5th EDITION

Guidelines for the clinical management of **HIV infection in Myanmar**

National AIDS Programme, Department of Public Health
Ministry of Health and Sports, Myanmar

2017

World Health Organization
Myanmar

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List of abbreviations

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
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
DTG	dolutegravir
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
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
PCP	*Pneumocystis jerovecii* 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 diagnostic test
STI	sexually transmitted infections
TG	transgender
TST	tuberculin skin test
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
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

Foreword

HIV is one of the priority public health issues in Myanmar. The country has been implementing a wide range of activities and services as national concern since 1989 with high political commitment.

A couple of years have passed since the last edition of the National guidelines for Clinical Management of HIV infection in 2014. During the time period, the WHO has published the Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infections: Recommendations for a Public Health Approach: Second Edition 2016.

In the meantime, Myanmar achieved major progress in expanding the coverage of HIV prevention among key populations and HIV treatment and care. Especially, antiretroviral treatment (ART) coverage doubled from 24% in 2012 to almost 50% in 2015. Part of this impressive achievement includes the shift of patients from private sector to the public sector – Government now manages nearly 56% of ART cases.

Despite the major progress, there remains a long way before accomplishing the vision of ending HIV as a public health threat by 2030. This vision is crucial in supporting Myanmar to achieve the Sustainable Development Goals (SDGs) and universal health coverage, by strengthening the leadership and enhancing public, private and community partnerships at all levels.

The Guidelines for the Clinical Management of HIV Infection in Myanmar: Fifth Edition augment and complement the 2014 Myanmar Guidelines published by the National AIDS Programme. In particular, it is recommended that all people living with HIV be provided with ART. With this recommendation, all limitations on eligibility for ART among people living with HIV are to be removed. The same once-per-day combination pill is now recommended for all adults living with HIV, including those with tuberculosis, hepatitis, and other co-infections. The Ministry of Health and Sports acknowledge the contribution of the Guidelines Drafting Team and the Peer Review Team, concerned programs including National Tuberculosis Program, and partner agencies.

These guidelines are for all healthcare personnel in the public and private sectors serving HIV patients in Myanmar. It should be stressed that the choice of the patients must be respected and a high degree of professionalism should be maintained at all times regardless of the situation or the premises. The guidelines are optimized for all health workers regardless of their experience or training and suitable for patients living anywhere in Myanmar to seek necessary treatment and care.

We are confident that these guidelines will be of immense help to further scale-up quality HIV treatment services throughout the country. The NAP is thus very pleased to issue the Guidelines for the Clinical Management of HIV infection in Myanmar, Fifth Edition.

(Dr Than Win)
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Summary of key recommendations

Chapter	Recommendation
1. Diagnosis of HIV	
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 diagnosis
HIV diagnosis in infants and children	
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. HIV virological assays used for the purpose of clinical diagnostic testing (usually at or after 6 weeks of age) 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. 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. All HIV exposed infants should have HIV virological testing at 4-6 weeks of age or at the earliest opportunity thereafter. If resources are available, addition of NAT at birth to existing early infant diagnosis (EID) testing approaches can be considered to identify HIV infection in HIV-exposed infants. 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. 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. Positive test result should be fast-tracked to the mother-baby pair as soon as possible to enable prompt initiation of ART. HIV-exposed infants who are well should undergo HIV serological testing at around 9 months of age. Infants who have reactive serological assays at 9 months should have a virological test to identify HIV infection and the need for ART. Infants with signs and symptoms suggestive of HIV infection should undergo HIV serological testing and, if positive, virological testing. 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.

Other priority populations	
Adolescents	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.
Key populations	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. 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.
2. Antiretroviral drugs for HIV prevention	
Oral pre-exposure prophylaxis for preventing 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
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: LPV/r or ATV/r • Alternative third drug: EFV 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: LPV/r • Age appropriate alternative third drug: can be ATV/r, RAL, DRV, EFV or NVP A full 28-days 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.

3. 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/mm³
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 adolescents (10–19 years of age)	Initiate ART in all adolescents living with HIV, regardless of WHO clinical stage and at any CD4 cell count As a priority, initiate ART in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with a CD4 count ≤350 cells/mm³
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: As a priority, initiate ART in • all children <2 years of age, • children younger than 5 years of age with WHO clinical stage 3 or 4 or CD4 count ≤750 cells/mm³ or CD4 percentage <25% and • children 5 years of age and older with WHO clinical stage 3 or 4 or CD4 count ≤350 cells/mm³.
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 8 weeks of treatment. HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/ mm³) should receive ART within the first two weeks of initiating TB treatment. ART should be started in any child with active TB disease as soon as possible and within 8 weeks following the initiation of anti-tuberculosis treatment regardless of the CD4 cell count and clinical stage.
What to start: first-line ART	
First-line ART for adults and adolescents	Recommended regimen: 2 NRTI + 1 NNRTI or 1 Integrase Inhibitor (INSTI) Preferred option: TDF + 3TC (or FTC) + EFV as a fixed-dose combination Alternative first line regimen: • AZT + 3TC + EFV • ABC + 3TC + EFV • TDF + 3TC (or FTC) + DTG

First-line ART for pregnant and breastfeeding women	Preferred regimen: TDF + 3TC (or FTC) + EFV as a fixed-dose combination Alternative first line regimen: • AZT + 3TC + EFV (or NVP) • TDF + 3TC (or FTC) + NVP
First-line ART for children aged 3 to 10 years of age	Preferred regimen: ABC + 3TC + EFV Alternative first line regimen: • ABC + 3TC + NVP • AZT + 3TC + EFV or NVP • TDF + 3TC (or FTC) + EFV or NVP
First-line ART for children younger than 3 years of age	Preferred first line regimen: ABC (or AZT) + 3TC + LPV/r Alternative first line regimen: ABC (or AZT) + 3TC + NVP
Monitoring the response to ART and diagnosing treatment failure	
Laboratory monitoring before and after initiating ART	Routine viral load monitoring can 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. 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 load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure. Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, two consecutive viral load measurements within a 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: 2 NRTI + 1 PI or 2 NRTI + 1 INSTI The following sequence of second-line NRTI options is recommended: After failure on a TDF + 3TC (or FTC)-based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens. After failure on an AZT or d4T + 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-based regimen, children younger than 3 years should be switched to a RAL-based second-line regimen. After failure of a first-line LPV/r-based regimen, children older than 3 years should be switched to a second-line regimen containing two NRTIs plus EFV or RAL. After failure of a first-line NNRTI-based regimen, children should be switched to a boosted PI-based regimen. LPV/r or ATV/r are preferred. 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. After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC).
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.
4. 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/mm³. 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/mm³). 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	Xpert MTB/RIF should be used as the initial diagnostic test in adults and children suspected of having HIV-associated TB or multidrug resistant TB. LF-LAM may be used to assist in the diagnosis of active TB in adult patients 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 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.
Isoniazid preventive therapy (IPT)	Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT. Adults and adolescents living with HIV who have an unknown or positive tuberculin skin test (TST) status and are unlikely to have active TB should receive at least 6 months of IPT. IPT should be given to such individuals regardless of the degree of immunosuppression, ART status, pregnancy and prior TB treatment history. 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. Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive 6 months of IPT (10 mg/kg/day). In general, IPT is not indicated for the HIV infected children who had completed prior IPT. However, IPT may be considered as in dividual case, for those at high risk of becoming re-infected and progressing to TB disease. In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive 6 months of IPT if the evaluation shows no TB disease.
Multidrug-resistant TB and HIV	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line antituberculosis drugs irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment.

Cryptococcal disease	Prompt lumbar puncture with measurement of CSF opening pressure by using spinal manometer and rapid CSF cryptococcal antigen (CrAg) assay or rapid serum CrAg (either LA or LFA) is the preferred diagnostic approach. The routine use of antifungal primary prophylaxis for cryptococcal disease in HIV-infected adults, adolescents and children with a CD4 count less than 100 cells/mm³, and who are CrAg-negative or where CrAg status is unknown, is not recommended prior to ART initiation. The use of routine serum or plasma CrAg screening in ART-naive adults, followed by pre-emptive antifungal therapy if CrAg-positive to reduce the development of cryptococcal disease, may be considered prior to ART initiation in patients with a CD4 count less than 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 2-5 weeks of induction and consolidation treatment with Amphotericin containing regimen.
Assessment and management of non-communicable diseases	Assessment and management of cardiovascular risk should be provided for all individuals living with HIV according to standard protocols recommended for the general population.
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 2016, extensive consultations and discussions were held in Naypyitaw and Yangon on the adaptation of the Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach (WHO, 2016), with active participation of all stakeholders. Under the leadership of the National AIDS Programme, the core writing group was formed and drafted these Guidelines for the clinical management of HIV infection in Myanmar: Fifth 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
- update on the initiation of ART
- new ARV drugs and regimens
- new recommendation on infant prophylaxis
- 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 and Sports.

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 QA mechanisms should ensure that people receive a correct diagnosis. QA 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.

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 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 IPT 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.

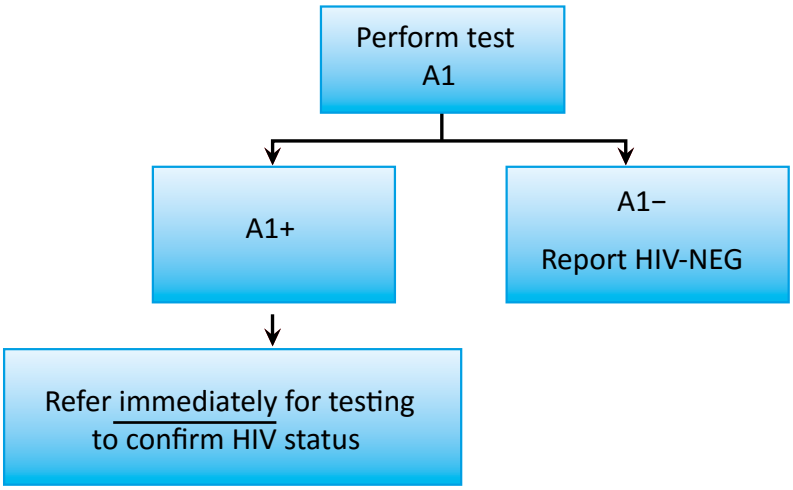
1.2. Laboratory diagnosis of HIV infection

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 RDT.

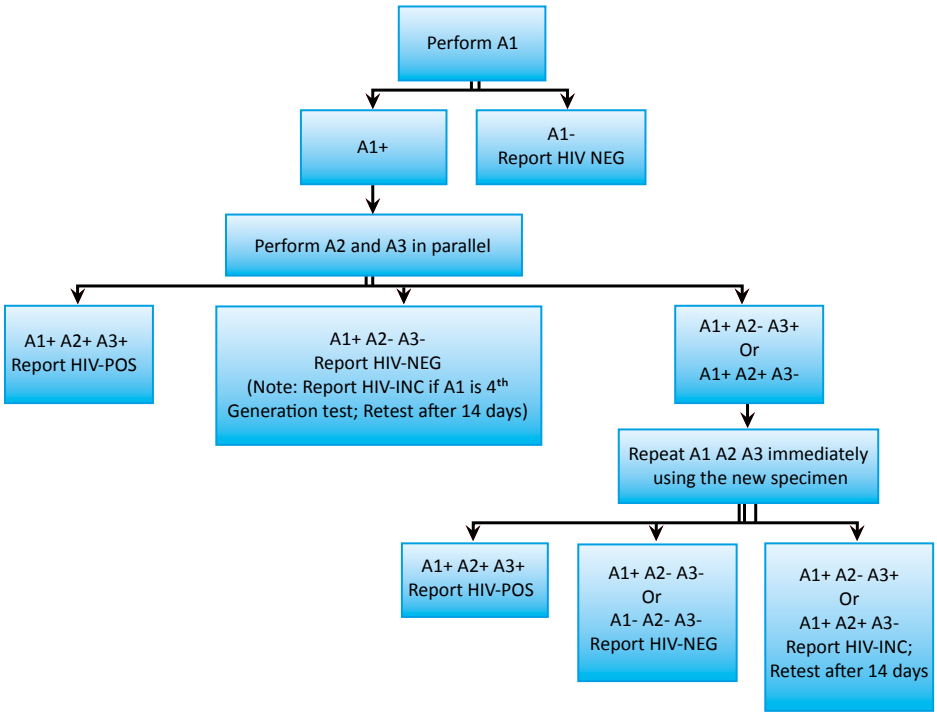
Figure 1. Testing algorithm for HIV screening



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.**

Figure 2. Testing algorithm for HIV confirmation



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 can 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%)

A3 = HIV 1/2 STAT-PAK (manufactured by Chembio Diagnostic Systems Ltd., USA) (SP) ICT (sensitivity 99% and specificity 100%)

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:

- All HIV exposed infant should have HIV virological testing at 4-6 weeks of age or at the earliest opportunity thereafter.
- 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.
- 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.

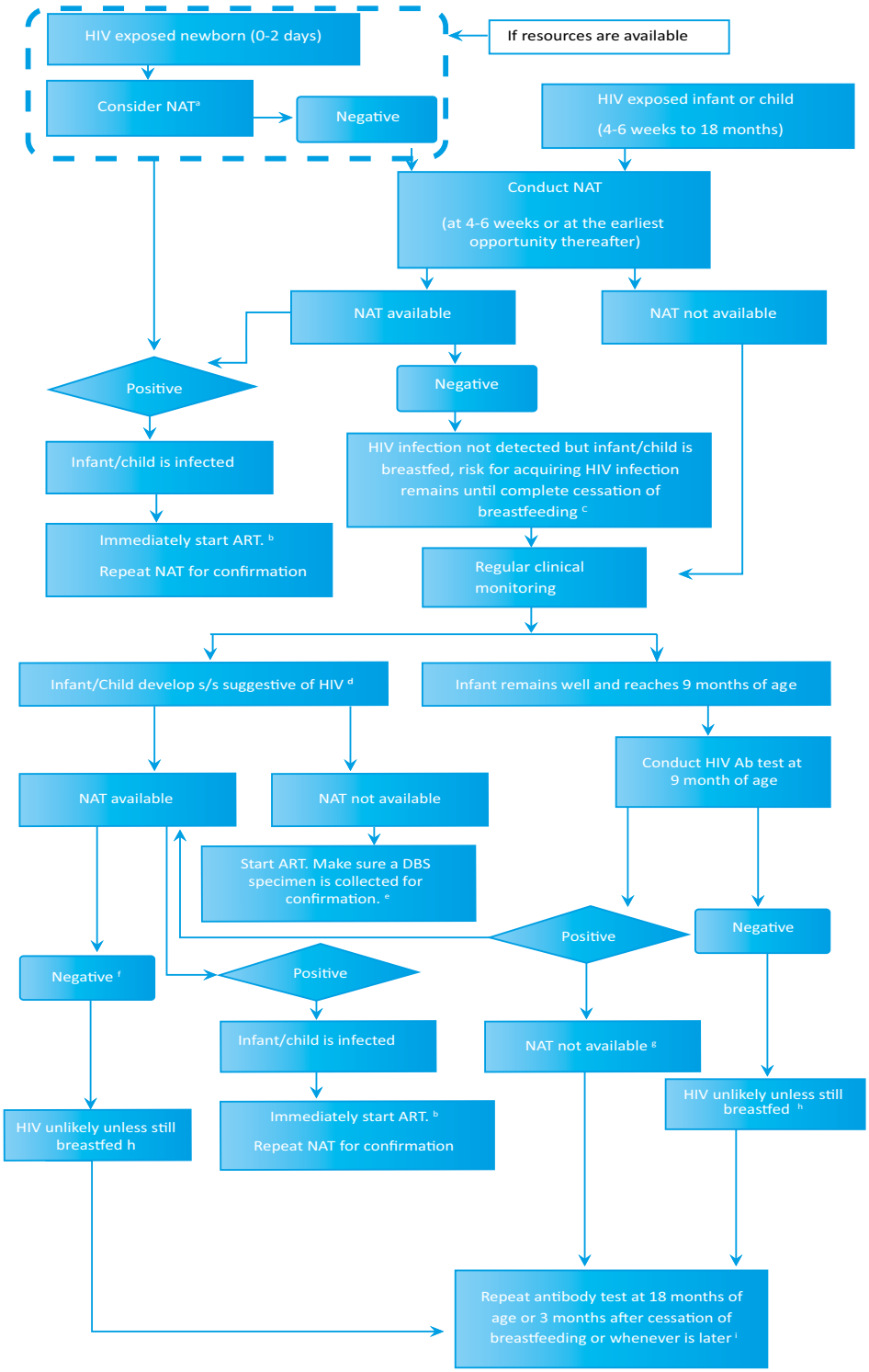
HIV virological assays used for the purpose of clinical diagnostic testing (usually at or after 6 weeks of age) have a sensitivity of at least 95% and ideally greater than 98%, and specificity of 98% or more under quality assured, standardized and validated laboratory conditions.

For children of 18 months of age or older, who are not on breastfeeding anymore, or who have stopped breastfeeding at least six weeks 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 early infant diagnosis



Important Notes:

[a] Based on these revised Guidelines addition of NAT at birth to the existing testing algorithm can be considered.

[b] 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 and re-testing after a first positive NAT is important to avoid unnecessarily treatment, particularly in settings with lower transmission rates. If the second test is negative, a third NAT should be done before interrupting ART.

[c] 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.

[d] Signs and symptoms suggestive of HIV (oral thrush, recurrent or severe bacterial infections such as pneumonia or sepsis, FTT/wasting or AIDS indicator condition http://www.who.int/hiv/pub/paediatric/infants2010/en/).

[e] If infant presents with signs and symptoms of HIV disease (see footnote d above) but NAT is unavailable, consider starting ART, especially if an antibody test is conducted and result positive at 9 months or later. A DBS specimen must be collected prior to starting treatment for later NAT testing to confirm HIV diagnosis, because subsequent diagnostic testing while already on ART might be difficult to interpret.

[f] If infant presents with signs and symptoms of HIV disease (see footnote d above) consider starting ART while waiting for NAT result. However, another DBS specimen should be collected prior to starting treatment for later NAT testing to confirm HIV diagnosis.

[g] Regular and periodic monitoring should be ensured while waiting for NAT to be available or for antibody testing to be conducted at 18 months. If infant presents with signs and symptoms of HIV disease should be managed as described previously (see footnote e).

[h] The risk of HIV transmission remains as long as breastfeeding continues. If the 9 months antibody testing is conducted earlier than 3 months after cessation of breastfeeding, infections acquired in the last days of breastfeeding may be missed so retesting at 18 months should be ensured for final assessment of HIV status.

[i] If breastfeeding beyond 18 months, final diagnosis of HIV status can only be assessed at the end of breastfeeding. If breastfeeding ends before 18 months, 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 < 18 months of age positive antibody testing requires NAT to confirm infection. If infant is > 18 months, negative antibody testing confirms infant is uninfected; positive antibody testing confirms infant is infected

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

A systematic review and metanalysis of PrEP trials containing TDF demonstrated that PrEP is effective in reducing the risk of acquiring HIV infection. The levels of protection did not differ by age, sex, regimen (TDF versus TDF+FTC) and mode of acquiring HIV (rectal, penile and vaginal exposure). The level of protection was strongly correlated with adherence.

- HIV testing is required before PrEP is offered and 3 monthly interval while PrEP is taken.
- 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.

2.2. 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-blood-stained 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.
- **PEP regimens for adults and adolescents:**
    - TDF + 3TC (or FTC) is the preferred backbone.
    - LPV/r or ATV/r is the preferred third drug.
    - EFV is the alternative third drug.
- **PEP regimens for children <10 years:**
    - AZT+3TC is the preferred backbone.
    - ABC+3TC or TDF+3TC can be considered as alternatives.
    - LPV/r is the preferred third drugs.
    - An age-appropriate alternative third drug can be identified among ATV/r, RAL, DRV, EFV and NVP.
- A 28 days prescription of antiretroviral drugs should be provided for PEP following initial risk assessment.
- 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 the exposed person 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.

2.3. 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:

  - o Targeted information and education: use various communication approaches
  - o 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.

3. Pre-ART care

3.1. Natural history of HIV infection

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

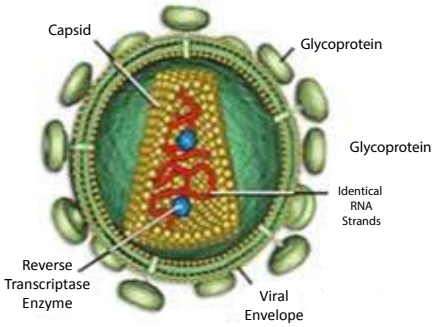
1. **Primary infection** (1 to 3 months): After infection, there is in general a first peak in HIV RNA copies and a steep decline in CD4 cells in the blood. These changes can be explained by the fact that during the early days, HIV can replicate without being controlled by the immune system. When the 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 4 and 5 show the structure of HIV virus and the typical course of untreated HIV infection.

Figure 4. Human immunodeficiency virus (HIV)

1983- HIV discovered

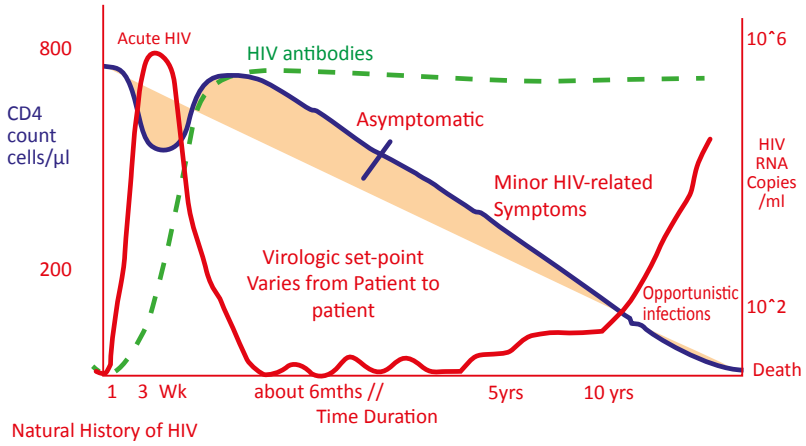
Human Immunodeficiency Virus(HIV) Anatomy



Robert Gallo
Discovered retroviruses

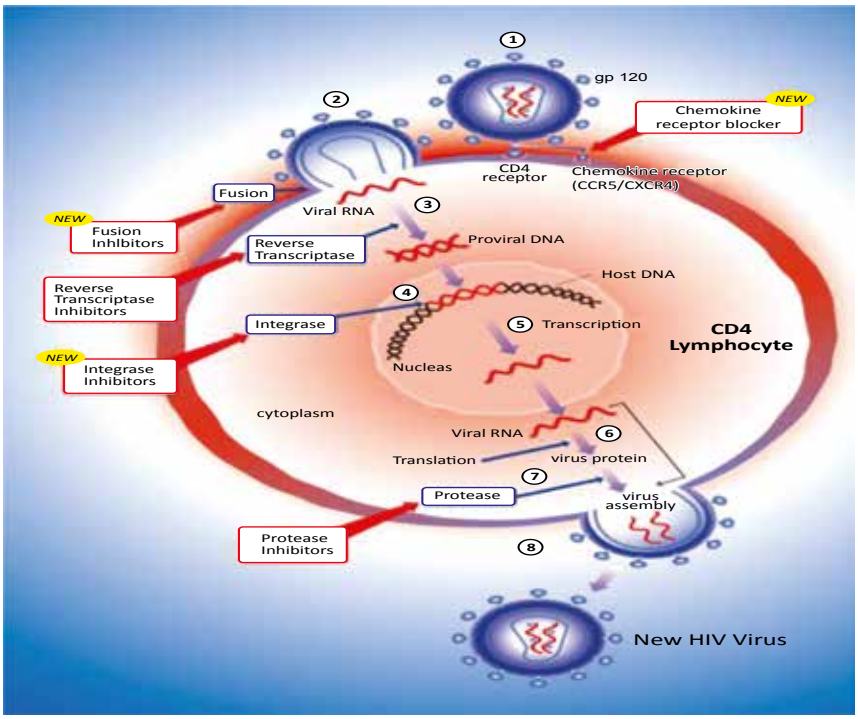
Luc Montagnier
Discovered HIV

Figure 5. 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 6 demonstrates the life cycle of HIV infection and site of action of ARV drugs.

Figure 6. Diagram of HIV life cycle and site of action of ARV drugs



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 • 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.

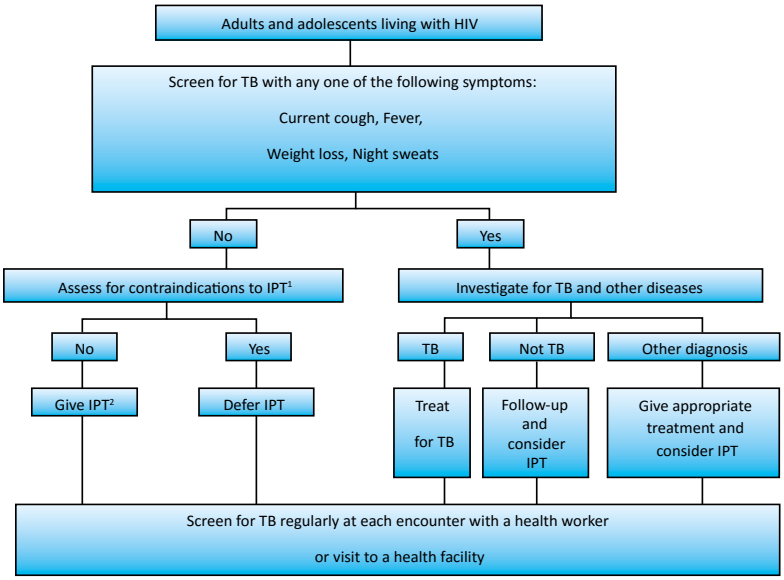
- Current cough
- Fever
- Weight loss
- Night sweat

Algorithm for TB screening and diagnosis of pulmonary TB/MDRTB in adults and adolescent living with HIV is shown in Fig 7 and Fig 8. Refer to the Guidelines for programmatic management of HIV/TB in Myanmar 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 9). 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 7: Algorithm for TB screening in adults and adolescents living with HIV



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

[2] IPT can be given regardless of prior TB treatment history. 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.

Figure 8: Diagnosis of pulmonary TB/MDR-TB in HIV-positive patients

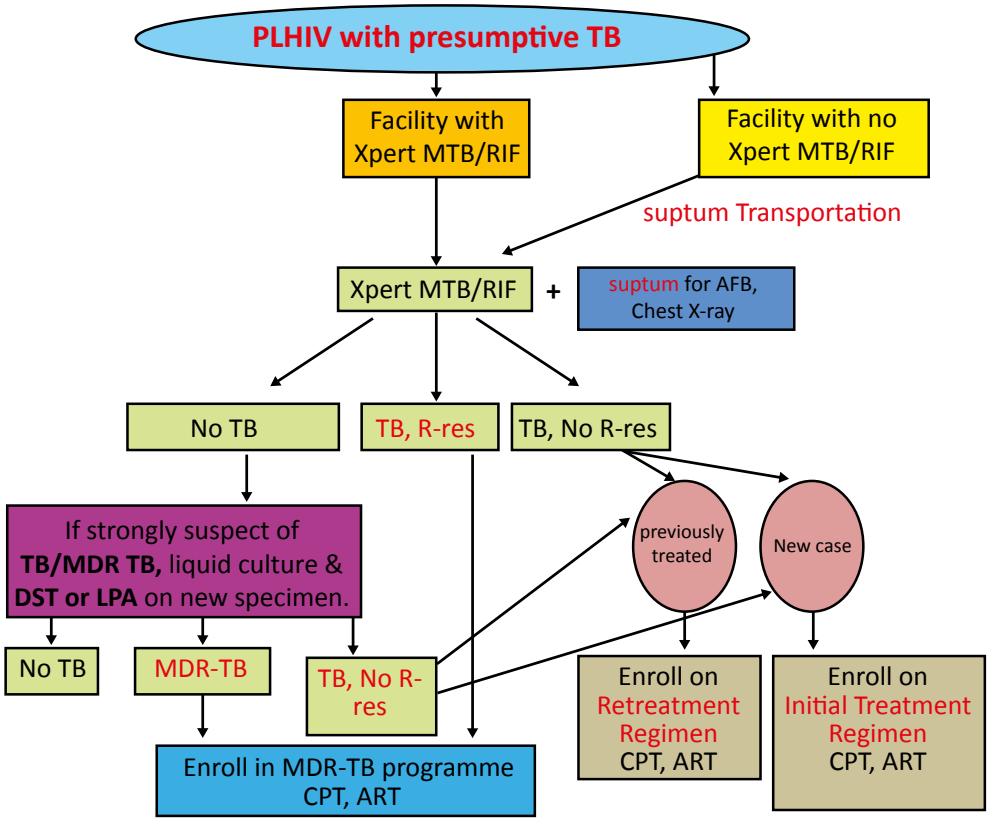
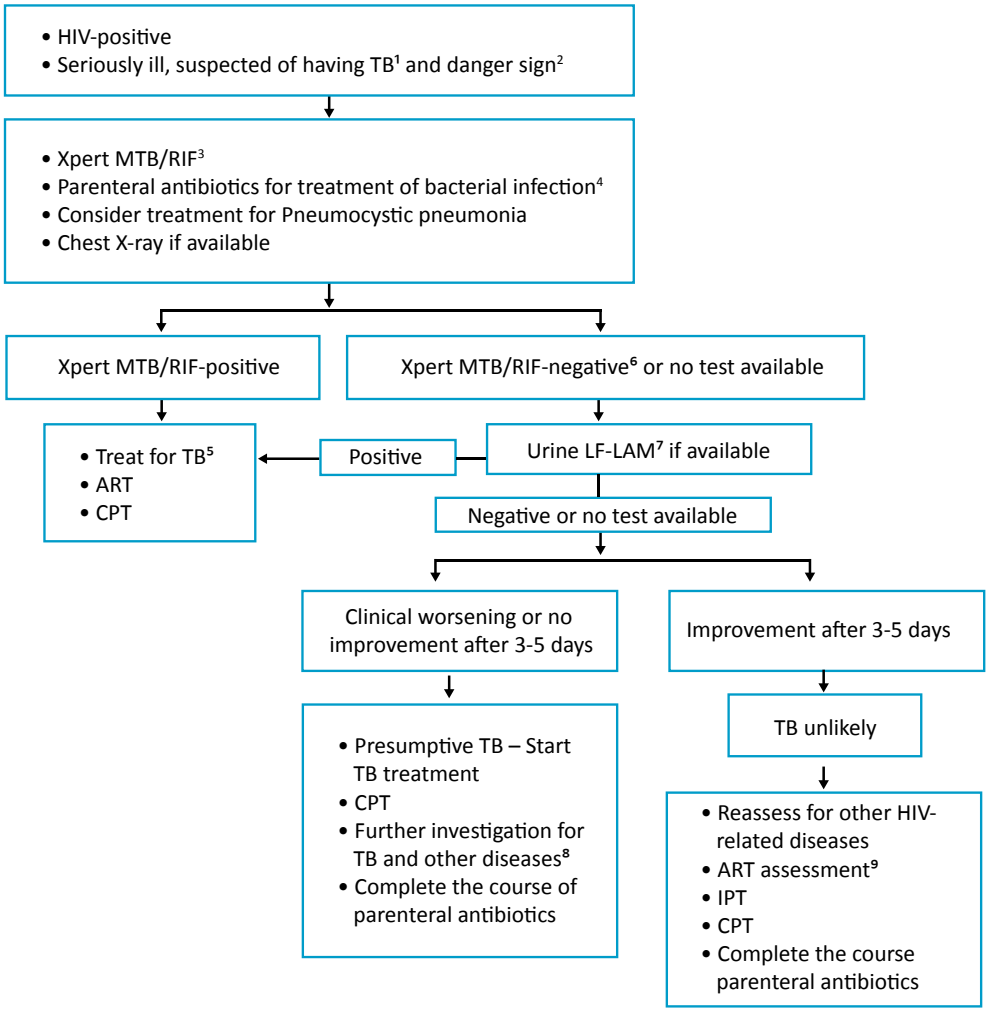


Figure 9: Algorithm for managing people living with HIV and suspected of having TB (seriously ill)



[1]Suspicion of TB is defined by the presence of any one of the following symptoms.

– For adults and adolescents living with HIV: current cough, fever, weight loss or night sweats.

– 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-resistant 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.

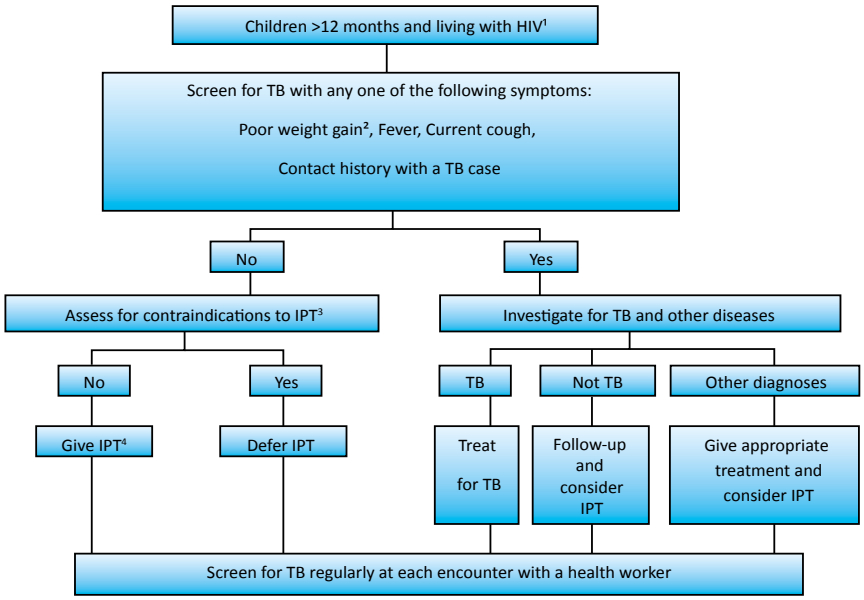
[6]If Xpert MTB/RIF shows negative results, the test can be repeated using a fresh specimen.

[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 and culture. If extrapulmonary TB is suspected, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed.

[9]ART should be recommended for all adults, regardless of CD4 cell count or clinical stage.

Figure 10: 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] 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).

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

[4] In general, IPT is not indicated for the HIV infected children who had completed prior IPT. However, IPT 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/mm³. One double-strength tablet daily of Cotrimoxazole daily is recommended (sulfamethaxazole 800 mg/ trimethoprim 160 mg= 960 mg).

Skin reaction is the commonest side effect with Cotrimoxazole. Other side effects 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 1. Criteria for initiating, discontinuing and monitoring Cotrimoxazole preventive therapy

Age	Criteria for initiation	Criteria for discontinuation [a]
HIV exposed infant	Give to all exposed infants, starting at 4–6 weeks after birth	Until the risk of HIV transmission ends or HIV infection is excluded.
Children and adolescents with HIV	Initiate in all regardless of WHO clinical stage or CD4 count. **As a priority, initiate in:** all less than 5 years of age; all older than 5 years of age with severe HIV disease (Stage 3 or 4) or CD4 count <350 cells/mm³	May be discontinued in 5 years of age and older who are clinically stable, with evidence of immune recovery [b] and/or viral suppression on ART.
Adults (including pregnant women)	Any WHO stage and CD4 count <350 cells/mm³ or WHO 3 or 4 irrespective of CD4	May be discontinued in those who are clinically stable[c], with evidence of immune recovery and/or viral suppression on ART [d].

[a] Discontinue if the person has Stevens-Johnson syndrome, severe liver disease, severe anaemia, severe pancytopenia or negative HIV status.

[b] Parameter for immune recovery in children when >5 years old: CD4 cell count >350 cells/mm³, with viral load suppression.

[c] Clinically stable adults are defined as those individuals on ART for at least one year without any new WHO clinical stage 2, 3 or 4 events.

[d] CD4 count >350 cells/mm³, with viral load suppression, is considered indicative of immune recovery.

3.5. Laboratory assessment for pre-ART

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

Table 2. Laboratory assessment for pre-ART

Recommended	Desirable
CD4 count[a]	Haemoglobin test[b]
	Serum creatinine and estimated glomerular filtration rate (eGFR)[b]
	ALT, AST[b]
	Cryptococcus antigen[b] if CD4 count is < 100 cell/mm³.
	Pregnancy test to assess if ART initiation should be prioritized for PMTCT[b]
	Screening of STI
	HBV serology
	HCV serology

[a] CD4 count is recommended for OI management but not necessarily for ART eligibility.

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

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
    - o past ability to attend clinic regularly
    - o past ability to take drugs regularly, e.g. co-trimoxazole prophylaxis
    - o past ability to complete full course of TB treatment if relevant
    - o adequate understanding of what is involved
- Treatment adherence, at least 95% to the recommended regimens, should be emphasized. This means that missing more than 3 doses per month (with 1 BD regimens) 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 3. Classification and dosage of ARV drugs

Generic name	Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Zidovudine (AZT)	250-300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir (TDF)	300 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)

Generic name	Dose
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 4. 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/mm³
Children and infants	**Initiate ART regardless of WHO clinical stage or at any CD4 count.** **As a priority, initiate those:** • All children under 2 years of age • Children younger than 5 years of age with WHO clinical stage 3 or 4 or CD4 count ≤ 750 mm³ or CD4 percentage <25% • Children 5 years of age and older with WHO clinical stage 3 or 4 or CD4 count ≤350 mm³.

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/mm³

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 including those who are currently on option B.**

In settings where ART initiation site is easily accessible from antenatal care;

- Life-long ART for all HIV(+) pregnant women and mother, mother-baby follow-up, infant prophylaxis and EID, and enrolment in pediatric ART

In settings where ART initiation site is NOT easily accessible from antenatal care;

- As first step, provide ARV drugs to prevent mother-to-child transmission of HIV to pregnant women within one week of HIV diagnosis (*This is similar to Option B in 4th edition of HIV Clinical Management Guideline, 2014)
- Throughout the antenatal care and post natal care follow-up, provide the mother with counseling, support and education on ART to ensure client's readiness to receive long ART
- At the same time link/refer to ART facilities for life-long ART as soon as feasible in consultation with the mother
- In case mother decides not to continue ARV for life long, make sure to continue ARV at least to one week after cessation of breast feeding
- These activities will ensure life-long ART for all HIV(+) pregnant woman and mother, mother-baby follow-up, infant prophylaxis and EID, and enrolment in pediatric ART

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/mm³ (if younger than 5 years) and CD4 count at or below 350 cell/mm³ (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 risks for TB infection increases within one or two years after HIV infection begins and it has been shown that it becomes significantly high when the HIV positive patient remains below CD4 count < 500 cell /mm³.

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 to 8 weeks of treatment.

HIV positive TB patients with profound immunosuppression (e.g. CD4 count less than 50 cells/mm³) should receive ART within the first 2 weeks of initiating TB treatment.

4.4. What to start: first-line ART

Table 5. 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 + 3TC (or FTC) + EFV [b]	AZT + 3TC + EFV TDF + 3TC (or FTC) + DTG [c] ABC + 3TC + EFV [d]
Pregnant or breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV TDF + 3TC (or FTC) + NVP ABC + 3TC + EFV [d]
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

[a] ART regimens for HIV+ TB cases are same as the regimens for HIV+ cases without TB

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

[c] Safety and efficacy data on the use of DTG in pregnant women, people living with HIV/TB coinfection and adolescents younger than 12 years of age are not yet available.

[d] ABC based regimen may be considered for pregnant women under special circumstances which may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons.

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

Table 6. Summary of first-line ART regimens in adults and adolescents

Preferred regimen	TDF + 3TC (or FTC) + EFV
Alternative regimens	AZT + 3TC + EFV TDF + 3TC (or FTC) + DTG ABC + 3TC + EFV

Remark: The above mentioned table includes recommended first-line ART regimens (both preferred and alternative) for initiation of ART. There may still be PLHIV who have been taking ART for a long period and maintained on other ART regimens mentioned below. They can be continued on these regimens if there is no indication to change.

- **TDF + 3TC (or FTC) + NVP**
- **AZT + 3TC + NVP**
- **ABC + 3TC + NVP**

TDF + 3TC (or FTC) + EFV

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. It is the preferred regimen when there is HIV/HBV co-infection where both TDF and 3TC have activity against HBV. It also avoids the potential hepatotoxicity of NVP. 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 (Cockcroft-Gaultformula). This combination is also preferred if there is HIV/TB co-infection and also in late stage disease when AZT had to be avoided because of anaemia.

AZT + 3TC + EFV

This is a preferred alternate first line regimen especially when TDF is contraindicated. It can well be used with TB and hepatitis co-infection where EFV provides benefits over NVP. There is a chance of the development of AZT associated anaemia which is most common in the first 6 months of treatment but which can occur any time, sometimes abruptly to dangerous Hb levels. Patients are warned to report immediately when severe pallor or shortness of breath develops. In advanced disease when there is anaemia (Hb< 10 g/dl) it is advisable to avoid AZT. It has been reported that baseline anaemia predicts development of AZT anaemia which supports baseline testing and avoidance of AZT if patient is anaemic.

[N.B. In advanced disease with very low CD4 counts and low BMI, anaemia is present in most patients. This anaemia is usually due to anaemia of chronic disease due to opportunistic infections or HIV itself, made worse by nutritional deficiencies (especially iron and folate deficiency) due to loss of appetite or chronic diarrhoea. Treatment of OIs and ART usually improves the anaemia but AZT itself is capable of causing bone marrow suppression and some patients may have a severe fall in Hb levels. With pre-existing anaemia of Hb<10 g/dl there is a risk of a further fall in Hb to dangerous level. Hb level is monitored at 4, 8 and 12 weeks of AZT therapy and the patient is advised to report if shortness of breath or severe pallor develops while on AZT therapy.]

TDF + 3TC (or FTC) + DTG

In 2015, a systematic review and network meta-analysis was conducted to assess direct and

indirect comparative evidence of the efficacy and safety of the integrase inhibitors (INSTI) including dolutegravir (DTG). The analysis showed moderate quality evidence that two NRTIs + INSTI was a generally more effective regimen (with higher viral suppression, CD4 cell recovery rate and lower risk of treatment discontinuation) than two NRTIs + EFV 600 mg. DTG has other clinical and programmatic advantages when compared with EFV 600 mg, including lower potential for drug interactions, a shorter median time to viral suppression and a higher genetic resistance barrier when compared to EFV and other ARV drugs. The safety and efficacy of DTG during pregnancy and among TB/HIV co-infected patient using rifampicin has not been established.

ABC + 3TC + EFV

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 both TDF and AZT as first-line ART.

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 but there are a few key differences in term of alternative regimens for first-line ART. DTG has not been studied significantly in pregnant women for it to be recommended as an alternative in this population. In addition, the efficacy of low-dose EFV in pregnancy has not been studied. As a result, alternative first line ART for pregnant and breastfeeding women includes only NVP in place of EFV and AZT in place of TDF.

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) + EFV which is same as adults.

For infants

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

Table 7. 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)
>6 weeks to 12 weeks		
	20 mg once daily (2 ml of syrup once daily or half [a] 50 mg tablet once daily)	No dose established for prophylaxis; use treatment dose 60 mg twice daily or 6 ml of syrup twice daily or a 60 mg tablet twice daily

[a]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 3-10 years of age

Table 8. Frist-line ART regimens for children 3-10 years of age

Preferred	**ABC + 3TC + EFV**
Alternative	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP

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 use of non-thymidine analogues – either ABC or TDF – in the first-line regimen to maximize the response to AZT in the second line ART; and
- the provision of treatment recommendations for older children that are aligned with those for adolescents and adults.

4.4.4. First-line ART regimens for children younger than 3 years

Table 9. Frist line ART regimen for children younger than 3 years

Preferred regimens	**ABC[a] or AZT + 3TC + LPV/r**
Alternative regimens	ABC or AZT + 3TC + NVP
Special circumstances [b]	ABC or AZT + 3TC + RAL[c]

[a] Based on the general principle of using non-thymidine analogues in the first-line regimens and thymidine analogues in the second-line regimens, ABC should be considered as the preferred NRTI whenever possible.

[b] Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug to drug interactions, drug procurement and supply management issues for other reasons.

[c] RAL is approved for use in infants and children from the age of 4 weeks, but there is very limited evidence to inform the use of raltegravir (RAL) as a first-line drug in infants and young children.

4.4.5. TB co-infection in children with HIV

Table 10. Summary of recommended ART regimens for children who need TB treatment

Recommended regimens for children and infants initiating ART while on TB treatment [a,b]		
Younger than 3 years	**Triple NRTI (AZT + 3TC + ABC) [c]**	
3 years and older	**Two NRTIs + EFV** or **Triple NRTI (AZT + 3TC + ABC)**	
Recommended regimen for children and infants initiating TB treatment while receiving ART [a]		
Child on standard NNRTI based regimen **(Two NRTIs + EFV or NVP)**	Younger than 3 years	**Continue NVP,** ensuring that the **dose is 200 mg/m².** or **Triple NRTI (AZT+ 3TC + ABC) [c]**
	3 years and older	If the child is **receiving EFV, continue the same regimen.** If the child is **receiving NVP, substitute with EFV.** or **Triple NRTI (AZT + 3TC + ABC) [c]**
Recommended regimen for children and infants initiating TB treatment while receiving ART [a]		
Child on standard PI-based regimen **(Two NRTIs + LPV/r)**	Younger than 3 years	**Triple NRTI (AZT + 3TC + ABC) [c]** or **Continue LPV/r, adding RTV to achieve the full therapeutic dose [d]**
	3 years and older	If the child has no history of failure of an NNRTI-based regimen: **Substitute with EFV [e]** or **Triple NRTI (AZT + 3TC+ ABC) [c]** or **Continue LPV/r, adding RTV to achieve the full therapeutic dose [d]** If the child has a history of failure of an NNRTI-based regimen: **Triple NRTI (AZT+ 3TC+ ABC) [c]** or Continue LPV/r adding RTV to achieve the full therapeutic dose [d] Consider consultation with experts for constructing a second-line regimen.

[a] Ensure optimal dosing of rifampicin based on dosing guidelines

[b] Substitute ARV drugs based on an age-appropriate ART regimen in line with nationally recommended first-line ART.

[c] Triple NRTI is only recommended for the duration of TB treatment; an age-appropriate PI or NNRTI based regimen should be restarted when rifampicin based therapy ends.

[d] Increase RTV until it reaches the same dose as LPV in mg, in a ratio of 1:1.

[e] Substitution of EFV should be considered as the preferred option and EFV could be maintained after TB treatment ends to enable simplification and harmonization with the ARV drug regimens used for older children.

4.5. Monitoring ARV toxicities and response to treatment

4.5.1. ARV toxicities

Table 11. 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 allele	Do not use ABC in the presence of HLA-B*5701 allele. 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 1A1*28 (UGT1A1*28) allele	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.

ARV drug	Major type of toxicity	Risk factors	Suggested management
AZT	Severe anaemia, neutropaenia	CD4 cell count of ≤200 cells/ mm³	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).
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)	For CNS symptoms, dose at night-time. Consider using EFV at a lower dose (400 mg/ day) or substitute with NVP or integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms. For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
	Convulsions	History of seizure	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	
	Severe skin and hypersensitivity reactions	Risk factor(s) unknown	
	Gynaecomastia	Risk factor(s) unknown	Substitute with NVP or another therapeutic class (integrase inhibitors or boosted PIs).

ARV drug	Major type of toxicity	Risk factors	Suggested management
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 misuse	
	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/mm³ in women or >400 cells/mm³ 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).

ARV drug	Major type of toxicity	Risk factors	Suggested management
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 BMI <18.5 or low body weight (<50 kg) notably in females Untreated diabetes Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	Substitute with AZT or ABC. Do not initiate TDF at eGFR <50 mL/min, uncontrolled hypertension, untreated diabetes, or presence of renal failure.
	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	

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]Using the Cockcroft-Gault (CG) or Modification of Diet in Renal Disease (MDRD) formulas for estimation. An onlinecalculator is available at http://nephron.com/cgi-bin/CGSI.cgi.

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

MDRD formula: eGFR = 175 X SerumCr–1.154 X age–0.203 X 1.212 (if patient is black) X 0.742 (if female).

4.5.2. Drug interactions

Antituberculosis drugs

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 children, using a triple NRTI regimen (such as AZT + 3TC + ABC) should also be considered. 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.

Rifampicin is known to significantly lower plasma concentrations of DTG, and increasing the dose to a twice-daily schedule may be necessary.

Drugs for Hepatitis C

Potential drug interactions should be considered when using ARV drugs and DAAs for HCV infection. Simeprevir and the combination of ombitasvir + paritaprevir + ritonavir plus dasabuvir should not be co-administered with any PI or NNRTI. 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 90 mg/day.

Antifungal agents

Itraconazole 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 and fluconazole) 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 12. Key ARV drug interaction and suggested management

ARV drug	Key interactions	Suggested management
AZT	Ribavirin and pegylatedinterferon alpha-2a	Substitute AZT with TDF
Boosted PI (ATV/r, DRV/r, LPV/r)	Rifampicin	Substitute rifampicin with rifabutin Adjust the dose of LPV/r or substitute with three NRTIs (for children)
	Halofantrine and lumefantrine	Use an alternative antimalarial agent
	Lovastatin and simvastatin	Use an alternative cholesterol-lowering agent
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Methadone and buprenorphine	Adjust methadone and buprenorphine doses as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	TDF	Monitor renal function
	Simeprevir	Use alternative DAA
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA

ARV drug	Key interactions	Suggested management
DTG	Carbamazepine, phenobarbital and phenytoin	Use alternative anticonvulsant agent
	Polyvalent cation products containing Mg, Al, Fe, Ca and Zn	Use DTG 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- or Zn-multivitamin supplements; mineral supplements, cation-containing laxatives and Al-, Ca- or Mg-containing antiacids. Monitor for virological efficacy
EFV	Amodiaquine	Use an alternative antimalarial agent
	Methadone	Adjust the methadone dose as appropriate
	Hormonal contraceptives	Use alternative or additional contraceptive methods to prevent HIV transmission and unintended pregnancies, as EFV may lower efficacy of some long-acting hormonal contraceptives
	Astemizole and terfenadine	Use an alternative antihistamine agent
	Simeprevir	Use alternative DAA
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA
NVP	Rifampicin	Substitute NVP with EFV
	Methadone	Adjust the methadone dose as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	Itraconazole and ketoconazole	Use an alternative antifungal agent
	Simeprevir	Use alternative DAA
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA

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 13. Recommended laboratory monitoring of ART

Phase of HIV management	Recommended	Desirable
HIV diagnosis	HIV testing (serology for adults and children 18 months or older; EID for children younger than 18 months) CD4 cell count[a] TB symptom screening	HBV (HBsAg) serology[b] HCV serology Cryptococcus antigen if CD4 cell count ≤100 cells/mm^3 [c] Screening for STIs Pregnancy test to assess if ART initiation should be prioritized to prevent HIV transmission to the child Assessment for major non-communicable chronic diseases and co-morbidities[d]
Follow-up before ART	CD4 cell count (every 6–12 months in circumstances where ART initiation is delayed)	
ART initiation		Haemoglobin test for starting AZT[e]* Serum creatinine and estimated glomerular filtration rate (eGFR) or starting TDF[f]* Alanine aminotransferase for NVP[g]* Pregnancy test Blood pressure measurement Baseline CD4 cell count
Receiving ART	HIV viral load (at 6 months and 12 months after initiating ART and every 12 months thereafter). If routine viral load is not available, targeted viral load testing is recommended. CD4 cell count every 6 months until patients are stable on ART	Serum creatinine and eGFR for TDF[f] Pregnancy test, especially for women of childbearing age not receiving family planning and on treatment with DTG or low-dose EFV
Suspected treatment failure	Serum creatinine and eGFR for TDF[f] pregnancy test, especially for women of childbearing age not receiving family planning and on treatment with DTG or low-dose EFV	HBV (HBsAg) serology[a,h] (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]CD4 count is recommended for OI management but not necessarily for ART eligibility.

[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]Can be considered in settings with a high prevalence of cryptococcal antigenaemia (>3%).

[d]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.

[e]Among children and adults with a high risk of adverse events associated with AZT (low CD4 or low BMI).

[f]Among people with a high risk of adverse events associated with TDF: underlying renal disease, older age group, low body mass index (BMI), diabetes, hypertension and concomitant use of a boosted PI or potential nephrotoxic drugs.

[g]Among people with a high risk of adverse events associated with NVP, such as being ART-naive, women with HIV with a CD4 count >250 cells/mm^3 and hepatitis C virus (HCV) coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity.

[h]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 14. 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/mm³ following clinical failure[b] or Persistent CD4 levels below 100 cells/mm³ **Children** Younger than 5 years Persistent CD4 levels below 200 cells/mm³ Older than 5 years Persistent CD4 levels below 100 cells/mm³	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.

Stopping CD4 count monitoring where viral load testing is available

Recent studies suggest that in situations where viral load testing is routinely available and individuals are virally suppressed, long-term CD4 cell count monitoring adds little value, and stopping the estimation of CD4 for monitoring purposes will have major cost savings.

4.6.1. Plasma HIV viral load

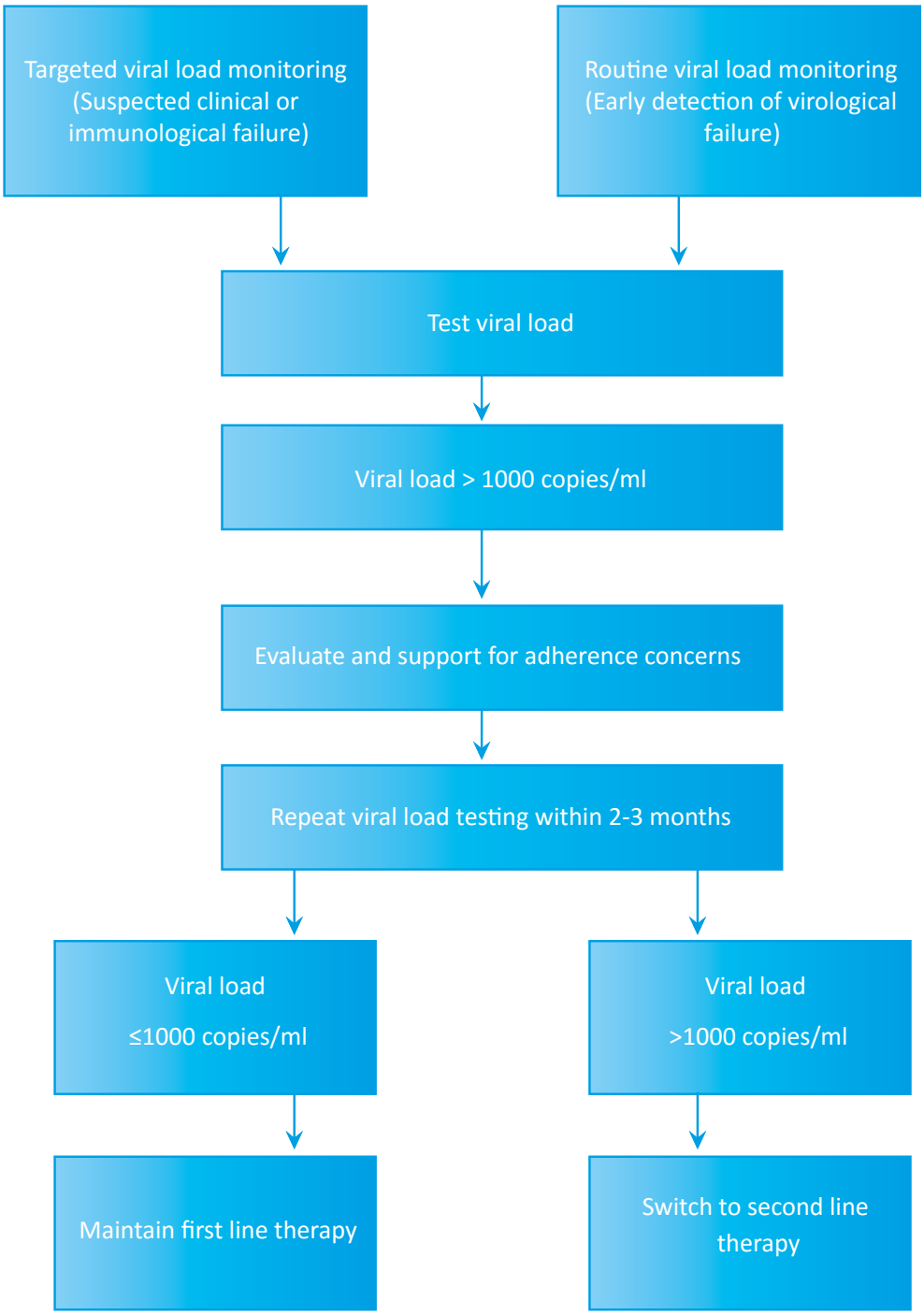
Plasma HIV viral load is measured using PCR (polymerase chain reaction) technology. The result is expressed as copies/ml. In HIV symptomatic or in late cases VL may be as high as 100,000- 1,000,000 copies/ml or more. Plasma viral load can be used to monitor therapeutic success of ART. It is the most 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 (50–1000 copies/mL) can occur during effective treatment but have not been associated with an increased risk of treatment failure.

Figure 11. Algorithm for defining treatment failure



4.6.2. Second line ART regimens

Table 15. Preferred second line ART regimen for adults, adolescents and pregnant women and children

Population		Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + ATV/r or LPV/r	2 NRTIs[b] + DRV/r[c] 2 NRTIs[b] + DTG[e]
		2 NRTIs + DTG		
Pregnant or breastfeeding women		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + ATV/r or LPV/r	2 NRTIs[b] + DRV/r
Children	Less than 3 years	2 NRTIs + LPV/r	2 NRTIs[b] + RAL	Maintain the failing LPV/r-based regimen and switch to 2 NRTIs[b] + EFV at 3 years of age
		2 NRTIs + NVP	2 NRTIs[b] + LPV/r	2 NRTIs[b] + RAL[d]
	3 years to less than 10 years	2 NRTIs + LPV/r[a]	2 NRTIs[b] + EFV	2 NRTIs[b] + RAL[d]
		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + LPV/r	2 NRTIs[b] + ATV/r[d]

[a] ATV/r can be used as an alternative PI for children older than 3 months of age.

[b] If ABC+ 3TC or TDF + 3TC (or FTC) was used in the first-line failing regimen, AZT + 3TC should be used in second-line and vice versa.

[c] RAL + LPV/r can be used as an alternative second-line regimen in adults and adolescents.

[d] DRV/r can be used as an alternative PI option in special situations.

[e] 2 NRTIs + DTG can also be used as an alternative second-line especially for patients failing with first-line regimen not including DTG.

A boosted protease inhibitor (bPI) plus two NRTIs are used for second line ART for adults, adolescent and also for children when NNRTI containing regimens were used in first line ART. In children using a PI-based regimen for first-line ART, switching to NNRTI or maintaining the PI regimen is recommended according with age. In some circumstances, dolutegravir (DTG) might be used for second line ART regimen as alternative option.

A simplified second line ART is recommended –

- If d4T or AZT has been used in first line therapy, use TDF + 3TC (or FTC) plus a boosted PI (LPV/r): for children - ABC+ 3TC+ boosted PI (LPV/r) can also be used.
- If TDF has been used in first line therapy, use AZT + 3TC plus a boosted PI (LPV/r) should be used as second line therapy. In children, if ABC has been used in first line therapy, use AZT + 3TC plus a boosted PI (LPV/r) should be used as second line therapy.
- If LPV/r cannot be used, Atazanavir/r is the alternate bPI for adults and children over 6 years of age.

Table 16. Summary of preferred second-line ART regimens for adults and adolescents

Target population	Preferred second-line regimen[a]	
Adults and adolescents	If d4T or AZT was used in first-line ART	TDF + 3TC (or FTC) + ATV/r or LPV/r [b,c]
	If TDF was used in first-line ART	AZT + 3TC + ATV/r or LPV/r [b,c]
Pregnant or breastfeeding women	Same regimens as recommended for adults and adolescents	
HIV and TB coinfection	If rifabutin is available	Standard PI-containing regimens as recommended for adults and adolescents
	If rifabutin is not available	Same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800 mg/200 mg twice daily)[d]
HIV and HBV coinfection	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)[b]	

[a] ABC and didanosine (ddI) can be used as NRTI back-up options but add complexity and cost without clinical advantages.

[b] DRV/r can be used as an alternative PI option.

[c] RAL + LPV/r can be used as an alternative second-line regimen (conditional recommendation, low-quality evidence).

[d] Standard LPV/r and RTV-boosted saquinavir (SQV/r) doses with an adjusted dose of RTV (that is, LPV 400 mg/ RTV 400 mg or SQV 400 mg /RTV 400 mg twice daily) can be used as alternative options.

3TC lamivudine, ATV atazanavir, AZT zidovudine, d4T stavudine, FTC emtricitabine, LPV lopinavir, NRTI nucleoside reversetranscriptase inhibitor, NVP nevirapine, PI protease inhibitor, r or RTV ritonavir, TDF tenofovir.

Table 17. Summary of recommended first and second line ART regimens for children

	Children (including adolescents)	First-line ART regimen	Second-line ART regimen
LPV/r-based first-line regimen	Younger than 3 years	ABC + 3TC + LPV/r	AZT or ABC+ 3TC + RAL[a]
		AZT + 3TC + LPV/r	
	3 years and older	ABC + 3TC + LPV/r	AZT + 3TC + EFV or RAL
		AZT + 3TC + LPV/r	ABC or TDF[b] + 3TC + EFV or RAL
NNRTI based first-line regimen	All ages	ABC + 3TC + EFV (or NVP)	AZT + 3TC + ATV/r or LPV/r[c]
		TDF[b] + 3TC (or FTC) + EFV (or NVP)	
		AZT + 3TC + EFV (or NVP)	ABC or TDF + 3TC[c] (or FTC) + ATV/r or LPV/r[c]

[a] If RAL is not available, no change is recommended unless in the case of advanced clinical disease progression or lack of adherence specifically due to poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered. Based on approval of the use of EFV in children less than 3 years, an EFV-based regimen could be considered as an alternative. However, more data are needed to inform how best to use EFV in this population.

[b] TDF may be given only to children older than 2 years.

[c] ATV/r can be used as an alternative to LPV/r in children older than 3 months. However, the limited availability of suitable formulations for children younger than 6 years, the lack of an FDC and the need for separate administration of the RTV booster should be considered when choosing this regimen.

3TC lamivudine, ABC abacavir, ATV atazanavir, AZT zidovudine, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NVP nevirapine, r ritonavir, RAL raltegravir, TDF tenofovir.

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.

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. Raltegravir (RAL) is an integrase inhibitor, a new drug with potent antiretroviral actions, but the cost is high. Dolutegravir (DTG) is an integrase inhibitor, and is currently approved for only children 12 years and older; however the studies are ongoing to determine dosing in younger children and approval for lower age groups is expected in the near future.

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 18. Summary of sequencing options for first, second, and third-line ART regimens in adults, adolescents, pregnant women and children

Populations	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (>10 years)	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r[a] 2 NRTI + DRV/r[b]	DRV/r [b] + DTG[c] (or RAL) ± 1–2 NRTIs
		2 NRTI + DTG[c]	DRV/r [b] + 2 NRTIs ± NNRTI
	2 NRTIs + DTG[c]	2 NRTIs + ATV/r or LPV/r	DRV/r [b] + 2 NRTIs ± NNRTI
		2 NRTI + DRV/r	Optimize regimen using genotype profile
Pregnant or breastfeeding women	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r[a]	DRV/r [b] + DTG[c] (or RAL) ± 1–2 NRTIs
		2 NRTIs + DRV/r[b]	
Children (0–10 years)	2 NRTI + LPV/r	If less than 3 years: 2 NRTIs + RAL[d]	RAL (or DTG)[f] + 2 NRTIs DRV/r[g] + 2 NRTIs DRV/r[g] + RAL (or DTG)[f] ± 1–2 NRTIs
		If older than 3 years: 2 NRTIs + EFV or RAL	
	2 NRTI + EFV	2 NRTIs + ATV/r[e] or LPV/r	

[a] RAL + LPV/r can be used as an alternative second-line regimen in adults and adolescents.

[b] In PI experienced patients, the recommended DRV/r dose should be 600 mg/100 mg twice daily.

[c] Safety and efficacy data on the use of DTG in adolescents younger than 12 years and pregnant women are not yet available.

[d] If RAL is not available, no change is recommended unless in the presence of advanced clinical disease progression or lack of adherence, specifically because of poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered. Based on approval of the use of EFV in children less than 3 years of age, an EFV-based regimen could be considered as an alternative. However, more data are needed to inform how best to use EFV in this population.

[e] ATV/r can be used as an alternative to LPV/r in children older than 3 months of age. However, the limited availability of suitable formulations for children younger than 6 years of age, the lack of an FDC and the need for separate administration of RTV booster should be considered when choosing this regimen.

[f] RAL can be used in children failing PI-based second-line treatment when DTG is not available and when RAL has not been not used in a previous regimen. DTG is currently approved only for children 12 years and older; however, studies are ongoing to determine dosing in younger children, and approval for lower age groups is expected in the near future

[g] DRV/r should not be used in children younger than 3 years of age.

ATV atazanavir, DRV darunavir, DTG dolutegravir, EFV efavirenz, LPV lopinavir, NNRTI non-nucleoside reverse-transcriptase inhibitor, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r ritonavir, RAL raltegravir.

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 states 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
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 "Three I's" for HIV/TB (intensified TB case finding, IPT, 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, miliary 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. Xpert MTB/RIF) 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 may 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 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 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, miliary 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. 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.

(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 National TB Programme.

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 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 IPT) 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.

Isoniazid preventive therapy (IPT)

Adults and adolescents with HIV who do not have any one of the symptoms of current cough, fever, weight loss, night sweats or lymph node enlargement have a very low probability of active TB and should be offered IPT. Those who report any one of these symptoms should be evaluated for TB and other diseases. 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. INH is given at a dose of 300 mg/ day regardless of prior TB treatment history. 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. It has been shown that INH resistance is not significantly associated with providing IPT.

Children living with HIV older than 12 months 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. However, IPT may be considered as individual case, for those at high risk of becoming re-infected and progressing to TB disease. 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 all.

Table 19. 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 jerovecii* pneumonia

Pneumocystis jirovecii (previously known as *Pneumocystis carinii*) is a fungus that causes pneumonia in patients with CD4 count<200/mm³. There is subacute onset and progression of exertional dyspnoea, non-productive cough and fever over days or weeks. The dry cough and the exertional dyspnoea are progressive and 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. 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/mm³ to prevent PCP. CPT is continued until the patient is clinically stable on ART at least one year and CD4 >350 cell/mm³.

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. Maintenance is with Pyrimethamine 25-50 mg/day plus Sulphadiazine 500 mg 6 hourly / day plus Leucovorin 10-25 mg/day. The higher dose is for those weighing >60kg; Leucovorin (folinic acid, not folic acid) is necessary to prevent bone marrow suppression due to Pyrimethamine. Maintenance treatment is necessary until the CD4 reaches 200/ mm^3 with ART.

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.

Prompt lumbar puncture with measurement of CSF opening pressure by using spinal manometer and rapid CSF cryptococcal antigen (CrAg) assay or rapid serum CrAg (either LA or LFA) is the preferred diagnostic approach. CSF opening pressure is typically very high.

Initiation of treatment is with i.v. Amphotericin 0.7 mg/kg plus Fluconazole 400 mg i.v./oral/ day for at least 2 weeks followed by consolidation with Fluconazole 400 mg po od for 8 weeks followed by maintenance of Fluconazole 200 mg OD until CD4 count rises to 200/mm^3 with ART. However in resource limited situations Fluconazole 800 mg/day (or more -1200 mg per day)

provides the only practical regimen for the first 2 weeks since it is more convenient, less toxic, less expensive and more easily available than Amphotericin. Itracozonale 200 mg BD in the consolidation and 200 mg OD in the maintenance phase may be used.

The routine use of antifungal primary prophylaxis for cryptococcal disease in HIV-infected adults, adolescents and children with a CD4 count less than 100 cells/mm³, and who are CrAg-negative or where CrAg status is unknown, is not recommended prior to ART initiation.

The use of routine serum or plasma CrAg screening in ART-naive adults, followed by pre-emptive antifungal therapy if CrAg-positive to reduce the development of cryptococcal disease, may be considered prior to ART initiation in patients with a CD4 count less than 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 2-5 weeks of induction and consolidation treatment with Amphotericin containing regimen.

Cryptococcal meningitis in HIV is associated with a high mortality and failure to manage elevated intracranial pressure is the most common cause. Intravenous mannitol may be used initially but removing the CSF until the pressure decreases 50% is more effective.

Immune reconstitution syndrome (IRIS) is sometimes seen following initiation of ART in cryptococcal meningitis. ART may also unmask cryptococcal meningitis.

5.1.5. *Penicillium marneffei* infection in HIV

Systemic infection with *Penicillium marneffei* (penicilliosis) is one of the common OIs 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/mm³. The lesions are papules with central umbilication. 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. Untreated systemic penicilliosis can lead to death. Severe infections have to be treated with intravenous Amphotericin infusion 0.7 mg/kg/day for 14 days followed by Itraconazole 400 mg for 10 weeks followed by secondary prophylaxis of 100 mg 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.

The differential diagnosis is disseminated histoplasmosis and disseminated cryptococcosis which can also present with similar skin lesions and which is also treated similarly with antifungal agents. Skin lesions may resemble molluscum contagiosum (pox virus) but this causes skin lesions only without systemic involvement.

5.1.6. Histoplasmosis infection in HIV infection

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/L, use of 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.

Management- amphotericin B IV 0.7 mg/kg/day x 3-10 days followed by Itraconazole 200 mg PO BD 12 weeks. Response is seen within 1 week. 50% will have blood culture negative about 2-4 weeks after starting treatment.

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 immuno-suppression 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 <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 *Sarcoptesscabiei* (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/mm³ 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 nitazoxanide 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, 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 < 350/mm³ 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/mm³. 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. Prevention, screening and management of other comorbidities

5.2.1. 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 aging.

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.

5.2.2. 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.

5.2.3. 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
- Opiod substitution therapy (OST)
- 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

5.2.4. 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 3TC, 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.

5.2.5. Sexually transmitted infections (STIs) and cervical cancer

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.

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. All women with HIV should therefore be screened for cervical cancer regardless of age. Immediate management of precancerous and cancerous lesions should be provided.

5.2.6. 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 flattering 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.

6. Atlas of HIV related conditions and opportunistic infections

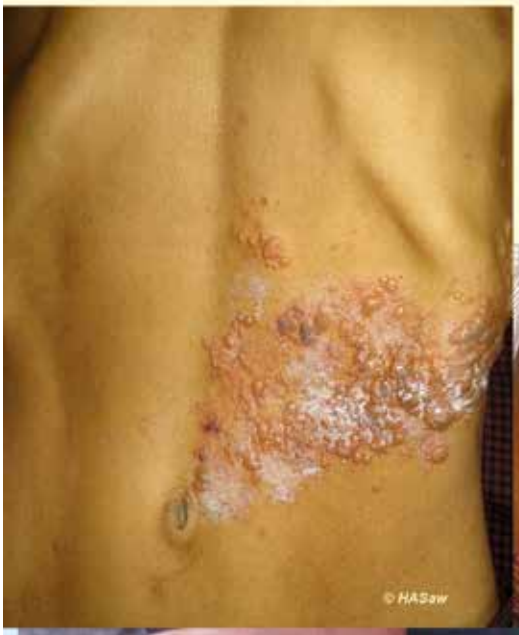
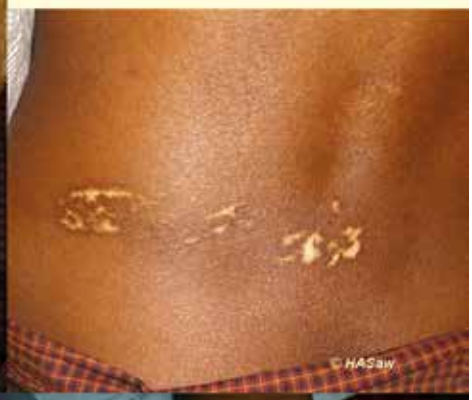
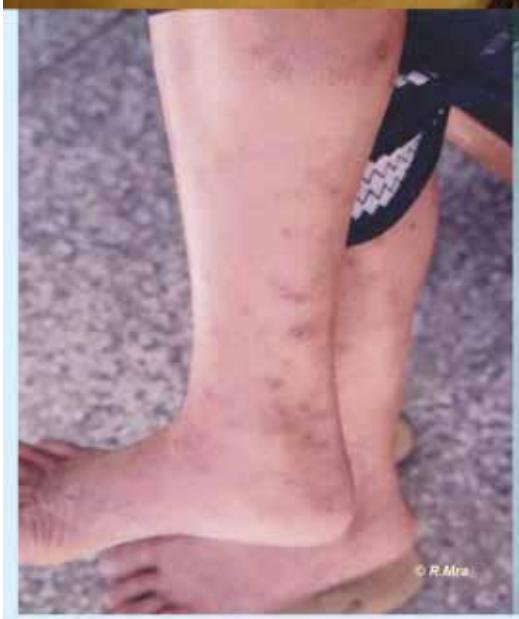


Fig (3.1-Left) Herpes zoster is usually an early manifestation of immunosuppression and usually occurs at around CD4 300/mm^3. It is seen as a painful vesicular eruption along a dermatone. It may be recurrent and is sometime multidermatomal.

Fig (3.2-Below) A herpes zoster scare is sometimes a clue to the presence of HIV infection.





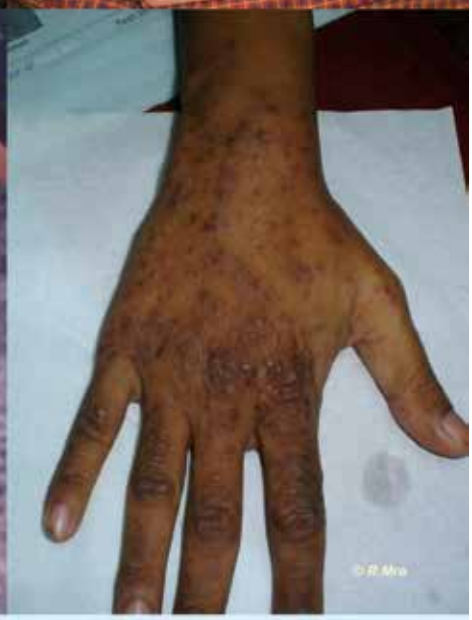


Fig (3.3-above left) & Fig (3,4- above right) Pruritic papular erutions are seen in the exposed parts of the limbs. Scratching produces infection and scarring. Pruritic papular eruption is thought to be due to allergic rection to insect bites. PPE is not scabies.

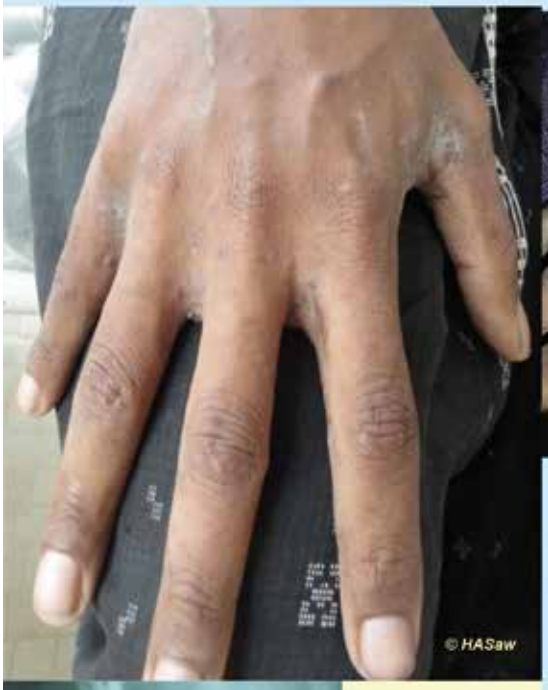


Fig.(3.5 - left)Scabies is caused by *Sarcoptes scabiei* mites burrow into the skin and is usually first seen in areas where the skin is thin e.g. webs of fingers and toes, genitalia and axillae. Scabies is intensely pruritic and the pruritis is worse at night. Scabies is not a sign of immunosuppression and is usually due to poor personal hygiene.

Fig.(3.6 - above right) 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.

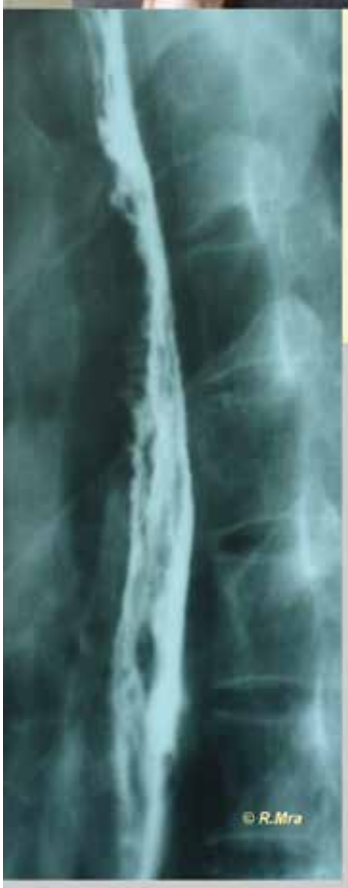
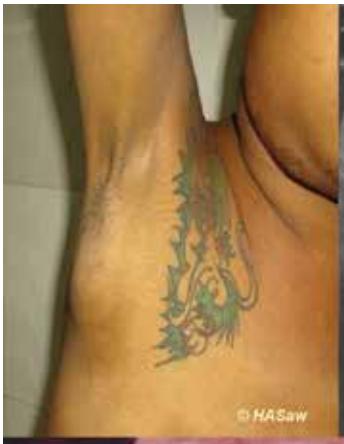
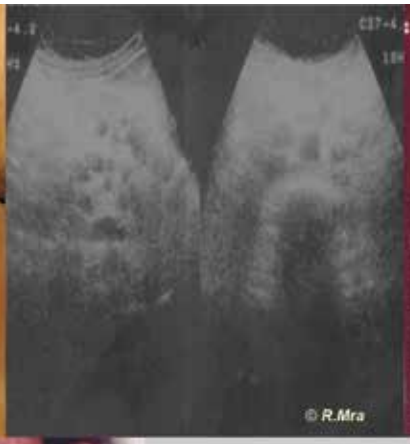


Fig.(3.7 - left) Barium swallow showing oesophageal thrush with mucosal ulcerations.

Fig.(3.8 & 3.9 - right) Oral thrush is due to *Candida albicans* in most cases and is usually seen as white plaques which can be easily scaped off (right) and sometimes as erythematous raw red areas (below right). There is soreness of the tongue and mouth. With advanced immunosuppression candidiasis extends into the oesophagus causing ulcerations and dysphagia. (left)





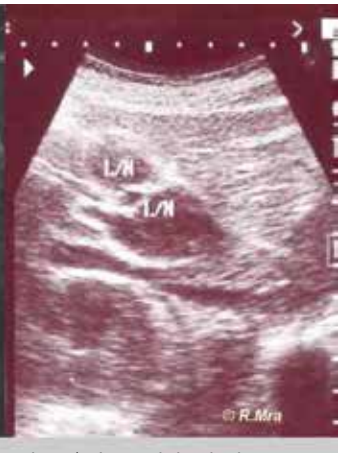


Fig.(3.12 & 3.13 - above) Intra-abdominal lymphadenopathy seen as hypoechoic areas on abdominal ultrasound examination. This is most commonly due to tuberculosis with advanced immunosuppression.

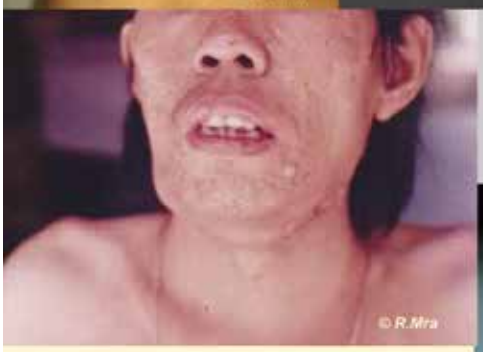
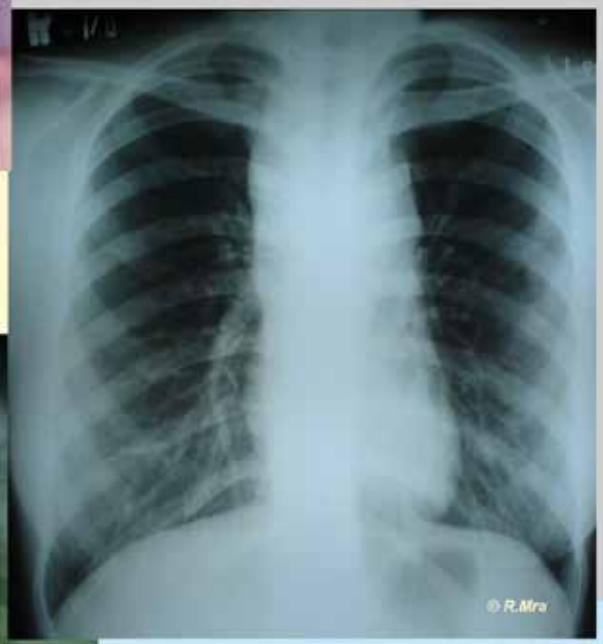


Fig.(3.10 & 3.11 - above) Tuberculosis commonly manifests as lymphadenopathy in HIV/AIDS.



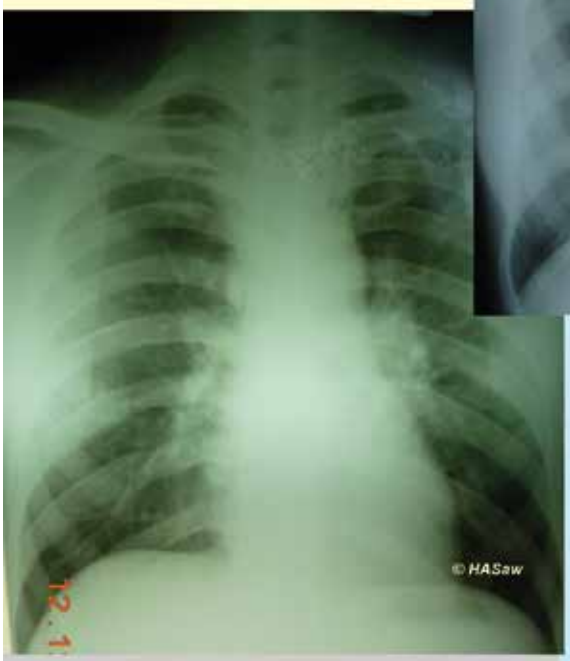


Fig.(3.14 - above) & Fig.(3.15 - left) Chest x-ray showing mediastinal lymphadenopathy (above) and hilar lymphadenopathy (left). This is most commonly due to tuberculosis in HIV/AIDS especially if associated with prolonged fever, weight loss and night sweats. Lymphoma is a differential diagnosis but is less common than TB.

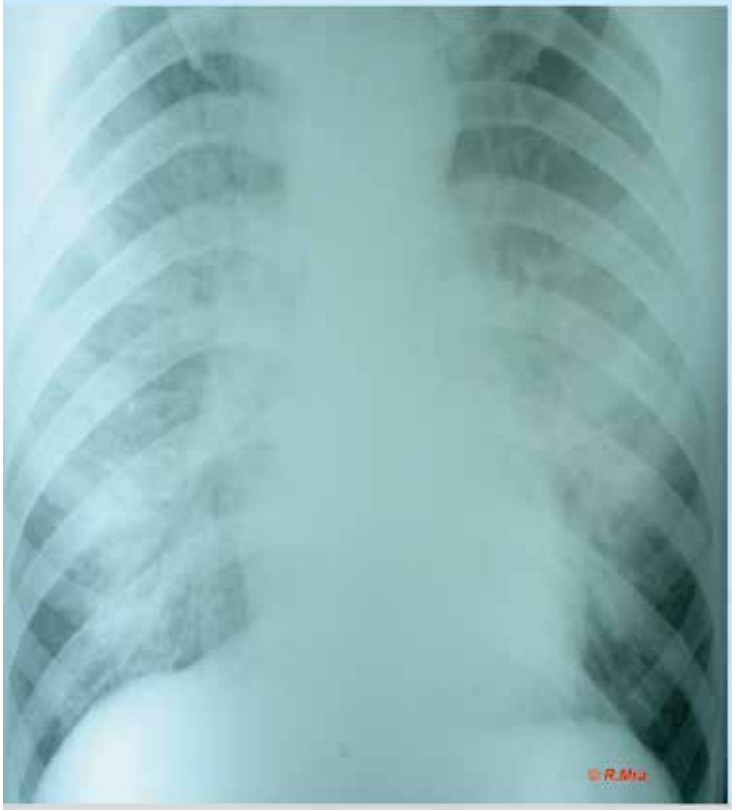
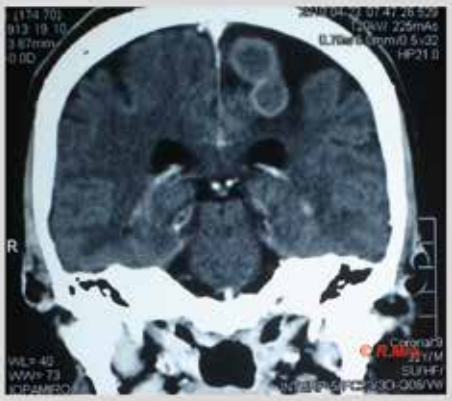
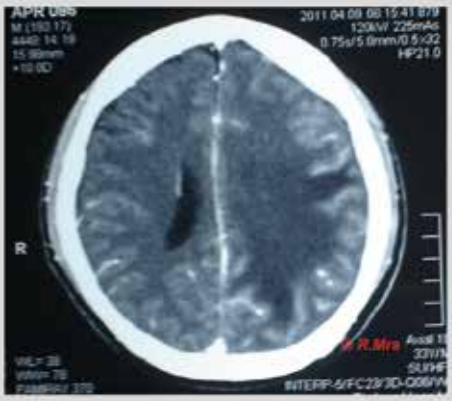


Fig.(3.16) The patient presented with a low grade fever, dry cough and shortness of breath which had become progressively more severe over the past 3 weeks. The dyspnoea became worse after the slightest movement and cyanosis developed on exertion. There were very few lung signs. An urgent chest X-ray showed diffuse pulmonary infitraties 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).

Fig. (3.17 - below left) 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 patiemt made a complete recovery and is now well on ART.

Fig. (3.18 - below right) 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.





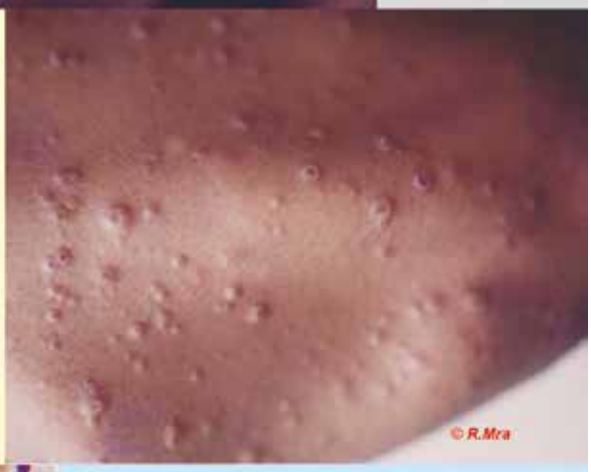


Fig. (3.19) Penicilliosis seen on the face (above) and skin (right).
Umbilicated papular eruptions first appear on the face and spreads to the limbs and trunk. The skin lesions are prominent but this is a systemic fungal infection involving the organs and bone marrow.

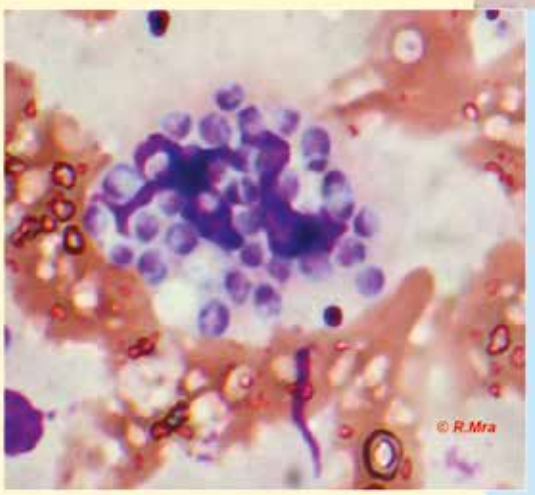


Fig. (3.20 right) Diagnosis is easily made by puncturing and scraping the papules and staining the smear on a glass slide with Leishman's or Giemsa's stain. Fungal bodies are seen inside macrophages with a characteristic central septation. (Oil immersion lens).

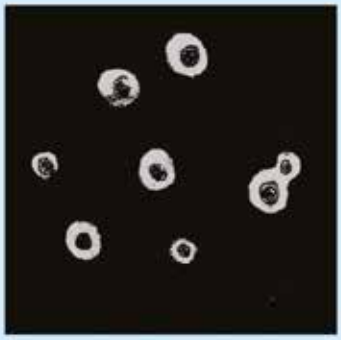


Fig. (3.23-above) India ink preparation of CSF showing yeast cells of *Cryptococcus neoformans* with unstained thick capsules and budding (sketch).

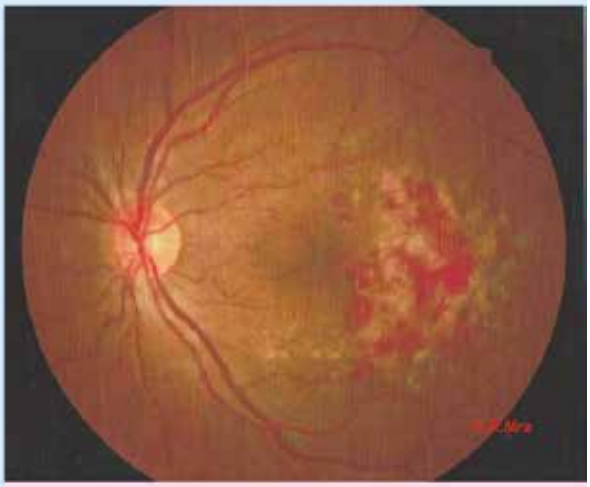


Fig. (3.24 - above) CMV retinitis showing haemorrhagic necrosis of the retina with exudates ("scrambled eggs and tomato ketchup appearance"). Involvement of the macula area causes blindness.

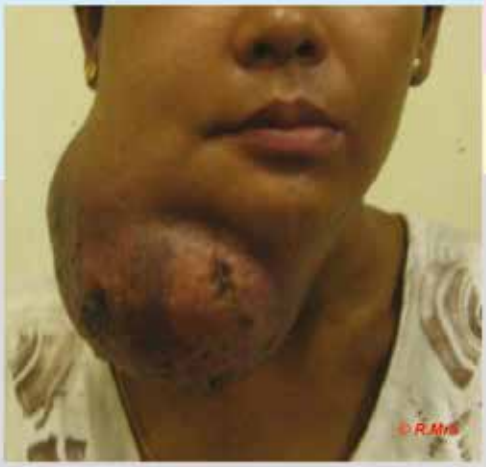
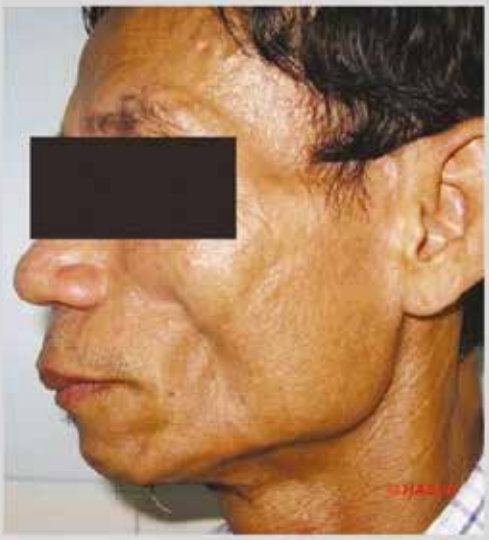
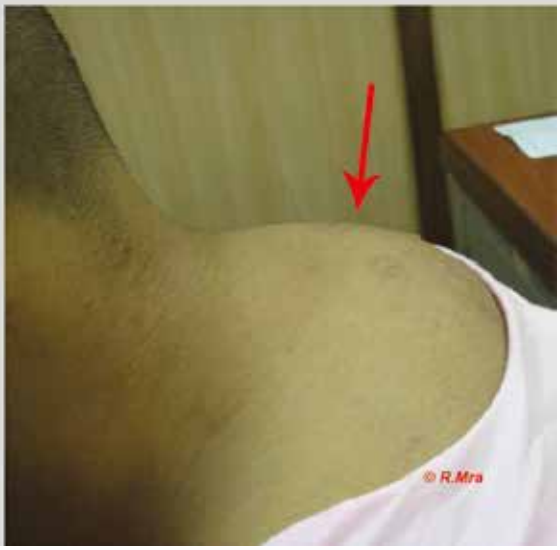


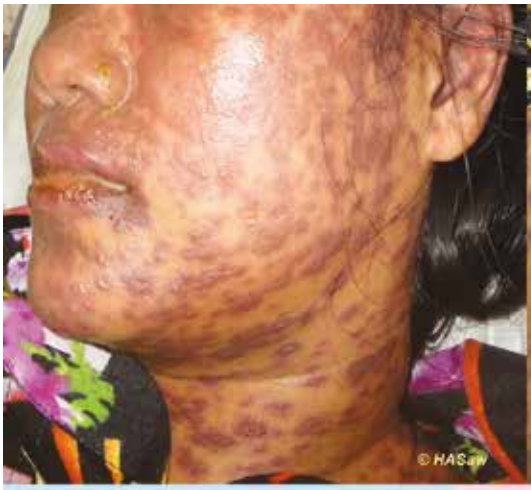
Fig. (3.25 - left) HIV associated lymphoma is a high-grade B cell non-Hodgkin lymphoma.

Fig. (3.26 - below left) Lipoatrophy of face caused by long-term stavudine therapy. Lipoatrophy is also seen in arms, legs and buttocks.

Fig. (3.27 - below right) Lipo-hypertrophy seen in the dorso-cervical region causing a "buffalo hump" appearance. Lipo-hypertrophy is also seen in the breast and abdomen. Lipodystrophy is a common complication seen with long term stavudine therapy.







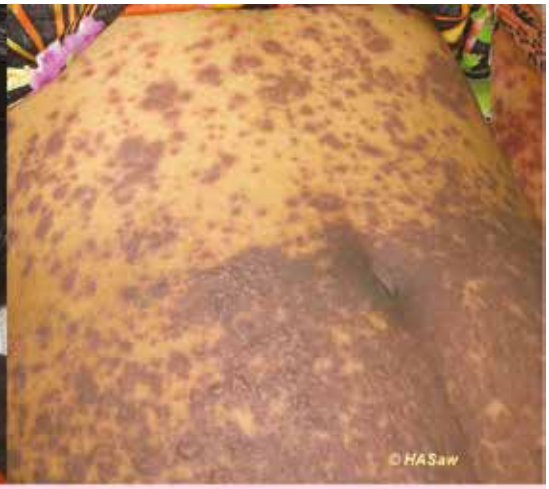
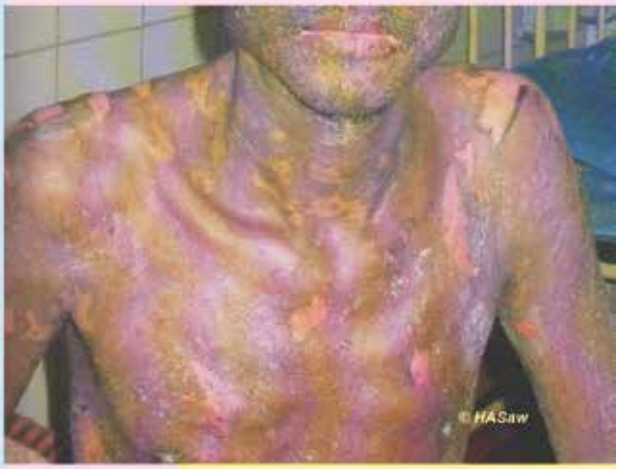


Fig. (3.28-above left) & Fig.(3.29-above right) Stevens-Johnson syndrome due to nevirapine involving the whole body as well as mucous membrane. This is a recognized complication of NVP and can occure at all levels of immunosuppression but particularly in women with CD4 count > 250/mm^3.

Stevens-Johnson syndrome can be also a rare complication of other drugs e.g rifampicin, co-trimoxazole.

Fig (3.30 - right). Toxic epidermal necrolysis due to neviraphine.



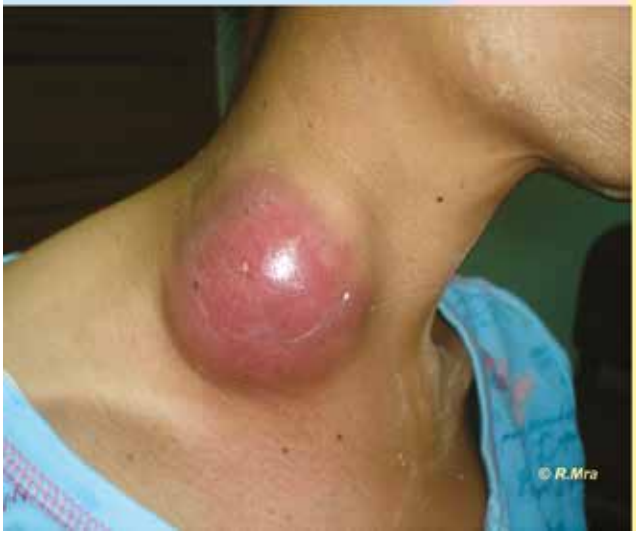


Fig. (3.31-left) Immune reconstitution Inflammatory sydrome or IRIS. This patient had a CD4 count of 50/mm^3. There was a small lymph node at the root of the neck. TB treatment was started for pulmonary tuberculosis and ART started 2 weeks later. After one month symptoms worsened and the cervical lymph node had become enlarged, painful and then gradually became fluactuant. 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. Treating late HIV disease

Majority of patients with HIV in resource limited countries will still present with late HIV disease with CD4 counts < 100/mm³ or <50/mm³. 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 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. All attempts for a microbiologic diagnosis should be made including sputum smears for AFB, Gene Xpert, sputum culture and lymph node aspirate smears. Urinary LF-LAM may assist in the diagnosis of TB in patients with signs and symptoms of TB who have a CD4 cell count < 100 cells/mm³, or HIV positive patients who are seriously ill regardless of CD4 count. The diagnosis may or may not be confirmed but in very ill cases, treatment for tuberculosis will have to be started presumptively if there is a strong clinical suspicion and this may very well be lifesaving. The response to anti-TB treatment is usually good.

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.

In late HIV disease, OIs have to be diagnosed and treated first before starting ART. Starting ART without diagnosing and treating OIs can be disastrous due to the risk of immune reconstitution inflammatory syndrome (IRIS) if ART is started at the same time as the treatment of OI. The exact time to start ART in OIs is not exactly established but vigilance and close observation is necessary in managing late cases.

In patients with pulmonary TB/HIV co-infection with CD4 counts <50 cells/mm³, early ART

initiation within 2 weeks of TB treatment initiation was associated with better AIDS-free survival, albeit with increased risk of IRIS. Exacerbation of symptoms and signs can be due to IRIS or to the simultaneous occurrence of another OI. Multiple OIs may occur at the same time and IRIS can also unmask more OIs. Drug reactions or drug resistance are also a possibility. Close monitoring is the key to successful management of late HIV disease.

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/mm³ 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/mm³) 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 2-5 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)

8. Annexes

Table 20. Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing for infants and children 4 weeks of age and older [a]

Drug	Strength of tablets (mg)	Number of tablets by weight band morning and evening										Strength of adult tablet (mg)	Number of tablets by weight band	
		3.0–5.9 kg		6.0–9.9 kg		10.0–13.9 kg		14.0–19.9 kg		20.0–24.9 kg			25.0–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
AZT/3TC[a]	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
AZT/3TC/ NVP[a]	Tablet (dispersible) 60 mg/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg/ 150 mg/200 mg	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600 mg/ 300 mg	0.5	0.5
ABC/3TC	Tablet (dispersible) 120/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600 mg/ 300 mg	0.5	0.5

[a] For infants younger than 4 weeks of age, see Table 23 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolize medication. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birthweight infants.

Table 21. Simplified dosing of child-friendly solid and oral liquid formulations for once-daily dosing for infants and children 4 weeks of age and older[a]

Drug	Strength of tablet (mg)	Number of tablets or capsules by weight band once daily					Strength of adult tablet (mg)	Number of tablets or capsules by weight band once daily
		3.0–5.9 kg	6.0–9.9 kg	10.0–13.9 kg	14.0–19.9 kg	20.0–24.9 kg		25.0–34.9 kg
EFV[b]	Tablet (scored) 200 mg	–	–	1	1.5	1.5	200 mg	2
ABC/3TC	Tablet (dispersible) 60/30 mg	2	3	4	5	6	600 mg/ 300 mg	1
ABC/3TC	Tablet (dispersible) 120/60 mg	1	1.5	2	2.5	3	600 mg/ 300 mg	1
ATV[c]	Capsules 100 mg	–	–	1	2	2	300 mg	2 (100 mg)[d] or 1 (300 mg)
TDF[e]	Oral powder scoops 40 mg/scoop	–	–	3	–	–	300 mg	1 (200 mg)[d] or 1 (300 mg)
	Tablets 150 mg or 200 mg	–	–	–	1 (150 mg)	1 (200 mg)		

[a] For infants younger than 4 weeks of age, see Table 23 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolize medication. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birthweight infants.

[b] EFV is not recommended for children younger than 3 years and weighing less than 10 kg. The United States Food and Drug Administration approved EFV for use for children younger than 3 years weighing more than 3.5 kg during the finalization of WHO guidelines (3.5–5.0 kg: two 50-mg capsules;

5.0–7.5 kg: three 50-mg capsules; 7.5–15.0 kg: one 200-mg capsule), but more data are urgently needed to inform recommendations for using EFV in this age group.

[c] ATV is only approved for use for children 3 months and older. ATV single-strength capsules should be administered with RTV 100 mg for all weight bands. The ATV powder formulation enables administration of ATV to infants and children as young as 3 months. Infants and children weighing 5–10 kg should be administered 200 mg of ATV powder (4 packets, 50 mg per packet) with 80 mg of RTV oral solution (5 ml). http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206352s003,021567s038lbl.pdf

[d] 200 mg should be used for weight 25.0–29.9 kg and 300-mg tablets for 30.0–34.9 kg.

[e] TDF is only approved for use for children 2 years and older. Target dose: 8 mg/kg or 200 mg/m² (maximum 300 mg). The Paediatric Antiretroviral Working Group developed this guidance to harmonize TDF dosing with WHO weight bands and to reduce the numbers of strengths to be made available. The WHO generic tool was used based on the target dose provided by the manufacturer's package insert. In accordance with the standard Paediatric Antiretroviral Working Group approach, dosing was developed ensuring that a child would not receive more than 25% above the maximum target dose or more than 5% below the minimum target dose.

Table 22. Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing for infants and children 4 weeks of age and older [a]

Drug	Strength of tablets (mg) or oral liquid (mg/ml)	Number of tablets or ml by weight-band morning (AM) and evening (PM)										Strength of adult tablet (mg)	Number of tablets by weight band	
		3.0–5.9 kg		6.0–9.9 kg		10.0–13.9 kg		14.0–19.9 kg		20.0–24.9 kg			25.0–34.9 kg	
		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
NVP[b]	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200 mg	1	1
LPV/r[c]	Tablet[d] 100 mg/ 25 mg	–	–	–	–	2	1	2	2	2	2	100 mg/ 25 mg	3	3
	Pellets[e] 40 mg/ 10 mg	2	2	3	3	4	4	5	5	6	6	100 mg/ 25 mg	3	3
DRV[f]	Tablet 75 mg	–	–	–	–	3	3	5	5	5	5			
RAL	Chewable tablets 25 mg	–	–	–	–	3	3	4	4	6	6	400 mg	1	1
	Chewable tablets 100 mg	–	–	–	–	–	–	1	1	1.5	1.5	400 mg	1	1
	Granules[g] (100 mg/sachet)	0.25	0.25	0.5	0.5	–	–	–	–	–	–		–	–
Liquid formulations														
AZT	10 mg/ml	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	–	–	–	–	–	–	–
ABC	20 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	–	–	–	–	–	–	–
3TC	10 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	–	–	–	–	–	–	–
NVP[b]	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	–	–	–	–	–	–	–
LPV/r[c]	80/20 mg/ml	1 ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml	–	–	–
DRV[f]	100 mg/ml	–	–	–	–	2.5 ml	2.5 ml	3.5 ml	3.5 ml	–	–			

[a] For infants younger than 4 weeks of age, see Table 23 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolize medication. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exists on the dosing of ARV drugs for preterm and low-birth-weight infants.

[b] NVP dose escalation with half dose for 2 weeks when initiating ART is still recommended to avoid toxicity from high initial NVP levels. However, secondary analysis from the (CHAPAS)-1 trial recently suggested that younger children have a lower risk of toxicity, and consideration can be given to starting with a full dose (Fillekes Q et al. Is nevirapine dose escalation appropriate in young African HIV+ children? 20th Annual Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, USA, 3–6 March 2013 (http://retroconference.org/2013b/Abstracts/46904.htm, accessed 15 May 2015). More definitive evidence is expected from an ongoing trial.

[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.

[d] The adult 200/50 ml tablet could be used for children 14.0–24.9 kg (1 tablet in the morning and 1 tablet in the evening) and for children 25.0–34.9 kg (2 tablets in the morning and 1 tablet in the evening)

[e] The LPV/r pellets formulation should not be used for infants younger than 3 months. More details on the administration of LPV/r pellets is available at http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30-September-2015.pdf.

[f] DRV must be administered with 0.5 ml of RTV 80 mg/mL oral suspension if the child weighs less than 15 kg and with RTV 50 mg solid formulation for children weighing 15–30 kg.

[g] RAL granules are approved for use for children as young as 4 weeks, but the feasibility and acceptability of such formulations has not been widely investigated, and concerns have been raised regarding administration in resource-limited settings. The bioequivalence of RAL chewable tablets dispersed in liquid is currently being explored, and more guidance will be provided as soon as additional evidence becomes available.

Table 23. Drug dosing of liquid formulations for twice-daily dosing for infants younger than 4 weeks of age [a]

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

[a] There is limited experience with initiating treatment among newborns living with HIV <2 weeks of age, with few pharmacokinetic data to fully inform accurate dosing for drugs other than AZT during a time that renal and liver functioning is rapidly maturing , and LPV/r solution should not be given to infants aged <2 weeks, making management of HIV treatment in newborns challenging.

In addition, reliable pharmacokinetic data for preterm infants are available only for AZT, with uncertainty of dosing for NVP and 3TC; LPV/r solution should not be given in preterm infants until they have reached 42 weeks of gestational age. This guidance will be updated when more evidence is available from ongoing trials.

[b] Do not use LPV/r solution for infants <2 weeks of age. LPV/r pellets should not be used for infants younger than 3 months. More details on the administration of LPV/r pellets is available at http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30- September 2015.pdf.

Table 24. Simplified dosing of isoniazid and co-trimoxazole prophylaxis for infants and children who are at least 4 weeks of age

Drug	Strength of tablet or oral liquid (mg or mg/5ml)	Number of tablets or millilitres by weight band once daily					Strength of adult tablet (mg)	Number of tablets by weight band
		3.0–5.9 kg	6.0–9.9 kg	10.0–13.9 kg	14.0–19.9 kg	20.0–24.9 kg		25.0–34.9 kg
Isoniazid	100 mg	0.5	1	1.5	2	2.5	300 mg	1
Co-trimoxazole	Suspension 200/40 per 5 ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	–	–
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	–	–
	Tablets (scored) 400/80 mg	–	0.5	0.5	1	1	400 mg/ 80 mg	2
	Tablets (scored) 800/160 mg	–	–	–	0.5	0.5	800 mg/ 160 mg	1
Isoniazid + co-trimoxazole + B6[a]	Tablets (scored) 300 mg/960mg/25mg	–	–	–	0.5	0.5	960 mg/ 300 mg/ 25 mg	1

[a] This formulation is currently awaiting regulatory approval, and a scored talet(480mg/150mg/12.5 mg) is also being developed.

Table 25. Potential overlapping and additive toxicities of ART and anti-TB treatment

TOXICITY	ANTIRETROVIRAL AGENT	ANTI-TB AGENT	COMMENTS
Skin rash	**ABC, NVP, EFV, d4T** and 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.

TOXICITY	ANTIRETROVIRAL AGENT	ANTI-TB AGENT	COMMENTS
Central nervous system (CNS) toxicity	**EFV**	**Cs,** H, Eto/Pto, FQ	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	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 others	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.
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).

TOXICITY	ANTIRETROVIRAL AGENT	ANTI-TB AGENT	COMMENTS
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).
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.
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	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.

TOXICITY	ANTIRETROVIRAL AGENT	ANTI-TB AGENT	COMMENTS
Lactic acidosis	**d4T, ddI,** 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.

TOXICITY	ANTIRETROVIRAL AGENT	ANTI-TB AGENT	COMMENTS
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.

Note: Abbreviation of anti-TB drugs	
Amk	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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