3	4	5	6		
	Dispersible scored tablet 10 mg	0.5	1.5	2	2.5	3		

[a] See Table 33 for dosing recommendations for infants younger than four weeks old. Doses for this age group are reduced to account for the decreased ability to excrete and metabolize medications. For infants who are at least four weeks old but weigh less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birth-weight infants.

[b] EFV is not recommended for children younger than three years and weighing less than 10 kg.

[c] At the time of this update, the United States Food and Drug Administration approved TAF film-coated tablets for children older than six years for use in unboosted regimens such as with DTG. The United States Food and Drug Administration tentatively approved a fixed-dose combination containing TAF/FTC/DTG (TAF 25 mg, FTC 200 mg, DTG 50 mg) that can be used once daily for children and adolescents living with HIV weighing at least 25 kg.

[d] ATV is only approved for children three months and older. ATV single-strength capsules should be administered with RTV 100 mg for all weight bands 10 kg and above. ATV powder formulation has limited availability in low- and middle-income countries but enables ATV to be administered to infants and children as young as three months. Infants and children weighing 5–<15 kg should be administered 200 mg of ATV powder (four packets, 50 mg per packet) with 80 mg of RTV oral solution (1 mL) *(14)*.

[e] ATV 300 mg with RTV 100 mg for 25–<30 kg is recommended based on the findings from the PRINCE-2 study.

[f] DRV in combination with RTV should be used for children older than three years, once daily when this is used without previous exposure to PIs. Although the approved dosing for 30–<35 kg is 675 mg, preliminary data from adult studies suggest that even lower DRV doses may be effective, and the 600 mg dose was therefore extended to the entire 25- to <35 kg weight band.

[g] RTV should only be use as a boosting agent in combination with ATV or DRV or to super-boost LPV/r when given with concomitant rifampicin for TB (see Table 34).

[h] At the time of this update, the United States Food and Drug Administration approved 5 mg dispersible tablets and tentatively approved 10-mg scored dispersible tablets for treatment-naive or treatment-experienced INSTI-naive children at least four weeks old and weighing at least 3 kg, based on data from the IMPAACT 1093 trial *(4)* and ODYSSEY *(16)*. The United States Food and Drug Administration and European Medicines Agency approved simplified dosing of the DTG 50 mg film-coated tablets for all children weighing ≥20 kg. DTG dispersible tablets and DTG film-coated tablets are not bioequivalent; 30 mg of DTG dispersible tablet corresponds to 50 mg of DTG film-coated tablets. DTG 50 mg film-coated tablets are preferred for children who have reached 20 kg (unless they cannot swallow tablets). Safety monitoring remains important given the current limited experience with this dosing. For adolescents living with HIV weighing more than 30 kg, a fixed-dose formulation of TDF 300 mg, 3TC 300 mg and DTG 50 mg (TLD) can be used and is preferred.

Table 32. Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing for infants and children four weeks of age and older [a]

Drug	Strength	Number of tablets or mL by weight-band morning (AM) and evening (PM)										Strength of adult tablet	Number of tablets by weight band	
		3-<6 kg		6-<10 kg		10-<14 kg		14-<20 kg		20-<25 kg			25-<35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
Solid formulations														
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
LPV/r[b]	Tablet 100 mg/25 mg	–	–	–	–	2	1	2	2	2	2	–	3	3
	Pellets 40 mg/10 mg	2	2	3	3	4	4	5	5	6	6		–	–
	Granules 40 mg/10 mg sachet	2	2	3	3	4	4	5	5	6	6		–	–
DRV[c]	Tablet 75 mg	–	–	–	–	–	–	5	5	5	5	400 mg	1	1
RTV[d]	Tablet 25 mg	–	–	–	–	–	–	2	2	2	2	100 mg	1	1
	Tablet 50 mg	–	–	–	–	–	–	1	1	1	1			
RAL[e]	Chewable tablets 25 mg	1	1	2	2	3	3	4	4	6	6	400 mg	1	1
	Chewable tablets 100 mg	–	–	–	–	–	–	1	1	1.5	1.5			
Liquid formulations														
AZT	10 mg/mL	6 mL	6 mL	9 mL	9 mL	12 mL	12 mL	–	–	–	–	–	–	–
ABC[f]	20 mg/mL	3 mL	3 mL	4 mL	4 mL	6 mL	6 mL	–	–	–	–	–	–	–
3TC	10 mg/mL	3 mL	3 mL	4 mL	4 mL	6 mL	6 mL	–	–	–	–	–	–	–
LPV/r[b]	80 mg/20 mg/mL	1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL	2.5 mL	2.5 mL	3 mL	3 mL	–	–	–
DRV[c]	100 mg/mL	–	–	–	–	2.5 mL	2.5 mL	3.5 mL	3.5 mL	–	–	–	–	–
RTV[d]	80 mg/mL	–	–	–	–	0.5 mL	0.5 mL	0.6 mL	0.6 mL	–	–	–	–	–
RAL[e]	10 mg/mL (Oral granules for suspension: 100 mg/ sachet)	3 mL	3 mL	5 mL	5 mL	8 mL	8 mL	10 mL	10 mL	–	–	–	–	–

[a] See Table 33 for dosing recommendations for infants younger than four weeks. Doses for this age group are reduced to account for the decreased ability to excrete and metabolize medications. For infants who are at least four weeks old but weigh less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern, but uncertainty still exists on the dosing of ARV drugs for preterm and low-birth-weight infants.

[b] Although ABC dose represents a significant increase compared with the neonatal dose, this dose was designed to match the recommended dose for the solid formulation above.

[c] LPV/r liquid requires a cold chain during transport and storage. The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. Adult 200/50 mg tablets could be used for children weighing 14–<25 kg (one tablet in the morning and one in the evening) and for children weighing 25–<35 kg (two tablets in the morning and one in the evening). The LPV/r pellet formulation should not be used for infants younger than three months. More details on the administration of LPV/r pellets are available. This dosing schedule applies to equivalent solid dosage forms such as LPV/r granules, which can be used from two weeks of age. Since the supply is currently constrained, both pellets and granules should be discouraged for children weighing more than 14 kg, who should receive LPV/r 100/25 mg tablets instead. Information on LPV/r formulations for children is available.

[d] DRV to be used for children older than three years must be administered with 0.5 mL of RTV 80 mg/mL oral suspension if they weigh less than 15 kg and with RTV 50 mg (using 25 mg or 50 mg solid formulation) for children weighing 15–<30 kg. RTV 100-mg tablets can be used as a booster if lower-strength RTV tablets are not available, based on limited experience suggesting good acceptability and tolerability.

[e] RTV should only be used at this dose as a boosting agent in combination with ATV or DRV.

[f] RAL granules are approved from birth. The feasibility and acceptability of such formulations have not been widely investigated, and concerns have been raised about administration in resource-limited settings. Because of the administration challenges presented by the granule formulation, the Paediatric Antiretroviral Working Group endorsed the use of the 25 mg chewable tablets as dispersible for infants and children older than four weeks and weighing at least 3 kg. This was largely based on in vitro data on solubility and bioequivalence between tablets and granules and on considering the limited availability of adequate alternatives for this age group. However, the findings from a feasibility and acceptability assessment conducted in South Africa demonstrate that administering RAL granules in rural settings is feasible as long as it is supported by adequate training and counselling.

Table 33. Drug dosing of liquid formulations for infants younger than four weeks of age [a]

Drug	Strength of oral solution		2-<3 kg		3-<4 kg		4-<5 kg	
			AM	PM	AM	PM	AM	PM
AZT	10 mg/mL		1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL
ABC	20 mg/mL		0.4 mL	0.4 mL	0.5 mL	0.5 mL	0.6 mL	0.6 mL
NVP	10 mg/mL		1.5 mL	1.5 mL	2 mL	2 mL	3 mL	3 mL
3TC	10 mg/mL		0.5 mL	0.5 mL	0.8 mL	0.8 mL	1 mL	1 mL
LPV/r[b]	80 mg/20 mg/mL		0.6 mL	0.6 mL	0.8 mL	0.8 mL	1 mL	1 mL
	Granules 40 mg/10 mg sachet		–	–	2	2	2	2
RAL	10 mg/mL (Oral granules for suspension: 100 mg/ sachet)[c]	<1 week	0.4 mL (once daily)[c]		0.5 mL (once daily)[c]		0.7 mL (once daily)[c]	
		>1 week	0.8 mL	0.8 mL	1 mL	1 mL	1.5 mL	1.5 mL

[a] To avoid dose changes over a short period of time and to minimize the likelihood of errors, all ARV drugs except for RAL (dose change after week 1), should be dosed based on weight when treatment starts and maintained until four weeks of age (weight gain is limited during the first four weeks of life). Pharmacokinetic data for preterm infants are available only for AZT; there are limited data and considerable uncertainty of appropriate dosing for NVP, RAL and 3TC for preterm and low-birth-weight infants. In addition, LPV/r solution should not be given to preterm infants until they have reached 42 weeks gestational age, because of the risk of adverse effects. This guidance will be updated when more evidence on solid LPV/r formulations is available from ongoing trials.

[b] Do not use LPV/r solution for infants aged younger than 2 weeks of age. LPV/r pellets should not be used for infants younger than three months. More details on administering LPV/r pellets is available. Because of lack of clinical data to fully inform the use of LPV/r granules for newborns, these dosing recommendations were developed based on the current United States Food and Drug Administration approval (supporting use of LPV/r granules from two weeks) and considering the substantial uncertainty, especially for neonates weighing 2–3 kg. If no other formulation exists, one sachet twice a day could be considered for neonates older than two weeks who weigh 2–3 kg to minimize the risk of potential toxicity with overdosing.

[c] RAL granules for oral suspension should be used for newborns weighing at least 2 kg and be administered once a day during the first week of life and twice a day afterwards.

Table 34. ARV drug dose adjustment for children receiving rifampicin-containing TB treatment [a]

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or mL by weight-band morning (AM) and evening (PM)										Strength of adult tablet	Number of tablets by weight band	
		3-<6 kg		6-<10 kg		10-<14 kg		14-<20 kg		20-<25 kg			25-<35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
DTG[b]	5 mg dispersible tablets	1	1	3	3	4	4	5	5	6	6	50 mg film-coated tablets	1	1
	10 mg scored dispersible tablets	0.5	0.5	1.5	1.5	2	2	2.5	2.5	3	3			
	50 mg film-coated tablets	–	–	–	–	–	–	–	–	1	1			
RAL	10 mg/mL (Oral granules for suspension: 100 mg/ sachet)	6 mL	6 mL	10 mL	10 mL	16 mL	16 mL	20 mL	20 mL	–	–	400 mg	2	2
	Chewable tablets 25 mg	2	2	4	4	6	6	8	8	–	–			
	Chewable tablets 100 mg	–	–	–	–	–	–	2	2	3	3			

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or mL by weight-band morning (AM) and evening (PM)										Strength of adult tablet	Number of tablets by weight band	
		3-<6 kg		6-<10 kg		10-<14 kg		14-<20 kg		20-<25 kg			25-<35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
LPV/r[c] (with additional RTV)	Oral solution[d] 80/ 20 mg/mL	1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL	2.5 mL	2.5 mL	3 mL	3 mL	–	–	–
	Pellets[e] 40 mg/10 mg	2	2	3	3	4	4	5	5	6	6	–	–	–
	Granules 40 mg/10 mg sachet	2	2	3	3	4	4	5	5	6	6	–	–	–
	Tablet 100 mg/25 mg	–	–	–	–	2	1	2	2	2	2	100 mg/25 mg	3	3
RTV[f]	Tablet 100 mg	–	–	–	–	1	1	1	2	1	2	100 mg	2	2
	Tablet 50 mg	–	–	–	–	2	2	3	3	3	3			
	Tablet 25 mg	–	–	–	–	4	4	6	6	6	6			
	Oral solution 80 mg/ mL	0.8 mL	0.8 mL	1.2 mL	1.2 mL	1.5 mL	1.5 mL	2 mL	2 mL	2.3 mL	2.3 mL	–	–	–
	Powder 100 mg/packet	–	–	1	1	1	1	1	2	1	2	–	–	–

[a] The adapted dose of the ARV drugs needs to continue until two weeks after rifampicin treatment ends, since the enzyme-inducing effect of rifampicin slowly fades away after discontinuing the drug.

[b] The United States Food and Drug Administration recommended administering the weight-based DTG dose twice daily if taken with rifampicin based on its customary approach of extrapolating drug– drug interaction data from adults. Direct pharmacokinetic data in children support the use of DTG twice daily for children weighing more than 25 kg. The Paediatric Antiretroviral Working Group highlights the need to continue to collect confirmatory evidence for lower weight bands but endorses immediate uptake of twice-daily dosing of DTG when taken with rifampicin for all children (at least four weeks of age and weighing at least 3 kg).

[c] The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. An adult 200/50 mg tablet could be used for children weighing 14–<25 kg (one tablet in the morning and one in the evening) and for children 25–<35 kg (two tablets in the morning and one in the evening).

[d] LPV/r liquid requires a cold chain during transport and storage.

[e] The LPV/r pellet formulation should not be used for infants younger than three months. More details on administering LPV/r pellets is available. The dosing schedule provided applies to equivalent solid dosage forms that may become available such as LPV/r granules, which the United States Food and Drug Administration has approved for from two weeks of life.

[f] Suggested RTV dose for super-boosting to achieve the same dose as LPV in mg, in a ratio equal or approaching to 1:1. This dosing approach is supported by a study that explored this approach for young children receiving LPV/r. RTV oral solution dosing is based on the dosing tested in the trial that supports the use of super-boosting.

Table 35. Simplified dosing of isoniazid and co-trimoxazole prophylaxis for infants and children at least 4 weeks old

Drug	Strength of paediatric tablet or oral liquid	Number of tablets or mL by weight band once daily					Strength of adult tablet	Number of tablets by weight band
		3-<6 kg	6-<10 kg	10-<14 kg	14-<20 kg	20-<25 kg		25–<35 kg
Isoniazid	100 mg	0.5	1	1.5	2	2.5	300 mg	1
Co-trimoxazole (sulfamethoxazole and trimethoprim)	Suspension 200 mg/ 40 per 5 mL	2.5 mL	5 mL	5 mL	10 mL	10 mL	–	–
	Tablets (dispersible) 100 mg/20 mg	1	2	2	4	4	–	–
	Tablets (scored) 400 mg/80 mg	–	0.5	0.5	1	1	400 mg/80 mg	2
	Tablets (scored) 800 mg/160 mg	–	–	–	0.5	0.5	800 mg/160 mg	1
Isoniazid/ (sulfamethoxazole and trimethoprim)/ B6	Tablets (scored) 300 mg/(800 mg/ 160 mg) /25 mg	–	–	–	0.5	0.5	300 mg/ (800 mg/ 160 mg)/ 25 mg	1

Table 36. Weight-based fixed dose DTG-based Regimens

Weight Band	Number of Tablets Per Day	
	pABC/3TC 120/60 mg + pDTG 10 mg	pALD: ABC/3TC/DTG 60/30/5 mg
3 to 5.9 kg	1 + 0.5	Separate pABC/3TC and pDTG tablets will still be used
6 to 9.9 kg	1.5 + 1.5	3
10 to 13.9 kg	2 + 2	4
14 to 19.9kg	2.5 + 2.5	5
20 to 24.9 kg	3 + 1 DTG (50 mg) tablet	6

Table 37. Potential overlapping and additive toxicities of ART and anti-TB treatment

TOXICITY	ANTIRETROVIRAL AGENT	ANTI-TB AGENT	COMMENTS
Skin rash	ABC, NVP, EFV, d4Tand others	H, R, Z, PAS, Fluoroquinolones, and others	Do not re-challenge with ABC (can result in life-threatening anaphylaxis). Do not re-challenge with any agent that may have caused Stevens-Johnson syndrome. Also consider co-trimoxazole as a cause of skin rash if the patient is receiving this medication. Thioacetazone is contraindicated in HIV because of the risk of life-threatening rash.
Central nervous system (CNS) toxicity	**EFV**	**Cs,** H, Eto/Pto, FQ Lfx, Mfx, Dlm, Am, Cs, Mpm Bdq, Eto/ Pto, H, Pa	EFV has a high rate of CNS side effects (dizziness, impaired concentration, depersonalization, abnormal dreams, insomnia and confusion) in the first 2–3 weeks of use, but typically resolve on their own. If these effects do not resolve, consider substitution of the agent. At present, there are limited data on the use of EFV with Cs; concurrent use is the accepted practice as long as there is frequent monitoring for central nervous system toxicity. Frank psychosis can occur with Cs but is rare with EFV alone; other causes should always be ruled out.

Depression	EFV	**Cs,** FQ, H, Eto/Pto Lfx, Mfx, Dlm, Am, Cs, Mpm Bdq, Eto/ Pto, H, Pa	Severe depression can be seen in 2.4% of patients receiving EFV. Consider substitution of EFV if severe depression develops.
Headache	AZT, EFV	Cs, Bdq	Rule out more serious causes of headache, such as bacterial meningitis, cryptococcal meningitis, central nervous system toxoplasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration may help. Headaches secondary to AZT, EFV and Cs are usually self-limited.
Nausea and vomiting	RTV, d4T, NVP, and most others	Eto/Pto, PAS, H, Bdq, E, Z and Dlm	Persistent vomiting and abdominal pain may be a result of developing lactic acidosis (especially common with long-term d4T use) and/or hepatitis secondary to medications.
Abdominal pain	All antiretrovirals have been associated with abdominal pain	Eto/Pto, PAS	Abdominal pain is a common adverse effect and often benign; however, abdominal pain may be an early symptom of severe side effects, such as pancreatitis, hepatitis or lactic acidosis (especially common with long-term d4T use.
Diarrhoea	All protease inhibitors, ddI (buffered formulation)	Eto/Pto, PAS, FQ	Diarrhoea is a common adverse effect. Also consider opportunistic infections as a cause of diarrhoea, or *Clostridium difficile* (pseudomembranous colitis).
Hepatotoxicity	NVP, EFV, all protease inhibitors (RTV > others), all NRTIs	H, R, E, Z, Bdq, PAS, Eto/ Pto, FQ	Also see Section on hepatotoxicity treatment related to second-line anti-TB drugs. When severe, stop both the ART and TB medications, and restart the TB medications first. Also consider co-trimoxazole as a

			cause of hepatotoxicity if the patient is receiving this medication. Also rule out viral aetiologies as cause of hepatitis (hepatitis A, B, C, and CMV).
Lactic acidosis	AZT, 3TC	Lzd	If an agent has caused hyperlactataemia (i.e. high lactate) or lactic acidosis, replace it with an agent less likely to cause lactic acidosis. Note: the goal should always be early detection and management of hyperlactataemia to prevent development of lactic acidosis.
Renal toxicity	TDF (rare)	Aminoglycosides, Cm	TDF may cause renal injury with the characteristic features of Fanconi syndrome, hypophosphataemia, hypouricaemia, proteinuria, normoglycaemic glycosuria and, in some cases, acute renal failure. **Avoid TDF in patients receiving aminoglycosides or Cm. If TDF is absolutely necessary, serum creatinine and electrolytes should be monitored frequently (at least every two weeks).** Even without the concurrent use of TDF, HIV-infected patients have an increased risk of renal toxicity secondary to aminoglycosides and Cm. Frequent creatinine and electrolyte monitoring is recommended. In the presence of renal insufficiency, antiretrovirals and anti-TB medications need to have their doses adjusted.

Electrolyte disturbances	TDF (rare)	**Cm, amino-glycosides**	Diarrhoea and/or vomiting can contribute to electrolyte disturbances. Even without the concurrent use of TDF, HIV-infected patients have an increased risk of both renal toxicity and electrolyte disturbances secondary to aminoglycosides and Cm.
Bone marrow suppression	AZT	**Lzd,** R, Rfb, H	Monitor blood counts regularly. Replace AZT if bone marrow suppression develops. Consider suspension of Lzd. Also consider co-trimoxazole as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if the patient is receiving co-trimoxazole.
Dysglycaemia (disturbed blood sugar regulation)	**Protease inhibitors**	**Gfx,** Eto/Pto	Protease inhibitors tend to cause insulin resistance and hyperglycaemia. Eto/Pto tends to make insulin control in diabetics more difficult, and can result in hypoglycaemia and poor glucose regulation.
Arthralgia	**Indinavir, other protease inhibitors**	**Z, BDQ**	Protease inhibitors can cause arthralgia and there have been case reports of more severe rheumatologic pathology. Arthralgias are very common with Z and has been reported as one of the most frequent adverse effects (>10%) in controlled clinical trials with Bdq.

QT Prolongation	ART has been associated with QTc prolongation	**Bdq, Mfx, Gfx, Cfz,** Lfx, Ofx, Dlm	ARV therapy does appear to confer a significant increased risk of QTc prolongation in HIV-positive patients but data is sparse. The additive effects of combining ART with the known second-line anti-TB drugs in respect to QTc prolongation is not known.

Note: Abbreviation of anti-TB drugs

Am	Amikacin
Amx/Clv	Amoxicillin/clavulanate
Bdq	Bedaquiline
Cm	Capreomycin
Clr	Clarithromycin
Cfz	Clofazimine
Cs	Cycloserine
Dlm	Delamanid
E	Ethambutol
Eto	Ethionamide
Ipm	Imipenem/Cilastatin
H	Isoniazid
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
Ofx	Ofloxacin
PAS	p-aminosalicylic acid
Pto	protionamide
Z	Pyrazinamide
Rfb	Rifabutin
R	Rifampicin
S	Streptomycin
Thz	Thioacetazone

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