THE CLINICAL MANAGEMENT OF HIV INFECTION IN MYANMAR

GUIDELINES

National AIDS Programme
Department of Health, Ministry of Health,
Myanmar

2014

World Health Organization
Country Office for Myanmar

GUIDELINES
FOR THE CLINICAL MANAGEMENT OF HIV INFECTION IN MYANMAR

FOURTH EDITION

National AIDS Programme
Department of Health, Ministry of Health, Myanmar

2014

Contents

List of tables

List of figures

Peer review team members

1.	Prof. Rai Mra	Professor Rtd.	Myanmar Medical Association
2.	Prof. Mya Thida	Professor and Head, O&G	University of Medicine 1
3.	Dr. Htin Aung Saw	Associate Professor	Wabagi Specialist Hospital
4.	Dr. Thandar Lwin	Director Disease Control	Department of Health
5.	Dr. Myint Shwe	Deputy Director	National AIDS Programme
6.	Dr. Htun Nyunt Oo	Assistant Director	National AIDS Programme
7.	Dr. Aung San	Sr Consultant Physician	Mingaladon Specialist Hospital
8.	Dr. Khin Yi Oo	Deputy Director	National Health Laboratory
9.	Dr. Aung San Oo	Sr consultant Physician	Pyin Oo Lwin General Hospital
10.	Dr. Mar Mar Aye	Sr consultant Physician	Mandalay General Hospital
11.	Dr. Kyaw Thu	Sr consultant Physician	Nay Pyi Taw 1000 bedded Hospital
12.	Dr. Par Par	Sr consultant Physician	Mandalay Teaching Hospital
13.	Dr. Htar Kyi Swe	Jr Consultant Physician	Mandalay General Hospital
14.	Dr. Sabai Phyu	Sr consultant Physician	Thakayta Specialist Hospital
15.	Dr. Khin Thant Zin	Sr consultant Paediatrician	Nay Pyi Taw 1000 bedded Hospital
16.	Dr. Aye Aye Khaing	Consultant Paediatrician	Mingaladon Specialist Hospital
17.	Dr. Ohnma Mon	Consultant Paediatrician	Mandalay Children Hospital
18.	Dr. Vimlesh Purohit	Medical Officer (HIV/AIDS)	WHO
19.	Ms. Phavady Bollen	Technical Officer (HIV/AIDS)	WHO
20.	Mr. Eamonn Murphy	Country Director	UNAIDS
21.	Dr. Faisal Mansoor	Program Officer	UNOPS
22.	Dr. Htin Aung	National Technical Officer	WHO

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 (ZDV)
BD	twice daily
bPI	boosted protease inhibitor
CD4 count	CD4+ T-lymphocyte count
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
d4T	stavudine
DBS	dried blood spot
ddI	didanosine
EFV	efavirenz
FTC	emtricitabine
Hb	haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HCT	HIV counselling and testing
HIV	human immunodeficiency virus
HSV	herpes simplex virus
IDV	indinavir
INH	isoniazid

IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir
LPV/r	ritonavir boosted lopinavir
MTCT	mother-to-child transmission (of HIV)
MDR-TB	multidrug-resistant tuberculosis
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OD	once a day
PCP	Pneumocystiscariini&jiroveciipneumonia
PEP	post exposure prophylaxis
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
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
RLC	resource limited country
RLS	resource limited situation
RTV	ritonavir
SQV	saquinavir
TG	transgender
TST	tuberculin skin test
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
VL	viral load

Foreword

Three years have passed since the last National guidelines for Clinical Management of HIV infection were updated in the Myanmar context. During that time period, the WHO has published the CONSOLIDATED GUIDELINES in June, 2013 and March 2014 SUPPLEMENT TO THE 2013 CONSOLIDATED GUIDELINES ON THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION: Recommendations for a public health approach. In the meantime, Myanmar's concerted efforts against HIV/AIDS with the unwavering help of the UN agencies, national and international non-governmental organizations have been gaining ground due to the relentless endeavours of all the stakeholders involved. However, there still remains some disparate guidance on the ART use for adults, children, pregnant and breast feeding women, and special populations. In order to leverage the recently gained ground and move further forward, it is imperative that an update is published, disseminated and followed unequivocally.

This update will both augment and complement the 2011 Myanmar Guidelines published by the National AIDS Programme. In Myanmar, a country with limited resources and capacity, the available resources must be best employed to achieve the best possible solutions for People Living with HIV. With this in mind, evidence based recommendations have also been made in PMTCT; PEP and coinfection with HBV and HCV.

The Update is meant for all healthcare personnel in the public and private sectors serving HIV patients in Myanmar. However, it must be stressed again that the choice of the patients must be respected and a high degree of professionalism is maintained at all times regardless of the situation or the premises. The guidelines are optimized for all medical doctors regardless of their experience or training and suitable for patients living anywhere in Myanmar to seek necessary treatment and care. The wide range of available medical facilities and resources would thus be utilized to their fullest potential for the greatest good, anytime and anywhere within Myanmar.

We are confident that these guidelines will be of immense help to expand and enhance the scope and scale-up of Myanmar's ART programmes. The NAP is thus extremely pleased to issue the Guidelines for the Clinical Management of HIV infection in Myanmar, Fourth Edition.

National AIDS Programme
Department of Health

Summary of key recommendations for ART in the new guidelines

I. When to start?

1.	**Adults and Adolescents**	
	i.	HIV positive individuals – CD4 ≤500 cells/mm^3; priority to those with CD4 less than 350/mm^3
	ii.	WHO clinical stage 3 or 4 irrespective of CD4 cell count
2.	**Pregnant and breastfeeding women**	
	i.	All pregnant and breastfeeding women with HIV should initiate triple ARV as soon as possible
	ii.	If the woman is eligible for treatment, continue ART for life long If the woman is not eligible, choose option B (discontinue ARV 1 week after cessation of breastfeeding) or option B plus (continue life long ART) (For detail information please refer to section 3.1.2)
	iii.	Prophylaxis for HIV exposed infants All infants regardless of feeding mode – daily NVP for 6 weeks
	iv.	Infant feeding– recommendation for known HIV-infected women – to choose between formula feeding or exclusive breastfeeding
3.	**Children**	
	i.	Initiate ART in all HIV infected children less than 5 years
	ii.	For children more than 5 years, follow same criteria as adults.
4.	**Special Populations**	
	i.	HIV/TB coinfection– Treat all HIV/TB coinfected individuals irrespective of CD4 count; ART to be started 2 to 8 weeks after start of TB treatment
	ii.	HIV/HBV coinfection – Provide ART to HBV/HIV coinfected if ALT level 2.5 timesmore than the upper limit of normal.
	iii.	Sero discordant couples – Treat all sero discordant couples irrespective of CD4 count.
	iv.	Key populations – Treat all irrespective of CD 4 count (Key populations include FSWs, MSMs, TGs and PWIDs)

II. What ART to start?

Adults and Adolescent	
i.	HIV positive ARV naïve adults and adolescents – TDF+3TC (FTC)+EFV is the preferred first line regimen, unless there is any contraindication.
ii.	If the preferred first line cannot be used, the alternate first line regimen, in order of preference are: AZT+3TC+EFV; AZT+3TC+NVP: ABC+3TC+EFV
Pregnant and breastfeeding women	
iii.	Life long ART as well as prophylaxis ARV – same as Adult and adolescent
Co-infections	
iv.	HIV/TB coinfection – Same as above ; ART to be started 2 to 8 weeks after start of TB treatment ;
v.	HIV/HBV coinfection – TDF+3TC+EFV; alternative TDF+3TC+NVP
Children (see algorithm and table in text)	
vi.	Age less than 3 years (Table 5)
vii.	Age from 3-10 years (Table 6)
viii.	Age over 10 years (Table 6)

Note: ABC can be kept as backup option if AZT or TDF cannot be used.

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 infection and remain at risk to their own health and of unknowingly passing their virus on 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.

There were several meetings carried out in Naypyitaw and Yangon, with participation from all stakeholders and technical support from WHO local representatives and visiting consultants. The consensus reached was used to develop the Myanmar national guidelines 2014, based on the WHO CONSOLIDATED GUIDELINES in June, 2013 and March 2014 SUPPLEMENT TO THE 2013 CONSOLIDATED GUIDELINES ON THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION: Recommendations for a public health approach. The finalized guidelines have now been made available for use by all healthcare personnel.

The new guidelines will provide flexibility and versatility for all healthcare providers and accommodate the decentralized approach being undertaken by the National AIDS Programme (NAP). The notable changes include:

- Updates on the Initiation of ART
- New drugs/regimens
- New recommendations on PMTCT
- Considerations for co-infection with TB, HBV and HCV
- PEP updates

It must be noted that the guidelines are meant for the operational level and are kept in line with the existing Myanmar context. The clinicians' own judgement and consideration should be the dominant factor when options are prioritized for the optimal treatment.

1. Diagnosis of HIV infection

HIV counselling and testing (HCT)

HIV counselling and testing is widely available in Myanmar at healthcare facilities including: ART centers/sites AIDS/STD clinics, antenatal care settings, TB clinics and Methadone maintenance therapy clinics. It is also available at drop in centers and outreach services for key affected population. There will be amended HCT guidelines in 2015 when the National Review on HCT is performed.

HIV Counselling

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

- The risks for transmission and how HIV can be prevented.
  The reasons why HIV testing is being recommended. The benefits and consequences of HIV testing; in the case of pregnant women the risks of transmitting HIV to infants and possibility of preventing this
- The testing process
- Assurance about confidentiality and the right to decline the HIV test
- The meaning of the test results in understandable language

Post-test counselling

- Clients should be counselled for a positive or a negative result and have the result explained
- Clients should be assured of confidentiality

In case of positive results, the counsellor needs to:

- Provide emotional support
- Assess the individual's ability to cope
- Assess the social support available
- Explain how to prevent HIV transmission to uninfected or untested partners
- Encourage individuals to share their HIV status with their sexual partners and to have them also tested for HIV
- Refer the individual for clinical monitoring and follow up and to evaluate the need for ART

In case of negative results, the counsellor needs to:

- Encourage the HIV negative individual to adopt safe practices (e.g. condom use)
- Explain that the individual has to be tested again in 6 to 8 weeks in case the first test was performed during the "window period".
- Explain that a negative test performed during the "window period" may not mean that the individual is definitively uninfected.

HIV testing

HIV test is recommended for

1. For all patients whose clinical presentations might result from underlying HIV infection
2. Most at risk population (Key affected population with high risk behavior)
3. All pregnant women attending antenatal care setting
4. Sexual partners of HIV positive persons.
5. Early Infant Diagnosis (EID)

Diagnosis of HIV infection

The diagnosis of HIV infection can be carried out by detecting any of the following:

- Antibodies to HIV
- HIV nucleic acid (RNA/DNA)

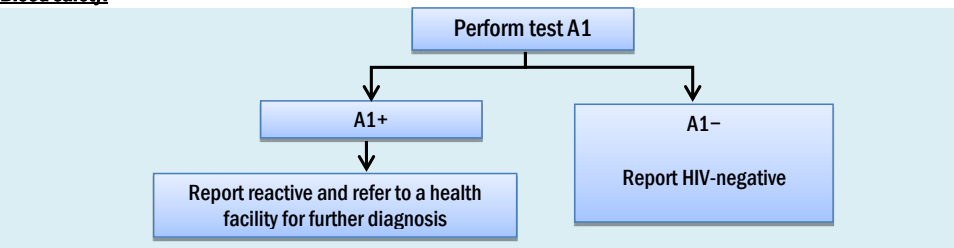
The most commonly used method for the diagnosis of HIV infection is detection of anti-HIV antibodies in serum or plasma. It is economical, rapid and can be performed easily in most laboratories.Although HIV antibody tests nowadays have a high degree of sensitivity and specificity there is no perfect HIV antibody tests and therefore the diagnosis of HIV infection is based on a multi-test algorithm for detecting antibodies to HIV.

Diagnostic testing involves initial screening withWHO prequalifiedhighly sensitive tests and confirmatory testing with highly specific tests. The assays used should be based on different principles and/or different antigens. Three testing strategy is used for clinical diagnosis includingPMTCT. A1, A2, A3 represent three different assays (Figure 1). Indeterminate results are retested 14 days later on a new specimen and if it isindeterminate again, can be repeated at 6 months and if still indeterminate, it should be refered to the reference center for Western Blot test. However molecular methods (nucleic acid testing by PCR) can be used to resolve 2 indeterminate test results.

HIV-exposed infants and children younger than 18 months should be tested within four to six weeks of birth. Virological test, using dried blood sopt (DBS) specimen,can confirm HIV infection in children younger than 18 months. For children of 18 months of age or older, who are not on breastfeeding anymore, can be diagnosed with standard HIV serological tests. HIV testing algorithm for infants born to HIV infected mother is shown in Figure 2.

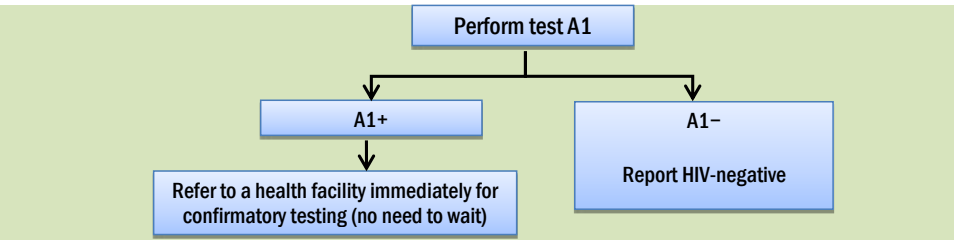
Figure :1 HIV testing for Blood Safety and diagnosis

Blood safety:

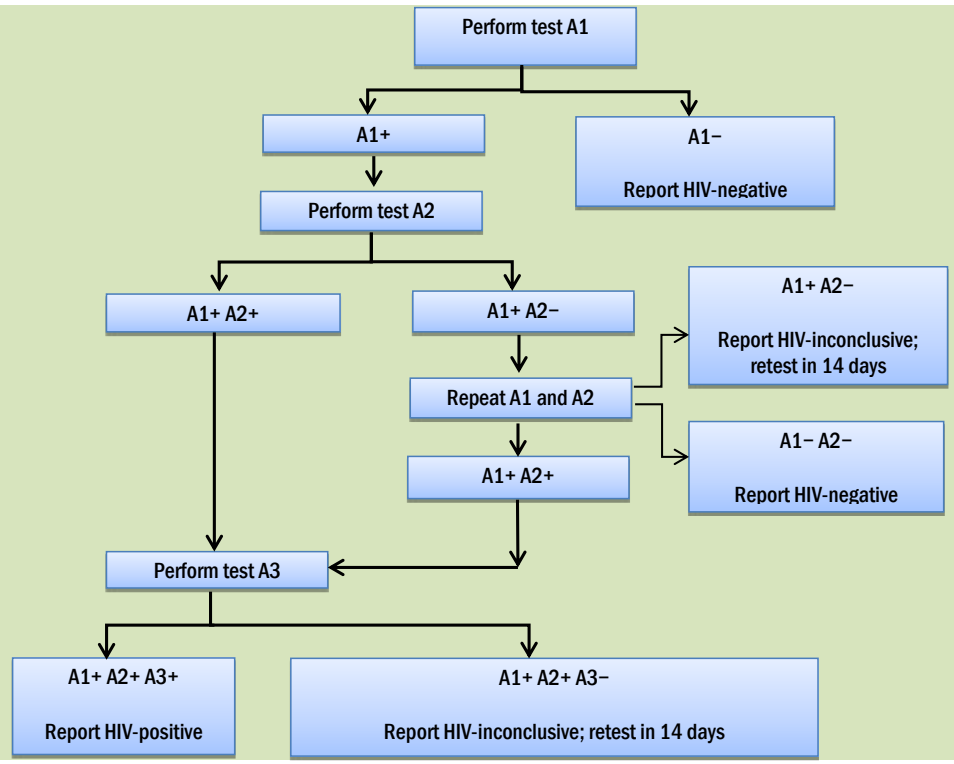


Diagnosis:

Community outreach, community based, private general practitioners, and health facilities that do not have a certified laboratory

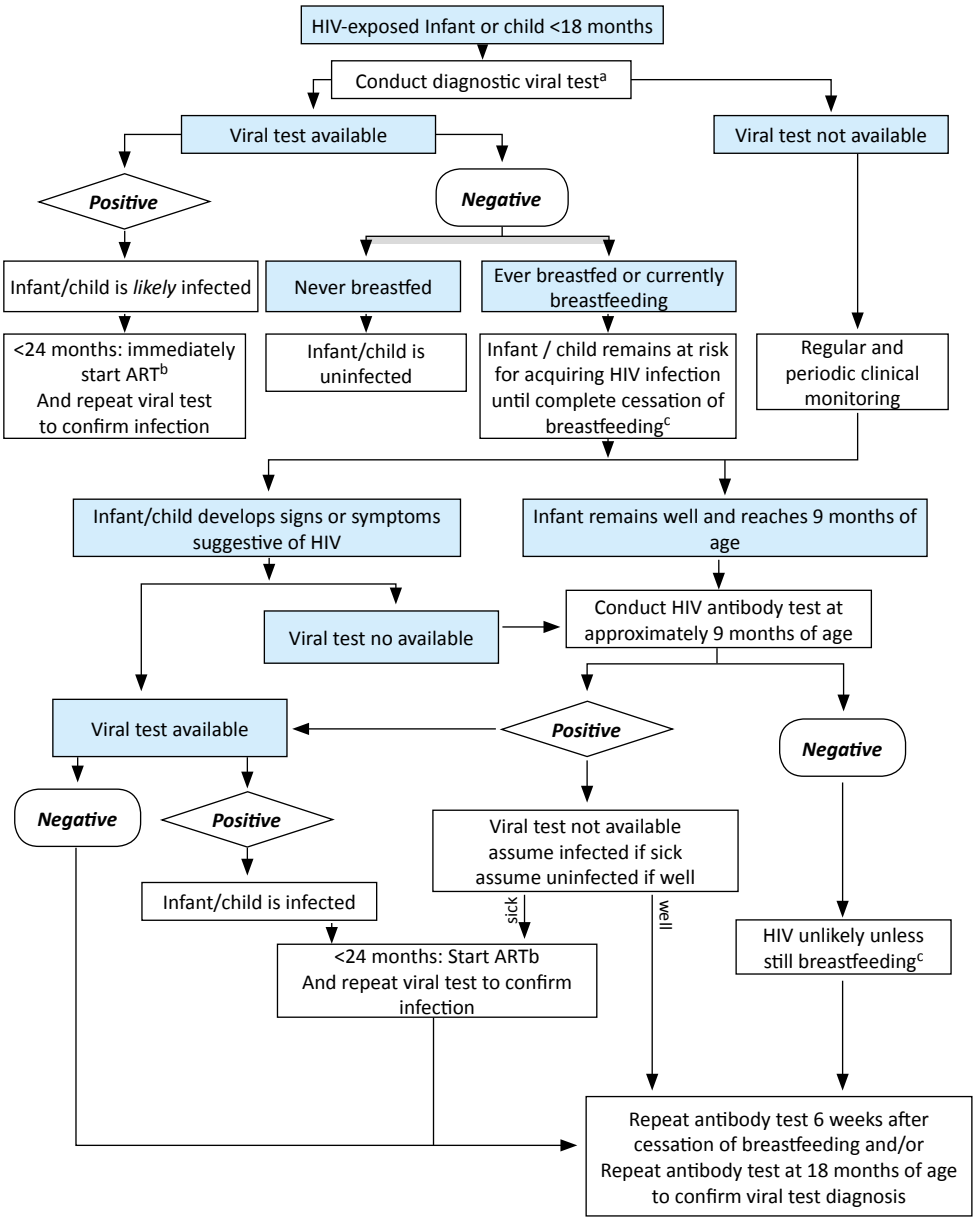


Hospitals, Laboratories, health centers, and other facilities with laboratory capacity



A1=Determine (D) ICT, A2=Uni-gold (UG) ICT, A3=Stat Pak (SP) ICT

Figure 2:Algorithm for early infant diagnosis



a) For newborns, test first at or around birth or at the first postnatal visit (usually 4–6 weeks).

b) Start ART, if indicated, without delay and at the same time, retest to confirm infection.

c) The risk of HIV transmission remains as long as breastfeeding continues.

2. Pre-ART care

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

The revised WHO clinical staging of HIV disease is designed to be used in patients with confirmed HIV infection. Along with CD4 count testing, where available, the staging system is used to guide decisions on when to start opportunistic infection (OI) prophylaxis and when to start and switch ART.

Table 1: WHO clinical staging of HIV disease in adults and adolescents

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 Fungal nail infections	Unexplained persistent hepatosplenomegaly Papular pruritic eruptions Extensive wart virus infection Extensive molluscumcontagiosum Recurrent oral ulcerations Unexplained persistent parotid enlargement Lineal gingival erythema Herpes zoster Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Fungal nail infections
Clinical stage 3	
Unexplainedsevere weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for >1 month Unexplained persistent fever (intermittent or constant for >1 month)	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 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 × 10^9/l) and/ or chronic thrombocytopaenia (<50 × 10^9/l)	Persistent oral candidiasis (after first 6 weeks of life) Oral hairy leukoplakia Acute necrotizing ulcerative gingivitis or periodontitis Lymph node TB Pulmonary TB Severe recurrent bacterial pneumonia Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including bronchiectasis Unexplained anaemia (<8.0 g/dl), neutropaenia (<0.5 × 10^9/l) or chronic thrombocytopaenia (<50 × 10^9/l)
Clinical stage 4	
HIV wasting syndrome *Pneumocystis jiroveci* pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary TB Penicilliosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonarycryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection	Unexplained severe wasting, stunting or severe malnutrition[b] not responding to standard therapy *Pneumocystis jiroveci* 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) Extrapulmonary TB Penicilliosis Kaposi sarcoma Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy

Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonaryhistoplasmosis, coccidioidomycosis) Recurrent septicaemia (including nontyphoidal*Salmonella*) Lymphoma (cerebral or B-cell non-Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy	Cytomegalovirus infection; retinitis or cytomegalovirus infection affecting another organ, with onset at age more than 1 month Extrapulmonarycryptococcosis, including meningitis Disseminated endemic mycosis (extrapulmonaryhistoplasmosis, coccidioidomycosis, penicilliosis) Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis Disseminated non-tuberculous mycobacterial infection Cerebral or B-cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy HIV-associated cardiomyopathy or nephropathy

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

2.2 TB screening

Screen for TB to see there is any of the following symptoms;

- Current cough
- Fever
- Weight loss
- Night sweats
- Lymph node enlargement

2.3 Management of opportunisticinfections and prophylaxis

Cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis is a very important part of the management of a patient with HIV. It is recommended for all symptomatic individuals (WHO clinical stages 2, 3 or 4)

including pregnant women. Where CD4 count is available, Cotrimoxazole prophylaxis is recommended for individuals with CD4 count of ≤ 350/mm^3. One double-strength tablet daily of Cotrimoxazole daily is recommended (sulfamethaxazole 800 mg/ trimethoprim160 mg= 960 mg).

Since the most common initial side effect of Cotrimoxazole and antiretroviral therapy especially NVP and EFV is rash, it is recommended to start Cotrimoxazole prophylaxis first and to initiate ART two weeks later if the individual does not develop rash with Cotrimoxazole.

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 drug related adverse effects are not common and typically occur within the first few weeks 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.

2.4 Laboratory assessment

Laboratory assessment for pre- ART	
Hb g/dl	Baseline
CD4 count	Baseline
Fasting blood sugar	Baseline
ALT, AST	Baseline Desirable
Creatinine (for Cr clearance calculation)	Baseline Desirable
HBs Ag, HCV Ab	Baseline Desirable
Urinalysis (proteinuria, glucosuria)	Baseline
Chest X- rays	Baseline if indicated

CD4 count

CD4+ T lymphocytes or T helper cells are subsets of lymphocytes (CD stands for clusters of differentiation; numbers represent specific subsets) that play a vital role as co-ordinators of the body's immune response. CD4 cells are the primary target of HIV. Loss of CD4 cells results in weakening of the immune response and the ability of the host to respond to foreign antigens, rendering the host susceptible to infections and ultimately leading to the acquired immune deficiency syndrome.

CD4 counts are monitored to assess immune suppression and disease progression in HIV infected persons and decisions to start prophylaxis of opportunistic infections. Changes in CD4 cell counts are an important indicator of the response to ART. The CD4 count is the most important key marker for initiation and also used together with the Viral Load for monitoring of ART response.

Other factors that affect the CD4 count besides the HIV disease process are – diurnal changes (higher in the evening), modest decrease during acute infections and major surgery and decrease during corticosteroid administration. Deceptively high CD4 counts are seen in HTLV-1 coinfection and after splenectomy.

CD4 counts may vary with the method used. Using the CyflowPartec counter (which is commonly used) the normal CD4 count ranges from 430 to 1600/mm3. When interpreting CD4 counts it is important to follow the trend rather than specific values since there may be some degree of physiological and analyticalfluactuations. In adults the absolute number of CD4 cells is counted but in infants and young children the CD4 percentage (of total lymphocytes) is more informative. The CD4 count can be repeated every 3 to 6 months according to the situation. Result of a CD4 count that is not consistent with prior trends should be repeated before making any clinical decisions.

2.5 Adherence - important measures when starting ART

- Patients should understand
    - that ART is suppressive therapy
    - that ART is life-long
    - that near perfect adherence is necessary to prevent ART resistance
    - that there are possibilities of side effects
- Assessment of patient readiness should be carried out before starting ART (ART should never be prescribed casually at the first visit).

Treatment adherence counselling

- Establish trusting relationship
- Provide necessary information and advice
- Identify and encourage peer/family/friends/community/support groups participation
- Try to fit in ART into patients lifestyle and daily events
- Discuss cost if patient/family/friends have to pay
- Discuss need for regular follow up; patient's address, how he will attend clinic, who will help, cost of travel
- Assess readiness and commitment of patients for ART
    - past ability to attend clinic regularly
    - past ability to take drugs regularly, e.g. co-trimoxazole prophylaxis
    - past ability to complete full course of TB treatment if relevant
    - adequate understanding of what is involved
- Treatment adherence, at least 95% to 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.
- Patients should not take prescription and go away.

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 visit check -

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

Use fixed dose combination (FDC) pills if possible. Use of FDCs reduces pill burden and improves adherence.

In children also there are fixed dose combinations that are available as dispersible tablets. The details of the pediatricregimens based on weight bands and the dispensing guidance is enclosed in table 14a to 14e in Annexes.

3. Antiretroviral therapy

Goals of Antiretroviral Therapy

- Improvement in 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
- Minimize side effects of drugs
- Reduce HIV transmission

3.1 When to start antiretroviraltherapy

Table2: Summary of recommendations on when to start ART in adults, adolescents, pregnant and breastfeeding women and children

<table>
<tr><td rowspan="7">Adults and adolescents</td><td colspan="2">Initiate ART if CD4 count ≤500 cells/mm^3</td></tr>
<tr><td colspan="2"><u>As a priority</u>, initiate ART in everyone with severe/advanced HIV disease (clinical stage 3 or 4) or CD4 count ≤350 cells/mm^3</td></tr>
<tr><td rowspan="5">Regardless of CD4 count and clinical stage</td><td>Pregnant and breastfeeding women with HIV; Decide on when to stop (Option B) or Continue (Option B plus). Refer to the text.</td></tr>
<tr><td>Active TB disease</td></tr>
<tr><td>HBV coinfection with severe chronic liver disease</td></tr>
<tr><td>HIV-positive individual in a serodiscordantcouples (to reduce HIV transmission risk)</td></tr>
<tr><td>Key populations including FSWs, MSMs, TGs and PWIDs</td></tr>
<tr><td rowspan="2">Children ≥5 years old</td><td colspan="2">Initiate ART if CD4 count ≤500 cells/mm^3</td></tr>
<tr><td colspan="2"><u>As a priority</u>, initiate ART in all children with severe/advanced HIV disease (clinical stage 3 or 4) or CD4 count ≤350 cells/mm^3</td></tr>
<tr><td rowspan="2">Children 1–5 years old[a]</td><td colspan="2">Initiate ART in all regardless of CD4 cell count and clinical stage</td></tr>
<tr><td colspan="2"><u>As a priority</u>, initiate ART in all HIV-infected children 1–2 years old or with severe/advanced HIV disease (clinical stage 3 or 4) or with CD4 count ≤750 cells/mm^3 or <25%, whichever is lower.</td></tr>
<tr><td>Infants <1 year old[a]</td><td colspan="2">Initiate ART in all infants regardless of CD4 cell count and clinical stage</td></tr>
</table>

[a]Initiate ART in all HIV-infected children below 18 months of age with presumptive clinical diagnosis of HIV infection.

3.1.1 Starting ART in adults and adolescents

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

- All patients with CD4 counts of <500/mm3 irrespective of the WHO clinical stage; Priority to be given to those with CD4 count less than 350/mm3
- All patients with WHO clinical stage 1 and 2 should be tested for CD4 counts to decide when to start ART
- All patients with WHO clinical stage 3 or 4 irrespective of CD4 count

It is also recommended to initiate ART in people with active TB disease and HBV coinfection with severe liver disease (ALT levels more than 2.5 times the normal), all children younger than five years living with HIV andHIV-positive individual in a serodiscordant couples, regardless of CD4 cell count.

There is insufficient evidence and/or favourable risk–benefit profile to support initiating ART at a CD4 cell count >500 cells/mm^3 or regardless of CD4 cell count or WHO clinical stage in the following situations: individuals with HIV older than 50 years, individuals with HIV-1 infected or coinfected with HIV-2, individuals with HIV coinfected with HCV and key populations with HIV with a high risk of transmission (such as people who inject drugs, men who have sex with men, transgender people and sex workers). ART initiation in these populations should therefore follow the same principles and recommendations as for other adults with HIV.

There is insufficient evidence and/or favourable risk-benefit profile to support initiating ART in everyone coinfected with HIV and HBV with a CD4 count >500 cells/mm^3 or regardless of CD4 cell count or WHO clinical stage. Initiating ART regardless of CD4 count is therefore recommended among people with evidence of severe chronic liver disease, who are at greatest risk of progression and mortality from liver disease. For people without evidence of severe chronic liver disease, ART initiation should follow the same principles and recommendations as for other adults.

People with WHO clinical stage 1 and 2 will be usually in the asymptomatic stage or will only have signs or symptoms not severe enough to seek medical advice. However it is now recognized that some of them will have low CD4 counts of $\leq$350/mm^3. Therefore CD4 counts become very important in the new guidelines and attempts should be made to measure CD4 counts in all cases for success of ART.

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.

In the long run however providing ART at CD4 counts of ≤500/mm^3 will be beneficial not only for the individual patient but also more cost effective since there will no longer be any need to hospitalize patients or to treat opportunistic infections and because of reduction in morbidity and mortality.

For these reasons wider access to HIV testing and CD4 count measurements become important and provider initiated counselling and testing should be carried out on a wider scale.

While increased access to CD4 testing is a priority, the lack of a CD4 count should not be a barrier to the initiation of ART.

N.B. When starting ART in WHO clinical stage 3 and 4, opportunistic infections should be diagnosed and treatment started before starting ART.

3.1.2 Starting ART in pregnant women

All pregnant and breastfeeding women with HIV should initiate triple ARV as soon as possible.

Deciding on Duration of ART started to pregnant and breastfeeding women:

The decision whether to stop or continue ART, in pregnant and breastfeeding women who are on ARV, should be made after assessment of treatment eligibility for her own health and counselling with the patient during breastfeeding.

If the CD4 count of the pregnant women is less than 500/mm^3 or if she has WHO stage 3 or 4 illness, the ART should be continued as she is eligible for treatment like any other HIV positive individual.

Ifthe CD4 count is more than 500/mm^{3}and she does not have WHO stage 3 or 4 illness, ART can be continued lifelong (Option B plus) or can be stopped at 1 week after cessation of breast feeding (Option B) depending on patient's choice.

For infants born to HIV infected mother, regardless of feeding mode, daily NVP should be administered for 6 weeks.

3.1.3 Starting ART in children

Infants and young children have an exceptionally high risk of poor outcomes from HIV infection. Up to 52% of children die before the age of two 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. It is therefore recommended that:

- ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count
    - Infants diagnosed in the first year of life
    - Children infected with HIV one year to less than five years of
- ART should be initiated in all HIV-infected children five years of age and older with CD4 cell count < 500 cells/mm^3, regardless of WHO clinical stage
- ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count.
- ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection

3.1.4 Starting ART in co-infections

HIV/TB coinfection

HIV/TB coinfection –All patients with HIV and active TB should be started on ART irrespective of CD4 count.

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 /mm^3.

It is recommended that ART be initiated in people with active TB irrespective of the CD4

ART Recommendations for HIV/TB coinfection

- Start ART in HIV infected individuals with active TB irrespective of CD4 count.
- Start TB treatment first followed by ART as early as 2 weeks and not later than 8 weeks.
- Use EFV as the preferred NNRTI in patients started on ART while on TB treatment.

HIV and Hepatitis B coinfection

Individuals with HIV/HBV coinfection have an increased risk of developing chronic HBV infection; an increased risk of fibrosis and increased risk of death compared to HBV infected individuals without HIV infection. Therefore it would be beneficial to start ART in all HIV/HBV coinfected individuals who require treatment for their HBV infection (i.e. chronic active hepatitis) irrespective of the CD4 count or the WHO clinical stage. Therefore, it is recommended to initiate ART in all HIV/HBV coinfected patients irrespective of CD4 count if the serum ALT level is more than 2.5 times upper limit of the normal. In such situations TDF and 3TC (or FTC) containing ART combinations should be used since both these agents have activity against HBV. The new preferred first line regimen contains both these drugs and hence, is useful in harmonizing the first line treatment across this group as well. Recommendations include-

- Catch-up hepatitis B immunization strategies should be instituted in settings where infant immunization has not reached full coverage.

Considerations for People who inject drugs (PWID),current guidance on the use of ART for treatment of HIV infection in adults and adolescents applies to people living with HIV who inject drugs. When ART is provided in a supportive environment, people who inject drugs have treatment outcomes similar to others' outcomes.

HIV and Hepatitis C coinfection

Hepatitis C (HCV) coinfection is associated with accelerated progression of liver disease and increased risk of death in HIV positive persons. The effect of HCV on HIV disease progression however is uncertain. HCV infection is difficult to treat in a public health setting as interferon injections and ribavirin have to be used. Ribavirin causes drug interactions with AZT, ABC, d4T, ddI and ATV. The initiation of ART in HIV/HCV coinfected people should follow the same principles and guidelines as for ART treatment of HIV infections without HCV coinfection. Patients should be closely monitored for increased risk of drug toxicities. All HIV positive patients with HBV or HCV coinfection should avoid alcohol and other hepatotoxic drugs.

- Assessment for antiviral treatment of all adults and children with chronic HCV infection is recommended, including for people who inject drugs (strong recommendation, moderate quality of evidence).
- New guidelines will be out within a short time with more effective and sensitive as well as shorter course regimens.

Notes-

- WHO guidelines on HBV prevention, treatment and care came out in 2015 and screening strategies for hepatitis B and C will be available in 2016.

- WHO HCV guidelines provide detailed guidance on treatment and care.
- There are challenges in diagnosing and treating active HCV infection in certain populations such as people who inject drugs, particularly in settings with limited access to HCV antibody and RNA assays, diagnostic tools for staging of liver disease and HCV therapy. People receiving ART and HCV drugs require close monitoring for possible drug interactions.

3.2 What ART combination to start

Classification of Antiretroviral Drugs

Nucleoside Reverse Transcriptase Inhibitors (NRTIs):

Zidovudine (ZDV) (also known as azido thymidine or AZT)
Lamivudine (3TC)
Emtricitabine (FTC)
Abacavir(ABC)
Nucleotide Reverse Transcriptase Inhibitor -
Tenofovir(TDF)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

Nevirapine (NVP)
Efavirenz (EFV)
Etravirine(ETR) **

Protease Inhibitors (PIs):

Lopinavir (LPV)
Ritonavir (used to boost other PIs only)
Ritonavir boosted lopinavir (LPV/r)
Ritonavir boosted Atazanavir (ATV/r)
Atazanavir (ATV)
Darunavir(DRV)**

IntegraseInhibitor:

Raltigravir (RAL)**

**** Recommended 3rd line drugs**

Table 3: Summary of first-line ART regimens for adults, adolescents, pregnant and breastfeeding women and children

First-line ART	Preferred first-lineregimens	Alternativefirst-lineregimens
Adults and adolescents (including pregnant and breastfeeding women and adults with TB coinfection and HBV coinfection)	TDF+3TC (orFTC) +EFV	AZT + 3TC + EFV AZT + 3TC + NVP ABC + 3TC + EFV[a]
Children ≥3 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP
Children <3 years	ABC (or AZT) +3TC + LPV/r	ABC + 3TC + NVP AZT + 3TC + NVP

[a]ABC based combinations 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 ofsignificant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons.

3.2.1 ART regimens in adults and adolescents

Table 4: Summary of first-line ART regimens for adults

First-line ART for adults (including pregnant and breastfeeding women and people with TB coinfection and HBV coinfection)	
Preferred regimens	TDF + 3TC (or FTC) + EFV
Alternative regimens (in order of preference)	AZT + 3TC + EFV AZT + 3TC + NVP ABC + 3TC + EFV

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 coinfection 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 coinfection 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 coinfection where EFV provides benefits over nevirapine. 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 folatedeficiency) 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.]

EFV is sometimes associated with giddiness, insomnia and nightmares which usually disappear after a few days.

The safety of EFV is now established in pregnancy. Hence, it can be used in pregnant women.

AZT + 3TC + NVP

This is an alternate to preferred first line regimen for treatment naive patients. This is widely available in a fixed dose combination. NVP sometimes causes serious side effects. It is not advisable to use NVP together with Rifampicin since Rifampicin causes reduced NVP levels. NVP is associated with the occurrence of skin rash, Stevens-Johnson syndrome and hepatotoxicity. If severe side effects occur NVP should be discontinued permanently and not restarted.

In women with CD4 count >250/mm^3(or in men with CD4 >400/mm^3) NVP is not advised; it should be used with caution, if other choices are not available, since there may be an

increased risk of hypersensitivity and hepatotoxicity. Close monitoring is advised in the first 12 weeks of therapy with NVP. Patient taking NVP should be advised to report immediately if nausea, fever, rash or jaundice develops.

NVP is started with 200 mg OD dose for 2 weeks (lead-in dose) after which it is increased to the usual dose of 200 mg BD. This will allow NVP to induce its own metabolism (enzyme auto-induction); if NVP is started 200 mg BD straight away there may be very high drug levels with toxicity. NVP containing regimens are contraindicated for prophylaxis in HIV negative persons.

ABC + 3TC + EFV

This is another alternate first line regimen that is recommended under the Myanmar National guidelines. A very small proportion of patients who cannot tolerate both TDF and AZT can be put on this regimen.

NRTIs not to be used together

- AZT + d4T (antagonism)
- d4T + ddI (overlapping toxicities)
- 3TC + FTC (interchangeable)
- TDF + ddI + any NNRTI (early rate of virological failure)

3.2.2 Prevention of mother-to-child transmission (PMTCT)

WHO recommends a four-pronged approach to a comprehensive PMTCT strategy:

1. Primary prevention of HIV infection among women of childbearing age
2. Preventing unintended pregnancies among women living with HIV
3. Preventing HIV transmission from women living with HIV to their infants
4. Providing appropriate treatment, care, and support to mothers living with HIV, their children and families

Maternal prophylaxis

The recommended regimen, for both ARV prophylaxis as well aslife longART, is TDF/3TC(FTC)/EFV or alternate first line same as adult.

Infant prophylaxis

The recommended regimen for infant prophylaxis is NVP and the following table shows the detail dosage of NVP.

Table 8: Simplified infant prophylaxis NVP dosing recommendations

Infant age	Daily dosing
Birth[a] to 6 weeks[b] • Birth weight 2000–2499 g • Birth weight ≥2500 g	 10 mg once daily 15 mg once daily
>6 weeks to 6 months[c]	20 mg once daily
>6 months to 9 months	30 mg once daily
>9 months until breastfeeding ends	40 mg once daily

[a]Low-birth-weight infants should receive mg/kg dosing; the suggested starting dose is 2 mg/kg once daily.

[b]Recommended for 6 weeks, but 4 weeks may be considered in settings with replacement feeding.

[c]Dosing beyond 6 weeks of age in special situations in which prolonged dosing of up to 12 weeks should be considered (such as the mother having had limited ART and not being likely to be virally suppressed; the infant is identified as HIV exposed after birth and is breastfeeding.

Table 9: Scenarios for maternal and infant ARV prophylaxis

Scenario	Maternal ARV prophylaxis	Infant ARV prophylaxis	Duration of infant ARV prophylaxis
Mother diagnosed with HIV during pregnancy	Initiate maternal ART	NVP	6 weeks
Mother diagnosed with HIV during labour or immediately postpartum and plans to breastfeed	Initiate maternal ART	NVP	6 weeks; consider extending this to 12 weeks
Mother diagnosed with HIV during labour or immediately postpartum and plans replacement feeding	Refer mother for HIV care and evaluation for treatment	NVP	6 weeks
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is breastfeeding	Initiate maternal ART	NVP	Perform infant PCR early infant diagnosis test and then immediately initiate 6 weeks of NVP – strongly consider extending this to 12 weeks
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is not breastfeeding	Refer mother for HIV care and evaluation for treatment	No drug	Do HIV PCR test in accordance with national recommendations on early infant diagnosis; no infant ARV prophylaxis; initiate treatment if the infant is infected
Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to continue)	Determine an alternative ART regimen or solution; counsel regarding continuing ART without interruption	NVP	Until 6 weeks after maternal ART is restarted or until 1 week after breastfeeding has ended

First-line ART for pregnant and breastfeeding women and ARV drugs for their infants

The ideal first-line regimen for pregnant and breastfeeding women with HIV is available as a fixed-dose combination; is safe for both pregnant and breastfeeding women and their infants; is well tolerated; has low monitoring requirements and a low drug-resistance profile; is compatible with other drugs used in clinical care; and is harmonized with the recommendations for non-pregnant adults. The regimen of TDF + 3TC (or FTC) + EFV is available as a once-daily fixed-dose combination and is the recommended first-line regimen for adults because of simplicity, increasing affordability and efficacy against HBV.

Safety of EFV in pregnancy

There had been concerns in the past over the use of efavirenz in pregnancy due to the early data suggesting birth defects, including anencephaly, microphthalmia and cleft palate among primates with EFV exposure in utero and some isolated case reports and retrospective clinical data on neural tube defects among humans. However, the recent evidence as well as recommendation from WHO have suggested that it is safe to useEFV during pregnancy. Evaluation of prospectively collected data in humans is reassuring. Studies of live births to women receiving EFV in the first trimester and found no increase in overall birth defects and no elevated signal for EFV compared with other ARV exposure in pregnancy.

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, 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.

3.2.3 ART regimens for children

The recommendation for the choice of first line regimen in children is based on the age. Therefore, the recommendations are provided for two groups:

a. Children less than 3 years

b. Children over 3 years including adolescent

ART regimen for children less than 3 years age: Optimizing first-line ART in children younger than three years is critical to achieving effective and rapid control of viral replication in the context of high viral load and rapid infant growth. Considerations that may require alternative therapeutic approaches include the limited availability of drugs in appropriate formulations, the long-term toxicities of ARV drugs, difficulty with adherence and the possibility of pre-existing viral resistance because of ARV drug exposure for PMTCT. Young children with HIV who are exposed to NNRTIs used for PMTCT have demonstrable viral Resistance, which compromises the response to NVP-containing first-line ART. The selection of paediatric regimen for this group takes into consideration the following:

- A LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than three years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with a NVP-based regimen
- Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained
- For infants and children infected with HIV younger than three years, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted.
- For infants and children infected with HIV younger than three years, the NRTI backbone for an ART regimen should be ABC or AZT + 3TC

Table 5: Summary of first-line ART regimens for children younger than three years

Preferred	ABC[a] or AZT + 3TC + LPV/r[b]
Alternative	ABC[a] or AZT + 3TC + NVP
Special circumstances	d4T[c] + 3TC + LPV/r d4T[c] + 3TC + NVP

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

[b]Using LPV/r oral liquid should be avoided in premature babies (born one month or more before the expected date of delivery) until 14 days after their due date or in full-term babies younger than 14 days of age. Dosing for children younger than 6 weeks should be calculated based on body surface area.

[c]Because of the limited options available for children younger than three years, d4T is still included among the recommended NRTIs, but its use should be restricted to the situations in which toxicity to AZT is suspected or confirmed and ABC cannot be used. The duration of therapy with this drug should be limited to the shortest time possible.

ART Regimen for children more than 3 years age: The selection of paediatricregimen for this group takes into consideration the following:

- For children infected with HIV three years and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative
- For children infected with HIV three years to less than 10 years old (or adolescents less than 35 kg), the NRTI backbone for an ART regimen should be one of the following, in preferential order:
  - ABC + 3TC
  - AZT or TDF + 3TC (or FTC)
- For adolescents infected with HIV (10 to 19 years old) weighing 35 kg or more, the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in preferential order:
  - TDF + 3TC (or FTC)
  - AZT + 3TC
  - ABC + 3TC

Table 6: Summary of recommended first-line ART regimens for children and adolescents

	Children 3 to 10 years or Adolescents <35 kg	Adolescents (10 to 19 years) ≥35 kg
Preferred	ABC[a] + 3TC + EFV	TDF + 3TC (or FTC) + EFV[a]
Alternatives	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Special circumstances	d4T[b] + 3TC + EFV d4T[b] + 3TC + NVP	ABC + 3TC + EFV ABC + 3TC + NVP

[a]These recommendations apply to children and adolescents who are initiating first-line ART. Children and adolescents who are already taking ABC-containing regimens can safely substitute TDF for ABC, if this is needed for programmatic reasons. Children and adolescents who are on d4T-containing regimens without evidence of treatment failure can safely substitute ABC or TDF for d4T. Despite a lack of direct evidence, consideration can also be given to substituting ABC or TDF for AZT with the goal of simplifying and harmonizing treatment regimens across age groups. Including TDF in initial ART regimens for children with HBV coinfection offers the potential advantage of reducing the selection of HIV resistance to 3TC that may compromise future options for HBV treatment.

[b]d4T use should be restricted to situations in which toxicity to AZT is suspected or confirmed and access to ABC or TDF is lacking.The duration of therapy with this drug should be limited to the shortest time possible.

3.2.4 TB co-treatment in children and adolescents with HIV

TB is one of the most common opportunistic infections affecting children with HIV. Selecting regimens that are compatible with TB therapy is therefore essential. It should be noted that Rifampicin and LPV/r or NVP be avoided. The various recommended strategies for managing TB in HIV infected children is summarized below:

Table 7: Summary of recommended ART regimens for children and adolescents who need TB treatment

Recommended regimens for children and adolescents initiating ART while on TB[a] treatment[b]		
Younger than 3 years		Two NRTIs + NVP, ensuring that dose is 200 mg/m^2 or Triple NRTI (AZT + 3TC + ABC)[c]
3 years and older (including adolescents)		Two NRTIs + EFV or Triple NRTI (AZT + 3TC + ABC)[c]
Recommended regimen for children and infants initiating TB[a] treatment while receiving ART		
Child on standard NNRTI-based regimen (two NRTIs + EFV or NVP)	**Younger than 3 years**	Continue NVP, ensuring that dose is 200 mg/m^2 or Triple NRTI (AZT + 3TC + ABC)[c]
	3 years and older (including adolescents)	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]
Child on standard PI-based regimen (two NRTIs + LPV/r)	**Younger than 3 years**	Triple NRTI (AZT + 3TC + ABC)[c] or Substitute NVP for LPV/r, ensuring that dose is 200 mg/m^2 or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose[d]
	3 years and older (including adolescents)	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; consider 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 consider adding RTV to achieve the full therapeutic dose[d] Consider consultation with experts for constructing a second-line regimen

[a]Ensure optimize dosing of Rifampicin based on new 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. Based on the findings from the ARROW trial, this regimen should be considered as the preferred option for children younger than three years who are receiving an LPV/r-based regimen when starting TB treatment. It should also be considered as the preferred regimen for children older than three years with a history of failure of an NNRTI-based regimen.

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

[e]Substitution with 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.

3.3 Monitoring ARV toxicities and response to treatment

3.3.1 ARV toxicities

AZT - severe anaemia can develop and sometimes very suddenly any time but especially during the first 6 months; warn patients about pallor and severe shortness of breath; stop AZT; can recover if mild but may need erythropoietin or blood transfusions; substitute with TDF.

d4T – the side effects of lipodystrophy, hyperlipidaemia, peripheral neuropathy and lactic acidosis develop over time; not advisable in first line regimens; if used initially, switch with AZT or TDF; should not use d4T for extended periods of time.

TDF – potential for renal toxicity; check creatinine (creatinine clearance), proteinuria, glucosuria.

NVP – always use lead-in dose (200 mg OD x 2 weeks and continue 200 mg BD); watch out for rash, Stevens-Johnson syndrome, hepatotoxicity especially during first 3 months; stop NVP immediately and if reactions severe, can be fatal; may require special care. Do not use NVP again. Change regimen. NVP toxicity may occur at all stages of immune suppression but is more common in women with CD4 > 250/mm^3 and in men with CD4 > 400/mm^3.

EFV – can have insomnia, nightmares, and severe giddiness at start of treatment but usually goes away after one or 2 weeks. The main type of toxicity of EFV is central nervous system side effects, which typically resolve after a few weeks. However, in some cases, they can persist for months or not resolve at all. Advise night time dose; do not take with food to minimize side effects.

N.B. – When stopping NVP or EFV continue NRTI backbone (2 drugs) for at least 7 days to cover the long half-life of NNRTI decay and reduce the risk of NNRTI resistance.

Table 10: Adult dosage and important side effects of first line ARV drugs

ARV drug	Adult Dosage	Side effects
NRTIs -		
AZT	300 mg BD	Bone marrow suppression, severe anaemia (any time), gastrointestinal intolerance, Skin and nail pigmentation
3TC	150 mg BD 300 mg OD	Generally well tolerated Acute exacerbation of hepatitis may occur if it is withdrawn in HBV coinfected patients who stop 3TC
FTC	200 mg OD	Generally well tolerated, cutaneous hyperpigmentation Acute exacerbation of hepatitis may occur if it is withdrawn in HBV coinfected patients who stop FTC
d4T	30 mg BD	Lipodystrophy can be severe; hyperlipidaemia especially hypertriglyceridemia Peripheral neuropathy Lactic acidosis
ddI	400 mg OD (>60 kg) 250 mg OD (<60 kg)	Pancreatitis, lactic acidosis, peripheral neuropathy, hepatitis, hepatic steatosis
ABC	300 mg BD	Hypersensitivity reactions
TDF (NtRTI)	300 mg OD	Renal toxicity, decrease in bone density Acute exacerbation of hepatitis may occur if it is withdrawn in HBV coinfected patients who stop TDF
NNRTIs-		
NVP	200 mg BD, initially 200 mg OD x 2 wks	Hypersensitivity reaction Rash Stevens-Johnson syndrome Hepatic toxicity Hyperlipidaemia
EFV	600 mg OD	Similar to NVP but milder and less frequent Giddiness in first few days, can be severe

Table 11: Monitoring ART in those at higher risk of adverse effects

ARV drug	Major toxicity	High-risk situations
AZT	Anaemia, neutropenia	Anaemia at baseline, CD4 < 200/mm^3, BW < 50 kg
TDF	Renal dysfunction	Underlying renal disease, age > 40 yr, BW < 50 kg, diabetes, hypertension, PI or nephrotoxic drugs
EFV	Psychiatric illness	Depression or psychiatric illness
NVP	Hepatotoxicity	HCV and HBV coinfection

In children, a weight based drug dosage is recommended. There are fixed drug combinations now available as dispersible tablets for paediatric formulations and WHO has recommended using them according to weight bands. The dosing details for the children are provided in the Annexes (Table 22a to Table 22e).

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

Table 12: Summary of the major toxicities of the commonly used drugs, risk factors for these toxicities and suggested management

ARV drug	Major types of toxicity	Risk factors	Suggested management
ABC	ABC hypersensitivity reaction	Presence of HLA-B*5701 gene	If ABC is being used in first-line ART, substitute with TDF or AZT or d4T If ABC is being used in second-line ART, substitute with TDF
AZT	Anaemia, neutropaenia, myopathy, lipoatrophy or lipodystrophy Lactic acidosis or severe hepatomegaly with steatosis	Baseline anaemia or neutropaenia CD4 count of <200 cells/mm^3 BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues Obesity	If AZT is being used in first-line ART, substitute with TDF or ABC If AZT is being used in second-line ART, substitute with d4T
d4T	Peripheral neuropathy, lipoatrophy or lipodystrophy Lactic acidosis or severe hepatomegaly with steatosis, acute pancreatitis	Older age CD4 count of <200 cells/mm^3 Concomitant use of isoniazid or ddI BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues Obesity	If d4T is being used in first-line ART, substitute with TDF or AZT or ABC If d4T is being used in second-line ART (after TDF or ABC are used in first-line ART), substitute with AZT

ARV drug	Major types of toxicity	Risk factors	Suggested management
EFV	Persistent central nervous system toxicity (such as abnormal dreams, depression or mental confusion) Hepatotoxicity Convulsions Hypersensitivity reaction, Stevens-Johnson syndrome, potential risk of neural tube defects Male gynaecomastia	Depression or other mental disorder (previous or at baseline) Daytime dosing Underlying hepatic disease – HBV and HCV coinfection Concomitant use of hepatotoxic drug History of seizure Risk factors unknown	NVP. If the person cannot tolerate either NNRTI use boosted PIs
LPV/r	Electrocardiographic abnormalities (PR and QT interval prolongation, torsades de pointes) QT interval prolongation Hepatotoxicity Pancreatitis Risk of prematurity, lipoatrophy or metabolic syndrome, dyslipidaemia or severe diarrhoea	People with pre-existing conduction system disease Concomitant use of other drugs which may prolong the PR interval Congenital long QT syndrome Hypokalaemia Concomitant use of drugs that may prolong the QT interval Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs Advanced HIV disease Risk factors unknown	If LPV/r is used in first-line ART for children, use an age-appropriate NNRTI (NVP 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, use ATV/r or DRV/r. If boosted PIs are contraindicated and the person has treatment failure with NNRTI in first-line ART, consider integrase inhibitors
NVP	Hepatotoxicity Severe skin rash and hypersensitivity reaction (Stevens-Johnson syndrome	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs Pregnant women CD4 > 250 cells/mm^3 in women CD4 >400 cells/mm^3 for men First month of therapy (if lead-in dose is not used) Risk factors unknown	EFV. If the person cannot tolerate either NNRTI use boosted PIs

ARV drug	Major types of toxicity	Risk factors	Suggested management
TDF	Tubular renal dysfunction, Fanconi syndrome Decreases in bone mineral density Lactic acidosis or severe hepatomegaly with steatosis Exacerbation of hepatitis B (hepatic flares)	Underlying renal disease Older age BMI <18.5 (or body weight <50 kg) Untreated diabetes mellitus Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI History of osteomalacia and pathological fracture Risk factors for osteoporosis or bone loss Prolonged exposure to nucleoside analogues Obesity Discontinuation of TDF	If TDF is being used in first-line ART, substitute with AZT or d4T or ABC If TDF is being used in second-line ART (after d4T + AZT use in first-line ART), substitute with ABC or ddI Not applicable

Monitoring 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 incase 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).

Common adverse effects of ARV drugs include fat maldistribution, hyperlipidaemia, lactic acidosis, hepatotoxicity, impaired glucose tolerance, pancreatitis and peripheral neuropathy and these are due to mitochondrial toxicity.

Lipodystrophy consists of two components viz. fat accumulation and lipoatrophy. Fat accumulation is seen in the upper back (buffalo hump), the breasts, within the abdominal cavity and in subcutaneous tissue. Metabolic syndrome may also develop. Lipoatrophy causes loss of subcutaneous fat in the face, extremities and buttocks. Lipodystrophy can be disfiguring and may not be reversible. Lipodystrophy is seen with ART; Stavudine is the commonest cause of lipoatrophy and it may be caused to a lesser extent by AZT and ddI. Fat accumulation is seen more commonly with PIs.

Lactic acidosis/Hepatic steatosis– can complicate NRTIs usually due to d4T. Severe lactic acidosis is less common but can be lethal.
Insulin resistance is common with PIs but diabetes is less common except in those with a family history.
Hyperlipidaemia especially hypertriglyceridaemia can be due to HIV infection with or without ART but more often with ART; this can increase the risk of cardiovascular disease. AZT, d4T and PIs are especially responsible. Lovastatin and simvastatin should not be used with PIs because of drug interaction.
Osteoporosis and avascular necrosis of the femoral head may be seen in patients on long term ART.

3.3.2 Drug interactions

Many of the commonly recommended ARVs have several key drug interactions. It is important to know these as PLHIV on ART will also be taking other medications for other ailments and diseases.

The most common examples include interactions of Rifampicin with PIs, antifungals with NVP; AZT with ribavirin and HCV treatment; EFV with anti-malaria drugs (like artemisinin based combination); methadone and ARV interactions; ARV interaction with steroids and oral contraceptives; PIS and NNRTIs with certain antihistamines; PI interaction with statins.

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 receiving methadone and EFV should be monitored closely, and those experiencing opioid withdrawal may need to adjust their methadone dose.

Concomitant use of boosted PIs and NNRTI with some antihistamine agents (such as astemizole and terfenadine) has been associated with severe and life-threatening reactions, such as cardiac arrhythmia. Alternative antihistamine agents include loratidine and cetirizine.

WHO recommends using statins for people with a 10-year cardiovascular risk exceeding 30%. Boosted PIs may lead to increased concentrations of lovastatin and simvastatin. Increased concentrations may increase the risk of developing serious adverse events such as myopathy (including rhabdomyolysis). Alternative dyslipidaemia agents should be used to prevent severe toxicity among people with HIV.

Table 13: Key ARV drug interactions and suggested substitutions

ARV drug	Key interactions	Suggested management
AZT	Ribavirin and peg interferon alfa-2a	First-line: substitute AZT with TDF Second-line: substitute AZT with d4T
Boosted PI (ATV/r, LPV/r)	Rifampicin	Substitute Rifampicin with Rifabutin
	Lovastatin and simvastatin	Adjust the PI dose or substitute with three NRTIs (for children)
	Estrogen-based hormonal contraception	Use an alternative dyslipidaemia agent
	Methadone and buprenorphine	Use alternative or additional contraceptive methods
	Astemizole and terfenadine	Adjust methadone and buprenorphine doses as appropriate
		Use alternative antihistamine agent
EFV	Amodiaquine	Use an alternative antimalarial agent
	Methadone	Adjust the methadone dose as appropriate
	Estrogen-based hormonal contraception	Use alternative or additional contraceptive methods
	Astemizole and terfenadine	Use an alternative anti-histamine agent
NVP	Rifampicin	NVP with EFV
	Itraconazole and ketoconazole	Use an alternative antifungal agent
	Estrogen-based hormonal contraception	Use alternative or additional contraceptive methods
	Astemizole and terfenadine	Use an alternative antihistamine agent

3.3.3 Monitoring response to ART

Clinical assessment and laboratory tests play a key role in assessing individuals before ART isinitiated 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 coinfections and noncommunicable diseases.

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

Table 14: Recommended Laboratory Monitoring of ART

Laboratory monitoring of ART	
Hb (For AZT)	Baseline and at 4, 8, 12 weeks ; every 6 months desirable
CD4 count	Baseline and every 6 months
Plasma viral load : targeted	At 12 months after the ART initiation and as needed only to confirm virological failure
Chest X- rays	When indicated
Urinalysis (proteinuria, glucosuria)	Baseline and Every 6 months if TDF used
Creatinine (for Cr clearance calculation)	Every 6 months if TDF used especially in high risk patients
ALT, AST	Every 6 months (if NVP used at 4,8 12 weeks) desirable but not compulsory
Fasting blood sugar	Every 6 months desirable
Lipid profile (at least cholesterol and triglyceride)	Every 12 months (desirable)

Table 15: Summary of laboratory monitoring for response to and toxicity of ARV drugs before, during and after initiating ART in adults and children

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis	HIV serology, CD4 TB screening	HBV (HBsAg) serology[a] HCV serology *Cryptococcus* antigen if CD4 ≤100 cells/ mm[3b] Screening for sexually transmitted infections Assessment for major noncommunicable chronic diseases and comorbidities[c]
Follow-up before ART	CD4 (every 6–12 months)	

Phase of HIV management	Recommended	Desirable (if feasible)
ART initiation	CD4	Haemoglobin test for AZT[d] Pregnancy test Blood pressure measurement Urine dipsticks for glycosuria and estimated glomerular filtration rate and serum creatinine for TDF[e] Alanine aminotransferase for NVP[f]
Receiving ART	CD4 (every 6 months) HIV viral load (6-12 months after ART initiation/ targeted)	Urine dipstick for glycosuria and serum creatinine for TDF[c]
Treatment failure	CD4 HIV viral load	HBV (HBsAg) serology[a] (before switching ART regimen if this testing was not done or if the result was negative at baseline)

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

[b]Can be considered only in settings with a high prevalence of cryptococcalantigenaemia (>3%).

[c]Consider assessing the presence of chronic conditions that can influence ART management such as hypertension and other cardiovascular diseases, diabetes and TB.

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

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

[f]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 HCV coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity.

3.4 When to switch to second line ART

When the first line ART regimen fails it becomes necessary to switch to second line ART.

Second line regimens are expensive – about 5 to 10 times more than the standard first line ART regimen. Therefore utmost attempts must be made to optimize adherence and prevent resistance to first line regimens.

ART switching-

- Where available , use viral load (VL) to confirm treatment failure
- A persistent VL of > 1000 copies/ml confirms treatment failure
- Where VL is not available, use immunological criteria (CD4 count) to confirm clinical failure.

Table 16: WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens in adults and children

Failure	Definition	Comments
Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodefiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndromeoccuring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure
Immunological failure	**Adults and adolescents** CD4 count falls to the baseline (or below)**or** Persistent CD4 levels below 100 cells/ mm^3 **Children** *Younger than 5 years* Persistent CD4 levels below 200 cells/ mm^3 or <10% *Older than 5 years* Persistent CD4 levels below 100 cells/ mm^3	Without concomitant or recent infection to cause a transient decline in the CD4 cell count

Failure	Definition	Comments
Virological failure	Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support	An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed Assessment of viral load using DBS and point-of-care technologies should use a higher threshold

Virologicalfailure (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 regimento be less effective as the viral load gets higher and more drug resistant clones to remaining NRTIs develop.

The cost of a single viral load test is less than the cost of one month's supply of a second line regimen. However expensive equipment is required and the test requires expertise to perform. Efforts should be made to make viral load measurements as much as possible to maximize ART.

ART can be started without doing VL but its use is actually necessary to diagnose ART failure, in a timely manner. While expensive, VL has the potential to save the cost of expensive second line drugs by confirming they are needed.

Routine viral load strategy for failure and switching

The objective of the routine VL strategy is to detect virological failure early, leading to adherence interventions or changes in therapy that will limit ongoing viral replications, reduce the risk of accumulation of resistance mutations and protect the drug susceptibility of second line and subsequent ART regimens.

Routine viral load testing, every 12 months -

- If VL > 1000 copies/ml, take adherence interventions.
- Then repeat VL.
    - o If VL < 1000 copies/ml, do not switch to second line.
    - o If VL > 1000 copies/ ml, switch to second line.

Targeted viral load testing

Targeted VL testing can limit unnecessary switching to expensive second line ART. In resource limited settings, it can be carried out only when there is suspected clinical or immunological failure. In such a case –

- If VL > 1000 copies/ml, take adherence interventions
- Repeat VL
    - o If VL < 1000 copies/ml, do not switch to second line
    - o If VL > 1000 copies/ml, switch to second line.

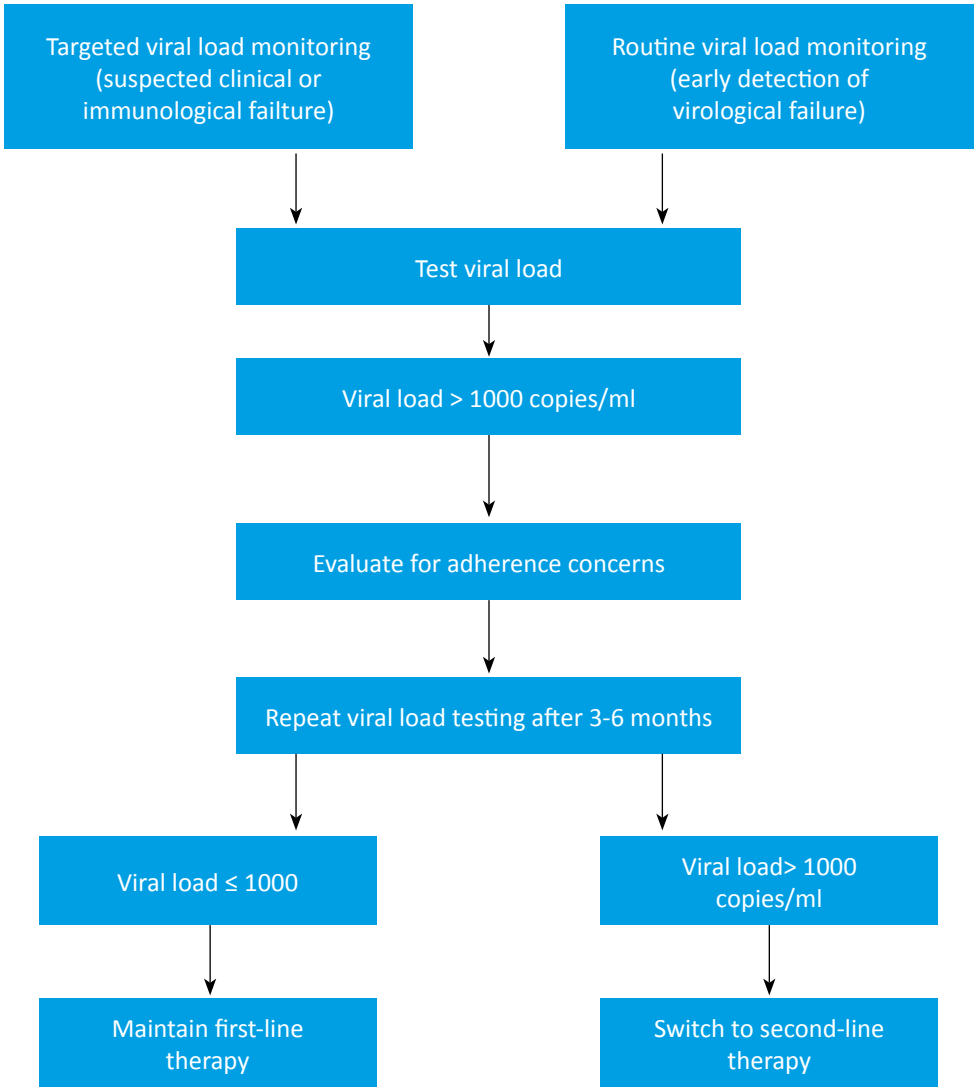
3.4.1 Plasma HIV viral load

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. The lowest level of detection is <50 copies/ml or 400-500 copies/ml depending on the sensitivity of the test. 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(<50 c/ml). 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 VL below 50 c/ml almost eliminates orsubstantially 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 its importance in monitoring ART cannot be over emphasized and attempts are needed to make this test widely available. However lack of VL facilities does not preclude effective ART.

Figure 3: Algorithm for defining failure to treatment using viral load testing



3.4.2 Second-line ART regimens

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.

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.

Use of PIs (Protease inhibitors)

Boosted PIs (bPI) provide most of the antiretroviral activity in second line regimens. Only boosted PIs are recommended for use. Ritonavir is a PI which acts as an inhibitor of cytochrome enzymes involved in metabolism of protease inhibitors. Thus it can reduce the dose (reduced side effects) and increase interval between doses of PIs (improve compliance) with which it is combined (PI/r). Ritonavir is not used by itself as a PI.

Among the PIs, use of Indinavir is no longer recommended as this causes serious problems with renal stones especially in tropical climates.

ATV/r has the advantage of once daily dosing, and it does not because PI cross-resistance.

NRTIs in second-line ART-

- Residual activity of first-line NRTIs (with the possible exception of 3TC or FTC) is more likely the earlier ART failure is detected and switching is started. (Thus the importance of viral loads). Any new NRTI may be compromised in the second line regimen if there is late switching after ART failure because of the development of cross resistance among NRTIs.(Cross resistance of ARV drugs may develop within the same class).
- 3TC may remain useful in second line regimens even if there is resistance as such a strain may protect potential NRTI options and avoid PI monotherapy.
- ABC and ddI are not recommended as preferred options in second line regimens for adults.

Table 17: Protease inhibitors, dose and side effects

Protease Inhibitor	Dose	Important side effects
Ritonavir (RTV)	Only used to boost other PIs in doses of 100 – 400 mg a day	GI intolerance mainly, dyslipidaemia
Lopinavir/r (LPV/r)	400/100 mg BD 800/200 mg OD (OD for treatment-naïve patients)	GI intolerance; dyslipidaemia
Atazanavir/r(ATV/r)	300/100 mg OD	jaundice
Darunavir/r(DRV/r)	600/100 mg BD	Hepatotoxicity, rash, dyslipidaemia

3.5 Third-line ART regimens

- Plans should be made for third-line therapy that consider costs, sustainability and equitable access to ART
- Third line regimens should include new drugs likely to have anti-HIV activity such as second-generation NNRTIs, PIs and integrase inhibitors.
- Patients on a failing second-line regimen with no new options should continue with a tolerated regimen.

While there is need to plan for third-line ART, because of financial constraints in resource limited countries, priority should be on expanding access to first line ART and failing that access to second line ART. Boosted Darunavir (DRV/r) has potent anti-HIV activity and has excellent activity against HIV strains that are resistant to other PIs.

Etravirine (ETR) 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.

In trials combination of these agents has been used effectively. In resource limited countries the availability is uncertain.

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.

Important drug interactions

Drug interactions should be checked when prescribing ARVs.

Many drugs are metabolized in the liver by cytochrome enzymes. A drug which induces the cytochrome liver enzyme that metabolizes another drug reduces the therapeutic concentrations of the second drug. A drug which inhibits the cytochrome enzyme used by another drug increases the concentration of the second drug.

Rifampicin is a potent enzyme inducer and it reduces the drug levels of NNRTIs (NVP> EFV), PIs, ethinylo estradiol, clarithromycin among others. Rifampicin should not be used with NVP. Rifabutin causes less enzyme induction.

All PIs are enzyme inhibitors and ritonavir is the most potent. Ritonavir increases the drug levels of benzodiazapines, opiate analgesics, carbamezapine, clarithromycin, cisprapridеand quinine, sometimes to toxic levels. However RTV increases the activity of glucoronyl transferase enzyme and therefore reduces the levels of ethinylo estradiol. Other PIs also cause increase levels of sidenafil, tricyclic antidepressants, statins, diltiazem and clarithromycin.

The enzyme inhibitor action of RTV is made use of by combining with other PIs so that the dose of PIs can be reduced and the interval of dosing increased. This reduces the toxicity of PIs and also improves compliance (e.g. LPV/r, ATV/r)

RTV as well as azole antifungals (especially ketoconazole) and clarithromycin by causing enzyme inhibition increases the drug levels of antihistamines terfenadine and astemizole which can result in cardiotoxic side effects and these should not be used together.

Anticonvulsants (phenobarbitone, phenytoin, carbmezapine) as enzyme inducers decrease the levels of many PIs, and PIs acting as enzyme inhibitors may increase the drug levels of some anticonvulsants (carbamezapine)– drug interaction acting both ways.

Azole antifungals and PIs may also interact both ways increasing the drug levels of each other.

NNRTIs decrease the drug levels of anticonvulsants, clarithromycin andethyniloestradiol.

Drug interactions can be sometimes complex. Warfarin levels can be decreased or increased by NNRTIs or PIs.

NRTIs do not use the cytochrome P450 enzyme and do not cause drug interactions through this enzyme system but may affect GI absorption or renal elimination.

(For details refer to www.aidsinfo.nih.gov; www.hivinsite.com ; www.hiv-druginteractions.org)

3.6 Updates on post-exposure prophylaxis (PEP)

Post-exposure Prophylaxis (PEP) is a short-term antiretroviral treatment to reduce the likelihood of HIV infection after all potential exposure. Within the Health sector, PEP should be provided as a part of a comprehensive universal precautions package that reduces staff exposure to infectious hazards at work. There already is a joint WHO/ILO guideline on PEP to prevent HIV infection, published March, 2007. However, the recent developments in infection patterns, most notably sexual assault, isolated or episodic injecting drug use and consensual sexual exposure warrant attention and consideration. The global consensus is that the evidence on efficacy of PEP/PrEP, the available strategies and clear operational guidelines be reviewed and that the Focus should be on risk rather than exposure type with a single guideline for all.

Preferred recommendations for adults, adolescents and children are:

- Alignment with recommendations for ART
- Emphasis on simplification to support completion rates
- Full course prescription (28 day)
- Adherence support

When considering the eligibility for PEP, the Best Practice Guidance is

1. PEP should be offered, and initiated as early as possible, preferably within 6 hours to all persons with a HIV exposure, andwithin a window of 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:

    1. Bodily fluids (semen, cervico-vaginal secretions, blood)
    2. Mucous membranes
    3. Percutaneous injury with contaminated sharps

4. Exclusions for PEP would include:

    1. Index patient positive from another source
    2. Source is HIV negative

5. In some settings with high background HIV prevalence, all eligible exposures may be considered for PEP without a risk assessment.

It is, therefore, imperative that HIV post-exposure prophylaxis policies reinforce the importance of primary prevention and risk prevention counseling in all settings where HIV could be transmitted.

Either 2 or 3 drug combinations may be prescribed. The following drug combinations can be used. A third drug, for example, Protease Inhibitor can be added. Updated guidelines and recommendations need to be followed.

It should be noted that the final recommendations and guidelines are available in "December 2014 supplement to the WHO 2013 consolidated ARV guidelines"which will be a supplement to the National guidelines.

Table 18: Recommended ART regimens for PEP

Adults & adolescents	Drugs
Preferred	TDF+3TC (FTC)
Alternative	AZT+3TC
Children (≤ 10 years)	Drugs
Preferred	AZT+3TC
Alternative	TDF+3TC (FTC) ABC+3TC

4. Opportunistic infections in HIV/AIDS

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.

Cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis is a very important part of the management of a patient with HIV. It is recommended for all symptomatic individuals (WHO clinical stages 2, 3 or 4) including pregnant women. Where CD4 count is available, Cotrimoxazole prophylaxis is recommended for individuals with CD4 count of $\leq 350/mm^3$. One double-strength tablet daily of Cotrimoxazole daily is recommended (960 mg = 800 mg sulfamethaxazole + 160 mg trimethoprim).

Since the most common initial side effect of Cotrimoxazole and antiretroviral therapy especially NVP and EFV is rash, it is recommended to start Cotrimoxazole prophylaxis first and to initiate ART two weeks later if the individual does not develop rash with Cotrimoxazole.

Skin reaction is the commonest side effect with Cotrimoxazole. Other side effects are bone marrow toxicity and hepatotoxicity. Side effects can be monitored clinically. Patients starting Cotrimoxazole are advised to stop the drug if an adverse effect is suspected and to report to the nearest clinic. Erythema and a mild maculopapular rash may be observed and antihistamines given but if there is vesiculation, mucosal ulceration and exfoliative dermatitis, Cotrimoxazole should be stopped immediately and discontinued permanently. However drug related adverse effects are not commonand typically occur within the first few weeks of starting prophylaxis. Clinical monitoring is usually sufficient. The safety of Cotrimoxazole in long-term use has been established.

Cotrimoxazole can be discontinued as prophylaxis when the CD4 count rises above 350 cells/mm^3 with ART for at least six months.

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 there is no other alternative in a resource limited setting. 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. Routine screening for G6PD is usually not carried out a resource limited setting.

Table 19: Criteria for initiating, discontinuing and monitoring Cotrimoxazole preventive therapy

Age	Criteria for initiation	Criteria for discontinuation[a]
HIV-exposed infants	Give to all exposed infants, starting at 4–6 weeks after birth	Until the risk of HIV transmission ends or HIV infection is excluded
<1 year	Universal	Until 5 years of age regardless of CD4% or clinical symptoms[c] or Never
1–5 years	WHO clinical stages 2, 3 and 4 regardless of CD4 % or Any WHO stage and CD4 <25% or Universal[b]	Never *(A-IV)*
≥5 years, including adults	*Any WHO stage and CD4 count <350 cells/mm^3* *or* *WHO 2,3 or 4 irrespective of CD4 level*	*CD4 ≥350 cells/mm^3 after 6 months of ART[c]*

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

[b]Universal regardless of CD4 percentage or clinical stage in settings with high HIV prevalence, high infant mortality due to infectious diseases and limited health infrastructure.

[c]If initiated primarily for *Pneumocystis* pneumonia or toxoplasmosis prophylaxis.

4.1 Major opportunistic 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

Table 20: Correlation between CD4 count and HIV associated OIs and conditions

CD4> 500/mm^3	
• Acute primary infection • Persistent generalized lymphadenopathy	• Recurrent vaginal candidiasis
CD4<500/mm^3	
• Pulmonary tuberculosis • Pneumococcal pneumonia • Herpes zoster • Oropharyngeal candidiasis • Oral hairy leukoplakia • Extra-intestinal salmonellosis	• HIV associated ITP (Immune thrombocytopenia) • Cervical intra-epithelial neoplasia II-III • Kaposi's sarcoma (rare in Myanmar)
CD4<200/mm^3	
• Extrapulmonary/military tuberculosis • *Pneumocystis carinii (jirovecii)* pneumonia • Oesophageal candidiasis • Mucocutaneous herpes simplex • *Cryptosporidium* (diarrhoea) • *Microsporidium*(diarrhoea)	• HIV associated wasting • Peripheral neuropathy
CD4<100/mm^3	
• Cerebral toxoplasmosis • Cryptococcal meningitis • Penicilliosis (*Penicillium marneffei)* • Non-Hodgkin lymphoma • Primary CNS lymphoma	• HIV associated dementia • Progressive multifocal leukoencephalopathy
CD4<50/mm^3	
• CMV retinitis/gastrointestinal disease	• Disseminated *Mycobacterium avium intracellulare* disease

4.1.1 HIV/TB coinfection

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 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. Before there is profound immunosuppression (usuallyCD4 count > 200/mm^3) the usual picture of pulmonary tuberculosis with apical infiltrations, cavitation and fibrosis is found. With advancing degrees of immunosuppression i.e. with falling CD4 count,pulmonary TB changes in clinical pattern. There are less apical infiltrations or cavitation. There can be infiltrations in the middle or lower lobes, the chest X-ray appearance may become atypical or non-specific. Sputum smears are less likely to be AFB positive as immunosuppression advances. In the chest X-ray the hilar and mediastinal glands become enlarged.

In advanced immunosuppression there is extrapulmonary spread of tuberculosis. Pleural effusions and pericardial effusions, military TB, TB meningitis, TB of bone especially vertebra with psoas abscess may occur.

Widespread lymphadenopathy due to TB is a common presentation in HIV late stages. The cervical, axillary, hilar and mediastinal glands are involved. Intra-abdominal lymph nodes become enlarged which may occur in isolation or occur together with lymphadenopathy elsewhere. Ultrasound examination of the abdomen is a very useful investigation in patients with HIV to diagnose intrabdominal 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 tuberculosis will depend on the clinical symptoms, and sputum smears for AFB should always be performed; sometimes a biopsy may be necessary e.g. in a lymph node.

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

Tuberculosis in HIV patients is treated just like TB in immunocompetent 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 months in case of tuberculous meningitis, military TB and spinal TB with neurological involvement.The response to treatment is usually very good; in most cases, fever subsides and there is some clinical improvement usually in two weeks time.

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 also refer to the guidelines on clinical management of TB/HIV coinfection, (including IP, use of Gene Xpert machines and MDR TB) by NTP)

ART Recommendations for HIV TB coinfection

- Start ART in HIV infected individuals with active TB irrespective of CD4 counts.
- Start TB treatment first followed by ART as early as 2 weeksand not later than 8 weeks.
- Use EFV as the preferred NNRTI in patients started on ART while on TB treatment.

ART drug interaction with Rifampicin

Rifampicin induces the metabolism of NVP lowering drug levels which can lead to resistance. Therefore EFV is advised instead of NVP in patients taking TB treatment with Rifampicin who are given ART. The alternative is to use ABC instead of a NNRTI (“triple nukes” – AZT + 3TC + ABC) but this is less preferable than EFV.

Similarly Rifampicin induces the metabolism of protease inhibitors, so that boosted protease inhibitors in standard doses are not to be used together with Rifampicin.

The other alternative is to substitute Streptomycin for Rifampicin but this involves giving daily injections and this may not always be possible.

A super boosted dose of ritonavir to increase level of PIs (Ritonivir 400 mg instead of the usual dose of 100 mg to boost the PI) or doubling the usual PI/r dose can be employed if an alternative to Rifampicin is not available, but these measures are associated with greater toxicity and require more frequent and close monitoring.

Rifabutin can be used as an alternative to Rifampicin for those on ART especially if second line ART with boosted PIs is used. Rifabutin has minimal effect on bPI unlike Rifampicin. The suggested dose of Rifabutin with a bPI is 150 mg 3 times/ week. Rifabutin is not yet generally available.

MDR-TB in HIV

There is a risk of MDR-TB in patients with HIV and ideally all TB/HIV coinfected patients should have drug sensitivity tests for anti-TB drugs; this is not yet possible on a wide scale at the present. All HIV patients with suspected MDR-TB should have sputum tested with GeneXpert. Those tested positive for MDR TB should be referred to MDR TB treatment centers. ART is indicated in all MDR-TB/HIV coinfected patients regardless of CD4 counts. MDR-TB in HIV patients carries a poor prognosis. Treatment is difficult and costy. History of inadequate treatment for tuberculosis is the strongest risk factor for MDR-TB.

Isoniazid prophylaxis in HIV

Adults and adolescents with HIV who ***do not have any one of the symptoms of current cough, fever, weight loss or night sweats 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. 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 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.

Table 21: 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

4.1.2 *Pneumocystis jerovecipneumonia*

Pneumocystis jirovecii (previously known as *Pneumocystis carinii)* is a fungus that causes pneumonia in patients with CD4 count<200/mm^3. There is subacute onset and progression of exertional dyspnoea, non productive cough and fever over days or weeks. 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 tables TDS for 3 weeks. Alternative is pentamidineiv 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 RLS and mortality can be high. Cotrimoxazole prophylaxis is continued until the CD4 count rises to >200/mm^3 with ART. Cotrimoxazole prophylaxis is given to all patients in WHO stage 3 or 4 or in those with any WHO stage and CD4 < 350 cells/mm^{3}to prevent PCP.

4.1.3 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/mm^3 it usually causes cerebral abscesses due to reactivation of latent cysts

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.

4.1.4 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, fungal blood culture may be positive but the diagnosis can be easily made from CSF stained with India ink which will show yeast cells with characteristic thick walls. There may be very little CSF pleocytosis; the protein is raised; 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 week sfollowed 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. Itraconazole 200 mg BD in the consolidation and 200 mg OD in the maintenance phase may be used.

Cryptococcal meningitis in HIV is associated with a high mortality and failure to manage elevated ICP 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.

4.1.5 *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 faceand upper body and become generalized throughout the body. It is seen usually when the CD4 count is <100/mm^3. The lesions are papules with central umbilication. 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. Voriconazole can be also used.

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.

4.2 Other conditions and opportunistic infections in HIV

4.2.1 Seroconversion illness or Acute HIV syndrome

This usually occurs 3 to 6 weeks after infection with HIV and about half of all patients may experience this syndrome. It causes a flu-like illness with fever, skin rash, lymphadenopathy, pharyngitis and myalgia and resolves spontaneously in most cases. In some patients it may be more severe with meningitis or encephalitis. It represents a burst of viraemia. This is followed by a prolonged period of clinical latency.

4.2.2 Clinical latency

The length of time from infection to the development of clinical disease varies but in most patients it is from 6 to 10 years. However during this period HIV disease with active virus replication is ongoing. The rate of disease progression is directly related with HIV viral load or RNA levels, those with high VL progressing more rapidly. A small proportion of patients known as *slow progressors* show a very slow decline of CD4 counts even longer and a tiny subset know as *elite controllers* show VL <50 copies/ml with very little signs of disease progression.

4.2.3 PGL (Progressive Generalized Lymphadenopathy)

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

Differential diagnosis of lymphadenopathy in a patient 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

4.2.4 Herpes zoster

It is one of the early manifestations of immunosuppression; even though there is a risk at all strata of CD4 count it is usually seen when the CD4 count falls to $\leq 350/mm^3$. Sometimes it can be multidermatomal. Diagnosis is clinical from the appearance of painful vesicular eruptions along the distribution of a dermatomal nerve. Herpes zoster involving the cornea can cause blindness and when the nasociliary branch of the 1st division of the Vth 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.

4.2.5 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.

4.2.6 Pruritic papular eruptions

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.

4.2.7 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.

4.2.8 Candidiasis

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

4.2.9 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.

4.2.10 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 alarge ulcer > 1 cm can be deep, painful, prolonged and interferes with eating. Triamcinalone paste can be used to relieve the pain; a tapering dose of prednisolone may be tried. Response to ART is very good.

4.2.11 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.

4.2.12 Diarrhoea

Diarrhoea, intermittent or prolonged is a common complication. It is caused by common bacteria such asshigella, 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 ileoceacal junction but usually this will not be possible. The condition responds very well to anti-TB treatment.

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

4.2.13 Cytomegalovirus (CMV)

CMV can cause pneumonitis, oesophagitis, enteritis, cholecystis and encephalitis in patients withHIV but an important complication is CMV retinitis which is usually seen in patients with CD4 count < 50/mm^3. 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). In resource limited settings treatment is difficult and very expensive. Ganciclovir or Foscarnet iv is required to stop visual loss and intravitreous injections of Ganciclovir or Foscarnet may be effective as secondary prophylaxis. CMV antibodies are present in > 90% of the population.

4.2.14 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.

4.2.15 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/mm^3 can reduce the prevalence of malaria in the population. There is no evidence however that malaria has a significant effect on clinical progression of HIV.

4.2.16 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.

4.2.17 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.

4.2.18 HIV related tumours or opportunistic tumours in HIV

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

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

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

Cancer cervix - 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. Atlas of HIV related conditions and opportunistic infections

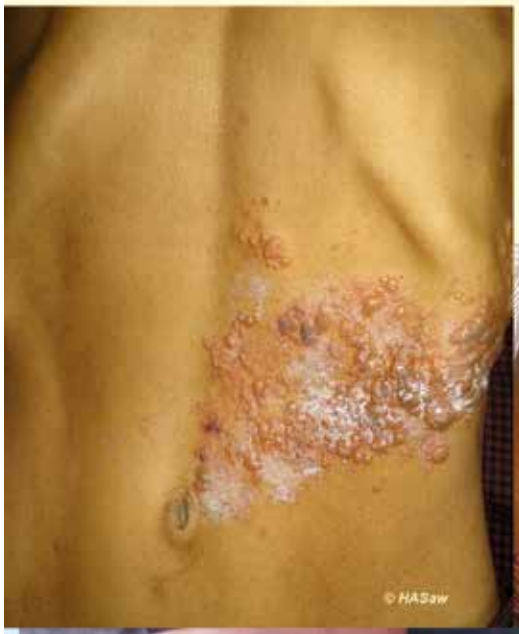
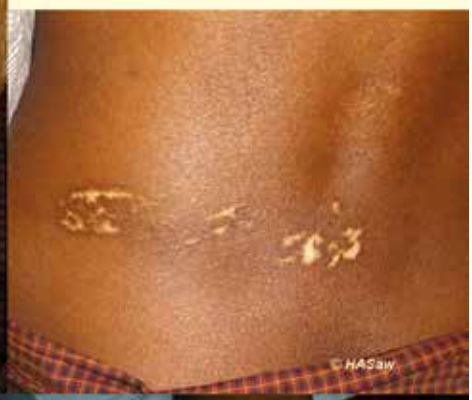
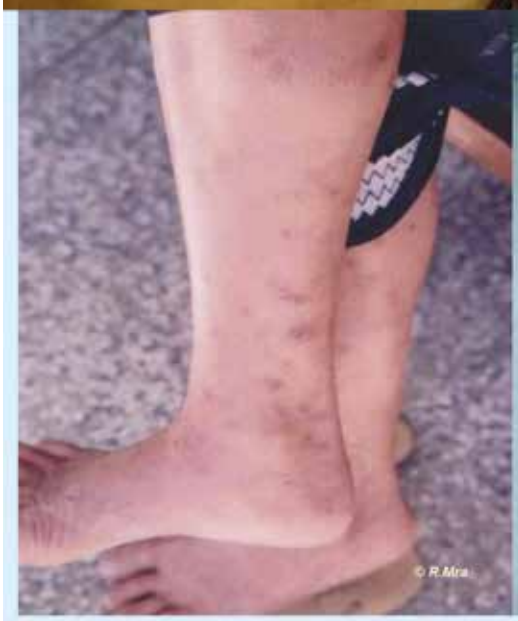


Fig. (3.1- left) Herpes zoster is usually an early manifestation of immunosuppression and usually occurs at around CD4 300/mm3. It is seen as a painful vesicular eruption along a dermatone. It may be recurrent and is sometimes multidermatomal.

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





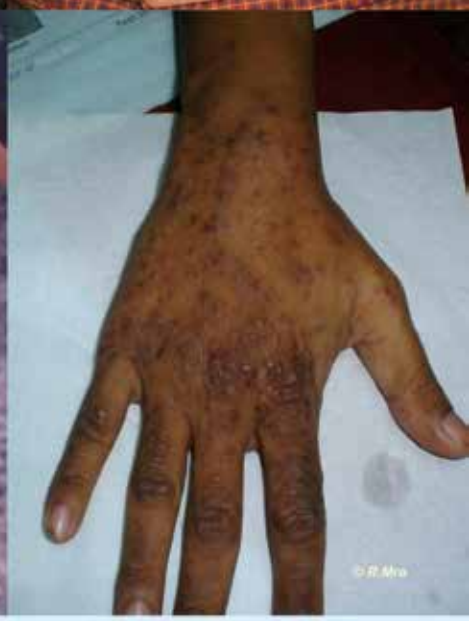


Fig (3.3-above left) & Fig.(3.4 –above right) Pruritic papular eruptions are seen in the exposed parts of the limbs. Scratching produces infection and scarring. Pruritic papular eruption is thought to be due to allergic reaction to insect bites. PPE is not scabies.

Fig.(3.5 - left)Scabies is cause by *Sarcoptes scabei* mites which 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.

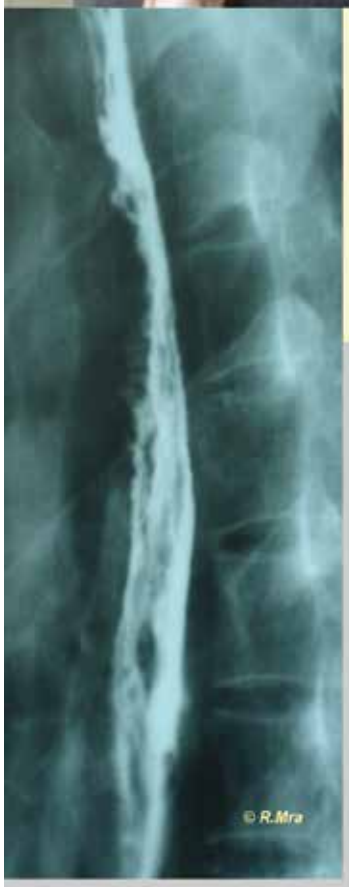
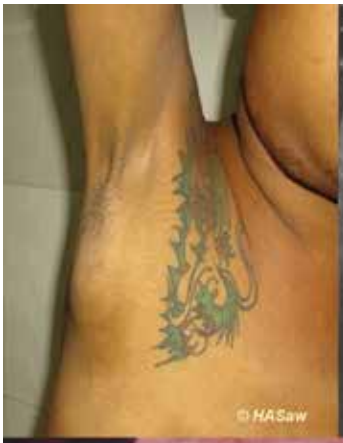
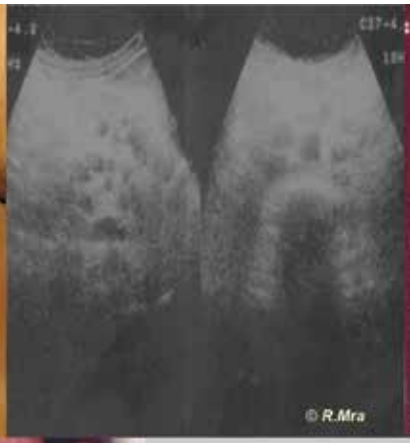


Fig. (3.7 - left) Barium swallow showing oesophageal thrush with mucosal ulcerations.

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)





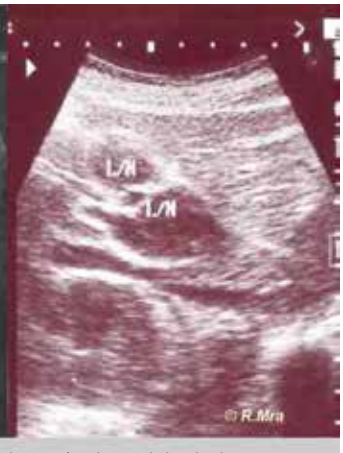


Fig.(3.12 & 3.13 - above). Intra-abdominal lymphadenopathy seen as hypoechoic areas on abdominal ultrasound examination. This is most commonly due to tuberculosis with advanced immunosuppression.

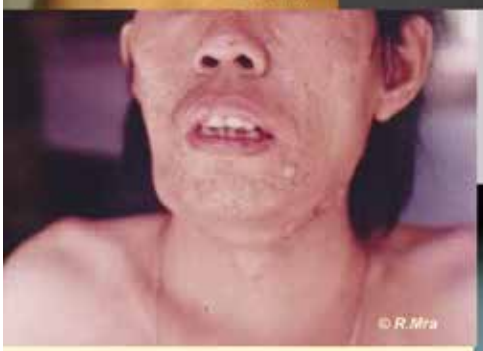
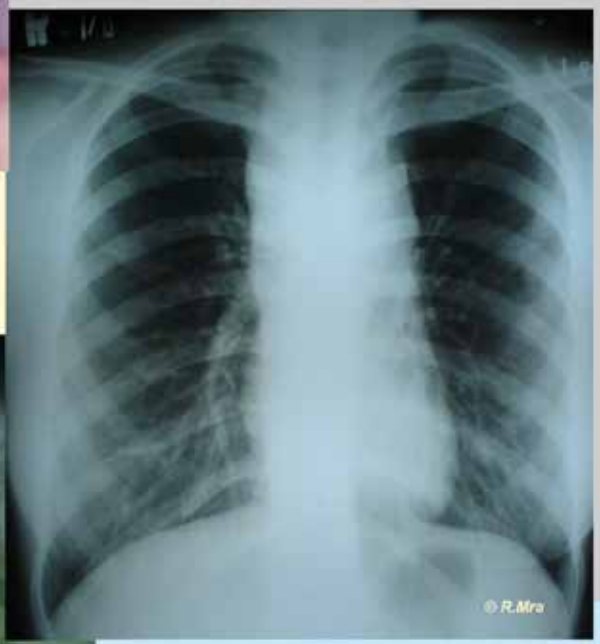


Fig.(3.10 & 3.11 - above) Tuberculosis commonly manifests as lymphadenopathy in HIV/AIDS.



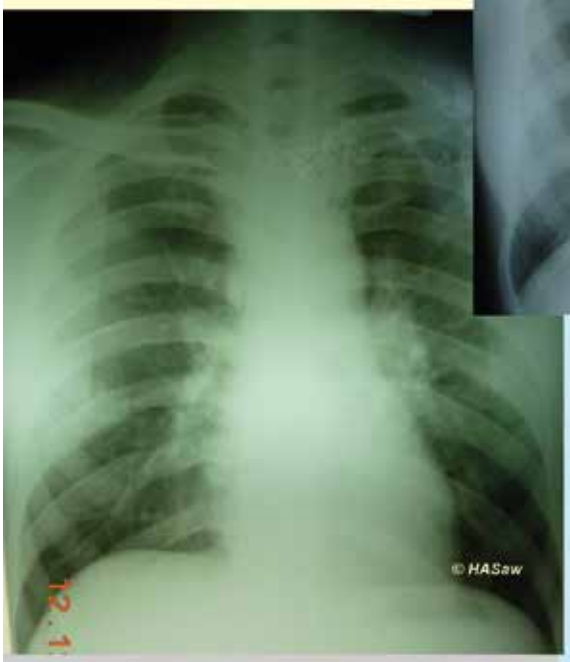


Fig.(3.14- above) & Fig. (3.15– left)Chest x-ray showing mediastinal lymphadenopathy (above) and hilar lymphadenopathy (left). This is most commonly due to tuberculosis in HIV/AIDS especially if associated with prolonged fever, weight loss and night sweats. Lymphoma is a differential diagnosis but is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

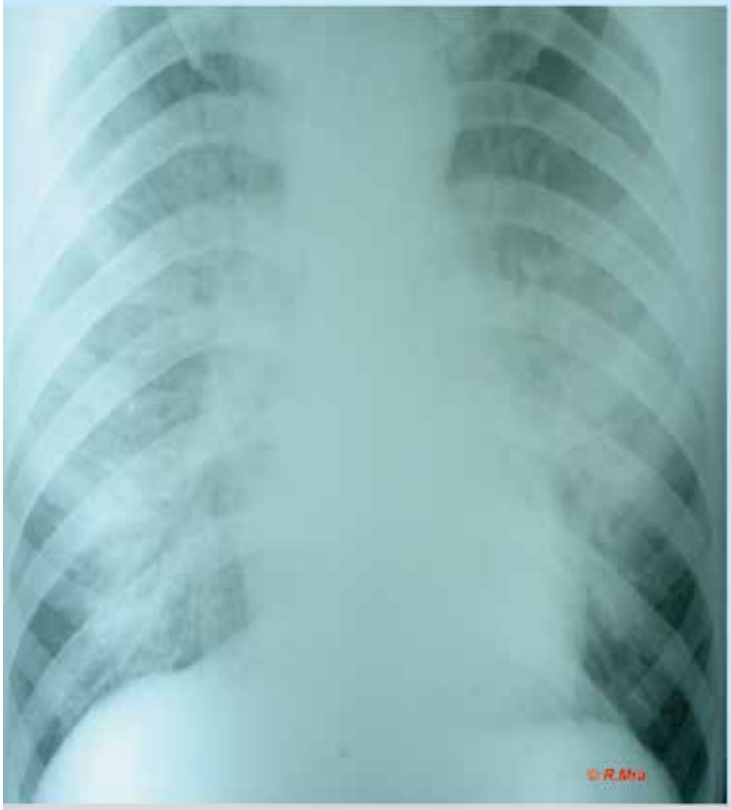
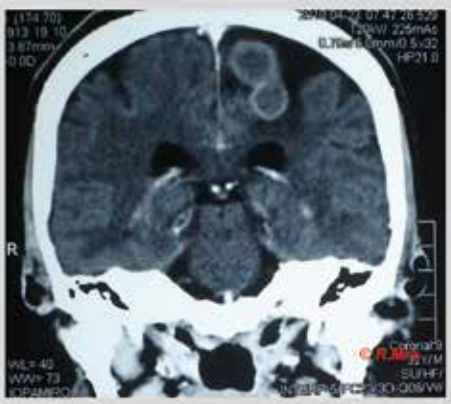
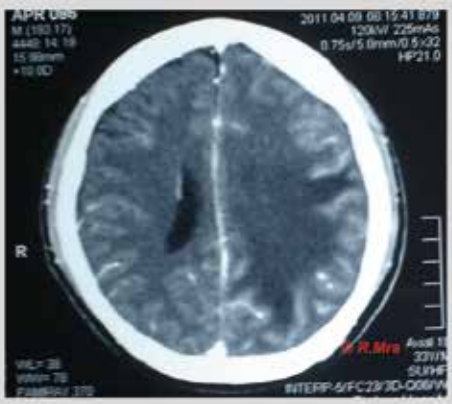


Fig. (3.16) The patient presented with a low grade fever, dry cough and shortness of breath which had become progressively more severe over the past 3 weeks. The dyspnoea became worse after the slightest movement and cyanosis developed on exertion. There were very few lung signs. An urgent chest X-ray showed diffuse pulmonary infiltraties fanning out from the hilar region and sparing the apices and lower regions. The clinical and radiological picture are typical of pneumocystis pneumonia (due to *Pneumocystis jeroveci).* 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 patient 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 settings treatment for cerebral toxoplasmosis is started on clinical grounds alone; one should look for a response to treatment for the clinical diagnosis.





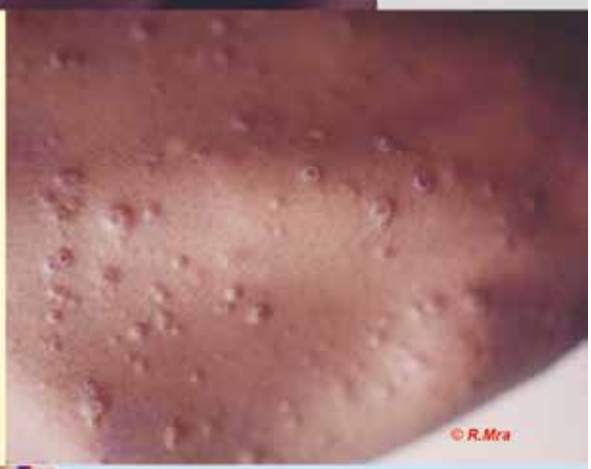


Fig. (3.19) Penicilliosis seen on the face (above)and skin (right).
Umbilicated papular eruptions first appear on the face and spreads to the limbs and trunk. The skin lesions are prominent but this is a systemic fungal infection involving the organs and bone marrow.

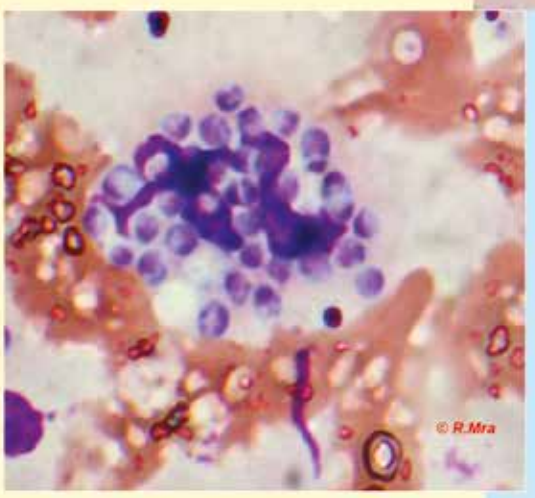


Fig. (3.20 right) Diagnosis is easily made by puncturing and scraping the papules and staining the smear on a glass slide with Leishman's or Giemsa's stain. Fungal bodies are seen inside macrophages with a characteristic central septation. (Oil immersion lens).

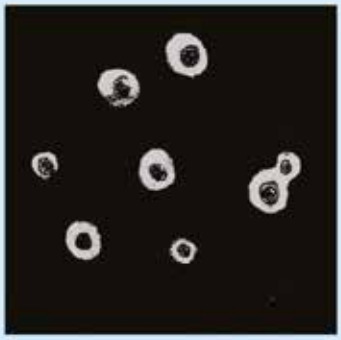


Fig. (3.23-above) India ink preparation of CSF showing yeast cells of *Cryptococcus neoformans* with unstained thick capsules and budding (sketch).

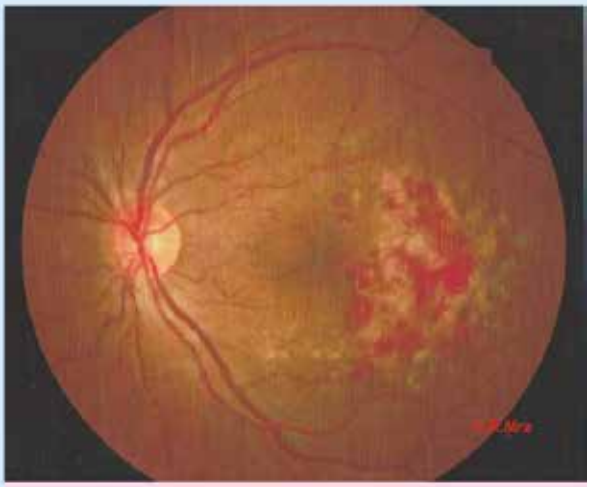


Fig. (3.24 - above) CMV retinitis showing haemorrhagic necrosis of the retina with exudates ("scrambled eggs and tomato ketchup appearance"). Involvement of the macula area causes blindness.

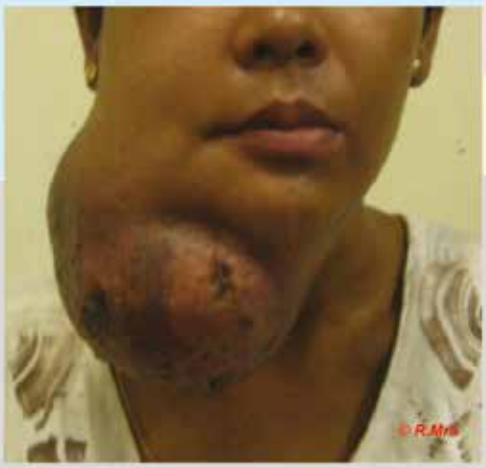
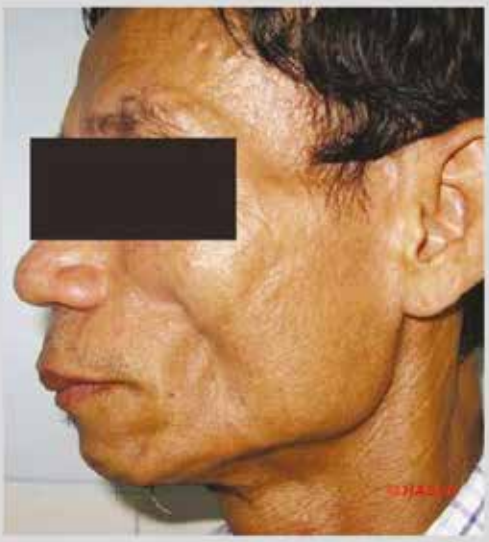
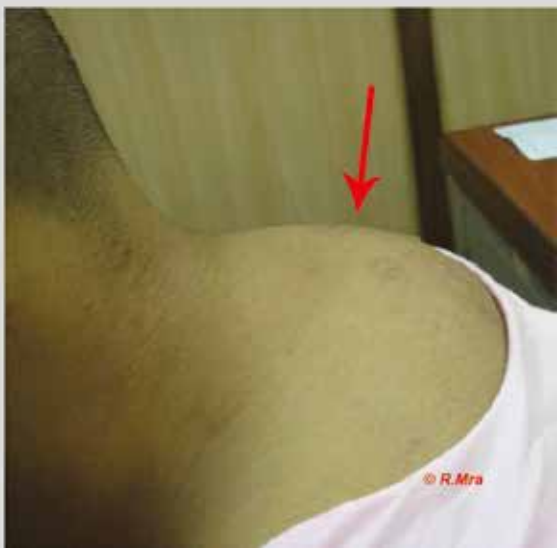


Fig. (3.25 - left) HIV associated lymphoma is a high-grade B cell non-Hodgkin lymphoma.

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.





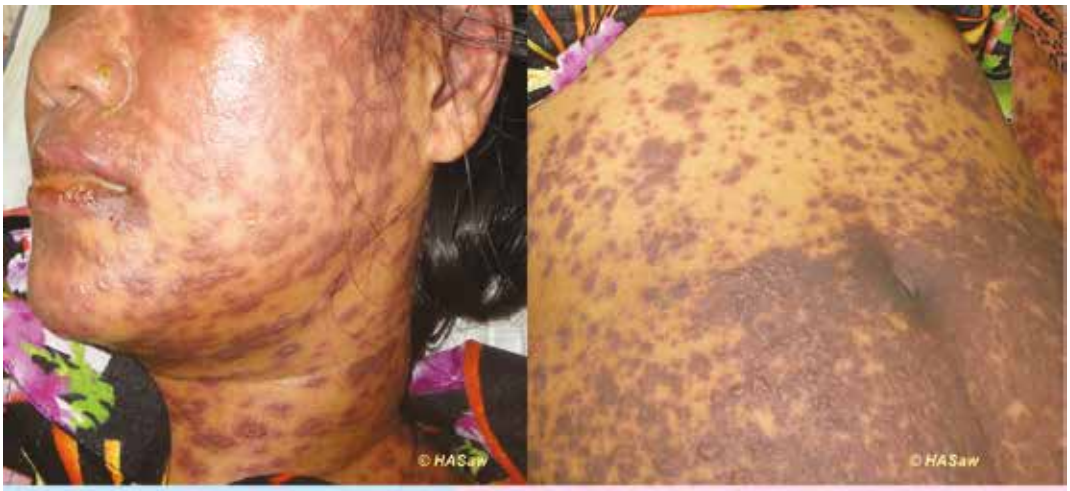
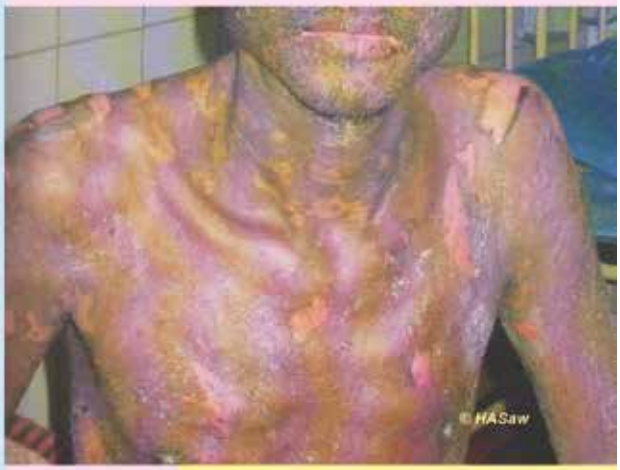


Fig. (3.28 - above left) & Fig.(3.29 - above right).
Stevens-Johnson syndrome due to nevirapine involving the whole body as well as mucous membrane. This is a recognized complication of NVP and can occur at all levels of immunosuppression but particularly in women with CD4 count > 250/mm3(see text).Stevens-Johnson syndrome can be also a rare complication of other drugs e.g. rifampicin, co-trimoxazole
Fig. (3.30 - right). Toxic epidermal necrolysis due to nevirapine.



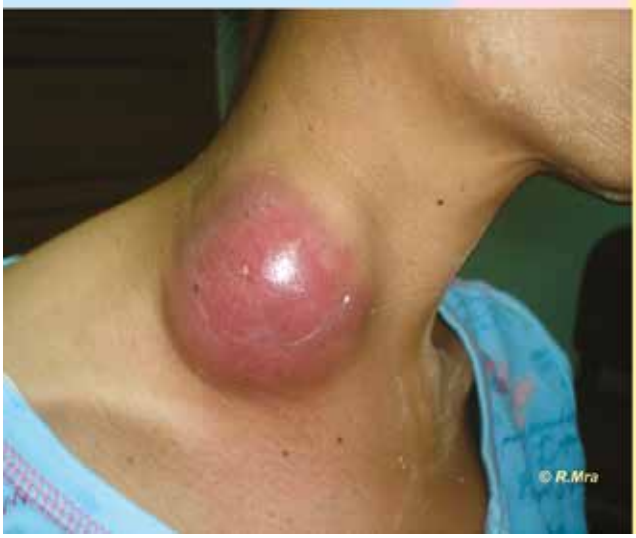


Fig. (3.31 - left) Immune reconstitution inflammatory syndrome or IRIS. This patient had a CD4 count of 50/mm3. There was a small lymph node at the root of the neck. TB treatment was started for pulmonary tuberculosis and ART started 2 weeks later. After one month symptoms worsened and the cervical lymph node had become enlarged, painful and then gradually became 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.

6. Treating late HIV disease

Majority of patients with HIV in resource limited countries will still present with late HIV disease with CD4 counts < 100/mm^3 or <50/mm^3. They will usually have fever > 1month, 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, sputum culture, lymph node aspirate smears and 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 OIsfollowed 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 or resultsfrom 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

ART will have to be started soon after treating OIs and in tuberculosis this will be at 2 weeks or not later than 8 weeks. This is because of 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/mm^3, early ART initiation within 4 weeks of TB treatment initiation was associated with better AIDS-free survival, albeit with increased risk of IRIS. However, in patients with CD4 ≥50 cells/mm^3, delaying initiation of ART to the first 4 weeks of continuation phase of TB reduced the risk of IRIS and drug switches without compromising AIDS-free survival.

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. 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 may be associated with paradoxical exacerbation of the OI that is being diagnosed and treated after starting ART.

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,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

- Treatment naïve at start of OI treatment

- Short interval between OI treatment and ART

For this reason a brief delay is advisable in starting ART after the treatment of OI is started to control the OI. This delay may be 2 to 8 weeks in tuberculosis depending on the situation. In late disease with very low CD4 counts usually < 50/mm^3 delaying ART too long could be dangerous because of the risk of disease progression and this has to be balanced against the risk of IRIS.

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.

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 developing countries, IRIS is most commonly associated with TB. 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 liquefective 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. 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)

7. Annexes

Figure 4: Lifelong ART for all pregnant and breastfeeding women with HIV (Option B+)

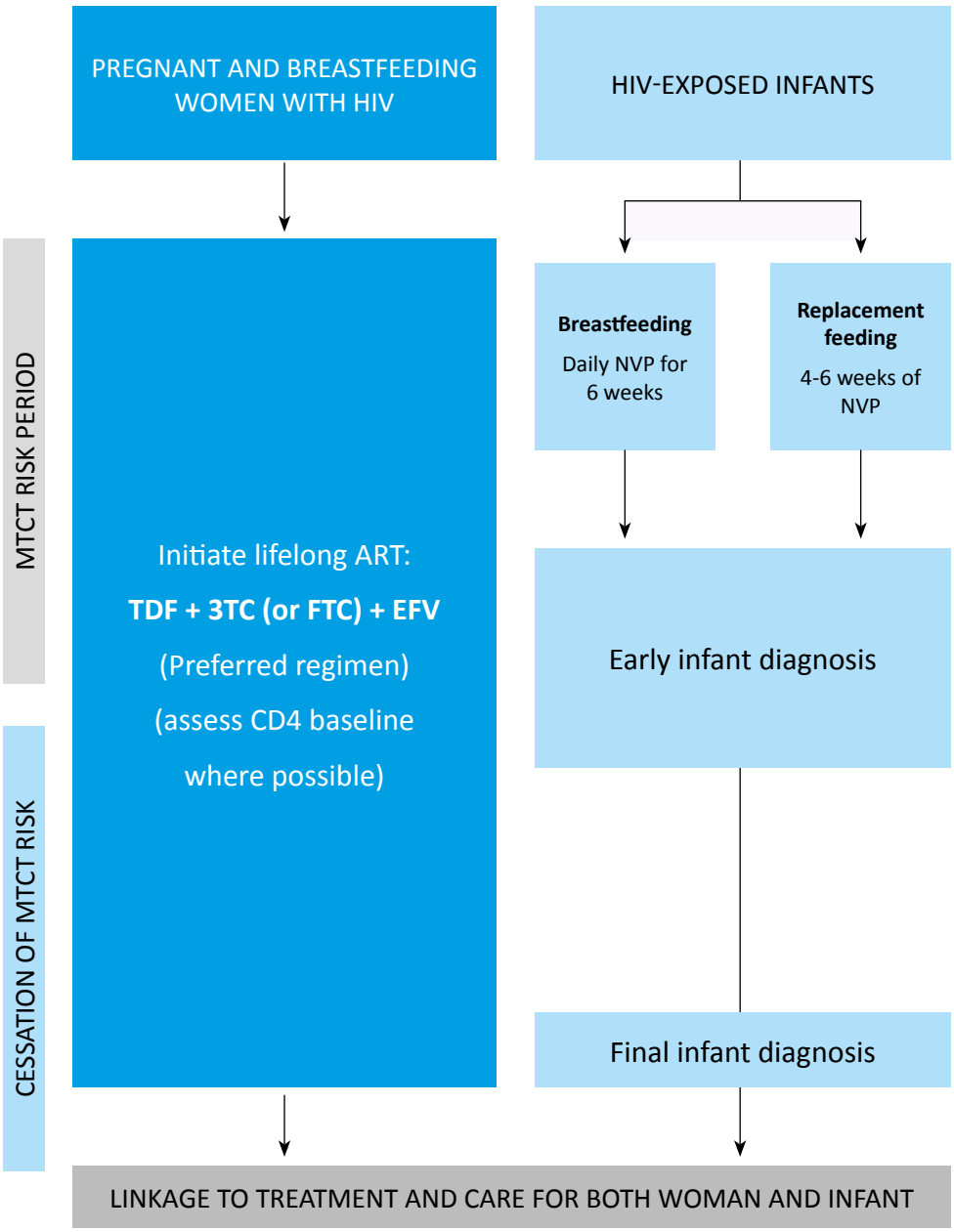


Figure 5: ART for women with HIV during pregnancy and breastfeeding (Option B)

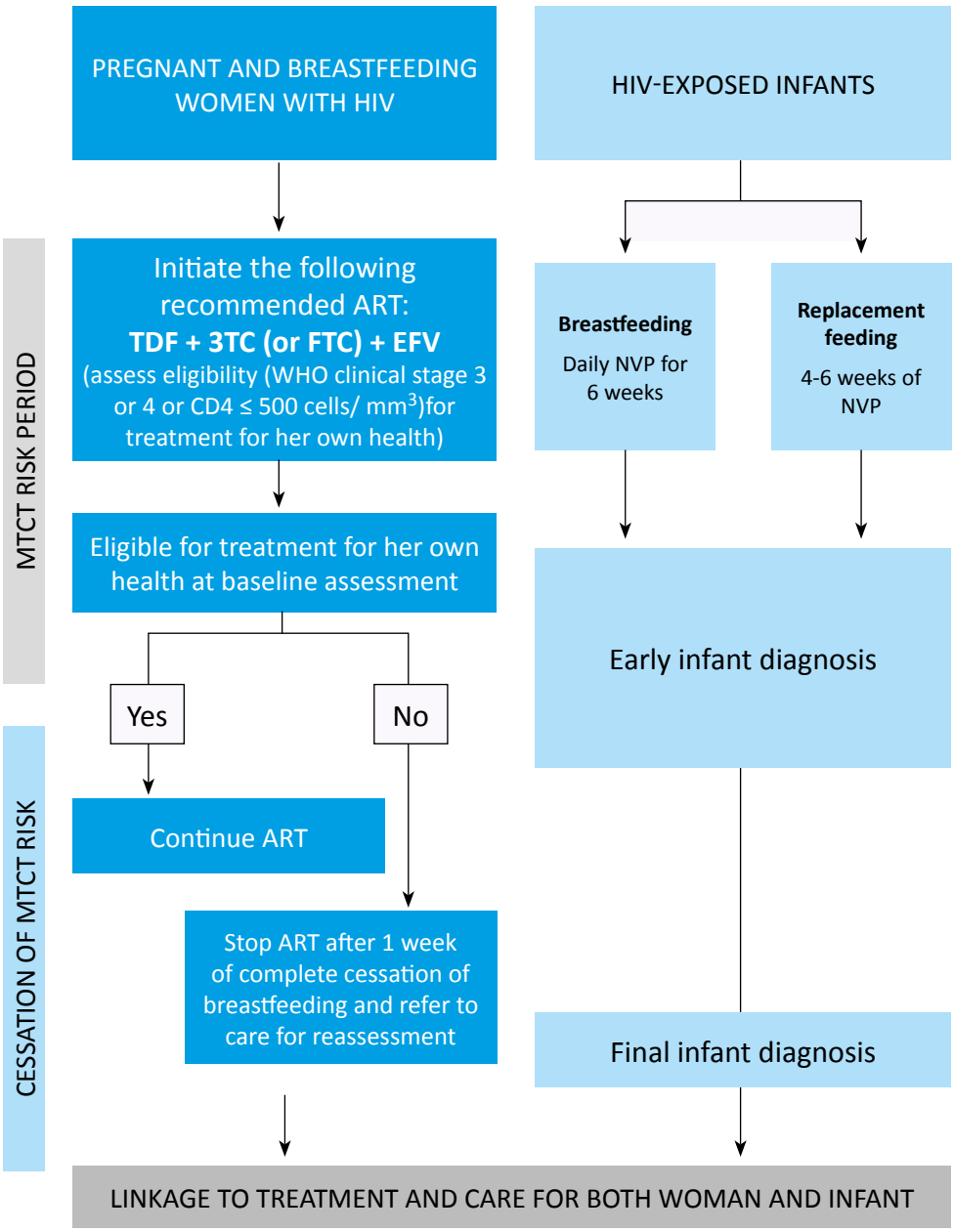
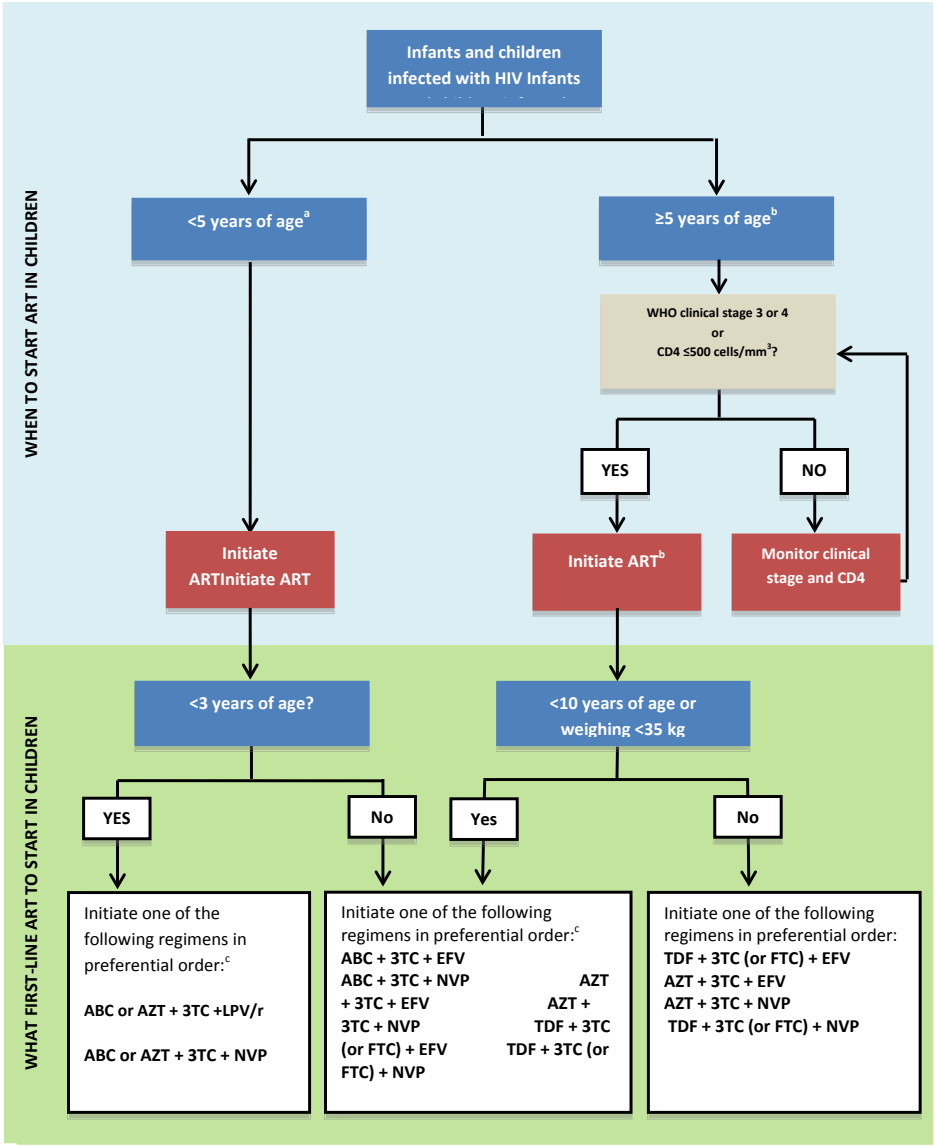


Figure 6: Algorithm for the 2014 recommendations for children



[a] If this recommendation to treat all children between one and under five years of age is not adopted: initiate ART with WHO clinical stage 3 and 4 or with CD4 count ≤750 cells/mm^3 or <25%, whichever is lower, regardless of WHO clinical stage

[b] If this recommendation is not adopted ART should be initiated at WHO HIV clinical stage 3 and 4 or with CD4 count ≤350 cells/mm^3 regardless of WHO clinical stage

c Special note: d4T use should be restricted to those situations where there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The durationof therapy with this drug should belimited to the shortest time possible.

In children, a weight based drug dosage is recommended. There are fixed drug combinations now available as dispersible tablets for paediatric formulations and WHO has recommended using them according to weight bands. The dosing details for the children are provided in following table:

Table 22a: Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing among children

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	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
AZT + 3TC	Tablet (dispersible) 60 mg + 30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 + 150	1	1
AZT + 3TC + NVP	Tablet (dispersible) 60 mg + 30 mg + 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 + 150 + 200	1	1
ABC + AZT + 3TC	Tablet (dispersible) 60 mg + 60 mg + 30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 + 300 + 150	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 + 300	0.5	0.5
d4T + 3TC	Tablet (dispersible) 6 mg + 30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30 + 150	1	1
d4T + 3TC + NVP	Tablet (dispersible) 6 mg + 30 mg + 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	–	4	4

Table 22b: Simplified dosing of child-friendly solid formulations for once-daily dosing in children

Drug	Strength of tablet (mg)	Number of tablets or capsules by weight band once daily					Strength of tablet (mg)	Number of tablets or capsules by weight band once daily
		3–5.9 kg	6–9.9kg	10–13.9 kg	14–19.9 kg	20–24.9 kg		25–34.9 kg
EFV[a]	Tablet (scored) 200 mg	–	–	1	1.5	1.5	200	2
	Tablet (double scored)[b] 600 mg	–	–	one third	one half	two thirds	600	2/3
ABC + 3TC	Tablet (dispersible) 60 + 30 mg	2	3	4	5	6	600 + 300	1

a EFV is not recommended for children younger than 3 years and weighing less than 10 kg.

b The double-scored tablet has two score lines on one side of the tablet and one score line on the other side, enabling the tablet to be divided into thirds and halves as needed.

Table 22c: Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing

Drug	Strength of tablets (mg) or oral liquid (mg/ml)	Number of tablets by weight-band morning and evening										Strength of tablet (mg)	Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
Solid formulations														
3TC	Tablet (dispersible) 30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	150	1	1
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
NVP[a]	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200	1	1
LPV/r[b]	Tablet (heat stable) 100 mg + 25 mg	–	–	–	–	2	1	2	2	2	2	100 + 25	3	3
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[a]	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	–	–	–	–	–	–	–
LPV/r[b]	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	–	–	–

a 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 2013). More definitive evidence is expected from an ongoing trial.

b 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 or crushed.

Table 22d: Simplified harmonized dosing for currently available TDF formulations for children

Drug	Size of powder scoop (mg) or strength of tablet (mg)	Number of scoops or tablets by weight band once daily					Strength of adult tablet (mg)	Number of tablets by weight band
		3–5.9 kg	**6–9.9 kg**	**10–13.9 kg**	**14–19.9 kg**	**20–24.9 kg**		**25–34.9 kg**
TDF[a]	Oral powder scoops 40 mg/scoop	–	–	3	–	–	300 mg	1 (200 mg)[b] or 1 (300 mg)
	Tablets 150 mg or 200 mg	–	–	–	1 (150 mg)	1 (200 mg)		

[a]Target dose: 8 mg/kg or 200 mg/m^2 (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.

[b]200-mg tablets should be used for weight 25–29.9 kg and 300-mg tablets for 30–34.9 kg.

Table 22e: Simplified dosing of isoniazid (INH) and co-trimoxazole (CTX, sulfamethoxazole (SMX) + trimethoprim (TMP)) prophylaxis

Drug	Strength of tablet or oral liquid (mg or mg/5 ml)	Number of tablets or ml by weight band once daily					Strength of adult tab (mg)	Number of tablets by weight band
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg		25–34.9 kg
INH	100 mg	0.5	1	1.5	2	2.5	300 mg	1
CTX (SMX + TMP)	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	–	one half	one half	1	1	400 + 80 mg	2
	Tablets (scored) 800 + 160 mg	–	–	–	one half	one half	800 + 160 mg	1
CTX+ INH+ B6[a]	Tablets (scored) 960 mg + 300 mg + 25 mg	–	–	–	one half	one half	960 mg + 300 mg + 25 mg	1

This formulation is currently awaiting regulatory approval, and a scored junior tablet (480 mg + 150 mg + 12.5 mg) is also under development.

8. References

1. National AIDS/STD prevention and control programme. Guidelines for the clinical management of HIV infection in adults and adolescents. Third edition. Department of Health, Yangon, 2011.

2. WHO. Consolidated Guidelines for Treating and Preventing HIV infection. Recommendations for a public health Approach, July 2013.

3. WHO. Consolidated guidelines document on HIV prevention, diagnosis, treatment and care for key populations, July 2014.

4. WHO. March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.

5. WHO. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. Geneva, World Health Organization, 2010.

6. WHO. Post-exposure prophylaxis to prevent HIV infection. Joint WHO/ILO guidelines on post-exposure prophylaxis (PEP) to prevent HIV infection. Geneva, World Health Organization, 2007.