

MSF HIV/TB clinical guide



2015

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2015

Includes WHO and South African national guidelines



MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

Acknowledgements

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This is the 8th edition of the MSF HIV/TB clinical guide. The first edition was developed for use in primary health care level HIV clinics opened by Médecins Sans Frontières (MSF) in the township of Khayelitsha, Cape Town, South Africa. It successfully became a practical reference tool for nurses and doctors in the clinics in Khayelitsha, and later in the MSF projects located in the rural areas of Lusikisiki in the Eastern Cape and Morija, Lesotho. This latest edition, has evolved to provide a more comprehensive approach to clinical HIV/TB care while helping clinicians remain informed and up-to-date in the context of rapid developments in the field of HIV care and treatment, including the regular updates of national and international guidelines.

The objectives of this book

- to assist clinicians' decision making in the management of HIV/TB-related conditions (adults and children), especially in resource-limited settings
- to provide accurate information on the management of ART patients and common HIV-related conditions
- to provide a primary focus on the WHO guidelines but also include national ART guidelines for comparison
- to form the syllabus of the MSF HIV/TB e-learning course.

An online pdf version (updated) of the book will be available on the SAMU website (www.samumsf.org) for download.



Welcome to the 8th edition of the MSF HIV/TB guide.

This now-famous image celebrates a bright day in December 2002, when Nelson Mandela came to visit our clinics in Khayelitsha. He came to offer political support, while we were confronted with strong HIV denialism from the National Government. He left people in no doubt regarding his personal convictions when, without hesitation, he swiftly put on the HIV positive T-shirt, an image which made world headlines.

By endorsing this T-shirt, he identified with the political struggle to gain access to ARVs. To have the world's foremost statesman come to a destitute township like Khayelitsha, take off his shirt and don a strongly political T-shirt symbolised in one gesture what we had tried to do for a couple of years: make ARV treatment accessible to the poorest and most affected, as close as possible to where they live, in a country still completely divided along socio-economic lines.

“After climbing a great hill, one only finds that there are many more hills to climb.” Nelson Mandela

This is what this clinical guide is about: it aims at motivating and equipping primary care health staff with necessary knowledge to treat HIV-related conditions and initiate adults, children, pregnant women on ARVs within their own clinic, even if they have no support available from a specialised health care centre. It aims to support HIV care at the grassroots level.

When we drafted the first edition of this guideline in 2000, we had no idea if we would succeed in such a tremendous challenge. This is the 8th edition and, in the meantime, major progress has been made in Khayelitsha: 28 000 on ART, including 3 500 children and a mother-to-child transmission rate reduced to 1.3%.

Similar exponential coverage has taken place nationwide, despite a much later start. This has had an immediate impact on reducing mortality by 27% in the last 5 years; increasing life expectancy in KwaZulu-Natal (KZN), a high HIV burden province, from 49.2 years in 2003 to 60.5 years in 2011.

These figures are definitely impressive, but many challenges remain, mostly qualitative ones: we have to find innovative ways to keep initiated patients in long-term care with undetectable HIV viral loads and, even more, we need to reduce new infections, particularly in young women, and eliminate vertical transmission; all of this in the absence of an effective vaccine, probably for the next decade.

This guideline is not close to becoming obsolete; despite impressive ART coverage, as we still see late presenters with advanced opportunistic infections coming to our clinics and hospitals. These patients often require high-level diagnostic and treatment procedures and, for this reason, a complement to this guide, aimed at addressing such complex cases referred for hospital care, will be soon released.

‘AIDS is a war against humanity’, said Nelson Mandela on that day in 2002. In making his symbolic gesture, he offered his own humanity to head the battle while giving many the courage to fight our worst enemies: stigmatisation and ignorance.

Let us together continue on this path, striving together to provide an increased quality of care to the people.

This guideline is dedicated to the memory of Madiba.

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*Completed 13 years at Ubuntu clinic Khayelitsha.
Nkosi Sis Lizzie.*

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How to use this book

- 1 Register on the SAMU website (www.samumsf.org) to be notified if book chapters have been updated.
- 2 Read the chapter overviews for an indication of the content flow.
- 3 The appendices include the most recent WHO guidelines and National (SA) guidelines.
- 4 Take note of the highlighted boxes and caution icons for important information.
- 5 'Referral' icons are highlighted to assist in decision-making with regard to referring to experienced HIV clinicians/specialists/next level of care.
- 6 Make notes in this book to enhance knowledge retention.
- 7 Provide feedback on typos or information errors using the email on the SAMU website.

Our current management strategies for HIV-related conditions will be confirmed or rejected by observational research in the future. We hope the reader will acknowledge this, and we would be grateful for any comments to make the next edition even better. Have a good read!

Useful web addresses

World Health Organisation (WHO)
www.who.int/hiv/pub/guidelines/en/

AIDSMAP
www.aidsmap.com

Drug Interactions
www.hiv-druginteractions.org

SA HIV Clinicians Society
www.sahivsoc.org

AIDSinfo
www.aidsinfo.nih.gov/guidelines/

Report stockouts
www.stockouts.org

Disclaimer

Drug dosages have been thoroughly checked but some errors may have been overlooked. Unless otherwise stated, drug dosages are for oral administration and recommendations are for the non-pregnant adult who is not breastfeeding.

Please consult your national formulary or drug manufacturers information before prescribing medication.

The authors and the publishers do not accept responsibility or legal liability for any errors in the text or for the misuse or misapplication of material in this work.



What the icons mean



Important information



Caution/Danger



Refer to a website



Refer to the WHO guidelines



Refer to your national guidelines



Information regarding children



Refer the patient to a specialist or hospital



See an Appendix at the back of the book for more information

Abbreviations

3TC	lamivudine	CXR	chest X-ray
ABC	abacavir	d4T	stavudine
ADA	adenosine deaminase (a test done on pleural fluid to detect TB)	ddl	didanosine
AEB	accidental exposure to blood	DR-TB	drug resistant TB (used in this guide to mean at least rifampicin resistance)
AFASS	affordable, feasible, accessible, safe and sustainable	DST	drug-sensitivity testing
AFB	acid-fast bacilli (the tuberculosis germ)	EFV	efavirenz
AIDS	acquired immunodeficiency syndrome	ELISA	enzyme-linked immunosorbent assays
ALT/ALAT	alanine aminotransferase (a liver blood test)	EPTB	extra-pulmonary tuberculosis (TB outside of the lungs)
ART	antiretroviral therapy	ESR	erythrocyte sedimentation rate
ARVs	antiretrovirals	FBC	full blood count
ATV	atazanavir	FNAB	fine needle aspiration biopsy
AZT	zidovudine (occasionally also written as 'ZDV')	FQ	fluoroquinolone
BCG	Bacillus Calmette-Guérin	FTC	emtricitabine
BD	twice daily	GERD	gastro-oesophageal reflux disease
BMI	body mass index (used to classify adults as overweight or underweight)	HAART	highly active antiretroviral therapy
BSA	body surface area (sometimes used to calculate ARV dosages in children)	Hb	haemoglobin
CCM	cryptococcal meningitis	HBsAg	hepatitis B surface antigen
CLAT/CRAG	A test for detection cryptococcal meningitis	HBV	hepatitis B virus
CMV	cytomegalovirus	HCV	hepatitis C virus
CNS	central nervous system	HCW	health care worker
COPD	chronic obstructive pulmonary disease	HIV	human immunodeficiency virus
Cr	creatinine	HIVAN	HIV-associated nephropathy
CrCl	creatinine clearance (a measure of kidney function)	HPV	human papilloma virus
CRP	C-reactive protein (a blood test that measures inflammation)	HSR	hypersensitivity reaction
CSF	cerebrospinal fluid	HSV	herpes simplex virus
CTX	cotrimoxazole (Bactrim®, Cotrim®, Purbac® or Cozole®)	IC	infection control
		IM	intramuscular
		IMCI	integrated management of childhood illnesses
		INH	isoniazid (one of the TB drugs)
		IPT	isoniazid prophylaxis therapy
		IRIS	immune reconstitution inflammatory syndrome
		IV	intravenous (same as 'drip')

KS	Kaposi's sarcoma (a cancer)	PLHIV	person living with HIV/AIDS
LFT	liver function test	PML	progressive multifocal leucoencephalopathy
LIP	lymphoid interstitial pneumonitis	PMTCT	prevention of mother-to-child transmission (of HIV)
LP	lumbar puncture (to diagnose meningitis)	PN	peripheral neuropathy
LPV/r	lopinavir/ritonavir (Kaletra® or Aluvia®)	PO	per os
LRTI	lower respiratory tract infection	PPD	purified protein derivative (used in TB skin testing)
MAC	mycobacterium avium complex	PPE	papular pruriginous eruption (a common itchy rash)
MCS	microscopy, culture and sensitivities	PrEP	pre-exposure prophylaxis
MDR-TB	multi-drug resistant tuberculosis	prn	as required
MER	more efficacious regimen	Pt.	patient
MMC	male medical circumcision	PTB	pulmonary tuberculosis (TB of the lungs)
MSF	Médecins Sans Frontières (French for 'doctors without borders')	PWID	people who inject drugs
MTCT	mother-to-child transmission (of HIV)	QID	four times a day
NB	<i>note bene</i> is Latin, meaning 'note well' or 'pay special attention to the following'	RIF	rifampicin
NNRTI	non-nucleoside reverse transcriptase inhibitor ('non-nukes')	RPR	test for syphilis
NRTI	nucleoside reverse transcriptase inhibitor ('nukes')	RTV	ritonavir
NTM	non-tuberculous mycobacteria	RUQ	right upper quadrant
NVP	nevirapine	SCC	smear and culture control
OD	once daily	SSRI	selective serotonin re-uptake inhibitor
OI	opportunistic infection	STI	sexually transmitted infection
ORS	oral rehydration solution	TB	tuberculosis
PAP smear	test for detection of cervical cancer	TBM	tuberculous meningitis
PCP	<i>Pneumocystis jirovecii</i> pneumonia (a life-threatening OI)	TDF	tenofovir
PCR	polymerase chain reaction (a laboratory test)	TDS	three times a day
PEP	post-exposure prophylaxis	TST	TB skin testing
PI	protease inhibitor	URTI	upper respiratory tract infection
PID	pelvic inflammatory disease	UTI	urinary tract infection
PITC	provider-initiated testing and counselling	VDRL	test for syphilis
		VL	viral load
		WHO	World Health Organisation
		XDR-TB	extensively drug-resistant tuberculosis

HIV overview

Global HIV epidemic: statistics

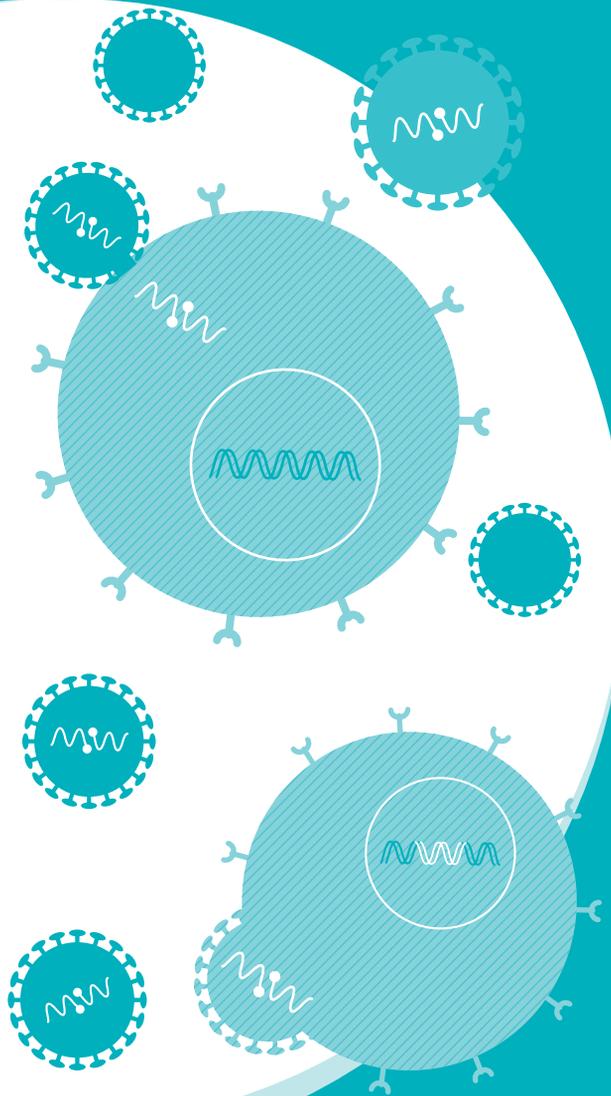
HIV lifecycle

HIV natural evolution

HIV treatment

HIV prevention

Post-exposure prophylaxis (PEP)



Global HIV epidemic: statistics

Countries in sub-Saharan Africa have been hardest hit by the global HIV epidemic. At the end of 2011, 34 million people worldwide were living with HIV, of whom 23.5 million were living in sub-Saharan Africa. The scale up of people on antiretroviral therapy (ART) has been substantial, with 9.7 million receiving ART in low- and middle-income countries by the end of 2012. Despite this success, there were still 2.5 million new infections and 1.7 million AIDS-related deaths, globally, in 2011.

Routes of HIV transmission

The majority of people acquire HIV through one of the following routes:

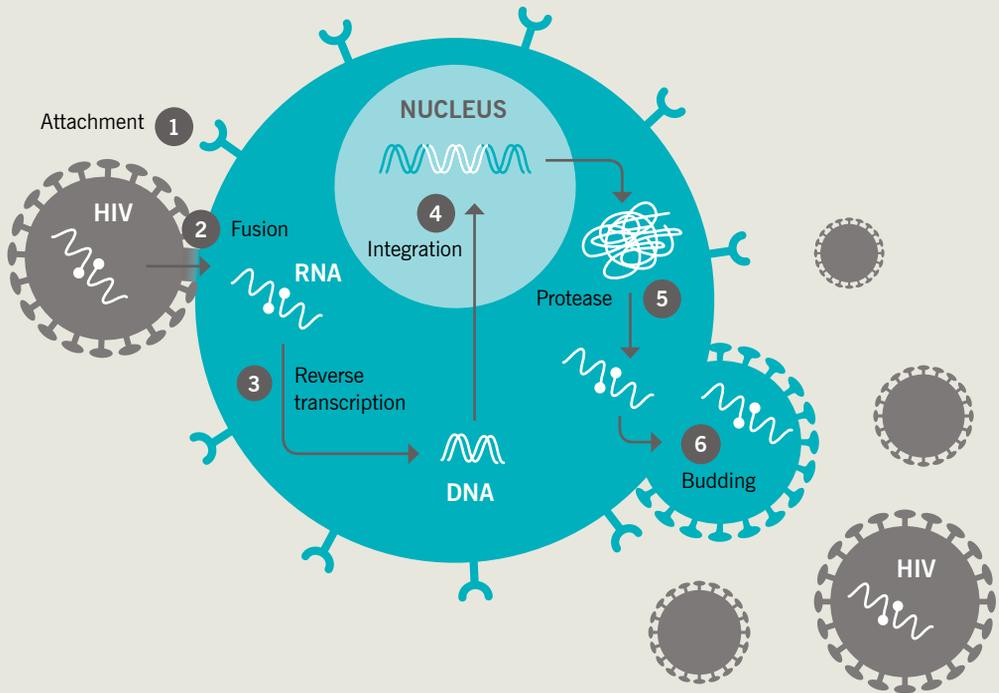
- sexual contact (the main route of transmission in Africa)
- *in utero* (before birth) or during delivery
- through breastfeeding
- through using contaminated needles (mostly in intravenous drug users; more common in Eastern Europe and Russia)
- through blood or blood products (NB: Rare when donor blood is carefully screened).

HIV lifecycle

There are six important phases (see Figure 1.1) that HIV must go through before new HIV particles can be produced. These are:

1. **Attachment:** HIV attaches to the CD4 (and CCR5/CXCR4) receptors of the host's CD4 cell.
2. **Fusion:** HIV fuses with the cell wall and enters the cell.
3. **Reverse transcription:** Viral RNA is transformed into viral DNA by an enzyme called reverse transcriptase. The drug classes known as nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) act at this level, by preventing this process.
4. **Integration:** Inside the nucleus of the CD4 cell, viral DNA is integrated into the cell's genome, and then new material required to form individual HIV particles is made. The integrase inhibitors act at this point of the cycle.
5. **Protein production and protease function:** Large proteins are broken into smaller proteins to become functional; the protease inhibitor (PI) drug class acts at this stage.
6. **Maturation and budding:** This is the final process, during which new HIV particles are released.

Figure 1.1 Lifecycle of HIV



HIV natural evolution

Following infection, HIV slowly makes a person's immune system weak over many years. This progressive 'immunodeficiency' roughly correlates with a gradual drop in the CD4 cell count (test) – a type of white blood cell. As the CD4 count drops, certain infections and other illnesses are more likely to appear, see Table 1.1 below.

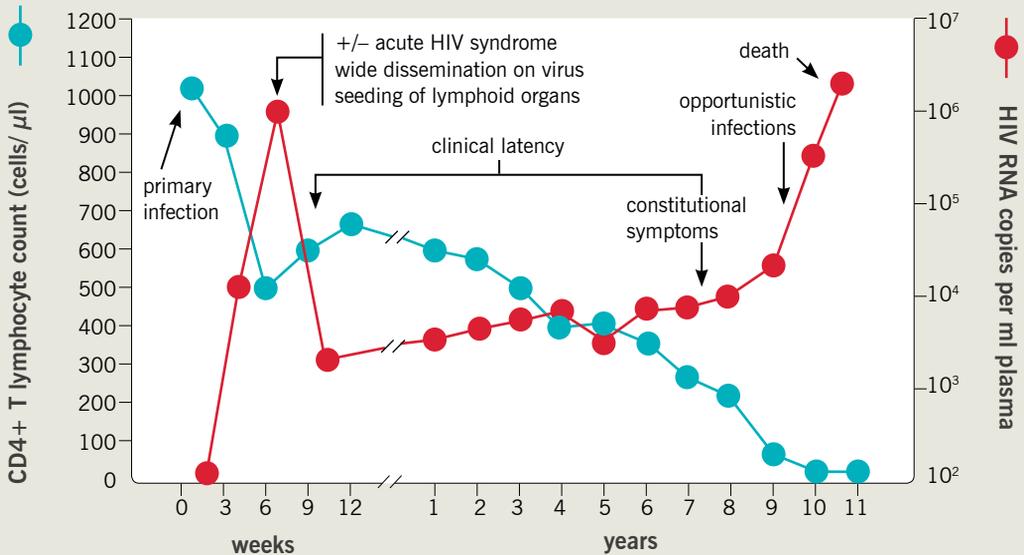
As their immune systems weaken and they suffer from more frequent and severe infections (and cancers), we classify adults and children into different **clinical stages** of HIV infection. All health care professionals (and patients) should be knowledgeable about the different stages of HIV as the World Health Organisation (WHO) classifications are valuable tools in our clinics (see Appendix 1).

Figure 1.2 shows the relationship between the amount of HIV virus in the blood and the level of the CD4 cell count, from the time of infection through to the development of AIDS and finally death, in a person without access to antiretroviral therapy.



See Appendix 1

Figure 1.2 Typical course of HIV infection



Source: Modified from Fauci AS et al. 1996. *Ann. Intern Med.* 124:654

Most people who are newly infected with HIV do not immediately know that they have become infected. **Usually, HIV-infected persons develop antibodies to HIV antigens six weeks to three months after being infected. This time is known as the ‘the window period’.** People are highly infectious during this early period because the viral load is very high – and yet they are probably unaware of their condition, and generally do not have any symptoms. Importantly, during the window period HIV antibody tests (ELISA) will be negative.

Seroconversion refers to when a person who has been recently infected with HIV first tests sero-positive for HIV antibodies. A positive antibody test should always be confirmed with a separate test. Some people have a ‘glandular fever-like’ illness (fever, rash, joint pains and enlarged lymph nodes) at the time of acute primary infection. Occasionally, acute infections of the nervous system (e.g. aseptic meningitis, radiculitis, encephalitis and myelitis) may occur.

The HIV DNA PCR test is used in children under 18 months old. It can also be used in special circumstances in adults.

HIV infection before the onset of symptoms

In the natural history of HIV infection in adults, there is often a long, silent period of HIV infection before the disease progresses to AIDS (WHO clinical stage 4 and/or CD4 <200). An adult person infected with HIV may have no symptoms for up to ten years or more (i.e. ‘**slow-progressors**’). However, in some adults and in the vast majority of children who are perinatally infected (during pregnancy and birth), there can be a rapid progression to late-stage disease and death. Most perinatally infected children present with symptoms before the age of two years. Some

children, particularly if infected during the breastfeeding period, will remain well for several years.

Progression from HIV infection to HIV-related diseases and AIDS

Without treatment, all HIV-infected people will ultimately develop HIV-related diseases and AIDS. This progression depends on the type (HIV1 or HIV2) and strain of the virus and certain host characteristics.¹

Factors that may cause faster progression include:

- age less than 5 years
- age over 40 years
- presence of other infections (especially tuberculosis)
- possibly genetic (hereditary) factors.

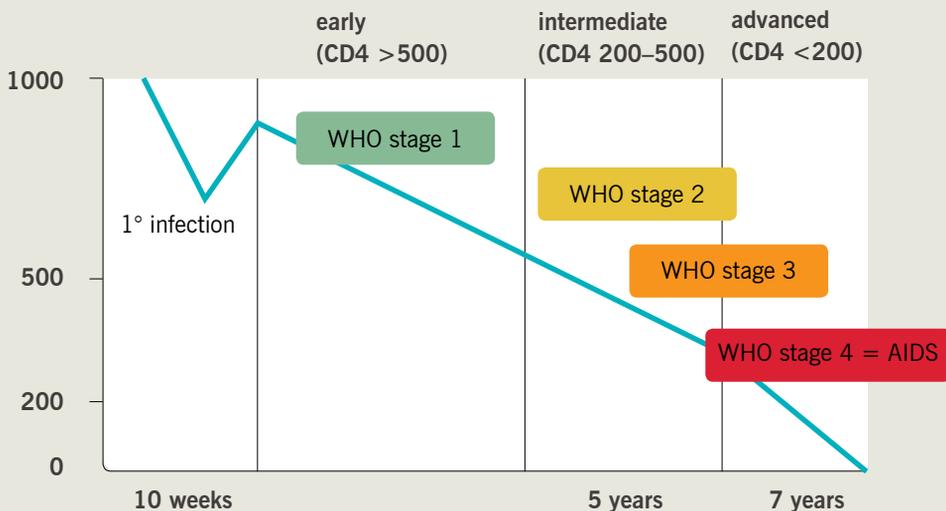
HIV infects both the central and the peripheral nervous system early in the course of infection, which can cause a variety of neurological and neuropsychiatric conditions.

Figure 1.3 and Table 1.1 shows the relationship between the level of CD4 cells over time and the likelihood of developing specific opportunistic infections (OIs). This will also be linked to the clinical staging of disease (see Appendix 1).



See Appendix 1

Figure 1.3 Deterioration linked to loss of CD4 cells



¹ HIV1 is the dominant type in sub-Saharan Africa and, unless mentioned otherwise, the focus of this book. HIV2 is less virulent, more common in West Africa and inherently resistant to NNRTIs.

Early recognition and treatment of OIs is therefore vital. People do not die from HIV; they die from infections (and sometimes cancers). If we diagnose these conditions early, and give proper medical treatment, we can avert many deaths. Early recognition of tuberculosis (TB) is especially important.

Table 1.1 Risk of opportunistic infections (OIs) and other HIV-related conditions by CD4 cell count

CD4 count	Condition
Any CD4 count	Persistent generalised lymphadenopathy (PGL) Parotid gland enlargement Herpes zoster (shingles) Tuberculosis Bacterial pneumonia Cervical intraepithelial neoplasia (CIN) Vulvo-vaginal candidiasis Chronic anaemia HIV-related thrombocytopenia Lymphocytic interstitial pneumonitis (LIP) commonly seen in children
<200 cells/ μ L (when severe OIs begin to appear)*	Oral candidiasis (i.e. thrush) Oesophageal candidiasis Oral hairy leukoplakia (OHL) Pneumocystis jiroveci pneumonia (PCP) Cryptosporidiosis Lymphoma (non-CNS) Kaposi's sarcoma (KS) HIV-associated dementia
<100 cells/ μ L	Toxoplasmosis Cryptococcal meningitis (CCM) Cytomegalovirus infection (eye) Wasting syndrome
<50 cells/ μ L	Non-tuberculosis mycobacterial (NTM) infection Lymphoma (CNS) Progressive multifocal leukoencephalopathy (PML) Cytomegalovirus infection (brain or disseminated)

* It is possible to have a patient with a very low CD4 count who is still in clinical stage 1, i.e. without any symptoms. There are also a few clinical stage 4 conditions (HIV-related lymphoma, Kaposi's sarcoma, cardiomyopathy, and nephropathy) that may occur at higher CD4 counts.

HIV treatment

Prophylaxis

Proper medical care in the later clinical stages also includes prevention of serious infections (also known as prophylaxis).

People living with HIV (PLHIV) need regular preventive doses of the antibiotic cotrimoxazole in the later stages of HIV infection. Cotrimoxazole prophylaxis prevents PCP, toxoplasmosis and malaria and common protozoal infections, like *Isospora* and *cyclospora*. (See Appendix 2A for indications and criteria for discontinuation.)

Some individuals may also benefit from isoniazid preventative therapy (IPT) to help prevent TB.

Fluconazole prophylaxis is sometimes given to prevent cryptococcal meningitis in patients with CD4 < 100.



See Appendix 2A

Antiretrovirals (ARV)

When an HIV-positive person's immune system has become too weak, we use antiretrovirals (ARVs) to 'stop HIV from growing', which, in turn, allows the immune system to recover. This is how ARVs prevent unnecessary deaths in patients with advanced HIV infection. Note that only HIV-positive adults and older children who are in the later stages of HIV infection (stage 3 or 4) or have a CD4 < 500 need ARVs. For HIV-positive infants less than 5 years, early treatment, regardless of clinical or immunological stage, has proved to be beneficial with a 75% reduction in mortality for children under 2 years in a South African study (CHER study team 2008). (See Table 5.4 on page 64.)

Summary of treatment interventions used to prevent death from HIV/AIDS

1. Early voluntary counselling and testing (VCT) in order to know one's HIV status early, so that treatment interventions can take place early.
2. **Counselling** in order to allow a person to accept being HIV positive.
3. **Education and counselling** about the HIV lifecycle, the different clinical stages of HIV infection, CD4 counts, viral load, possible OIs and sexual health.
4. Good **nutrition**: most importantly, a healthy diet, but – if possible – includes supplementation with micronutrients (vitamins and minerals).
5. Early **diagnosis** and prompt **treatment** of OIs, especially TB.
6. **Prevention** of OIs with cotrimoxazole (and other medications) and prevention of TB with IPT
7. **ARVs** to lower the HIV viral load and allow a person's immune system to recover.

8. **Monitoring** for any **side effects of ARVs** in the short and long term.
9. **Prevention** of transmission of HIV, including prevention of mother-to-child transmission (PMTCT).
10. **Ongoing adherence counselling** and support, including **support groups**.
11. **Monitoring for resistance** that HIV can develop against ARVs.

HIV prevention

Effective practices to reduce transmission of HIV are:

- Use barrier methods, i.e. male and female condoms.
- Introduce safer sexual practices: delay sexual debut; reduce concurrent partners.
- Treat sexually transmitted infections (STIs), especially herpes simplex virus (HSV). (See page 148.)
- Introduce medical male circumcision (MMC), which decreases the acquisition of HIV by approximately 60%.
- Apply PMTCT. (See Chapter 4.)
- Practise **exclusive breastfeeding** for the first six months, followed by supplementary feeding and weaning at 12 months, if an alternative source of milk is available. Formula feeding can be considered if it is affordable, feasible, acceptable, sustainable and safe for the entire first six months.
- Introduce needle and syringe exchange programmes for people who inject drugs.
- Screen blood donors and test blood products.
- Provide post-exposure prophylaxis (PEP) for occupational exposure to HIV and rape victims.
- Pre-exposure prophylaxis (PrEP) may now be used in certain high-risk groups, such as serodiscordant couples, people who inject drugs (PWID), men who have sex with men (MSM) or commercial sex workers (CSW).

Post-exposure prophylaxis (PEP)

Figure 1.4 MSF OCB PEP protocol

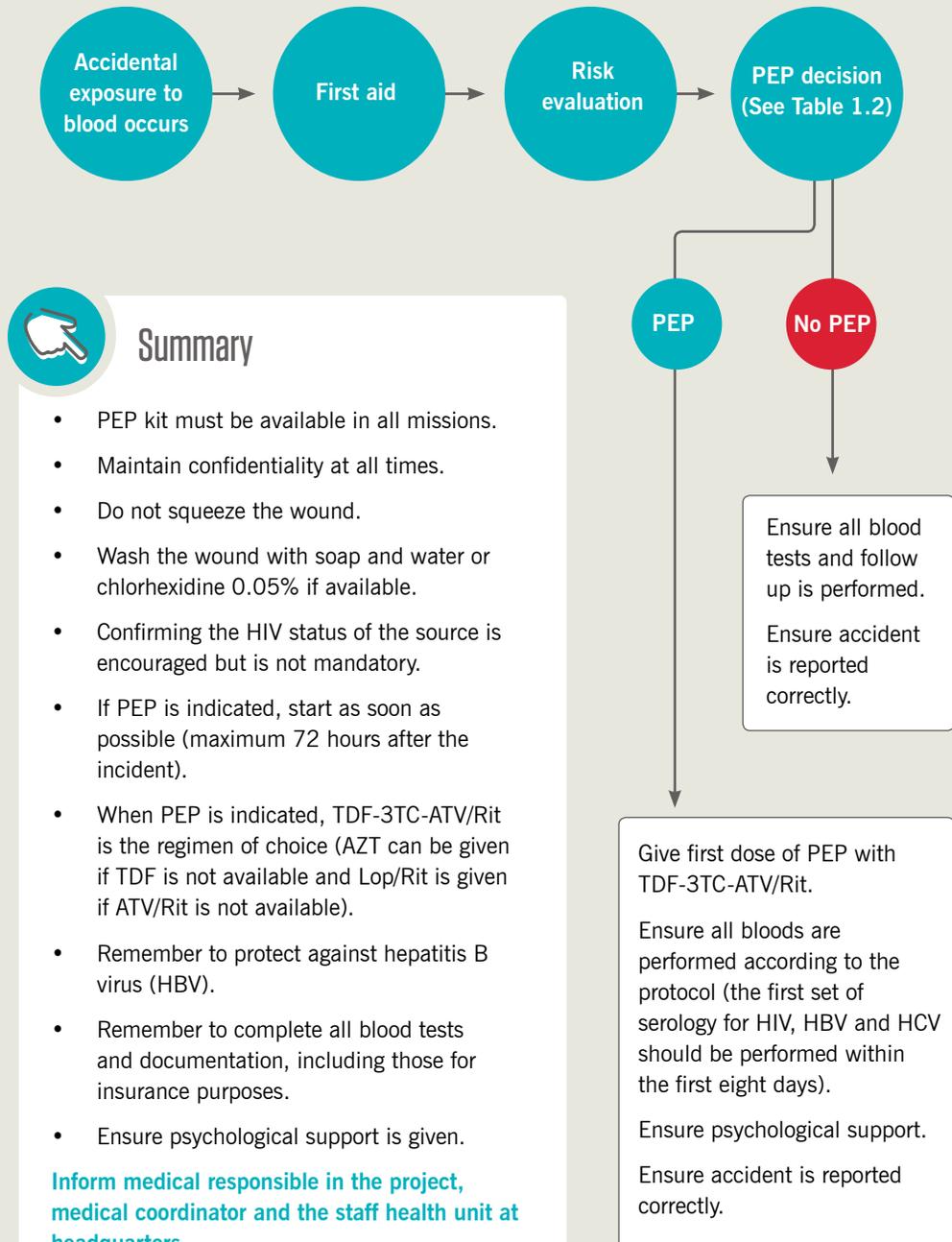
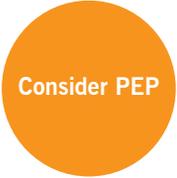


Table 1.2 To decide who needs PEP

Type of exposure	HIV status of source patient unknown	Source is HIV positive	Source is HIV negative but HIV prevalence > 1% OR source patient in high risk group (commercial sex worker, MSM, injecting drug user)
<ul style="list-style-type: none"> Any needle stick injury Any cut from a scalpel contaminated with blood Deep wound with a material contaminated with blood Mucous membrane or damaged skin in contact with a significant amount of blood Any rape 			
<ul style="list-style-type: none"> Bite Scratch Contact with blood on undamaged skin Contact with other body fluids not containing blood (CSF, saliva, urine) 			



Check www.samumfsf.org for most recent PEP guideline.

Ways in which exposure occurs

Health care workers are at risk of accidental exposure to blood (AEB) or other body fluids through:

- percutaneous injury with a needle or another sharp instrument
- exposure to blood or body fluids via mucous membranes (eye, mouth) or non-intact skin (wound, dermatitis, abrasion).

What to do in case of occupational exposure

If an occupational exposure happens to you or to one of your colleagues, treat this as an **emergency**:

- **Immediately** let the wound bleed (without squeezing), wash both the wound and surrounding skin with water and soap (without scrubbing) and then rinse.
- If you received an exposure involving the eyes or mucous membranes: rinse the exposed area immediately with an isotonic saline solution for ten minutes. Antiseptic eye drops can also be used for eye exposure. If none of these solutions are available, use clean water.
- If the source patient is known, offer a test for HIV.
- Offer an HIV test to the person exposed in order to exclude **pre-existing** HIV infection. If positive refer for HIV care.
- To decide who needs PEP, see Table 1.2 above.



Refer to your MSF section PEP guidelines for more details

- Start PEP **as soon as possible** (ideally within one or two hours, not later than 72 hours after exposure). If patient >35kg and >10 years old, **give tenofovir (TDF) 300 mg + lamivudine (3TC) 300 mg + atazanavir 300 mg /ritonavir 100 mg (ATV/r) once a day.**

If TDF is not available, use zidovudine (AZT).

If ATV/r is not available, use Lopinavir/r (LPV/r).

If neither ATV/r or Lpv/r are available, start with TDF + 3TC + EFV.

Do not use NVP.

- **The important thing is not to delay treatment.**
- All these PEP regimens should be taken for one month.
- **Notify** your supervisor (and/or a medical doctor) of the incident.
- **HIV test to be repeated at months 1, 3 and 6.**
- Follow the full monitoring guideline (see Table 1.3) to screen for other infection as a result of the exposure (i.e. hepatitis B and C) and possible side effects of the ARVs.

Table 1.3 Full monitoring guideline for PEP

Timetable	In people taking AEB prophylaxis	In people not taking AEB prophylaxis
Consider before starting PEP To be done within eight days of the AEB.	HIV, HBV, HCV Creatinine clearance if on TDF Hb if on AZT ALT Pregnancy test	HIV, HBV, HCV
Day 15	Clinical follow up of tolerance and signs of seroconversion Hb if on AZT ALT Creatinine clearance if on TDF	
Month 1	Clinical follow up of signs of seroconversion Hb if on AZT ALT Creatinine clearance if on TDF HIV	Clinical follow up of signs of seroconversion HIV
Month 3	HIV, HBV, HCV ALT	HIV, HBV, HCV ALT
Month 6	HIV, HBV, HCV ALT	HIV, HBV, HCV ALT

Assessment and follow-up of the HIV patient

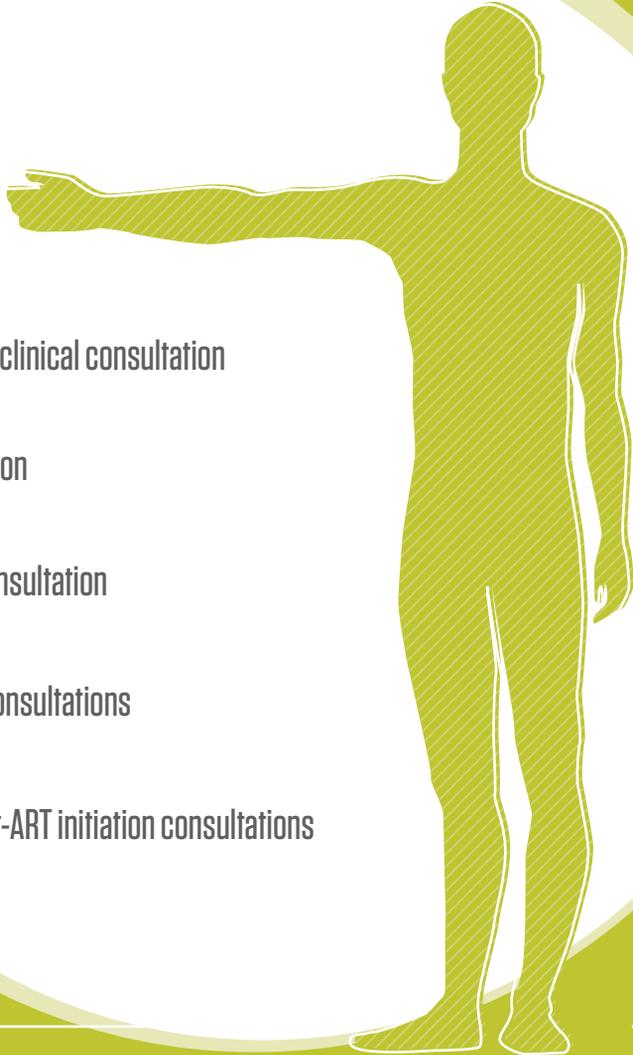
The aims of the clinical consultation

First consultation

Follow-up consultation

Further consultations

Post-ART initiation consultations



The aims of the clinical consultation

The aims of the consultation are different for those patients pre- and post-initiation of ART.

Table 2.1 Overview of general consultation principles

Pre-ART	Post-ART initiation
<p>To prevent, diagnose and treat common OIs. In the very ill or late-presenting patient, this may require hospitalisation.</p> <p>To determine clinical and immunological criteria for ART initiation and the timing of initiation.</p> <p>To assess patient readiness for ART and refer for appropriate counselling.</p> <p>To provide appropriate follow-up consultations and prescribe appropriate medications for prophylaxis (e.g. cotrimoxazole, INH).</p>	<p>First weeks (+/- 4 weeks) post-ART initiation:</p> <p>Ask targeted questions regarding possible ARV-related side effects based on the patient's ART drug profile. Early side effects include headache, nausea, rash, diarrhoea, hepatitis and psychiatric symptoms.</p> <p>Observe for any clinical deterioration, which may indicate immune reconstitution inflammatory syndrome (IRIS) or a new OI.</p> <p>Longer-term follow-up focuses on:</p> <p>Early detection and treatment of possible late-onset side effects. The presence of these side effects may require drug substitutions.</p> <p>Detection of new OIs or reoccurrence of pre-existing OIs, which may indicate immune failure.</p> <p>If possible, monitor with HIV viral load (VL) testing as this is the best early objective indicator of treatment failure. CD4 testing and clinical exam are used for monitoring 'response to therapy' if VL testing is not available.</p> <p>Adherence to medication is very important and must be screened for through questioning, pill counts or pharmacy refill.</p>
<p>In all consultations it is most important to note:</p> <ol style="list-style-type: none"> 1. WHO clinical staging: new or reoccurring condition/s, and if treated or not (especially the presence of TB). 2. Last known CD4 count: this indicates severity of immune deterioration, predicts what OIs can occur, and suggests time to recovery. A patient with a very low CD4 count (<100 cells/μl) is known as an 'HIV late presenter' (see Appendix 16), and will need special care in the discerning of symptoms, the clinical exam and the interpretation of investigations (e.g. CXR, CRP, FBC, CrAg). In a patient on ARVs, if the patient presents with signs or symptoms of new OIs or is virologically detectable (VL >1000) then a CD4 should be checked to assess the current immune response. 3. Timeline of events e.g. onset of symptoms, investigations and treatment thus far: many patients will have multiple conditions and treatments and the timing will assist the clinician in discerning more accurately a working diagnosis, appropriate treatment and probable outcome for the patient. 4. Prioritisation: listing all of the current medical problems in a prioritised 'problem list' can help to ensure that the most serious problems are promptly addressed. 	



See Appendix 16

First consultation

History of present illness

- Check for chief complaint ('the main problem today'): What? Since when? Where? How? and aggravating conditions.
- History of the present illness: make a note of the timeline of significant events related to the chief complaint.
- Are there associated constitutional symptoms? Loss of appetite (LOA), loss of weight (LOW), night sweats (NS).
- It is important to remember that symptoms may appear mild or absent in patients with very low CD4 counts.
- Screen for pregnancy.

Past history (TB, OIs or other conditions)

- Tuberculosis (TB):
 - Past history: duration and adherence to treatment. Don't forget to ask if the treatment was for drug-sensitive TB or a multidrug-resistant (MDR) strain.
 - Recent/current contact with a TB case, and whether drug-sensitive or drug-resistant.
 - Current TB symptoms, investigations and/or treatment regimen.
- Any past or current OIs that will influence WHO clinical staging.
- Other conditions, e.g. epilepsy, diabetes, hypertension, rheumatoid arthritis. This is important as symptoms may overlap with those of OIs and significant drug interactions may occur between ART and their respective treatments.
- Psychiatric history: prior depression, anxiety, etc.
- Prior exposure to any ARVs (including PMTCT and PEP interventions). Also, the patient may have been initiated on ART in another clinical setting (GP/ Clinic/Hospital) and it is important to enquire directly for this information.
- Allergies e.g. to cotrimoxazole, sulphur, penicillin.

Family history

Children? Partner? All tested for HIV? Any on treatment?

Social history

Information gathered in this category has important implications for adherence to ART.

- Disclosure of HIV status and outcome of the disclosure.
- Employment status (nature of employment) and source of income.
- Psychological support (family, friends, etc.).
- Alcohol / drug history.



See Appendix 3



See Appendix 24

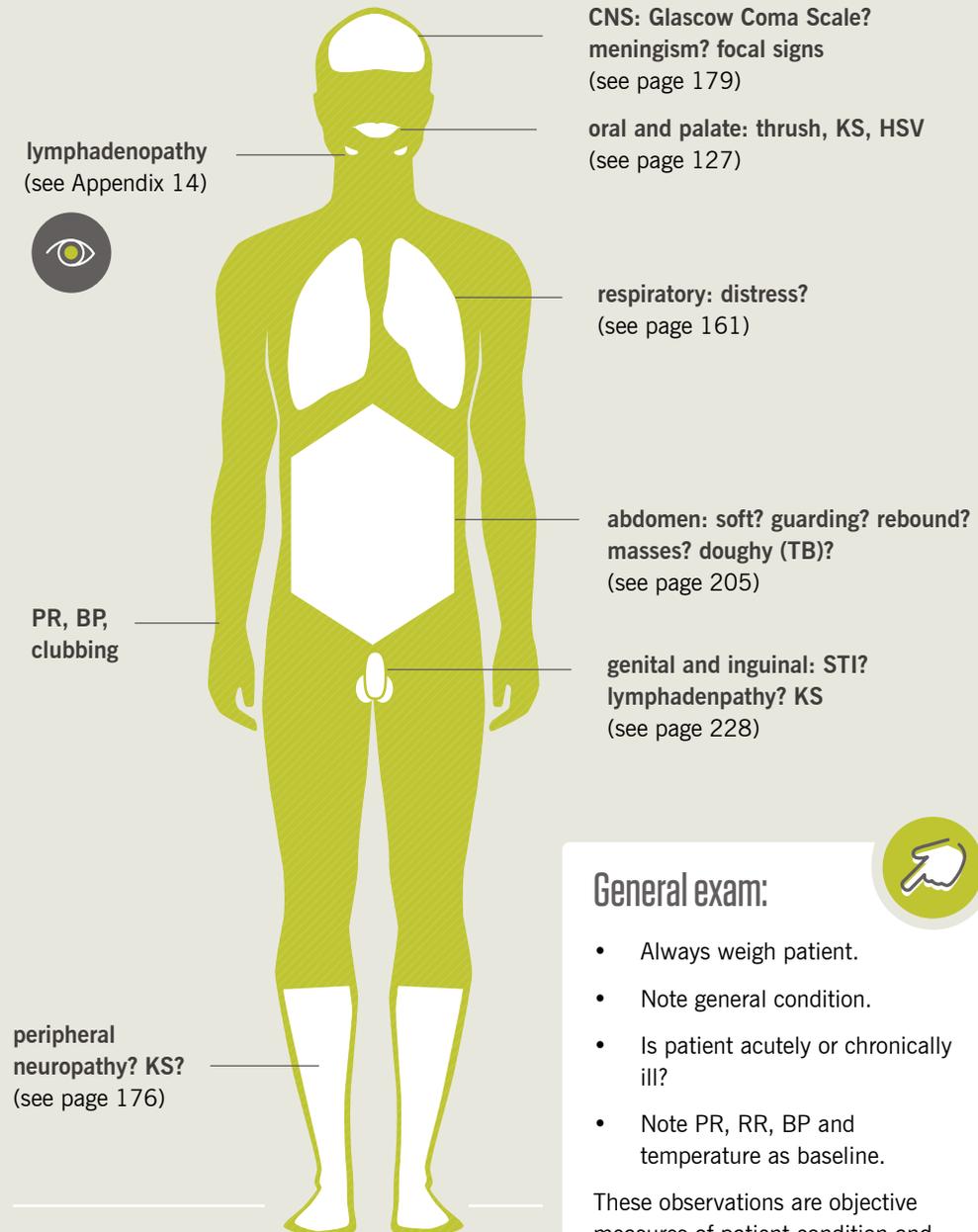
Review of systems

- Refer to Appendix 3.
- Identify any recent weight loss.
- Screen for symptoms of sexually transmitted infections (STIs). Ask specifically about penile or vaginal discharge and ulcers, as patients will not usually volunteer this information.
- Screen for symptoms of TB.
- Screen for symptoms of depression. (See Appendix 24.)

Physical examination

- What is the patient's general condition?
- Does this person look stable or unstable? (If unstable, you will have to spend more time with this person and/or refer to hospital.)
- Check the vital signs (heart rate, respiratory rate, oxygen saturation, blood pressure, temperature).
- Check weight and height at first visit and calculate body mass index ($BMI = W/H^2$, where weight is in kilograms and height is in meters).
- Check weight at each and every follow-up visit.
In children, check weight, height and head circumference at each visit. Plot these measurements on the standard growth charts.
- A thorough examination of all body systems is necessary to exclude OIs.

Figure 2.1 General examination



**CNS: Glasgow Coma Scale?
meningism? focal signs**
(see page 179)

oral and palate: thrush, KS, HSV
(see page 127)

lymphadenopathy
(see Appendix 14)

respiratory: distress?
(see page 161)

**abdomen: soft? guarding? rebound?
masses? doughy (TB)?**
(see page 205)

**PR, BP,
clubbing**

**genital and inguinal: STI?
lymphadenopathy? KS**
(see page 228)

**peripheral
neuropathy? KS?**
(see page 176)

General exam:

- Always weigh patient.
- Note general condition.
- Is patient acutely or chronically ill?
- Note PR, RR, BP and temperature as baseline.

These observations are objective measures of patient condition and are useful clinical parameters in assessment of improvement and deterioration.



Remember to check for the following common signs on examination, as they will help you to decide which WHO clinical stage to put the patient in.

- Signs of wasting or weight loss (stage 2, 3, or 4, depending on the degree).
- Rashes (PPE, current or former herpes zoster – both stage 2).
- Lymphadenopathy.
- Pallor/anaemia: chronic anaemia may relate to undiagnosed TB (stage 3 or 4, depending on site) or HIV itself (stage 3).
- Oral examination: look for oral thrush, oral hairy leukoplakia, and gingivitis (all stage 3) or Kaposi's sarcoma – check palate (stage 4). **Oral thrush together with painful swallowing should raise suspicion of oesophageal thrush (stage 4).**
- If the CD4 count is <100 cells/ μ L, perform a retinal examination through dilated pupils to look for signs of disseminated TB, toxoplasmosis, cytomegalovirus (CMV), etc.

Investigations

The cost, availability and protocols for investigations are different in various clinics, hospitals and countries. **Laboratory investigations are only useful if results are acted upon.**

Point-of-care tests

- Fingerprick test for haemoglobin (Hb) to confirm anaemia.
- Urine dipstick: may indicate urinary tract infection (UTI) if blood and/or nitrites are present; or, if protein present (more than 1+), may indicate HIV-associated nephropathy (HIVAN), which presents as nephrotic syndrome. (See page 222.)

Blood tests

A number of 'baseline' blood tests should routinely be ordered, the exact ones of which will depend on the national guidelines and the particular ARVs making up the first-line ART regimen. Table 2.2 distinguishes between 'preferred' and 'minimum' baseline tests.

Notes:

1. Those presenting with advanced HIV infection (i.e. CD4 count <100 cells/ μ l) will require some additional baseline tests, even if asymptomatic, as they are at risk of certain OIs. Screening for these allows for early diagnosis and management.
2. Clinically unwell patients will require additional investigations, depending on their symptoms and signs.



See National Guidelines

Table 2.2 Minimum and preferred baseline tests

Minimum	Preferred	Other indications
<p>CD4 count: Some countries do not test for a CD4 count when ART initiation criteria have already been established with clinical staging. However, a CD4 test is advisable in very ill or hospitalised patients as it assists with OI diagnosis and prognosis and ideally is performed so screening of late presenters can be carried out.</p> <p>Creatinine and calculation of CrCl if patient to be started on TDF. (See page 221 for CrCl calculation.)</p> <p>Some countries do not recommend creatinine testing at baseline. If this is the case in your setting, targeted baseline testing should be considered for:</p> <ul style="list-style-type: none"> • elderly patients • patients with pre-existing renal disease • diabetes • hypertension • patients on nephrotoxic medication. <p>FBC in patients who will receive AZT.</p> <p>ALT if patient to be initiated on NVP.</p>	<p>FBC</p> <p>Creatinine</p> <p>ALT</p> <p>RPR/VDRL</p> <p>CD4 count</p> <p>VL (viral load) is done as baseline in children as confirmation in some countries.</p> <p>Urine pregnancy test in women of child-bearing age.</p>	<p>If clinically anaemic, take Hb. (See Appendix 30)</p> <p>If urine dipstick abnormal, consider a creatinine.</p> <p>If symptom/signs of hepatitis or hepatomegaly take ALT.</p> <p>HepBsAg if the patient is found to have abnormal liver function tests e.g. ALT > 40.</p> <p>Most countries now test for HepBsAg later if/when the patient is on TDF and 3TC and needs a change in the ARV regimen.</p> <p>CRP is useful in confirmation of inflammation and monitoring response to treatment, e.g. TB</p> <p>ESR is not considered useful in an HIV patient.</p>
<p>If the baseline CD4 count is < 100 cells/μl:</p> <ul style="list-style-type: none"> • Screen for subclinical TB with one of the following (as TB disease is common in this group and smear microscopy not sensitive enough): GeneXpert, TB culture; and/or Determine TB LAM. • Adults should be screened for cryptococcal disease with a cryptococcal antigen (CrAg) test, which can be done on blood or plasma (in addition to CSF). If the patient has headache or any other symptoms of meningitis are present, a lumbar puncture (LP) is indicated. (See page 179.) 		





www.samumsf.org
(search for films on xrays)

X-rays

If available, a chest x-ray (CXR) is particularly useful in patients with:

- dry, chronic cough
- past or recent history of pulmonary TB (PTB), for follow-up purposes.

A CXR is indicated in the following patients:

- acutely ill with a respiratory complaint
- severely short of breath (SOB)
- has suspected abdominal or meningeal TB.

See Appendix 17A for CXR presentations of TB in people living with HIV.



See Appendix 17A

Diagnosis

Compose a problem list with any OIs and other diagnoses that are present. For example:

1. HIV, clinical stage 3
2. PTB
3. oral thrush
4. UTI



See Appendix 1

Clinical staging: Stage the patient following the WHO clinical staging system (see Appendix 1). Clinical staging gives an idea of how sick a person living with HIV/AIDS has ever been. The stage can increase with new, more serious HIV-related conditions, but cannot decrease, even with improved health after ART initiation.

Treatment

Stabilise all patients who are severely ill. This may need to be done before a thorough history and examination.

When deciding on treatment you should consider if the patient requires immediate or delayed referral (i.e. to a higher level of care – doctor, specialist) for investigation or treatment purposes e.g. lumbar puncture (LP) for suspected meningitis. If the patient already meets any ARV eligibility criteria, be sure to state this in the referral note. This assists the hospital clinician with ARV treatment decisions.

Potential indications for urgent up-referral/discussion prior to initiation or when on therapy:

- eGFR less than 60 ml/min
- Hb less than 8 g/dl
- BMI less than 18.5 kg/m²
- in a patient with TB, poor response to TB treatment.



Refer patient

If patient does not require referral, consider:

1. **Is this patient eligible for ART and when should it preferably be initiated?**
2. Which conditions can I treat? (e.g. a lower respiratory tract infection – LRTI – with a broad-spectrum antibiotic; PPE with a mild steroid cream and anti-histamine)
3. Which OIs can I treat? (e.g. oral candidiasis – thrush – with nystatin suspension)
4. Prescribe cotrimoxazole (CTX) for prevention of certain OIs if in clinical stage 2, 3 or 4 or CD4 <350 cells/ μ l (adults). See Appendix 2A for criteria to start and stop CTX for children and adults.
5. Should I offer any other prophylaxis? (e.g. isoniazid – INH – to prevent active TB disease)
6. Ensure adequate nutrition (i.e. advice on diet and supplementation with vitamins when indicated) and provide therapeutic food according to national nutritional guidelines.



See Appendix 2A

Counselling

Reassure patient that infection with HIV is a treatable condition.

- Emphasise the importance of regular follow up and the benefit of prophylaxis and treatment.
- Provide counselling on family planning and condom use (male and female).
- Initiate ART preparation counselling according to your local guidelines



See National Guidelines

Follow-up consultation

Review of symptoms

- Follow up on TB and/or other OIs identified and managed at first consultation.
- Follow up on specific drug-related side effects.
- If no symptoms, educate patient to return early in the future if certain symptoms do develop.

Physical examination

- Does this person look stable or unstable? (If unstable, you will have to spend more time with this person and/or refer to hospital.)
- Check vital signs if necessary.
- Check weight (at every visit).
- Do thorough examination to exclude new OIs and TB.

Treatment

- If patient is already taking CTX and/or INH, check adherence and tolerance.
- Treat any opportunistic infection.

Counselling

- ART preparation counselling will be required as per counselling guide and local protocols.

Further consultations



See Appendices 4A, 4B & 4C

Further consultations will depend on whether the patient is eligible for and initiated on ARVs. The frequency of follow-up visits depends on the clinical stage and baseline CD4 count, and timing of ARV initiation. If the adult or child is eligible for ART (see Appendices 4A, 4B, and 4C), continue with counselling about ARVs.

Patient ineligible for ART:

- If not eligible for ART, the person still requires regular follow up, including **advice on HIV prevention**.
 - Patient must be educated as to the **symptoms of common OIs** e.g. oral candida or TB and advised to seek medical advice if they get ill.
 - Prevent new OIs with **cotrimoxazole**, if not already started (see Appendix 2A for indications).
 - Remember to **check weight and WHO stage** at every visit.
 - Perform (or refer women for) a **PAP smear**, if one was not done during the last year. A negative PAP smear will need a repeat every three years or as per national guideline.
 - Prevent active TB disease by means of **INH prophylaxis**, if clinically indicated. (Follow national guidelines on INH prophylaxis.)
 - Ideally, the following high-risk contacts should be assessed by a clinician, even if there are no obvious symptoms (since TB disease can be subtle):
 - children <5 years of age
 - all HIV-positive household contacts.
- NB: If active TB disease is not suspected, these high-risk contacts should be offered isoniazid preventive therapy (IPT).**
- If the patient is not yet eligible for ARVs, repeat **CD4 every 6 months**.



See Appendix 2A



See National Guidelines

Patient eligible for ART – timing of initiation

Age, pregnancy, clinical conditions and CD4 are the main determinants of the timing of ART initiation. In general, most patients should be initiated in 4–8 weeks. However, certain groups of patients are at higher risk of morbidity and mortality and require 'fast-tracking'. **Fast tracking means that ART must be initiated within 1–2 weeks, regardless of drug readiness counselling being completed.** Counselling can be completed post-ART initiation.

Fast-tracking criteria may differ between settings (see Appendices 4B and 4C for country-specific recommendations) but the following patients are generally considered:

- pregnant and breastfeeding women
- clinical stage 4 disease
- CD4 count <200 cells/ μ l
- TB co-infection with CD <50 (with the exception of TBM).

Note: ART initiation should be delayed for 4–6 weeks in those treated for cryptococcol and TB meningitis, due to the risk of life-threatening intracranial IRIS. (See page 41 for more details.)

The patient is advised to bring a person they can trust (treatment assistant) so that both can receive any necessary counselling.



See Appendices 4B, 4C

Post-ART initiation consultations

(See Table 2.1 on page 14.)

General principles

Remember to check weight at every visit.

- Prevent new OIs with cotrimoxazole, if not already started (see Appendix 2A for indications).
- Perform (or refer women for) a PAP smear, if one was not done during the last year; a negative PAP smear will need a repeat every three years or as per national guideline.
- Discuss family planning options. Despite some prior concern that efavirenz (EFV) may cause birth defects if taken in the first trimester, 'review of the available data and programmatic experience provides reassurance that exposure to EFV in early pregnancy has not resulted in increased birth defects or other significant toxicities'.² Thus, female patients can continue on this drug, if discovered to be pregnant.



See Appendix 2A

2 WHO. 2012. *Technical update on treatment optimization: use of efavirenz during pregnancy: a public health perspective*. Acknowledgement: Ford, Vitoria and Shaffer. http://whqlibdoc.who.int/publications/2012/9789241503792_eng.pdf

- Recent changes, including changes in residence, telephone numbers, surnames, new sexual partners and disclosure(s) need to be explored.
- **CD4 count** can be rechecked 12 months following initiation, then yearly (or according to local protocol). In countries where VL monitoring is available, there is a move toward dropping CD4 monitoring in patients with CD4 above 350.
- **HIV viral load (VL) testing:** If available, the VL should be checked 3–6 months after ART initiation (according to local protocol) and then yearly. **All detectable viral loads require an enhanced adherence assessment (see page 36).**

HIV and TB

- Screen household contacts of PTB patients.
- Prevent active TB disease by means of INH prophylaxis, if clinically indicated. (Follow national guidelines on INH prophylaxis.)
- If the patient is on TB therapy, check the TB card to ensure that the person is adhering to treatment, that follow-up sputum specimens have been taken and that culture and sensitivity results (to look for drug-resistant TB) are available, if taken.
- Patients on ARVs who are initiated on TB treatment may need the ARV regimen modified to accommodate this (see page 104).

(For national guidelines, see Appendix 18.)



See National Guidelines
(Appendix 18)

Antiretroviral therapy

Antiretroviral therapy (ART)
and objectives of treatment

ARV mechanism of action

Classes

Summary process of ART initiation

General principles

Preparation for ART

Post ART management:

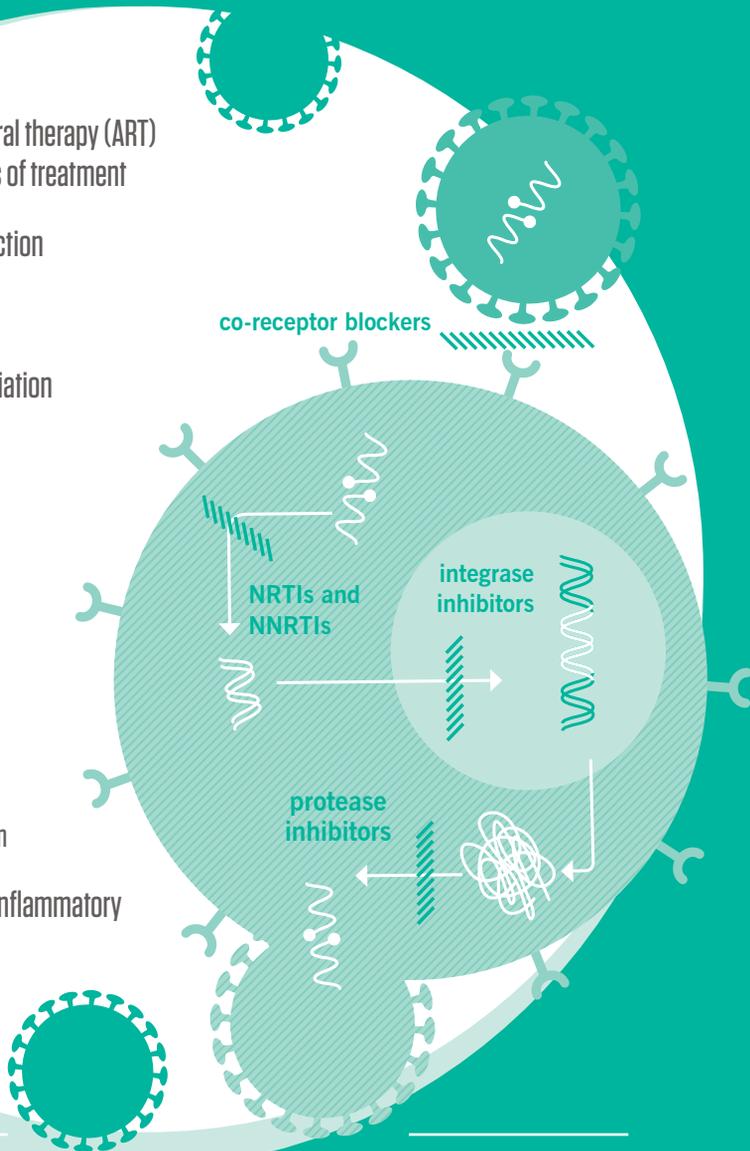
Monitoring ART response and
diagnosing treatment failure

Changes to the ART regimen:

Substitution for ART side-effects

Switch for failure of ART regimen

Immune Reconstitution Inflammatory
Syndrome (IRIS)



Antiretroviral therapy (ART) and objectives of treatment

ARVs are the standard of care for HIV treatment worldwide. ARVs do not eradicate HIV, but block its replication, which then allows the immune system to recover its strength. Put more simply, ARVs 'stop HIV from growing'. By doing so, opportunistic infections become less frequent and less severe, and the person's clinical condition markedly improves.

Principle objectives of antiretroviral therapy (ART) include:

- **Prolong life expectancy and improve quality of life:** 'In South Africa, life expectancy increased from 54 to 60 years between 2005 and 2011, largely due to ART scale-up'.³
- **Reduce HIV viral load:** The aim is to reduce viral load replication to an undetectable limit, thereby providing the best protection against viral toxicity and immunological destruction.
- **Improve the CD4 count, reflecting an immunological improvement:** Such immunological recovery is individually variable but the majority of patients improve rapidly in the first few (1–3) months, with a more gradual recovery thereafter. In a small percentage of patients, the CD4 count will not significantly increase although the immune function may improve.
- **Reduce opportunistic infections (OIs) and other HIV-related conditions.**
- **Reduce transmission of HIV:** Studies have shown that HIV-positive patients on ART with a suppressed viral load have a significant reduction in transmitting the virus to HIV-negative partners. 'ART has contributed to the global decrease of 20% in the estimated number of new infections between 2001 and 2011'.⁴

Therefore, the earlier ART is initiated (with the new international threshold being CD4 of 500 cells/ μ l, according to the WHO), the greater the individual benefit in terms of immune protection (fewer OIs, less frequent hospitalisations and deaths) and the greater the public health benefit as a result of decreasing transmission.



The WHO provides guidance on HIV treatment and these are updated regularly to encompass new scientific evidence, which informs the public health response globally. The WHO thus informs national country guidelines, which have to consider cost and implementation challenges.

This book includes WHO guidelines and specific country guidelines (current at the time of printing), but always check for updates to your current national guidelines. They can be downloaded for print here www.samumsf.org.



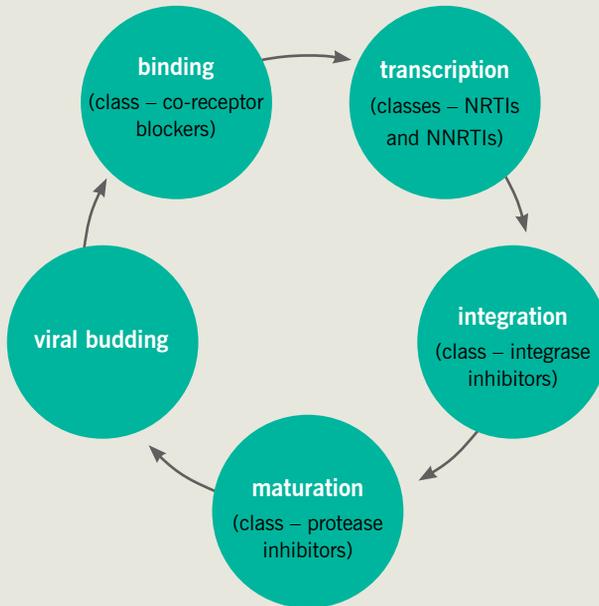
www.samumsf.org

3 WHO. 2013. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. ISBN 978 92 4 150572 7.

4 Ibid

ARV mechanism of action

Figure 3.1 HIV lifecycle and drug classes



ARVs target the HIV lifecycle at different enzymes and receptors. Single or dual therapy (i.e. with just one or two ARVs) is not adequate to suppress replication in the long term, as the virus adapts/mutates rapidly. However, the use of three drugs, termed highly active antiretroviral therapy (HAART), which essentially mixes different classes of ARVs, has been found to be most effective.

Classes

Nucleoside/tide reverse transcriptase inhibitors (NRTIs):

- tenofovir (TDF)
- lamivudine (3TC)
- zidovudine (AZT)
- stavudine (d4T)
- didanosine (DDI)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

- nevirapine (NVP)
- efavirenz (EFV)



See Appendix 5A

Protease inhibitors (PI)*:

- lopinavir/ritonavir
- atazanavir/ritonavir
- darunavir/ritonavir

* all PIs boosted with ritonavir

(See Appendix 5A: ARV classes, drugs and 'need-to-know' facts.)

Summary process of ART initiation

Figure 3.2 Assessment for ART

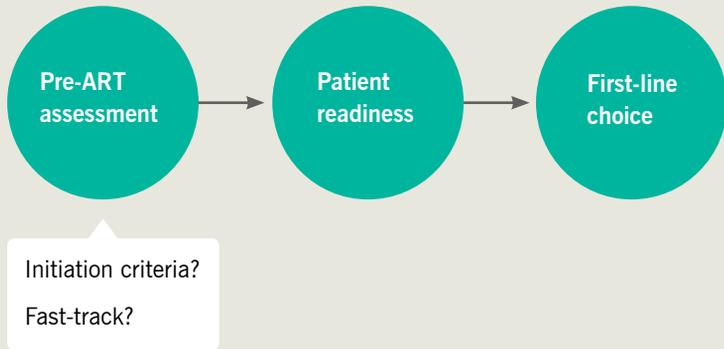
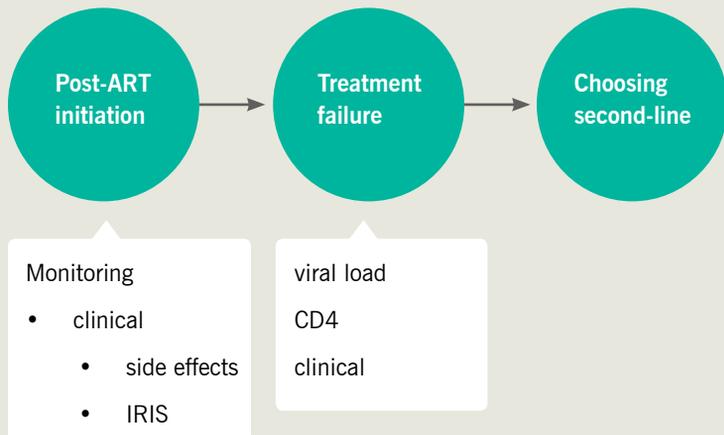


Figure 3.3 ART monitoring



General principles

Not all HIV-infected people need ARVs at the time you first see them.

Results of clinical staging and CD4 count testing are used to decide when to start ARVs for adults and older children (see Appendices 4A, 4B and 4C).

ARVs can be given for:

- treatment – ART
- prevention – PMTCT, post-exposure prophylaxis or PEP (e.g. post-rape), pre-exposure prophylaxis or PrEP (e.g. in an HIV-negative, commercial sex worker).



See Appendices 4A, 4B and 4C

Triple therapy (also known as HAART)

For treatment purposes, three ARV drugs are given together ('triple therapy') to prevent HIV developing resistance to individual ARVs. This concept is similar to that seen in TB treatment, where multiple TB drugs are given simultaneously to stop TB (and to avoid resistance to TB drugs).

If someone develops resistance to ARVs it means that those three ARVs won't be effective ever again for that person, even if the ARVs are subsequently taken faithfully. The only chance the person then has to lower the HIV 'viral load' is to start taking three new ARVs (known as 'second-line' treatment).

Preparation for ART



Treat any OIs (especially TB) before starting treatment with ARVs. Thoroughly assess for OIs (especially TB), other HIV-related conditions – such as anaemia and peripheral neuropathy (PN) – and contraceptive issues before deciding on the first-line regimen. See Appendix 6 for an ART initiation checklist. Always try to stabilise the patient as best as possible (by treating TB and other OIs, and improving nutrition) before starting ARVs.



See Appendix 6

Assessing and counselling for treatment readiness is very important but this period should not be extended unnecessarily. In certain high-risk patients this phase should be **fast-tracked** (i.e. ART initiation within two weeks) as a matter of urgency, with counselling continuing post-initiation.

Patient support is needed to enable a person to take ARVs faithfully every day. The person (or caregiver, in the case of a child) must live in a stable, supportive environment, must believe in the usefulness of ARVs and must be motivated to take them. She/he should be encouraged to attend a support group for people living with HIV. She/he should have disclosed her/his HIV status to at least one person in whom they trust.

Pre-ART

1. Does the patient meet initiation criteria?



See National Guidelines
(Appendix 4B and 4C)

Table 3.1 World Health Organisation ART eligibility criteria

(See Appendix 4B and 4C for national guidelines.)

Adults and adolescents	WHO 2013
When to start ART	<p>As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤ 350 cells/μl (strong recommendation, moderate-quality evidence).</p> <p>ART should be initiated in all individuals with HIV with CD4 count > 350 cells/μl and ≤ 500 cells/μl, regardless of WHO clinical stage (strong recommendation, moderate-quality evidence).</p> <p>ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations ***:</p> <ul style="list-style-type: none"> • Individuals with HIV and active TB disease (strong recommendation, low-quality evidence). • Individuals coinfecting with HIV and HBV with evidence of severe chronic liver disease (strong recommendation, low-quality evidence). • Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (strong recommendation, high-quality evidence). • All pregnant and breastfeeding women.



Refer patient

*** Other serious conditions may also be considered for HAART (**discuss with experienced clinician**).⁵

- HIV-related conditions: These include: LIP, HIVAN, thrombocytopenia (platelets < 50), polymyositis or HIV vasculopathy.
- HIV-unrelated conditions: chronic hepatitis B or non-AIDS malignancies.

2. Must the patient be fast-tracked?



Those requiring fast-tracking (i.e. ART initiation within 1–2 weeks of being eligible)*:

- HIV-positive women who are pregnant or breastfeeding
- Patients with low CD4 (i.e. <200 cells/ μ l)
- Patients in clinical stage 4, irrespective of CD4 count
- Patients with TB/HIV co-morbidity with CD4 count <50 cells/ μ l.

* This excludes patients with TB meningitis and cryptococcal meningitis.

Check your national guidelines for details as they may differ.



See National Guidelines

3. Are there any specific conditions I must be aware of?



In patients with **cryptococcal meningitis** or **TB meningitis**, defer ART for four to six weeks, to avoid life-threatening intracranial IRIS. This recommendation is based on the increased mortality for these conditions when a patient is initiated earlier on ART.

Check your national guidelines for details as they may differ.



See National Guidelines

4. Is the patient ready?

The patient is ready when:

- The patient is ready to commit to long-term antiretroviral therapy.
- Ideally, the patient is willing to **disclose HIV status** in confidence to a person who agrees to act as the patient's 'treatment assistant'. However, if no treatment assistant is available, this should not be a reason to delay starting ART (**strongly recommended but not mandatory**).
- Exclude or treat alcohol abuse.

5. When should counselling start?

Start counselling sessions as soon as patient meets clinical or CD4 criteria for ARV initiation (see Table 3.1 above). Do not wait until the clinical workup is completed. Pre-ART counselling sessions should be completed by the date set by the clinician. Duration for counselling sessions to be completed depends on the level of CD4, whether there is TB co-infection or whether use of ARVs is for PMTCT. The final session is usually given on the day of initiation.

Counselling sessions should include disclosure and information on: positive living and the basics of HIV; testing the CD4 count; the need for cotrimoxazole prophylaxis; the ARV treatment plan; adherence; and treatment side effects. A Patient Education and Counselling Guide can be found at www.samumfsf.org



www.samumfsf.org

6. What are the baseline laboratory results?

The clinical assessment and the baseline laboratory results will influence the choice of the first-line ART regimen. In some circumstances/settings, ARVs may have to be initiated without any baseline blood test results.



See Appendix 16



See Appendix 26C



See Appendices 6–8

Take blood for:

- **CD4 count** – to determine eligibility for ART initiation (to consider fast-tracking) as well as to indicate the likelihood of underlying conditions (see late presenter management, Appendix 16) and risks for IRIS (see page 41).
- **creatinine and to calculate creatinine clearance (CrCl)** according to the formula in Appendix 26C. It is essential to calculate the CrCl in patients with age >50 years, weight <50 kg, or serum creatinine >100. The tables in Appendix 26C allow you to estimate the CrCl if calculation is difficult. In some settings, the laboratory calculates the CrCl and reports it with the creatinine result.
- **ALT if nevirapine is going to be used.** Check HBsAg if baseline ALT >40 (or whenever considering discontinuation of TDF). Note that routine screening for HBsAg is not necessary if the first-line regimen includes TDF and 3TC (provided that the CrCl is >50 mL/min).
- **FBC if the patient is to be started on AZT** or there are clinical indications.

See Appendix 6 for an ART initiation checklist.

See Appendices 7A, 7B, 7C, and 7D for a list of laboratory tests recommended by WHO at baseline and during monitoring of those on ART, as well as country-specific recommendations.

See Appendix 8 for management of abnormal laboratory results.

Choosing the drugs to be used in the first-line regimen

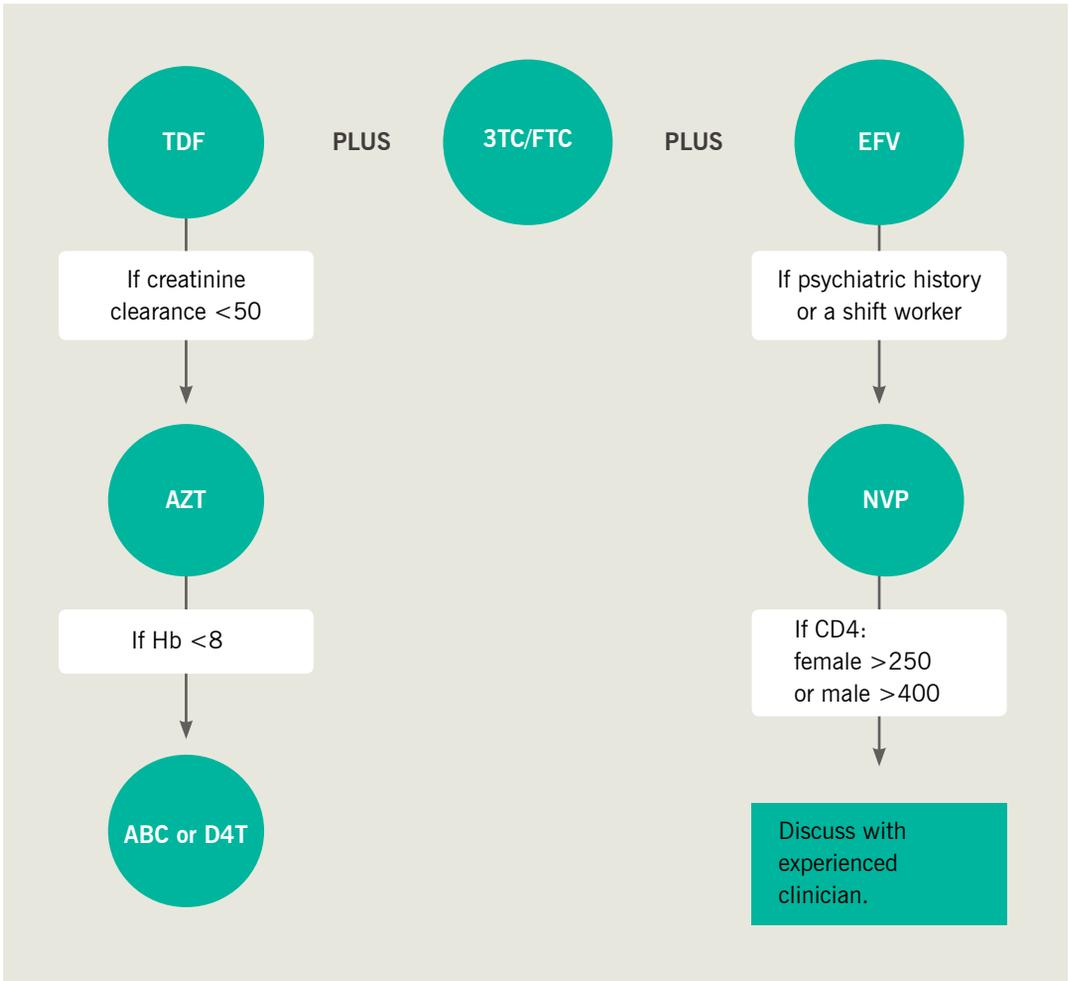
A first-line ART regimen typically consists of two NRTIs plus one NNRTI. The perfect ARV regimen would be one tablet once a day (i.e. a fixed-dose combination of the three ARVs) and would have no side effects. It exists as one tablet taken once a day TDF/3TC/EFV. It is the preferred first-line regimen because of its better profile for side effects and its compatibility with TB treatment.

If there are contraindications to the TDF/3TC/EFV regimen, then we proceed as indicated below.



Algorithm 3.1 Choosing a first-line flowchart

(See Appendix 5A for dosages.)



See Appendix 5A for dosages.

See Appendix 9A for first-line ART regimens as recommended by WHO.

See Appendices 9C and 9D for national guidelines on first-, second- and third-line ART regimens in adults and adolescents.

Please check page 104 for discussion of TB and ART.



See Appendices 9A, 9C, 9D

Post ART management

Monitoring ART response and diagnosing treatment failure

After initiation of ART, patients must be monitored for:

- development of IRIS (see page 41)
- possible side effects
- response to ART and development of resistance.

Monitoring for possible ARV-related side effects

Clinical and laboratory monitoring should be performed frequently in the first few months after ART initiation, in order to diagnose and manage any short-term side effects early. See Chapter 6 on side effects on page 73.

(See Appendices 7A, 7B, 7C and 7D.)



See Appendices 7A–D

Monitoring for efficacy (success) of ART

The measurement of the success of treatment with ARVs can be done in three ways:

1. clinically (by monitoring for subsequent infections)
2. immunologically (by monitoring CD4 counts)
3. virologically (with viral loads).



'Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure (strong recommendation, low-quality evidence). If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure (strong recommendation, moderate-quality evidence).'⁶

Clinical monitoring

Allow 4–8 weeks on ARVs until the first positive effects are seen: weight gain, improvement in general health and fewer new infections. After starting ARVs, opportunistic infections can still occur, especially if the baseline CD4 count was <100 cells/ μ l. Infections can also worsen several weeks after ART initiation, a situation called immune reconstitution inflammatory syndrome (IRIS). (See page 41.)

⁶ WHO. 2013. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. ISBN 978 92 4 150572 7.

- Look for signs of infection, particularly TB, at each visit.
- Check weight.
- Investigate weight loss >1.5kg in 4 weeks.

CD4 monitoring

Treatment with ARVs interrupts the lifecycle of HIV, so HIV ‘stops growing’ and the destruction of CD4 cells is halted. The CD4 count then slowly rises (usually to a level well above 200 cells/ μ l). However, this can take many months or years, and will only continue if the person is correctly taking the ARVs. This level of 200 is important, since most OIs occur when the CD4 count is below 200, and until that threshold is reached, chemoprophylaxis against infections (e.g. cotrimoxazole) is still required.

Viral load

This blood test measures how much HIV is in a person’s blood. It does not measure how the person is feeling or how high the CD4 count is. After several months of ARVs (usually no more than six), the HIV viral load should fall to undetectable levels. This undetectable level (also known as LDL or ‘lower than detectable’ limit) is important, since it means that the HIV has stopped replicating as a result of the ARVs. Where viral loads are available, they are used both to monitor response to therapy and make decisions about switching to a second-line ART regimen. In some settings, viral load is performed routinely. However, if resources are constrained, viral load testing will only be performed if triggered by clinical, immunological or adherence criteria. (See Algorithm 3.2 on page 39.)

What are the possible reasons for a detectable viral load?

- The patient has poor adherence to the medication.
- The patient is taking the ARVs incorrectly.
- The patient is taking other medication, which is reducing the effectiveness of the ARVs (this can occur with both TB medicines and traditional medicines).
- The blood sample was mixed up with that of another patient.
- The patient is suffering from an inter-current illness (TB, common cold, etc.), which boosts replication of HIV. We call this a ‘blip’ in the viral load.
- Frequent vomiting or diarrhoea, which prevents absorption of ARVs into the body.
- The patient was infected with a resistant virus (i.e. primary resistance).
- The patient’s HIV has developed resistance to the antiretroviral medication (i.e. failure of the current ART regimen).



See Appendix 12



Poor adherence remains the commonest cause of virological failure. See Appendix 12 for an example of an adherence worksheet.

Risk factors include:

- Non-disclosure of status – patients often have to hide medication from family members.
- Lack of insight, due to insufficient patient education, or may possibly be due to cognitive impairment.
- Depression – always screen for depression in a patient with virological failure.
- Substance abuse.
- Adolescents and young adults.

Practical tips for providing increased adherence support to patients:

- Ensure patient understands what a viral load is.
- Provide reasons for acquiring a high viral load.
- Allow patient to conclude what the cause is of their high viral load.

Discuss possible solutions to their adherence problem:

- Choose an appropriate time to take your ARVs.
- Always take a missed dose as soon as you remember.
- Carry a few days extra supply of ARVs in your handbag at all times.
- Use reminders like your cell phone alarm, regular TV programmes, or family/friends.
- Plan for trips and holidays by asking for extra supply of ARVs from your clinic.

Table 3.2 Monitoring on ART

Monitoring on ART	Purpose
Increase in clinical stage.	To monitor response to ART.
CD4 count test at month 6, one year on ART and then every 6 months.	To monitor response to ART.
If available, VL at month 3 or 6 (according to local protocol) and then yearly.	To monitor response to ART; To identify problems with adherence; To decide when to switch to a second-line ART regimen.
ALT if on NVP and develops rash or symptoms of hepatitis.	To identify severity of NVP toxicity.
FBC at month 1, 2, 3 and 6 if on AZT.	To identify severity of AZT toxicity.
If available and feasible, creatinine (and calculate CrCl) at month 6, 12 and then every 12 months.	To identify TDF toxicity.
Fasting cholesterol, triglycerides, and glucose at month 3, month 12 and then yearly if on PIs.	To identify LPV/r toxicity.

Changes to the ART regimen

Changes to the ART regimen may be required for several reasons. Some people may experience a major side effect to one ARV, requiring substitution of that ARV. In some cases a whole regimen fails (usually due to earlier problems with adherence).

Substitution for ART side effects

Change only the one 'culprit' drug. However, before substitution, check the VL (or last VL if done in the previous six months) to see if the patient may have treatment failure. **Never substitute a single drug in a failing regimen.**

What is 'tail protection' for NNRTI drug interruption?

- NNRTIs have a long half-life. Whenever we have to stop EFV or NVP, it's advisable to continue drugs with a shorter half-life (e.g. TDF/3TC or d4T/3TC) for 7 days, to help avoid emergence of HIV resistance to the NNRTI, so that it remains an option in the future.
- Likewise, when we have to stop **all ARVs** (e.g. in case of lactic acidosis), and it's not possible to continue one of the NRTIs, it's better to give 'tail protection' for NNRTIs with a double dose of Lopinavir/rit (i.e. 4 tablets of LPV/r BD) for

7–10 days. A double dose is used because of an interaction between LPV/r and the NNRTI.

- Stopping TDF abruptly in a person with active hepatitis B infection (i.e. HBsAg+) is contraindicated. In case of a life-threatening condition (but different from drug-induced hepatitis, e.g. emergency surgery) necessitating interruption of all ARVs, an experienced clinician should manage the case. Withdrawal of TDF for few days is allowed, under close surveillance. Re-introduce TDF (and 3TC) as soon as possible.

Switch for failure of ART regimen

(See Appendix 11A.)

The regimen has to be changed to a second-line regimen because the HIV in that particular person's body has developed resistance to all three ARVs.

Note that one HIV mutation (M184V) both acts against 3TC and has a crippling effect on the virus itself; therefore, if virological failure is confirmed, 3TC should be continued, even as we switch the other two drugs that were in the failing first-line regimen.

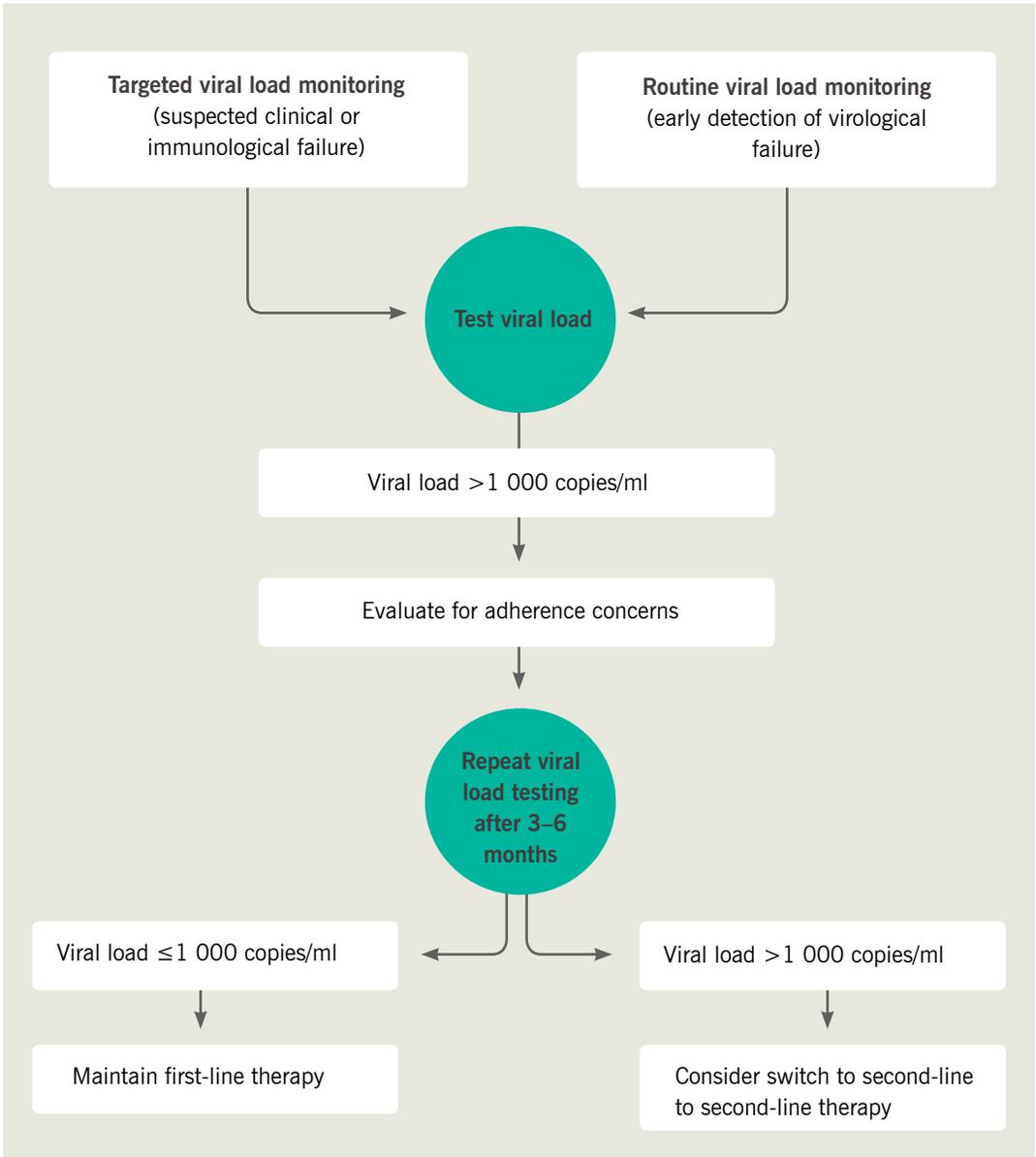
If the patient was on a NNRTI (NVP or EFV) in the first-line regimen, the second-line regimen has to include a protease inhibitor (eg. Lop/rit or ATZ/r) as the HIV will now contain an NNRTI mutation that makes the virus resistant to both of these NNRTI drugs (i.e. cross-resistance).

Changing ART regimens is a serious decision. The nurse, counsellor and HIV doctor should discuss each case before changing regimens. The first-line regimen is always a person's best chance at maintaining an undetectable viral load; we must do our best to help people on first-line ARVs to adhere to their treatment. Always try to correct a problem with adherence before considering switching to a second-line regimen. However, in a patient with confirmed virological failure and poor immunity (e.g. CD4 < 100 cells/ μ l) and/or is ill with a new OI (e.g. now clinical stage 4), **switching to a second-line ART regimen is more urgent.**



See Appendix 11A

Algorithm 3.2 Viral load testing strategies to detect or confirm treatment failure and switch ART regimen in adults, adolescents and children⁷



See Appendix 13B for national guidelines on viral load monitoring and second-line switching.



See Appendix 13B

Second-line ART in adults

The adult patient on a second-line ART regimen will thus take:

- TDF/3TC (or TDF/FTC) once daily or AZT/3TC twice daily, together with LPV/r (or ATV/r) twice daily. **Remember to check for presence of active hepatitis B (i.e. HBsAg+) before stopping tenofovir (TDF).**
- 3TC (lamivudine) is maintained in the second-line regimen due to its crippling effect on HIV viral replication, even if resistance to 3TC has already developed.
- LPV/r. If a patient on LPV/r develops diabetes or severe dyslipidemia (see Appendix 10A and 10B), involve an experienced clinician. A change from LPV/r to atazanavir/ritonavir (ATV/r) can be considered if:
 - patient has high cholesterol
 - patient has raised fasting glucose
 - patient unable to tolerate LPV/r due to gastro-intestinal side effects.



See Appendix 10B and 10B

LPV/r and TB treatment

(Refer to page 104.)

- Patients starting rifampicin should have the dose of LPV/r **doubled** gradually over two weeks, to 800 mg lopinavir + 200 mg ritonavir twice daily.

If TB is diagnosed while on LPV/r:

- Week 0: Start TB treatment and increase LPV/r to 600/150 mg twice daily.
- Week 1: give LPV/r 800/200 mg twice daily.

If LPV/r needs to be started while on TB treatment:

- Week 0: Start LPV/r 400/100 mg twice daily.
- Week 1: Give LPV/r 600/150 mg twice daily.
- Week 3: Give LPV/r 800/200 mg twice daily.

Such high doses of LPV/r can predispose to side effects such as gastro-intestinal upset and hepatitis. In addition to careful clinical monitoring for symptoms of hepatitis, ALT should be monitored routinely. (See page 80: *Management of drug-induced hepatitis.*)

- Continue with double-dose LPV/r (or with super-boosted LPV/r) for 2 weeks after rifampicin-containing TB therapy is stopped.



Alternatively, instead of doubling the dose of LPV/r, additional ritonavir (an extra 300 mg 12 hourly in adults) can be used to 'super-boost' the existing dose of LPV/r in those patients taking a TB regimen that includes rifampicin. In children on rifampicin taking LPV/r, additional ritonavir is needed and LPV/r should not be double-dosed.

ATV/r and TB treatment

ATV/r cannot be used with rifampicin. It can be co-prescribed with rifabutin.

If rifabutin is not available temporarily switch to LPV/r as described above.

Third-line ART (or ‘salvage therapy’) in adults

Patients failing second-line therapy have few treatment options and require consultation with an experienced HIV clinician.

Most patients suspected of having second-line ART failure actually have adherence issues. With enhanced adherence support, the majority of suspects will have a re-suppressed VL on the same second-line regimen. Only a minority will actually need to be switched to third-line ART.

Suspected second-line ART failure is almost always due to poor adherence and every effort should be made to address this:

- Diagnose and treat OIs.
- Diagnose and treat depression.

Address side effects aggressively, e.g. LPV/r can cause severe diarrhoea and nausea which can lead to poor adherence. (See *Practical tips for providing increased adherence support to patients* page 36.)



Refer patient

Immune Reconstitution Inflammatory Syndrome (IRIS)

When ARVs are initiated there is an expected favourable immune recovery/reconstitution. In some patients, this immune reconstitution is complicated by a disproportionate inflammatory response to a pre-existing disease/condition. Clinically, this manifests as a worsening of symptoms or clinical status several weeks after starting ART.

There are two types of IRIS:

- **Unmasking IRIS:** This means a previously undetected ‘subclinical’ infection presents shortly after initiation of ART with new and frequently unusual manifestations. Thus it is very important to diagnose OIs before ARV initiation; however, it is very challenging in those patients with very low CD4 count as symptoms/signs may be mild or even absent.
- **Paradoxical IRIS:** This refers to an OI that was successfully controlled and on continued treatment, which worsens a few weeks after start of ART.

Timing of IRIS:

The majority of IRIS begins between two weeks and three months, but it can occur up to nine months.

Risk factors for IRIS:

- low CD4 count at initiation (<100 cells/ μ l)
- short duration between treatment of an OI and initiation of ART.

Diagnosis:

IRIS is a diagnosis of exclusion; as such there is no test for IRIS.

We need to exclude other conditions that may mimic IRIS:

- new OIs
- untreated or partially treated OIs – poor adherence? drug resistance?
- drug reactions.

For a diagnosis of paradoxical IRIS: If on OI treatment (e.g. TB), there must have been a symptomatic improvement on that treatment before ART initiation, prior to the worsening, for the diagnosis to be an option.

Management:

- Most IRIS is mild and self-limiting and will resolve with proper treatment of the OI, continuing ARVs and symptomatic treatment (fever, pain) with paracetamol and NSAIDs.
- In moderate/severe cases of IRIS, steroids must be considered.
- For TB IRIS see page 41; for crypto IRIS see page 188.
- Life-threatening IRIS is rare; but when it occurs, ARVs must be discontinued.

(See www.samumsf.org for IRIS presentation.)



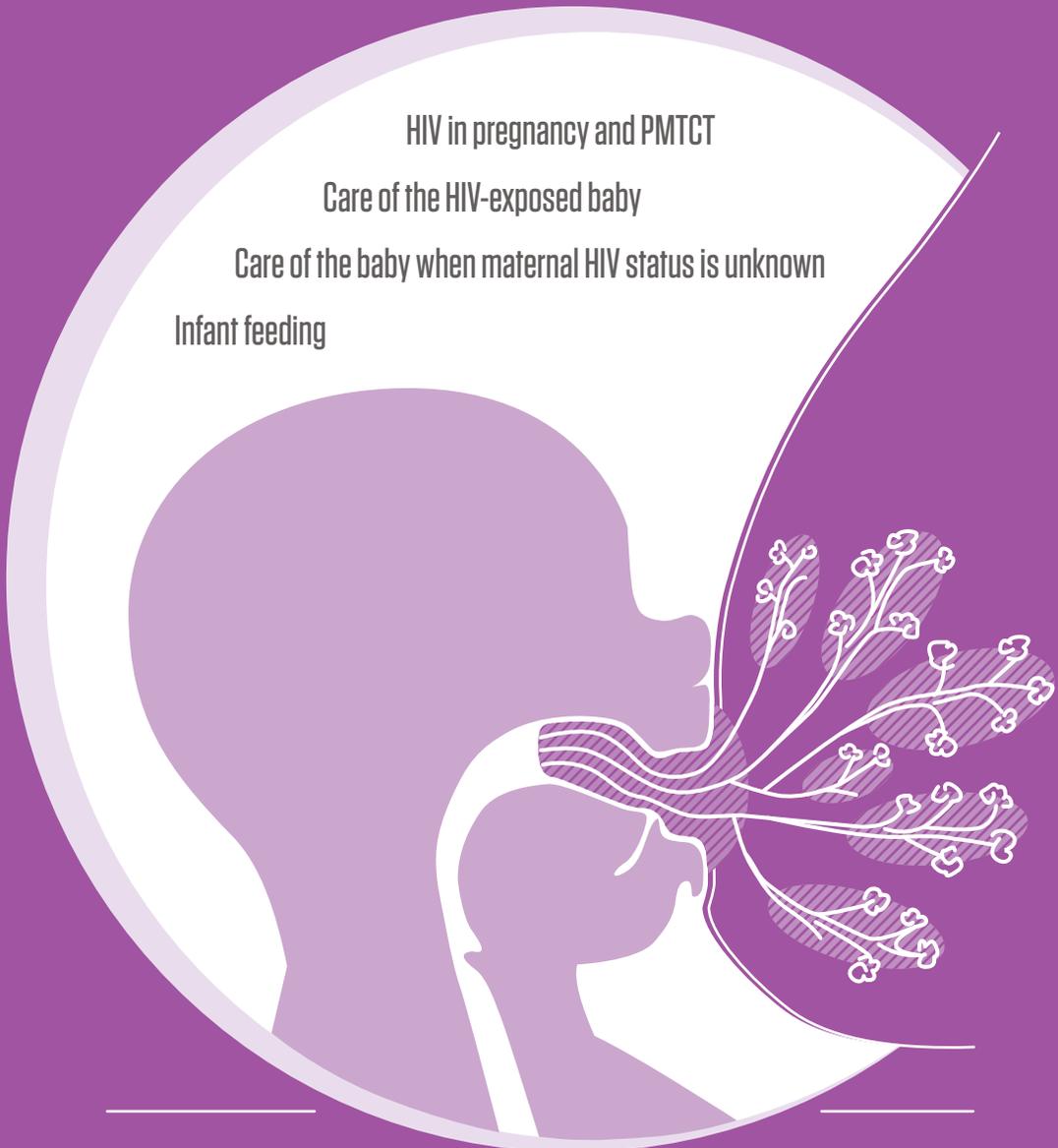
Prevention of mother-to-child transmission (PMTCT)

HIV in pregnancy and PMTCT

Care of the HIV-exposed baby

Care of the baby when maternal HIV status is unknown

Infant feeding



Algorithm 4.1 Management of HIV-positive pregnant women

Antenatal care

All HIV positive pregnant women need:

- CD4, creatinine and clinical staging.
- screening for TB and if active TB is excluded consider giving IPT.¹
- CTX for stages 2, 3, 4 or CD4 <350.
- screening for syphilis and other STIs.
- folic acid daily in the first trimester; multivitamin daily; ferrous sulphate if HB <11.0.
- standard antenatal care according to national protocol.



Antenatal first visit

- Start all HIV positive pregnant women on TDF 3TC EFV on the same day they test positive.²
- EFV is safe to use in the first trimester.
- If creatinine clearance at subsequent visit is <50ml/min, change TDF to AZT if HB >8g/dl. If HB <8 g/dl, use ABC.



Continue antenatal care visits and ART visits according to local protocol, ensuring delivery of a comprehensive PMTCT adherence package, including adherence to ART, a delivery plan and feeding advice.



Labour and delivery

- Continue TDF 3TC EFV once a day during labour and delivery.
- If a woman presents and tests positive in labour, start TDF 3TC EFV immediately.
- As soon as the baby is born, NVP syrup should be given daily according to the dose in Table 4.1.



After delivery the mother:

- continues TDF 3TC EFV for life.³
- should receive postnatal care package.
- should receive ongoing counselling on adherence and infant feeding.
- should exclusively breast feed for 6 months.

After delivery the baby:

- continues on NVP syrup for six weeks.⁴
- should receive DNA PCR testing at or before 6 weeks, according to national guidelines.
- should be exclusively breast fed.
- should start CTX from 6 weeks until proven to be HIV negative.

Notes:

1 For details on the duration and dose of INH, refer to your national TB guidelines or the 2014 MSF *TB guide*.

2 In case TB treatment is required, wait 2-4 weeks on TB treatment before starting on TDF 3TC EFV.

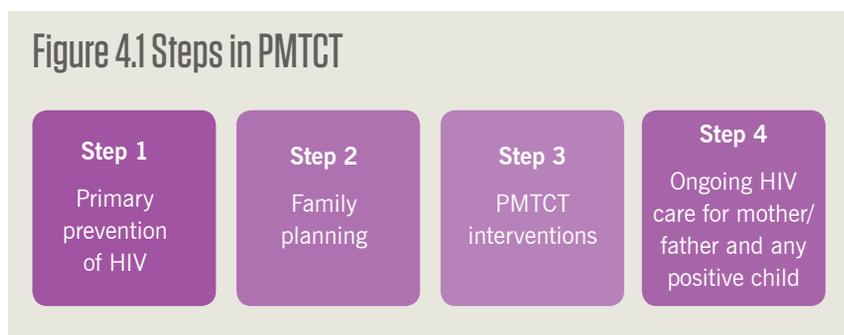
3 In some settings women may be given the choice to stop ART depending on their CD4. Consult local guidelines.

4 If the baby vomits within one hour of initial dose, repeat prophylaxis.

HIV in pregnancy and PMTCT

HIV poses some major challenges to the clinician managing pregnant women. Not only do we want the mother to have a healthy pregnancy, but we also want to prevent the baby from becoming infected with HIV before, during, and after delivery.

Prevention of mother-to-child transmission of HIV (PMTCT) can be divided into a number of steps shown in Figure 4.1.



Family planning

An essential step of PMTCT is effective family planning. All HIV-positive women should have access to family planning and at each visit women should be asked what method of family planning they are using. Long-acting, reversible methods of contraception are recommended (e.g. Depo-Provera injection, implant).

It must be remembered that, although family planning is important, women with HIV are able to become pregnant and deliver healthy HIV-negative children. Advice on preferred timing of pregnancy (ideally when on ART for 6–12 months and when the viral load is undetectable) should be discussed with all women and their partners.

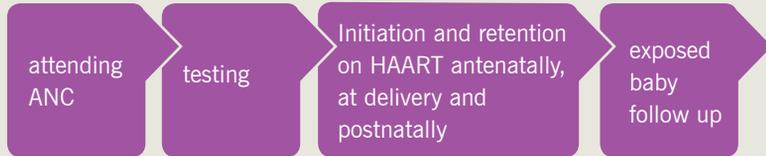
PMTCT interventions

Organisation of services for PMTCT: aiming for a ‘one-stop’ service

Once an HIV-positive woman becomes pregnant, PMTCT interventions start at the first antenatal visit and continue until the baby has a definitive HIV-negative test at 18 months of age or 6 weeks after complete cessation of breast feeding, whichever comes first. In order to maximise retention for both mother and child, HIV/ART services and antenatal care should be integrated as a **one-stop service**. Likewise, the mother and her exposed baby should be consulted together until the child has a definitive diagnosis (see Algorithm 4.2) usually in the MCH department and/or ‘under-5 clinic’. Visits should be coordinated so that the mother can receive her ART whilst the baby is examined, receives cotrimoxazole, is tested according to the algorithm and receives vaccinations according to the EPI schedule.

Interventions related to PMTCT can also be broken down into a number of steps, often referred to as the 'PMTCT cascade' (see Figure 4.2). This starts from ensuring antenatal attendance, HIV testing, initiating and retaining the pregnant woman on ART through to the testing and retention in care of the infant exposed to HIV. All steps need to be monitored to ensure maximal coverage of any PMTCT intervention.

Figure 4.2 Attacking the leaks in the cascade



Diagnosis of HIV in pregnant women

- 'Opt-out' HIV testing should be done at the first ANC visit, along with the other antenatal tests. If the woman decides to 'opt out' of HIV testing, individual counselling should be performed, and HIV testing offered at every visit until the status is known.
- If the woman tests negative initially, she should be retested in the third trimester of pregnancy, according to national guidelines.
- Testing should be done during labour for all pregnant women with unknown HIV status, or immediately after delivery, if not possible during labour.
- It is important that women who tested negative during antenatal care and at delivery are re-tested during the breastfeeding period.
- Partners should be encouraged to test at every visit. If the woman tests negative and the partner positive (i.e. a serodiscordant couple), he should be offered ARVs regardless of CD4 count, in order to reduce the risk of transmission of HIV to the pregnant woman. (Check your local guidelines on the treatment of serodiscordant couples.)



See National Guidelines

Management of HIV-positive pregnant women

- All pregnant women should be started on three antiretroviral drugs as soon as they are identified as being HIV positive, whether this is during antenatal care or at delivery. Women who present and test HIV positive while breastfeeding should also be offered immediate ART.
 - According to WHO's PMTCT recommendation, ART is given lifelong to all pregnant HIV-positive women (Option B+), i.e. ART should be continued throughout pregnancy, delivery, and breastfeeding and should not be stopped.

- In some countries or circumstances, ART can be discontinued in those women not meeting the usual ART eligibility criteria (e.g. baseline CD4 count <500 cells/ μ l) once the risk of transmission is gone (Option B).
- Refer to your national policy on which option to follow in your setting.
- Triple therapy for all pregnant women (Option B and B+) is currently being phased in, in many settings, replacing management of HIV-positive pregnant women according to Option A (as previously recommended by WHO in 2010).
- The first-line ART regimen of choice for pregnant women is TDF + 3TC + EFV. Note that EFV is now considered safe for women in the first trimester.⁸
- If at a subsequent visit the baseline CrCl is shown to be <50 ml/min, substitute TDF with AZT (as long as the Hb is >8 g/dl). Note that this will be rare, as 1% or less of HIV-positive pregnant women will have a CrCl <50 ml/min. Where there is no access to creatinine monitoring TDF should still be given as this is the safest drug to give.
- The rate of loss to follow up is high in pregnant women on ART and so it is essential that thorough counselling is performed. At the first visit, the emphasis should be that taking the ART during pregnancy, delivery and breastfeeding will keep your baby HIV negative. During subsequent visits, the benefits for maternal health and for reducing transmission can be discussed further. See www.samumfsf.org for PMTCT counselling material in the PMTCT toolkit.
- ARVs for the HIV-exposed newborn (= a type of PEP):
 - All babies born to an HIV-positive mother should receive NVP syrup daily for 6 weeks according to the dosing in Table 4.1.
 - At 6 weeks the NVP syrup can be stopped and cotrimoxazole syrup started according to the dosing in Table 4.2.
- If a mother and baby present after delivery, the mother should be offered HIV testing. If tested positive, she should be started on ART immediately, using TDF + 3TC + EFV. The baby should be tested using DBS PCR and then started the same day on NVP syrup according to the dosing in Table 4.1. NVP syrup should be continued for six weeks.
- Unless formula feeding is '100% available, feasible, affordable, sustainable and safe' (AFASS) for a minimum of six months, all babies should be exclusively breast fed for the first six months. See section on infant feeding, page 52 below.



See National Guidelines



www.samumfsf.org

8 WHO. June 2012. *Technical update on treatment optimisation: Use of efavirenz during pregnancy. A public health perspective*. Acknowledgement: Ford, Vitoria and Shaffer. http://whqlibdoc.who.int/publications/2012/9789241503792_eng.pdf



See National Guidelines

Monitoring of ARV treatment in pregnant women

Monitoring for ART toxicities is no different for pregnant women. See Chapter 2, and refer to your national guidelines for more information.

Viral load monitoring is the strategy of choice to monitor the response to ART, especially in pregnant and breastfeeding women. If feasible, consider more frequent (e.g. six-monthly) viral load monitoring during the period of pregnancy and breastfeeding.

CD4 count monitoring may be continued six monthly if required by national protocol. Interpretation of the percentage drop in CD4 count for those women starting with high CD4 counts is difficult and has limited use in identifying cases of suspected ART failure. A CD4 count <100 cells/ μ l or below baseline can be taken as a sign of immunological failure ideally, to be confirmed with virological testing.



See National Guidelines



For pregnant and breastfeeding mothers on effective ARV treatment, the risk of MTCT is minimal. Ensuring the mother has good adherence to ART is essential. If HIV viral load (VL) testing is available, consider more frequent testing for pregnant and breastfeeding mothers and ensure enhanced adherence counselling is performed if the VL result is not suppressed. Refer to your local guidelines on the use of VL.



Care of the HIV-exposed baby

Routine care

- Every infant born to an HIV-positive mother should receive NVP once a day (according to weight) for 6 weeks post delivery (see Table 4.1). NVP prophylaxis can be stopped at 6 weeks if the mother continues to take triple therapy or if the infant is exclusively formula fed.
- At 6 weeks, all HIV-exposed babies should be commenced on cotrimoxazole syrup according to weight (see Table 4.2). Cotrimoxazole should only be stopped after a confirmed negative HIV test has been performed 6 weeks after cessation of breastfeeding.
- For late PMTCT presenters mothers should be tested for HIV and, if positive, started on TDF + 3TC + EFV. The baby should have a DBS PCR test performed and immediately be started on NVP syrup (dosing according to Table 4.1) for six weeks.
- Follow-up of the HIV-exposed baby in the first year should be monthly. Clinic visits for mother and child should ideally coincide, i.e. a 'one-stop service' and the child should also receive Expanded Programme on Immunisation (WHO EPI) vaccinations at the same scheduled visits.
- Weight, height and ideally head circumference should be plotted on the standard centile charts at each visit.

Table 4.1 NVP infant dosing guide

Drug	Birth weight or age	Dose	Quantity (once daily)
NVP syrup (10 mg/ml)	Birth to 6 weeks 2 000–2 499 g* birth weight	10 mg/day	1 ml
	Birth to 6 weeks ≥2.5 kg birth weight	15 mg/day	1.5 ml
	6 weeks to 6 months	20 mg/day	2 ml
	6 months to 9 months	30 mg/day	3 ml
	9 months to end of breastfeeding	40 mg/day	4 ml

* Infants weighing <2 000 g should receive mg/kg dosing; the suggested starting dose is 2 mg/kg once daily.

Note: Premature babies need reduced dosing.

Table 4.2 Cotrimoxazole prophylaxis dosing guide

Drug	Strength of tablet or oral liquid (mg or mg/5ml)	3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg	25–34.9 kg
CTX	Suspension 200/40 per 5ml	2.5ml	5ml	5ml	10ml	10ml	-
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	-
	Tablets (scored) 400/80 mg	-	half	half	1	1	2
	Tablets (scored) 800/160 mg	-	-	-	half	half	1

- The baby should be examined and history taken for any TB signs, symptoms or contacts. For more information on how to examine an infant, see Chapter 5.
- Immunisations should be given as per national standard EPI schedule for HIV-exposed infants. If the baby is confirmed HIV positive, consult MSF immunisation guidelines and local protocols regarding administration of BCG and measles vaccine.
- Give a multivitamin containing vitamin A until HIV infection is excluded or, if unavailable, give mega-dose vitamin A as in Table 4.3.

Table 4.3 Dosage of vitamin A

Age of HIV-exposed or infected child	Dosage of Vitamin A	Schedule
6–12 months	100 000 IU	a single dose between 6 and 11 months of age
> 12 months	200 000 IU	a single dose at 12 months, then every 6 months until the age of 5 years



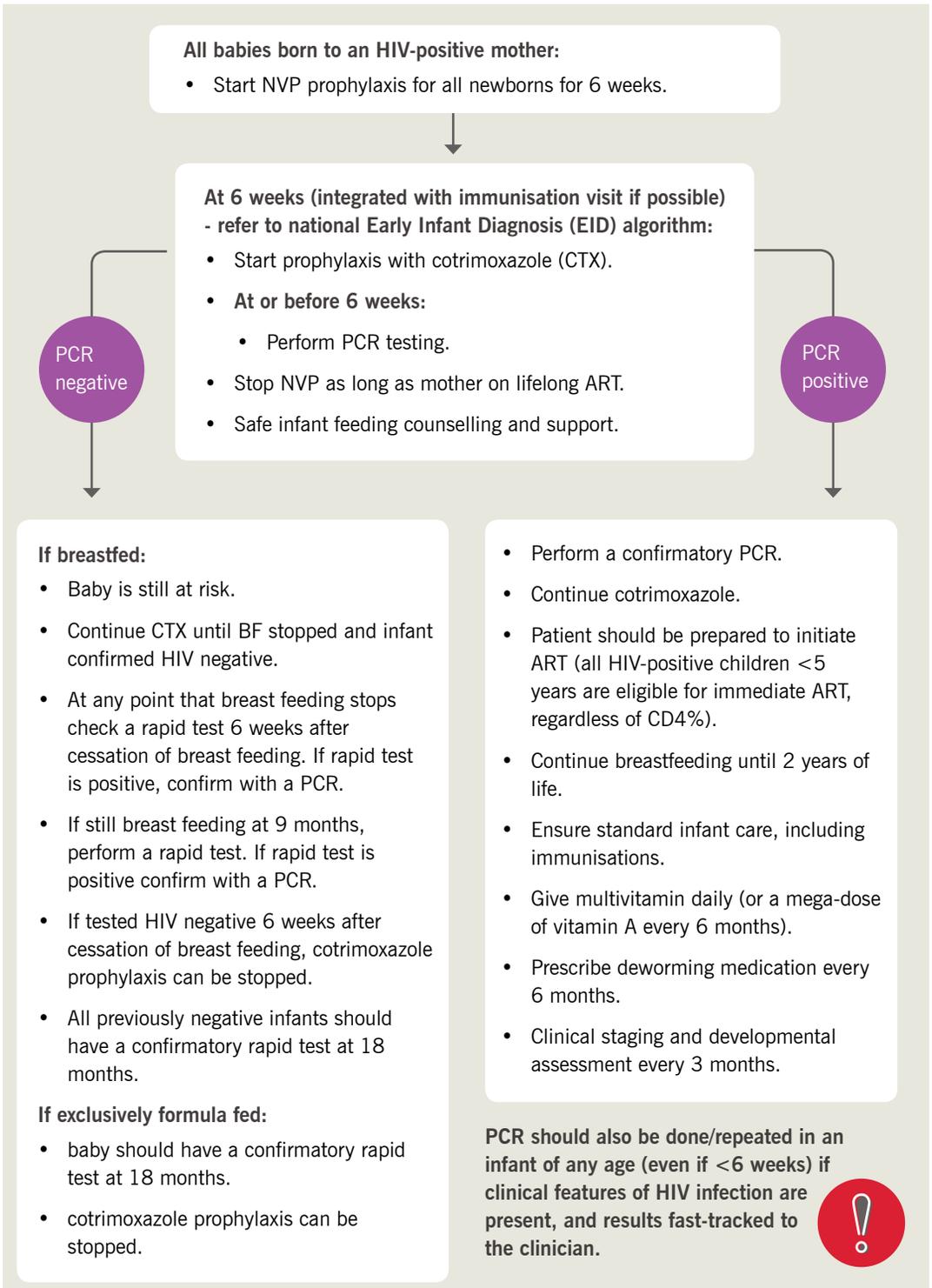
See National Guidelines

- Test for HIV as per Algorithm 4.2. This testing algorithm may vary according to setting. Refer to your local guidelines. The essential thing is that any positive PCR is confirmed either with a repeat PCR, or in some settings, HIV viral load testing.

Care of the baby when maternal HIV status is unknown

- **Abandoned babies:** If the mother's HIV status is unknown, perform an HIV rapid test as soon as possible:
 - If the rapid test is positive, initiate NVP syrup for 6 weeks and perform a DNA PCR test. If the baby is more than 6 weeks old at presentation, start cotrimoxazole prophylaxis.
 - If the rapid test is negative, do not give NVP syrup, but schedule the baby for a PCR test at 6 weeks anyway.
 - For these cases, access to formula feeding should be made available.
- The above management also applies to other cases in which the maternal status is unknown, including cases in which the mother is indisposed due to severe illness, coma, mental illness or death.

Algorithm 4.2 Management of HIV-exposed babies when mother on triple ART during breast feeding



Infant feeding

General considerations



www.samumsf.org

Counselling on infant feeding should be started during the antenatal period and continued postnatally. For details see www.samumsf.org for the PMTCT counselling guide.

Unless formula feeding is '100% available, feasible, affordable, sustainable and safe' (AFASS) for a minimum of six months, all babies should be exclusively breast fed for the first six months. Exclusive breastfeeding for six months is the usual recommendation for all resource poor settings in which we work.

Discourage mixed feeding as it increases the risk of childhood infections and the risk of HIV transmission.

For breastfeeding mothers:

- Within one hour of delivery ensure correct latching occurs (enough areola in the mouth) to prevent cracked and sore nipples.
- Mother to check the baby's mouth regularly for sores.
- Assess mother's nutritional status. Check BMI. Refer to dietician if necessary.
- No bottles, teats or pacifiers.

Formula feeding does need to be made available in situations where the mother is too sick to breastfeed or where the child has been orphaned.

If formula feeding is chosen:

- Advise patient to strap breasts to inhibit milk supply. Advise patient on management of breast engorgement: express milk, apply cold cloths.
- At each visit ensure patient can mix formula properly and is cleaning utensils adequately. Give clear guidance regarding volumes and frequency of feeding needed at each age.
- Discuss dangers associated with bottle-feeding. Discuss and demonstrate cup feeding as a recommended alternative to bottle feeding.
- Discuss home support for avoiding all breastfeeding; ensure that the woman has a carer/supporter outside the health facility to help her avoid all breastfeeding.

Exclusive breastfeeding during the first 6 months of life means that the baby gets **only** breast milk (no formula, tea, water, cereal, traditional medicines), oral polio vaccine and cotrimoxazole prophylaxis. Medications prescribed at the health centre or hospital to treat inter-current medical problems are also allowed. Likewise, exclusive formula feeding means baby gets only formula (no breast milk.).

Before 6 months of age, the infant does not need any food other than milk to grow. After 6 months, complementary foods are necessary for the infant's growth and should be introduced even though the breastfeeding mother is encouraged to continue breastfeeding beyond 6 months.

Weaning from breast milk is recommended at 12 months. Weaning **does not have to be rapid**. Remember that the baby is still protected via the mother's antiretroviral therapy (assuming that the HIV viral load has fallen to undetectable). If another source of milk is not available, breastfeeding can be continued. If the baby tests positive for HIV, breastfeeding can continue for up to two years.



HIV in children

How do children acquire HIV?

Disease progression

Which children should be tested for HIV?

Assessment and follow up of HIV-exposed
and infected children

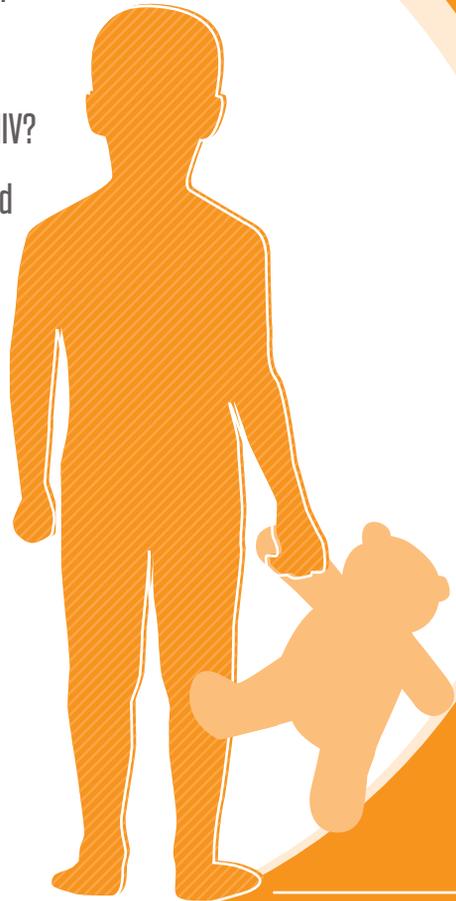
Treatment with ARVs

Adherence

Process of disclosure

Measuring response to therapy

Switching to second-line ART:
when and to what?



With a little practice you will find that caring for children with HIV is not so difficult, even though they are not simply 'little adults'. As they grow, children's emotional, intellectual and social needs change. Importantly, **doses of medications must be constantly adjusted to the child's weight.**

Remember to communicate with children the way you would communicate with them in your home. Making children feel at ease is essential. Simple gestures count, like calling the child by his name, asking her about a favourite hobby or a best friend, and involving him in the discussion (not only the caregiver).

For adolescents and young adults peer support becomes increasingly important. Having staff members who are non-judgmental and who take into account the specific medical and psychosocial needs of this age group is essential, in order to achieve good adherence.



HIV exposed

This term is used for children born to HIV-infected mothers, when the child's status is not yet confirmed. Diagnostic tests are needed to determine the HIV status.

HIV infected

This term implies that definitive testing has been done to confirm HIV infection.

- A positive HIV DNA PCR (which detects viral DNA) is diagnostic in infants and children under the age of 18 months. It is standard practice to confirm a first positive PCR result by repeating HIV testing, either with another PCR test, or with an HIV viral load (consult your national guidelines).
- For children above 18 months of age, **two positive rapid HIV tests** (which detect antibodies) are adequate to confirm HIV infection. Such antibody tests are generally not used before 18 months of age, since the child's blood can still contain some of the mother's antibodies, and it is not possible to know for sure if the antibodies are the child's or the mother's.

Age categories for adolescents and young adults

- Young adolescents: 10–14 years
- Older adolescents: 15–19 years
- Young adults: 20–24 years



See National Guidelines

How do children acquire HIV?

More than 90% of HIV infection in children is acquired through mother to child transmission during pregnancy, labour and delivery, and later through breastfeeding. Thus it is important to implement effective strategies for PMTCT (see Chapter 4). Other ways children can become infected are: through transfusion with contaminated blood; sexual abuse; or injury with contaminated sharp objects, such as razors, needles or non-sterile circumcision instruments. As children become adolescents, risk factors for HIV become the same as those found in adults.

The risk of HIV transmission through breastfeeding can be reduced if the HIV-positive mother is on lifelong ART. These children require an age-appropriate HIV test following cessation of breastfeeding after the ‘window period’ (see Algorithm 4.2 on page 51). A final rapid test should also be performed at 18 months for all HIV-exposed children.

Disease progression

Infants and children have an immature immune system and are thus less able to suppress HIV viral replication once infected. Hence, HIV disease can progress much more rapidly in infants and children than it does in adults. This is particularly true for infants less than 12 months of age. If untreated, approximately 40% of HIV-infected children will die by their first birthday, and 50% will have died by the age of two.



The goal is to manage HIV-infected infants and children BEFORE they get sick. All HIV-exposed infants and children <18 months should be tested according to Algorithm 4.2 on page 51, and, if found to be positive, started immediately on ART. If a child <18 months is showing symptoms/signs of HIV infection that fit criteria for presumptive diagnosis for HIV infection (see page 65) then treatment should be started whilst waiting for the test result – unless the result can be available within 1–2 weeks.

Which children should be tested for HIV?

Unfortunately, HIV diagnosis in children is often delayed. In addition to thinking more about testing children, it is important to look out for signs and symptoms that suggest HIV infection; if an infant is not growing and developing well (‘failing to thrive’) and/or has frequent diarrhoea or lung infections, then the child should be tested or re-tested for HIV. If the PCR result is delayed and the infant has symptoms/signs of HIV infection, do not wait for the PCR result: prepare to start the child on ART immediately.

Opportunities for testing children, including those who are ‘well’ (in addition to following the early infant diagnosis algorithm for known exposed babies) are

in EPI/vaccination clinics and 'under five' clinics. Many children – particularly if they were infected during the breastfeeding period – may present late in the course of HIV infection. Provider-initiated testing and counselling (PITC) should also be offered to children and adolescents in all health facilities, in inpatient and outpatient settings. Moreover, testing of family members of index cases should be done as soon as possible after the family member is diagnosed.



Remember to initiate counselling and testing for HIV for the following children:

- all children known to be HIV-exposed (Algorithm 4.2)
- infants with unknown or uncertain HIV exposure being seen in health care facilities at or around birth or at the first postnatal visit, or other child health visit
- children with HIV-positive parents or siblings
- children diagnosed with TB, severe pneumonia or severe malnutrition
- orphans, abandoned children, and children in whom maternal status is unknown (see page 50)
- children with signs and symptoms of HIV infection⁹, including children with pneumonia, persistent diarrhoea, ear discharge (acute or chronic), very low weight for age, oral thrush, parotid enlargement, generalised lymphadenopathy.
- children who have experienced or been at risk of sexual assault (see page 242).

Assessment and follow up of HIV-exposed and infected children

Birth history

- PMTCT regimen use by mother and baby
- mode of delivery (C-section or vaginal)
- complications
- feeding choice.

⁹ According to the IMCI 2008 classification (*Integrated management of childhood illnesses for high HIV settings: chart booklet*.) IMCI is a joint WHO/UNICEF initiative.

Interim history

- changes or new illness since last visit
- child's appetite and feeding practices
- any new developmental milestones or loss thereof
- TB and other illnesses in the household
- new medication
- adherence to previously prescribed medications (e.g. cotrimoxazole prophylaxis).

Parental concerns

- Note: Parents often recognise problems first.

Social and psychosocial history

- maternal health
- source of income
- support structures, availability of a second caregiver
- disclosure to child and to others (see page 69 for general guidelines on disclosure to children and for tools of disclosure see www.samumsf.org)
- problems with substance abuse, family violence
- assess understanding of issues.



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Tips for the physical examination

- If possible, examine the child in the presence of caregiver.
- Engage the child (not only the caregiver).
- Observation is very important.
- Be creative and adaptable; use play when possible.
- Perform potentially uncomfortable procedures last (such as mouth and ear examinations).
- Children should be undressed for all physical examinations.
- Ear, nose and throat (ENT) examination is essential. **(To look in the ears and mouth you will need an otoscope and a tongue depressor.)**
- Poor growth is one of the most important indicators of HIV disease in HIV-exposed babies and of disease progression in HIV-infected children.

- Document weight, height and head circumference on the centile charts and note any decline across the centiles.
- Weight should be plotted at every visit for all children.
- Length, head circumference (HC), should be plotted monthly for infants < 1 year.
- For children 1 year and older, height and HC should be measured and plotted every 3 months (HC up to 3 years).
- Perform a full systems examination, keeping in mind diagnoses that influence clinical staging.
- Look for physical changes indicating HIV involvement, e.g. enlarged liver or spleen, thrush, lymphadenopathy, dermatitis, linear gingival erythema (red band gingivitis).
- Timing of the next follow-up assessment should be targeted according to history and previous findings.



See Appendices 27 and 28

Growth and nutrition

(See Appendix 27 and Appendix 28.)

Growth progression is one of the best indicators of a child's overall health.

- Monitor weight, length/height, head circumference and nutritional status (weight/height or mid-upper arm circumference, oedema).
- Plot these parameters on growth charts.
- Conduct routine deworming every 6 months:

Age	Weight	Albendazole
12 up to 24 months	< 10 kg	200 mg single dose
>24 months	10 kg or more	400 mg single dose

- Advise parents about safe food preparation (e.g. washing hands, sterilising teats and other utensils, using clean water, preparing one feed at a time, etc.).
- Advise care givers about improving the nutritional value of meals, e.g. adding vegetable oil, margarine or peanut butter to the child's porridge, samp, rice or potatoes.
- If child is failing to thrive, look for treatable causes and manage these appropriately, e.g. chronic diarrhoea, TB, malnutrition.
- Food supplementation or therapeutic feeding may be indicated (follow national nutrition guidelines).



See National Guidelines



Monitoring growth in children is essential.

Severe acute malnutrition

Children with severe acute malnutrition must be identified and managed correctly, including giving therapeutic feeding.

Stunting in children

Stunting means that children are not growing well in height. A child may appear to be proportional (normal weight-for-height) but still be stunted (height-for-age <third centile). Chronic malnutrition in the HIV-infected child can cause this to happen. This is another reason why it is so important to measure all the growth parameters of children, including weight and height (and head circumference for the child <3 years) and to evaluate these (by plotting them on curves, e.g. weight-for-age, weight-for-height and height-for-age).

Developmental assessment

- Measuring and plotting head circumference can help to identify microcephaly (head circumference below -2 standard deviation for age and sex) or poor brain growth (stagnation and failure of the head circumference to grow).
- Abnormal development should raise concern of HIV disease progression or treatment failure.
- Loss of previously attained milestones could be a sign of HIV encephalopathy: in this case, refer immediately for ART.
- Ask the caregiver about the child's achievements and their concerns.

Table 5.1 Developmental checklist

1 month	Raises head, alert to sound, makes crawling movements.
2 months	Holds head at midline, lifts chest off the table, smiles.
4 months	Rolls front to back, laughs.
6 months	Sits supported, babbles.
9 months	Pulls to stand.
12 months	Walks alone, uses single words.
18 months	Can remove garment, scribble, run.

Table 5.2 Developmental warning signs

6 weeks	No eye contact, no smile, poor suck, floppy excessive head lag.
6 months	Doesn't reach for object with both hands, no response to sound, poor social response to people.
10 months	Unable to sit unsupported, hand preference, fisting. Persistence of primitive reflexes.
12 months	Unable to bear weight on legs.
18 months	No walking. No single word with meaning.

Dental evaluation

Dental caries (tooth decay) and periodontal disease are common in HIV-infected children of all ages.

- Advise and encourage good oral hygiene.
- Refer to dentist when indicated.

Management of inter-current medical problems

These include common childhood infections, skin conditions, tuberculosis, etc. These are discussed in detail in other chapters.

Immunisation

- All children should be immunised according to the national immunisation schedule and according to the WHO Expanded Programme on Immunisation (EPI).
- Immunisation is of vital importance in preventing and reducing the severity of some conditions in HIV-infected infants.



Hepatitis B vaccine: all newborns should be vaccinated within 24 hours of life. Monovalent vaccine should be used for birth dose. Pentavalent vaccines can be given subsequently.

Pneumococcal vaccine: Pneumococcal conjugate vaccine (PCV 10 or 13) should be given to all HIV-infected or HIV-exposed children under 5 years of age, regardless of immune status.

If Hepatitis B and PCV are not part of the EPI programme, strong lobbying should be performed so they are added.

BCG vaccination

- BCG vaccination should routinely be given to newborns at birth, except if the mother has pulmonary TB. In this case, INH prophylaxis therapy (IPT) should be given to the baby (if asymptomatic) for 6 months according to protocol (see page 111).
- If BCG vaccination is delayed because the mother has TB, the HIV-uninfected, exposed infant may receive vaccination 2 weeks after completion of IPT (provided active TB is excluded).
- A child who is known to be HIV-infected should not receive BCG.
- HIV-exposed infants who receive BCG should be closely followed to provide early identification and treatment of any BCG-related complication.

Cotrimoxazole (CTX) prophylaxis

(Also see Appendices 2A and 2B.)

If taken regularly, CTX protects against:

- pneumonia, especially PCP
- cerebral toxoplasmosis
- certain types of diarrhoea
- other bacterial infections, such as UTI
- malaria.

HIV-exposed infants:

- Cotrimoxazole should be given to all HIV-exposed infants from 6 weeks of age.
- Cotrimoxazole can be stopped after a definitive HIV-negative test (at least 6 weeks after cessation of breast feeding).

HIV-infected infants:

- Cotrimoxazole should be given to all HIV-positive infants age <1 year until the age of 5 years.
- After the age of 5 years, cotrimoxazole may be stopped as per the adult guidelines (e.g. two consecutive CD4 counts >350 or 200 cells/ μ l after a minimum of 12 months on ART). Refer to your national guidelines.
- Cotrimoxazole should be given according to the weight of the child (see Table 5.3).



See Appendix 2A and 2B



See National Guidelines

Table 5.3 Cotrimoxazole prophylaxis dose

Formulation of CTX	3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg	25–34.9 kg
Suspension 200/40 mg 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	-	Half	Half	1	1	2
Tablets (scored) 800/160 mg	-	-	-	Half	Half	1

Treatment with ARVs

When to start ART in children¹⁰

- ART should be initiated in all HIV-infected children below five years of age, regardless of WHO clinical stage or CD4 cell count.
- ART should be initiated in all HIV-infected children five years of age and older with a CD4 count <500 cells/ μ l.
- ART should be initiated in all children infected with HIV with severe or advanced 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 (See page 65), if virological testing is not available or results are delayed by more than 1–2 weeks.



See National Guidelines
(Appendix 4B)

(For national guidelines see Appendix 4B.)

Table 5.4 When to start ART in children

Age	When you start
Infants (<1 year)	Treat all individuals.
1 year to <5 years	Treat all individuals (children \leq 2 years or with WHO stages 3 or 4 or CD4 count \leq 750 cells/ μ l or <25% as a priority).
5 years and above	WHO stages 3 or 4 or CD4 \leq 500 cells/ μ l (CD4 \leq 350 cells/ μ l as a priority).

¹⁰ WHO. 2013. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. ISBN 978 92 4 150572 7.

Presumptive diagnosis of HIV in infants under 18 months

Criteria for presumptive diagnosis for initiation of ART in infants <18 months of age where virological confirmation of infection is not available:

- infant is HIV antibody positive (ELISA or rapid test), and
- diagnosis of any AIDS-indicator condition(s) can be made, or
- infant is symptomatic with two or more of the following:
 - oral thrush (recurrent or chronic)
 - severe pneumonia
 - severe sepsis.

Other supporting factors supporting the diagnosis include:

- recent HIV-related maternal death or advanced HIV disease in the mother
- CD4 <20%.



Integrated Management of Childhood Illnesses (IMCI)¹¹ definitions:

Oral thrush: Creamy white to yellow soft small plaques on red or normally coloured mucosa, which cannot easily be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender.

Severe pneumonia: Cough or difficult breathing in a child with chest indrawing, stridor or any of the IMCI general danger signs; i.e. lethargic or unconscious, not able to drink or breastfeed, vomiting, and presence or history of convulsions during current illness; responding to antibiotics.

Severe sepsis: Fever or low body temperature in a young infant with any severe sign such as fast breathing, chest in-drawing, bulging fontanel, lethargy, reduced movement, not feeding or sucking breast milk, convulsions.



If a child is sick a PCR can be taken at any time to confirm diagnosis. However, do not wait for DNA PCR results to start ARVs in a sick infant who fulfils the criteria for presumptive diagnosis of HIV infection. Start ARVs immediately.

¹¹ According to the IMCI 2008 classification (*Integrated management of childhood illnesses for high HIV settings: chart booklet*.) IMCI is a joint WHO/UNICEF initiative.

What ART to start in children



See National Guidelines
(Appendix 9B)

Table 5.5 shows which first-line ART regimens are recommended by WHO for children according to their age and weight. Note that recommendations may vary slightly from country to country, due to availability of paediatric formulations. Refer to Appendix 9B for national guidelines.

- For children older than 10 years and weighing >35kg the preferred regimen is the same as for adults: TDF + 3TC + EFV.
- For children 3 years to 10 years, plus adolescents weighing <35kg, use ABC + 3TC + EFV.
- For all children <3 years of age, use ABC or AZT together with 3TC and lopinavir/ritonavir (LPV/r). In settings where LPV/r is not yet available to all children <3 years, it must be given in priority to babies who received NVP or whose mothers were exposed to any ARVs as part of a PMTCT intervention. If the mother did not undergo PMTCT and LPV/r is not readily available, then the regimen of choice is ABC or AZT, together with 3TC and NVP.

Table 5.5 WHO first-line regimens

First-line ART	Preferred first-line regimens	Alternative first-line regimens ^{a b}
Adults (including pregnant and breastfeeding women and adults with TB and HBV coinfection)		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Adolescents (10 to 19 years) ≥35 kg	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP ABC + 3TC + EFV (or NVP)
Children 3 years to less than 10 years and adolescents <35 kg	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

Notes:

- For adolescents, using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used and to the shortest time possible, with close monitoring. For children, d4T use should be restricted to the situations in which there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible.
- ABC or boosted PIs (ATV/r, DRV/r, LPV/r) can be used in special circumstances.

Baseline clinical and laboratory investigations prior to initiation of ART in children

Baseline investigations may vary in different settings. (Refer to Appendix 7B for national criteria.)

Some elements that will be common throughout are:

- child's height and weight, head circumference and nutritional status
- clinical staging
- screening for TB symptoms
- developmental level
- CD4 count (or CD4 % if <5 years)
- FBC for all children at baseline
- ALT (if planning to use an NVP-based regimen)
- Creatinine if planning to use TDF.



See National Guidelines
(Appendix 7B)

Notes on prescribing ARVs in children

- Dosing must be based on weight or body surface area (BSA). Therefore it is **essential** that the child is properly weighed at each visit and the dose adjusted.
- Giving the child too little medication for his/ her weight will cause the HIV to more quickly develop resistance.
- Giving the child too much medication for her/his weight will increase the risk of drug-related side effects.



Do not:

- copy the dose your colleague wrote at the last visit.
- weigh the child by getting the mother to stand on the scale with and without the baby.

Salter scales should be available in all clinics to weigh the baby accurately.

- ARV dosing charts based on the child's weight should be used (see Appendix 5B and 5C).
- NVP is prescribed once daily for two weeks at initiation (i.e. the induction phase) followed by twice daily thereafter.
- Switch from syrups to tablets/capsules as soon as possible.
- LPV/r syrup denatures unless it is kept in a cool, dry place at a temperature <25° C. It should not stay out of the fridge for more than 42 days, so ask the caregiver to refrigerate it if possible. If not possible, an alternative is to keep it in a cool clay pot. A heat stable formulation will be available soon.



See Appendix 5B & 5C

- Young children who start on a LPV/r based regimen should remain on the same regimen even after reaching three years or ten kilograms unless a substitution of one ARV or switch to second-line regimen is indicated for reasons of toxicity or treatment failure, respectively.
- Avoid using LPV/r oral liquid 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. The calculation for dosing children younger than six weeks should be based on body surface area.

Adherence

In non-urgent cases, try to get an idea of any challenges there may be with respect to adherence, prior to initiating ART in the child. Note whether:

- The child attends the booked visits for ART preparation on time, with the caregiver.
- The caregiver gives current medications regularly and appropriately to the child (e.g. cotrimoxazole or TB medicines). The following 4 key questions should be addressed:
 - Who will be administering the medications?
 - What medications will be given?
 - When will medications be given?
 - How will medications be given?

The nurse or counsellor should observe how the caregiver prepares/gives the medication.

Note that all HIV-positive children should already be on cotrimoxazole prophylaxis, which gives an opportunity to assess adherence.

Adherence poses additional challenges in children for several reasons. Some of these are:

- The young child is dependent on his/her caregiver to administer the medication at the right time and in the right dosages.
- Fewer fixed-dose combinations (FDCs) for children exist. (Soon fixed-dose combinations for the PI-based regimens and a paediatric formulation for TDF will become available.)
- Sometimes the child must take syrups which he/she may not like the taste of.
- The caregiver may change and the child has to get used to a new person.

Assess adherence at every visit and use every interaction with the caregiver and child to re-enforce the absolute need for adherence. Also remember that just because a child is adherent today, does not mean that he/she will stay adherent. In particular, as children become adolescents, adherence can become a new challenge.



Ongoing education and support of families

Providing ongoing counselling for the child and caregiver is essential. Adapted paediatric counselling tools are available at www.samumfsf.org.

Process of disclosure



Disclosure

Disclosure to a child about his or her HIV status is VERY important and can be a major factor in how the child adheres to treatment.

Disclosure is the process by which the child learns about his/her HIV status. One can distinguish between **partial** disclosure (giving the child information about what is happening in his/her body without naming the virus and the disease) and **full** disclosure (telling the child he/she is infected with HIV and giving him/her all the information needed about HIV).

For all children <12 years, it is usually recommended to use **progressive** disclosure, starting with partial disclosure. All 6–9 year olds should have reached partial disclosure, in which children are given information about what is happening in their body without naming the disease. Full disclosure, where the disease is then named as HIV should be achieved by the age of 12.

Caregivers are often very hesitant to disclose to the child. Some of the common reasons for this hesitance (among many others) are:

- belief that the child is too young to know
- fear that the child cannot maintain a secret
- shame – the mother may feel ashamed to talk to the child about the transmission of the disease.

There are many reasons why a child should be told he/she is HIV positive. Some of these are:

- Honesty is important in the child-caregiver relationship.
- Children often know the truth before we expect or think they do.
- Children often cope with the truth better than we anticipate.
- Secrecy may be associated with increased behavioural problems.
- Disclosure can provide the child with a sense of control over their lives.
- Children should know why they go to the hospital and have blood taken regularly.
- It's their right to know.

- If they know their status, they can protect others from infection.
- Knowing their status gives the child permission to talk openly about HIV with caregivers.

Nurses, doctors, and counsellors have an important role to play in helping caregivers through the process of disclosure. This can take time.

Start the disclosure process¹² as early as possible; at the latest, when the child starts asking questions. The longer we wait, the bigger the risk of losing the child's trust. The more the secret lasts, the more difficult it will be to break the silence.

Provide information about:

- being sick
- going to the doctor
- the body
- blood circulation
- germs and getting sick
- our defences (immune system)
- the immune system needing assistance from drugs
- the specific virus the child has (name the virus and the illness: HIV)
- the CD4 count (and/or viral load if available)
- transmission and non-transmission of HIV
- sexual relations and condoms use.

Discuss with the child with whom the secret should be shared.

Always achieve total disclosure before adolescence.

Measuring response to therapy

Clinical, CD4 and viral load monitoring

We measure the success of ARVs in children in the same way as we measure it in adults. In children, we often notice clinical improvement quite rapidly. The child will gain weight and he/she will feel much better. Usually, the caregiver will notice a big improvement in the child's progress once ARVs are started. Often the caregiver will be the first one to tell you that the child is now playing, not sick as often, and doing things she/he wasn't able to do before.

Don't forget to weigh the child at every visit and plot the child's weight on a growth curve. This is one of the most sensitive indicators of treatment success.



If the child is getting worse in the first months of treatment instead of getting better, you must suspect IRIS: look carefully for any undiagnosed OIs, especially TB.

How the child is developing can help us decide when the child needs ARVs (see section on HIV encephalopathy, page 194) and it will help us see how the ARVs are working. It is important to ask the caregiver how the child is progressing and assess the child's development every three months by using the developmental checklist (Table 5.1, page 61).

Similar to adults, the child's CD4 count should gradually increase on ARVs and the viral load should become undetectable. Frequency of viral load testing should be according to the viral load algorithm (see page 39 and Appendix 13B). In some contexts testing may be more frequent for children – refer to national guidelines (Appendix 7B).



See Appendix 13B



See National Guidelines
(Appendix 7B)

Table 5.6 Definitions of clinical, immunological and virological failure in children

Failure	Definition
Clinical failure	New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 or 4 condition with exception of TB) after 6 months of effective treatment.
Immunological failure	Younger than 5 years: Persistent CD4 levels below 200 cells/ μ l or <10%. Older than 5 years: Persistent CD4 levels below 100 cells/ μ l.
Virological failure	Plasma viral load above 1000 copies/ml, based on two consecutive viral load measurements after 3 months, despite adherence support.

Side effects

ART-associated side effects occur in children as well as adults. Fortunately, they are seen less commonly in children. However, this means that they may be missed when they do occur. Vigilance and proper education given to the caregiver can help avoid this. For more information on side effects and management see section on side effects, see Chapter 6.

Switching to second-line ART: When and to what?

The same viral load follow-up criteria apply to children and adults, and children should be considered for second-line treatment if the repeat viral load after 3 months is >1000 copies/ml, despite enhanced adherence support. In-depth assessment of adherence is essential and often includes a home visit in the context of a child failing ART. The decision to switch a child to second-line ART should be made by a multidisciplinary team composed of a clinician (doctor, clinical officer), nurse and counsellor.



General considerations prior to defining treatment failure in children:

- Check the child has been on therapy for at least 24 weeks.
- Check adherence first. This is the most common reason for treatment failure.
- Who is the caregiver? Are there multiple caregivers? Would it be useful to do a home visit?
- If it is not possible to improve adherence, attempt directly observed therapy (DOT) with a health care worker or another adult living in the same house.
- Treat any inter-current opportunistic infections.
- Exclude IRIS.
- Ensure adequate nutrition.



See WHO Guidelines
(Appendix 13A)



See National Guidelines
(Appendix 9B)

Which second-line art regimen?

The choice of second-line ART regimen will depend on the age of the child and which first-line ART combination has been used. Appendix 13A outlines the WHO second-line regimen options according to age and the initial first-line regimen used. These regimens may vary according to your setting. See Appendix 9B for national guidelines.

Side effects of ART

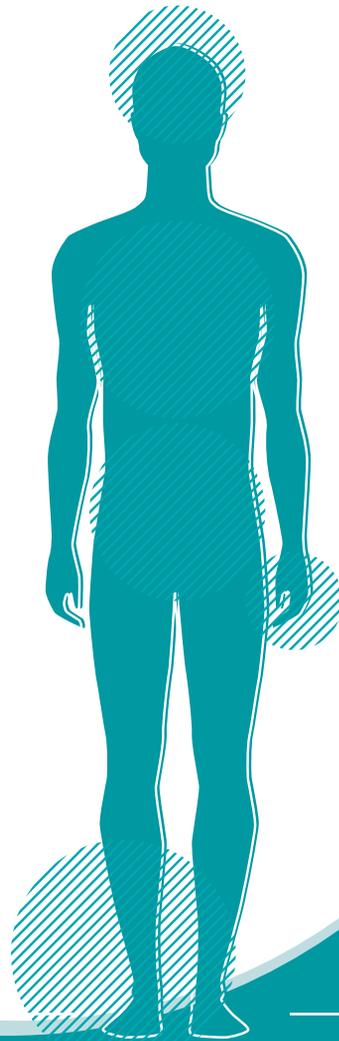
Approach to management of side effects

Common side effects of ARVs

Serious side effects of ARVs

Other possible late side effects

Common drug interactions



Approach to management of side effects

If a patient presents with a new symptom (rash, fever, abdominal pain, weight loss), you should ask the following questions:

1. What, since when and how is the symptom improving or worsening over time? (See Appendix 10A for common presentations of symptoms.)
2. Is the symptom related to:
 - ARVs?
 - other medication used to treat OIs (TB drugs/amphotericin B for CCM/cotrimoxazole)?
 - other medical condition?
3. How severe is the side effect (grades 1 → 4)? (See Appendix 10B.)
4. Should the ARV be decreased, stopped or substituted?
5. How do I counsel the patient?



See Appendix 10A



See Appendix 10B



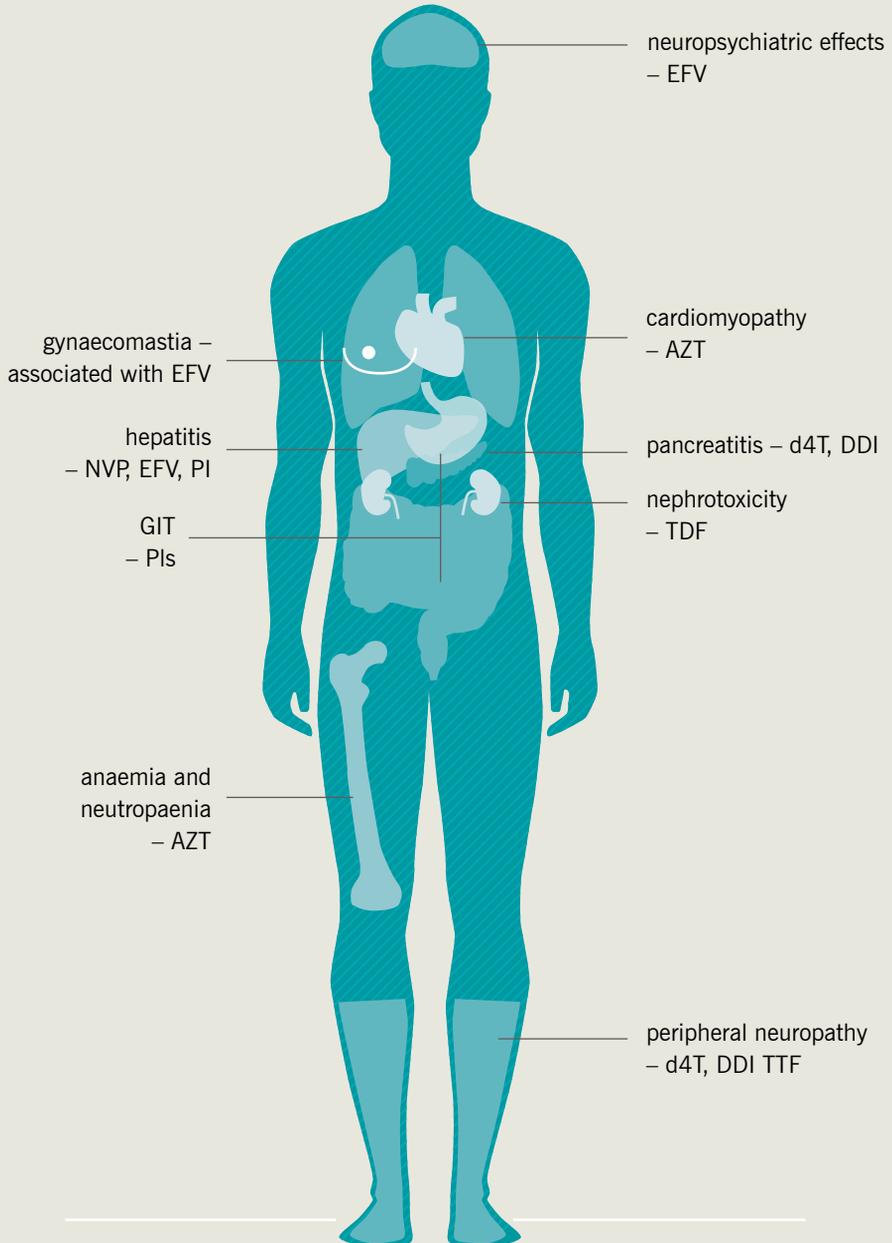
- Not every person starting ARVs will suffer from side effects. Only some patients will experience side effects and each patient should be educated about the symptoms they may experience.
 - Instruct the patient to report any side effects early and not to stop any drugs without consulting the nurse or doctor first.
 - Side effects are more common in severely immune-compromised (CD4 <200) patients. One exception to this is nevirapine (NVP) and hepatitis.
 - Side effects can be the result of a number of different drugs used to treat or prevent OIs, which may complicate the diagnosis and management, e.g. a drug rash may be related to NVP, TB medications or cotrimoxazole.
 - A careful drug history (illustrated with a timeline) is of the utmost importance to make the correct diagnosis. However, if the side effect is very severe, all potential causal drugs should be stopped.
 - Side effects can also be classified into those occurring early vs those occurring late. (See Appendix 10A.)
 - Side effects can be graded (1 → 4) to help differentiate between minor and major problems. (See Appendix 10B).



See Appendices 10A & 10B

Look at the following diagram for a quick overview of common ARV-related side effects and the drugs that cause them.

Some of the side effects of ART are listed in the figure below.



Common side effects of ARVs

The following side effects are more commonly seen in those on ARVs:

Nausea and vomiting

- All drugs can cause nausea and vomiting, but it is more commonly seen with DDI, AZT, and protease inhibitors (PIs).
- Nausea already occurs in some HIV patients to some extent. It can become worse when ARVs are initiated, but ARV-related nausea is usually 'self-limiting' (resolves on its own after several weeks of therapy). There is usually no treatment needed. (Metoclopramide 10 mg three times daily as required may help if the nausea is severe.)
- Change of drug intake times may help to some extent (for example, DDI can be tried two hours after breakfast instead of one hour before breakfast).
- The more drugs a patient has to take, the more likely there is to be nausea and vomiting (for example, when a person must take ARVs and TB drugs together).
- If the ARVs are regurgitated, tell the patient to take the pills again two hours later. If the vomiting is very severe or does not stop, then the patient must be clinically assessed.



Take immediate action if the vomiting:

- is associated with serious symptoms such as fever, severe rash, and/or jaundice (must **exclude hepatitis**).
- is very severe and does not stop over several days (correct any dehydration).
- is associated with abdominal/epigastric pain (must **exclude pancreatitis and hepatitis**).
- occurs in patients who are >4–6 months on ARVs (especially d4T and DDI) and is associated with weight loss (must **exclude high lactate levels before lactic acidosis develops, see Algorithm 6.1**).

Rash

(See Chapter 9 Dermatology.)

- Rash is a typical side effect of the NNRTI class of ARVs. It is most commonly a concern with nevirapine (NVP); sometimes with efavirenz (EFV) or with cotrimoxazole.
- It typically occurs during the first 2–6 weeks of treatment, and is much more common with NVP than EFV. For this reason, only half of the usual dose of NVP is given during the first two weeks of treatment.

- Always recheck the 'liver blood test' (ALT) when you see a rash that might be associated with NVP.
- NVP can be continued in the presence of a mild rash (see below) by an experienced nurse or doctor.

For a mild rash:

- Continue the 'culprit drug' (usually NVP); consider extending the lead-in dosing, but see the patient every 2–3 days.
- Chlorpheniramine 4 mg three times daily as required may help reduce itching.
- Topical steroid such as betamethasone ointment may help (but do not use oral steroids).
- If in doubt about what to do, consult an experienced clinician.



Refer patient



Take immediate action (including substitution of the culprit drug) if the rash:

- is associated with serious symptoms such as fever, vomiting, or jaundice (must **exclude hepatitis**).
- is associated with a significant increase of ALT (>5 times the upper limit of normal for ALT, which works out to approximately ALT >200 in an adult).
- progresses and becomes **very severe** (with scaling and skin erosion).
- involves **mucous membranes** ('Stevens-Johnson rash').

All these patients need to be referred to hospital.



Refer patient

Dizziness and 'light-headedness'

- Can occur with efavirenz and zidovudine (AZT) and may be of particular concern to shift workers, e.g. long-distance drivers, security guards.
- If symptoms due to efavirenz, no specific action needed, except counselling as to the duration the side effect is likely to be experienced. This is why efavirenz is prescribed at bedtime.
- If the dizziness does not disappear after six weeks, EFV may need to be substituted with nevirapine.
- See Appendix 10B for other possible **psychological** side effects due to EFV.
- If there is a concern about anaemia causing the dizziness (sometimes occurring with AZT), check the haemoglobin and assess the need for blood transfusion (and substitution with another ARV) **if the Hb is low**.



See Appendix 10B

Peripheral neuropathy (PN)

(See Chapter 11 Neurological conditions.)

- Occurs most commonly with stavudine (d4T) and didanosine (DDI)



This possible side effect can become very debilitating if overlooked. Always question a patient taking d4T about painful feet and substitute with another ARV early.

- Never use d4T and DDI together, since this increases the likelihood of PN (and other side-effects).
- If a patient is on d4T and has symptoms of PN, substitute the d4T with another drug (usually TDF). This change should be made no matter the severity of the PN. It should be made sooner rather than later, as patients may have persistent neuropathic pain and/or difficulties walking if left for too long.
- Always check CrCl before starting TDF.
- Never substitute a single ARV if you suspect treatment failure and/or viral load is detectable.
- Treat PN as described in Chapter 11 Neurological conditions.

Serious side effects of ARVs

The following possible side effects are potentially fatal if missed or ignored:¹³

- Anaemia – AZT
- Nephrotoxicity (renal impairment) – TDF
- Hepatitis – NVP, EFV, or protease inhibitors (PIs)
- Hypersensitivity reaction – ABC, NVP
- Hyperlactataemia and lactic acidosis – d4T, DDI, AZT

Nephrotoxicity

(See Chapter 14 Renal disease in HIV.)

Nephrotoxicity is a **rare side effect** of tenofovir (TDF).

The risk of nephrotoxicity is higher in patients with:

- with underlying kidney damage
- with co-morbidities (diabetes, hypertension)
- using other nephrotoxic medication (chronic NSAIDs or aminoglycosides).

13 Southern African HIV Clinicians Society. 2012. Guidelines for antiretroviral therapy in Adults. *SAJHIVMED* 13 (3) <http://www.sahivsoc.org/upload/documents/Southern%20African%20Journal%20of%20HIV%20Medicine,%20Vol%2013,%20No3.pdf>



Note: Patients with MDR-TB who are taking an anti-TB injectable in the intensive phase (e.g. aminoglycosides) should avoid TDF. These at-risk patients should have a dipstick (check for proteinuria) or, preferably, the creatinine clearance (CrCl) calculated, and should avoid TDF if CrCl < 50 ml/min.

In adults taking TDF, renal function should be routinely monitored by calculating the creatinine clearance (CrCl).

Haematological toxicity

Haematological abnormalities are frequently encountered in HIV patients. Common causes include undiagnosed OIs (TB), drugs (ARV and OI drugs), HIV-related malignancies and the HIV virus itself.

A careful clinical assessment should be made regarding drug history, specifically AZT use (including traditional medications and herbs) and the detection of underlying, underdiagnosed OI's.

Drugs often implicated:

- AZT – anaemia (macrocytic), neutropaenia
- d4T – anaemia (macrocytic), neutropaenia (less common than with AZT)
- cotrimoxazole – anaemia, neutropaenia, thrombocytopaenia (often when used in high treatment doses).

(See Table 6.1 below.)

Other common causes:

- TB – anaemia (normocytic)
- Kaposi's sarcoma – anaemia (microcytic)

In patients with low CD4, **bone marrow infiltration** caused by Mycobacterium avium complex (MAC), fungal infections or lymphomas could lead to a **pancytopenia (anaemia, neutropaenia, thrombocytopaenia)**.

Table 6.1 Guidelines for managing haematological toxicity (mainly AZT-induced)

Hb	>8 g/dl Monitor.	7.0–7.9 Repeat 4 weeks. Reduce AZT 200 mg bd or consider switching AZT.	6.5–6.9 Repeat 2 weeks. Consider switching AZT.	<6.5 Switch AZT.
Neutrophils	1–1.5x10 ⁹ /l Repeat 4 weeks.	0.75–1.0 Repeat 2 weeks.	0.50–0.75 Repeat 2 weeks. Consider switching AZT.	<0.5 Switch AZT.

Hb = haemoglobin; AZT = zidovudine.



See Appendix 30

Hepatitis (inflammation of the liver)

- Hepatitis can occur **acutely** (associated with fever and rash as described above with NVP) or more **chronically** (with d4T or Ritonavir). For acute NVP-induced hepatitis, see also Appendix 10B.
- Hepatitis is more common when ARVs are used at the same time as TB medication and it may be difficult to assess which drugs are responsible. (See page 103 for management of TB/HIV hepatitis.)
- If the hepatitis is mild, then monitor the ALT regularly to ensure that it is not worsening.
- If the ALT result is becoming progressively higher, then the culprit ARV must be substituted with a new drug.
- If you suspect that a patient has severe hepatitis (**ALT >5 times upper limit of normal, jaundice and/or abdominal pain**), then **refer to hospital immediately**. This patient will need testing to exclude underlying HBV and HCV, full LFTs and an INR to check synthetic function of the liver. The patient may require an ultrasound. Depending on the severity, all drugs are discontinued and may require a stepwise re-challenge.
- ATV/r may cause jaundice but this is not due to hepatitis. If ALT and Hep screen is normal, the patient should not be concerned and ATV/r can be continued.



Refer patient

Table 6.2 Guidelines for managing hepatotoxicity

ULN*	<2.5 x ULN	2.5 - 5 x ULN	>5 x ULN
alanine transaminase (ALT)	Monitor.	Repeat at 1 week.	Discontinue relevant drug(s).
alkaline phosphatase (ALP)	Monitor.	Repeat at 2 weeks.	Ultrasound. Consider biopsy.
Bilirubin	Repeat at 1 week.	Discontinue relevant drug(s).	Discontinue relevant drug(s).

* ULN = upper limit of normal. Any elevations with symptoms of hepatitis (nausea, vomiting, right upper quadrant pain) should be regarded as an indication to stop relevant drugs.

Symptomatic hyperlactataemia and lactic acidosis¹⁴

This side effect has become less common with fewer patients starting ART with d4T and with the use of lower doses. However, clinicians should remain vigilant in patients receiving d4T and be aware that this side effect can occur with all other NRTIs, although very rare with ABC, TDF, 3TC and FTC. Mildly elevated lactate is not uncommon in patients treated with NRTIs, but is generally asymptomatic. Asymptomatic elevated lactate does not predict the development of lactic acidosis; it is therefore unnecessary to monitor levels in asymptomatic patients.



The potential of NRTIs to cause elevated lactate varies (from most likely to least likely):

stavudine/didanosine > zidovudine >
tenofovir/emtricitabine/lamivudine/abacavir.

Lactic acidosis is a serious, rare, potentially fatal side effect of NRTIs, most commonly associated with d4T, particularly when combined with DDI. Symptomatic hyperlactataemia without acidosis is more common, but seldom seen with the safer NRTIs recommended. (See Algorithm 6.1 on page 82.)



High lactic acid might also be caused by any situation of circulatory or respiratory failure (e.g. shock, severe infection, severe pneumonia). All these conditions have to be detected early and managed appropriately in order to prevent mortality.

14 Southern African HIV Clinicians Society. 2012. 'Guidelines for antiretroviral therapy in adults.' *SAJHIVMED* 13(3) <http://www.sahivsoc.org/upload/documents/Southern%20African%20Journal%20of%20HIV%20Medicine,%20Vol%2013,%20No3.pdf>

Algorithm 6.1 Risk factors and treatment for hyperlactataemia

The combination of d4T and DDI is associated with a high risk of symptomatic hyperlactataemia or lactic acidosis (particularly in pregnancy). This combination should therefore be avoided. Symptoms are non-specific and include nausea and vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

Risk factors and management for hyperlactataemia include:

female gender

obesity

the use of NRTIs for >6 months

the development of NRTI-induced peripheral neuropathy or fatty liver.

A raised lactate of >5 mmol/l together with metabolic acidosis confirms the diagnosis of lactic acidosis.

Lactate <5 mmol/l and bicarbonate >20 mmol/l and minor symptoms.

Lactate >5 mmol/l and bicarbonate >15 mmol/l.

Lactate >5mmol/l and bicarbonate <15 mmol/l.

Low serum bicarbonate (<20 mmol/l) is the most sensitive marker of acidosis. Associated abnormalities include elevated ALT and AST, lactate dehydrogenase and creatinine kinase. Treatment is supportive. High-dose riboflavin (50 mg) and L-carnitine may be used (no evidence for either intervention). Management depends on the lactate and bicarbonate concentrations.

NRTIs should be switched to agents less associated with hyperlactataemia: TDF or ABC (if these are unavailable, then AZT could be used) plus FTC or 3TC. Symptoms and serial lactate should be monitored for several months (lactate levels decrease slowly over weeks).

NRTIs should be discontinued and the patient should be admitted. If the patient is on an NNRTI regimen, a boosted PI should be added. If the patient has already failed an NNRTI and is on a boosted PI, RAL and/or etravirine (ETV) should be added, if available, or the patient should be continued on the boosted PI only. When lactate has normalised, the patient should be switched to TDF or ABC with 3TC or FTC, as above.

NRTIs should be discontinued and the patient should be admitted, preferably to an intensive care unit. If the patient is on an NNRTI regimen, a boosted PI should be added. If the patient has already failed an NNRTI regimen and is receiving a boosted PI, RAL and/or ETV should be added, if available, or the patient should be continued on a boosted PI only. Bicarbonate replacement is controversial, but most experts would use this strategy to partially correct severe acidosis. Broad-spectrum antibiotics are recommended as sepsis can mimic NRTI-induced lactic acidosis (this can be discontinued if procalcitonin is normal). On recovery, all NRTIs should be avoided in future regimens (some experts would be prepared to use safer NRTIs, as above).¹⁵

15 For further guidance: Southern African HIV Clinicians Society. 2006. 'Guidelines for the prevention, diagnosis and management of NRTI-associated symptomatic hyperlactataemia and lactic acidosis'. *Southern African Journal of HIV Medicine* 7: 8-15.

Hypersensitivity reaction (HSR) due to abacavir (ABC)

Caregivers must be warned about potential but rare (3%) hypersensitivity reaction (ABC HSR) which may include:

- fever (80% of cases)
- rash (70%, but often mild, non-pruritic and unnoticed)
- gastro-intestinal and respiratory symptoms (18% have cough, pharyngitis, dyspnoea)
- constitutional non-specific symptoms (myalgia, generalised malaise).

ABC should be stopped permanently if hypersensitivity reaction occurs, and never be re-challenged (recurrence might be fatal).

It's very easy to mistake a common viral infection for an HSR due to ABC, but the following can help:

- HSR usually occurs in the first six weeks after initiation on ABC (mainly first ten days).
- Symptoms worsen just after every new dose (and with every subsequent dose).
- Symptoms usually resolve after 48 hours from discontinuation.
- Never initiate ABC if the patient already has a fever or cough.
- Be cautious when initiating a patient on NVP and ABC at the same time. In the case of severe allergy, it would be difficult to ascertain the culprit drug, and a re-challenge would be too dangerous.
- Decision about stopping ABC should only be made by a health care provider (not by the patient himself or herself).
- The patient has to be given a 'patient alert card' to be shown, in case of symptoms, to any health care provider he/she might consult, to make the health care provider aware that he/she is taking ABC.)

Pancreatitis

- Didanosine (DDI) is the most common cause (d4T and 3TC occasionally).



Pancreatitis can be life-threatening.

- If possible check the serum amylase +/- lipase level whenever someone on ARVs presents with **abdominal/epigastric pain**.
- If in doubt, **admit to hospital for investigations**.
- Treatment is supportive.



Refer patient

Other possible late side effects

Lipodystrophy (fat redistribution)

- Can occur with PIs or NRTIs (especially d4T).
- Lipohypertrophy (fat accumulation): Patient will present with increased fat around the abdomen, breasts and/or back of neck.
- Lipoatrophy: Decrease in fat in face, limbs and buttocks. Strongly correlated to d4T, DDI and AZT. Caused by mitochondrial toxicity.
- Always occurs in patients who are on long-term ARV therapy.
- Can be disturbing and stigmatising for the patient, which may affect negatively on adherence.
- Management of lipoatrophy: Changing the offending ARV (d4T to TDF) may lead to improvement (but substitution is allowed only if the latest VL is undetectable and adherence isn't a concern). Patient must be counselled that a change in ARVs may not resolve the condition.
- Management of lipohypertrophy: There is no good evidence to support the switching of ARVs in patients with fat accumulation.

Hyperglycaemia and diabetes mellitus

- Can occur with protease inhibitors (PIs).
- Consider screening those on LPV/r with yearly fasting glucose levels.
- Management is similar to that of diabetes.
- The offending ARV may need to be changed (e.g. LPV/r to ATV/r).

Hyperlipidemia

- A person's triglyceride and cholesterol levels often rise when taking a protease inhibitor (such as LPV/r). Even if screening for raised lipids is not possible or statin drugs are not available, simple advice such as cessation of smoking and the benefits of a healthy diet and exercise should be discussed. This is especially important for patients who have hypertension, diabetes, existing cardiovascular disease or a strong family history of cardiovascular disease.
- If triglycerides are high, fibrates are the treatment recommended as there are fewer drug interactions.

Common drug interactions

One drug can change the blood or tissue level of another by affecting its absorption, distribution, metabolism (processing in the body) or elimination. Some interactions can result in significant changes in drug levels. This may require the dose of one or more drugs to be changed or to use another drug altogether.



The NNRTIs and PIs are metabolised in the liver by a complex enzyme system called the cytochrome P450 system. These classes have the most interactions as many drugs are metabolised by this enzyme system, most notably: TB drugs, contraceptives, anti-epileptics and warfarin.



www.hiv-druginteractions.org

Useful website: www.hiv-druginteractions.org

Practical advice¹⁶

- If you're unsure – check to see for possible interactions.
- Use drugs from a class which does not have interactions. If not possible, use a drug from the interacting class which has a different metabolism.

Rifampicin

Co-administration with NVP or PIs reduces some ARV drug concentrations. EFV is the drug of choice when co-administration of TB treatment is required. In case LPV/r is used, the dosage needs to be doubled (return to the normal dose two weeks after the end of anti-TB treatment) or additional ritonavir syrup added (see page 40). Switch patients to double dose LPV/r for the duration of TB treatment. Atazanavir/ritonavir cannot be prescribed with rifampicin and rifabutin will need to be used.

Contraception (oral)

The effectiveness of low-dose oral contraception is reduced if taken with NVP, EFV or PIs. High dose oral or injectable contraceptive is preferred. Injectables include medroxyprogesterone acetate (Depo-Provera) given every 12 weeks or norethisterone (Noristerat) given every 8 weeks along with barrier protection. Barrier methods and LARC (long-acting reversible contraception such as implants and intrauterine devices) are also recommended.

Emergency contraception:

Women on enzyme-inducing drugs (e.g. rifampicin, NNRTIs, PIs) should use 3 mg of LNG (levonorgestral) or 3 tabs of Ovral (0.5 mg of levonorgestrel and 100 µg of ethinylestradiol) now and 3 tabs 12 hours later.¹⁷

¹⁶ Professor Gary Maartens

¹⁷ South African Department of Health. 2013. *National Contraception Clinical Guidelines*.

Anti-epileptics (phenytoin/carbamazepine)

Epilepsy is more frequent in persons living with HIV than in the general community and anticonvulsants are often used in the treatment of neuropathic pain.

Co-administration of carbamazepine, phenytoin and phenobarbitone with NVP, EFV or LPV/r should be avoided, due to changes in drug levels in the blood. Instead, sodium valproate is the recommended choice or the newer antiepileptics such as levetiracetam or lamotrigine.

In case of PN due to d4T, vitamin B₆ (if deficiency suspected) and/or amitriptyline should be used as treatment instead of anti-epileptics.

Ketoconazole

Blood levels are significantly lowered with use of NVP. Use of the systemic anti-fungal agent fluconazole is preferred.

Benzodiazepines

Benzodiazepines should be avoided with EFV, and especially PI's, due to increased risk of sedation.

Complementary and alternative medications (CAMS)

Over-the-counter and traditional herbal treatments should be avoided with all ARV drugs, as they might lead to inadequate drug concentrations.

St. John's Wort, a popular herbal remedy for treating mild depression, reduces the plasma concentrations of all ARV drugs. Other CAMS that affect ARVs are garlic supplements, Sutherlandia and hypoxis (African potato).

Warfarin

Interactions can occur between warfarin (used in persons to help prevent clot formation), rifampicin, the PIs and NNRTIs. Frequent, careful monitoring of the INR is recommended.

Anti-malarials

Co-administration of amodiaquine with efavirenz is contra-indicated. There are no interactions between anti-malarials and the NRTIs. Levels of artemisinins may be slightly lowered by co-administration with NNRTIs, so close observation of patient response is needed.

Drug-sensitive and drug-resistant tuberculosis

Tuberculosis

Types of active TB disease

Five 'I's to reduce the burden of TB in PLHIV

Clinical presentation of extrapulmonary TB

Evaluating for active TB disease in PLHIV

TB management

TB treatment and ARVs

TB in children

Isoniazid preventive therapy (IPT)

TB infection control

Drug-resistant tuberculosis (DR-TB)



Tuberculosis

Tuberculosis is the most common cause of morbidity and mortality in people living with HIV. It is caused by the organism *Mycobacterium tuberculosis* (MTB), which is transmitted through the air via infectious respiratory droplets that originate from a person with active **pulmonary** disease, most commonly as a result of **coughing**.

It is important to distinguish between **infection** with MTB and active **disease** due to MTB. Upon inhalation of MTB, a person with a healthy immune system will 'control' it, such that in most cases the MTB remains latent, with only a 10% **lifetime** risk that it will ever develop into active TB disease. However, those with weakened immune systems, such as young children and people living with HIV (PLHIV), are less able to control the MTB and have an approximate 10% risk per year that the Mycobacterium will begin to replicate uncontrollably, leading to active TB disease and the development of symptoms.

- When TB disease involves the lungs (i.e. **pulmonary TB** or PTB), a person will have coughing and certain other 'constitutional' symptoms, e.g. loss of appetite, loss of weight, fever and night sweats.
- TB disease can also spread and cause active disease outside the lungs in almost any organ in the body – called **extrapulmonary TB** (EPTB). The symptoms and signs of EPTB will depend on exactly which organ is involved (e.g. headache if TB meningitis, effusion if joint involvement, etc.).

Types of active TB disease

It is helpful to think of active TB disease according to the following:

- smear-positive pulmonary TB, the most infectious form
- smear-negative pulmonary TB, which is more difficult to diagnose, often leading to a dangerous delay in initiation of treatment
- extrapulmonary TB (EPTB), which is also difficult to diagnose, and requires good and thorough clinical assessment.

Each of the above 3 types of TB disease can be caused by either drug-sensitive or drug-resistant (DR-TB) strains. DR-TB requires a longer duration of treatment.



If drug-sensitive TB treatment is given to someone with DR-TB, it is likely to make the drug resistance worse.



TB and HIV together = 'double trouble'.

The clinical presentation and diagnostic approach are different when someone with active TB is co-infected with HIV. This is because active TB disease presents differently in the presence of a weakened immune system.

Pulmonary TB is more difficult to diagnose using smear microscopy:

- Since immune systems are weaker in PLHIV, there is less cavity formation in the lungs in response to active TB disease.
- As a result, HIV-positive people tend to cough up fewer TB germs, not enough to be seen on microscopic examination, so their smear microscopy results are often reported as 'negative', despite the presence of active TB.

Therefore, never tell PLHIV, who have symptoms of TB but 'negative' smear results, that they do not have TB. They may have active TB, but need other tests to prove it.

TB disease is more often located outside of the lungs in HIV-positive people i.e. extra-pulmonary TB (EPTB).

For the above reasons, a clinician will have to frequently order **additional investigations** in order to prove the diagnosis of active TB. Fortunately, there are a number of newer diagnostic tests that can assist with this. Since PLHIV are at risk of rapid clinical deterioration due to active TB, clinicians need to avoid excessive delays in diagnosis.

Five 'I's to reduce the burden of TB in PLHIV

A number of different strategies can be employed to reduce the burden of TB in PLHIV in your setting:

1. **intensified case-finding (ICF)** through TB symptom screening at each visit of a PLHIV to a health facility, plus screening strategies within the community
2. **isoniazid preventive therapy (IPT)** to prevent development of active TB disease
3. **TB infection control (IC)** measures to reduce the risk of transmission to others
4. **integration** of TB and HIV services in high-burden settings to improve outcomes
5. earlier **initiation** of ART, i.e. at higher CD4 counts, to help prevent development of active TB disease

The 2nd, 3rd, and 5th 'I's directly prevent the occurrence of new cases of active TB, while the 1st and 4th ones indirectly do so.



TB and HIV services should be integrated in settings where both diseases are common.

Approximately 10% of people living with HIV develop active TB **every year**, while up to 70% of those receiving treatment for TB are HIV-positive in high HIV burden settings (whether they know it or not).

Integration of HIV and TB services helps to reduce overall morbidity and mortality, both by reducing diagnostic delay of TB in HIV patients, and by encouraging TB patients to know their HIV status, which in turn allows for earlier care and treatment of other HIV-related conditions. In addition, integration allows for more efficient use of human resources for health, as it prevents some duplication of work that currently exists in parallel TB and HIV programmes.

Some of the objectives of TB/HIV integration include:

- **Screening for TB symptoms in all children and adults living with HIV at every visit to a health facility (including at HIV testing sites, antenatal clinics, etc.),** followed by rapid evaluation for active TB disease in all those who are coughing or who have at least one other TB symptom.
- **All people receiving TB treatment know their HIV status.**
- All HIV-positive people with pulmonary or extrapulmonary TB (drug-sensitive or drug-resistant TB) being initiated on ART.

Clinical presentation of pulmonary TB

Typical presentation

The presentation of active TB disease affecting the lungs generally differs between those in the early stages of HIV infection and those in the late stages. A contact history with a known TB case is a strong indicator of underlying TB in the presence of symptoms. Symptoms of pulmonary TB (PTB) in those having mild immunodeficiency (i.e. higher CD4 counts) are similar to those experienced by HIV-negative patients:

- chronic cough (≥ 2 –3 weeks), not fully responding to antibiotics
- loss of appetite
- recent unintentional weight loss (≥ 1.5 kg within 4 weeks)
- drenching night sweats
- fever ≥ 2 weeks
- general weakness and tiredness
- chest pain – the position of which (left or right) could indicate the presence of a pneumonitis or pleural effusion
- sometimes haemoptysis (blood in the sputum when coughing).

Atypical presentation

With more **advanced** immunodeficiency (i.e. lower CD4 counts), an HIV-positive person with PTB is likely to present with different symptoms:

- general malaise and weakness (**deterioration has been severe if the patient is having difficulty with activities of daily living i.e. washing themselves, making food**)
- looks 'really sick'
- significant weight loss (>10% of previous body weight)
- less coughing, which tends to be dry (i.e. no cough)
- shortness of breath
- anemia
- often associated with disseminated TB (i.e. miliary TB) and/or extrapulmonary TB (meaning involvement of any organ outside of the lungs).

Clinical presentation of extrapulmonary TB

The clinical presentation of extrapulmonary TB (EPTB) will depend on the organ system in which the active TB disease is present. Since pulmonary TB can occur simultaneously with EPTB, sputum specimens should be sent for TB investigations if possible (if dry cough, perform sputum induction).

Table 7.1 Clinical presentation of EPTB

(Table continued on next page.)

Site	Symptoms	Investigations	Other
Meninges (covering the brain and spinal cord)	Headache/confusion and fever, leading to vomiting, stiff neck and loss of consciousness.	Lumbar puncture and investigation of CSF (protein, glucose, cell count, AFB, TB culture, GeneXpert – plus India ink, CrAg/CLAT, VDRL).	TB meningitis is common in children, in whom symptoms tend to be non-specific (e.g. drowsiness, irritability).
Lymph nodes (see Appendix 14) 	One or more enlarged (e.g. >2 cm), painless nodes in the neck, axillae, or inguinal areas.	<ul style="list-style-type: none"> • Needle aspiration if node is fluctuant (= easy) • Fine needle aspirate cytology (FNAC) if not fluctuant (= not so easy) • See Appendix 4 in 2014 MSF <i>TB Guide</i>. 	TB-related lymphadenopathy can also occur inside the chest or abdominal cavities.

Site	Symptoms	Investigations	Other
Pericardium (i.e. TB pericarditis)	Chest pain and symptoms related to heart failure (shortness of breath, peripheral oedema, and sometimes abdominal swelling).	Chest x-ray. Echocardiogram.	
Pleural effusion (often one-sided)	Chest pain (often unilateral) and shortness of breath.	Chest x-ray. Pleural tap for: <ul style="list-style-type: none"> • straw-coloured fluid suggests TB vs pus (empyema) • TB investigations • ADA • albumin. 	<ul style="list-style-type: none"> • AFB often not found in pleural fluid in TB-related pleural effusion. • In a high TB burden setting, a clinical diagnosis of TB can be made upon finding of a one-sided pleural effusion in a PLHIV and having TB symptoms. • A high ADA with lymphocytosis in pleural fluid is indicative of TB. • NB: The differential diagnosis of a bilateral pleural effusion is wider.
Abdominal	Non-specific symptoms (e.g. alteration in bowel habit) that can include pain and distension due to ascitic fluid.	Abdominal ultrasound. Ascitic tap for: <ul style="list-style-type: none"> • TB investigations • ADA • albumin. 	A 'doughy' abdomen is sometimes described on palpation as being suggestive of abdominal TB.
Spine (also known as Pott's disease)	Localised pain, followed by deformation.		Destruction of the spine may lead to neurological symptoms and signs.
Joint	Swelling, but not so much pain, usually involving a hip, knee or elbow		
Note that active TB disease can involve almost any organ in the body: kidneys, adrenal glands, thyroid, breast, genitals, skin, etc.			
Miliary TB (also known as disseminated TB)	Constitutional symptoms (fever, weight loss) which can lead to serious morbidity if it goes undiagnosed.	Choroidal tubercles on fundoscopic exam. Determine TB LAM of urine (if CD4 <100). Miliary pattern on chest x-ray.	Also known as disseminated TB, caused by haematological spread of bacilli throughout the body.



Clinical danger signs

Clinical danger signs requiring urgent hospital referral include:

- severe respiratory distress (e.g. from pulmonary TB with/without bacterial superinfection)
- severe wheezing; not responding to bronchodilators (consider severe airway compression)
- headache (especially if accompanied by vomiting), irritability, drowsiness, neck stiffness and convulsions (consider TB meningitis)
- big liver and spleen (consider disseminated TB)
- breathlessness and peripheral oedema (consider pericardial effusion or 'fluid around the heart')
- distended abdomen with ascites (consider abdominal TB)
- acute angulation of the spine (consider TB of the spine).

Screening for TB in PLHIV

Intensified case finding (ICF) for TB can help increase the chances of early detection; **TB symptom screening** should be performed **routinely** in PLHIV, in health facilities and within the community. Screening for TB is easy, and can be performed in less than 30 seconds by any trained health care worker.

- **Caregivers of children** should be asked about current cough, fever, poor weight gain and contact history with a TB case.
- **Adults and adolescents** should be asked about the presence of four symptoms: current cough, fever, weight loss and night sweats.

All children and adults found to have one or more TB symptoms during the screening process need to be **evaluated for TB** using a setting-specific **TB diagnostic algorithm** (see pages 97 and 98).

Those infected with HIV but not reporting one or more symptoms are unlikely to have active TB disease and should be considered for isoniazid preventive therapy or **IPT** (see page 110 for more on IPT).¹⁸

Important exceptions are those being 'worked up' to start ART; in this group, 'subclinical TB' is common, which implies the need for **routine** TB investigations even in the absence of TB symptoms.¹⁹

18 WHO. 2010. *Guidelines for intensified TB case-finding and IPT for people living with HIV in resource constrained settings*. http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf

19 Rangaka, M. *Tuberculosis Screening and Intensified Case Finding at an Integrated HIV/TB Clinic in Khayelitsha, Cape Town*. IAS 2009 poster. <http://www.ias2009.org/pag/Abstracts.aspx?AID=3397>

Evaluating for active TB disease in PLHIV

A **TB diagnostic algorithm** specific to your setting should already exist (if not, get together with your colleagues and create one.). Such algorithms help to standardise the diagnosis of TB using clinical examination and locally available investigations, with or without a course of antibiotics, and are especially helpful in diagnosing **smear-negative PTB** without unnecessary delay. For examples of TB diagnostic algorithm, see Algorithms 7.1 (smear microscopy as first test) and 7.2 (GeneXpert as first test) on pages 97 and 98.

1. Always perform a good physical **examination** in an adult or child whom you suspect has active TB.
2. Send two sputum samples for testing with **GeneXpert** (preferred) and/or **smear microscopy**. Make sure the patient provides sputum from the lungs, and not saliva from the mouth. Although early morning sputum has traditionally been requested, there is now sufficient evidence that a **same-day** diagnostic approach (i.e. 'spot-spot') is equivalent in terms of diagnostic accuracy. Thus, efforts should be made, whenever possible, to diagnose TB on the same day of presentation.²⁰
3. If concomitant bacterial infection is suspected, prescribe an antibiotic while waiting for the sputum test results (amoxicillin in a typical adult dosage of 500 mg, 3 times daily or, if allergic to penicillin, erythromycin 500 mg, 4 times daily).
4. If GeneXpert detects MTB or if acid-fast bacilli (AFB) are seen on smear microscopy, start TB treatment.
5. It is important to note that if GeneXpert does not detect MTB and if AFB are not seen under a microscope, the person may still have active TB disease. If TB symptoms persist (despite the antibiotic), **other investigations** are necessary. These investigations will depend on the person's symptoms/signs and on which ones are available in your setting.

Investigations

1. **Chest x-ray** – note that CXR presentations of TB in PLHIV 'are now well characterised and should no longer be considered atypical for TB in HIV prevalent settings'.²¹ These include:
 - miliary or diffuse shadowing
 - large heart (especially if symmetrical and rounded)
 - pleural effusion
 - enlarged lymph nodes inside the chest.

20 WHO. 2011. 'Same-day diagnosis of tuberculosis by microscopy', *Policy Statement*.

21 WHO. 2007. *Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary TB among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings*. http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.379_eng.pdf

If the chest x-ray and clinical picture are consistent with active TB, then the patient should be started on TB medication without delay, and the response to TB treatment monitored.

See Appendix 17B for a 'tick sheet' that can assist non-radiologists in the interpretation of paediatric chest x-rays through systematic review and recording, particularly with respect to findings suggestive of active TB disease.



See Appendix 17B

2. Repeat **GeneXpert** (if available).
3. Other molecular test or TB culture (if available).
4. **Determine TB LAM** is a newer lateral flow assay (i.e. 'dipstick') test of the urine that can identify disseminated TB antigen. However, this test should be reserved for those with low CD4 counts, since its sensitivity is poor at higher CD4 counts.
5. If one or more large and/or chronically infected lymph nodes (LN) are present in the neck, axillae or groin, which have not responded to a course of antibiotics, TB-related lymphadenopathy is very likely.
 - If the LN is fluctuant, **needle aspiration** is a relatively straightforward procedure to obtain a specimen for testing.
 - If the LN is not fluctuant, fine needle aspiration cytology (**FNAC**) should be performed.
 - If a pleural effusion is present, perform **thoracentesis** ('pleural tap') in order to look at the pleural fluid and exclude empyema.
 - **Ultrasound** is useful to detect abnormalities suggestive of abdominal TB (enlarged para-aortic nodes, ascites, splenic hypodensities) or TB pericarditis (pericardial effusion).
6. If the number of investigations is limited in your setting such that they do not allow you to prove a diagnosis of TB, but the person continues to have TB symptoms and is clinically deteriorating, it is acceptable to initiate **empiric** TB treatment. However, it is important to continue trying to confirm the diagnosis of TB and to monitor closely the response to therapy.
7. If the person is at risk of DR-TB, a specimen must be sent for drug sensitivity testing (DST). If GeneXpert is not available in your setting, then you should arrange for TB **culture + DST**. Note however that a culture/DST result could take up to two months.
8. **Don't forget to start all TB patients on cotrimoxazole prophylaxis and initiate ART in order to prevent other opportunistic infections (OIs), plus pyridoxine (vitamin B6) to reduce the risk of peripheral neuropathy.**



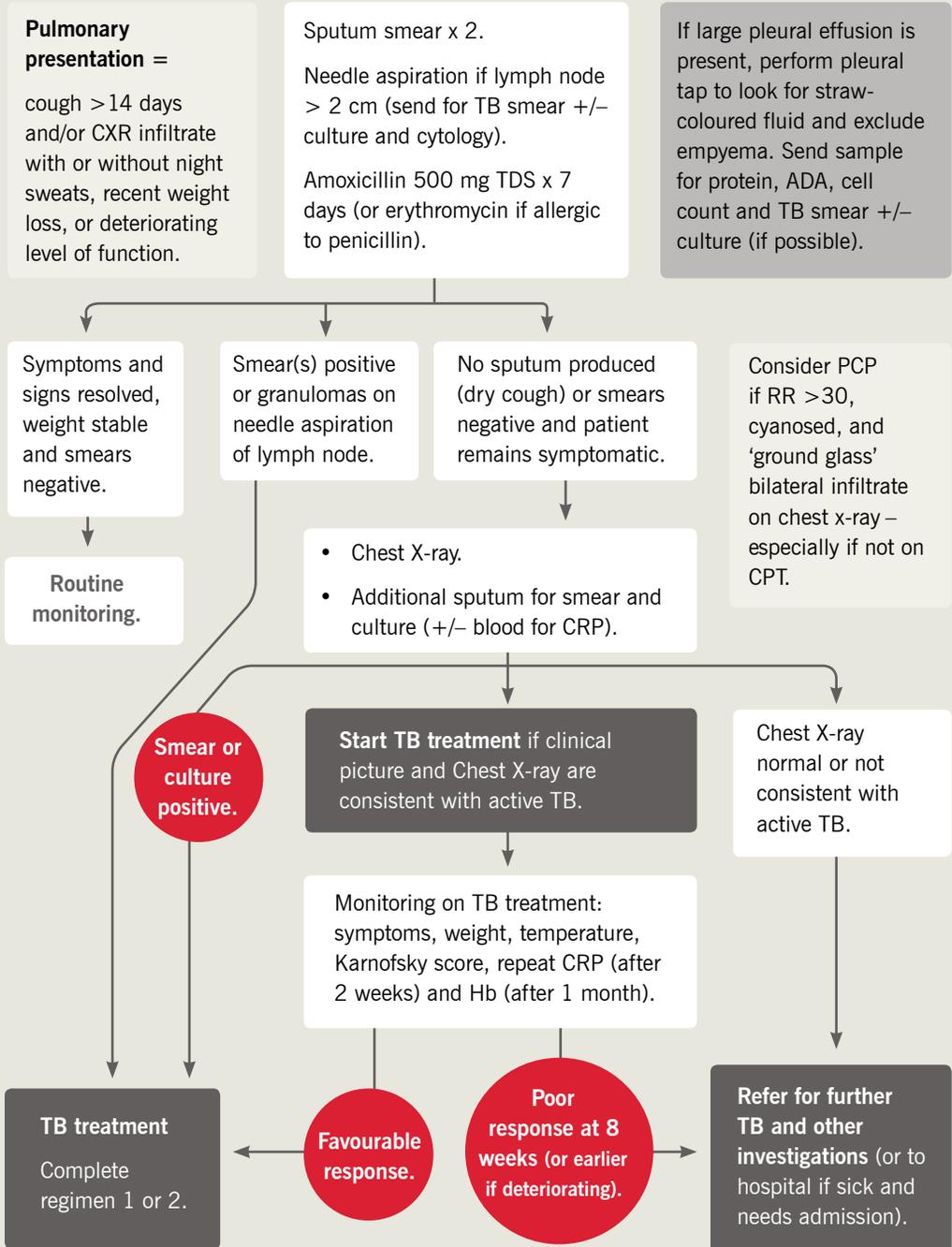
Xpert MTB/RIF (also known as 'GeneXpert')

GeneXpert is a new molecular diagnostic tool that can detect the DNA of MTB in sputum (and certain extrapulmonary specimens) within two hours. It has a number of advantages compared to smear microscopy:

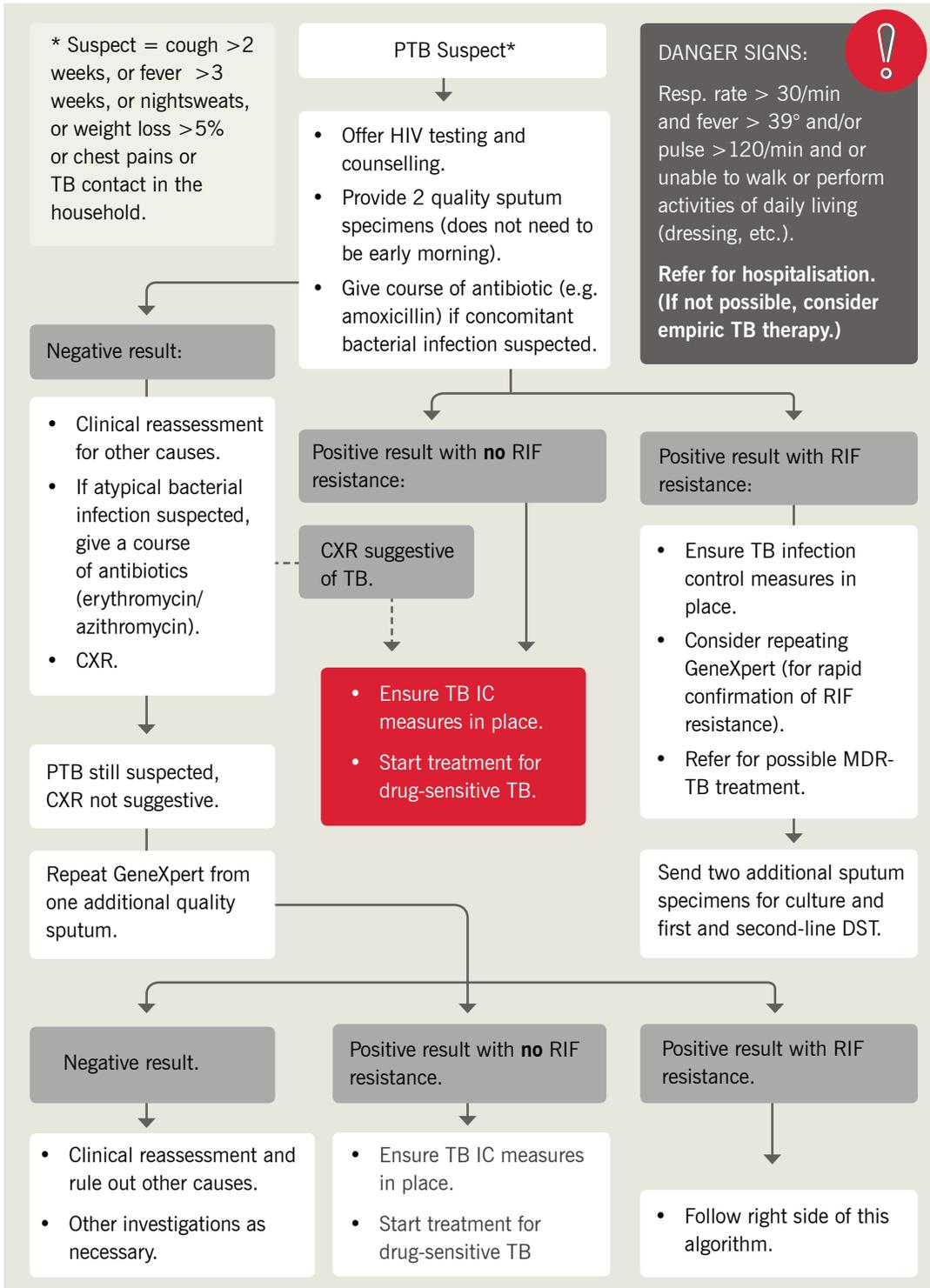
- It has a higher sensitivity than smear microscopy and will often detect TB in smear-negative samples: In controlled clinical validation trials, one GeneXpert test was able to detect MTB in 72.5% of 'smear-negative, culture-positive' cases. In demonstration studies, the overall sensitivity of a single GeneXpert test in culture-proven cases of TB was 91%; in comparison the sensitivity of a single direct smear microscopy was 60%. Since GeneXpert is not 100% sensitive, clinicians must be aware that it may be necessary to repeat GeneXpert testing if TB is still suspected and there has been a negative result.
- Access to GeneXpert testing is likely to reduce the need for CXR in your setting.
- GeneXpert is fully automated and does not require a high-level laboratory.
- It can also detect rifampicin resistance in less than two hours, which is a much quicker turn-around-time compared to culture and drug sensitivity testing (DST), which can take up to eight weeks.

Algorithm 7.1 Smear-negative algorithm for management of HIV-positive patients suspected of having TB (pulmonary presentation with or without enlarged lymph nodes)

Note: This algorithm to be used in settings where GeneXpert is not available for diagnosis.



Algorithm 7.2 TB diagnostic algorithm in settings where GeneXpert is available for use as the initial diagnostic test





Clinical staging of TB patients co-infected with HIV

In HIV-positive patients, a diagnosis of **pulmonary TB (PTB)** means that the adult or child is in clinical stage 3 of HIV infection (see Appendix 1).

Children with **extrapulmonary TB (EPTB)** are all considered to be in clinical stage 4, except for those with lymph node TB, who remain in clinical stage 3.

All adults with EPTB are considered by the World Health Organisation (WHO) to be in clinical stage 4.

Note that patients having a **pleural effusion** together with PTB should be classified as clinical stage 4; this is because a pleural effusion, although inside the chest cavity, remains outside of the lungs. Using the same logic, those people with TB **pericarditis** or TB **lymphadenopathy** are also classified as being in clinical stage 4.

Children and adults with a **miliary** pattern on chest x-ray have disseminated TB, which being a type of EPTB, means that they are all in clinical stage 4.



See Appendix 1

TB management

TB treatment regimens

Drug-sensitive TB can be **cured** relatively inexpensively, using a combination of 4 or more anti-TB drugs.

- **New TB cases** are patients who have never been treated for TB before (or have taken anti-TB drugs for <1 month). They are prescribed a Category I TB treatment regimen for a total of 6 months, consisting of a 2-month intensive phase with four drugs: [rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E)] followed by a 4-month continuation phase with rifampicin and isoniazid (RH). Sputum smear monitoring should be performed at 2 months, 5 months, and at end-of-treatment for all PTB cases (and EPTB cases with pulmonary involvement).
- **Retreatment cases** are patients who have received one month or more of anti-TB drugs in the past. They have traditionally been prescribed a Category II treatment regimen for a total of 8 months, consisting of 2 months of RHZE plus streptomycin injections, 1 month of RHZE, and 5 months of RHE. Sputum smear monitoring should be performed at 3 months, 5 months and at end-of-treatment for all PTB cases (and EPTB cases with pulmonary involvement).
- **Dosages** for all of the first-line anti-TB drugs mentioned above are based on the child's or adult's weight. See Table 7.2 for a summary of the dosages for these individual drugs.

- **Fixed-dose combinations (FDCs)** are commonly available in 4-in-1, 3-in-1, and 2-in-1 combinations; these reduce pill burden and can improve adherence. If not available in your national TB guidelines, tables showing the daily dose of anti-TB drugs using FDCs can be found in Appendix 8 of the 2014 MSF *TB Guide*.²²

Table 7.2 Dosages of first-line anti-TB drugs

Drug	Dosage		Other information
	Child <30 kg	Adults and children >30 kg	
Isoniazid (H)	10 mg/kg once daily (maximum 300 mg daily).	5 mg/kg once daily.	Maximum dose 300 mg daily. Do not give to those with severe liver disease.
Rifampicin (R)	15 mg/kg once daily.	10 mg/kg once daily.	Should be taken on an empty stomach. Maximum dose 600 mg daily. May cause orange-red discoloration of body fluids.
Pyrazinamide (Z)	35 mg/kg once daily.	25 mg/kg once daily.	Maximum dose 2000 mg daily. In those with renal impairment, give 25 mg/kg/dose, 3 times per week.
Ethambutol (E)	20 mg/kg once daily.	15 mg/kg once daiy.	Maximum dose 1200 mg daily. In those with renal impairment, give 15–25 mg/kg/dose, 3 times per week.



Notes on treatment of drug-sensitive TB

1. Settings with access to GeneXpert (or other rapid DST) should be **phasing out the use of Category II treatment regimens**: a person with a prior history of TB treatment who is diagnosed as having active TB, using GeneXpert, can, in many cases, take Category I TB treatment, as long as GeneXpert does not detect rifampicin (R) resistance (and as long as mono-resistance to isoniazid is not suspected).
2. GeneXpert is currently only recommended for **diagnosis** of TB. Those diagnosed with active TB, using GeneXpert, still need to have 'response to therapy' **monitored** using smear microscopy.
3. **Rifampicin interacts** with a number of other medications. Be particularly careful if the patient is taking:
 - warfarin (higher dose needed)
 - contraceptives (decreased efficacy)
 - fluconazole (decreased levels)
 - certain ARVs (decreased levels of nevirapine and most protease inhibitors).

An excellent, evidence-based resource to help clinicians to recognise and avoid drug-drug interactions is maintained by the University of Liverpool and available for free at the following web address: www.hiv-druginteractions.org/

4. For all patients receiving **isoniazid** (abbreviated as INH or just 'H') in a TB treatment regimen, give pyridoxine (vitamin B₆) to help prevent peripheral neuropathy:
 - adults and children >5 years: 10 mg OD
 - children <5 years: 5–10 mg OD.



www.hiv-druginteractions.org

Monitoring the response to TB therapy

All those on TB treatment need to be monitored for a **response to therapy**.

- The basis for monitoring is a **good clinical examination**.
- Those improving on treatment for PTB will show improvement of **symptoms**: less coughing, night sweats, and improved appetite.
- There will be an improvement in the person's general condition, including an increased ability to perform activities of daily living.
- More objectively, there should be **weight gain** (another important reason to check the weight at every visit).

- Follow-up sputum specimens are collected routinely during treatment and at the end of treatment in order to check for the presence of AFB using **smear microscopy**.
- If a person on TB treatment is not clinically improving, especially if the TB diagnosis was made empirically, a thorough reassessment and new investigations are necessary. The differential diagnosis includes:
 - drug-resistant TB (DR-TB)
 - bacterial pneumonia
 - bronchiectasis with bacterial superinfection
 - lung abscess or empyema
 - PCP
 - disseminated fungal infections (e.g. cryptococcosis)
 - *Nocardia*
 - Non-tuberculous mycobacteria (NTM)
 - Kaposi's sarcoma (KS)
 - Other cancers, including bronchial carcinoma and lymphoma
 - Congestive heart failure.
- Don't forget that immune reconstitution inflammatory syndrome (IRIS) can cause temporary worsening of TB symptoms several weeks after initiation of ART.
- Poor adherence, malabsorption, TB paradoxical reactions and drug-related adverse events could also contribute to a lack of clinical improvement.

For more details on monitoring response to TB therapy with sputum testing, including management according to smear results, see your national TB programme guidelines or Section 9.4 in the 2014 MSF *TB Guide*.

Possible adverse events due to first-line TB drugs

Each of the drugs used to treat drug-sensitive TB may result in adverse events (i.e. side effects). Whether they be minor side effects (e.g. nausea) or major ones (e.g. hepatitis), all side effects need to be diagnosed and managed early, so as not to negatively affect adherence.

The international standard for those on drug-sensitive TB treatment is to **clinically** monitor for such side effects, not with routine laboratory testing. However, in those at high risk for specific adverse events, it is prudent to monitor with suitable laboratory investigations (e.g. ALT regularly in a person with a pre-existing liver problem).

Some of the more common possible side effects due to first-line anti-TB drugs and their general management are outlined in the table below. Note that sometimes it will not be possible to know for certain which drug is responsible for a specific side effect. Also, make sure to rule out other causes for the symptoms (e.g. a new infection), instead of automatically blaming it on a TB drug.

Table 7.3 Possible side effects due to first-line anti-TB drugs and their general management

Possible side effect	Drugs likely responsible	Suggested management (See also Appendix 22) 	Comment
Nausea and vomiting	All	Ensure hydration. Give anti-emetic 30 minutes prior to TB treatment.	Nausea and vomiting generally subside over time. Always rule out other causes.
Peripheral neuropathy (PN)	H E	Pyridoxine.	Pyridoxine should routinely be given to all those being initiated on TB treatment in an effort to prevent PN. If possible, avoid concomitant use of d4T. (See page 176 in Chapter 10 Neurological conditions.)
Orange urine	R	None.	It is important to warn the person at the time of initiation to expect this.
Rash	S, E, Z, R, H (in order of likelihood, from most to least)	Stop TB therapy if any concern of a generalised hypersensitivity reaction (e.g. mucous membrane involvement), and re-introduce drugs in a stepwise fashion, starting with the least likely drug. (See the 2014 MSF <i>TB Guide</i> for more details.)	In addition to mucosal involvement, monitor closely for general signs (fever, headache, vomiting, etc.), as these may represent a generalised hypersensitivity reaction, which can result in mortality (especially if the culprit drug is not discontinued).
Renal toxicity	S	Replace/discontinue likely offending drug.	Reduce dosages of all renally excreted drugs according to CrCl.
Optic neuritis	E	Replace/discontinue Ethambutol.	Early diagnosis depends on screening with the Ishihara test at each visit (see Appendix 21B).
Hepatitis	Z (most likely), H R E	Stop TB therapy if hepatitis is moderate or severe, and re-introduce drugs individually while monitoring liver function closely, with least likely drug introduced first. (See the 2014 MSF <i>TB Guide</i> for more details.) In those who are severely ill with TB, such that stopping therapy would be too risky, some clinicians continue TB therapy with anti-TB drugs known to be less toxic (e.g. streptomycin or amikacin 15 mg/kg daily, moxifloxacin 400 mg daily or levofloxacin 750 mg daily, and ethambutol 800–1 200 mg daily) until resolution of the hepatitis (normal bili/ALT < 100) allows for the reintroduction of other drugs from the initial regimen.	It helps to grade the level of hepatotoxicity as follows: – mild: ALT < 5 times normal (no jaundice) – moderate: jaundice or ALT 5–10 times normal – severe: jaundice or ALT > 10 times normal Example of re-challenge regimen: Day 1: Start rifampicin (normal doses). Day 8: Add isoniazid (normal doses). Day 15: Add pyrazinamide (normal doses) – clinician's discretion. Rechallenge should not be attempted if the hepatitis resulted in hepatic failure. Consult an expert for further management.

TB treatment and ARVs

1. If an adult or child already on ARVs is diagnosed with TB, the ARV regimen may need to be modified according to Table 7.4.
2. If TB infection is present before the person has been initiated on ART, the following notes apply:
 - All HIV-infected adults and children with active TB disease are eligible for ART.
 - Start TB treatment first.
 - For the choice of ARVs in the ART regimen, refer to Appendices 9A to 9D and Table 7.4.
 - Those at high risk of mortality should be initiated on ART within two weeks if possible. See Table 7.5 for the optimal **timing** of ART initiation if the person is already on TB treatment.
 - If the person is clinically stable and has a higher CD4 count, **some clinicians prefer to delay ART until just after the intensive phase of drug-sensitive TB treatment (i.e. 2 months) unless other serious HIV-related conditions are present (e.g. KS)**. This reduces the pill burden, the risk of additive drug side effects and the risk of IRIS.²³



See Appendices 9A to 9D

23 Southern African HIV Clinicians Society. 2012. *Guidelines for antiretroviral therapy in Adults*. SAJHIVMED 13(3) <http://www.sahivsoc.org/upload/documents/Southern%20African%20Journal%20of%20HIV%20Medicine,%20Vol%2013,%20No3.pdf>

Table 7.4 Changes to ARV regimen if TB treatment needed

Current regimen includes	Change drug to	Patient group
NVP	EFV	Non-pregnant adults. Pregnant women in the 2nd or 3rd trimester
	Double dose LPV/r* (outdated).	Pregnant women in the 1st trimester.
	Different options: <ul style="list-style-type: none"> • Use a triple NRTI regimen (e.g. ABC + 3TC + AZT), returning to the other regimen once TB treatment has been completed. • LPV/r super-boosted with additional ritonavir. • Use NVP up to dose of 200 mg/m². 	Children <3 years or <10 kg.
LPV/r ****	Double dose of LPV/r*.	Adults.
	LPV/r boosted with additional ritonavir.	Children.
Atazanavir/ritonavir (ATV/r)****	Temporarily change to LPV/r (as above).	All, since ATV/r cannot be used with rifampicin.
d4T	Consider change to TDF** to reduce the risk of peripheral neuropathy, unless patient requires an anti-TB injectable (e.g. Am/Km, Cm, S).	Adults and older children*** (provided CrCl >50 ml/min and VL if available is undetectable).

Notes:

- * Continue double dose LPV/r (or additional ritonavir) for two weeks after stopping the rifampicin-containing TB regimen.
- ** Do not substitute one drug (e.g. d4T to TDF) if patient is suspected of failing ART.
- *** According to the WHO, 'TDF seems to be efficacious in children and adolescents aged 2 years to <18 years at the current US FDA-approved doses. The benefits of using TDF in children need to be balanced against the potential risk of toxicity'. But the current lack of paediatric formulations limits the use of TDF to older children weighing >35 kg.
- **** Since it causes less enzyme induction compared to Rifampicin, Rifabutin can be used together with protease inhibitors such as LPV/r and ATV/r. If available, change Rifampicin to Rifabutin. (For more information on the use of Rifabutin, see Chapter 12 and Appendix 9 in the 2014 MSF *TB guide*.)

Table 7.5 Timing of ART initiation in an adult already on treatment for TB

Clinical situation	Timing of ART initiation
All TB cases with CD4 count <50 cells/ μ l (except TB meningitis)	Within 2 weeks if possible.
TB meningitis	Between 4–6 weeks (NB: Risk of intracranial IRIS).
Pregnant women	<ul style="list-style-type: none"> • Within 2 weeks if CD4 <50 cells/μl. • If clinically stable, try to wait until the end of the 1st trimester, then initiate with EFV). • Otherwise within 8 weeks.
Young children (especially <1 year of age)	Within 2 weeks if possible.
All TB cases with CD4 count >50 cells/ μ l	Between 2–8 weeks*.
All DR-TB cases	Within 2 weeks if possible.



See Appendix 19

- * If the person is clinically stable and has a higher CD4 count, some clinicians prefer to delay ART until just after the intensive phase of drug-sensitive TB treatment (i.e. 2 months) unless other serious HIV-related conditions are present (e.g. KS). This reduces the pill burden, the risk of additive drug side effects, and the risk of IRIS.

(See Appendix 19 for an approach to patients who deteriorate on TB treatment.)



TB in children

- All HIV-infected children with active TB disease are eligible for ART.
- Begin ART as soon as TB drugs are tolerated (preferably within two weeks), irrespective of clinical stage, in case of MDR/XDR-TB, very low CD4 percentage (i.e. <5–10%), and/or <1 year of age.
- If TB treatment and ARVs are being taken at the same time, changes may be necessary to the ART regimen (see Table 7.4 above).
- Monitor for drug interactions.
- Monitor for side effects, especially hepatitis.
- Since the patient will be taking a large number of tablets, ensure adequate counselling is done in order to maintain adherence.

Special considerations for TB/HIV co-infected children

Clinical presentation of TB in children

- Common presenting symptoms of TB disease in children include:
 - persistent cough > 14 days
 - fever >38°C for over 1 week (after excluding other causes of fever)
 - weight loss or failure to gain weight (don't forget to look at the 'Road to Health' card)
 - unusual fatigue (e.g. not able to play as usual).
- Extrapulmonary presentations of TB (EPTB) are common in children. Symptoms will depend on the part of the body involved:
 - A visible mass in the neck, not responding to a course of antibiotics and without a visible local cause probably represents lymph node TB in a high TB burden setting.
 - Other common presentations of EPTB in younger children include meningitis and miliary/disseminated disease.
 - Osteoarticular TB disease is more common in older children.
 - See Table 7.1 above for other presentations of EPTB.

Active screening

- Active screening for TB disease in HIV-infected children is essential at each and every visit.
- Ask the child's caregiver about poor weight gain, fever or current cough – if none of these are present, then the child is unlikely to have active TB, and can be considered for IPT (see later in this section).²⁴
- Always ask about contact with an adult with active TB disease (see Algorithm 7.3 below).

Diagnosis

Diagnosis of TB in children is difficult, especially in the HIV-positive child. Other pulmonary conditions may present with symptoms similar to TB (bacterial pneumonia, fungal pneumonia, LIP, etc.). If the child is able to produce sputum, it is often paucibacillary (i.e. containing few TB germs), so sputum smears are often reported as 'negative'.

Thus, we need to use many pieces of information to make the diagnosis of TB in a child: contact history and clinical presentation are most important. Other investigations may also help: a child over five years old is generally old enough to

24 WHO. 2010. *Guidelines for intensified TB case-finding and IPT for people living with HIV in resource-constrained settings*. http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf

try to produce sputum, whereas in the younger child, induced sputum (preferred) or gastric aspirate will have to be considered. Depending on local resources, CXR, TB skin testing and needle aspiration of large, fluctuant lymph nodes should be performed.

- **Induced sputum or gastric aspiration** can increase the yield of sputum production (see below) in facilities where there are trained staff to perform these.
- A raised, thickened area >5 mm in diameter following a **TB skin test (TST)** in an HIV-positive child is considered a positive result. It tells us that the child has inhaled TB at some point in the past; however, it does not necessarily mean that the child currently has active TB disease. A TST result is just another clue that can help us to make a diagnosis of active TB. **Remember, though, that a negative test does not exclude active TB.**



- **CXR**s are even more difficult to interpret in HIV-infected children, and can be normal in up to one third of those with active TB. **The eye of an experienced clinician is often needed to make a diagnosis and TB should not be diagnosed from the CXR alone.** The most common feature on x-ray is **hilar lymphadenopathy**. Other features may also be present, including alveolar consolidation, cavitation or miliary pattern.



www.samumfsf.org



A miliary pattern in a child who does not look sick most likely means the child has lymphoid interstitial pneumonia (LIP), not disseminated TB.

Check www.samumfsf.org for videos on reading Paediatric x-rays.

- **Needle aspiration** of fluctuant lymph nodes ≥ 1 cm is relatively straightforward, so should be performed without hesitation, and aspirated material sent in a sputum container for microscopy, molecular testing (e.g. GeneXpert) and/or culture. Fine-needle aspiration of non-fluctuant lymph nodes is more difficult. See Appendix 4 in the 2014 MSF *TB Guide* for details on fine needle aspirate cytology (FNAC).

The following can help to improve the yield of TB tests on sputum in children:

- Induced sputum collection: First give a bronchodilator (e.g. salbutamol), followed by nebulisation with hypertonic saline solution. An older child will then usually be able to expectorate sputum; if not, suctioning of the pharynx will be necessary to obtain a specimen for testing, as in younger children. (Check www.samumfsf.org for sputum induction videos.)
- Gastric washings or gastric aspirates are commonly performed procedures, but require a child to be fasting overnight.
- Send specimens for microscopy, molecular testing (e.g. GeneXpert) and/or culture.



www.samumfsf.org



Remember to keep a **high index of suspicion for TB in a child**. In other words, if you think the child might have TB, be sure to investigate further.

If an HIV-positive child has persistent TB symptoms after a course of antibiotics, even if there is no known history of contact and/or the TB skin test is negative, strongly consider a diagnosis of TB.

If CXRs are not available, and the child has chronic symptoms and a known TB contact, strongly consider initiating empiric TB treatment (sputum collection should be attempted whenever possible).

The presence of certain **findings on clinical examination** in children with TB symptoms in a high TB prevalence area is enough to warrant immediate **initiation of TB treatment**:

- non-painful lymphadenopathy with fistula
- angle deformity of the spine.

Management

- Management of TB is the same as for HIV-negative children.
- Children with certain types of EPTB (e.g. TB meningitis and of the joint) are often given a prolonged duration of treatment (e.g. up to 12 months).
- Ethambutol is now considered safe for children of any age, including little risk of ocular toxicity, provided that it is correctly dosed at 20 mg/kg/day.
- Thus, 4 drugs (including ethambutol) should be used in the intensive phase of treatment.
- Streptomycin should be avoided in children, due to the risk of irreversible auditory nerve damage.
- Inpatient management should be considered for children that are seriously ill.
- Nutritional support is very important, especially if the child is malnourished.
- The child needs CTX prophylaxis and enrolment for ART (see Table 7.5 on page 106 for timing of ART initiation).
- Pyridoxine to help prevent peripheral neuropathy: give 5–10 mg daily for those <5 years, and 10 mg daily for those >5 years.



If the child's symptoms worsen despite TB therapy, questions to ask include:

- Are the TB drug dosages correct for the child's weight?
- Is the child being given the medication appropriately?
- If the child is severely malnourished, is this being managed appropriately?
- Is there a reason to suspect drug-resistant TB (e.g. index case is known to have DR-TB, is a relapse case, or is also not responding to therapy)?
- Has the child developed IRIS (if on ARVs)?
- Is there another reason for the child's illness, other than or in addition to TB?

Perform a thorough clinical assessment and investigate.

Prevention of TB infection and disease

TB prevention should be a focus of every HIV/TB program. A series of TB infection control (IC) measures help to prevent transmission of MTB to others, while isoniazid preventive therapy (IPT) can be used to prevent the development of active TB disease in individual adults and children living with HIV.

Isoniazid preventive therapy (IPT)

In adults

IPT involves prescribing a single TB medication, isoniazid (INH), for six months or more, in order to prevent development of active TB disease for up to two years. For details on eligibility and the duration/dose of INH, refer to your national TB guidelines or the 2014 MSF *TB Guide*.



Before using INH, one must be certain that the person does not have active TB; or else the situation will be made worse, as giving INH monotherapy to a person with active TB would promote resistance of the TB organism against INH.

The following criteria exclude a patient from consideration for IPT:

- Symptoms and/or signs of TB, i.e. patients who are currently ill with new or worsening cough, with or without sputum production, haemoptysis, night sweats, fever or measured weight loss of more than 5%.
- The person is unlikely to adhere to IPT.
- The risks outweigh the potential benefits (e.g. the presence of jaundice or active hepatitis).
- The strain of TB is unlikely to be sensitive to isoniazid.



Of note, health care workers in high TB-burden settings are a group of adults in whom WHO strongly recommends the use of INH preventive therapy.



In children

IPT should be offered to the following children:

1. Contacts of PTB cases:
 - all HIV-positive (and HIV-exposed) children <15 years
 - all HIV-negative children under 5 years of age
 - newborns of smear-positive mothers.
2. HIV-positive children between 1–15 years, regardless of contact history.
3. HIV-positive children <15 years, post-TB treatment (i.e. as secondary prophylaxis).

Note: Unlike adults, TB skin testing (TST) does not have a role in determining which child will benefit from IPT. TST can, however, be used to evaluate a child for active TB disease.

- Children on INH prophylaxis should receive pyridoxine to avoid PN
 - >5 years, 10 mg OD
 - <5 years, 5–10 mg OD.
- The dose of INH for preventive therapy in children is 10 mg/kg/day for 6 months (see Table 7.6 below).
- For details on the duration and dose of INH in children, refer to your national TB guidelines or Chapter 16 in the 2014 MSF *TB Guide*.

Table 7.6 Dosage recommendations for IPT in children

Body weight	Daily isoniazid (INH) 100 mg tablet
2–3.4 kg	¼ tablet
3.5–6.9 kg	½ tablet
7–9.9 kg	1 tablet
10–14.9 kg	1 and ¼ tablet
15–19.9 kg	1 and ½ tablet
20–24.9 kg	2 tablets
25–29.9 kg	2 and ½ tablets
≥30 kg	3 tablets

TB infection control

TB infection control (IC) refers to a set of measures/controls that can reduce the transmission of TB.

1. **Administrative controls.** These are the most important and include:
 - Prompt identification of infectious TB cases (e.g. cough triage and 'fast track' for coughing patients).
 - Physical separation of patients known or suspected of having TB (e.g. a person with pulmonary TB should sleep in a separate room while infectious).
 - Coughing patients to wear surgical masks.
 - Patients to be instructed about cough hygiene.
 - Infection control policy and functioning infection control committee to be in place.
 - Infection control risk assessment to be undertaken in all health care facilities.
2. **Environmental controls:**
 - Maximise natural ventilation.
 - Avoid being downwind from an infectious patient.
 - Maximise the amount of natural light in a room.
 - NB: In resource-limited settings, mechanical ventilation and UV lamps are not the priority.
3. **Personal respiratory protection:**
 - At-risk staff to wear N95 respirator masks.

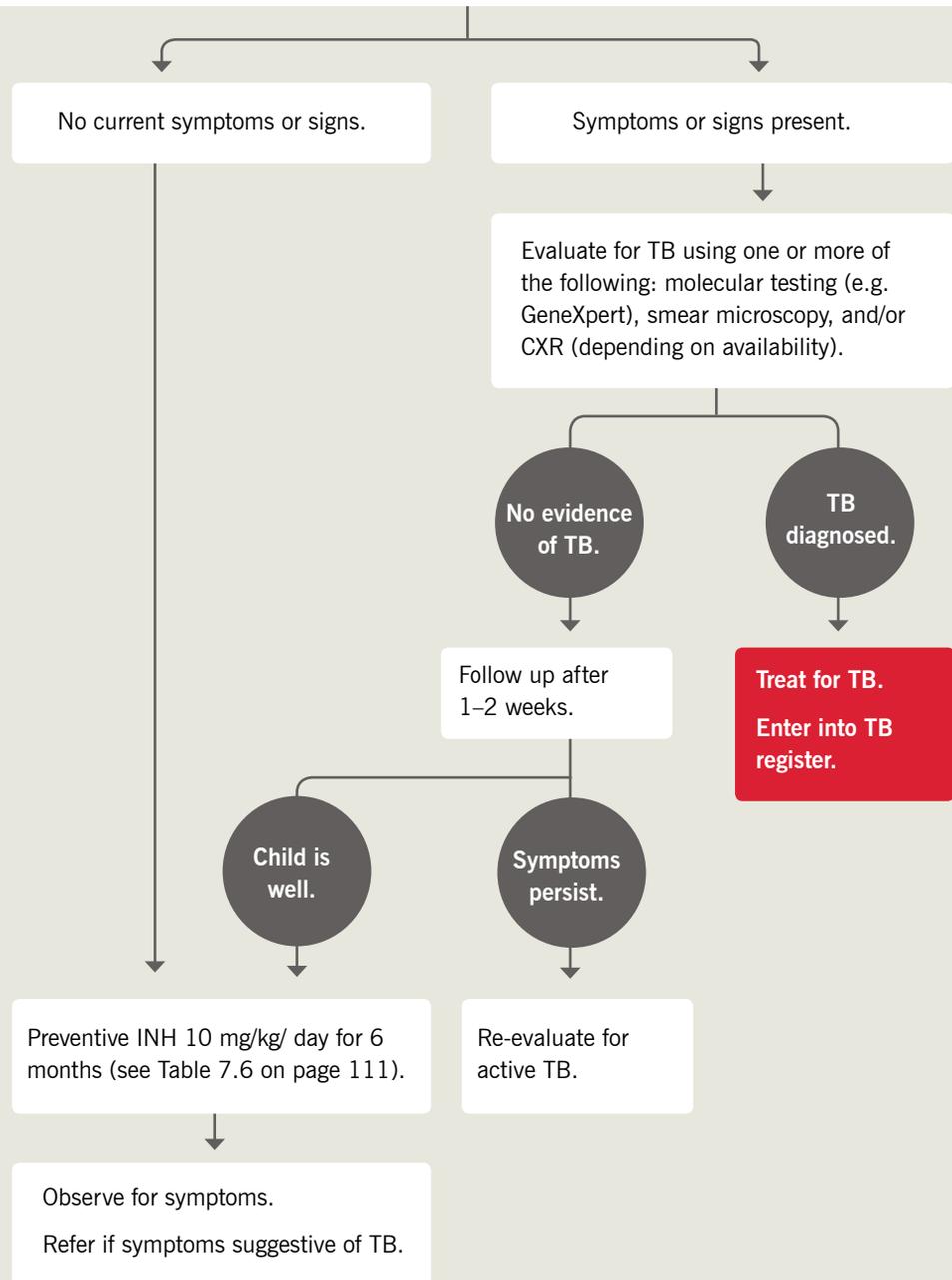


The most effective way to prevent TB transmission is through **early diagnosis and treatment** of active TB disease. TB patients quickly become non-infectious once started on an effective treatment regimen.

Algorithm 7.3 Management of an HIV-infected child contact of a known case of active TB

Documented TB exposure in an HIV-infected child

Close contact with any TB patient, where close contact is defined as any household contact or contact outside the household that is of sufficient duration to pose a high risk of infection.



Drug-resistant tuberculosis (DR-TB)

Drug-resistant TB (DR-TB) is an increasingly recognised threat. Worldwide, 3.7% of new cases and 20% of previously treated cases are estimated to be due to TB strains that are multidrug-resistant.²⁵ However, it is important to note that the rate of DR-TB varies considerably by region, and that the vast majority of DR-TB cases currently go undiagnosed (and therefore untreated).

If someone on TB treatment in your setting has been adherent to their treatment but is not improving, one of the first diagnoses to think of and to rule out is DR-TB. Known contacts of patients with DR-TB who present with TB symptoms should also be investigated for DR-TB, particularly if HIV positive or <5 years.

Classification of DR-TB

DR-TB can be classified into four categories:

1. **Mono-resistant:** Resistance to **one** of the first-line anti-TB drugs: ethambutol (E), rifampicin* (R), isoniazid (H), pyrazinamide (Z).
2. **Polydrug-resistant (PDR):** Resistance to **two or more** of the first-line drugs, but not R and H together (see MDR below).
3. **Multidrug-resistant (MDR):** Resistance to at least R and H.**
4. **Extensively drug-resistant (XDR):** Resistance to **R, H and one or more** of the anti-TB injectable drugs (**capreomycin, kanamycin, amikacin**) and any of the fluoroquinolones (e.g. **ofloxacin**).

Notes:

- * Note that rifampicin mono-resistance is treated similarly to a case of MDR-TB.
- ** The term 'pre-XDR' is informally used to refer to MDR-TB strains that have additional resistance to either an injectable or a fluoroquinolone (i.e. halfway between MDR and XDR-TB).

Clinical presentation

What are the symptoms of DR-TB?

The symptoms of DR-TB are the same as those of drug-sensitive TB (DS-TB) – see page 90.

DR-TB patients may present with cough, weight loss, fatigue, night sweats, chest pain and/or more atypical symptoms if they are HIV positive with advanced immunodeficiency.

Who gets DR-TB?

Transmission of DR-TB is the same as drug-sensitive TB – i.e. airborne. Anyone can get DR-TB but certain people are more at risk, including:

- a person who has been in close contact with someone with DR-TB (especially if living in the same household)
- health care workers, including laboratory workers and auxiliary staff (e.g. hospital cleaners)
- those in congregate settings: miners, prisoners and prison guards
- those with a history of TB drug use: relapse after treatment; return after default; treatment failure (greatest risk); history of using poor or unknown quality of drugs; history of illness or other medications that interfere with TB drug absorption
- those with weakened immune systems (since at increased risk for all forms of TB).

How is DR-TB diagnosed?

(See Table 7.7 on page 116.)

Although DR-TB can be suspected clinically, the actual diagnosis of DR-TB has to be made in a laboratory. When a person is suspected to have DR-TB, one or more specimens is sent for smear microscopy, molecular testing and/or culture and drug sensitivity testing (DST).

Which people need to have one or more specimens sent for DST (i.e. active case finding for DR-TB)?

- all re-treatment TB cases
- patients on TB treatment who remain sputum smear positive after 3 months
- symptomatic close contacts of confirmed DR-TB cases
- symptomatic individuals from known high-risk groups:
 - health care workers
 - other employees of health care facilities (e.g. cleaners)
 - laboratory workers
 - those in congregate settings (e.g. prisoners, miners).



Remember: Rifampicin resistance detected by GeneXpert needs to be confirmed by DST, since GeneXpert can sometimes give a 'false positive' RIF result and it is important to know about resistance to additional drugs.

Table 7.7 Testing for DR-TB

Test	Role	Time to result	Other
Xpert MTB/RIF (i.e. GeneXpert)	Can detect rifampicin (RIF) resistant strains of MTB.	<2 hours	Rifampicin resistance detected by GeneXpert needs to be confirmed by DST (especially true for low prevalence settings) since GeneXpert can sometimes give a 'false positive' result.
Line Probe Assay (LPA), also known as 'Hain test'	Used to detect H and R resistant strains in smear- and culture-positive specimens (but not smear-negative ones).	<2 hours	Not yet validated for DST of second-line drugs.
Culture/DST, also known as phenotypic DST	Can be used to detect resistance to first-line drugs (H, R, Z, E, S).	2–3 weeks if liquid culture (e.g. MGIT). >1 month if solid culture (L-J).	DST results to H, R, FQs and injectables tend to be reliable and reproducible. DST of other drugs is much less reliable.
	Can be used to detect resistance to second-line drugs (injectables, FQs, etc.).	Even longer, since second-line DST is usually performed sequential to first-line DST.	There is cross-resistance between the injectables amikacin (Am) and kanamycin (Km), and also capreomycin (Cm) but less so.
Smear microscopy	Determines level of infectiousness in those with PTB: <ul style="list-style-type: none"> • Smear-positive PTB patients are more infectious. • Smear-negative PTB patients are less infectious. 		Note that EPTB patients are not infectious (unless they have co-existing PTB).

Assessing a DR-TB patient

History:

It is important to get detailed information about:

- the TB treatment history (for each episode of TB) and to understand if there were adherence issues in the past
- a history of exposure to a known case of DR-TB
- any conditions that can weaken the immune system (HIV infection, diabetes mellitus, renal disease, malignancies or chronic malabsorption syndrome)
- the psychosocial context of the patient.

Physical exam should be comprehensive:

- weight and body mass index.

Baseline investigations:

- repeat smear, culture and DST prior to starting DR-TB treatment
- HIV screening (if not already done) and CD4 count if found to be HIV-positive
- chest x-ray
- pregnancy test (if of child-bearing age)
- audiometry (baseline, within 3–7 days if possible, and monthly during the intensive phase of treatment)
- potassium
- serum creatinine and calculate creatinine clearance (CrCl)
- full blood count, or at least haemoglobin (Hb)
- liver blood test – ALT
- Thyroid-stimulating hormone – TSH
- fasting blood glucose (FBG)
- urinalysis
- colour vision test if on ethambutol or linezolid (using Ishihara test in Appendix 21B)
- Electrocardiogram (ECG) in settings where clofazamine and newer TB drugs (bedaquiline, delamanid) being used.

Infection control

Infection control in the home of the patient will need a detailed initial assessment, in order to reduce the risk of transmission to others in the household during the period of infectivity.

All **close contacts** need to be screened for TB symptoms. All contacts <5 years should be assessed by a clinician and assessed regularly for a total of two years. See page 93 for more information on contact tracing.



See Appendix 21B

Individualised **counselling** should be provided by a trained DR-TB counsellor, using a standard model for information giving and education of patient and family.

Management of DR-TB

Standardised regimens are usually recommended in the guidelines of national TB programmes (NTP). For example, the standardised regimen for **multidrug-resistant TB (MDR-TB)** mentioned in the 2011 South African guidelines includes an intensive phase of kanamycin/amikacin, moxifloxacin, ethionamide, terizidone, and pyrazinamide (taken at least six times per week) followed by a continuation phase that includes the latter four oral drugs.

For strains having advanced resistance, e.g. **extensively drug-resistant (XDR) TB**, the treatment regimen will likely have to be **individualised**, based on the results of DST and treatment history.

The principles of DR-TB treatment can be summarised as in Table 7.8.

Those with **mono- and poly-drug-resistant TB** (apart from mono-resistance to RIF, which is treated similarly to MDR-TB) are often treated for lesser durations, e.g. 9–12 months. See Chapter 11 in the 2014 MSF *TB Guide* for further details.

Table 7.8 Principles of DR-TB treatment

(See Appendix 20 for drug dosages.)



1	Aim to have at least four second-line anti-TB drugs likely to be effective in a DR-TB regimen.
2	Start by choosing an injectable drug (from Group 2) based on the DST result and treatment history. <ul style="list-style-type: none"> • kanamycin • amikacin • capreomycin
3	Then add a fluoroquinolone (FQ, Group 3), ideally a later generation one: <ul style="list-style-type: none"> • moxifloxacin • levofloxacin
4	Add at least two bacteriostatic drugs from Group 4: <ul style="list-style-type: none"> • ethionamide (or prothionamide) • cycloserine • para-aminosalicylic acid (PAS) <p>Choice is based on treatment history and side effect profile.</p> <p>Note that all three of these drugs may have to be included in order to have four second-line drugs likely to be effective.</p>
5	If the regimen does not yet contain four second-line drugs likely to be effective, add Group 5 drugs: <ul style="list-style-type: none"> • bedaquiline (if available) • linezolid • clofazimine • amoxicillin/clavulanic acid • high-dose isoniazid (in certain circumstances)
6	Add Group 1 drugs as follows: <ul style="list-style-type: none"> • Pyrazinamide (Z) is added routinely, unless resistance has been documented or there is intolerance. • Ethambutol (E) is not routinely added, unless it is likely to be effective.
7	The duration of the intensive phase of DR-TB treatment (i.e. the phase containing the injectable) is guided by culture results: until at least four months after the TB culture becomes negative, or at least eight months, whichever is longer.
8	The total treatment duration is also guided by culture results: at least 18 months after the culture becomes negative. The duration may need to be further extended in chronic cases having extensive pulmonary damage.
9	A combination of sputum smear microscopy and culture should be used to monitor response to therapy, together with clinical assessment.
10	All HIV-infected DR-TB patients should receive ART, irrespective of CD4 count, and as early as possible following initiation of anti-TB therapy.

Source: Modified from Figure 10.1 in the 2014 MSF *TB Guide*.

Model of care for DR-TB treatment

Patients with MDR-TB should be treated using mainly **ambulatory care** rather than models of care based principally on hospitalisation.²⁶ Treatment should be directly observed (i.e. DOT); if the person lives far from the health facility, then a community-based '**treatment supporter**' can be trained to provide such support close to the person's home.

Adherence and psychosocial support are very important in a DR-TB programme, as are the provision of '**enablers**' (e.g. food and transport) to ensure that a person with MDR-TB can successfully complete the entire course of treatment.

If the patient is clinically unstable or if there are significant psychosocial difficulties, admission to a health facility may be required initially (or later if the patient suffers from a serious adverse event).

TB infection control measures should be employed in the home (or health facility) during the initial period of infectiousness, in order to reduce the risk of transmission to others.

The basic principles of MDR-TB treatment include:

- The treatment regimen should include a minimum of **four drugs that are likely to be effective, preferably five to six**.
- Whenever possible, include first-line anti-TB drugs that are likely to be effective.
- Do not rely on drugs to which resistance is suspected but cannot be confirmed due to unreliable DST. For example, if a patient was taking Z and failed a Category I or II regimen (i.e. smear and culture positive) the strain of MTB is likely to be resistant to Z. These drugs may be included if tolerated, but cannot be relied upon as effective.
- Extrapulmonary DR-TB is treated using the same strategies (and duration) as pulmonary DR-TB.

HIV and DR-TB

The risk of mortality is higher in a DR-TB patient co-infected with HIV; thus it is important to make the diagnosis early and start DR-TB treatment early. All HIV-positive DR-TB patients are eligible for ART, regardless of CD4 count.

If a patient with DR-TB is co-infected with HIV, then the ARV tenofovir (TDF) is best avoided during the intensive phase of treatment, due to the additional risk of nephrotoxicity from both TDF and the second-line injectable drug (i.e. amikacin/kanamycin, capreomycin).

Patient support

Support of DR-TB patients is of paramount importance and should be offered throughout treatment.

A DR-TB patient can have difficulty adhering to the prolonged treatment regimen for a number of reasons, including:

- psychological distress
- social problems
- knowledge and beliefs regarding the purpose of treatment
- separation from family/friends
- adverse events (due to medication or other reasons)
- inconsistent immediate effect
- lack of trust in the provider.

Strategies to support patients with these numerous difficulties are many, but a basic package of support should include:

- DR-TB patients should receive sufficient **information and education** about their disease and its treatment to enable them to have some responsibility for their own outcome. It is very important that patients understand that if they do not adhere to their treatment, they risk amplifying the resistance of their strain of DR-TB, such that it may become less treatable, and the strain can be passed on to their families.
- **Psychological support** – individually and/or in groups.
- Intense **medical support** to treat side effects of drugs, addictions, other medical conditions, psychiatric disease and other pre-existing conditions or results of treatment.
- **Social support**, including ‘enablers’ such as social grants, food, accommodation, and transport, plus other needs of the patients and their families. It is important that these resources are accessible in the community.
- Some **flexibility** in treatment delivery to enable patients to stay adherent.

Early identification of DR-TB treatment interruption

If a person interrupts DR-TB treatment, he or she should be traced immediately and the reasons for interruption explored. Every effort should be made to help the patient resume treatment and prevent a similar occurrence in the future.

Each DR-TB programme needs to have a good **monitoring system** in place to identify treatment interruption promptly (i.e. within 1–2 days). DR-TB patients that miss clinic visits should receive a phone call and/or home visit in order to determine the reason(s) for this.

Monitoring someone on DR-TB treatment

Drug-related adverse events are more common with the use of second-line anti-TB drugs. Patients on treatment for DR-TB need to be monitored carefully to identify any such adverse events early and assess response to therapy. Such close monitoring is crucial to improve the chance of a successful outcome.



See Appendix 21A

Adverse events: Second-line anti-TB drugs are associated with a number of different adverse events, from minor to life threatening. It is the responsibility of the health care worker to be aware of all potential adverse events of these drugs and monitor their patients appropriately. (See Appendix 21A for a monitoring schedule for MDR-TB patients.)

Response to therapy: If a person is responding well to DR-TB treatment, then smear and culture results should 'convert' from positive to negative within the first few months. **Conversion is officially defined as two consecutive negative culture results collected at least one month apart.**

It is also important to monitor patients for the further development (known as '**amplification**') of drug resistance, hence the need for a repeat DST if culture remains positive after four months of treatment or becomes positive again after conversion).

Monitoring programme:

- At the start of DR-TB treatment, the patient should be assessed daily (by the person directly observing therapy) for any side effects to medication.
- A clinician should see the patient at least weekly during the first month and more often if any problems develop. Once stable, the clinician can see the patient every two weeks in the first three months, followed by monthly visits.
 - Check the patient's **weight** at each clinic visit.
 - In between monthly visits to the clinician, other DR-TB team members will see the patient and should signal any concerns.
- **Thyroid stimulating hormone (TSH)** every six months (every three months if HIV positive) to screen for hypothyroidism if on ethionamide (Eto) and/or para-aminosalicylic acid (PAS).
- Check creatinine and calculate **creatinine clearance** monthly while on an injectable.
- **Potassium** is very important to monitor monthly while an injectable anti-TB drug is being given:
 - Check magnesium if hypokalemia (= low potassium) has been detected.
- **Audiometry** monthly to screen for hearing loss during the injectable phase. If audiometry is not available, patients must at the very least be actively asked at each visit if they are experiencing any problems with hearing.
- Screen for optic neuropathy monthly using the **Ishihara test** in anyone on linezolid or ethambutol. See Appendix 21B.



See Appendix 21B

- Check haemoglobin monthly in those on linezolid or other drugs that can cause anaemia.
- ALT should be checked every 1–3 months in patients receiving pyrazinamide and those at risk of hepatitis (and as necessary in anyone having symptoms of hepatitis).
- Electrocardiogram (ECG) monitoring will be necessary if drugs are being used, especially in combination, which can prolong the QT interval: clofazimine, moxifloxacin, and the newer TB drugs (bedaquiline, delamanid).
- **Smear and culture** monthly.
- Repeat DST if:
 - culture remains positive at four months
 - patient is clinically deteriorating
 - culture becomes positive again after conversion.
- Chest x-ray can be rechecked after 6 months of treatment.



Adverse events are more frequent in patients taking second-line anti-TB drugs and potentially more severe than in patients taking first-line anti-TB drugs. Early recognition and aggressive management of all adverse events is essential, whether they are minor or major (life-threatening), to avoid treatment default.

Continuation phase monitoring

- Examination by clinician monthly unless there is a medical necessity to see the patient more often. Other DR-TB team members see the patient in between and signal any concerns to the clinician.
- Patient's weight should be checked monthly.
- ALT, FBC, creatinine if clinically indicated.
- TSH levels every six months in patients on PAS and/or ethionamide.
- Repeat Ishihara test monthly if on ethambutol or linezolid.
- Smear and culture done monthly.
- DST if:
 - patient is deteriorating clinically
 - culture remains positive or culture becomes positive again after conversion.



See Appendix 22

Adverse events related to drugs used in DR-TB regimens

Side effects occur more commonly with second-line anti-TB drugs, compared to first-line anti-TB drugs. Patients (and their treatment supporters) need to be informed of symptoms of these side effects and when to notify the health care provider.

Timely and aggressive management of all adverse events is essential, whether they are minor (non-life-threatening) or major (life-threatening). (See Appendix 22 and page 118, *Management of DR-TB*).

Contact tracing related to DR-TB

All household contacts and others having a long duration of exposure, especially if in the same indoor space, are at risk of having inhaled the DR-TB strain and developing active disease (the latter especially if having a weakened immune system).

Asymptomatic adult contacts

WHO does not recommend routine use of second-line drugs for chemoprophylaxis in cases where patients have had contact with DR-TB. Asymptomatic adult contacts should be advised that they have been exposed to a drug-resistant (DR) strain of TB, advised of the symptoms of TB and, if they develop any of these symptoms, advised that they must go to their clinic and report that they have been in contact with DR-TB. By doing this, they will be investigated for active DR-TB disease with smear microscopy, culture and DST.

Symptomatic adult contacts

Symptomatic contacts should be evaluated for DR-TB, with GeneXpert (result within days) and/or traditional culture and DST (result within weeks).



Paediatric contacts

All child contacts of DR-TB cases should be evaluated for active TB disease by a clinician. This includes:

- Thorough review of **symptoms**: Symptoms of TB in children can be non-specific, e.g. chronic cough or wheeze, failure to thrive and recurrent fevers.
- Clinical examination to look for:
 - any change in weight
 - signs of TB on examination e.g. enlarged lymph node(s), respiratory signs, pleural effusion, ascites, etc.
- The following investigations should be considered, even if no symptoms or obvious signs of TB, especially in contacts <5 years of age and HIV-infected children of any age:
 - TB skin testing (TST)
 - chest x-ray (AP and lateral)

- culture and DST: If the child is young and/or cannot expectorate, sputum induction or gastric aspiration should be performed.



All MDR and XDR-TB patients co-infected with HIV should be initiated on ARVs after two weeks, regardless of CD4 count.

Oral pathology

Oral health

Oral candidiasis (oral thrush)

Oesophageal candidiasis
(oesophageal thrush)

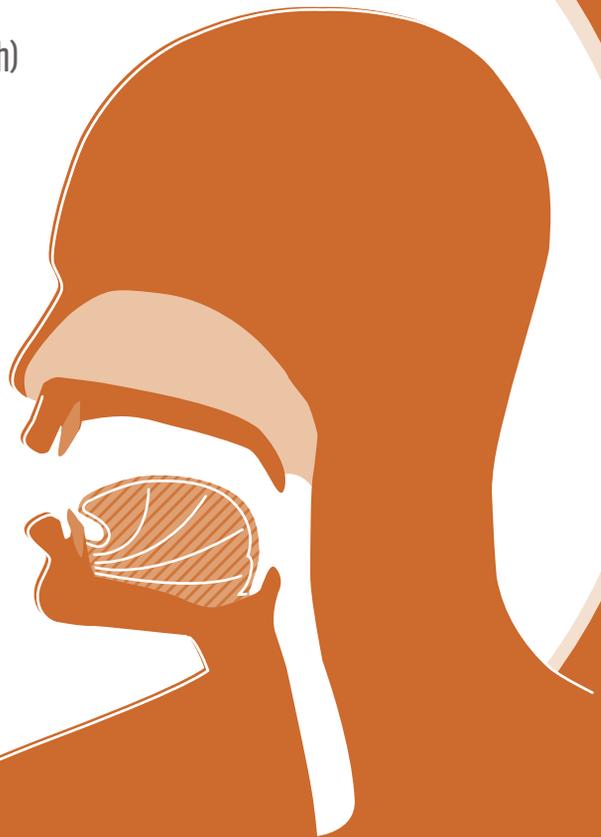
Angular stomatitis (cheilitis)

Oral ulcers

Oral hairy leukoplakia

Kaposi's sarcoma (KS)

Necrotising gingivitis



Oral health

A thorough oral exam is indicated in every patient and is particularly important for WHO clinical staging relating to ARV initiation:

Stage 3: oral candidiasis, oral hairy leukoplakia (OHL)

Stage 4: oesophageal candidiasis, HSV >1 month; oral KS (check palate)



Danger signs for referral include a patient who cannot open his/her mouth or is unable to swallow liquids and solids.

Basic oral hygiene is important to prevent infections of the oral cavity, as these occur with increased frequency in HIV-positive people. This includes:

- Regular brushing and flossing of teeth.
- Do not share a toothbrush.
- Advise a visit to the dentist if gum disease or dental cavities are present.

Oral candidiasis (oral thrush)



See Appendix 1

Oral candidiasis is caused by a yeast called *albicans*. It occurs in newborns, the elderly and those who have very weak immune systems ie. the very young, the very old, and the very sick. **It is a serious sign in HIV-infected patients as it indicates advanced immunodeficiency.** It places an adult and a child (more than 1 month old) in clinical stage 3 of HIV infection (see Appendix 1).

Clinical presentation

Oral candidiasis has two presentations:

- Pseudomembranous presentation ('thrush'): white patches (which can be removed with a tongue depressor) surrounded by a reddish border; these involve mostly the inner mucosa of the mouth, the pharynx and the inner lips.
- Thrush may present as a reddish discoloration and burning of the hard palate ('atrophic thrush'). This may be difficult to diagnose.

Patients often complain of having 'no taste'.

Ask about 'painful swallowing' and 'difficulty swallowing', which suggests co-existing oesophageal candidiasis (see page 129).

Management

- Nystatin oral suspension 1 ml qds to be swished around the mouth for as long as possible.

- If the thrush still persists then use: nystatin tablets, 500 000 IU, 1 sucked 4 times a day for 5 days or amphotericin B lozenges sucked 6 hourly for 5 days.
- Prescribe fluconazole 200 mg once daily for one week if the thrush is severe or recurrent.
- Oral candidiasis in a child (> 1 month old) or if persistent/severe, is strongly suggestive of HIV infection. See WHO AIDS clinical case definition on page 65.
 - In infants, it is sometimes accompanied by a candidal napkin rash. Prescribe nystatin drops, 1 ml 4 times daily for 7 days +/- 30 minutes after feed for 7 days. Continue for 48 hours after disappearance.
- If no response/poor response, add miconazole (Daktarin®) gel 4–6 hourly for 7–14 days.
- Treat refractory candidiasis with fluconazole 3 mg/kg/day for up to 21 days.



All patients with oral thrush should be assessed for ARVs.

Oesophageal candidiasis (oesophageal thrush)

Since the oesophagus (the muscular tube carrying food from the mouth to the stomach) cannot be visualised on physical examination, a diagnosis of oesophageal thrush is not easy to make. Usually, the clinician has to rely on a good history to make such a diagnosis.

Clinical presentation

- Oesophageal thrush must be suspected when someone with a low CD4 count complains of difficulty swallowing, or pain on swallowing, especially if oral candidiasis is present.
- In immunocompromised patients, it is often associated with a critical decrease in food intake, and consequent weight loss.
- Other possible causes of painful and difficult swallowing include:
 - gastro-oesophageal reflux disease (GORD)
 - infection of the oesophagus with cytomegalovirus (CMV consider this if CD4 <50.)
 - an oesophageal ulcer which can be either idiopathic (i.e. aphthous ulcer) or related to HSV
 - Kaposi's sarcoma (KS).

Management

- **The patient must be enrolled for ARVs as soon as possible.**
- Prescribe fluconazole 200–400 mg daily for 10–14 days, then check the response to treatment after 7 days.
 - If there is a good response, then oesophageal candidiasis is the likely diagnosis and the patient is then considered to be in clinical stage 4. Continue the fluconazole for 10 days to 2 weeks.
- If fluconazole is not effective after one week, consider other causes:
 - The majority of those with CMV-related oesophagitis will develop CMV retinitis as well. So if CMV retinitis is seen on fundoscopic examination (see Appendix 15), IV ganciclovir/valgancyclovir should be initiated.
 - If HSV is thought to be responsible, prescribe acyclovir 400 mg three times daily for 10 days.
- If none of the above treatments are effective, then the patient should be referred for endoscopy (i.e. a medical procedure to visualise the oesophagus) if at all possible.



See Appendix 15



Oesophageal thrush only occurs at low CD4 counts (i.e. <200 cells/ μ l).

If someone with a high CD4 count is complaining of retrosternal pain but is not sick (and not losing weight), that person does not have oesophageal thrush (and is therefore not in stage 4). The diagnosis in this case is more likely to be 'reflux' requiring antacids (not fluconazole).



Management in children

- Oesophageal candidiasis is difficult to diagnose in infants. Suspect it if the infant has oral candidiasis associated with excessive crying and/or refusal to feed.
- Treat with fluconazole 3 mg/kg/day for 21 days.
- If there is no improvement after 7 days, and HSV is suspected, prescribe acyclovir for 10 days. Use dose appropriate for children.
- The child needs admission to hospital if he/she does not tolerate food and/or has signs of dehydration.

Angular stomatitis (cheilitis)

Angular stomatitis is usually caused by *Candida* or sometimes bacteria.

Clinical presentation

- Involvement of the corners of the mouth, presenting as a fissure (or 'crack').
- Can be painful.

Management

- Keep dry and avoid mechanical irritation.
- Nystatin/clotrimazole cream or oral gel twice daily for 10 days is very effective.

Oral ulcers

Oral ulcers may be due to:

- **Aphthous ulcers** ('canker sores'): one or more ulcers on the mucosa of the mouth, the inner lips, and sometimes the tongue.
 - Cause unknown.
 - Very persistent and very painful (10 days).
 - Symptomatic treatment with pain relief.
 - If severe or deep, a topical steroid or steroid inhaler (aimed at the lesion) may be tried.
 - A short course of prednisone 30 mg is indicated in severe disease or oesophageal involvement.²⁷
- HSV: May present as shallow ulcers and/or blisters which are painful, extensive and/or recurrent.
 - Avoid acidic foods.
 - Pain relief: Paracetamol with codeine or/and NSAID.
 - Give acyclovir 400 mg three times daily for 5–10 days in case of HSV.

Syphilis: less painful – treat as per protocol.

Oral hairy leukoplakia

Oral hairy leukoplakia (OHL) is caused by Epstein-Barr Virus (EBV). OHL is specific to HIV infection, and indicates immunosuppression. It occurs mostly in adults and places a person in clinical stage 3 of HIV infection.

Clinical presentation

Very typical appearance: white raised vertical lines ('Adidas stripes') on the sides of the tongue.

Management

No treatment is necessary. OHL often disappears after ARVs are initiated.

Kaposi's sarcoma (KS)

Clinical presentation

- Purplish fleshy swelling on the roof of the mouth or gums.
- May often bleed.
- If KS is present on the palate or oral cavity it may be indicative of pulmonary KS or gastro-intestinal (GI) involvement as well. Investigate with a chest x-ray, especially if any respiratory symptoms.

Management

- Patient should be referred for antiretroviral treatment immediately.
- Patient should be referred to assess eligibility for chemotherapy (the treatment of choice is IV pegylated liposomal doxorubicin. If this is not available intravenous BV (bleomycin and vincristine) or ABV may be considered.)

Visit www.samumsf.org for most recent KS protocol.



Necrotising gingivitis

Clinical presentation

- This is an inflammation of the gingiva.
- It may lead to tooth loss, severe pain and foul smelling breath.

Management

- Oral hygiene.
- Antiseptic mouthwashes.
- Antibiotics: metronidazole 400 mg TDS for 7 days or clindamycin 600 mg TDS for 7 days.
- Pain management.
- This is a stage 3 condition, so the patient should be referred for antiretroviral treatment.



Oral candidiasis (oral thrush)



Oral hairy leukoplakia



Kaposi's sarcoma



Necrotising gingivitis

Dermatology

Approach to an HIV-positive person
with a skin complaint

Adverse drug eruptions

Seborrhoeic eczema

Papular pruritic eruption (PPE)

Eosinophilic folliculitis

Warts

Xerosis

Impetigo

Herpes simplex virus (HSV 1&2)

Varicella zoster virus/Chicken pox

Shingles/zoster

Molluscum contagiosum

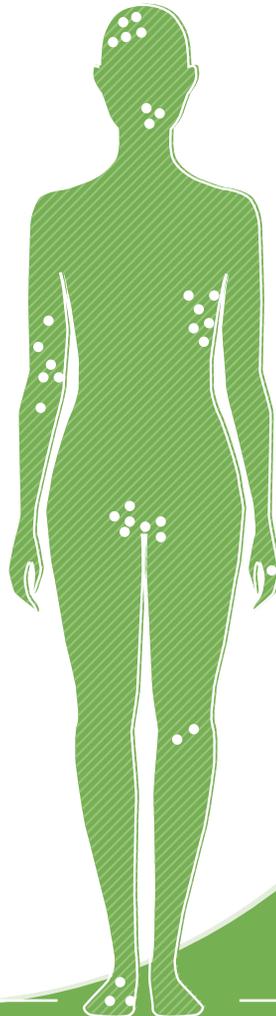
Psoriasis

Kaposi's sarcoma (KS)

Bacillary angiomatosis (BA)

Tinea

Scabies



Skin conditions are very common in people living with HIV and are often the first presenting features of HIV infection. Table 9.1 describes the common causes of skin pathology in the HIV patient.

Table 9.1 Skin diseases in HIV infection based on pathogenesis

(See also pages 158–159.)

Skin infections	Bacterial Folliculitis Impetigo Syphilis Cutaneous tuberculosis Atypical mycobacterium Bacillary angiomatosis
	Fungal Dermatophytosis Candidiasis Deep fungal infections - Cryptococcus, Histoplasmosis Penicilliosis
	Viral Human Papilloma Virus (HPV) Molluscum contagiosum Herpes zoster Herpes simplex Cytomegalovirus EBV
	Arthropod Scabies
Inflammatory conditions	Xeroderma and ichthyosis Seborrhoeic dermatitis Pruitic papular eruption Eosinophilic folliculitis Psoriasis Atopic eczema
Cutaneous malignancy	Kaposi's sarcoma Non-Hodgkin's lymphoma
Miscellaneous group	Acute seroconversion syndrome Drug reactions (lipodystrophy, nail and hair changes) Granuloma Annulare
Adverse drug reactions	Steven's Johnson Syndrome (SJS) Toxic Epidermal Necrolysis (TEN) Fixed drug eruption DRESS (drug reaction with eosinophilia and systemic symptoms) Lichenoid Photo-exacerbated reactions



See Appendix 1

Many common skin conditions are prominent in the WHO clinical staging (see Appendix 1) especially in WHO Stages 2 and 3. Table 9.2 describes skin conditions as related to CD4 count and therefore it is important to know the clinical (WHO) and immunological (CD4) status of the patient to make an accurate diagnosis.

Table 9.2 Mucocutaneous disorders stratified by CD4 count

(See also pages 158–159.)

CD4 range (per μL)	Skin diseases
>500	<ul style="list-style-type: none"> • Acute retroviral syndrome • Oral hairy leukoplakia • Vaginal candidiasis • Seborrhoeic dermatitis • Psoriasis • Kaposi's sarcoma
200–500	<ul style="list-style-type: none"> • Oral thrush • Herpes zoster • Herpes simplex • Refractory psoriasis • Hypersensitivity to nevirapine • Condyloma acuminatum • Tinea infection • Verruca vulgaris
100–200	<ul style="list-style-type: none"> • Disseminated herpes simplex • Refractory seborrhoeic dermatitis • Eosinophilic folliculitis • Pruritic papular eruption • Molluscum contagiosum • Extensive Kaposi's sarcoma
<100	<ul style="list-style-type: none"> • Cutaneous penicilliosis • Bacillary angiomatosis • Herpes simplex: large and unhealing • Cutaneous cryptococcus • Giant mollusca • Disseminated cytomegalovirus • Acquired ichthyosis

Source: <http://www.info.gov.hk/aids/pdf/g190htm/21.htm>

Approach to an HIV-positive person with a skin complaint

(See pages 158–159 for images.)

In approaching the HIV patient with a skin complaint a detailed evaluation of symptoms is mandatory. This history should especially be related to the:

- CD4 count – opportunistic infections are more likely to occur with CD4 <200 μ l.
- Medication – ARV, TB and cotrimoxazole are common causes of adverse drug reactions and could prove fatal.

Algorithm 8.1 Evaluation of symptoms

Detailed history (Hx) and examination (Ex)

- evolution of symptoms
- itch
- pain
- asymptomatic
- fever
- sore throat
- conjunctivitis
- mucositis

**Rash with pain/
discomfort**
+/- pain
+/- fever
+/- recur in
same place

grouped vesicles; red base

HSV1 and 2

dermatomal distribution

Zoster

recur in same or new
place +/- tender, dusky

**Fixed drug eruption
(FDE); consider viral
exanthem**

**But if any epidermal necrosis or dusky purple areas,
it is important to exclude adverse drug reaction
(ADR). ADR can be potentially fatal and therefore
needs special attention to allow early diagnosis,
management and/or referral.**



Refer patient

Epidermal necrosis and/or erythroderma

Consider laboratory investigations: FBC, differential count (eosinophilia), ALT, AST

<10% BSA (body surface area) epidermal necrosis + 2 mucous membranes

Stevens-Johnson Syndrome (SJS)

≥ 30% BSA epidermal necrosis

TEN (toxic epidermal necrolysis)

90% ≥ erythrodermic, ± systemic symptoms e.g. increased eosinophils

DRESS (drug reaction with eosinophilia and systemic symptoms)

Fixed drug eruption (FDE)

Rash and no/minimal itch

- Consider intractable pruritis, especially if no visible rash.
- Exclude systemic cause of itch, e.g. renal failure, thyroid disease and anaemia.

scalp: scaly patches, black dots, hairloss.

tinea

trunk and limbs: annular lesions, active edge

purple macules, papules or nodules

Kaposi's sarcoma (KS) or bacillary angiomatosis

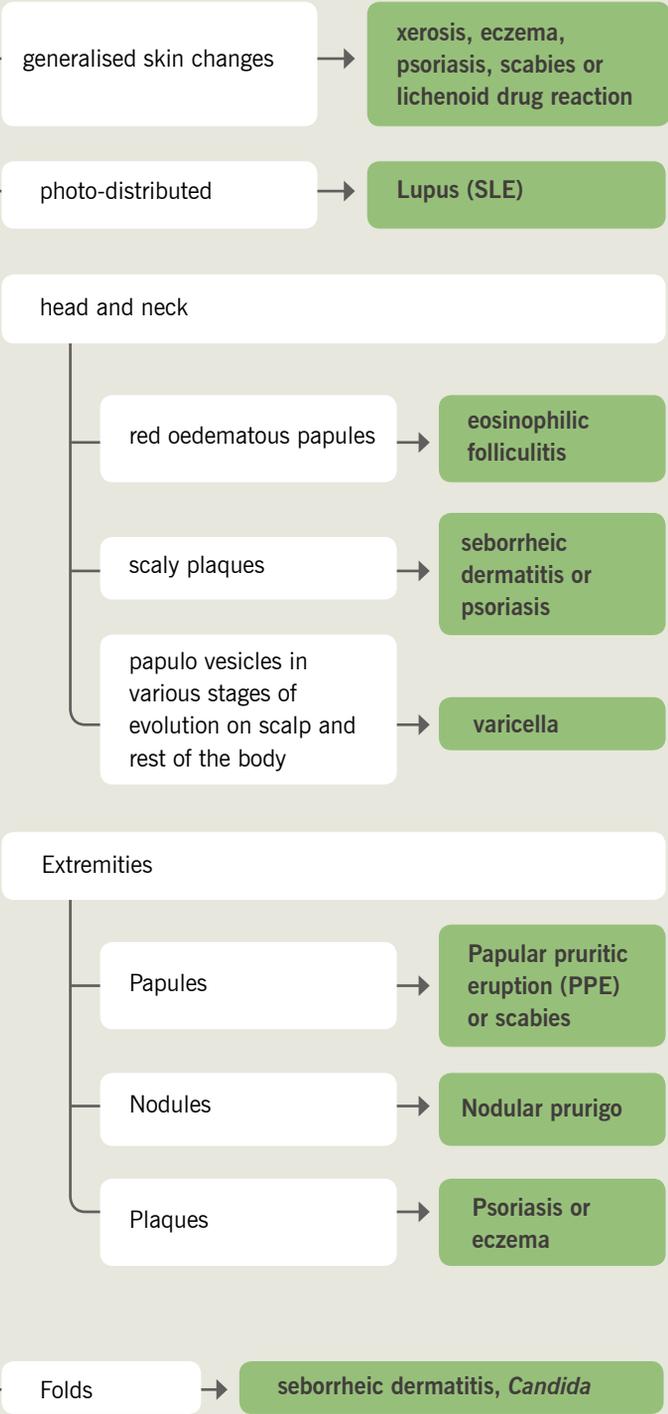
dimpled/umbilicated

molluscum or Cryptococcus (NB: check CD4)

palms and soles: +/- papulosquamous.
rest of the body

secondary syphilis

Rash and itch



Adverse drug eruptions

- All drugs have potential side effects, which often manifest on the skin.
- They can range from mild to life threatening and may involve single drugs or drug combinations.
- In the settings of HIV and TB, some of the following drugs are commonly implicated as culprits:
 - (a) **ARVs**
 - (i) nevirapine – usually in first three weeks of treatment, often just after increasing dose to 200 mg PO twice daily
 - (ii) efavirenz
 - (iii) lamivudine (3TC)
 - (iv) zidovudine (AZT)
 - (v) abacavir
 - (vi) etc.
 - (b) **cotrimoxazole** (for PCP and other prophylaxis)
 - (c) **TB drugs**
 - (d) Others – **anti-epileptics** (e.g. carbamazepine, phenobarbitone), **NSAIDS**, **allupurinol**, etc.

When a patient presents with a rash and fever, with or without conjunctivitis and constitutional symptoms, the 'knee jerk' reaction would be to blame it on a viral exanthem, but always consider a drug reaction as it may be life threatening.

Taking a good history and doing a good physical examination is key to the diagnosis.

Key features of some drug eruptions

- (a) **Fixed-drug eruptions** (e.g. NSAIDS, tetracyclines, phenolphthalein laxatives):
 - Nummular or coin-shaped hyperpigmented areas.
 - May be localised or extensive.
 - May blister.
 - Usually recurs on same place \pm new ones.
 - Stop the offending drug.

NB: Refer patients with extensive disease, seen as serious drug eruption.



Refer patient



Refer patient

(b) **Lichenoid drug eruptions and photodermatitis** (e.g. thiazides, TB drugs, chloroquine, Bactrim®):

- Patients develop lichenoid pigmentation (slate grey/blue color) of skin, sometimes in more photo-distributed areas but can be generalised.
- Stop offending drug and refer.



(c) **Drug hypersensitivity syndrome/DRESS**

- Erythroderma or diffuse morbilliform eruption involving 90% or more of skin.
- Fever with or without associated lymphadenopathy (cervical, suboccipital).
- \pm Eosinophilia (check FBC/DIFF).
- \pm Nephritis and pneumonitis (check BP, urine dipstick, CXR).
- Usually starts approximately 3 weeks after the start of medication.
- **Stop the offending drug.**
- **This is a serious adverse drug eruption, so refer urgently.**



Refer patient



(d) **Stevens-Johnson syndrome and Toxic Epidermal Necrolysis:**

- These are serious adverse drugs eruptions. They involve epidermal necrosis to varying degrees from less than 10% to more than 30% body surface area, involving at least 2 or more mucous membrane, e.g. eyes, mouth or genitalia.
- Usually starts as an abrupt onset of dusky purple macules areas with pain on shedding of skin secondary to pressure, leaving red weepy areas suggestive of burn (positive Nikolsky's sign)
- **NB: Stop the offending drug. Refer urgently, requires in-hospital management.**



Refer patient

Seborrhoeic eczema

This is a common scaling and sometimes weeping rash that typically involves inflammation in areas rich in sebaceous 'oil secreting' glands **common in HIV infection**.

Key features

- Most common on face, ears, scalp, chest and body folds.
- Infantile and adult forms exist.
- Sharply demarcated patches that are pink or red.
- Yellow to brown flaky 'greasy' scales, \pm vesiculation and crusting.
- Usually has a mild course and little discomfort.
- When a patient presents with widespread, erythrodermic disease and/or therapy resistant disease this may be a pointer to check the patient for immunosuppression.

Management

Scalp

- Use cetamagrocol cream, olive oil, or 5% salicylic acid in emulsifying ointment on scalp overnight to soften scale crust.
- Wash out and shampoo e.g. Selenium sulphate, tar, ketoconazole shampoo.
- Keep hair short, easier to manage.
- For inflammation of scalp, use mild to moderate potency cortisone gel or lotion e.g. Synalar® gel or Betnovate® scalp lotion.

Skin

- Better to use formulation in cream, lotion or gel form.
- Face: 1% hydrocortisone cream.
- Flexures and rest of body: 10% betamethasone cream.
- Treat secondary infections.
- NB: Please refer severe cases for dermatologist opinion.

Infants

- Skin: 1% hydrocortisone cream.
- Scalp: 2% salicylic acid, 2% sulphur precipitate in aqueous cream and apply overnight.



Refer patient



Papular pruritic eruption (PPE)

Often reported as one of the most common rashes seen in HIV infection. This is a form of prurigo and a diagnosis of exclusion as it is often lumped as a mixed bag of conditions with insect bite reactions, eosinophilic folliculitis and pityrosporum folliculitis, etc.

May represent a spectrum of pruritic disorders.

Key features

- Chronic pruritis, symmetrically distributed non-follicular sterile papules and pustules. More on extensor surface of limbs, but also trunk and face; sparing palms and soles and mucous membranes, in the absence of other definable causes in an HIV infected individual.
- Initial non-descript red papules may become pigmented and hyperkeratotic.
- Often the presenting sign of HIV and is more common when the CD4 count is <200 cells/ μ l.

Management

- Exclude other causes e.g. scabies.
- Very resistant to treatment.
- Topical potent cortisone e.g. betamethasone, topical tar preparations e.g. LPC.
- Oral antihistamines.
- If no response, refer to dermatologist for possible phototherapy.

Eosinophilic folliculitis

- One of the more characteristic and common pruritic dermatoses associated with HIV infection.
- A similar eruption occurs in HIV-negative individuals, called Ofuji's disease.

Key features

- Edematous, red, skin-coloured papules and pustules.
- Pruritic.
- Can involve face, scalp, neck and trunk.
- Cultures are negative; may have peripheral eosinophilia.
- Skin biopsy shows eosinophils around hair follicles and sebaceous glands may be recalcitrant to treatment; topical steroids, antihistamines and antifungals have been used for symptomatic relief.
- Severe cases may require phototherapy or oral retinoids.
- May fluctuate and improve with initiation of ART.

Warts

Caused by direct skin-to-skin contact or inoculation with the human papilloma virus (HPV), with different subtypes responsible for different variants of genital and non-genital warts.

Type of wart	Common HPV type
common	2, 4, 29
plantar/ palmar	1, 2, 4, 10
flat	3, 10
anogenital	6, 11, 42, 44
oncogenic subtypes associated with malignancy	16, 18, 31, 33, 35

Key features

- Single or multiple skin-coloured papules that may coalesce to form a plaque.
- Flat or raised and smoothed or roughened surfaces.
- Localised or extensive.
- Common on hands, face, feet, genitalia.

- On genitalia known as 'condylomata accuminata' and may assume a cauliflower-like appearance.
- May last months to years and regress spontaneously if immunity normal.
- In immunosuppressed host, warts have the tendency to be florid and recur post-treatment.
- May present in such a way as a manifestation of immune reconstitution inflammatory syndrome (IRIS), especially post-initiation of ART.

Diagnosis

- Clinical appearance.
- Clues to diagnosis: black dots on surface of wart which are actually thrombosed blood vessels.
- Histological appearance on biopsy (usually not needed).
- Serotyping.

Management

Non-genital warts

Reassure as they generally resolve spontaneously or with improved immune status. For children and flat warts, this may take time.

Various methods for treatment of individuals for genital warts include:

- wart paint (1 part salicylic acid, 1 part lactic acid, 3 parts collodion)
- cryotherapy
- electrocautery and curettage
- trichloroacetic acid
- imiquimod cream .

Genital warts

- Podophyllin 25% in tincture of benzoic compound (TBCO); apply every one to two weeks. Ensure protection of surrounding non-involved skin with Vaseline. Fix with talcum or French powder; advise patient to wash off after 4 hours.
- Imiquimod cream applied 3 times/week to affected areas for up to 16 weeks.

NB: Refer complicated cases to dermatologist or gynaecologist.



Refer patient

Xerosis

Abnormally dry skin. ('Xero' is a Greek word meaning 'dry'.)

May result from endogenous and exogenous factors, including dry climate, frequent showering, detergents, malnutrition, thyroid disease and hereditary cause, like ichthyosis vulgaris, etc.

Key features

- Dull, dry, rough, scaly skin.
- May have associated pruritis.
- In severe cases may exhibit a 'fish scale' or 'crazy paving' pattern of cracked, dry skin.
- May have associated asteatotic eczema/eczema craquele.
- Common in HIV infection (>20% of cases).

Management

- Modify daily routine e.g. take shorter showers or baths with lukewarm water. Moisturise regularly, at least 3 to 4 times/day with e.g. emulsifying ointment or cetomagrocol.
- If underlying eczema, may need topical cortisone.
- NB: Exclude other underlying causes of xerosis (as mentioned above).

Impetigo

Common, contagious superficial infection of the skin, more often seen in children.

It is caused by both *B-haemolytic streptococci* and *staphylococci*, e.g. *Streptococcus pyogenes* and *Staphylococcus aureus*. This is more commonly seen in areas of high humidity and poor living condition and may develop post insect bites, sites of minor trauma or complicated conditions, such as eczema and scabies.

Key features

Non bullous impetigo

- Due to *Streptococcus* and *Staphylococcus*.
- Yellow to honey-coloured crusts, overlying an erosion.

Bullous impetigo

- Blisters, flaccid or with cloudy content +/- erythema.
- Caused by *staphylococci* that produce exfoliative toxins.

Management

- Soak off crusts with lukewarm water.
- For localised lesions use antibacterial creams e.g. povidone iodine, mupirocin or fusidic acid.
- For more extensive lesions, consider oral antibiotics e.g. flucloxacillin.
- Advise patients on anti-staphylococcal measures.
- Infected contacts should be treated.
- Resistant cases may need bacterial swabs for culture and sensitivity.

Herpes simplex virus (HSV 1 & 2)

- Forms part of the human herpes virus family which include: VZV, EBV, CMV and HHV8.
- HSV 1 & 2 are transmitted via close physical contact through a break in the mucocutaneous surface with that of an infected individual.
 - HSV 1 – orolabial lesions.
 - HSV 2 – genital lesions.

Key features

- Grouped vesicles on an erythematous base that may evolve to painful erosions and ulcers, ± secondary crusting.
- May appear pustular, ± scalloped borders.
- Affected areas include lips, nose, tongue, oropharynx, buccal, gingival and anogenital areas.
- May have a prodrome of burning and tingling.
- Usually recurs at same site due to reactivation of latent virus migrating back via nerves to primary site of infection.

Diagnosis

- clinical features
- Tzanck smear for multinucleate giant cells
- viral culture and PCR.

Management

- Prevention:
 - Avoid skin-to-skin contact during flare.
 - Advise use of condoms in genital herpes.
- Orolabial lesions can be treated with symptomatic treatment e.g. zinc sulphate in aqueous solution topically and sulphadiazine cream to prevent secondary infection. Topical antivirals, e.g. acyclovir or penciclovir cream may be used but are of limited value.

Oral antiviral agents are indicated for:

- immunosuppressed patients
- ocular lesions (NB: Refer to ophthalmologist)
- eczema herpeticum in atopic eczema
- genital lesions with frequent recurrences.

Oral antivirals e.g. acyclovir are optimally used if started within 72 hours of start of lesions.

Adjust dose of acyclovir if creatinine clearance is <50 ml/min. (See Appendix 25.)



Refer patient



See Appendix 25

Varicella zoster virus/Chicken pox

VZV (HHV-3)

- Varicella or 'chicken pox' is the infection with the VZV and may later reappear during periods of stress or depressed immunity as a secondary phenomenon of 'shingles' (also known as 'zoster').
- It is most common in children and is contagious.
- It is spread via direct contact with lesions or respiratory secretions.

Key features

- Mild prodromal symptoms with rash appearing 2–3 days later.
- Initial lesions usually appear on the face and scalp then spread to trunk and limbs; can involve mucosa.
- Pruritic papulovesicular lesions (can be pustular) evolve over days to become scabs and crusts, with or without scars.
- Lesions usually form successive crops in various stages of evolution.



- Children with immunosuppression may have larger extensive lesions and are more likely to complicate. Immunosuppressed patients and primary infection in adulthood may be complicated by hepatitis, encephalitis, etc. **NB: Monitor closely for signs.**

- The patient is infectious for approximately 4 days before rash the appears until 4 days after crusting of all lesions.

Diagnosis

- clinical features
- clue – lesions in scalp
- Tzanck smear
- viral culture or PCR.

Management

- Isolate child or adult if possible until all lesions have crusted over.
- Patients with normal immunity can be treated symptomatically with antipyretics, antihistamines, calamine lotion and tepid baths.
- If started within 72 hours of cutaneous eruption, acyclovir has been shown to decrease duration and severity of infection.
- Treat secondary bacterial infection.
- Prevention and post exposure prophylaxis (PEP) with varicella immunoglobulin (VZIG) is recommended for all immunocompromised individuals with first time exposure to varicella and must be given within 96 hours of exposure.

NB: Refer to hospital if:

- appropriate medication not available
- disseminated infection suspected (pneumonia, jaundice, neurological findings, etc.)
- dehydrated, ill patients.



Refer patient

Shingles/zoster

- Due to reactivation of VZV (chicken pox), during periods of a weakened immune system (e.g. during stress, old age, HIV infection).
- Often described as the 'belt of roses from hell' or 'dew drops on a rose petal'.

Key features

- ± Prodrome of intense pain, tingling, tenderness, hyperesthesia in more than 90% of patients.

- Rarely, pain is not followed by a rash (zoster sine herpette).
- Commonly forms grouped vesicles on an erythematous base base, unilateral, **following a dermatome**, usually trunk but can affect face and other areas.
- May heal with scarring and post herpetic neuralgia (PHN).
- When patients are immune suppressed, rash may be atypical, generalised, cross nerve roots, persistent crusted and verrucous lesions.
- Disseminated cutaneous disease, defined as more than 20 vesicles outside area of primary or adjacent dermatomes and/or visceral involvement. Approximately 5% of patients with zoster will experience a recurrence, usually in same dermatome.



Is herpes zoster contagious?

Direct contact with a cutaneous lesion may result in transmission of primary varicella (chicken pox) to a susceptible host but not zoster itself.

Should I be concerned about zoster involving the nose ('Hutchinson sign')?

- Lesions involving tip side or root of nose indicates involvement of the trigeminal nerve and should alert you to the possibility of ocular involvement.

NB: Refer to ophthalmologist.

- **Ramsay-Hunt syndrome:** triad of cutaneous zoster involving auditory canal, auricle, ipsilateral facial palsy and excruciating ear pain.



Refer patient

Diagnosis

- clinical features
- Tzanck smear
- viral culture and PCR.

Management

- Pain control – (paracetamol ± Codeine, add Amitriptyline if not adequate).
- Acute vesicles – calamine lotion.
- Eroded areas – Sulphadiazine cream or Povo-Iodine cream.
- Treat secondary infection if present.
- Ocular lesion – add eye lubricant or chloramphenicol ointment.
- Oral acyclovir if rash present less than 72 hours, especially in those who are immunocompromised and ocular or auditory disease, and refer to appropriate specialist.

Molluscum contagiosum

- Pox virus infection.
- Common especially in children and immunocompromised individuals.
- Transmitted through skin-to-skin contact and can be spread sexually.

Key features

- Umbilicated skin coloured papules (with central dimples), that can occur anywhere on skin surface.
- May be extensive, coalesce, persistent and resistant to treatment in immunocompromised patients.
- Must be differentiated from cryptococci and dimorphic fungi – if misdiagnosed, risk of cryptococcal meningitis.
- May present as part of IRIS, post initiation of ART.

Diagnosis

- Clinical features.
- Usually you can express the white molluscum body with a needle or curette.
- 'Henderson Patterson body' has a characteristic histological appearance on microscopy and staining.

Management

- Reassure patient (usually resolves with ARVs in HIV setting but may get worse before getting better).
- Individual lesions may improve spontaneously but can be treated with wart paint, cryotherapy, trichloroacetic acid. If no improvement, refer for possible ARVs.
- If extensive, manual removal with curettage, ± electrocautery is also a viable option.

Psoriasis

- Papulosquamous condition of the skin that may involve skin, scalp, nails and joints.
- Overall incidence not increased in HIV, but the clinical presentation may be more dramatic and the patients may be more recalcitrant to treatment.
- Patients have a genetic predisposition set off by various triggers, e.g. infections (stress), drugs (B-blockers, lithium), stress, etc.

Key features

- Red to purple papules and plaques with a silvery scale.
- Usually little or no pruritis; may vary.
- More extensor surfaces on arms and legs, but also abdomen, back, scalp, palms and soles.
- Can involve folds ('inverse psoriasis').
- Can be pustular or erythrodermic; patient then usually more febrile and ill looking. (NB: Refer to dermatologist.)
- May develop psoraitic arthritis (refer to rheumatologist).
- Perform scratch test (see page 159).



Refer patient

Diagnosis

- Clues
 - Nails: pitting, onychodystrophy, onycholysis.
 - Skin: Silvery scale – elicit with orange stick \pm Auspitz sign if scale removed with bleeding points underneath.
 - Scalp: Thick stuck-on scales, can form 'limpets'.
 - Koebner phenomenon: Psoriasis developing at sites of physical trauma.
- Biopsy – for histology (characteristic).

Management

- Refer to dermatologist to initiate treatment if extensive disease.

Table 9.3 Topical treatments

Examples of topical treatments applied to:	
Skin on trunks and limbs	5% LPC (liquor picis carbonis) 5–10% crude coal tar 5–10% salicylic acid in white soft vaseline, modified Adamsons ointment
Body folds	diluted cortisone, e. g. 10% betamethasone cream
Scalp	selenium sulphide, tar, shampoos, salicylic acid preparations, cortisone lotion or gel

- Severe cases must be referred for specialist management and may require initial hospital inpatient care.
- Dermatologist may add phototherapy or systemic retinoids and such patients may require ART irrespective of CD4 count if disease is extensive and recalcitrant.
- Children can be started on 1% hydrocortisone but should be referred to a dermatologist.



Refer patient

Kaposi's sarcoma (KS)

- Vascular tumour due to infection of vascular endothelium by human herpes virus-8 (HHV-8) in the setting of HIV.
- KS can occur in non-immune suppressed individuals.
- KS lesions signify clinical stage 4 disease.

Key features

- Violaceous to purple, macules, patches, papules, nodules and plaques.
- Single or multiple with a smooth or scaly, hyperkeratotic, ulcerated or haemorrhagic surface.
- Often on palate but can affect trunk, limbs, nose, genitals, etc.
- KS sometimes associated with lymphedema of associated leg.



www.samumfsf.org



Patients with KS should be sent for early ART initiation, regardless of CD4 count.

See KS protocol on SAMU website: www.samumfsf.org

Management

- Palate and general skin examination.
- Assess for signs of organ involvement, e.g. pleural effusion, chronic cough, blood in stools and ascites.
- Investigations: CXR, \pm abdominal ultrasound.
- Initiate ART as soon as possible.
- Refer to oncologist to assess need for chemo or radiotherapy.



Refer patient

Bacillary angiomatosis (BA)

Key features

- Gram negative bacillary disease caused by bartonella henselae (found in cat fleas) and bartonella quintana (found in the human body louse); can involve skin as well as lymph nodes, liver, spleen and bone.
- Cutaneous and subcutaneous lesions can be solitary or multiple violaceous papules and nodules.
- The vascular looking lesions may mimic KS.
- Organisms can sometimes be demonstrated with a Warthin-Starry silver stain on histological specimens.

Management

- Prevention: Individuals with HIV should avoid contact with cats, especially kittens, to minimise risk of acquiring BA (as well as toxoplasmosis).
- Antimicrobial: Mainstay of treatment is erythromycin and doxycycline but other macrolides have been used.

Tinea

- Dermatophyte infection of the skin caused by fungi that live off keratin found in skin, hair and nails.
- Common dermatophytes include trichophyton, epidermophyton and microsporum.
- Scalp – T. Capitis.
- Body – T. Corporis.
- Feet – T. Pedis.
- Spread via infected humans, animals and soil.

Main features

- **Trunk, face and limb** will have annular lesions with a raised, red or vesicular, scaly edge (so called 'active edge') with central healing.
- **Scalp:** Round scaly patches with partial hair loss; ± Black dots or broken hairs; Less common – diffuse scaling or boggy, inflamed masses (kerion).

Diagnosis

- Clinical suspicion.
- Scrape for microscopy with 10–20% KOH (potassium hydroxide preparation).
- Look for fungal hyphae on skin and endo- or ectothrix in hair.

Management

- Localised cutaneous lesions can be treated with topical Whitfield ointment, imidazole cream, or terbinafine cream. If in toe web spaces, keep area dry. Change socks often, encourage open shoes, talcum powder.
- More extensive disease needs oral medication, e.g. griseofulvin or fluconazole.
- Scalp disease: needs oral antifungal treatment (e.g. children griseofulvin 10–20 mg/kg for 6 weeks. Wash with betadine shampoo. Topical antifungals are not effective.
- Nails require oral therapy, fungal nail infection is a stage 2 disease.

Scabies (*sarcoptes scabies var hominis*)

The scabies mite is an obligate human parasite spread via close skin-to-skin contact, e.g. handshakes, sexual contact, infected clothing and bedding/fomites and can stay alive for more than 48 hours off human skin.

Key features

- Pruritis – usually worse at night, can take up to one month to manifest on first exposure and can manifest within 24 hours on re-infestation.
- The rash ranges from burrows, papules, nodules to pustules involving hands, feet, **webspaces**, axillae, abdomen, genitalia, trunk, limbs.
- Face usually spared.
- Infants, rash can be seen on palms and soles, \pm pustules on scalp and face.

Diagnosis

- Clinical features.
- Find burrows; scrape check under oil on microscope for mite, body parts, eggs and faecal material.



What is Norwegian scabies?

- Massive infestation of mites proliferate to produce a thick greyish crust. This seems to be in response to an inadequate host of immune response.
- Scratching may be absent as itching is variable.
- Commonly seen in immunosuppressed patients, elderly living together in close confines of a home, mental illness, etc.

Management

- Treatment should include patient and all close physical contacts, regardless, whether they are itching or not.
- Topical benzoyl benzoate lotion from shoulder down – wash off after 24 hours and repeat treatment in 7–10 days.
- In children (6 months–5 years) a 50% dilution of this may be used (diluted 1:1 with equal amounts of water).
- For infants less than 6 months, 5% sulphur ointment used nightly for 3 days.
- Other topical treatments include 5% permethrin cream, gamma benzene hexachloride (not ideal in children), crotamiton cream.



- Persistent and severe case will require oral ivermectin.
- Treat pruritis with oral antihistamines, \pm dilute topical steroids as often it is accompanied by an eczematous rash.
- Wash clothing, bed sheets in hot water; when not possible, leave items sealed in a bag for 10 days.
- Post-treatment itching may persist for a further 2-4 weeks.

Table 9.4 Key conditions with clinical clues

Tinea	Annular lesions with an active edge and central clearing.
Herpes 1 and 2	Grouped vesicles on an erythematous base, \pm prodrome and pain. Recurs in same area.
Shingles	Grouped vesicles on an erythematous base; usually linear – in a dermatome.
Molluscum contagiosum	Dimpled papules, central umbilication. NB: Check CD4 count; if <200 exclude cryptococcus.
KS	Purple, red papules, macules, nodules.
Chickenpox	Papulovesicles at various stages of evolution; itchy on scalp and rest of body.
Fixed drug eruption	Dusky to pigmented coin-shaped hyperpigmented lesion. May blister. Recurs in same areas.
Scabies	papules and burrows with nocturnal itch
Stevens Johnson Syndrome	epidermal necrosis, dusky skin, conjunctivitis and mucositis



Stevens-Johnson syndrome



Tinea



Herpes (eczema herpeticum)



Herpes zoster



Molluscum contagiosum



Cryptococcus



Kaposi's sarcoma (KS)



Varicella (chickenpox)



Fixed drug eruption



Extensive FDE



Scabies



Papular pruritic eruption (PPE)



Psoriasis



Psoriasis scratch test



Bacillary angiomatosis



Seborrheic dermatitis

Pulmonary conditions

Introduction to
pulmonary conditions

Community-acquired
pneumonia

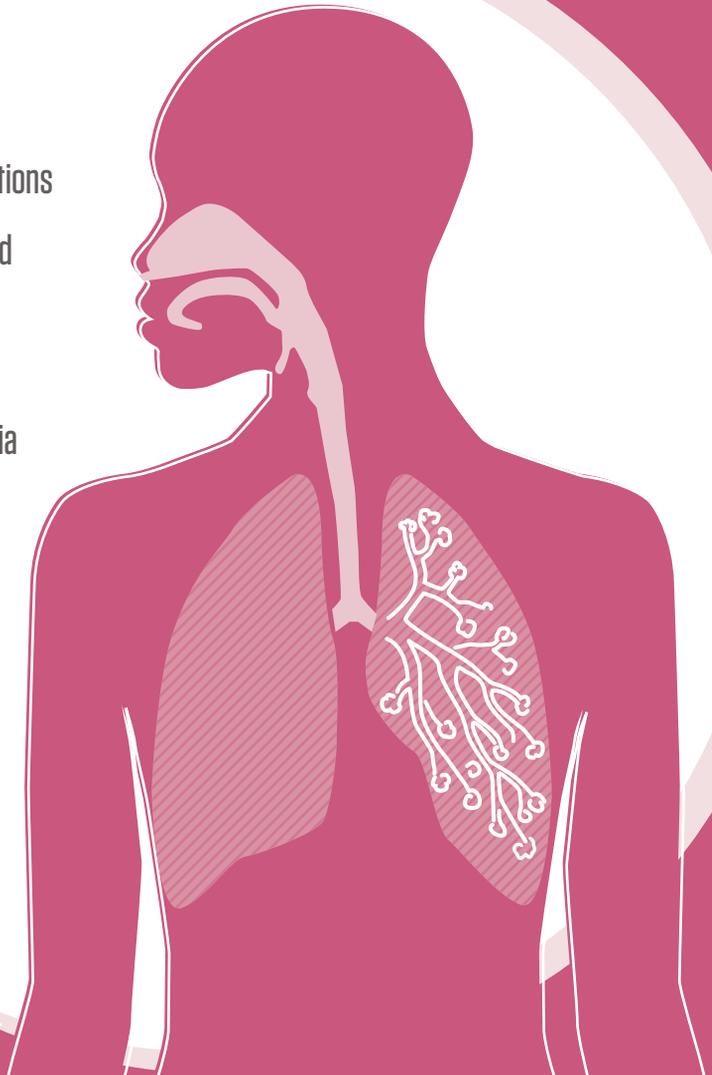
Children

Pneumocystis pneumonia
(PCP)

Tuberculosis

Lymphoid interstitial
pneumonitis (LIP)

Pulmonary Kaposi's
sarcoma (KS)



Introduction to pulmonary conditions

Common pulmonary diagnoses

The three most common pulmonary diagnoses in HIV-positive people are:

- pulmonary tuberculosis (PTB)
- lower respiratory tract infections (LRTIs)
- acute bronchitis (often viral) vs bacterial pneumonia
- *Pneumocystis jirovecii* pneumonia (PCP).

Clinical presentation

The foundation for any diagnosis is a good history and physical examination, especially when a person is sick. If someone presents with a respiratory complaint, make sure to 'ask and look' for all of the following important respiratory symptoms and signs (see also Appendix 3).

Remember that multiple pathologies can occur at the same time in 'late presenters' who have seriously compromised immune systems.

- cough: productive vs dry
- chest pain:
 - ask which side of the chest is involved, as this will help to localise the pathology (LRTI, effusion, etc)
 - also ask if it is worse on deep breathing (= pleuritic, suggesting pleural involvement)
- haemoptysis (blood in sputum)
- dyspnea (shortness of breath)
- tachypnea (fast breathing determined by examination)
- reduced air entry on one side on auscultation, which could represent:
 - pleural effusion (dull to percussion)
 - pneumothorax (hyper-resonant on percussion)
- constitutional symptoms (fever, night sweats, weight loss), which may indicate active TB disease, NTM (e.g. MAC) or malignancy.

Note that **different pulmonary conditions** tend to have different presentations:

- Acute onset (<2 weeks) is more likely to be found in:
 - acute bronchitis
 - bacterial pneumonia
 - *Pneumocystis jirovecii* pneumonia (PCP), which has a sub-acute onset, but eventual rapid deterioration.



See Appendix 3

- Chronic onset (>2 weeks) is more likely to be found in:
 - pulmonary TB
 - pulmonary Kaposi's sarcoma
 - chronic obstructive pulmonary disease (COPD)



It is important to quickly recognise those who are **severely ill**, who will have one or more of the following signs:

- respiratory rate ≥ 30 breaths/minute (adults)
- breathlessness at rest or while talking
- prominent use of the breathing muscles
- agitated or confused
- unable to walk unaided.

Management of a breathless patient

If the person is seriously short of breath, he/she will need rapid treatment:

- Oxygen (40% by face mask if possible, or at least 4 L/min via nasal prongs).
- If you have access to a pulse oximeter, this can guide the amount of oxygen.
- Antibiotics to treat any bacterial cause: ceftriaxone 1 g IM or IV.
 - If unavailable, give amoxicillin 1 g orally.
 - If allergic to penicillin, give erythromycin 500 mg orally.
- Take sputum specimens for TB testing (since TB is such a common cause of respiratory symptoms in those with HIV):
 - Molecular testing if available (e.g. GeneXpert).
 - +/- Smear microscopy.
 - +/- Determine TB LAM on urine to detect disseminated TB antigen.
- Refer the same day for chest x-ray and admission to hospital.



Refer patient

Table 10.1 Association of pulmonary infections with different CD4 strata²⁸

Most pulmonary infections occur with increasing frequency at lower CD4 counts.

CD4 cell counts when infection first occurs	Pulmonary infections		Non-infectious pulmonary conditions
>500 cells/ μ l	Acute pharyngitis, bronchitis, sinusitis	URTI symptoms	Lymphoid interstitial pneumonitis (LIP) – see page 171.
	Pneumonia (see pages 165–171)	Productive cough +/- blood. High temperature. +/- Dyspnea while walking. +/- Unilateral chest pain.	Kaposi's sarcoma (often with CD4 <100). See page 172. Spontaneous pneumothorax – associated with PCP, LIP and KS.
	PTB (<i>occurs at all CD4 count strata but with increasingly atypical presentations as the CD4 decreases. See below.</i>)	Cough (dry or productive). Fever, night sweats, LOA and LOW. May have pleuritic chest pain. Respiratory rate can be normal. Enquire about close TB contact.	Chronic lung disease. Pulmonary embolus. Pulmonary hypertension. Bronchogenic carcinoma. Non-Hodgkin lymphoma.
200-500 cells/ uL	Recurrent bacterial pneumonia	As above.	
	Varicella zoster pneumonitis	Associated with rash.	
100-200 cells/ uL	PCP (see page 168)	High mortality rate. Common in patients not on cotrimoxazole preventive therapy (CPT). Dry cough, hypoxia on exertion. +/- high temp. High respiratory rate. Subacute presentation but may worsen quickly. Watch for PCP in HIV-exposed or infected infants, regardless of the CD4 count.	
	Disseminated TB	See Table 7.1 on page 91	

²⁸ Table adapted from Hanson DL, Chu SY, Farizo KM, Ward JW. (The Adult and Adolescent Spectrum of HIV Disease Project Group.) 1995. 'Distribution of CD4+ T lymphocytes at diagnosis of acquired immunodeficiency syndrome-defining and other human immunodeficiency virus-related illnesses.' *Arch Intern Med* 155:1537–42.

<100 cells/uL	Disseminated MAC	Low CD4, pancytopenia, diarrhoea, abdominal pain, +/- hepatosplenomegaly.
	Fungal pneumonia (Aspergillosis, Candida, Cryptococcus, Histoplasmosis)	Look for associated rashes in patients with very low CD4 counts. CLAT positive in cryptococcal disease. Treatment – amphi B (for all causes) if severe, otherwise: fluconazole for Cryptococcus; itraconazole for Histoplasmosis and Aspergillus.
	Herpes simplex pneumonitis	
	CMV pneumonitis	Patient often ill with multisystem disease e.g. retinitis, oesophagitis, colitis, hepatitis and encephalitis. Often bilateral opacification on CXR. Check for CMV retinitis. Treatment – IV gancyclovir.

* Most pulmonary infections occur with increasing frequency at lower CD4 counts.

Community-acquired pneumonia

The most common causative agents for bacterial pneumonia include *Streptococcus pneumoniae* and *Haemophilus influenzae*. *Staphylococcus aureus* and gram-negative bacteria are less commonly involved. *Pseudomonas aeruginosa* tends to be a nosocomial (i.e. hospital acquired) infection.

Since pneumonia can occur in anyone regardless of HIV status, it is not considered an opportunistic infection (OI). But those infected with HIV are more likely to suffer from pneumonia (as well as all other infections found frequently in the general population) due to their weakened immune systems.

Bacterial pneumonia is a rare disease in adults below the age of 40; its occurrence suggests that a person unaware of her/his HIV status might be seropositive.

Clinical presentation

Bacterial pneumonia typically presents more acutely than TB, with the following symptoms and signs:

- productive cough, often with yellow or greenish sputum
- high temperature
- unilateral chest pain
- localised crepitations on auscultation.



Note that an infection caused by *Pseudomonas* is often described as having a 'sweet smell'.

Management

- In the presence of clinical 'danger signs', admission to hospital is necessary.
- Danger signs: resp. rate > 30 , breathless at rest or while talking, BP $< 90/60$, agitation or confusion, prominent use of breathing (accessory) muscles.
- Otherwise, outpatient management can be initiated using the following empiric antibiotics:
 - amoxicillin in a typical adult dose of 500 mg three times daily for 7–10 days
 - erythromycin in a typical adult dose of 500 mg four times daily for 7–10 days can be used in the presence of an allergy to penicillin.



Note: **Fluoroquinolones (e.g. ciprofloxacin) should not routinely be used to treat lower respiratory infections**, since these antibiotics are active against TB. Their routine use in 'coughing patients' will contribute to the development of drug-resistant strains in a setting.

- If a person does not respond to a course of antibiotics, then investigations will be necessary, including an evaluation for active TB or other pulmonary disease process (e.g. PCP).



Children

Bacterial pneumonia is very common in young children, and even more so in those infected with HIV. A child can die from bacterial pneumonia even after ARVs have been initiated, so you must be vigilant. Use the following IMCI guidelines to classify pneumonia into simple or severe.

Simple pneumonia

- Fast breathing without chest indrawing or stridor when calm, and without any clinical danger signs (unlike 'severe pneumonia' – see below).
- Commonly treated with amoxicillin 25 mg/kg/dose three times daily for 7 days (see Table 10.2 below).
- Reassess within 2 days of starting antibiotics.



Tachypnea (fast breathing) in children is defined as:

- 60 breaths or more per minute in children aged <2 months
- 50/minute or more in children aged 2–11 months
- 40/minute or more in children aged 12 months – 5 years.

N.B. The respiratory rate should be measured during one full minute in young children.

Table 10.2 Amoxicillin dose in children

Given three times a day					
Weight (kg)	Dose (mg)	Syrup	Syrup	Capsule 250 mg	Age
		125 mg/5 ml	250 mg/5 ml		
3.5–4.9	125	5 ml	2.5 ml		1–3 months
5–6.9	175	7 ml	3.5 ml		3–6 months
7–10.9	250	10 ml	5 ml		6–17 months
11–13.9	375	15 ml	7.5 ml	1 capsule	18 months–2 years
14–24.9	500	20 ml	10 ml	2 capsules	3–6 years
25–34.9	750			3 caps	7–10 years
≥35	1 000				≥ 11 years



Refer patient

Severe pneumonia

- If a child presents with **chest indrawing** or **stridor when calm**, or any clinical danger sign (**tachypnea**, **difficulty feeding**, **convulsions**, **lethargy** or **central cyanosis**), the child needs emergency care and admission to the hospital.
- Prior to hospital referral, administer oxygen by mask.
- Give the child a first dose of ceftriaxone IV or IM at a dose of 75 mg/kg:
 - 3–5 kg: 250 mg (1 ml)
 - 6–9 kg: 500 mg (2 ml)
 - 10–14 kg: 750 mg (3 ml)
 - 15–25 kg: 1 g (2 ml in each thigh).
- Check for hypoglycaemia with a point-of-care glucometer if possible.
- For HIV-exposed or HIV-infected children, especially those <1 year of age, initiate therapy with high-dose cotrimoxazole (CTX) in addition to the treatment described above, since *Pneumocystis pneumonia* (PCP) cannot be excluded and is rapidly fatal if untreated. See page 170 for management of PCP in children.
 - Severely immunocompromised children over one year of age who have not been on CTX prophylaxis should also be treated for both PCP and bacterial pneumonia.
- Total treatment duration (IV and oral) for severe bacterial pneumonia is typically 10–14 days.

Pneumocystis pneumonia (PCP)

PCP is an opportunistic infection of the lungs caused by the organism *Pneumocystis jirovecii*. Always think of PCP if one of the major symptoms is progressive **shortness of breath**, more so than coughing. People living with HIV and who have a CD4 ≤ 200 cells/ μ l are at risk, especially those who have not been taking cotrimoxazole preventive therapy (CPT).

Clinical presentation

- **Dyspnea (shortness of breath)** caused by hypoxemia (low oxygen) is the main symptom.
 - Initially this occurs only on exertion, but later also at rest.
 - The patient can progress to severe dyspnea quite quickly.
 - Hypoxemia can be confirmed with the use of a pulse oximeter device.
- Tachypnea (fast breathing).
- Nasal flaring.

- Cough which is non-productive (i.e. 'dry') and which tends to develop over several weeks.
- Fever is not always present, but when it is, can be very high.
- Chest x-ray is often **non-specific** but may show a widespread interstitial ('ground-glass') infiltrate that is more pronounced in the lower lobes.

Management

If the patient is not very dyspneic, there is strong clinical presumption of PCP and good home support, consider outpatient treatment as follows:

- **High-dose cotrimoxazole (CTX)**, where the dose is based on the adult's weight:
 - 100 + 20 mg/kg per day in divided doses.
 - Thus, a typical dose for an adult >56 kg is 4 x 480 mg tablets every 8 hours (i.e. 12 x 480 mg each day).
 - For 21 days duration.
- In adults with an **allergy** to CTX, dapson 100 mg/day + trimethoprim 300 mg/day may be used, or clindamycin 600 mg qds + primaquine 15–30 mg od for 14 days may be used.
- Add prednisone 80 mg/day for 5 days, then 40 mg/day for 5 days, and then taper until discontinued.
- Give folic acid 5 mg daily whenever a person is taking high-dose cotrimoxazole, since CTX depletes the body of folic acid.
- Monitor for CTX-associated rash, as this is very common.
- See the patient at least **twice per week**.

If severely dyspneic/hypoxic or if not responding:

- Refer immediately to hospital, since there is a risk of respiratory failure.
- Investigate for other HIV-related conditions, including active TB disease.
- Remember that more than one condition can exist at the same time, especially in 'late presenters' with low CD4 counts.



Refer patient

Follow-up

- If the symptoms of PCP have resolved after three weeks of treatment with high-dose cotrimoxazole, don't forget to continue giving a maintenance (preventive) dose of cotrimoxazole (960 mg once daily), or the PCP can recur. See Table 10.3 on page 171 for further details.



An adult or child who has suffered from PCP is in the final clinical stage of HIV infection (i.e. stage 4 or AIDS) and must be enrolled for ARVs as soon as possible.



Children

PCP is common in HIV-infected children less than 1 year in age. In older children, it is seen mainly in severely immune-compromised children not on cotrimoxazole preventive therapy (CPT).



See Appendix 29

Clinical presentation

- PCP in children typically presents with:
 - tachypnea (see Appendix 29 for normal vital parameters in children)
 - dyspnea (severe difficulty in breathing)
 - cyanosis
 - sudden onset of fever, although this is not always present; the child may be without fever or have a low grade temperature.
- Chest auscultation is less specific and important compared to the degree of respiratory distress.
- The chest x-ray may show a diffuse interstitial infiltrate.
- PCP is frequently seen in children who are not taking cotrimoxazole prophylaxis, but it is important to note that being on CPT does not exclude the diagnosis, especially in an infant, or a child with low CD4 count.

Management

- Children with PCP initially require inpatient management.
- Cotrimoxazole 100 + 20 mg/kg/day given in divided doses (i.e. three or four times a day) for 21 days. See weight-based dosages in Table 10.3 below.
- The first dose of CTX should be given prior to hospitalisation. In hospital, the CTX should be administered intravenously four times a day.
- Once the child begins to improve and can be managed as an outpatient, CTX can be administered orally three times daily.
- Treatment with cotrimoxazole can be given in addition to the usual treatment for pneumonia (e.g. amoxicillin).
- In severe cases, add prednisolone 1mg/kg/dose twice daily for 5 days, then 1 mg/kg/dose once daily for 5 days, then 0.5 mg/kg/dose once daily for 5 days.
- After completion of treatment, secondary prophylaxis with cotrimoxazole is important.
- If the child is allergic to cotrimoxazole, dapsone 2 mg/kg/day can be given as an alternative for prophylaxis.

Table 10.3 High-dose CTX for treatment of PCP in children

Weight (kg)	Dose given 4 times a day		Dose given 3 times a day	
	Syrup (200 + 40 mg/5 ml)	480 mg tab	Syrup (200 + 40 mg/5 ml)	480 mg tab
Less than 5	2.5 ml		4 ml	
5–9.9	5 ml		7 ml	
10–14.9	7.5 ml		10 ml	1 tab
15–21.9	10 ml	1 tab	15 ml	1½ tab
> 22	15 ml	1½ tab		2 tabs

Tuberculosis

Tuberculosis is a very common opportunistic infection in people living with HIV (PLHIV). It is an airborne infectious disease caused by the organism *Mycobacterium tuberculosis* (MTB).

Upon inhaling MTB, a person with a healthy immune system will control the MTB, such that there is only a 10% risk of it ever developing into active TB disease in that person's lifetime. However, those with weakened immune systems, such as young children and PLHIV, are less able to control the MTB and have a much higher risk of developing active TB disease, both in the lungs (**pulmonary TB**) and outside the lungs (**extrapulmonary TB**). Instead of a 10% lifetime risk, PLHIV develop active TB disease at a rate closer to 10% per year. Thus, when a person living with HIV presents with cough and other pulmonary symptoms, pulmonary TB (PTB) always needs to be ruled out.

To make matters worse, **drug-resistant TB** (DR-TB) is a growing threat that is commanding more and more resources to diagnose and treat. For more details on this most common cause of morbidity and mortality in PLHIV, see Chapter 7.



See Chapter 7

Lymphoid interstitial pneumonitis (LIP)

Lymphoid interstitial pneumonitis (LIP) is not an opportunistic infection, but a chronic condition of the lungs of unknown cause that occurs in 25–40% of children who acquired HIV at the time of birth. The presence of symptomatic LIP means that the child is in clinical stage 3 disease.

Clinical presentation

- LIP is often asymptomatic but at times presents with a chronic cough.
- It is important to recognise this condition because the clinical picture (chronic cough) and chest x-ray (interstitial infiltrate similar to a miliary pattern) can easily be mistaken for TB.



- Signs to look for in a child with LIP are: **enlargement of the parotid glands, hepatosplenomegaly** and finger **clubbing**.

Remember: A child can have both LIP and active TB disease. So making a diagnosis of LIP does not mean that you have excluded the diagnosis of TB. In general, it is helpful to remember that a child with LIP will not be very sick unless he/she has severe progressive LIP (seen usually in a child who is not on ARVs).

Management

- LIP improves with antiretroviral therapy (ART).
- Specific treatment (including oral steroids) is needed only in severe progressive cases, i.e. children who have oxygen saturation consistently <92% and/or those who develop signs of right-sided heart failure.
- If the child becomes febrile or acutely symptomatic, give amoxicillin 25 mg/kg/dose TDS for 10–14 days (to treat bacterial super-infection).
- At the same time, investigate for TB (sputum testing, etc.). If TB has been ruled out, then a prolonged course of oral steroids can be considered. However, these should be prescribed in consultation with an experienced clinician/paediatrician.



Refer patient

Pulmonary Kaposi's sarcoma (KS)

Pulmonary Kaposi's sarcoma is a serious diagnosis with a poor prognosis, even in patients on ART.

Clinical presentation

- Suspect pulmonary KS whenever a patient with cutaneous or oral KS lesions is having respiratory symptoms. Pulmonary KS can, however, occur when cutaneous lesions are absent.
- Pulmonary KS may have a similar presentation as pulmonary TB (PTB) or PCP.
- Pleural effusion is common (and often blood-stained).
- Chest x-ray is non-specific, but may show 'flame-shaped' haemorrhages extending from the hilar regions.

Management

- In patients with cutaneous or oral KS lesions, who have pulmonary symptoms, it is still necessary to rule out active PTB.
- Arrange for sputum samples to be sent for TB testing (GeneXpert, smear microscopy).

- Perform a CXR if possible.
- Any pleural effusion should be 'tapped' if present and the appearance of the pleural fluid noted. Consider sending the fluid for TB testing, protein analysis (or ADA), culture and sensitivity, and, if available, cytology.
- The presence of blood in the pleural effusion suggests pulmonary KS.
- Ideally, those suspected to have pulmonary KS should be referred for bronchoscopy and biopsy, if possible.
- Once confirmed, pulmonary KS requires treatment with chemotherapy:
 - The most efficacious treatment is IV pegylated liposomal doxorubicin (PLD).



Refer patient

Neurological conditions

Peripheral neuropathy (PN)

Meningitis in PLHIV

Bacterial meningitis

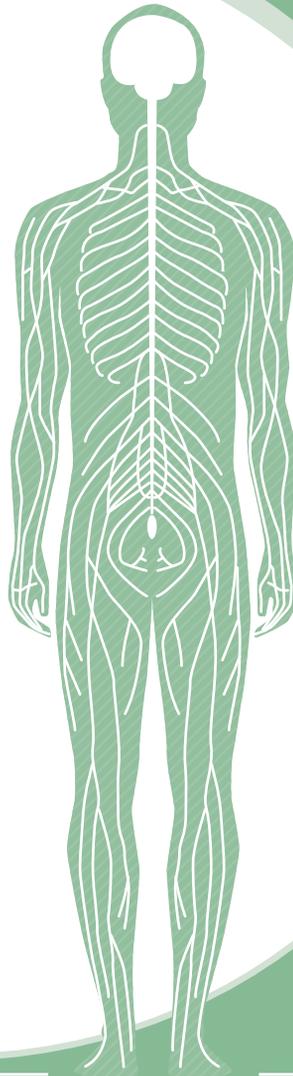
Cryptococcal meningitis

TB meningitis (TBM)

Cerebral toxoplasmosis

HIV encephalopathy/dementia

Cerebral stroke



Peripheral neuropathy (PN)

Peripheral neuropathy (PN) is a condition that frequently affects HIV-positive individuals, occurring in one-third of patients with CD4 <200 cells/ μ l. It can have many different causes, including HIV infection itself, vitamin deficiencies (B₆, B₁₂, thiamine, etc.) and be a side effect of different drugs, including ARVs (d4T or DDI), TB drugs (INH) and those used to treat other HIV-related conditions (e.g. vincristine for KS). Drug-related neuropathies usually present after the first month of treatment. Additional causes of PN include diabetes and alcohol abuse.

Clinical presentation

- Decreased sensation in a 'glove and stocking distribution' (hands and feet), although symptoms related to the feet are most common (especially the soles).
- Presenting as 'pins and needles', or a burning sensation.
- Can also be described as 'cold feet' at night with cramps, mainly in the legs.
- May lead to motor signs in prolonged cases (so test and note ankle and knee jerk reflexes at presentation).
- Can lead to significant disability if prolonged, which may be irreversible.

Prevention of PN

Try to **prevent** PN in those taking the anti-TB drug isoniazid (abbreviated as INH or just H). Ensure that **pyridoxine** is always prescribed simultaneously. The following doses of preventive pyridoxine are recommended:

- Children <5 years: 5–10 mg OD.
- Adults and children >5 years: 10 mg OD.²⁹
- If only 25 mg tablets are available, these should be prescribed 3 times per week.
- If an adult (15 years or older) on d4T needs TB treatment containing INH, consider substituting d4T with TDF (as long as the CrCl is >50 ml/min).



NB: If the patient is being prescribed an anti-TB injectable, avoid co-administration of TDF due to the additive risk of renal toxicity seen with anti-TB injectables and TDF. Instead, use another NRTI (e.g. AZT).

- Remember: If there is any suspicion of virological failure, never change just one ARV.

General management of PN

Impairment will progressively worsen and may be permanent if not treated promptly. It is best to treat peripheral neuropathy aggressively by removing or treating the underlying cause and providing symptom relief.

- What is the clinical distribution and severity?
- Exclude diabetes and alcoholism as causes.
- Check drugs: are there medications that are commonly implicated, e.g. isoniazid, d4T, or DDI?
- Treat underlying cause e.g. vitamin B₆ deficiency, drug substitution.
- Provide symptomatic pain relief.
- Verify that symptoms are symmetrical. If the symptoms are asymmetrical or associated with other neurological signs (e.g. weakness of an extremity) or loss of function, it is necessary to rule out other causes, which could be intracerebral or related to the spinal cord or peripheral nervous system. Perform a thorough neurological examination (including fundoscopy for papilledema), consult a specialist and/or arrange for appropriate investigations e.g. CT, MRI or nerve conduction studies.
- Test for glucose in the urine (or check capillary blood glucose, ideally fasting) to check for diabetes.
- Ask about alcohol consumption, and if excessive, arrange counselling.

Drug substitutions

- If an adult on d4T develops symptoms of PN, **no matter the severity**, substitute d4T with TDF if possible (or AZT if CrCl < 50 ml/min), provided that there is no suspicion of virological failure. (See page 37 for ARV substitution/switching.)
- If the person is taking d4T, DDI, or other ARV likely to cause mitochondrial toxicity (including AZT), check the lactate level, since PN can be associated with hyperlactatemia, which, if not detected early, can become life-threatening lactic acidosis. (See Chapter 6 for side effects of ART.)
- If the patient is on DDI and develops PN, substitute DDI with another ARV. If DDI is being used as part of an 'old' second-line ART regimen (AZT + DDI + LPV/r) you can substitute DDI with 3TC. Otherwise, consultation with other clinicians will likely be required in order to determine the most appropriate substitute ARV.

Vitamin B₆/ Pyridoxine?

If **vitamin B₆ deficiency** is suspected to be contributing to the PN and/or the patient abuses alcohol, give pyridoxine in a **treatment dose**:

- Start at 50 mg once daily (at night).
- As necessary, increase pyridoxine up to 150 mg orally once daily.



See Appendix 23

Analgesia

Treat the PN according to its severity.

- Start by prescribing basic analgesics (e.g. paracetamol or ibuprofen)
- If additional analgesia is needed, use the principles of the analgesic ladder (see Appendix 23) and review after two weeks.
 - If improvement, continue specific treatment.
 - If no improvement, especially if the patient is not on ARVs, look for other causes and reassess the patient's clinical stage.

Analgesics can be prescribed to adults as follows:

- Paracetamol 500–1000 mg four times daily as required, or,
- Paracetamol + codeine 1–2 tablets four times daily as required (only if PN is severe).
- Note that ibuprofen and other NSAIDs should not be used in those taking TDF, or have a history of renal impairment.
- Amitriptyline 25–100 mg at night (if PN is **moderate-severe**) may be helpful as an adjuvant therapy (i.e. used together with analgesics); start with 25 mg at night and increase progressively by 25 mg up to a maximum of 100 mg if necessary.



Do not use carbamazepine as there are significant interactions with ARVs.

- The newer anticonvulsants gabapentin and lamotrigine are another option that have been shown to provide pain relief in HIV-related sensory neuropathy conditions.



Children

- Although PN is less common in children than in adults, its diagnosis in children is not easy. The child sometimes complains of pain in the legs, or refuses to walk.
- Assessment of the child's motor function against developmental milestones can give an indication if the child has PN.

Prevention of PN in a child on INH

- Pyridoxine: in children who are <5 years, give 5–10 mg OD; in children who are >5 years, give 10 mg OD.
- If the child is on d4T and is assessed as having PN (no matter the severity), substitute d4T with another ARV (e.g. AZT or TDF) as long as there is no suspicion of virological failure, +/- the HIV viral load is undetectable.

- If vitamin B₆ deficiency is suspected, treat with higher dosages of pyridoxine:
 - In those <5 years, give 25 mg/day.
 - In those >5 years, give 50 mg/day.
- In severe cases, consult with a paediatrician or experienced clinician and consider amitriptyline in older children: in children of 6–12 years, consider 10 mg at bedtime; for children over 12 years, consider 25 mg, plus paracetamol 15 mg/kg as needed, three to four times/day.

Meningitis in PLHIV

Since meningitis is relatively common in people living with HIV, all clinicians need to have a high 'index of suspicion' for it. The high risk of morbidity (i.e. irreversible neurological sequelae) and mortality from meningitis requires that protocols be in place to prevent delays in diagnosis and treatment. Each and every adult and child with symptoms and/or signs of meningitis needs a prompt lumbar puncture (LP) and the cerebrospinal fluid (CSF) tested for a variety of possible causes:

- fungal (*Cryptococcus neoformans*, *coccidioidomycosis*, *histoplasmosis*)
- tuberculosis
- bacterial (*Streptococcus pneumoniae* by far the most common cause, followed by *Neisseria meningitidis* and *H. influenza B*)
- *Listeria monocytogenes*, *E. coli*, and Group B *Streptococcus* should also be considered in neonates
- viral (HIV itself, herpes zoster, mumps)
- syphilis.

It is important to note that multiple infections can occur at the same time. Viral meningitis (sometimes called 'aseptic meningitis') is a diagnosis of exclusion; apart from good nursing care, it does not require specific management, and has a good prognosis.

Clinical presentation of meningitis

Meningitis should be suspected in the presence of one or more of the following symptoms:

- progressive headache, not fully responding to analgesics
- neck pain
- altered mental state (disoriented, confused)
- photophobia (= extreme sensitivity to light)
- nausea and vomiting
- new-onset seizures
- irritability
- poor feeding in infants and children.





Possible signs include:

- fever and other signs of generalised infection: hepatomegaly, splenomegaly, rash
- stiff neck (but not always present)
- Brudzinski's sign (= flexion of the hips when the neck is flexed with the patient supine)
- Kernig's sign (= pain in the lower back when the knee is extended with the patient supine and the thigh flexed at the hip)
- papilledema on retinal examination (= increased intracranial pressure)
- focal neurological signs, which may be due to a space-occupying lesion or cerebral stroke
- hypotonia may be present in infants.

Diagnosis

A **lumbar puncture** (LP) must be performed as soon as possible at the hospital and the CSF sent for the following investigations:

- cell count
- protein
- glucose
- TB tests:
 - direct microscopy (but only positive in <10% of case)
 - GeneXpert (more sensitive, especially following centrifugation)
 - and/or TB culture
- bacterial culture
- India ink, CLAT, and/or CrAg
- VDRL.

After the LP, start empiric treatment for bacterial meningitis (since there is high mortality if not treated early) with an intravenous antibiotic such as ceftriaxone, in a dose according to local guidelines (which will depend on local levels of resistance to *Strep pneumoniae*).



1. According to WHO, raised intracranial pressure (ICP) is **not** a contraindication to LP. Instead, clinical contraindications include: significant coagulopathy or suspected **space occupying lesion** based on focal neurological signs, recurrent seizures, or confirmed on CT scan.³⁰ Other contraindications include major spinal deformity and consistent patient refusal.
2. **If cryptococcal meningitis is suspected, LP relieves severe symptoms of raised intracranial pressure, so is essential for both diagnosis and management of patient.**
3. Testing of other types of specimens (e.g. direct microscopy or GeneXpert testing of sputum, Determine TB LAM on urine, CrAg on blood) may help to establish the cause of the meningitis, especially if LP is not feasible.

Table 11.1: Distinguishing between the different causes of meningitis

	Cryptococcal	Tuberculosis	Bacterial	Viral
CD4 count*	Low	Any, but more common with lower	Any	Any
Onset	Chronic	Sub-acute	Acute	Acute
CSF appearance	Clear	Usually clear	Turbid	Clear or bloody
Cells	Lymphocytes	Lymphocytes	Elevated number of cells, mainly neutrophils	Lymphocytes
Glucose (mg/dl)	Normal or slightly low	Low	Low	Normal
Protein**	Mildly elevated. Pandy positive or negative.	Elevated. Pandy positive.	Elevated. Pandy positive.	Normal or high. Pandy positive or negative.
Other	India ink usually positive. CrAg (CLAT or LFA) very sensitive. Often a high opening pressure.	AFB not seen 90% of the time. GeneXpert has moderate sensitivity in CSF.		Viral meningitis is a diagnosis of exclusion.

* A cell count of zero cannot exclude TB meningitis, cryptococcal meningitis, or bacterial meningitis.

** The Pandy test is used to detect high protein in CSF. For further details, see Appendix 5 in the 2014 MSF *TB guide*.

Bacterial meningitis

Bacterial meningitis refers to infection causing acute inflammation of the 'meninges' (or coverings) of the brain and spinal cord; it can be caused by one of a number of bacteria, especially *Streptococcus pneumoniae* and, less commonly, *Neisseria meningitidis*.

Clinical presentation



Bacterial meningitis can occur at any CD4 count and is characterised by **acute** onset of symptoms. In addition to the signs mentioned above, look for evidence of a petechial rash on the body (associated with *Neisseria meningitidis*).

Specific management of bacterial meningitis



If the person is sick and **bacterial** meningitis is suspected, and it is not possible to perform an LP for whatever reason, do not delay in giving an antibiotic. While waiting for transfer of the patient, give the first dose of empiric treatment using intravenous ceftriaxone as soon as possible in order to reduce the risk of mortality.

Definitive treatment for bacterial meningitis is based on the bacterial culture and sensitivity results. While waiting for those results, empiric treatment in HIV-positive adults should be given according to local guidelines. Ceftriaxone is a good choice for initial therapy in a dose that will depend on local levels of resistance to *Strep pneumoniae*.



Children

- Bacterial meningitis can be difficult to diagnose early in young children. Symptoms can include: fever, headache, lethargy/coma, irritability, abnormal cry, poor feeding and vomiting, stiffness of the neck, convulsions. In infants, the fontanelle may be bulging (although not always present).



- Check your hospital protocol for preferred medications and dosages in your setting.

- In the absence of a hospital protocol, the following can be used as an initial guide:
 - Children <3 months: Preferred treatment ampicillin and ceftriaxone.
 - IV ampicillin (**check local protocol for dose**) and ceftriaxone 100mg/kg loading dose then 80mg/kg once daily.
 - Note that ampicillin, unlike ceftriaxone, is also active against *Listeria monocytogenes*.
 - Ceftriaxone is contra-indicated in premature neonates who have hyperbilirubinaemia.
 - Children ≥ 3 months: Usual dose of ceftriaxone is IM or slow IV, 50–75mg/kg/daily given in a single dose or 2 divided doses. Maximum 2g per dose. Doses over 50mg/kg by infusion only. (SAMF 11th edition)



NB! In certain paediatric meningitis treatment protocols, this dose is increased up to 100mg/kg/daily. It is important to check your local protocol for dosage guidance.

- If intravenous (IV) is difficult to establish, the initial doses can be given IM.

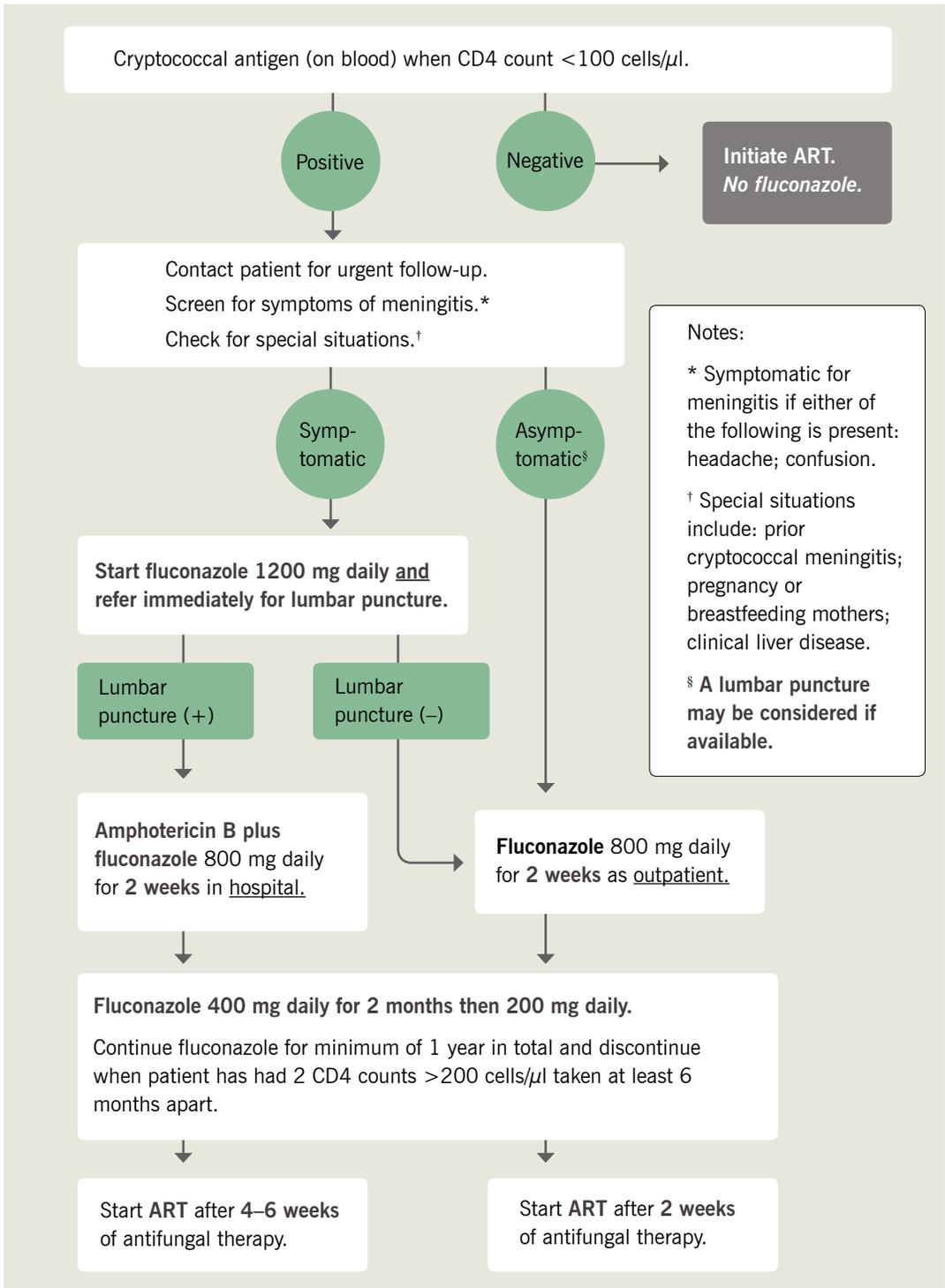
Cryptococcal meningitis

Cryptococcal meningitis (CCM) is caused by the fungus *Cryptococcus neoformans*. The risk of developing CCM is greatest among PLHIV having a CD4 count <100 cells/ μ l. It places an adult or child into WHO clinical stage 4. CCM is not contagious.

Clinical presentation

While many of the symptoms described for meningitis (above) are likely to be present, they are usually milder and less acute in onset with CCM. Severe headache is often the main presenting symptom.

During physical examination, the presence of papilledema indicates increased intracranial pressure (ICP). Also, be sure to look for cryptococcal skin lesions that may appear over the body (which can look similar to those of *molluscum contagiosum*).

Algorithm 11.1 Screening for CCM in late presenters (CD4 <100)³¹

31 Govender NP and Meintjes G (chairpersons) et al. Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update. *S Afr J HIV Med* 14(2):76–86. DOI:10.7196/SAJHIVMED.930

Screening

Even if asymptomatic, all those with a CD4 count <100 cells/ μ l should routinely have a blood specimen tested for cryptococcal antigen (CrAg), since they are at increased risk and may have 'subclinical' cryptococcal disease.

- If CrAg+, an LP should be performed whenever feasible, despite being asymptomatic, in order to identify subclinical cases of meningitis.
- If CrAg+ and LP is not feasible, give 'pre-emptive' anti-fungal therapy: the WHO recommends using **fluconazole 800 mg/day for two weeks, followed by 400 mg/day for eight weeks**, followed by continued maintenance with fluconazole 200 mg/day.³²
- Continue 200 mg of fluconazole until the CD4 count is >200 cells/ μ l on 2 separate occasions at least 6 months apart **and** after at least one year. ART can be initiated 4 weeks after antifungal therapy.

Diagnosis

In all those in whom meningitis is suspected, lumbar puncture should be performed and cerebrospinal fluid (CSF) sent for a number of tests (see above). Cryptococcus can be detected using any of the following tests on CSF: India ink stain (less expensive, but less sensitive), cryptococcal latex agglutination test (CLAT), and the cryptococcal antigen (CrAg) lateral flow assay. In resource-limited settings, it may be preferable to test first with India ink stain (a 'rule in' test) and if negative, immediately test with CLAT or CrAg.

Be sure to **measure the opening pressure** with a CSF manometer (normally between 10–20 cm H₂O). If the pressure is elevated and the cause is unknown, remove only 5 ml of CSF initially. If you do not have access to a manometer, you can use IV tubing that has been marked using a tape measure and attached to an IV pole.³³

However, if the CSF pressure is elevated and Cryptococcal meningitis is strongly suspected (e.g. CD4 <100 , symptomatic, +/- blood specimen result is CrAg+), 20-30 mls of CSF can be removed. See page 187 for more details on 'therapeutic taps'.

Specific management of CCM

The foundation of treatment for CCM is amphotericin B, as this medication is fungicidal. In addition to this and other medications, good nursing care and therapeutic lumbar punctures (to reduce high intracranial pressure) help to limit morbidity and mortality.

Important: Pre-hydration and electrolyte replacement prior to administration of amphotericin B substantially reduces renal and other toxicities.

32 WHO. 2011. Rapid advice on diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children.

33 WHO. 2011. *IMAI District clinician manual: Hospital care for adolescents and adults.*

Table 11.2 Summary of amphotericin B toxicity prevention, monitoring and management³⁴

Scenario	Recommendations
Administration of amphotericin B deoxycholate*	<ul style="list-style-type: none"> Amphotericin B powder should be reconstituted in sterile water; inject the calculated volume of reconstituted drug in water into 1 litre of 5% dextrose water and administer within 24 hours. Amphotericin B can be administered via peripheral IV line if the solution contains ≤ 0.1 mg amphotericin B in 1 ml of 5% dextrose water. A test dose is unnecessary. The solution should be infused over at least 4 hours.
Prevention of amphotericin B deoxycholate-related toxicities	<ul style="list-style-type: none"> Patients should be pre-hydrated with 1 litre of normal saline containing 1 ampoule of potassium chloride (20 mmol) infused over 2 hours before the amphotericin B infusion.[†] Twice-daily oral potassium and daily oral magnesium supplementation should be administered (adults). To minimise the risk of phlebitis, lines should be flushed with normal saline after amphotericin B infusion is complete and the infusion bag should not be left attached to the IV administration set after infusion is complete.
Monitoring	<ul style="list-style-type: none"> Baseline and twice-weekly creatinine and potassium (and magnesium, if available). Baseline and weekly haemoglobin. Fluid input and output monitoring.
Management of toxicities	<ul style="list-style-type: none"> If creatinine doubles, then 1 dose of amphotericin B may be omitted or pre-hydration can be increased to 1 litre 8-hourly. If creatinine remains elevated or repeatedly rises, then amphotericin B should be stopped and fluconazole used as suggested in recommendation 3 (baseline renal impairment section). Febrile reactions can be treated with paracetamol (1 g) 30 minutes before infusion (if severe, hydrocortisone (25 mg IV) can be given before subsequent infusions).

IV = intravenous.

* For adolescents and children, drugs should be calculated by body weight.

† For children and adolescents, normal saline, with 1 ampoule of potassium chloride (20 mmol) added per litre of fluid, should be infused at 10–15 ml/kg over 2–4 hours (not more than 1 litre prior to amphotericin B administration). If saline is unavailable, then other parenteral rehydration solutions that already contain potassium can be used, e.g. Darrow's solution or Ringer's lactate.

- Intensive phase in adults consists of IV amphotericin B, 0.7–1.0 mg/kg/day for 5–7 days, plus fluconazole 800 mg/day for 2 weeks.
 - Followed by a consolidation phase of fluconazole 800 mg daily for another 8 weeks.
 - Followed by a maintenance phase of fluconazole 200 mg daily (= secondary prophylaxis).
 - If available, the more expensive **liposomal** amphotericin B (3 mg/kg/day) should be considered, as it is associated with less toxicity and greater efficacy.³⁵
- If IV amphotericin B is not available, give adults fluconazole 1200 mg/day in a 2-week intensive phase, followed by fluconazole 800 mg/day in an 8-week consolidation phase, followed by a maintenance phase (= secondary prevention) with fluconazole 200 mg/day.
- If flucytosine is available, this should be combined with fluconazole when amphotericin B is not available, as this combination is superior to the use of high-dose fluconazole alone.³⁶
- **All patients with cryptococcal disease must be initiated on ART, but only after there is a sustained clinical response to anti-fungal therapy, in order to avoid life-threatening intracranial IRIS. An appropriate delay is generally 4–6 weeks in those following CMM treatment.**
- During follow-up, some patients will present with recurring/persisting headaches and will need a repeat LP. These headaches may be related to high CSF pressure due to the original diagnosis of CCM or may be caused by IRIS (if recently initiated on ART).
- High intracranial pressures due to CCM should be aggressively managed with **repeated therapeutic LPs**, as this can improve patient outcomes and will alleviate headaches better than most analgesics.
 - Measure the opening pressure during each LP using a CSF manometer or IV (as above). Normal pressure is usually 10–20 cm H₂O.
 - Patients with an opening pressure >25 cm H₂O should have removal of approximately 20–30 ml of CSF, with the goal being to reduce the opening pressure to <20 cm H₂O.
 - Such patients should have repeated daily LP until the opening pressure has stabilised in the normal range for three or more consecutive days.

35 WHO. 2011. *Rapid advice on diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents, and children.*

36 Jackson A et al. 'Flucytosine plus high dose fluconazole is superior to high dose fluconazole alone: results of a randomized trial comparing cryptococcal meningitis treatments in Malawi'. 5th IAS Conference on HIV Pathogenesis and Treatment: Abstract no. LBPEB02. www.iasociety.org/Abstracts/A200722785.aspx

- If once daily LP is not adequate to control severe symptoms (severe headache, visual symptoms, and cranial nerve abnormalities), twice daily lumbar punctures can be performed. If this does not control symptoms, an indwelling lumbar drain can be inserted if local expertise is available to manage.³⁷
- In the absence of clinical improvement, it will be necessary to try to exclude cryptococcal resistance (e.g. against fluconazole) and investigate for the presence of other causes (including additional infectious causes).

Secondary prophylaxis

Fluconazole should be continued in adults and adolescents for a period of time in order to prevent the meningitis from coming back. This is referred to as secondary prevention. The fluconazole can be discontinued once the following conditions have been met: the patient is stable on ART and has had anti-fungal maintenance treatment for at least one year, and the CD4 count is >200 cells/ μ l (preferably on 2 measurements taken 6 months apart).



Fluconazole is teratogenic, so women on prophylaxis should be advised to delay any pregnancy until fluconazole prophylaxis can be safely discontinued. Reliable contraception in addition to condoms should be advised. However, if a pregnant woman needs fluconazole as treatment or prophylaxis, the benefits outweigh the risks.



Recurrence of CCM symptoms

Patients may present with symptoms weeks to months after completing CM treatment.

Possible causes include:

- discontinuation of fluconazole prophylaxis
- fluconazole-resistant CM (needs CSF culture)
- cryptococcal meningitis IRIS.

Ill-patients will require an LP and to be re-treated with amphotericin B. Expert opinion will be required regarding therapeutic LPs and possible steroid administration.



Children

- Intensive phase in adolescents and children consists of IV amphotericin B, 0.7–1.0 mg/kg/day for 5–7 days, plus fluconazole 12 mg/kg/day (up to 1 200 mg/day) for 2 weeks.

- Followed by a consolidation phase of fluconazole 12 mg/kg/day (up to 800 mg/day) for another 8 weeks.
- Followed by a maintenance phase of fluconazole 6 mg/kg/day (up to 200 mg/day) as secondary prophylaxis.
- In children aged 2–5 years, secondary prophylaxis with fluconazole can be discontinued if the child is stable on ART and anti-fungal maintenance treatment for at least one year, and has a CD4 count >25% (preferably on 2 measurements taken 6 months apart).
- It is not currently recommended to discontinue secondary prophylaxis in children aged <2 years.

TB meningitis (TBM)

Tuberculosis commonly causes extrapulmonary (EP) disease in people living with HIV, both in children and adults. When it involves the meninges, brain and spinal cord, a person is said to be suffering from tuberculous meningitis (TBM). This form of TB can occur at any CD4 count (although more common at lower ones).

Other forms of TB, both pulmonary and EP (e.g. disseminated TB or abdominal TB) often accompany TBM.

Clinical presentation

Symptoms of TBM are progressive (usually over >5 days) with a less acute presentation than that of bacterial meningitis. Signs to watch for, that are associated with TBM, include:

- cranial nerve weaknesses (palsies), e.g. the third cranial nerve
- choroidal tubercles on fundoscopic exam (representing disseminated TB).

Diagnosis

- Lumbar puncture should be arranged urgently, looking for biochemical markers in the CSF (high protein and low glucose).
 - Acid-fast bacilli (AFB) are seen <10% of the time in CSF, so the diagnosis will have to be suggested by other tests.
 - TB culture is more sensitive, but the result will take many weeks.
 - Molecular testing (e.g. GeneXpert) of CSF is more sensitive than AFB staining, especially if the CSF is centrifuged; discuss with your local laboratory.
- Other investigations to consider include sputum testing (since pulmonary and EPTB can co-exist), chest x-ray (looking for a miliary pattern), and Determine TB LAM (a relatively new test that detects TB antigen in urine).



See National Guidelines

Management of TB meningitis

- See your national TB programme (NTP) guidelines for treatment details.
- The duration of treatment for TBM is often extended up to 12 months due to uncertain penetration of anti-TB drugs into the central nervous system (CNS).
- A course of steroids should be considered in all those with TBM to help reduce intracranial pressure: prednisolone (or its precursor prednisone) for 6–12 weeks (according to severity of symptoms and clinical response):
 - 2–4 mg/kg/day PO in children (to maximum of 60 mg daily) for 4 weeks then tapered over 2 weeks.
 - 1.5 mg/kg/day in adults to a maximum of 60 mg PO daily (**please check your local guideline**).
 - All steroids should be tapered over the final 2 weeks of their use.
- Those with TBM should begin ART depending on CD4 count (see Table 7.5).

Cerebral toxoplasmosis

Cerebral toxoplasmosis ('toxo') is caused by the reactivation of *Toxoplasma gondii* cysts in those with severely weakened immune systems, which have been lying dormant in the brain (following a mild 'primary infection' occurring earlier in the person's life). Note that toxoplasmosis almost always occurs in a person with a CD4 count <100 cells/ μ l.

Clinical presentation of 'toxo'

- Symptoms include headache, and sometimes fever.
 - **Focal neurological symptoms** such as one-sided weakness or paralysis.
 - Encephalitis-like symptoms, such as decreased levels of consciousness and confusion occur less frequently.
 - New-onset seizures.
- **Focal signs** can include:
 - Hemiplegia or hemiparesis.
 - Ataxia and difficulty walking.
 - Fundoscopic examination may reveal focal lesions in the choroid/retina and/or papilledema indicating increased intracranial pressure. (See Appendix 15.)



See Appendix 15

Diagnosis of 'toxo'

Ideally, all those with suspected toxoplasmosis (or other space occupying lesion) should receive a **CT scan** of the head, since lumbar puncture is contraindicated.

Toxo lesions typically show up on the CT scan as 'ring enhancing' lesions, although such lesions are not specific and could also represent tuberculoma or lymphoma.

Toxo serology testing is only partially useful, since it cannot prove a diagnosis of toxoplasmosis. The presence of toxo IgG shows that the patient has previously been infected with toxoplasmosis, and could therefore have reactivated disease; if the IgG is negative, the patient has not previously been infected and therefore cannot have reactivation disease. Thus, toxo IgG serology is a 'rule out' test, i.e. it is not that useful if the result is positive; but if toxo IgG is negative, it excludes toxo as a cause for the symptoms. Since toxo IgM antibodies are detectable early after infection, but can persist for a long time, they do not have a useful role, and should not be tested.

In settings where these tests are not readily available (or the toxo IgG serology is positive), **empiric** treatment for presumed cerebral toxoplasmosis **based on symptoms** is an option: if there is then a good clinical response to 'toxoplasmosis' treatment, then this corroborates the diagnosis.

The differential diagnosis of focal neurological symptoms and signs includes lymphoma, tuberculoma, and stroke. Chest x-ray and TB testing (e.g. GeneXpert) should be performed to investigate these other possibilities.

Management

Specific treatment

For suspected cerebral toxoplasmosis, treat with:

- **High-dose** cotrimoxazole: A typical dose for adults is 4 single strength tablets (i.e. 4 x 480 mg) twice daily for 4 weeks, followed by two tablets twice daily for 4–12 weeks.
- The patient should be advised to drink plenty of fluids, since such large doses of cotrimoxazole can cause renal dysfunction.
- Add folic acid 5 mg daily, since high-dose cotrimoxazole inhibits folate synthesis.
- **All patients with cerebral toxoplasmosis must be enrolled to start ARVs.**
- Because treatment for cerebral toxoplasmosis is with oral medication, the person can be treated at primary care level (unless clinically unstable). If there is no improvement after 2–3 weeks, it is necessary to consider other disease processes such as a tuberculoma, lymphoma, or stroke.

Secondary prevention

Continue with the usual 960 mg daily of cotrimoxazole prophylaxis until the person is stable on ART and the CD4 count is >200 cells/ μ l on two consecutive measurements.



Children

- High dose cotrimoxazole (sulfamethoxazole + trimethoprim). Check dosing for age/weight.



Remember: Toxo lesions generally resolve within three weeks of starting treatment. If an HIV-positive patient with focal neurological signs (and a low CD4 count) does not respond to empirical anti-toxoplasmosis treatment, the cause is probably not toxoplasmosis and the patient should undergo further assessment.

If resources are limited in your setting, consider empiric TB treatment (a full course), since a cerebral tuberculoma is another treatable cause of such symptoms.

CNS lymphoma can only be diagnosed definitively with a brain biopsy and is untreatable.

Stroke results in a focal neurological deficit without an encephalitic-type picture or fever. Causes include ischemia, haemorrhage, neurosyphilis, TB meningitis, and HIV vasculopathy.

HIV encephalopathy/dementia

About 10% of HIV-positive patients used to develop dementia in the late stages of the disease (i.e. CD4 <200 cells/ μ l). Increased access to ART has since decreased the risk of dementia. If HIV encephalopathy does occur, the person is considered to be in clinical stage 4 (i.e. AIDS).

Clinical presentation

Patients with HIV encephalopathy will present with:

- Progressive memory loss and concentration, and their families may report strange behaviour.
- Low mood (depression) can also occur.
- They may have motor problems and develop an abnormal walking pattern and poor balance.
- Incontinence may also develop.
- It is very important to exclude any infectious cause of dementia (e.g. CMV encephalitis, TB disease, or toxoplasmosis). HIV encephalopathy is a diagnosis of exclusion.

Tools have been developed, known as HIV dementia scales (HDS) to screen for and aid in diagnosis of HIV-associated dementia.

Table 11.3 International HIV dementia scale (IHDS)

Test	What to do	How to score
Memory-registration:	Give four words to recall (<i>dog, hat, bean, red</i>) – 1 second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.	
1. Motor speed	Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.	4 = 15 in 5 seconds 3 = 11–14 in 5 seconds 2 = 7–10 in 5 seconds 1 = 3–6 in 5 seconds 0 = 0–2 in 5 seconds
2. Psychomotor speed	Have the patient perform the following movements with the non-dominant hand as quickly as possible: <ul style="list-style-type: none"> • Clench hand in fist on flat surface. • Put hand flat on surface with palm down. • Put hand perpendicular to flat surface on the side of the fifth digit. • Demonstrate and have patient perform twice for practice. 	4 = 4 sequences in 10 seconds 3 = 3 sequences in 10 seconds 2 = 2 sequences in 10 seconds 1 = 1 sequence in 10 seconds 0 = unable to perform
3. Memory-recall	Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (<i>dog</i>); piece of clothing (<i>hat</i>); vegetable (<i>bean</i>); color (<i>red</i>).	Give 1 point for each word spontaneously recalled. Give 0.5 points for each correct answer after prompting. Maximum – 4 points.
<p>Total IHDS Score: This is the sum of the scores on items 1–3. The maximum possible score is 12 points.</p> <p>A patient with a score of ≤ 10 should be evaluated further for possible dementia.</p>		

Management

- Perform a comprehensive neurological examination.
- If possible, refer patient for a lumbar puncture/CT scan.
- If these are normal, start ART. Refer same week for ARVs.
- The family must be involved in treatment support and be part of the counselling sessions; patients with HIV dementia are generally unable to take charge of their treatment themselves.
- Response to ARVs is often good, and improves the long-term prognosis.

In patients with a poor response to the standard first-line regimen (TDF/3TC/EFV), AZT/3TC/NVP may be a better alternative as this regimen has improved CNS penetration.

- Offer supportive measures for both patient and family.



Children

HIV encephalopathy has a different natural history in children. It is an important condition to recognise in children because early ARV initiation can significantly diminish the long-term negative consequences that the child will suffer.

Clinical presentation

Suspect HIV encephalopathy if:

- the child's head circumference (HC) is not growing, or
- developmental milestones are delayed or the child has lost milestones that he/she had previously acquired (e.g. a child who was able to sit upright and now is unable to).



This is another reason why it is so important to measure, record, and plot on a graph the HC of every child <3 years of age, and to assess developmental milestones of all children. Don't forget to ask the caretaker how the child is developing. She/he usually knows best.

Management

- Investigate for other causes. If HIV encephalopathy is suspected, ensure that ARVs are initiated.
- For the child with HIV encephalopathy, a multidisciplinary approach works best, including clinical management, psychosocial support and physiotherapy where feasible.

Cerebral stroke

PLHIV are living longer and longer on ART. As people age and become more likely to have risk factors (e.g. hypertension, diabetes, high cholesterol, smoking), there is an increased risk for cardiovascular diseases such as stroke, also known as 'cerebrovascular accident' (CVA). Be sure to screen PLHIV for such risk factors in your health facility.

Strokes can be ischemic (due to occlusion of the artery and lack of blood flow) or haemorrhagic in nature. Either can compromise surrounding brain tissue and lead to a permanent loss in brain function.

Diagnosis

Symptoms of stroke usually develop rapidly, over the course of a few seconds to minutes. Specific symptoms will depend very much on the area of the brain that is affected.

- Weakness: sudden loss of strength or sudden numbness in the face, arm or leg, even if temporary.
- Trouble speaking: sudden difficulty speaking or understanding, or sudden confusion, even if temporary.
- Vision problems: sudden trouble with vision, even if temporary.
- Headache: sudden severe and unusual headache (NB: Haemorrhagic cause more likely).
- Dizziness: sudden loss of balance, especially with any of the above.³⁸

Management

Stroke is a medical emergency. Ischemic strokes can be treated (and symptoms reversed) with IV thrombolytic medication, if given within 3 hours of onset on symptoms and proven on CT scan.

Some haemorrhagic strokes benefit from surgery.

Prevention

Strokes (including recurrences) can be prevented through control of risk factors (hypertension, diabetes, high cholesterol, smoking cessation) and the use of certain drugs, such as aspirin.

Psychiatric conditions

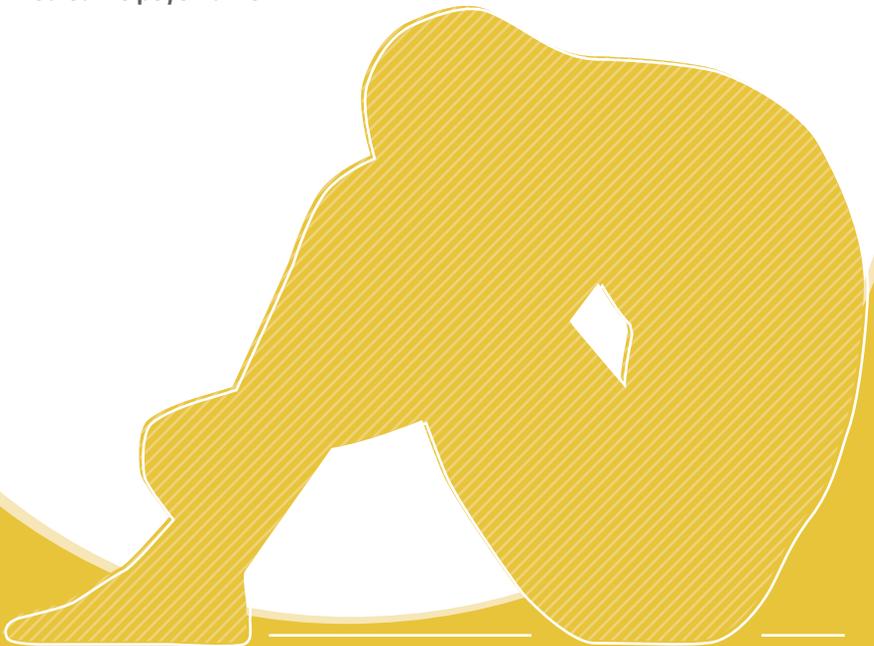
Depression

Generalised anxiety disorder (GAD)

Substance abuse disorders

Bipolar disorder

Psychosis: medical vs psychiatric





See Appendix 24

Mental health problems such as depression, anxiety, psychosis, delirium and substance abuse are more common in PLHIV and can be a significant contributor to poor adherence to treatment. Despite this, little attention is paid to mental health issues and they often go undiagnosed. A range of screening tools exist (see SAMISS tool in Appendix 24) and, at a minimum, patients should be asked about their mood and use of alcohol at each visit. Before making a psychiatric diagnosis, ensure that opportunistic infections, AIDS dementia complex and drug-related side effects have all been considered. If a patient has a psychiatric disorder, avoid prescribing efavirenz (EFV).



See Appendix 24



- Ask patients about their mood, alcohol and drug use using simple screening questions. See page 199.
- If you suspect a problem use more detailed screening questions and assess whether referral is required. See Appendix 24.
- Avoid using efavirenz in patients with psychiatric disorders.

Depression

Depression is very common and is under-diagnosed in people living with HIV. It can contribute to weight loss, poor adherence and loss to follow-up.

Clinical presentation

Depression is characterised by:

- persistent low mood
- low self esteem
- insomnia/hypersomnia
- reduced motivation
- unkempt or failing personal hygiene
- changes in appetite
- poor concentration, loss of libido (sexual appetite), low energy
- tearful or agitated
- difficulty adhering to medication
- increased alcohol intake
- decreased ability to function on a day-to-day basis
- may be related to a particular life event (= adjustment disorder).

Diagnosis of depression

Two basic but important questions should be asked:

- During the past month, have you felt like you were losing interest or pleasure in doing things?
- Have you felt down, depressed or helpless?

If the patient answers 'yes' to either of these questions, investigate further with a screening tool such as the Substance Abuse and Mental Illness Symptom Screener (SAMISS). See Appendix 24.



See Appendix 24

Depressed patients should have their suicide risk assessed and, if high, be referred immediately to psychiatric services. Note that the risk of suicidality is increased in those taking EFV in their first-line ART regimen.³⁹ Asking about suicide can be difficult. Possible ways of asking include:

- Has it ever become so (painful, frustrating, difficult, frightening) that you have thought about giving up? Have you thought about ending your life? Would you ever consider doing so? Under what circumstances have you considered this?
- Do you currently have any thoughts or plans to hurt yourself?

Management of depression

- Rule out an underlying medical cause for the depression (e.g. check thyroid function if feasible).
- Elucidate any potential cause for the depression: explore emotional and social issues.
- Refer to a counsellor, support group, social worker and/or a psychiatrist if necessary.
- If severe, organise, within the same week, an assessment of need for antidepressant medication.
- Amitriptyline has fewer interactions compared to other antidepressant medication. It can be prescribed at a starting dose of 50 mg nocte, and titrated up slowly as necessary.
- Selective serotonin reuptake inhibitors (SSRIs) may also be considered – e.g. citalopram in an initial dose of 20 mg, increasing to 40 mg if required – but caution should be taken due to interactions with commonly used ARVs (NNRTIs).
- If in doubt about possible drug interactions with ARVs, check the following website for quick and practical advice: www.hiv-druginteractions.org/



www.hiv-druginteractions.org

39 Mollan K. 'Hazard of Suicidality in Patients Randomly Assigned to Efavirenz for Initial Treatment of HIV-1: A Cross-Study Analysis'. Conducted by the AIDS Clinical Trials Group (ACTG). Oral Abstract Session: HIV Clinical Trials and Outcomes. <https://idsa.confex.com/idsa/2013/webprogram/Paper40032.html>

Generalised anxiety disorder (GAD)

Anxiety commonly occurs around the time of testing and HIV diagnosis, as well as with advancing disease.

Clinical presentation

- feeling excessively worried
- agitated
- poor sleep
- panic attacks
- obsessive behaviour
- compulsive thoughts.

Management

- Provide psychosocial support.
- Refer for counselling and involvement in a support group.
- If anxiety is severe or persists, medication can be considered (e.g. SSRIs or benzodiazepines).

Substance abuse disorders

Use of alcohol or other drugs (e.g. cannabis) is a common reason for poor adherence.

Clinical presentation

- injuries due to falls
- failure to fulfil work responsibilities
- getting into fights or trouble with the law
- difficulty with relationships
- symptoms of depression.

Diagnosis

Use the following CAGE questionnaire to screen for alcoholism:

- C** Have you ever felt you needed to **CUT** down on your drinking?
- A** Have people **ANNOYED** you by criticising your drinking?
- G** Have you ever felt bad or **GUILTY** about your drinking?
- E** Have you ever had to have a drink first thing in the morning (**EYE-OPENER**) to steady your nerves or get rid of a hangover?

If substance abuse is suspected, consider using a screening tool for depression (see Appendix 24).



See Appendix 24

Management

Assess patient for stressors and stigma and manage any depression or anxiety. Consider referral to existing local services that manage alcohol or substance abuse.

Bipolar disorder

Clinical presentation

Bipolar disorder is characterised by periods of mania (i.e. excessive excitement) or hypomania (lesser intensity) that may be followed with episodes of depression. During manic episodes, self-esteem may be abnormally elevated and there may be delusions of grandeur. The patient may be extremely talkative, have racing thoughts and a reduced need for sleep. Speech can become pressured, thoughts disorganised and auditory hallucinations may occur.

A useful screening question is: Have you had periods of feeling so happy or energetic that other people told you that you were talking too fast or were 'hyper'?

Management

If bipolar disorder is suspected, patients should be referred to psychiatry services. Lithium is the most commonly used first-line treatment.



Refer patient

Psychosis: medical vs psychiatric

It is not uncommon for a person living with HIV to present with **psychosis**, which can have a number of causes: **delirium**, medications, substance abuse (and consequent withdrawal), an undiagnosed opportunistic infection (OI), AIDS dementia complex, or a primary psychiatric disorder (e.g. schizophrenia). The confused HIV-positive patient presents a diagnostic challenge that will test your skills as a clinician.

Definitions

- **Psychosis:** A thought disorder in which there is loss of contact with reality, often associated with hallucinations or delusions.
- **Hallucinations:** Sensory perception in the absence of external stimuli, most often auditory or visual.
- **Delusions:** A false personal belief that is not subject to reason or contradictory evidence and is not explained by a person's usual cultural and religious concepts.
- **Delirium:** Fluctuating global cognitive impairment associated with behavioural abnormalities.

Psychosis is a symptom, not a diagnosis. The clinician must first and foremost rule out **delirium due to medical illness** as this carries a high risk of mortality. Causes of delirium include sepsis/infection, hypoxia, alcohol withdrawal, **drug toxicity** and hypoglycaemia. Think of delirium if your patient experiences any of the following:

- disturbance of consciousness
- appears agitated or aggressive
- change in cognition or a perceptual disturbance
- onset over hours to days, and tendency to fluctuate
- loss of the normal circadian rhythm.

There are a number of psychiatric causes of psychosis (see Table 12.1 below), which tend to have a more chronic onset.

Table 12.1 Distinguishing medical from psychiatric causes of psychosis

	Medical causes of psychosis (delirium)	Psychosis as a symptom of a psychiatric illness
Underlying illness	Sepsis or other infection Hypoxia Hypoglycaemia Drug-related Alcohol or substance abuse Substance withdrawal	Schizophrenia Mood disorders with psychotic features
Onset	Acute (over hours to days)	More chronic
Symptoms and signs	Often a fever and other signs of infection Tremor, agitation Fluctuating mental status Hallucinations (usually visual) Disruption of sleep-wake cycle	Impaired reality testing Delusions Hallucinations (usually auditory)
Orientation	Disoriented to time, place, and/or person	Not usually disoriented
Memory	Short-term memory loss	No memory loss
Attention	Difficulty paying attention	No difficulty
History of previous mental illness	Absent	Often present

Management of new-onset psychosis

- If possible, refer the same day to hospital.
- Manage in a calm environment.
- Since delirium usually has an underlying medical cause, it is important to investigate for an underlying cause.
- Perform a good clinical examination.
- Check for fever and rash.
- Listen carefully to the lungs.
- Check for stiff neck, papilledema, and focal neurological signs.



Refer patient

- Investigate thoroughly for medical causes:
 - underlying opportunistic infection
 - other infections (e.g. pneumonia, sepsis, UTI)
 - lung disease causing hypoxemia
 - consider LP to rule out CNS infection
 - medication-related side effects
 - alcohol or drug abuse.
- Check blood glucose level.
- Treat any hypoglycemia.
- NB: Give thiamine orally or by IM injection before starting any glucose infusion, if alcohol withdrawal is suspected.
- Provide face mask oxygen if hypoxic.
- Consider stopping any medication that may be exacerbating symptoms.
- While investigating for medical causes, diazepam 5 to 10 mg IM if very agitated or aggressive.
- If no medical cause found and psychosis thought to be of psychiatric origin, refer for psychiatric assessment.

Gastro-intestinal conditions

Diarrhoea

Acute diarrhoea

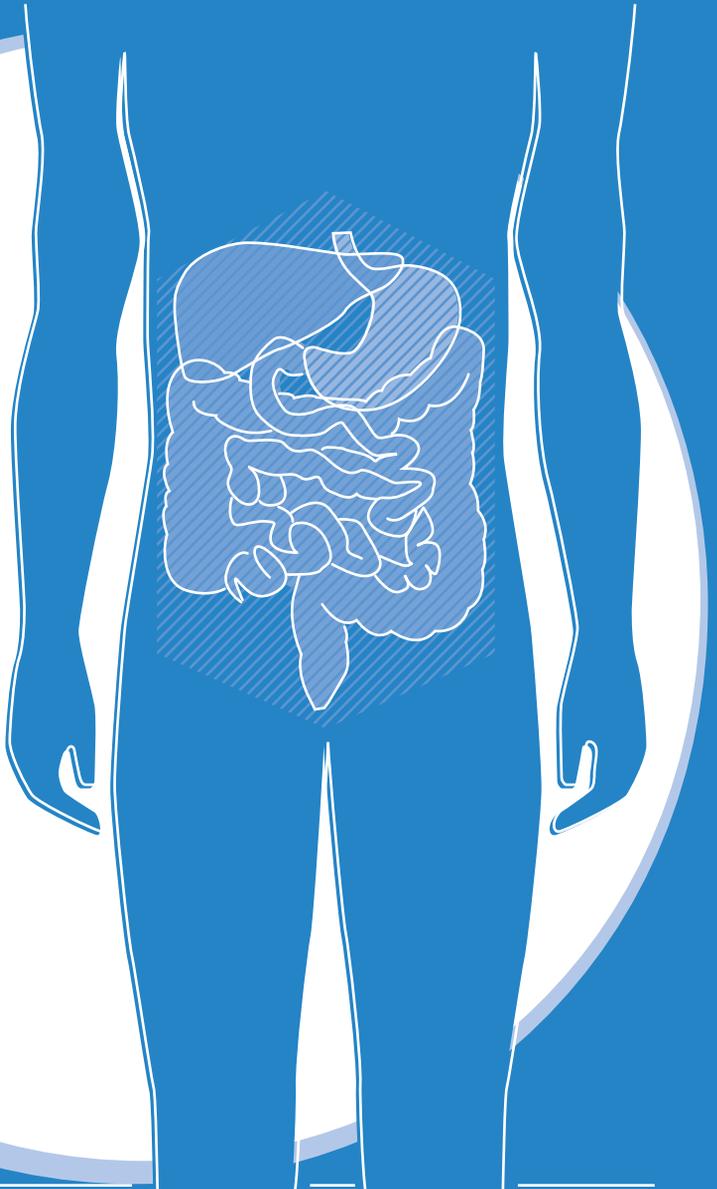
Chronic diarrhoea

Abdominal pain (no diarrhoea)

HIV and the liver

Hepatitis B co-infection

Hepatitis C co-infection



Gastro-intestinal (GI) conditions are common in people living with HIV for a number of reasons. HIV 'late presenters' often have GI symptoms when first seen, which can be due to a number of different opportunistic infections (OIs) or HIV itself. Common presentations are oral conditions (see page 127), acute and chronic diarrhoea, and abdominal pain.

Diarrhoea

Diarrhoea is very common in HIV-infected adults and children. Its presence influences the WHO clinical stage that the person is in, as follows:

Stage 3:

- unexplained chronic diarrhoea for >1 month for adults
- unexplained persistent diarrhoea for 14 days or more in children.

Stage 4:

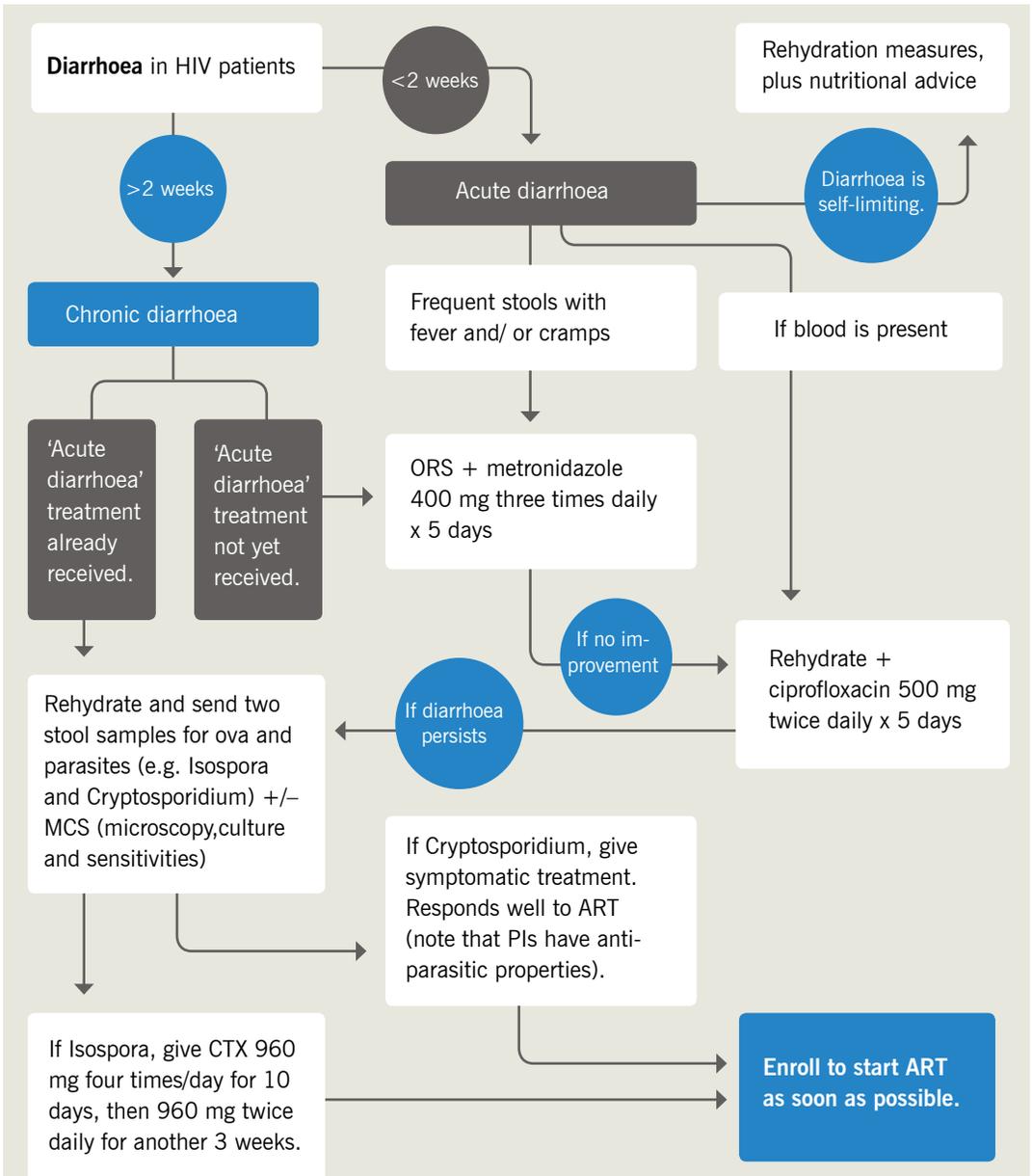
- HIV wasting syndrome (diarrhoea >1 month + >10% weight loss)
- Coccidian parasites:
 - chronic Isosporiasis
 - chronic Cryptosporidiosis.
- Other:
 - CMV oesophagitis or colitis
 - disseminated nontuberculous mycobacterial infection (e.g. MAC).

It is important to remember that all patients in clinical stage 4 or who have a CD4 count <200 cells/ μ l should be 'fast-tracked' for ART initiation.

On taking a clinical history, it is important that the clinician makes a **distinction between acute and chronic diarrhoea**, since these are managed differently. Other important symptoms to ask about include fever, blood in the stool, and abdominal pain.

On physical examination, check the vital signs, weight, and assess for severe dehydration: poor urine output, confusion or drowsiness and hypotension. Beware of any signs of electrolyte deficiency, including weakness (low K+) and tetany (low calcium).

Algorithm 13.1 Management of diarrhoea



Notes:

1. CTX = cotrimoxazole.
2. Always ensure good hydration; use IV fluids if necessary.
3. **Refer to hospital if:**
 - Bloody diarrhoea AND temperature above 38 degrees Celsius.
 - Signs of severe dehydration: poor urine output, confusion or drowsiness, hypotension.



Acute diarrhoea

Clinical presentation

Acute diarrhoea is characterised by:

- a duration of less than 2 weeks
- more than 3 loose stools/day
 - without significant weight loss
 - disappearing spontaneously or with appropriate treatment.

Two syndromes are to be noted:

1. **Gastroenteritic syndrome:** simple diarrhoea caused by viruses, bacteria (*E. coli*), food poisoning (*Staphylococcus*), or *Salmonella*.
2. **Dysenteric syndrome:** painful diarrhoea with **mucous and/or blood**, and rectal symptoms, caused by *Shigella*, *Amoeba enterolytica*, *Campylobacter* and some *E. coli* strains.

Note that there are some non-infectious causes of diarrhoea as well, including side effects to (many) drugs and food intolerance.

On clinical examination, check for fever and signs of **dehydration** (especially in children). (See Table 13.1 below.)



Table 13.1 IMCI classification of dehydration⁴⁰

Signs	Severe dehydration (2 of the following signs)	Some dehydration (2 of the following signs)	No visible dehydration
Level of consciousness	Lethargic or unconscious	Restless and irritable	Alert
Eyes	Sunken	Sunken	Not sunken
Ability to drink	Poor or unable	Eager, thirstily	Normal, not thirstily
Skin pinch (turgor)	Very slow return >2 seconds	Returns slowly <2 seconds	Returns immediately
Treatment	<ul style="list-style-type: none"> • Rehydrate with IV (or nasogastric tube). • Consider causes and treat. • Report cases. 	<ul style="list-style-type: none"> • Give fluid and food. • Immediately advise when to return. • Follow up in 5 days if not improving. 	<ul style="list-style-type: none"> • Treat at home. • Advise when to return. • Follow up in 5 days if not improving.

40 WHO. 2011. *IMAI District Clinician Manual: Hospital Care for Adolescents and Adults*.

Management

Rehydration

Rehydration is crucial. Tell patient to drink as much fluid as possible, and as often as possible. **Oral rehydration salts (ORS)** are best, but any fluid will do. **Sugar salt solution (SSS)** can be prepared according to the recipe below. If the person is unable to drink and/or severe vomiting is present, arrange for rehydration with intravenous fluid.

ORS is prepared by dissolving the contents of one sachet into one litre of clean or boiled water (after it has cooled).

SSS can be prepared according to the following recipe: One litre of clean boiled water + half a teaspoon of salt + 8 teaspoons of sugar. It is also recommended to add some potassium if possible (for example, by adding some orange or grapefruit juice).

Then give $\frac{1}{4}$ litre (1 full cup) every 15 minutes (for adults).

Make a new batch of ORS or SSS every day, and keep the ORS or SSS clean and cool.

Nutritional advice

Continue offering food, which is important especially for children (do not starve the patient). No special diet is needed, but very spicy food or very oily food should be avoided. Try rice, potatoes, maize porridge and bananas.



Antibiotic therapy

If the diarrhoea **improves on its own within one week**, then only rehydration and nutritional advice are necessary.

If acute diarrhoea **doesn't improve within one week**, then **empiric antibiotic therapy** is needed as follows (empiric means that no laboratory investigations, microbiology testing, or cultures are performed):

- If the person has frequent stools (>6 per day), together with a high temperature and/or bad cramps, then give:
 - cotrimoxazole 480 mg, 2 tablets twice daily x 5 days, AND
 - metronidazole 400 mg three times daily x 5 days.
- If there is **blood** in the stools, together with the above symptoms, or the diarrhoea is not improved with the above treatment, then give: ciprofloxacin 500 mg twice daily x 5 days.



Refer patient

Children

- Look for signs of dehydration and assess severity as per IMCI classification (see Table 13.1 above).
- Severe dehydration: give an intravenous bolus of 20 ml/kg of Ringer's lactate or normal saline rapidly. Refer urgently to hospital.
- Moderate dehydration: If not vomiting and able to tolerate oral feeds, give oral rehydration solution (ORS) 40 ml/kg over 4 hours. Increase the amount if the child wants more, and encourage the mother to continue breastfeeding where applicable, or to give any other fluids.
- For prevention of dehydration, caregiver needs to give 10 ml/kg of fluids after each loose stool:
 - Child age up to 2 years: 50–100 ml; Child age >2 years: 100–200 ml.
 - Use sugar salt solution, or if the child has already been rehydrated for 'severe dehydration' or 'moderate dehydration', use ORS.
 - Zinc supplements may lessen the duration of diarrhoea and stool frequency:
 - Age <6 months: 10 mg daily for 14 days; 6 months to 5 years: 20 mg daily.
- If blood in stool: ciprofloxacin 15 mg/kg/dose twice daily for 3 days.
- If not on exclusive breast milk, offer viscous fluids (e.g. soft porridge, yoghurt), sugar salt solution or ORS.
- Be cautious with rehydration in severely malnourished children.



See Appendix 29



Red flags

The following symptoms and signs in children require URGENT attention (see Appendix 29 for normal vital parameters in children):

- looks unwell or deteriorating
- altered responsiveness (e.g. irritable, lethargic)
- sunken eyes
- tachycardia (fast heart rate)
- tachypnea (breathing fast)
- poor fluid intake
- decrease in skin turgor.

Chronic diarrhoea

HIV itself can directly cause chronic diarrhoea, but other causes need to be excluded first before blaming the diarrhoea on the HIV. Tuberculosis (TB) can also cause diarrhoea, so this should actively be investigated with relevant/available tests, including CXR, Determine TB LAM, and molecular testing of sputum/other specimens.

At low CD4 counts (i.e. <50 cells/ μ l), the clinical stage 4 conditions of Mycobacterium avium complex (MAC), parasites (e.g. Cryptosporidium), and CMV colitis should be considered. A number of ARVs can cause chronic diarrhoea: didanosine (DDI), lopinavir/ritonavir and ritonavir.

In addition, the clinician needs to think of non-HIV related conditions such as hyperthyroidism, food intolerance, and inflammatory bowel disease (to name a few).

Clinical presentation

- Chronic diarrhoea is characterised by diarrhoea for **more than 2 weeks** and is often associated with significant **weight loss**.
- Physical examination should include fundoscopy, as this could reveal evidence of disseminated TB (i.e. choroidal tubercles) or CMV retinitis.

Management

Non-specific treatment:

- Rehydration as described above.
- Adults with unexplained chronic diarrhoea for more than one month are in no less than **WHO clinical stage 3**: start cotrimoxazole prophylaxis.
- **A person in clinical stage 3 is eligible to start ART, regardless of the CD4 count.**
- Nutritional advice as described above.
- If a person already on ARVs has ongoing diarrhoea and weight loss, consider active TB disease, other serious OIs, and other causes for the diarrhoea. Such patients require urgent and comprehensive investigation.

Specific treatment:

1. If the patient has **not** been treated at all for diarrhoea:
 - Empiric antibiotic treatment with high-dose cotrimoxazole and metronidazole as above (or ciprofloxacin if blood is present, as described above)
 - Check response to treatment after 3 days.

2. If the diarrhoea persists: **send two stool samples for ova and parasites (e.g. Isospora and Cryptosporidium) +/- MCS.**
3. Treat any infection that shows up in the stool investigation report:
 - Isosporiasis: give cotrimoxazole 480 mg, 2 tablets four times daily for 10 days, then 2 tablets twice daily for at least 3 weeks.
 - Cryptosporidiosis: rehydration therapy and nutritional advice as above; can try paromomycin if available (but expensive).
 - Since both Cryptosporidiosis and Isosporiasis represent clinical stage 4, **start preparing the patient to initiate ART.**
 - Note that protease inhibitors (PIs) have been shown to have anti-parasitic properties.
4. If the chronic diarrhoea has still not improved and the patient is severely immunocompromised, consider (re)investigating for other possibilities:
 - **Disseminated MAC:** can be confirmed by culture of blood or bone marrow. Clinical clues include:
 - low CD4 count (<50 cells/ μ l)
 - pancytopenia
 - constitutional symptoms: fever, night sweats, weight loss.
 - MAC (or other NTM) can also be indirectly diagnosed by finding a positive smear result and negative GeneXpert result on a sputum or other specimen, since GeneXpert is specific for MTB.
 - **CMV colitis:** a fundoscopic exam may help to establish this as the cause of the chronic diarrhoea, since it has been shown that 85% of people with extra-ocular CMV infection will develop CMV retinitis after a mean follow-up period of 6.4 months.⁴¹ (See Appendix 15 for a typical image of CMV retinitis.)
 - **Extrapulmonary/disseminated TB:** fundoscopy, chest x-ray, molecular testing (GeneXpert) of sputum and/or extrapulmonary specimens, plus Determine TB LAM on urine.
 - Microsporidiosis or Strongyloides stercoralis: try albendazole 400 mg daily for 2 weeks.
 - **'Fast-track' to start ART.**



See Appendix 15



Exercise caution with anti-diarrhoeal drugs.

Anti-diarrhoeal drugs must be used cautiously, as they slow the motility of the intestinal tract, which may result in harmful bacteria being retained (or 'kept inside'). The syndromic management of diarrhoea (described above) must be completed before considering anti-diarrhoeal drugs. In the event of a poor response

to syndromic management, the following anti-diarrhoeal drugs can be considered (while 'fast-tracking' the patient to start ART):

- loperamide 2 mg tablet after each episode of diarrhoea, up to 6 tablets a day, or
- codeine phosphate 30–60 mg up to four times a day.

Prescribing either of these drugs necessitates more frequent follow-up of the patient (i.e. every 2–3 days).

In a patient who has recently started an LPV/r-based regimen, diarrhoea (especially if not severe) might be related to these drugs: in this case, reassure the patient and treat symptomatically, since most of the time, the diarrhoea improves without changing treatment. If the diarrhoea does not improve, consider substituting LPV with atazanavir (ATV).

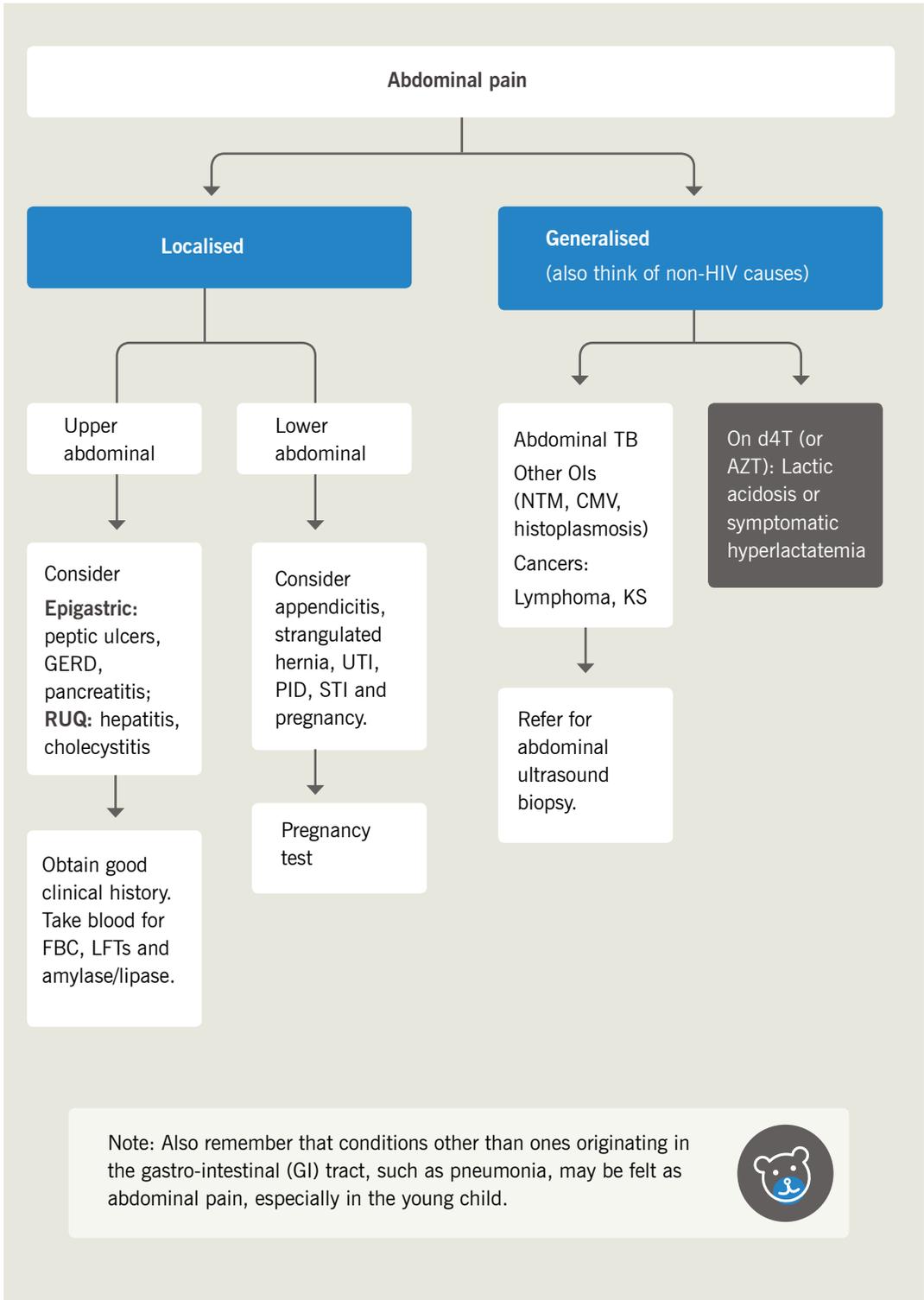
Children

- The foundation for management of diarrhoea in children is a good history and physical examination. Your auroscope will come in very handy here.
- Chronic diarrhoea is managed similarly in children as described above.
- If no pathogen is identified, give empiric treatment as follows: CTX 40 + 8 mg/kg per dose three times daily + metronidazole 10 mg/kg/dose three times daily for 5–7 days.
- Children with unexplained persistent diarrhoea for >14 days are in **no less than clinical stage 3**. Thus, cotrimoxazole prophylaxis is indicated, and the **child should be initiated on ART**.



Always assess children with acute or chronic diarrhoea for other infections: urinary tract infections (UTIs), sepsis, ear and throat infections, plus pneumonia can all be associated with diarrhoea.

Algorithm 13.2 Approach to abdominal pain



Abdominal pain (no diarrhoea)

(See Algorithm 13.2 for an approach to abdominal pain.)



Urgent

HIV with abdominal pain and one or more of the following signs signifies a severely ill patient requiring urgent attention:

- peritonitis (guarding or rigidity on abdominal examination)
- jaundice
- if on ARVs, especially d4T/ddI/AZT, any sign of lactic acidosis: see page 81.
- temperature $\geq 38^{\circ}\text{C}$

Organise same-day referral to hospital.



Refer patient



Remember

Always examine the lungs of a young child who complains of abdominal pain.

A child with pneumonia often complains of belly pain.



HIV and the liver

HIV clinicians need to be comfortable diagnosing and managing liver problems, as these commonly occur in people living with HIV. **Drug-related hepatitis** is not uncommon in those being treated with ARVs and/or TB medication, so it is important to have and use specific 'liver protocols' to manage such adverse events. (See page 80 for more details.)

Viral hepatitis shares modes of transmission with HIV, so people can become co-infected with HIV and hepatitis B and/or C. Thus, it is important to test for hepatitis B surface antigen (HBsAg) and hepatitis C antibody, if not routinely in high-risk groups and settings, then at least in the following scenarios:

- those having a baseline ALT >40
- anyone with jaundice or right upper quadrant abdominal pain.

Management of **hepatitis B** (HBV) co-infection is presented below, including why it is important to know the HBV status of any individual already on TDF/3TC and in whom these ARVs are being considered for discontinuation.

Hepatitis B co-infection

Hepatitis B virus (HBV) can cause serious acute problems, as well as chronic liver problems in those who develop chronic active infection (e.g. cirrhosis and hepatocellular cancer). Fortunately, certain ARVs (TDF, 3TC) are also active against HBV, which can ease management of those co-infected with HBV and HIV, albeit with one exception (see below).

In order to reduce the burden of HBV, many national departments of health have now added hepatitis B vaccination to their routine vaccination programme for children. It is important in high prevalence settings (any country in sub-Saharan Africa) that the first dose of hepatitis B vaccine is given with 72 hours of birth (ideally within 12 hours).

Diagnosis

A positive hepatitis B surface antigen result (HBsAg+) means that a person has active HBV infection, which can be transmitted to others. In settings where the usual first-line ART regimen includes TDF, **routine** testing for active HBV is not necessary in those being initiated on ARVs, since TDF and 3TC (or FTC) are active against both HIV and HBV and indicated for all HBsAg+ people living with HIV. However, HBsAg testing should still be considered in select cases (as above).

It is important to distinguish between the antigen test for HBV mentioned above and the antibody test. A positive hepatitis B antibody test could mean that either the individual has been infected with hepatitis B at some time in the past, or he/she has been vaccinated against hepatitis B. Thus, having antibodies against hepatitis B does not mean that a person has chronic active infection with hepatitis B.

If the HBsAg test result comes back as weakly positive, the test should be repeated.

Management

- Patients who are eligible for ARVs or are already on ARVs and have a HBsAg+ result need to be treated with tenofovir (TDF) and lamivudine (3TC).
- The 2013 WHO ART guidelines recommend that all those co-infected with HBV and who have severe chronic liver disease be initiated on ART, regardless of WHO clinical stage or CD4 count.
- When switching patients with chronic active hepatitis B infection to second-line ART regimens, **they need to remain on TDF and 3TC**. Sudden stoppage of TDF could cause a severe flare of the hepatitis, which can be life-threatening.



- If possible, check the creatinine and calculate the creatinine clearance (CrCl) before starting TDF.
- If it is not feasible to test for creatinine **routinely** in your setting, it should still be considered for those at risk of kidney disease (e.g. age >50 years, pre-existing renal impairment, hypertension and diabetes.)
- Patients with chronic active hepatitis B infection need to remain on TDF and 3TC indefinitely, even if they are switched to another ART regimen.

Hepatitis C co-infection

Clearance rates of **hepatitis C** (HCV) are lower in PLHIV (i.e. <15–30%) following acute infection, such that the majority of those infected with HCV develop chronic infection, followed by accelerated disease progression (compared to HIV-negative people). Treatments are available that can cure HCV, but these are expensive and difficult to take (since they have traditionally included interferon). Fortunately, newer and more effective treatments are becoming available. For more details on the management of HCV in PLHIV, see the *2013 MSF Hepatitis C Treatment Protocol and Programme Guidance for Resource-Limited Settings*.



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Renal disease in HIV

Tests used in the diagnosis and management of kidney disease

Renal diseases commonly encountered in primary care HIV clinic setting

Chronic Kidney Disease (CKD)

HIV-associated nephropathy (HIVAN)

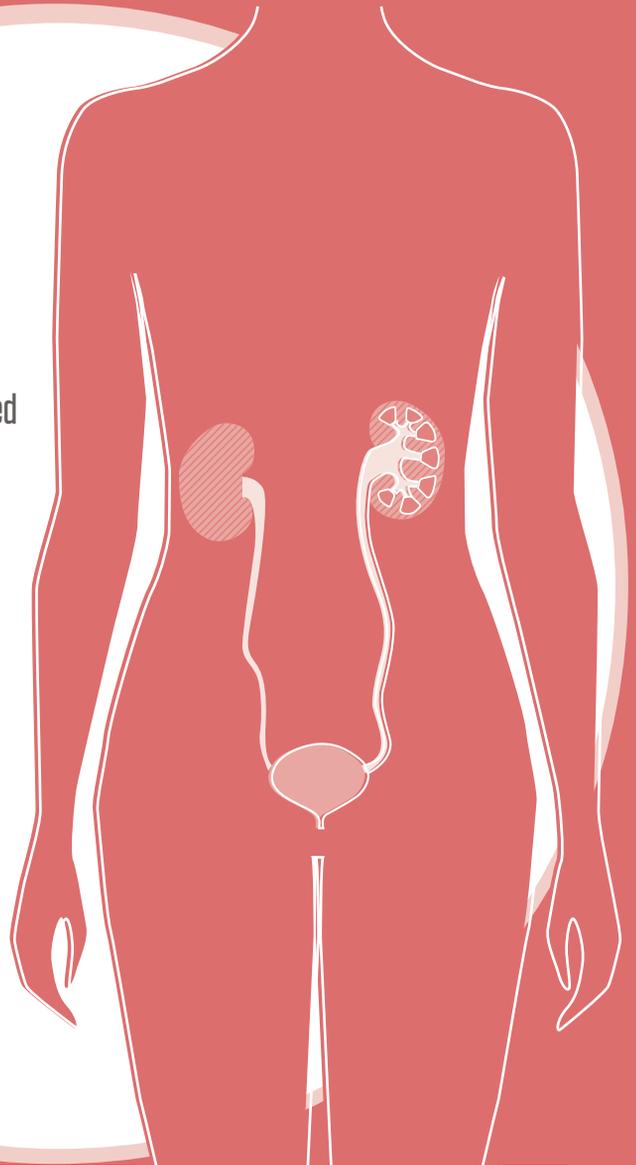
Acute kidney insult

Pre-renal causes

Intrinsic causes

Post-renal causes

Critical steps to take in safely managing renal disease in primary care



Kidney (renal) disease in patients often goes undetected because they do not present with obvious signs and symptoms.

Symptoms of kidney (renal) disease are often vague – mostly general malaise and nausea – but, as these are so frequent in HIV/TB, renal disease is often overlooked. When detected, it is usually on the basis of an abnormal laboratory test.

In the primary care HIV clinic, renal disease will be identified by a small range of signs, symptoms, and investigations:

- protein with or without blood in the urine
- elevated serum creatinine
- occasionally, ankle oedema
- occasionally, hypertension, nausea and vomiting, or a rash.

Failing to detect and manage renal disease in the early stages almost always leads to longer-term kidney damage that could have been prevented or lessened if treated earlier.

Tests used in the diagnosis and management of kidney disease

- **Urine dipstick:** The commonly used ones detect ten different things, of which the important ones in kidney disease are protein, blood and glucose. Nitrites and leukocytes are helpful in identifying urinary tract infections that can look like kidney disease.
- **Urine protein/creatinine ratio:** This is a test done on a simple urine test sent to a laboratory. It is a more accurate measurement of the amount of protein in the urine.

Interpretation: It is reported as g/mmol. Multiply the value by ten to give an approximate figure of grams of protein excreted per 24 hours, i.e. a urine protein/creatinine ratio of 0.1 means that about 1 g of protein is being excreted in the urine per 24 hours. This correlates roughly to 3–4+ proteinuria on dipstick testing.
- **Serum creatinine:** Creatinine is a natural chemical excreted in the urine daily. When the kidney starts to get sick this almost always results in the creatinine not getting cleared properly. The creatinine level therefore starts to rise.
- **Creatinine clearance (CrCl)/ Estimated Glomerular Filtration Rate (eGFR):** This is a calculation made using a formula and is a more accurate measurement of kidney **function** than the serum creatinine. It measures the kidney's ability to clear creatinine. A sick kidney almost always clears the creatinine more slowly, resulting in a rising serum creatinine and a dropping creatinine clearance (CrCl).



One formula to estimate the glomerular filtration rate (eGFR) or CrCl in ADULTS, modified from the Cockcroft-Gault formula, is as follows:

$$\text{eGFR} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l)}}$$

For females, multiply the result by 0.85 to better estimate the GFR.

The creatinine clearance must be evaluated every time. However it can be time-consuming in a busy clinic and calculating it for every patient is not necessary. Under the following circumstances the CrCl does not need to be calculated as the clearance is guaranteed to be within the normal range (more than 50 ml/min): If the patient's **weight > 50 kg, age < 50 years, creatinine < 100 (μmol/L) and non-pregnant.**

- **Kidney ultrasound:** This is not always available but, when it is, the findings can support a diagnosis. Chronic disease usually produces small kidneys (<9 cm) and acute disease like HIVAN or a drug reaction, often produces enlarged kidneys (>12 cm).

Renal diseases commonly encountered in primary care HIV clinic setting

Chronic kidney disease (CKD)

Common presentations seen in an ARV clinic are renal damage caused by hypertension and/or diabetes; and other known (previously diagnosed) renal disease. By the time a patient presents with elevated creatinine or proteinuria there is already significant renal disease.

However careful management from this point onwards can slow the progression to end stage renal disease (ESRD).

Diagnosis

- Diagnosis is usually made by finding elevated creatinine (ideally a few consecutive elevations a few months apart, indicating a more chronic state) with proteinuria and/or haematuria.
- There is frequently a mild anaemia (haemoglobin = 7–9 g/dl).
- An ultrasound, if obtainable, usually shows small kidneys (<9 cm).

Management

The following interventions have been shown to slow the progression of the damage:

- Stop smoking.
- Treat high blood pressure.
- Treat diabetes.
- Avoid NSAIDs.
- Start ARVs.
- Adjust renally excreted drug doses as needed (see Appendix 25).
- Monitor creatinine and urine six-monthly.
- Consider referral to or contact with more specialised help when the creatinine rises above 250.



See Appendix 25

HIV-associated nephropathy (HIVAN)

This is a kidney disease caused by the effect of HIV itself directly on the kidneys.

Key points:

- **There is always at least 2+ proteinuria, often much more.**
- The creatinine is frequently, **but not always**, elevated. At times it can rise rapidly with rapid progression to end stage renal disease (ESRD) within a few months.
- The CD4 count is often low, but can be more than 350 cells/ μ L. HIVAN is, however, always a clinical stage 4 disease requiring fast-tracking for ARVs.
- **There is rarely hypertension and oedema.**

Diagnosis

- Prevention and early detection of HIVAN is very important. If resources are adequate, this needs to be implemented at the primary care level with a routine baseline dipstick screening and serum creatinine measurement.
- The diagnosis can be confirmed only by biopsy but, as this is frequently not available, a presumptive diagnosis can be made as follows:
 - **In a setting where biopsy is not available, proteinuria (2+ or more) or a urine protein/creatinine ratio >1 , coupled with absence of hypertension and oedema, is enough for a presumptive diagnosis of HIV-associated nephropathy.**

Treatment

- Start ARVs as soon as possible, as there is clear evidence of their benefit.
- Protein damages the kidney so treat proteinuria with enalapril. Start with 2.5 mg bd and watch the blood pressure (as this can drop) and potassium (as this can rise, so check at one month).
- Continue to monitor the proteinuria and serum creatinine every three months for the first six months, then six monthly. It is important to calculate the CrCl as this will affect dose adjustments for certain medications (see Appendix 25).



See Appendix 25

Acute kidney insult

The commonest causes seen in the primary care setting are hypovolaemia, sepsis and drugs.

The fuller range of causes can be categorized as:

1. Pre-renal causes
2. Intrinsic causes
3. Post-renal causes

Once pre-renal and post-renal causes have been excluded, one is left with intrinsic causes, which are associated with high rates of morbidity and mortality.

1. Pre-renal causes

Main precipitants of pre-renal kidney failure, which act by decreasing blood pressure in glomerulus, include:

- sepsis
- hypovolaemia – especially in the presence of diarrhoea
- hypotension.

A mildly elevated serum creatinine (100–150 $\mu\text{mol/L}$) in the setting of dehydration is a common presentation in ill patients presenting for the first time to an HIV clinic (i.e. 'late presenters'). If the cause of the pre-renal failure is rapidly corrected, renal function can soon improve.

Treatment

Rehydrate, treat the sepsis and treat the diarrhoea. Because of the sensitivity of the kidney to hypo-perfusion, the patient will need intravenous (IV) fluids and preferably in-patient management until renal function has normalised.

2. Intrinsic causes

There are many different causes of intrinsic renal failure. The important ones in the HIV clinic are related to **drug reactions**, which will need more specialised input, but it is important to recognise such reactions early so that they can be referred or discussed.

Tenofovir (TDF) nephrotoxicity

- It occurs in less than 1% of patients starting on TDF and usually presents within weeks to months of starting the drug.
- It usually presents with rising creatinine but can also present with proteinuria, glycosuria, hypertension or oedema. The patient may also complain of myalgia related to hypokalaemia that can accompany a Fanconi syndrome.
- Risk factors include pre-existing, underlying kidney disease (hypertensive, diabetes) and co-administration of nephrotoxic medication e.g. aminoglycosides and NSAID use.
- In order to allow for early diagnosis, it is important to follow the guidelines that recommend serum creatinine measurement (and calculation of CrCl) at baseline, one month, four months and 12 months.
- Refer to national guidelines for local advice on creatinine monitoring. (NB: TDF is still the ARV of choice even when there is no access to creatinine as it is safer than AZT and D4T and is available as a once-a-day, fixed-dose combination.)



See National Guidelines

Treatment

Stop the TDF (check HepB status), replace it with another ARV, and monitor the CrCl in order to ensure a return to normal function, although there may be residual damage.

Cotrimoxazole and rifampicin toxicity

- These present similarly to an interstitial nephritis with symptoms such as a flu-like illness, flank pain, oliguria and fever. They both start within weeks to months of starting the drug.
- Rifampicin toxicity happens more commonly when rifampicin has been stopped and then restarted.



Refer patient

Treatment

As for tenofovir, treatment consists of stopping the drug and monitoring the CrCl in order to ensure a return to normal function. Cortisone may sometimes be necessary and this is best discussed with an experienced clinician.

3. Post-renal causes

In the HIV clinic, the commonest cause of post-renal failure is bilateral ureteric obstruction, due to large nodes as a result of TB lymphadenopathy. Occasionally, the nodes can be from a malignancy, such as cervical cancer or lymphoma. The clinical setting will alert the clinician and the diagnosis of post-renal failure will have to be confirmed with an ultrasound showing hydronephrosis.

Treatment

- Treat the underlying condition, whilst monitoring the renal function to ensure that it returns to normal.
- Consult with a specialist if possible as an urgent nephrostomy may be needed to take back-pressure off the kidneys.

Critical steps to take in safely managing renal disease in primary care

If an elevated creatinine is noted, first calculate the creatinine clearance and, if it is significantly reduced (i.e. less than 50 ml/min), specific steps need to be taken:

1. Avoid use of tenofovir (TDF) in the ARV regimen.
2. Adjust the doses of any ARVs that are renally excreted, e.g. 3TC or d4T (see Appendix 25). Please note: If the creatinine is not being cleared by the body, then certain drugs will not be properly cleared, resulting in toxic blood levels.
3. Find and manage the underlying kidney disease using the algorithms in Appendices 26A and 26B.



See Appendix 25



See Appendices 26A and 26B



Please note: Proteinuria with or without haematuria is often assumed to be due to a urinary tract infection (UTI). A UTI is more likely in the presence of nitrites and/or leukocytes. If the patient is treated for a UTI it is important that the urine is checked again to ensure that the protein has cleared. If proteinuria is still present following treatment of the UTI, this may be due to renal disease and it must be investigated further (see Appendix 26B).

For more a more detailed management guide for renal disease, view the training video and download the booklet 'Renal disease in primary care' from the website www.samumfsf.org/resources/



www.samumfsf.org

Reproductive health

Sexually transmitted
infections (STIs)

Protocol 1 (males): Urethral
discharge or dysuria

Protocol 2 (males or females):
Genital ulcer syndrome (GUS)

Protocol 3 (females): Vaginal
discharge syndrome (VDS)

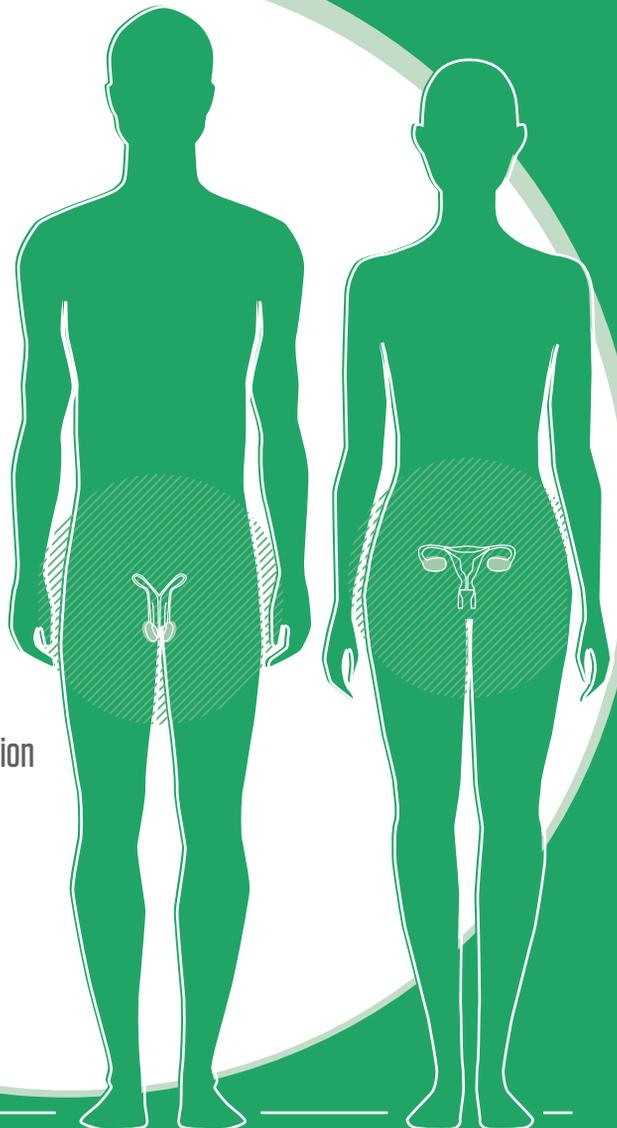
Protocol 4 (females): Lower abdominal
pain or cervical tenderness

Vulvo-vaginal candidiasis

Human papilloma virus (HPV) infection

Syphilis

Sexual assault



Sexually transmitted infections (STIs)

General principles

It is very important that STIs are diagnosed and treated in the general population, since they are a major risk factor for HIV transmission.

A syndromic approach is used for the management of STIs. This means that treatment is based on 'signs and symptoms' (syndromes), without using diagnostic tests to identify the precise cause of the infection. Syndromic management is cost effective and allows for early treatment (i.e. same day) of STIs. Since mixed infections are common, syndromic management covers the most likely organisms that may cause a specific symptom.

A good history is an important part of the four protocols below; assess the person's **risk factors for STI** (age <21, new partner, or multiple partners) and ask about any symptoms in the partner.

A physical examination should always be done to confirm the symptoms.

Treatment is then provided at the same visit based on results of the history and physical examination. A follow-up appointment in one week for reassessment should be regularly advised. Partner treatment is essential to avoid 'ping-pong' infections and ensure cure. Family planning and contraception needs (for both women and men) should be addressed. Ask about the last menstrual period and screen for pregnancy if indicated.



Always consider the six 'Cs' when dealing with STIs:

- Completion of prescribed medication and **Contact** tracing (of partner) to achieve **Cure**.
- **Counselling** to **Change** behaviour and encourage **Condom** use.

Approach to the partner with an STI:

- Offer syphilis screening and HIV testing to all partners.
- Partners who are symptomatic must be treated syndromically according to Algorithm 15.1.



Asymptomatic partner(s) of a patient with an STI should be treated based on the patient's STI diagnosis/syndrome.



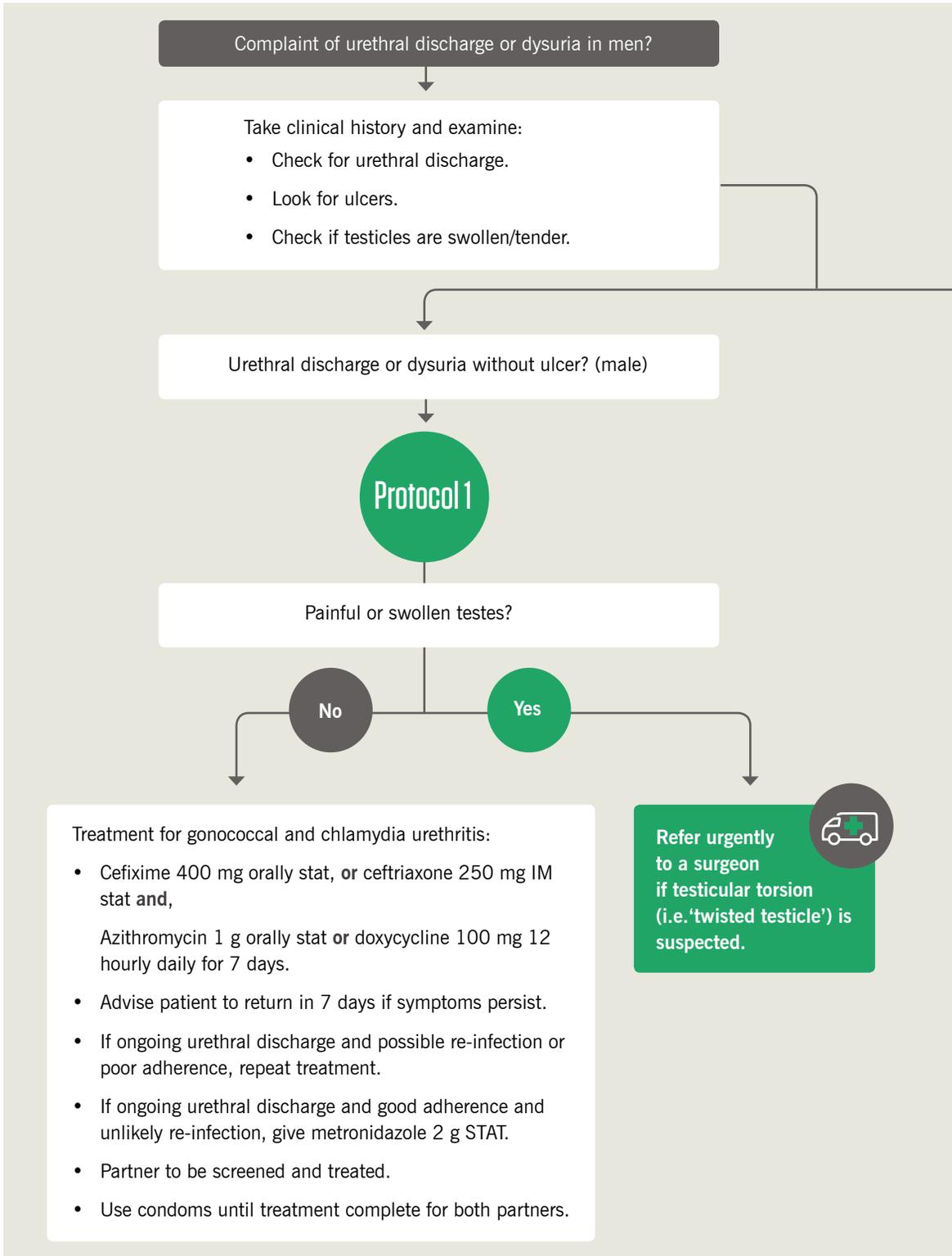
Resistance of gonorrhoea against ciprofloxacin is becoming common.

Therefore, ceftriaxone 250 mg by intramuscular injection (or cefixime 400 mg daily if available) is recommended to treat gonorrhoea in place of ciprofloxacin. Refer for further investigation if no improvement.



Refer patient

Algorithm 15.1 Syndromic STI management – protocols 1 and 2



Ulcer present? (in male or female)

Protocol 2

Ulcer with or without swollen inguinal lymph node?

Painful, small blisters?

Treatment for primary syphilis and chancroid:

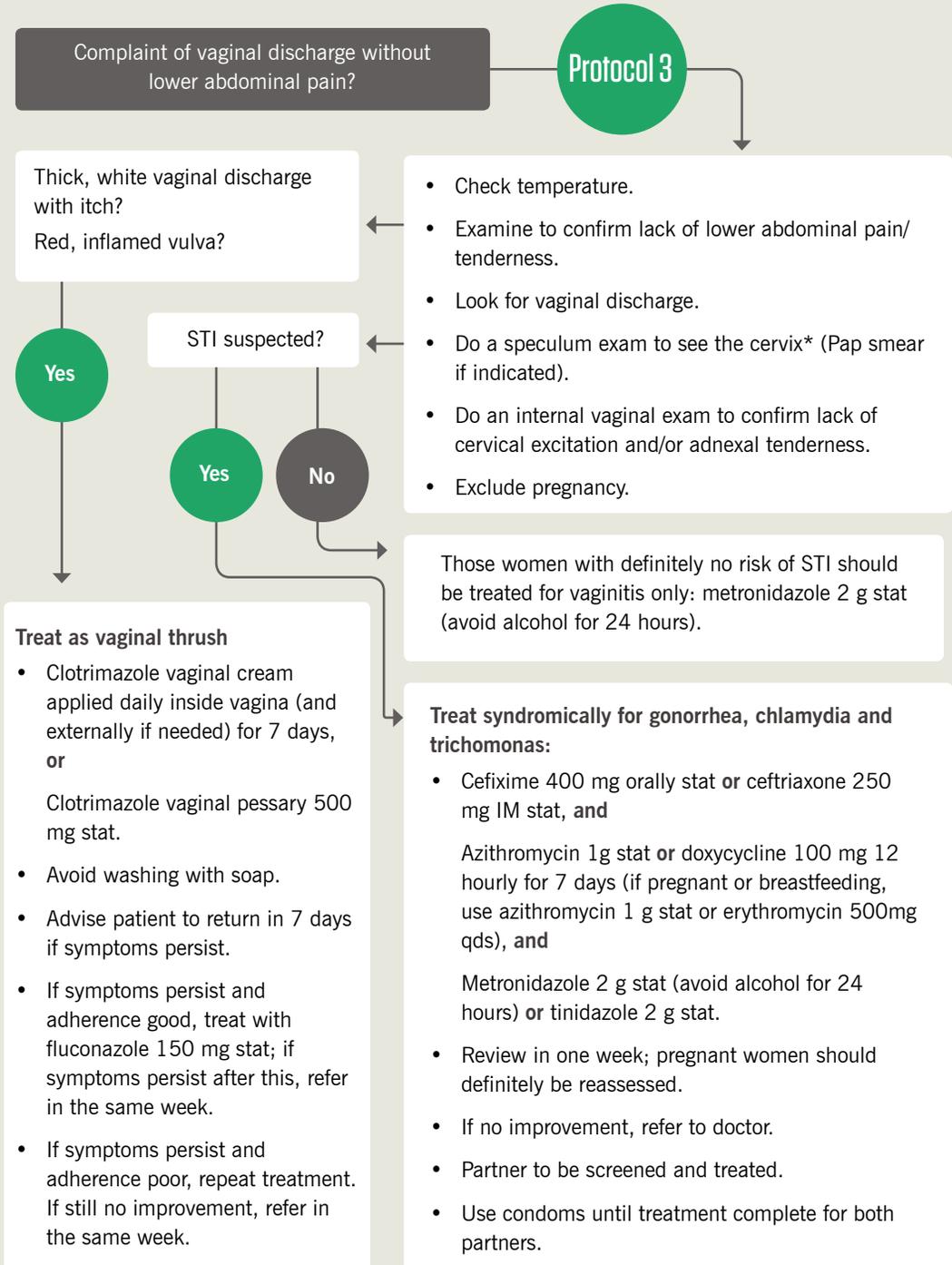
- Benzathine penicillin 2.4 MU IM stat, and Azithromycin 1g stat or erythromycin 500 mg 6 hourly for 14 days.
- If penicillin allergic, give erythromycin 500 mg 6 hourly for 14 days.
- Aspirate any fluctuant lymph node.
- Pain relief if indicated.
- Review after 7 days.
- If still present, but improving, repeat treatment.
- If no change, refer to doctor in the same week.
- Partner to be screened and treated.
- Use condoms until treatment complete for both partners.

Treatment for genital herpes simplex virus (HSV)

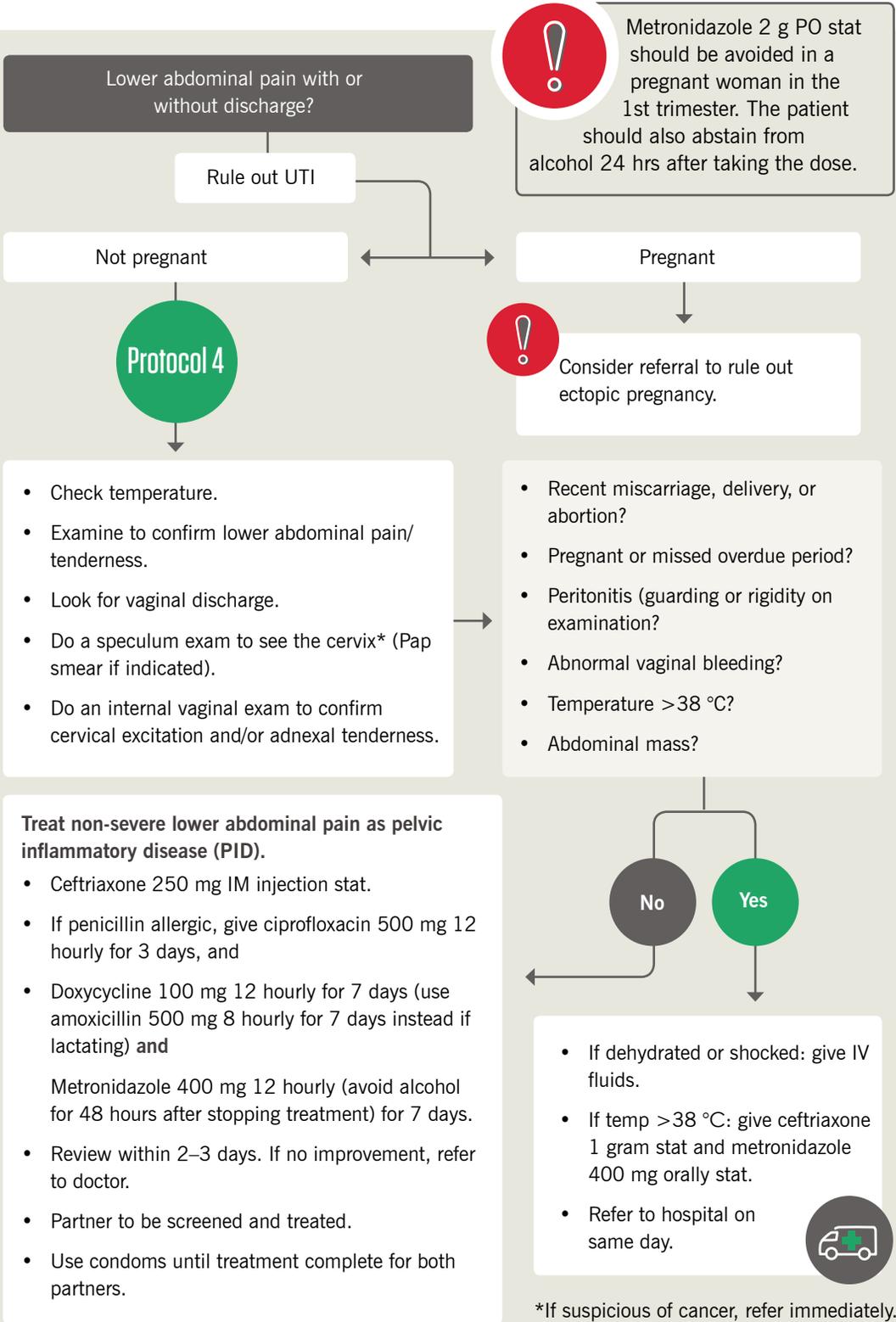
- Give pain relief if necessary.
- Keep lesions clean and dry.
- Acyclovir 400 mg 8 hourly for 7 days.
- Counsel that HSV infection is life long and that transmission can occur even if asymptomatic.

Algorithm 15.2 Syndromic STI management – protocols 3 and 4

(Exclude pregnancy, ideally with a pregnancy test, for any woman presenting with vaginal discharge or lower abdominal pain.)



*If suspicious of cancer, refer immediately.



Protocol 1 (males): Urethral discharge or dysuria

Treat syndromically for gonococcal and chlamydial urethritis.

A man with an STI usually complains of discharge and sometimes also dysuria (painful urination). Testicular pain may also signify an STI in males; rarely, testicular pain can result from torsion and this must not be missed (see below).

Assessment

- Confirm urethral discharge by examination.
- If a genital ulcer is present, use Protocol 2.
- If a painful or swollen testis is detected, refer to a surgeon at once if testicular torsion ('twisted testicle') is suspected. Testicular torsion is more likely in a male less than 18 years who is not sexually active, has no history of injury and no discharge on examination.



Refer patient

Management

- Treat urethral discharge or dysuria with: cefixime 400 mg orally stat or ceftriaxone 250 mg IM stat plus azithromycin 1 g orally stat or doxycycline 100 mg 12 hourly daily for 7 days. Advise patient to return in 7 days if symptoms persist.
- If ongoing urethral discharge or dysuria, decide if this is possible reinfection or it is poor adherence.
- If yes: repeat treatment: cefixime 400 mg orally stat or ceftriaxone 250 mg IM stat plus azithromycin 1 g orally stat or doxycycline 100 mg 12 hourly for 7 days.
- If not: give metronidazole 2 g stat. (Avoid alcohol for 24 hours.)
- Refer for further investigation if not resolved.



Refer patient

Protocol 2 (males or females): Genital ulcer syndrome (GUS)

The most common causes of genital ulceration are genital herpes simplex virus (HSV), syphilis and chancroid.

Assessment

- Confirm ulcer(s) by examination.
- Establish first if the patient has been treated for syphilis. If not, treat syndromically for primary syphilis and chancroid, both of which can present as a single ulcer with or without swollen inguinal lymph nodes.

- Note that syphilitic ulcers are painless whilst chancroid ulcers are usually painful.
- If there are multiple tiny, very painful blisters (that have become ulcers) and a history of recurrence of these blisters, the diagnosis is more likely to be herpes simplex virus (HSV), i.e. genital herpes.

Management

Syndromic treatment of a painless single ulcer, with or without swollen inguinal lymph nodes:

- Benzathine penicillin 2.4 million units IM injection stat and
- Azithromycin 1g orally stat or erythromycin 500 mg 6-hourly for 14 days. If penicillin-allergic, give erythromycin 500 mg 6-hourly for 14 days.
- Aspirate any fluctuant lymph node and send for microscopy and for AFB (GeneXpert) (since this procedure is easy, and there is always the possibility of active TB disease).
- Give pain relief if indicated.
- Review after 7 days.
- If still present but improving, repeat treatment:
 - Azithromycin 1g orally stat or erythromycin 500 mg 6 hourly for 7 days.
 - Aspirate any fluctuant lymph node.
 - Give pain relief if indicated and review after 7 days.
- If no change: refer to doctor same week.

Treatment of genital HSV

- Give pain relief if necessary.
- Keep lesions clean and dry.
- Acyclovir 400 mg 8 hourly for 7 days.
- Explain that herpes infection is life long and that transmission can occur even when asymptomatic.
- PLHIV who have an episode of genital herpes lasting more than one month are considered to be in clinical stage 4 and therefore are in need of cotrimoxazole prophylaxis and ART, regardless of CD4 count.



Refer patient

Protocol 3 (females): Vaginal discharge syndrome (VDS)

When a woman complains of a vaginal discharge (and/or burning or itching) it is important to distinguish between vaginitis (inflammation of the vagina) and cervicitis (inflammation 'higher up' of the cervix). It is also important to identify if a woman is pregnant, since some medications should not be used in pregnancy.

Assessment

- Confirm abnormal discharge by examination.
- Perform a speculum examination to visualise the cervix.
- Perform internal examination to check for 'cervical motion tenderness': If lower abdominal or cervical motion tenderness is present, treat for PID (see protocol 4).
- If lower abdominal pain or painful sexual intercourse: treat for PID (see protocol 4).
- Perform a Pap smear if indicated (see below): If suspicious of cancer (bleeding, ulcerated or fungating lesions or a palpable mass on the cervix), refer immediately.



Refer patient

Management

- Those women with definitely **no risk of STI**, treat for **vaginitis only**.
- If vaginal candidiasis (thrush) is suspected as the cause of the vaginitis (thick, white vaginal discharge with itch), give clotrimazole vaginal cream and tablets (see below).
- However, if no thick, white vaginal discharge is present, give metronidazole 2g stat. (Avoid alcohol for 24 hours.) If pregnant, give 400 mg TDS for 5 days.
- Young, sexually active women should be **treated syndromically for gonorrhoea, chlamydia and trichomonas**:
 - Cefixime 400 mg orally stat or ceftriaxone 250 mg IM stat, **AND**
 - Azithromycin 1 gram stat or doxycycline 100 mg 12 hourly for 7 days (if pregnant or breastfeeding, use amoxicillin 500 mg 8 hourly for 7 days instead), **AND**
 - Metronidazole 2 g stat (avoid alcohol for 24 hours after stopping treatment) or tinidazole 2 g stat. If pregnant, give metronidazole 400 mg TDS for 5 days.
- Pregnant women must be reviewed in one week. If there is no improvement, refer to the doctor.



Refer patient

Protocol 4 (females): Lower abdominal pain or cervical tenderness

Lower abdominal pain in women can be the result of many different problems, including complications of pregnancy. A thorough history and physical examination is necessary to determine the cause, as well as urine and pregnancy testing. Protocol 4 shows the syndromic management of **pelvic inflammatory disease (PID)**.

Assessment

- Check temperature.
- Is sexual intercourse painful (dyspareunia)?
- Examine to confirm lower abdominal pain/tenderness.
- Also perform an internal vaginal examination to confirm cervical motion and adnexal tenderness.
- Look for vaginal discharge.

Management

Severe PID



Give antibiotics as soon as possible; do not delay whilst waiting for transfer to hospital.

Refer to hospital urgently if:

- patient is very ill, cannot walk upright
- temperature $>38.5^{\circ}\text{C}$
- severe abdominal tenderness or pelvic mass
- abnormal vaginal bleeding
- pregnant (or missed or overdue period)
- recent miscarriage/delivery or abortion
- abdominal mass.

If **dehydrated** or in **shock**: give IV fluids.

If temp $\geq 38^{\circ}\text{C}$, give ceftriaxone 1 g IM stat and metronidazole 400 mg orally stat.



Refer patient

Low-grade PID

If none of the above symptoms and signs is present, then the PID can be considered low grade and treated with:

- Ceftriaxone 250 mg IM injection stat or Cefixime 500 mg PO stat, **AND**
- Doxycycline 100 mg 12 hourly for 7 days or (if pregnant or breastfeeding use amoxicillin 500mg 8 hourly for 7 days), **AND**
- Metronidazole 400 mg 12 hourly for 7 days (avoid alcohol for 24 hours after stopping treatment).
- Reassess in 3 days and refer to hospital if not improving.



Refer patient

Vulvo-vaginal candidiasis

Vulvo-vaginal candidiasis (also known as vaginal thrush or yeast vaginitis) is caused by a type of fungus (a yeast called *Candida*). It can occur in all women, regardless of HIV status. It is not an STI.

Vaginal thrush is more common in HIV-positive women for two reasons:

- HIV-positive women have weaker immune systems and are more likely to suffer from infections in general.
- HIV-positive women are more often on antibiotics to treat or prevent other infections; this disturbs the normal balance of organisms in a woman's body and allows the *Candida* yeast to 'overgrow'.

Clinical presentation

- burning or itching sensation in the vagina
- associated with a white thick discharge
- vulva is often inflamed and itchy.

Management

Topical therapies may be used depending on what is available in your clinic:

- Clotrimazole vaginal cream applied twice daily inside the vagina (and externally if needed) for 7 days.
- Clotrimazole vaginal tablet 500 mg stat, inserted high inside the vagina at night.
- Avoid washing with soap.
- Advise patient to return in 7 days if symptoms persist.
- If recurrences of vaginal thrush are common (usually >3 episodes) or the vaginal thrush is resistant to topical therapy:

- Oral treatment with fluconazole 150 mg stat dose should be effective.
- Fluconazole 50 mg daily for 7–10 days is also effective but patients are less likely to adhere.
- Or, repeat clotrimazole treatment (as above).
- Test for diabetes.
- If ongoing discharge, but no vaginal thrush on examination: consider protocol 3 (vaginal discharge syndrome).

Human papilloma virus (HPV) infection

1. Genital warts

Human papilloma virus (HPV) is a sexually transmitted virus. HPV types 6 and 11 can cause **genital warts** in men or women.

Clinical presentation

- HPV can present externally as genital warts (also known as ‘condyloma acuminata’): They start as small papules, which are often not noticed by the patient.
- Warts grow on moist surfaces and areas traumatised during sexual intercourse. They can be:
 - external: penile, vulva, perineum, perianal
 - internal: vagina, cervix.
- Genital warts can grow to become big cauliflower-like tumours.

Management

- The treatment of external genital warts is not easy.
 - One option is to protect the surrounding skin with petroleum jelly and apply 20% tincture of podophyllin or podophyllotoxin topical solution (5 mg/ml).
 - Apply twice daily for 3 consecutive days; treatment may be repeated at weekly intervals if necessary for a total of five 3-day treatment courses.
 - If not feasible for patient to self-apply, apply weekly at the clinic.
 - Do not apply podophyllin solution internally.
- Cryotherapy is the preferred treatment, if available. Laser therapy is an alternative treatment.
- Check for syphilis.

- If the genital wart lesions are too big and/or not responding, or podophyllin is not available, the patient can be referred for surgical treatment.
- Do not use podophyllin and podophyllotoxin during pregnancy.

2. Cervical cancer

HPV types 16 and 18 are the most common types of HPV that can lead to cervical intraepithelial neoplasia (CIN) in women, which are changes of the cervical cells that can progress over a number of years to cancer of the cervix. HPV is sexually transmitted. Pre-malignant changes and cervical cancer are more common in HIV-positive women and, hence, a Pap smear every 12 to 36 months is recommended in HIV-infected women, in order to screen for any cervical problems. The recommended frequency of the Pap smear will vary according to local guidelines and resources. If CIN is found early, these cervical problems can be treated before they develop into cancer.

Many countries are now starting to implement vaccination against HPV for adolescent girls, in order to protect them from developing cervical cancer. Refer to your local Expanded Programme on Immunisation (EPI) guidelines.



See National Guidelines

Screening for cervical cancer

Cervical cancer is the most common form of cancer in African settings.

Follow your national cervical screening protocol and manage results according to the guidelines.

Where cervical cytology is not available, visual inspection of the cervix using acetic acid (white vinegar) or Lugol's iodine (abbreviated as VIA and VILI respectively) can be implemented.

Inform your patient of symptoms of cervical cancer (abnormal bleeding, vaginal discharge) and instruct her to return should they occur. Give a clear appointment for when the next Pap smear should be.



See National Guidelines

Syphilis

A blood test for syphilis (VDRL) is recommended annually for all patients attending the HIV clinic.

Acquired syphilis is a complicated disease, having different stages and many different symptoms. Syphilis can also be transmitted from mother to child, which is called **congenital syphilis** in the newborn.

Clinical presentation

1. Early stage: primary or secondary signs present:
 - Primary: painless 'chancre' (ulceration) occurring during initial infection; this often goes unnoticed.
 - Secondary: various rashes on the body several months after primary infection, typically including the palms and soles, snail track ulcers in the mouth,

condylomata lata, constitutional symptoms and arthralgia. Any organ may be affected (e.g. meningitis, hepatitis, nephritis).

2. Latent stage: asymptomatic or absence of primary or secondary signs
3. Tertiary: late stage of infection causing skin, heart and neurological problems.

Syphilis may be asymptomatic, which is why screening is important.

Management

If syphilis is suggested by a positive VDRL result treat:⁴²

primary and secondary:		benzathine penicillin (2.4 MU IM as a single dose)
	or	erythromycin (500 mg 6 hourly) for 14 days (only for pregnant women, who must be given a course of doxycycline after delivery as erythromycin does not reliably treat syphilis),
	or	ceftriaxone 1 g daily for 14 days
	or	doxycycline (100 mg 12 hourly) for 14 days
latent syphilis in HIV positive patients:		benzathine penicillin (2.4 MU IM) at weekly intervals for 3 weeks
	or	erythromycin (500 mg 6 hourly) for 28 days (only for pregnant women, who must be given a course of doxycycline after delivery as erythromycin does not reliably treat syphilis)
	or	ceftriaxone 1 g daily for 14 days
	or	doxycycline (100 mg 12 hourly) for 28 days
neurosyphilis:		penicillin G (4 MU 4 hourly) for 14 days or by continuous infusion. Consider adding two doses of benzathine penicillin (2.4 MU IM; one week apart) after completion of IV therapy
	or	procaine penicillin (2.4 MU IM daily) plus probenecid (500 mg 6 hourly) for 14 days
pregnancy:		as above, but only penicillin reliably treats the baby – consider desensitisation in penicillin-allergic patients



See National Guidelines

Sexual assault

Sexual assault is often underreported. An open and non-judgmental attitude by the clinician is essential. Patients will probably not bring up a history of sexual violence unless they feel at ease. Be aware of more subtle signals that the person may send: for example, the patient may look depressed, or avoid eye contact when talking. The physical and psychological consequences of sexual assault are reduced through the provision of medical and mental health care.

Management of sexual assault

Management of sexual assault includes taking and documenting a thorough history and physical examination followed by 5 key steps (for full guidance on the management of sexual assault please refer to the MSF SGBV International guidelines on www.samumsf.org):

- HIV prevention (post-exposure prophylaxis or 'PEP')** if the patient presents within the first 72 hours and is HIV negative versus referral to an ART treatment centre if the patient is found to be already HIV positive.

For the HIV-negative individual, prophylaxis with ARVs (i.e. PEP) will be given as follows:

MSF recommends three-drug PEP for all cases of rape. (Consult local guidelines for national protocols):

 - TDF + 3TC (or FTC) + atazanavir 300/ritonavir 100 once daily for 28 days.
 - An alternative to TDF is AZT.
 - An alternative to atazanavir/ritonavir is lopinavir/ritonavir (Lpv/r).
- Testing for pregnancy and emergency contraception.** Levonorgestrel 1.5mg stat dose is given. Levonorgestrel is most effective if given within 72 hours of the event but has some evidence of efficacy up to 120 hours. If the woman is on any enzyme inducing drug (Rifampicin, a NNRTI, Ritonavir, Carbamazepine) the dose of levonorgestrel should be doubled to 3mg stat.
- STI treatment and prevention**, including hepatitis B vaccination if previously unvaccinated or did not previously complete the full course of hepatitis B vaccination.

STI prevention (non-pregnant adults and children >12 years):

- cefixime 400 mg stat dose
- metronidazole 2 g stat dose
- azithromycin 1 g stat (or doxycycline 100 mg twice a day for 7 days).

STI prevention (pregnant adults or pregnant adolescents >12 years):

- ceftriaxone 250 mg IM stat dose
- azithromycin 1 g stat or erythromycin 500 mg 4 times a day for 7 days
- metronidazole 400 mg tds for 7 days.

www.samumsf.org

4. Tetanus vaccination.
5. Trauma counselling.

Children

- Be aware of legal age of consent for HIV testing and HIV PEP in children.
- For children/adolescents >12 years, manage as above.
- Children <12 years preferably need to be managed at a specialised site where there is expertise in dealing with traumatised children and ART in children.
- For ARV prophylaxis (PEP) in children >40 kg and >6 years of age the adult regimens may be given. For drug dosages according to weight, refer to Appendix 5B. For children <40 kg and/or <6 years of age give:
 - AZT or ABC
 - 3TC
 - lopinavir/ritonavir (Lpv/r)
 - STI prophylaxis (see following 2 tables for dosages)
 - Cefixime (protects against *N. gonorrhoea*)
 - Azithromycin (protects against chlamydia)
 - Metronidazole or tinidazole (protects against trichomoniasis)



See Appendix 5B

Table 15.1 Children's prophylactic medications against gonorrhoea and chlamydia

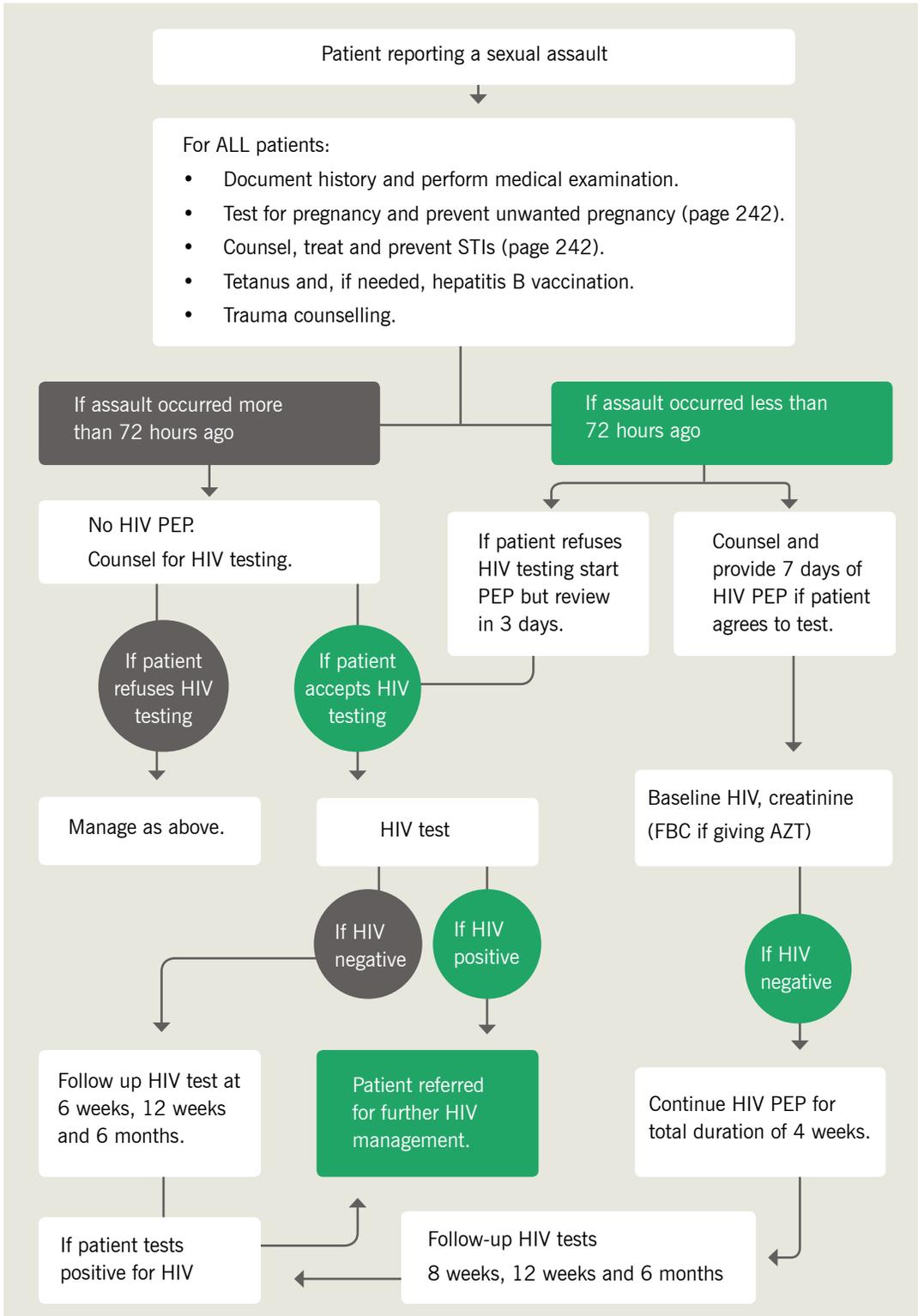
Children	Product	Presentation	Strength	Dosage	Duration
5–12 kg	cefixime	powder for suspension	100 mg/5 ml	8 mg/kg	stat dose
	azithromycin		200 mg/5 ml	20 mg/kg	
12–25 kg	cefixime	tablet or capsule	200 mg	200 mg	
	azithromycin		250 mg	500 mg	
25–45 kg	cefixime		200 mg	400 mg	
	azithromycin		250 mg	2 g	

Table 15.2 Children's prophylactic medications against trichomoniasis

Children	Product	Presentation	Strength	Dosage	Duration
<45 kg	tinidazole	tablet	500 mg	50 mg/kg (max 2 g)	stat dose
	metronidazole	+/- powder for suspension	250 mg or 500 mg or 125 mg/ml	30 mg/kg/day in 3 dosages	7 days

Algorithm 15.3 Management of sexual assault

(Also see Figure 1.4 on page 9 for MSF PEP protocol.)





Appendices

South African edition

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Appendix 1: WHO clinical staging of HIV disease in adults, adolescents and children

Adults and adolescents ^a	Children
Clinical stage 1	
Asymptomatic Persistent generalised lymphadenopathy	Asymptomatic Persistent generalised lymphadenopathy
Clinical stage 2	
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Seborrhoeic dermatitis	Unexplained persistent hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Herpes zoster Lineal gingival erythema Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Extensive wart virus infection Extensive molluscum contagiosum Unexplained persistent parotid enlargement
Clinical stage 3	
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than one month Unexplained persistent fever (intermittent or constant for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotising ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10 ⁹ /l) and/or chronic thrombocytopaenia (<50 x 10 ⁹ /l)	Unexplained moderate malnutrition ^b not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one month) Persistent oral candidiasis (after first 6 weeks of life) Oral hairy leukoplakia Lymph node tuberculosis Pulmonary tuberculosis Severe recurrent bacterial pneumonia Acute necrotising ulcerative gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5x10 ⁹ /l) or chronic thrombocytopaenia (<50 x 10 ⁹ /l) Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including bronchiectasis

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

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

- a In the development of this table, adolescents were defined as 15 years or older. For those aged less than 15 years, the clinical staging for children should be used.
- b For children younger than 5 years, moderate malnutrition is defined as weight-for-height <-2 z-score or mid-upper arm circumference ≥ 115 mm to <125 mm.
- c Some additional specific conditions can be included in regional classifications, such as penicilliosis in Asia, HIV-associated rectovaginal fistula in southern Africa and reactivation of trypanosomiasis in Latin America.
- d 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.

Appendix 2A: Cotrimoxazole prophylaxis

(also see Appendix 2B for desensitisation schedule)

Recommended dose/ Protection against	Indications to start	Indications to discontinue	If allergy or intolerance to cotrimoxazole
<p>Recommended dose</p> <p>Adults: CTX 960 mg od.</p> <p>Infants and children: dosage according to body weight (see Appendix 5B on page 258).</p> <p>If taken regularly, CTX protects against</p> <ul style="list-style-type: none"> • pneumonia, especially PCP • brain infections (toxoplasmosis) • certain types of diarrhoea • other bacterial infections, such as UTI • malaria. <p>CTX is a combination of two antibiotics: trimethoprim (TMP) and sulfamethoxazole (SMX).</p> <p>There are several trade names for CTX: Bactrim®, Septrim®, etc.</p>	<p>HIV-infected adults</p> <p>CD4 <350 cells/μl or clinical stages 2, 3 or 4.</p>	<p>HIV-infected adults</p> <p>On ARVs and CD4 >200 cells/μl on 2 consecutive occasions 3–6 months.</p> <p>In settings with high prevalence of malaria and/or severe bacterial infections (most low and low middle income countries), may be continued in adults with HIV infection, regardless of CD4 cell count and WHO clinical stage.</p>	<p>Non-severe side effects (grades 1 and 2):</p> <ul style="list-style-type: none"> • Desensitise adults (see Appendix 2B). • Desensitisation should not be done in children. <p>Grade 3 toxicity to CTX or desensitisation not successful:</p> <ul style="list-style-type: none"> • Dapsone 1.00 mg daily (protects against PCP, but limited protection against toxoplasmosis). • Therefore, add pyrimethamine 50 mg + folic acid** 25 mg weekly to protect against toxoplasmosis if available. <p>In case of severe reactions to CTX (grade 4 skin, liver, kidney or bone marrow toxicity), dapsone should not be used, as there may be cross-reactivity.</p> <p>Dapsone is safe in pregnancy.</p> <p>Dapsone (2 mg/kg/day) can be given to infants and children unable to tolerate CTX.</p> <p>** Note that folic acid is not the same as folic acid.</p>
<p>All HIV-exposed infants</p> <p>Starting at 6 weeks of age.</p>	<p>HIV-exposed infant</p> <p>Negative PCR or rapid HIV test at least 6 weeks after complete breastfeeding cessation and absence of clinical signs of HIV infection.</p>	<p>HIV-exposed infant</p> <p>Negative PCR or rapid HIV test at least 6 weeks after complete breastfeeding cessation and absence of clinical signs of HIV infection.</p>	
<p>HIV-infected children</p> <ul style="list-style-type: none"> • Under 5 years: • All >5 years: treat as adults = stages 2, 3 and 4 or CD4 <350 cells/μl. 	<p>HIV-infected children without previous PCP or toxoplasmosis*:</p> <ul style="list-style-type: none"> • Age 0–5: Do not stop cotrimoxazole. • Age >5: On ARVs and CD4 >200 cells/μl on 2 consecutive occasions 3–6 months apart. <p>HIV-infected children with previous PCP or toxoplasmosis*:</p> <ul style="list-style-type: none"> • <5 years: Do not stop. • >5 years: On ARVs and CD4 >200 cells/μl on 2 consecutive occasions 3–6 months apart. <p>* Children at risk of malaria should be maintained on CTX until that risk subsides.</p>	<p>HIV-infected children without previous PCP or toxoplasmosis*:</p> <ul style="list-style-type: none"> • Age 0–5: Do not stop cotrimoxazole. • Age >5: On ARVs and CD4 >200 cells/μl on 2 consecutive occasions 3–6 months apart. <p>HIV-infected children with previous PCP or toxoplasmosis*:</p> <ul style="list-style-type: none"> • <5 years: Do not stop. • >5 years: On ARVs and CD4 >200 cells/μl on 2 consecutive occasions 3–6 months apart. <p>* Children at risk of malaria should be maintained on CTX until that risk subsides.</p> <p>In settings with high prevalence of malaria and/or severe bacterial infections (most low and low middle income countries), may be continued in adults with HIV infection, regardless of CD4 cell count and WHO clinical stage.</p>	

Appendix 2B: Desensitisation with cotrimoxazole

Desensitisation can be offered rapidly or over a longer period of time.



Do not desensitise anyone who has had an anaphylactic reaction to cotrimoxazole or a severe skin rash such as Stevens-Johnson syndrome.

Do not attempt in children.

Desensitisation is usually about 60% effective. Rapid desensitisation ideally should be performed during the day in a setting where emergency resuscitation can be provided and adrenaline can be given. Observations during rapid desensitisation should take place every 30 minutes, before each dose is given, and should include temperature, pulse, and blood pressure.

If only mild rash or pruritus occurs, administer antihistamine (e.g. chlorpheniramine or promethazine) and continue. If more serious side effects occur, such as severe wheeze, severe or symptomatic hypotension, severe rash, and so on, discontinue desensitisation, manage appropriately, and do not try to restart desensitisation.

Once cotrimoxazole has been started, it can be continued indefinitely as long as no reactions are noted, but if the drug is stopped at any time, there may be a risk of reaction when it is restarted.

Using a 1 ml syringe, put 0.5 ml of paediatric cotrimoxazole 240 mg/5 ml syrup in 1 000 ml of 5% dextrose and mix well.

Give as follows:

Minutes	Quantity of above mixture given orally
0	1 ml (use 10 ml syringe)
30	10 ml (use 10 ml syringe)
60	100 ml (use 10 ml syringe)

Then switch to paediatric cotrimoxazole 240 mg/5 ml syrup in adults.

Minutes	Quantity
90	0.5 ml
120	5 ml
150	480 mg tablet
180	Start full prophylactic or therapeutic dose.

Appendix 3: Clinical review of symptoms and signs

Ask	Look
<p>If this is the first visit:</p> <p>Review medical history; particularly for TB, other opportunistic infections, and chronic problems.</p> <p>For all visits:</p> <ul style="list-style-type: none"> • How have you been? What problems have you had? • Have you had any of the following? If yes, ask for how long: <ul style="list-style-type: none"> • Headache? Fever? Night sweats? • Cough? • Nausea or vomiting? Poor appetite? • Mouth sores? • Abdominal pain? • Diarrhoea? • New skin rash? • Fatigue? • Signs of STI? • Tingling, numb, or painful feet/legs? • Any other pain? If yes, where? • Have you needed urgent medical care? If yes, ask for record/diagnosis. • Which medications are you taking and how often? • Assess adherence (if patient is on opportunistic infection prophylaxis and/or ART). • What problems have you had taking the medicines? How are you taking the medicines? • Are you taking any other drugs (traditional remedies, TB, ARV, illicit drugs, etc.). • How are things at home? • Has your partner been tested? • Have your children been tested? • Who knows about your diagnosis and how do you feel about someone attending with you for appointments? • Is there anything else you would like to talk about? • Access to/need for family planning? 	<p>In all patients:</p> <ul style="list-style-type: none"> • Look for pallor. If present, check haemoglobin level. • Look at the whites of eyes: are they yellow? • If CD4 <100, examine retinae through dilated pupils. • Look for oral thrush. • Listen to the lungs and palpate the abdomen. • Weigh, calculate, and record weight gain or loss. If weight loss >10%, ask for food intake and assess carefully for TB symptoms. • Take the height of adults at the first consultation and calculate BMI. Take the height of children at each consultation and calculate the ratio weight for height (W/H). • Estimate adherence. • If the patient is sad or has lost interest, assess for depression. • If any new symptoms: <ul style="list-style-type: none"> • Examine the relevant system and do further assessment of symptoms. • Measure temperature. • Check lymph nodes. • Look for a rash. • Look for evidence of violence.

(Recommendations in MSF programmes, Nov 2007. Source: Adapted from World Health Organisation. 2003. *Chronic HIV care with ARV therapy: Integrated management of adolescents and adults illness interim guide for first-level-facility health workers*. Geneva.)

Appendix 4A: WHO summary of recommendations on when to start ART in adults, adolescents, pregnant and breastfeeding women and children



Population	Recommendation
Adults and adolescents (≥ 10 years)	Initiate ART if CD4 cell count ≤ 500 cells/ μl : <ul style="list-style-type: none"> As a priority, initiate ART in all individuals with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤ 350 cells/μl.
	Initiate ART, regardless of WHO clinical stage and CD4 cell count: <ul style="list-style-type: none"> active TB disease HBV co-infection with severe chronic liver disease pregnant and breastfeeding women with HIV HIV-positive individual in a serodiscordant partnership (to reduce HIV transmission risk).
Children ≥ 5 years old	Initiate ART if CD4 cell count ≤ 500 cells/ μl : <ul style="list-style-type: none"> As a priority, initiate ART in all children with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤ 350 cells/μl.
	Initiate ART, regardless of CD4 cell count: <ul style="list-style-type: none"> WHO clinical stage 3 or 4 active TB disease.
Children 1–5 years old ^a	Initiate ART in all, regardless of WHO clinical stage and CD4 cell count: <ul style="list-style-type: none"> As a priority, initiate ART in all HIV-infected children 1–2 years old or with severe/advanced HIV disease (WHO clinical stage 3 or 4) or with CD4 count ≤ 750 cells/μl or $< 25\%$, whichever is lower.
Infants < 1 year old	Initiate ART in all infants, regardless of WHO clinical stage and CD4 cell count.

Appendix 4B: SA national guidelines: standardised eligibility criteria for starting ART regimens for infants and children



Criteria for initiating ART in children <10 years

Clinical criteria		Social criteria
age	Eligibility for Treatment	Social criteria are extremely important for the success of the programme and need to be adhered to. The principle is that adherence to treatment must be at least probable. <ul style="list-style-type: none"> At least one identifiable caregiver who is able to supervise the child for administering medication (all efforts should be made to ensure that the social circumstances of vulnerable children, e.g. orphans, are addressed so that they too can receive treatment) Disclosure to another adult living in the same house is encouraged so that there is someone else who can assist with the child's ART Treatment of mother/caregiver/other family member is to be actively promoted by ensuring same-site treatment or referral to the nearest treatment centre
Child less than 5 years	All children should be started on ART	
5 – 10 years	Symptomatic (stage 3 or 4) irrespective of CD4 count OR CD4 <500 cells/ μ l irrespective of WHO stage	
Criteria for fast-tracking (i.e. start ART within 7 days of being eligible) <ul style="list-style-type: none"> Children less than 1 year of age CD4 count <200 cells/μl or <15 % WHO clinical stage 4 MDR or XDR-TB 		

When to start ART in adolescents 10-15 years and <40kg

Criteria for initiation <ul style="list-style-type: none"> WHO stage 3 or 4 CD4 count \leq500 cells/μl
Fast-tracking (initiating ART within 7 days of being eligible) <ul style="list-style-type: none"> CD4 count of \leq200 cells/μl WHO stage 4 disease MDR/XDR-TB

Appendix 4C: SA national guidelines: standardised eligibility criteria for starting ART regimens for adults and adolescents



Eligible to start ART

CD4 count ≤ 500 cells/ μ l irrespective of clinical stage (Prioritise those with CD4 < 350 cells/ μ l)

OR

Severe or advanced HIV disease (WHO clinical stage 3 or 4), regardless of CD4 count

OR

Irrespective of CD4 count or clinical stage:

- Active TB disease (including drug-resistant and EPTB)
- Pregnant and breastfeeding women who are HIV-positive
- Known hepatitis B viral (HBV) co-infection
- Prioritise those with CD4 ≤ 350 cells/ μ l or advanced HIV disease

Timing of ART initiation

- ART should be started as soon as the patient is ready, and within at least 2 weeks of CD4 count being done
- In TB co-infection, start with TB treatment first, followed by ART as soon as possible and within 8 weeks
- If CD4 < 50 cells/ μ l initiate ART within 2 weeks of starting TB treatment, when the patient's symptoms are improving and TB treatment is tolerated
- If CD4 > 50 cells/ μ l initiate ART within 2-8 weeks of starting TB treatment
- In cryptococcal or TB meningitis: Defer ART initiation for 4-6 weeks

IMMEDIATE INITIATION:

- All HIV-positive pregnant or breastfeeding women, as long as no active TB



FAST TRACKING (within 7 days):

- Patients with CD4 < 200 cells/ μ l
- HIV stage 4, even if CD4 is not yet available

Appendix 5A: Classes, drugs and 'need-to-know' facts

Class	ARV	Formulation	Usual adult dose*	Specifics
NRTIs (nucleoside or nucleotide reverse transcriptase inhibitors)	TDF (tenofovir)	300 mg tablets	300 mg OD	Well tolerated but nephrotoxic in <1% of patients. Active against Hep B. Care must be taken to exclude Hep B when stopping TDF. CrCl must be >50 ml/min. Can be used from >= to 2 yrs in paediatric formulations.
	ABC (abacavir)	syrup (20 mg/ml) 300 mg tabs	300 mg twice daily	Hypersensitivity reaction in 3% of patients (less in those of African descent). No food restrictions. Tablet may be crushed (for children).
	3TC (lamivudine)	syrup (10 mg/ml) 150 mg tabs (also in combo with AZT, d4T and TDF)	150 mg twice daily (or 300 mg OD with TDF)	Well tolerated. Low genetic barrier to resistance but crippling effect when resistance is present. Active against Hep B.
	FTC (emtricitabine)	Usually in fixed dose combination with TDF.	200 mg OD	Well tolerated. Analogue of 3TC. May cause palmar rash.
	AZT (zidovudine)	syrup (10 mg/ml) 100 mg tabs 300 mg AZT (also in combo with 3TC)	300 mg twice daily	Capsules may be opened (children). Anaemia is a common side effect and may be severe.
	d4T (stavudine)	syrup (1 mg/ml) 15 mg caps 20 mg caps 30 mg caps	30 mg twice daily for all adults	All adults should now receive 30 mg of d4T, regardless of weight. Syrup must be refrigerated. Capsules may be opened (children). Watch for possible side effects of high lactate, peripheral neuropathy and lipodystrophy.
	ddl (didanosine)	25, 50, 100 mg tabs 250, 400 mg caps (enteric coated)	400 mg once daily if >60 kg; use 250 mg if <60 kg	TAKE ON AN EMPTY STOMACH. One hour before or two hours after food. Disperse 25 mg and 100 mg tabs in water (or chew). At least 2 tablets of appropriate strength must be used at any one time for adequate buffering.

* Paediatric dosages for all of the above ARVs can be determined using children's weights.

Class	ARV	Formulation	Usual adult dose*	Specifics
NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors) (low genetic barrier to resistance and if present confers class resistance)	NVP (nevirapine)	syrup (10 mg/ml) 200 mg tabs	200 mg once daily for the 1st 2 weeks, then 200 mg twice daily	Tablet may be crushed (children). Contra-indicated in females with CD4 >250 and in males with CD4 >350. Common early side effects include rash and hepatitis. The rash may lead to Stevens-Johnson Syndrome which may be fatal and requires hospitalisation. Nevirapine induces liver enzymes responsible for its own metabolism. Stepwise introduction helps to reduce the risk of skin rash and hepatitis. Interacts with fluconazole and TB medication rifampicin.
	EFV (efavirenz)	50 mg tabs or caps 200 mg tabs or caps 600 mg tabs	600 mg at night if >40 kg; use 400 mg if <40 kg NB: if on rifampicin, 600 mg should be prescribed.	Neuropsychiatric side effects are possible, so avoid in shift workers and pre-existing psychiatric conditions. Preferred NNRTI in TB patients. Taken at night to limit side effects. Avoid taking with fatty foods. Capsules may be opened (children). Tabs may not be chewed, divided or crushed. Studies suggests it is safe in the first trimester of pregnancy. ^a

a WHO. 2012. *Use of efavirenz during pregnancy.*

* Paediatric dosages for all of the above ARVs can be determined using children's weights.

Class	ARV	Formulation	Usual adult dose*	Specifics
PIs (protease inhibitors)	Kaletra® (lopinavir/ ritonavir or LPV/r)	syrup (80/20 mg/ ml) 125 mg tabs LPV 133 mg/r 33 mg caps	400/100 mg (= 3 caps) twice daily	Lopinavir is boosted by ritonavir. Capsules must be swallowed whole and not chewed, divided or crushed. Syrup and caps (not tabs) must be taken with food to enhance absorption and refrigerated until dispensed. Do not open capsules.
	Aluvia® = heat-stable lopinavir/ ritonavir (LPV/r)	250 mg tabs (LPV 200 mg/ ritonavir 50 mg))	400/100 mg (= 2 tabs) twice daily	Does not have to be taken with food. Common side effects: nausea and vomiting, diarrhoea. If patient is on rifampicin-containing TB regimen, the dose of LPV/r must either be doubled or 'super-boosted' with additional ritonavir.
	ATV (atazanavir) - always given with ritonavir. see below for FDC info.	150 mg tabs 200 mg tabs	300 mg (2 tabs of 150 mg) OD, together with 1 cap of 100 mg ritonavir (= 'boosted ATV') OR 400 mg (2 tabs of 200 mg) OD	To be stored at <25°C (but keep ritonavir caps in the fridge). To be taken with food. Always give boosted dose option if associated with use of TDF. Contra-indicated in those needing >20 mg a day of omeprazole. Should not be taken together with anti-acid medications (take ATV 2 hours before or one hour after). Common side effect is jaundice (not due to hepatitis) and if patient is otherwise well, can continue. Cases of allergic rash (usually not severe) and nephrolithiasis have been reported. Rifampicin decreases levels of ATV: avoid. Rifabutin is preferred TB treatment if prescribing ATV.
	ATV/r (atazanavir/ ritonavir) – it doesn't require a fridge.	FDC that contains ATV 300 mg and Rit 100 mg	1 tablet once a day	To be taken with food. Always give boosted dose option if associated with use of TDF. Contra-indicated in those needing >20 mg a day of omeprazole. Should not be taken together with anti-acid medications (take ATV 2 hours before or one hour after). Common side effect is jaundice (not due to hepatitis) and if patient is otherwise well, can continue. Cases of allergic rash (usually not severe) and nephrolithiasis have been reported. Rifampicin decreases levels of ATV: avoid. Rifabutin is preferred TB treatment if prescribing ATV.

Appendix 5B: SA antiretroviral drug dosing chart for children 2013



health

Department:
Health
REPUBLIC OF SOUTH AFRICA

	Abacavir (ABC)	Lamivudine (3TC)	Efavirenz (EFV)	Lopinavir/ritonavir (LPV/rtv)			
Target Dose	8mg/kg TWICE daily OR ≥10kg: 16mg/kg ONCE daily	4mg/kg TWICE daily OR ≥10kg: 8mg/kg ONCE daily	By weight band ONCE daily	300/75mg/m ² /dose LPV/rtv TWICE daily			
Available Formulations	Sol 20mg/ml Tabs 60mg (scored dispersible), 300mg (not scored), ABC/3TC 600/300mg	Sol. 10mg/ml Tabs 150mg (scored), 300mg, ABC/3TC 600/300mg	Caps 50,200mg Tabs 50,200, 600mg (not scored)	Sol. 80/20mg/ml Adult Tabs 200/50mg, Paeds Tabs 100/25mg			
Wt. (kg)	Currently available tablet formulations of abacavir (except 60mg), efavirenz,						
<3	Consult with a clinician experienced in paediatric ARV prescribing						
3-3.9	2ml bd	2ml bd	Avoid using when <10kg or <3 years: dosing not established	*1ml bd			
4-4.9							
5-5.9	3ml bd	3ml bd					
6-6.9							
7-7.9	4ml bd	4ml bd					
8-8.9							
9-9.9				*1.5ml bd			
10-10.9	Choose only one option:		200mg nocte (1x200mg cap/tab)	2ml bd			
11-13.9	6ml bd OR 2x60mg tabs bd	12ml od OR 4x60mg tabs od			6ml bd OR 12ml od		
14-16.9	8ml bd OR 2.5x60mg tabs bd	5x60mg tabs od OR 1x300mg tab od OR 15ml od	½ x150mg tab bd OR 8ml bd	1x150mg tab od OR 15ml od	Choose one option: -2.5ml bd -100/25mg paeds tabs : 2 bd -200/50mg adult tabs : 1 bd		
17-19.9							
20-22.9	10ml bd OR 3x60mg tabs bd	1x300mg tab + 1x60mg tab od	1x150mg tab bd OR 15ml bd	2x150mg tab od OR 1x300mg tab od OR 30ml od	Choose one option: -3ml bd - 100/25mg paeds tabs : 2 bd - 200/50mg adult tabs : 1 bd		
23-24.9		1x300mg tab + 2x60mg tabs od					
25-29.9	1x300mg tab bd	2x300mg tabs od OR 1xABC/3TC 600/300mg tab od	1x150mg tab bd	2x150mg tabs od OR 1x300mg tab od OR	Choose one option: - 3.5ml bd - 100/25mg paeds tabs : 3 bd - #200/50mg adult tabs : 1 bd + 100/25mg paeds tabs : 1 bd		
30-34.9				1xABC/3TC 600/300mg tab od		1xABC/3TC 600/300mg tab od	Choose one option: - 4ml bd - 100/25mg paeds tabs : 3 bd - #200/50mg adult tabs : 1 bd + 100/25mg paeds tabs : 1 bd
35-39.9							Choose one option: - 5ml bd - 200/50mg adult tabs : 2 bd
>40							
			600mg tab nocte				

od = once a day
(usually at night)
bd = twice a day* Avoid LPV/rtv solution in any full term infant <14 days of age and any premature infant <14 days after their due date of delivery (40 weeks post conception) or obtain expert advice.
Children 25-34.9kg may also be dosed with LPV/rtv 200/50mg adult tabs: 2 tabs am; 1 tab pm



Compiled by the Child and Adolescent Committee of the SA HIV Clinicians Society in collaboration with the Department of Health



Ritonavir boosting (RTV)	Stavudine (d4T)	Didanosine (ddI)	Nevirapine (NVP)	Zidovudine (AZT)	Target Dose
ONLY as booster for LPV/rtv when on Rifampicin TWICE daily (0.75xLPV dose bd)	1mg/kg/dose TWICE daily	180-240mg/m ² /dose ONCE daily	160-200 mg/m ² /dose TWICE daily (after once daily lead-in x 2 wks)	180-240mg/m ² /dose TWICE daily	
Sol. 80mg/ml	Sol. 1mg/ml Caps 15,20,30mg	Tabs 25,50,100mg (dispersible in 30ml water) Caps 250mg EC	Sol. 10mg/ml Tabs 200mg (scored)	Sol. 10mg/ml Caps 100mg Tabs 300mg (not scored), AZT/3TC 300/150mg	Available Formulations
LPV/rtv and AZT must be swallowed whole and NOT chewed, divided or crushed					Wt. (kg)
for neonates (<28 days of age) and infants weighing <3kg					<3
1ml bd	6ml	Avoid	5ml bd	6ml bd	3-3.9
1.5ml bd	7.5mg bd: open 15mg capsule into 5ml water: give 2.5ml	100mg od: (2x50mg tabs)	8ml bd	9ml bd	4-4.9
	10mg bd: open 20mg capsule into 5ml water: give 2.5ml	125mg od: (1x100mg + 1x25mg tabs)			5-5.9
1.5ml bd	15mg bd: open 15mg capsule into 5ml water	150mg od: (1x100mg + 1x50mg tabs)	10ml bd	1 cap bd OR 12ml bd	6-6.9
					7-7.9
2ml bd	20mg bd: open 20mg capsule into 5ml water (if the child is unable to swallow a capsule)	175mg od: (1x100mg + 1x50mg + 1x25mg)	1 tab am ½ tab pm OR 15ml bd	2 caps am 1 cap pm OR 15ml bd	8-8.9
					9-9.9
2.5ml bd	30mg bd	200mg od: (2x100mg tabs)	1 tab bd	2 caps bd OR 20ml bd	10-10.9
					11-13.9
3ml bd	30mg bd	250mg od: (2x100mg + 1x50mg tab) OR 1x250mg EC cap od	1 tab bd	1x300mg tab bd OR 1xAZT/3TC 300/150mg tab bd	14-16.9
					17-19.9
4ml bd	30mg bd	250mg od: (2x100mg + 1x50mg tab) OR 1x250mg EC cap od	1 tab bd	1x300mg tab bd OR 1xAZT/3TC 300/150mg tab bd	20-22.9
					23-24.9
					25-29.9
					30-34.9
					35-39.9
					>40

Weight (kg)	3-4.9	5-9.9	10-13.9	14-29.9	≥30
Cotrimoxazole Dose	2.5ml od	5ml od	5ml od	10ml or 1 tab od	2 tabs od
Multivitamin Dose	2.5ml od	2.5ml od	5ml od	5ml od	10ml or 1 tab od

Practical advice on administration of ARV drugs

Abacavir (ABC)

Caregivers must be warned about potential severe progressive hypersensitivity reaction which may include fever, rash, gastrointestinal and respiratory symptoms. If hypersensitivity occurs, it is usually during first six weeks of therapy, symptoms tend to worsen in the hours immediately after the dose and worsen with each subsequent dose.

Caregivers or patients should discuss symptoms early with the clinician rather than terminating therapy without consultation. ABC should be stopped permanently if hypersensitivity reaction occurs. Avoid combining ABC and NVP in a regimen and avoid concurrent initiation of ABC and co-trimoxazole. Tablets (except 60 mg) must not be chewed, divided or crushed; swallow whole with or without food.

Lamivudine (3TC)

Well tolerated, no food restrictions, oral solution may be stored at room temperature. Tablets are scored and can be easily divided; may be crushed and mixed with a small amount of water or food and immediately ingested.

Lopinavir/ritonavir (Kaletra® solution; Aluvia® tablets)

Dose is calculated on lopinavir component. Solution should be taken with food as increases absorption. Solution should be refrigerated; it however can be stored at room temperature up to 25°C for 6 weeks. May need techniques to increase tolerance and palatability: coat mouth with peanut butter, dull taste buds with ice, follow dose with sweet foods. Tablets must not be chewed, divided or crushed; swallow whole with or without food. Many drug interactions due to RTV inhibition of cytochrome p450.

Efavirenz (EFV)

EFV is not approved for children <3 years/<10 kg. Tablets must not be chewed, divided or crushed; swallow whole with or without food e.g. yoghurt or banana. Capsules may be opened and powder contents dispersed in water or mixed with a small amount of food (e.g. yoghurt) to disguise peppery taste and immediately ingested. Food, especially high-fat meals, increases absorption. Best given at bedtime to reduce CNS side-effects, especially during first 2 weeks. Consider drug-drug interactions.

Zidovudine (AZT)

No food restrictions and oral solution may be stored at room temperature. Capsules may be opened and powder contents dispersed in water or mixed with a small amount of food (e.g. yoghurt) and immediately ingested. Currently available tablets are not scored. Use with caution in children with anaemia due to potential for bone marrow suppression.

Ritonavir (RTV)

Only recommended use at present is as booster for lopinavir/ritonavir when co-administered with rifampicin-containing TB treatment. Increase RTV until it reaches the same dose as LPV in mg, in a ratio of 1:1. Should be taken with food. May be stored at room temperature, limited shelf life of 6 months. May need to use techniques described for Kaletra® to improve tolerance of bitter taste.

Nevirapine (NVP)

Once-daily dosing during the first 2 weeks of treatment reduces frequency of rash. If a mild rash occurs during the induction period, continue once daily dosing and only escalate dose to twice daily once the rash has subsided and the dose is well tolerated.

NVP should be permanently discontinued and not restarted in children who develop severe rash especially if accompanied by fever, blistering or mucosal ulceration. No food restrictions. Tablets can be crushed and mixed with a small amount of water or food and immediately ingested. Avoid NVP if rifampicin is being co-administered. Consider drug-drug interactions.



NEED HELP?

Contact the TOLL-FREE National HIV & TB Health Care Worker HOTLINE

0800 212 506 or 021 406 6782

Alternatively send an SMS or 'Please call me' to 071 840 1572

www.hivhotline.uct.ac.za

Appendix 5C: WHO Paediatric Dosing Chart

Urgently needed dosing strengths of drugs not yet available in child-friendly formulations

Drug	Formulation (mg)	Comments
DRUGS NEEDED FOR PMTCT		
NVP	20 mg scored tablet	Used for infant prophylaxis from 6 weeks onwards
DRUGS NEEDED FOR PAEDIATRIC ART		
LPV/RTV	40/10 mg sprinkle	Heat-stable formulation that will be equivalent to 0.5 ml of liquid and used to treat infants and children who are unable to take the paediatric tablet
ABC/3TC	Scored adult 300/150 mg tablet	Used in children >25 kg
ABC/3TC/NVP	60/30/50 mg	Triple FDC to align with the dual FDC
RTV	50 mg heat-stable sprinkle or tablet	Useful for co-administration with unboosted PIs and for super boosting when PIs need to be dosed with rifampicin
TDF/3TC	75/75 mg tab	
	Scored 300/300 mg tab	
DRV/RTV	Unclear	Current labelling calls for different ratios of DRV to RTV for different age brackets. It is unclear what the correct ratio should be to produce a co-formulated FDC, but this is a priority formulation
Raltegravir	Unclear	Raltegravir is not yet approved for paediatric use but this is highpriority formulation

See updated guidance on required paediatric formulations at <http://www.who.int/hiv/topics/paediatric/technical/en/index>.

Harmonized dosing schedules: Simplified table giving number of tablets of child-friendly solid formulations for morning and evening dosing

Drug	Strength of paediatric tab (mg)	Children 6 weeks of age and above								Strength of adult tab (mg)	Number of tablets by weight-band			
		Number of tablets by weight-band morning and evening									25 – 34.9 kg			
		3 – 5.9 kg		6 – 9.9 kg		10 – 13.9 kg		14 – 19.9 kg			20 – 24.9 kg		am	pm
SINGLE DRUGS														
AZT	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
ABC	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
NVP	50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200	1	1
ddl	25	2 ^a	2 ^a	3	2	3	3	4	3	4	4	25	5	5
COMBINATIONS														
AZT/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150	1	1
AZT/3TC/NVP	60/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150/200	1	1
ABC/AZT/3TC	60/60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/300/150	1	1
ABC/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	^b		
d4T/3TC	6/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150	1	1
d4T/3TC/NVP	6/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150/200	1	1
LPV/r ^c	100/25	NR	NR	NR	NR	2	1	2	2	2	2	100/25	3	3

a This dose of ddl is only appropriate for children 3 months of age or older and weighing between 5 kg and 5.9 kg.

b See ABC/3TC FDC dosing table.

c Higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, fos-amprenavir (FPV), rifampicin.

Simplified table giving ml of liquid formulation and number of tablets or capsules of adult solid formulation for morning and evening dosing

Drug	Strength of paediatric liquid (mg/ml) and adult tab/cap (mg)	Children 6 weeks of age and above											
		Number of tablets/capsules or ml by weight-band morning and evening											
		3 – 5.9 kg		6 – 9.9 kg		10 – 13.9 kg		14 – 19.9 kg		20 – 24.9 kg			
AZT	10 mg/ml; 300 mg	am 6 ml	pm 6 ml	am 9 ml	pm 9 ml	am 12 ml	pm 12 ml	am 0.5	pm 0.5	am 1	pm 0.5	am 1	pm 0.5
ABC	20 mg/ml; 300 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5	1	0.5
3TC	10 mg/ml; 150 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5	1	0.5
d4T	1 mg/ml; 15 mg or 20 mg	6 ml	6 ml	9 ml	9 ml	1 (15 mg)	1 (15 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)
NVP	10 mg/ml; 200 mg	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	1	1	1	0.5	1	0.5
ddl	10 mg/ml; 25 mg	3 ml ^a	3 ml ^a	5 ml	5 ml	6 ml	6 ml	4	3	4	3	4	4
LPV/r	80/20 mg/ml	1 or 1.5 ml ^b	1 or 1.5 ml ^b	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml	3 ml	3 ml

- a This dose of ddl is only appropriate for children 3 months of age or older and weighing between 5 kg and 5.9 kg.
- b LPV/r liquid: for 3 – 3.9 kg, use 1 ml a.m. and 1 ml p.m.; for 4 – 5.9 kg use 1.5 ml a.m. and 1.5 ml p.m. In addition, higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, FPV or rifampicin.

Simplified table giving number of tablets of child-friendly solid formulations for once-daily dosing

Drug	Strength of tab/cap (mg)	Number of tablets or capsules by weight-band once daily				Strength of tab/cap (mg)	Number of tablets or capsules by weight-band once daily
		3 – 5.9 kg	6 – 9.9 kg	10 – 13.9 kg	14 – 19.9 kg		
		Once daily	Once daily	Once daily	Once daily	Once daily	25 – 34.9 kg
SINGLE DRUGS							
EFV ^a	200 mg	NR	NR	1	1.5	1.5	200
ddl ^b	125 mg or 200 mg EC	NR	NR	1 (125 mg)	1 (200 mg)	2 (125 mg)	125 mg EC
							2

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

b ddl EC is not recommended for children weighing less than 10 kg; this dose is recommended only for those 10 kg and above.

NR = not recommended

EC = enteric coated

Appendix 6: ART initiation checklist

What is needed before giving a GREEN LIGHT for initiation?

Step 1: Psychologically ready for ART?

Check with counsellors.

Step 2: Rule out TB

- Current cough?
- Recent weight-loss?
- Drenching night sweats?
- Fever.
- Chest pains.
- Ask about contact with a case of active TB.
- Since 'subclinical TB' is common in those being 'worked up' for ART, send one or more specimens for TB testing, even in the absence of TB symptoms.^a

Step 3: Ask for symptoms of other opportunistic infections (current or in the past)

- Skin lesions: herpes zoster, PPE, seborrheic dermatitis, Kaposi's sarcoma.
- Headache, seizures: Meningitis: cryptococcal, TB or bacterial.
- Weight loss >10%.
- Fever >1 month.
- Diarrhoea >1 month.
- Pain when swallowing or difficulty swallowing: oesophageal candidiasis.
- Recurrent upper respiratory tract infections (URTIs)?
- Any other problem today?
- Any sexually transmitted infections (STIs)?

^a Rangaka. 2009. *Tuberculosis Screening and Intensified Case Finding at an Integrated HIV/TB Clinic in Khayelitsha, Cape Town*. IAS poster.

Step 4: Clinical examination

- Mouth: Oral thrush, necrotising gingivitis, oral sores, oral hairy leucoplakia, oral KS lesions, herpes, angular cheilitis.
- Skin: herpes zoster (scars), PPE, seborrheic dermatitis, KS, tinea (capitis, corporis, pedis, cruris), molluscum contagiosum, warts – genital ulcers or warts?
- Enlarged lymph nodes: TB, persistent generalised lymphadenopathy (PGL).
- Lung exam: crackles, percussion dull (consolidation) or stony dull (effusion).
- Hepatomegaly.
- If headache: neck stiffness?
- Children: Calculate weight for age (W/A) and height for age, check for developmental milestones.

Step 5: Clinical staging (stage 3 or 4?)

Step 6: Other conditions or medication?

e.g. epilepsy – drug-interactions.

Step 7: Discuss contraception and safe sex

Step 8: Laboratory

- CD4 count <500 (check national guidelines) cells/ μ l?
- Creatinine clearance >50 ml/min?
- Check haemoglobin (Hb) in child <12 years or if CrCl<50 ml/min, since AZT likely to be used.

Appendix 7A: WHO laboratory monitoring before and after initiating ART



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

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis	HIV serology, CD4 cell count TB screening	HBV (HBsAg) serology ^a HCV serology <i>Cryptococcus</i> antigen if CD4 count ≤ 100 cells/ μ l ^b Screening for sexually transmitted infections Assessment for major non-communicable chronic diseases and co-morbidities ^c
Follow-up before ART	CD4 cell count (every 6-12 months)	
ART initiation	CD4 cell count	Haemoglobin test for AZT ^d Pregnancy test Blood pressure measurement Urine dipsticks for glycosuria and estimated glomerular filtration rate (eGFR) and serumcreatinine for TDF ^e Alanine aminotransferase for NVP ^f
Receiving ART	CD4 count every 12 months if access to VL monitoring HIV viral load (at 6 months after initiating ART and every 12 months thereafter)	Urine dipstick for glycosuria and serum creatinine for TDF ^e
Treatment failure	CD4 cell count 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 co-infection and who therefore should initiate TDF-containing ART.
- b Can be considered only in settings with a high prevalence of cryptococcal antigenaemia (>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/ μ l and HCV co-infection. However, liver enzymes have low predictive value for monitoring NVP toxicity.

Appendix 7B: SA standardised monitoring for infants and children with HIV



At initial diagnosis of HIV	Purpose
Verify HIV status	Ensure that national testing algorithm has been followed
Document weight, height, head circumference (<2 yrs) and development	To monitor growth and development + identify eligibility for ART
Screen for TB symptoms	To identify TB/HIV co-infection
WHO clinical staging	To determine if child ≥ 5 years is eligible for ART
CD4 count testing	Children <5 years – Baseline and eligibility for fast-tracking, DO NOT wait for CD4 count to start ART
	Children ≥ 5 years – To determine eligibility for ART, fast-tracking and start cotrimoxazole prophylaxis as per national guideline
Hb or FBC	To detect anaemia – do Hb/FBC; to detect neutropenia – or FBC
At routine follow-up visits (non-eligible patients)	Purpose
Document weight, height and development	To monitor growth and development and assess clinical staging
Check that a CD4 count has been done in the last 6 months	To determine if patient has become eligible for ART
WHO clinical staging	To determine if patient has become eligible for ART and CPT
Screen for TB symptoms	To identify TB/HIV co-infection
At initiation of ART (Baseline)	Purpose
Hb or FBC	If less than 8 g/dl start ART and discuss with a specialist for opinion
CD4 count (if not performed in last 6 months)	Baseline assessment
Cholesterol + Triglyceride if on PI-based regimen	Baseline assessment
ALT (if jaundice or on TB treatment)	To assess for liver dysfunction

On ART	Purpose
Height, weight, head circumference (<2yrs) and development	To monitor growth and developmental milestones
Clinical assessment	To monitor response to ART and exclude adverse effects
CD4 at 1 year into ART, and then repeat only if clinically indicated	To monitor response to ART, stop cotrimoxazole prophylaxis as per national guideline
VL at month 6, 1 year into ART, then every 12 months	To monitor viral suppression response to ART; To identify treatment failure and to identify problems with adherence
Hb or FBC at month 1, 2, 3 and then annually if on AZT	To identify AZT-related anaemia
Cholesterol + Triglyceride at 1 year and then every 12 months if on PI based regimen	To monitor for PI-related metabolic side-effects
Clinical drug-related adverse events	To identify drug-related adverse events; If develops jaundice or rash on EFV or NVP do Liver function test and refer to specialist

What to start: ART first-line regimen for adolescents 10-15 years

First-line regimen		
Adolescent	Regimen	Comment
Weight <40 kg or age <15 years	ABC + 3TC + EFV	NVP can be used if EFV is contraindicated
Weight ≥40 kg and age ≥15 years	TDF + 3TC/FTC + EFV (Use FDC)	Use TDF if creatinine is >80mL/min with no proteinuria If <80 mL/min, use ABC+3TC+EFV and adjust dosages according to renal dysfunction, and discuss with expert

Appendix 7C: SA Standardised baseline monitoring (all adults/adolescents/pregnant and breastfeeding women)



Phase of HIV management	Purpose
HIV diagnosis	
Confirm HIV result with rapid antibody test if no test results are available	To confirm HIV-positive status in patients who present without documented proof of positive HIV status
WHO clinical staging if HIV-positive	To assess eligibility for ART and timing of initiation
CD4 count	To identify eligibility for ART (CD4 <500/ μ l) To identify eligibility for prioritisation (CD4 <350/ μ l) To identify eligibility for fast-tracking (CD4 <200/ μ l) To identify eligibility for cotrimoxazole (CD4 <200/ μ l) To identify eligibility for CrAg or CLAT (CD4 <100/ μ l)
Screen for pregnancy or ask if planning to conceive	To identify women who need ART for PMTCT and offer appropriate family planning
Assessment of hypertension and diabetes with blood pressure and urine glycosuria	To identify any concomitant chronic diseases
Screen for TB symptoms using the TB screening tool	To identify those suspected of TB and refer them for investigation and to assess eligibility for INH
Screen for HBV (HBsAg)	To identify those co-infected with HBV so that they can be initiated on ART regardless of CD4 count
Screening for STIs and syphilis	To identify and treat STIs
Weight and height in adolescent	To check if the weight is above or below 40kg to determine which ARV drugs to use
Cryptococcus Antigen (CrAg) test if CD4 <100 cells/ μ l	To assess if there is disseminated Cryptococcal infection and if fluconazole treatment/prophylaxis is indicated
Do Hb or FBC if requires AZT Creatinine if requires TDF ALT if requires NVP	To detect anaemia or neutropenia To assess renal sufficiency To exclude liver dysfunction
Fasting cholesterol and triglycerides if requires LPV/r	To identify at risk of LPV/r related hyperlipidaemia. If above 6 mmol/L, consider (ATV/r) instead of LPV/r (if available)

Phase of HIV management	Purpose
On ART	
Screen for TB symptoms at each visit	To identify TB/HIV co-infected
WHO clinical staging at every visit	To identify new OIs
Ask about side effects at each visit	To identify ARV related toxicity
CD4 at 1 year on ART	To monitor immune response to ART
VL at month 6, month 12 on ART and then every 12 months	To identify treatment failures and problems with adherence
ALT if on NVP and develops rash or symptoms of hepatitis	To identify NVP toxicity
FBC at month 3 and 6 if on AZT and then every 12 months	To identify AZT toxicity
Creatinine at month 3 and 6, month 12, then every 12 months if on TDF	To identify TDF toxicity
Fasting cholesterol and triglycerides at month 3 if on LPV/r	To identify LPV/r toxicity

Appendix 7D: Routine monitoring for adult ART patients (Western Cape Province, SA)



Developed by City of CT, MSF and Western Cape Government

	Before starting ARVs	Month 1	Month 2	Month 3	Month 4	Month 6	
For all ART patients	CD4 RPR CrCl CLAT (if CD4 <100) Pap smear (if >3 years since last)				VL		
Tenofovir (TDF) 300 mg OD	CrCl	CrCl			CrCl		
Lamivudine (3TC) 300 mg od or 150 mg bd							
Efavirenz (EFV) 600 mg Nocte							
Nevirapine (NVP) 200 mg bd	ALT	ALT (only if symptomatic)					

Fast-track (aim to start ART in <2 weeks) all patients with:

- CD4 <200
- Pregnant
- Stage 4 (excluding TB meningitis and Cryptococcal meningitis – start at 4–6 weeks)
- MDR/XDR TB

Eligibility for ART:

- All patients on TB Rx
- All patients with CD4 <350
- All patients WHO stage 4
- All pregnant women (Option B)*

Month 12 & Yearly	Yearly club monitoring	Common side effects	Comments
CD4 VL	CD4 VL		<p>Screen for TB at each visit.</p> <p>Pap smear 3 yearly if normal.</p> <p>If VL >1000, do intensive adherence counselling and repeat VL after 3 months.</p> <p>If VL >1000 on 2 consecutive tests and adherence addressed, switch to second-line.</p> <p>Use fixed dose combinations (FDCs) when possible*.</p> <p>Base monitoring of FDCs on individual ARVs in the combination.</p>
CrCl	CrCl	<p>Renal impairment: increased creatinine, peripheral oedema</p> <p>GI effects: (mild): nausea, vomiting, diarrhoea</p>	<p>TDF and 3TC should be used in patients who are Hep B positive.</p> <p>Check HepB (HBsAg) if switching off TDF.</p> <p>Continue TDF and 3TC if HBsAg positive and switching to second-line.</p> <p>Do not use if creatinine clearance <50 ml/min.</p>
		Side effects rare	<p>Dose adjust if CrCl <50 ml/min:</p> <p>If CrCl 10-50 ml/min, dose is 150mg OD.</p> <p>If CrCl <10 ml/min, dose is 50mg OD.</p>
		<p>CNS effects: dizziness, insomnia, nightmares, headaches, depression, psychosis (rare)</p> <p>GI effects: nausea, vomiting, diarrhoea</p> <p>Gynaecomastia</p>	<p>Always preferred over NVP unless there is a definite contraindication to EFV.</p> <p>Avoid prescribing with other psychoactive drugs or in patients who do shift work.</p> <p>If stopping all ART, provide 'tail coverage' for EFV by continuing 2 NNRTIs for 7 days or consider Aluvia®.</p>
		Rash: life threatening if involving mucosal membranes or accompanied with fever or symptoms of hepatitis	<p>Start with 200 mg OD and increase to 200 mg bd after 2 weeks.</p> <p>Do not start if, baseline CD4 >250 in females or CD4 >400 in males.</p> <p>Stop and never use again if patient develops severe rash or signs of hepatotoxicity.</p> <p>If stopping all ART, provide 'tail coverage' for NVP by continuing 2 NNRTIs for 7 days or consider Aluvia®.</p>

* From 1 April 2013. Subject to Department of Health recommendations.

***Creatinine clearance (CrCl) or eGFR**

$$\text{eGFR} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l})} \quad (\times 0.85 \text{ for females})$$

	Before starting ARVs	Month 1	Month 2	Month 3	Month 4	Month 6	
Zidovudine (AZT) 300mg bd	Hb or FBC/Diff Hep B (HBsAg) (if switching off TDF)	Hb or FBC/Diff	Hb or FBC/Diff	Hb or FBC/Diff		Hb or FBC/Diff	
Stavudine (d4T) 30 mg bd	Perform HepBsAg if switching from TDF						
Abacavir (ABC) 300 mg bd	Perform HepBsAg if switching from TDF						
Lopinavir-ritonavir (Aluvia®) 2 tab bd				Chol and TG and glucose (fasting)			
Atazanavir-ritonavir (Ataz / r) 300 mg/100 mg OD				Chol and TG and glucose (fasting)			
Didanosine (ddl) 400mg OD (250mg OD if <60 kg)							

NRTIs: TDF, 3TC, AZT, d4T, ABC, ddI

NNRTIs: NVP, EFV

PIs: Aluvia® (lopinavir-ritonavir), atazanavir-ritonavir

Month 12 & Yearly	Yearly club monitoring	Common side effects	Comments
		<p>Haematological effects: Anaemia, leucopenia, neutropenia</p> <p>Hepatotoxicity: abdo pain, nausea, vomiting, alt</p> <p>Lipodystrophy (rare)</p>	<p>Stop and do not use again if any of following occur after starting AZT: Hb <6.5, neutrophils <0.5, leucocytes <1, or increased ALT >200.</p> <p>If CrCl <10 ml/min dose is 300 mg OD.</p>
		<p>Lipodystrophy</p> <p>Peripheral neuropathy</p> <p>Hyperlactataemia / Lactic acidosis</p>	<p>Avoid use due to side effects unless TDF and AZT contraindicated.</p> <p>Switch promptly to TDF or AZT (or ABC) if patient has side effects and viral load is undetectable.</p> <p>Dose adjust if CrCl <50 ml/min: If CrCl 10-50 ml/min, dose is 15 mg bd. If CrCl <10 ml/min dose is 15 mg OD.</p>
		<p>Hyper-sensitivity reaction – look for 2 or more of: fever, rash (maculopapular or urticarial), cough, GI effects: nausea, vomiting, diarrhoea or abdominal pain</p>	<p>Only consider if TDF, AZT and d4T contraindicated.</p> <p>Stop immediately and do not use again if patient has hyper-sensitivity reaction - usually occurs in 1st 6 weeks but is very rare in the African population.</p>
Chol and TG and glucose (only if abnormal previously)	Chol and TG and glucose (only if abnormal previously)	<p>GI effects: diarrhoea (common)</p> <p>Metabolic disorders: Increased cholesterol, increased triglycerides, insulin resistance</p> <p>Lipodystrophy</p> <p>Headaches</p>	<p>Double the dose with TB treatment containing rifampicin.</p>
Chol and TG and glucose (only if abnormal previously)	Chol and TG and glucose (only if abnormal previously)	<p>Same as with lopinavir-ritonavir plus jaundice rash (maculopapular)</p>	<p>Mid to moderate rash can occur within 1st 3 weeks of therapy. Usually resolves within 2 weeks of onset.</p> <p>If severe rash develops, stop atazanavir.</p>
		<p>Peripheral neuropathy GI effects: Diarrhoea (mainly)</p> <p>Hyperlactataemia / Lactic acidosis CNS effects: Headache, Anxiety, Insomnia</p>	<p>Rarely used due to poor side effect profile.</p> <p>Advise patient to take at least one hour before or after food.</p> <p>Dose adjust if CrCl <50 ml/min: If CrCl 10–50 ml/min, dose is 200 mg OD (150 mg OD if weight <60 kg). If CrCl <10 ml/min, dose is 100 mg OD (75 mg OD if weight is <60 kg).</p>

Appendix 8: Management of abnormal blood results

Test	Normal result	Action required if result is abnormal
ALT	<40 IU/ml	<p>If ALT is abnormally high, need to identify the cause (test HBsAg, investigate for alcohol abuse, etc.). If possible, it would be useful to check other liver function tests (Alk phos, Bili).</p> <ul style="list-style-type: none"> • If ALT >100, EFV or LPV/r should be used instead of NVP; the ALT should be monitored closely over time. • If ALT 41-100, also need to monitor the liver function over time.
Hb	>10 g/dl	<p>If Hb <8.0 g/dl, assess carefully for active bleeding and opportunistic infections, especially TB.</p> <p>Consider giving iron and folic acid supplements and repeat Hb in 2–4 weeks.</p> <p>If no OI found, then use tenofovir or d4T instead of AZT when initiating ART.</p>
Hepatitis B surface antigen (HBsAg)	Negative	<p>Refer to doctor if HBsAg result is positive. Active hepatitis B requires use of TDF and 3TC (or FTC) in the first-line regimen.</p> <p>Once started, TDF and 3TC/FTC should ideally never be stopped in that person (see page 216).</p>
Creatinine clearance	≥90 ml/minute	<p>If CrCl <50 ml/min, identify and correct possible causes (dehydration, etc.). Discontinue any potentially nephrotoxic drugs (CTX, NSAIDs, etc.) See Appendix 26A Creatinine evaluation algorithm.</p> <p>Adjust doses of AZT, ddI, d4t and 3TC as necessary (see Appendix 25 Drug dosing adjustments in patients with renal impairment).</p> <p>Avoid tenofovir if CrCl is <50 ml/minute or in all cases of chronic renal failure (or renal failure that is new in onset, but not resolving).</p>  

Appendix 9A: WHO summary of first-line ART regimens for adults, adolescents, pregnant and breastfeeding women, and children



First-line ART	Preferred first-line regimens	Alternative first-line regimens ^{a b}
Adults (including pregnant and breastfeeding women and adults with TB and HBV co-infection)	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Adolescents (10 to 19 years) ≥ 35 kg		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP ABC + 3TC + EFV (or NVP)
Children 3 years to less than 10 years and adolescents < 35 kg	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 For adolescents, using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used and to the shortest time possible, with close monitoring. For children, d4T use should be restricted to the situations in which there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible.
- b ABC or boosted PIs (ATV/r, DRV/r, LPV/r) can be used in special circumstances.

Appendix 9B: SA national guidelines: standardised ART regimens for infants and children



First-line regimens for ART initiation in children

Child	Regimen	Comment
Children <3 years or older children weighing <10kg	ABC + 3TC + LPV/r	Doses are based on child's weight and need to be adjusted as the child grows
Children 3-10 years and >10kg Adolescents 10-15 years or <40kg	ABC + 3TC + EFV Children who started on ABC/3TC/LPV/r before 3 years must remain on same regimen at 3yr	Do not exceed maximum dosage If adolescents weight <40kg, align treatment with children's regimen
Children on d4T	Change all d4T to ABC	If VL suppressed: change to ABC If VL > 1000 copies/ml, manage as treatment failure If VL 50-1000 copies/ml, consult specialist
Children on ddl	Change all ddl to ABC	Change all regardless of VL

Second-line ART regimens for adolescents 10-15 years

Second-line regimen: Adolescents <15 years and <40kg		
First-line virological failure	Drugs	Comment
ABC/TDF + 3TC/ FTC + EFV	AZT + 3TC + LPV/r	Virological failure is 2 consecutive VL > 1000 copies/mL that are more than 1 month apart If VL > 1000 copies/mL: Include intensified adherence for a month Then repeat VL after 3 months of elevated VL If VL remains > 1000 copies/ml on NNRTI regimen or 10,000 copies/ml on PI regimen, then treat as virological failure Never switch only one drug in a failing regimen and do not continue therapy with a failing NNRTI regimen for prolonged periods as there is an increased risk of accumulating NRTI resistance mutations

Appendix 9C: SA national guidelines: standardised ART and ARV regimens for pregnant women who are HIV positive and their infants



Eligibility criteria for HIV-exposed infants

Mother	Infant regimen	Comment
Mother on lifelong ART	NVP at birth and then daily for 6 weeks	Mother has been on ART for >4 weeks prior to delivery
<p>Mother did not get any ART before or during delivery and tests HIV-positive >72hours post-delivery</p> <p>OR</p> <p>Mother newly diagnosed HIV-positive within 72 hours of delivery</p> <p>OR</p> <p>Mother started ART less than 4 weeks prior to delivery</p>	NVP as soon as possible and daily for 12 weeks (if infant is breastfed)	<p>12 weeks extended NVP is only necessary if the infant is being breastfed. Check feeding practice at the 6 week EPI visit to ensure infant receives correct duration of prophylaxis</p> <p>If mother received no ART before delivery, infant should receive birth PCR</p> <p>An additional HIV PCR test is required 4 weeks after NVP is discontinued</p> <p>This extended period of infant prophylaxis is required to allow time for maternal viral suppression. It takes up to 12 weeks for the viral load to become undetectable on ART</p>
<p>Breastfeeding mother diagnosed with HIV</p> <p>Start mother on a FDC immediately</p>	<p>NVP and AZT immediately</p> <p>If infant tests HIV PCR negative: stop AZT and continue NVP for 12 weeks and initiate ART immediately. If mother has received 12 weeks of ART then infant NVP can be stopped</p>	<p>Do HIV PCR and return for results in 7 days</p> <p>If infant <6 weeks, repeat HIV PCR at 6 weeks</p> <p>Additional HIV PCR 4 weeks after stopping NVP</p> <p>Infant HIV testing 6 weeks post-cessation of breastfeeding (either HIV PCR or ELISA, depending on age)</p>
Unknown maternal status for any reason, including orphans and abandoned infants	<p>Give NVP immediately*</p> <p>Test infant with rapid HIV test*</p> <p>If positive continue NVP for 6 weeks</p> <p>If negative discontinue NVP</p>	If rapid test is positive do an HIV PCR. If negative, repeat HIV PCR at 6 weeks. If HIV PCR positive, initiate baby on triple ART immediately and send confirmatory HIV PCR

Mother	Infant regimen	Comment
Mother with latest viral load >1000 copies/ml	Dual ARV for 6 weeks (NVP and AZT). Perform an HIV PCR at or shortly after birth	<p>PCR at birth, if negative follow up with a 6 week HIV PCR</p> <p>Manage the mother as per Table 7</p> <p>If repeat maternal viral load >1000 copies/ml then refer to/discuss telephonically with paediatric expert before the infant is 6 weeks old and prophylaxis is due to be discontinued</p> <p>Infants of mothers on 2nd or 3rd line regimens and VL>1000 should not be breastfed</p>
Non-breastfeeding mother diagnosed with HIV	<p>If more than 72 hours since delivery, no infant NVP</p> <p>Perform an HIV PCR, if positive initiate ART</p>	<p>Do HIV PCR, if <18 months</p> <p>Do rapid test if >18 months,</p> <p>Repeat PCR 6 weeks after last HIV exposure</p>

* If rapid HIV test can be done within 2 hours, then wait for HIV result before commencing NVP

Note: Remember to repeat the HIV PCR 6 weeks after breastfeeding cessation for all breastfed infants if < 18 months and a repeat HIV rapid test if > 18 months

ART regimens for pregnant and breastfeeding women

FIRST-LINE ART REGIMENS		
Population	Drugs	Comments
1st ANC visit		
All pregnant women not on ART (any gestational age)	TDF + 3TC (or FTC) + EFV Provide as fixed-dose combination (FDC)	If there is a contraindication to the FDC (Contraindication to TDF: renal insufficiency) Contraindication to EFV: active psychiatric illness): start AZT immediately and refer to Boxes 2 and 3
All breastfeeding women not on ART		
Pregnant women currently on ART	Continue current ART regimen Change to FDC if on individual first-line drugs and virally suppressed and no contraindications to FDC	Check a VL as soon as pregnancy diagnosed, regardless of when the last VL was done Patients with confirmed 2 nd or 3 rd line regimen failure should not breastfeed their infants
2nd ANC visit (1 week later)		
Pregnant women Creatinine $\leq 85 \mu\text{mol/l}$ and any CD4 cell count	Continue FDC	
Creatinine $> 85 \mu\text{mol/l}$ TDF contraindicated	Stop FDC, initiate AZT if Hb $\geq 7\text{g/dl}$	High-risk pregnancy: refer urgently for alternate triple therapy within 2 weeks, with dose adjustment if indicated, and investigation of renal dysfunction
Contraindication to EFV (active psychiatric illness)	Continue AZT until initiated on individual drugs TDF+3TC+NVP or LPV/r	Refer urgently for alternate triple therapy CD4 $< 250\text{cells}/\mu\text{l}$: NVP 200mg daily for 2 weeks, then 200mg BD CD4 $\geq 250\text{cells}/\mu\text{l}$ LPV/r 2 tablets 12 hourly
Labour		
Unbooked and presents in labour and tests HIV positive	sdNVP + sd Truvada and AZT 3-hourly in labour sdNVP + sd Truvada for C/S	Woman qualifies for lifelong ART Do creatinine and CD4 testing. Woman should get results at the 3-6 days visit
Emergency caesarean section in an unbooked woman with no ART	Start FDC next day regardless of CD4 cell count	
Post-Partum		
Mother diagnosed with HIV within 1 year post-partum or still breastfeeding beyond 1 year	Lifelong FDC initiated immediately	

Appendix 9D: SA national guidelines: standardised ART regimens for adults and adolescents



ART regimens for adolescent and adult pregnant and breastfeeding women

Population	Drug	Comments
Adolescents >15 years and weighing >40kg Adults All TB co-infection All HBV co-infection	TDF + 3TC (or FTC) + EFV provide as fixed-dose combination (FDC)	Replace EFV with NVP in patients: <ul style="list-style-type: none"> • With significant psychiatric co-morbidity or intolerance to EFV • Where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. night shift workers
Adults and adolescents on d4T	Change d4T to TDF (No patient must be on d4T)	Switch to TDF if virally suppressed and the patient has normal creatinine clearance, even if d4T well tolerated If VL > 1000 copies/mL, manage as treatment failure and consider switching to second line
Adolescents <15 years or weight <40kg	ABC + 3TC + EFV	If adolescent weight <40kg, align with paediatric regimen
Contraindication	Substitution drug	Comments
Contraindication to EFV: <ul style="list-style-type: none"> • Significant psychiatric co-morbidity • Intolerance to EFV • Impairment of daily function (shift workers) 	TDF + FTC (or 3TC) + NVP or LPV/r	If CD4 < 250 females and < 400 males, give NVP 200mg daily for 2 weeks, then 200mg BD CD4 ≥ 250 females and ≥ 400 males, use LPV/r 2 tablets 12 hourly
TDF contraindication: Creatinine clearance of <50 mL/min	ABC + 3TC + EFV (or NVP)	Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides MDR treatment

Appendix 10A: Early and late side effects of ARVs

Early side effects possible in the first 3 months

Symptom	Think of...	Important actions
Rash	Drug-related cause (NVP, cotrimoxazole, or TB drugs).	Grade the rash. Treat according to grade.
Nausea	If abdominal pain, think of pancreatitis or hepatitis.	See row below.
Vomiting	Pancreatitis Hepatitis	Correct any dehydration. Check lipase and ALT. Metoclopramide as required if severe.
Abdominal pain	Pancreatitis Hepatitis	Check lipase. Check ALT.
Weight loss	Not a side effect, but probably an undiagnosed OI (TB, chronic diarrhoea).	Investigate for TB. Send stool sample for investigation.
Confusion	Rule out infection before blaming this on efavirenz.	Refer for lumbar puncture. Consider changing efavirenz to another ARV (if no meningitis found).
Weakness	Anaemia (if on AZT)	Check haemoglobin (Hb).
Fever, constitutional symptoms, cough, sore throat, rash	Hypersensitivity reaction to abacavir (ABC) (See page 83).	If confirmed, stop ABC immediately and never re-try again. If doubtful, allow the patient to take one more dose and watch him/her carefully.

Late side effects possible after 3–6 months on ARVs

Symptom	Think of...	Important actions
Nausea with or without vomiting	High lactate	Check lactate level (refer to doctor if lactate level high).
Weight loss	Tuberculosis High lactate	Investigate for TB. Check lactate level. Consider need to substitute d4T.
Abdominal pain	High lactate Hepatitis Pancreatitis	Check lactate level. Check ALT. Check lipase level.
Shortness of breath	High lactate with lactic acidosis	Check lactate level and refer to doctor.
Painful, cold feet	Peripheral neuropathy (due to d4T or ddl).	Grade the PN and treat accordingly. Consider stopping d4T or ddl.
Fat redistribution	Lipodystrophy	Change d4T to another ARV.
Weakness	Anaemia (if on AZT)	Check haemoglobin (Hb).
Creatinine clearance <50 ml/min	TDF toxicity	After having ruled out treatable causes of acute renal insufficiency (dehydration due to fever, diarrhoea, protracted vomiting, etc.), change TDF to AZT.

Appendix 10B: Grading and management of possible side effects to ARVs

Symptoms (and diagnoses to consider, plus likely ARV responsible)	Grade 1	Grade 2	Grade 3	Grade 4
Painful feet	Mild, does not worry patient	Moderate, bothers patient	Symptoms day and night	Functional impairment (difficulty walking, etc.)
d4T-related peripheral neuropathy (also occurs with ddl)		<ul style="list-style-type: none"> Give amitriptyline 25 mg nocte. Patient should be switched to TDF (follow local protocol). 	<ul style="list-style-type: none"> Give amitriptyline 25 mg nocte. Patient should be switched to TDF (follow local protocol). 	URGENT: refer to doctor. <ul style="list-style-type: none"> Give amitriptyline 25 mg nocte. Check lactate level to rule out hyperlactatemia. 
Abdominal pain with or without nausea	Mild and transient (<24 hrs)	Food intake decreased (24–48 hrs)	Minimal food intake (>48 rs)	Patient too sick for outpatient treatment
d4T-related pancreatitis (short-term) or high lactate (long-term) NVP-related hepatitis	<ul style="list-style-type: none"> No treatment needed, but have patient return early if pain worsens. 	<ul style="list-style-type: none"> Encourage frequent small meals. Give metoclopramide 10 mg every 12 hours prn. Take blood for ALT and reassess in 2–3 days. 	<ul style="list-style-type: none"> Refer to doctor if ALT 3 x normal. Doctor to check lactate level if patient has been on d4T for more than 4 months, to rule out high lactate as the cause. 	<ul style="list-style-type: none"> Resuscitate patient and refer to hospital and doctor.

Symptoms (and diagnoses to consider, plus likely ARV responsible)	Grade 1	Grade 2	Grade 3	Grade 4
Vomiting	Once per day and/or lasting <3 days	<4 episodes per day and not dehydrated	Vomits >3 times per day, and dehydrated	Dehydrated and too sick for outpatient treatment
d4T-related pancreatitis (short-term) or high lactate (long-term) NVP-related hepatitis	<ul style="list-style-type: none"> Reassure patient, but have patient return early if worsens. Consider giving metoclopramide 10 mg every 12 hours prn. 	<ul style="list-style-type: none"> Give ORT. Encourage frequent small meals. Give metoclopramide 10 mg every 12 hours prn. Take blood for ALT and re-assess in 2–3 days. 	<ul style="list-style-type: none"> Give ORT. Give metoclopramide 10 mg every 12 hours prn. Refer to doctor. Doctor to check lactate level if patient has been on d4T for more than 4 months, to rule out high lactate as the cause. 	<ul style="list-style-type: none"> Refer to hospital and doctor.
Psychological	Dizziness	Vivid dreams	Mood changes or persistent disturbing dreams	Acute psychosis, hallucinations, confused behaviour
EFV	<ul style="list-style-type: none"> Reassure patient. Confirm EFV is being taken at night. 	<ul style="list-style-type: none"> Reassure patient. Symptoms will go away after few weeks. If symptoms persist after 6 weeks, refer or discuss with an experienced clinician. 	<ul style="list-style-type: none"> Confirm EFV is being taken at night and not with fatty foods. Refer to doctor if not settling. 	<ul style="list-style-type: none"> Refer to hospital. Perform lumbar puncture to rule out meningitis. Only restart ARVs when symptoms have fully resolved (use NVP instead of EFV).

Symptoms (and diagnoses to consider, plus likely ARV responsible)	Mild	Moderate	Severe
Skin rash	Red, itchy	Maculo-papular rash or dry scales	Blisters or moist loss of skin. Rash involves mucous membranes or eyes, with or without sloughing of skin
NVP (more commonly) EFV (but also consider TB meds or co-trimoxazole as possible causes)	<ul style="list-style-type: none"> Reassure, but have patient return early if worsens. Consider giving chlorpheniramine 4 mg every 8 hours prn, if itch is significant. 	<ul style="list-style-type: none"> Give aqueous cream with or without 0.1% betamethasone. Consider giving chlorpheniramine 4 mg every 8 hours prn. Check ALT, and reassess in 2–3 days. Patient to return early if rash worse, or abdominal pain. Consider switch to EFV 	<ul style="list-style-type: none"> URGENT: Refer to doctor same day. Doctor to decide when to stop ART with tail protection**. Give chlorpheniramine 4 mg every 8 hours as needed. When symptoms have resolved, restart ARVs, using a PI.
Creatinine clearance ml/minute	>50 ml/min	30–50 ml/min	<30 ml/min
TDF	<ul style="list-style-type: none"> Continue TDF. 	<ul style="list-style-type: none"> Check for urine infection and other reasons for dehydration. Treat possible causes and recheck creatinine after one week. If persistent, substitute TDF. 	<ul style="list-style-type: none"> Stop TDF. Refer to doctor.
Elevated ALT (in U/L)	50–100	100–200	>200
NVP (more commonly) EFV	Continue ARVs, but recheck ALT in one month	<ul style="list-style-type: none"> Continue ARVs if no other problem. Recheck ALT again after 2 weeks. Switch NVP to EFV (unless patient is in the first trimester of pregnancy). 	<ul style="list-style-type: none"> Refer to hospital. Check ALT frequently to ensure it returns to normal. Restart ARVs with EFV.



Symptoms (and diagnoses to consider, plus likely ARV responsible)	Mild	Moderate	Severe
Anaemia (low haemoglobin, in gm/dl)	8–9.4	6.5–7.9	<6.5
AZT	<ul style="list-style-type: none"> Examine patient to rule out bleeding, or serious problem (including active TB). If no problem, continue ARVs. Recheck Hb in 2 weeks. 	<ul style="list-style-type: none"> Examine patient to rule out bleeding, and refer to doctor for assessment. Stop AZT. If less than 6 months on ART change to TDF. 	<ul style="list-style-type: none"> Refer to hospital. Stop AZT. If less than 6 months on ART change to TDF.
Lipodystrophy	All		

** Tail-protection regimens for NNRTI drug interruption:

- Whenever we have to stop EFV or NVP, it's advisable to continue TDF/3TC or d4T/3TC for 7 days, to avoid emergence of HIV resistance.
- Likewise, when we have to stop all ARVs (e.g. in case of lactic acidosis), it's better to give a tail protection with a double dose of Aluvia® (that is 4 tabs twice daily) for 7–10 days. A double dose is given because of an interaction between LPV/r and the NNRTI.
- Stopping TDF in a HBsAg+ patient is contraindicated and a doctor should manage the case. In case of a life-threatening condition (but **different from drug-induced hepatitis** e.g. emergency surgery), necessitating interruption of all ARVs, withdrawal of TDF for a few days is allowed, under surveillance. Re-introduce as soon as possible.

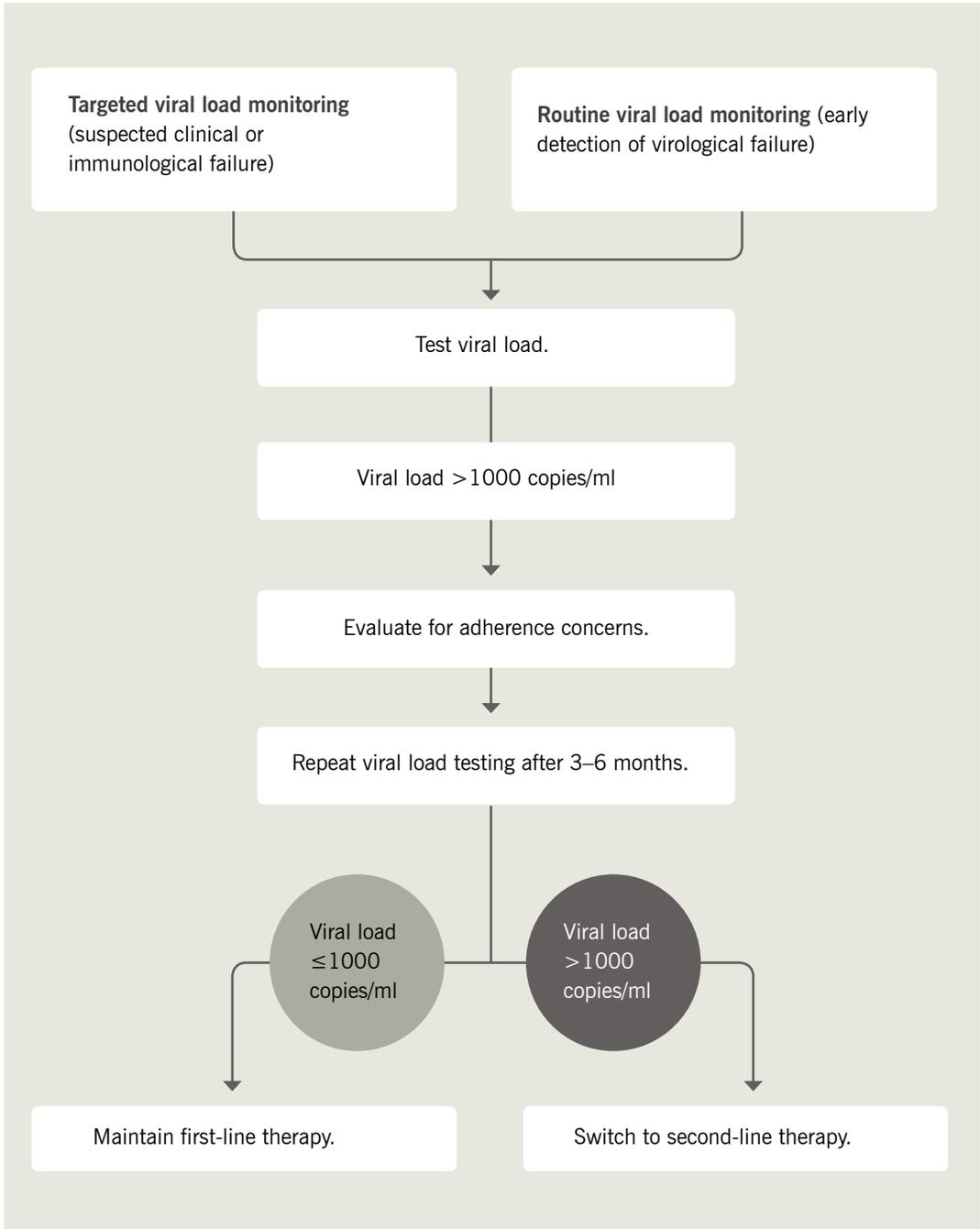
Appendix 11A: WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens



Failure	Definition	Comments
Clinical failure	<p>Adults and adolescents: New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment.</p> <p>Children: New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment.</p>	<p>The condition must be differentiated from immune constitution inflammatory syndrome occurring after initiating ART.</p> <p>For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure.^a</p>
Immunological failure	<p>Adults and adolescents: CD4 count falls to the baseline (or below).</p> <p>or</p> <p>Persistent CD4 levels below 100 cells/μl.</p>	<p>Without concomitant or recent infection to cause a transient decline in the CD4 cell count.</p> <p>A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure. The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure.</p>
	<p>Children: Younger than 5 years: Persistent CD4 levels below 200 cells/μl or <10%.</p> <p>Older than 5 years: Persistent CD4 levels below 100 cells/μl.</p>	
Virological failure	Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support.	<p>The optimal threshold for defining virological failure and the need for switching ART regimen has not been determined.</p> <p>An individual must have been taking ART for at least 6 months before it can be determined that a regimen has failed.</p> <p>Assessment of viral load using DBS and point-of-care technologies should use a higher threshold.</p>

^a See the list of clinical conditions associated with advanced or severe HIV disease associated with immunodeficiency in Appendix 1.

Appendix 11B: WHO algorithm of viral load testing strategies to detect or confirm treatment failure and switch ART regimen in adults, adolescents and children



Appendix 11C: Viral load monitoring for first-line regimens

Viral Load (VL)	Response
<p>NOTE: Always check hepatitis B before stopping TDF. If patient has chronic hepatitis B, stopping TDF may lead to a fatal hepatitis flare. If hepatitis B positive, TDF should be continued as a 4th drug in the second-line regimen</p>	
<400 copies/mL	<ul style="list-style-type: none"> • VL monitoring according to duration of ART and routine adherence support • Continue routine VL monitoring as it may be 12 monthly depending on how long patient is on treatment
400-1000 copies/mL	<ul style="list-style-type: none"> • Assess and manage adherence carefully • Repeat VL in 6 months and manage accordingly
>1 000 copies/mL	<ul style="list-style-type: none"> • Adherence assessment and intense adherence support • Repeat VL in 2 months and check HBV status and Hb, if not already done • If <1000 copies/mL, repeat in 6 months and then reassess • If >1000 copies/mL and adherence issues addressed, switch to second line therapy after checking HBV status and Hb

Appendix 12: Worksheet for combined adherence and clinical consultations

DATE SESSION 1:

Step 1: Review education

Viral load is: _____

High viral load is: _____

Suppressed viral load is: _____

Step 2: Patient's reason for high VL

Step 3: Review time meds taken

Problem with time: _____

Agreed-upon time: _____

Late/missed doses: _____

Step 4: Storing meds/extra doses

Usual storage place: _____

Emergency supply will be carried in: _____

Step 5: Motivation cards

Top 3 goals for the future: _____

Do you think your ARVs can help you achieve your goals for the future?

Brainstorm places to put stickers and other reminders. _____

Step 6: Patient's support system

Members of patient's support system _____

Step 7: Planning for substance use

What is your plan to make sure you take your ARVs if you use alcohol or drugs?

Step 8: Getting to appointments

How do you get to clinic? _____

Back-up plan to get to clinic: _____

Not able to come on date: _____

Step 9: Homework and way forward

Your VL will be repeated in _____ (which month)

Next visit date: _____

DATE SESSION 2:**Step 1: Discuss adherence difficulties/problems**

Review homework.

Adherence difficulties: _____

Problem solve: _____

Step 2: Mistakes in adherence

Thoughts to deal with mistakes AND learn from mistakes: _____

Step 3: Follow-up referral services*Did you attend?* _____*If yes, what was your experience?* _____**Step 4: Planning for trips**

Regular travel location: _____

Remind patient to plan for enough treatment.

In case of emergency: _____

Put file number into cellphone.

Step 5: Review and plan a way forward

Remind patient when VL will be repeated.

Next visit date: _____

DATE SESSION 3:**Step 1: Discuss adherence difficulties/problems**

Adherence difficulties: _____

Problem solve: _____

Step 2: Follow-up on referral services if appropriate*How is it going?* _____**Step 3: Take viral load**

...and any other blood tests needed.

Step 4: Plan a way forward

Discuss way forward if:

- VL result is low.
- VL result is high.

Next visit date: _____

DATE SESSION 4:**Step 1: Discuss viral load results****Suppressed: VL <400**

Congratulate patient.

Cover red sticker with green sticker.

Refer to adherence club: Y / N

Club number: _____

Give 2 months ART supply.

Not suppressed: VL >400

Refer to VL flowchart to assess regimen change.

If appropriate discuss new regimen, dosing schedule and possible side-effects.

Take baseline bloods, discuss with doctor.

Review previous sessions.

Discuss difficulties/problems

Problem: _____

Plan: _____

New dosing time: _____

Step 2: Plan a way forward

Next visit/club date: _____

SAMISS date: _____

Pos/Neg: _____

Referred to: _____

Appendix 13A: WHO summary of preferred second-line ART regimens for adults, adolescents, pregnant women and children



Second-line ART			Preferred regimens	Alternative regimens
Adults and adolescents (≥10 years), including pregnant and breastfeeding women			AZT + 3TC + LPV/r ^a AZT + 3TC + ATV/r ^a	TDF + 3TC (or FTC) + ATV/r TDF + 3TC (or FTC) + LPV/r
Children	If a NNRTI-based first-line regimen was used		ABC + 3TC + LPV/r ^b	ABC + 3TC + LPV/r ^b TDF + 3TC (or FTC) + LPV/r ^b
	If a PI-based first-line regimen was used	<3 years	No change from first-line regimen in use ^c	AZT (or ABC) + 3TC + NVP
		3 years to less than 10 years	AZT (or ABC) + 3TC + EFV	ABC (or TDF) + 3TC + NVP

- a DRV/r can be used as an alternative PI and SQV/r in special situations; neither is currently available as a heat-stable, fixed-dose combination, but a DRV + RTV heat-stable, fixed-dose combination is currently in development.
- b ATV/r can be used as an alternative to LPV/r for children older than six years.
- c Unless failure is caused by lack of adherence resulting from poor palatability of LPV/r.

Appendix 13B: South African guideline for switching to second-line ART regimens



Second-line regimen: adolescents ≥ 15 years and adults		
First-line virological failure	Drugs	Comments
Failing on a TDF-based first-line regimen	AZT + 3TC + LPV/r AZT + TDF + 3TC + LPV/r (If HBV co-infected)	If non-adherent, address causes of non-adherence If the VL > 1000 copies/mL at any point, intensify adherence and repeat VL in 2 months If VL remains at > 1000 copies/mL after 2 months, then switch to second line regimen
Failing on a d4T or AZT-based first line regimen	TDF + 3TC (or FTC) + LPV/r	
Dyslipidaemia (total cholesterol > 6 mmol/L) or diarrhoea associated with LPV/r	Switch LPV/r to ATV/r	
Anaemia and renal failure	Switch to ABC	

Third-line regimen for late adolescents and adults		
Failing any second-line regimen Decision should be based on expert consultation and genotype resistance, and supervised care	Most likely regimens may contain: Raltegravir, Darunavir/Retravirine adjusted according to genotype interpretation and patient history	An expert panel will manage patients failing on second-line therapy. The drugs for third-line will be managed centrally. Should take into account prior exposure and predictable mutations



Second-line ART regimens for children	
Failed first-line protease inhibitor (PI) based regimen	
Failed first-line PI-based regimen	Recommended second-line regimen
ABC + 3TC + LPV/r	Consult with expert for advice
d4T + 3TC + LPV/r	
Unboosted PI based regimen	
Failed first-line NNRTI-based regimen (discuss with expert before changing)	Recommended second-line regimen
ABC + 3TC + EFV (or NVP)	AZT + 3TC + LPV/r
d4T + 3TC + EFV (or NVP)	AZT + ABC + LPV/r

Appendix 14: Approach to lymphadenopathy, including fine needle aspiration (FNA)

Lymphadenopathy (enlarged lymph nodes) is often a result of infection but can also be caused by cancer (e.g. lymphoma or Kaposi's sarcoma). The lymphadenopathy can be generalised or localised. Do not confuse enlarged lymph nodes with swollen parotid glands (in the cheeks) or other swollen salivary glands (diffuse infiltrative lymphocytosis syndrome or DILS).

Causes of lymphadenopathy

Causes of generalised lymphadenopathy

- HIV itself (but often <2 cm in size) most commonly during acute seroconversion
- secondary syphilis.

Causes of localised lymphadenopathy:

- tuberculosis
- bacterial infection
- STIs (groin)
- Kaposi's sarcoma (KS)
- lymphoma
- cervical carcinoma (groin).

Symptom management

REMEMBER: Think of TB when a person presents with any enlarged lymph node that is chronic.

Clinical presentation

- swollen lymph nodes
- sometimes tender
- located in neck, axillae or groin.

Clinical examination

- Take body temperature.
- Assess for weight loss.
- Measure and note size of lymph nodes (fine needle biopsy indicated if >2 cm).
- Check all other lymph node areas (neck, axillae, groin).
- Check for liver or spleen enlargement.

Management

- Correct management depends on the specific diagnosis, so it is important to make an accurate diagnosis.
- A trial of antibiotic therapy is reasonable for localised, enlarged lymph nodes, especially while waiting for needle biopsy results: cloxacillin 250–500 mg four times daily x 5 days (depending on weight of adult).
- If the node is >2 cm in adults, needle aspiration should be performed by a trained clinician as follows:
 - If the node is fluctuant, aspiration is easy and can be performed by the nurse or doctor; liquid aspirate should be sent in a sputum jar for TB testing (AFB +/- culture).
 - If the node is not fluctuant, a **fine needle aspiration biopsy (FNAB)** should be performed by a trained clinician and the material sent on slides for AFB examination and cytology to rule out other possible causes (lymphoma, KS, etc.).
- Needle biopsy material should be sent for:
 - TB smear (AFB)
 - Cytology (to identify any lymphoma).

Fine needle aspiration biopsy (FNAB)

A FNAB allows cellular material from lymph nodes to be examined for microscopic evidence of TB or other pathology (fungal infections, lymphoma, etc.).

Equipment needed:

- gloves
- povidone-iodine solution (or alcohol swab)
- sterile gauze
- sterile needle (23 gauge is best)
- 10 ml syringe
- sterile water
- 2 microscope slides (frosted at one end)
- spray fixative
- pencil.

Fine needle aspiration technique:

- Label both microscope slides with patient identification and the date.
- Disinfect the skin overlying the lymph node with the povidone-iodine solution (or alcohol swab).
- With the needle attached to the syringe, draw some sterile water into the syringe.
- Immediately expel the water from the syringe (so that there is now a small 'coating' of water inside the needle and syringe).

- Immobilising the lymph node with one hand, insert the needle deep into the lymph node and pull back on the syringe plunger in order to create a vacuum (of about 2 ml).
- Without exiting the lymph node, withdraw and insert the needle several times at different angles in a 'back-and-forth' motion, all the while maintaining constant suction, in order to allow cells from the lymph node to enter the bore of the needle.
- Once material (or blood) appears in the needle hub, the aspiration should be stopped; the more cellular material aspirated, the better, since it improves the specificity and sensitivity of this diagnostic intervention.
- Release the negative pressure before removing the needle from the lymph node. If not, the aspirated material will enter the barrel of syringe and be less available for introduction onto the microscope slides.
- With the gauze, ask the patient to apply gentle pressure over the entry site.

Slide preparation

It is important to prepare the microscope slides **immediately** after aspiration as follows:

- Detach the needle from the syringe.
- Gently fill the syringe with air (while the needle is still detached).
- Reattach the needle to the syringe and quickly expel all of the 'air' while the needle tip is touching close to the frosted end of one of the slides. By doing so, moist cellular material will be released onto the slide.
- Gently place the second 'clean' slide face down over the slide with the aspirate on it.
- With the two slides now touching each other, move them in opposite directions in order to spread the cellular material across both slides simultaneously. Avoid pressing the slides together forcefully so as to avoid crushing the cells from the lymph node.
- Allow one slide to air dry.
- Spray the other slide with fixative.

Slide transport

The microscope slides must be well protected during transport to the laboratory.

Appendix 15: HIV-related conditions having retinal manifestations

Note: All patients with CD4 <100 cells/ μ l should have a fundoscopic examination performed through dilated pupils.



Photo credit: Dr Gary Holland

Figure 1: Active **CMV retinitis** typically appears as dense retinal whitening with an irregular border having satellite lesions, and sometimes showing haemorrhage. Blindness is imminent in this case since the retinitis is encroaching on both the fovea and optic disk.



Photo credit: Dr Emmett Cunningham

Figure 3: Tuberculosis can affect the choroid through haematogenous spread. The four grey-yellow nodules seen here are **choroidal tubercles**. Since they are deep to the retina, their borders are indistinct; note that retinal vessels can clearly be seen in front of two of these lesions. There are usually <5 in number, but may be up to 50.



Photo credit: Dr David Heiden

Figure 2: The area of dense retinal whitening situated inferonasal to the optic disk is a result of **primary toxoplasmosis**. Clinical correlation is important.



Photo credit: Dr Richard Imes

Figure 4: **Papilledema** with associated haemorrhage, which in this case was due to cryptococcal meningitis.

Appendix 16: Clinical management of HIV late presenters

HIV 'late presenters' are those that present for the first time in clinical stage 4 and/or with CD4 <100 cells/ μ l.

Late presenters need:

- A thorough clinical examination, including all 4 vital signs.
- Oxygen, if short of breath.
- Rehydration, if there is dehydration due to diarrhoea, vomiting, or other causes.
- Admission to hospital, if clinically unstable.
- If there is likely to be a delay in admission and a severe bacterial infection is suspected (e.g. pneumonia and/or sepsis), give the first dose of antibiotics parenterally (e.g. ceftriaxone IV or IM).

All HIV 'late presenters' need ART...

- Lumbar puncture (LP) should be performed if symptoms of meningitis.
- Even if no symptoms, screen with a rapid serum or plasma CrAg test.

Routinely perform fundoscopy as a number of HIV-related conditions have retinal manifestations (see Appendix 15).

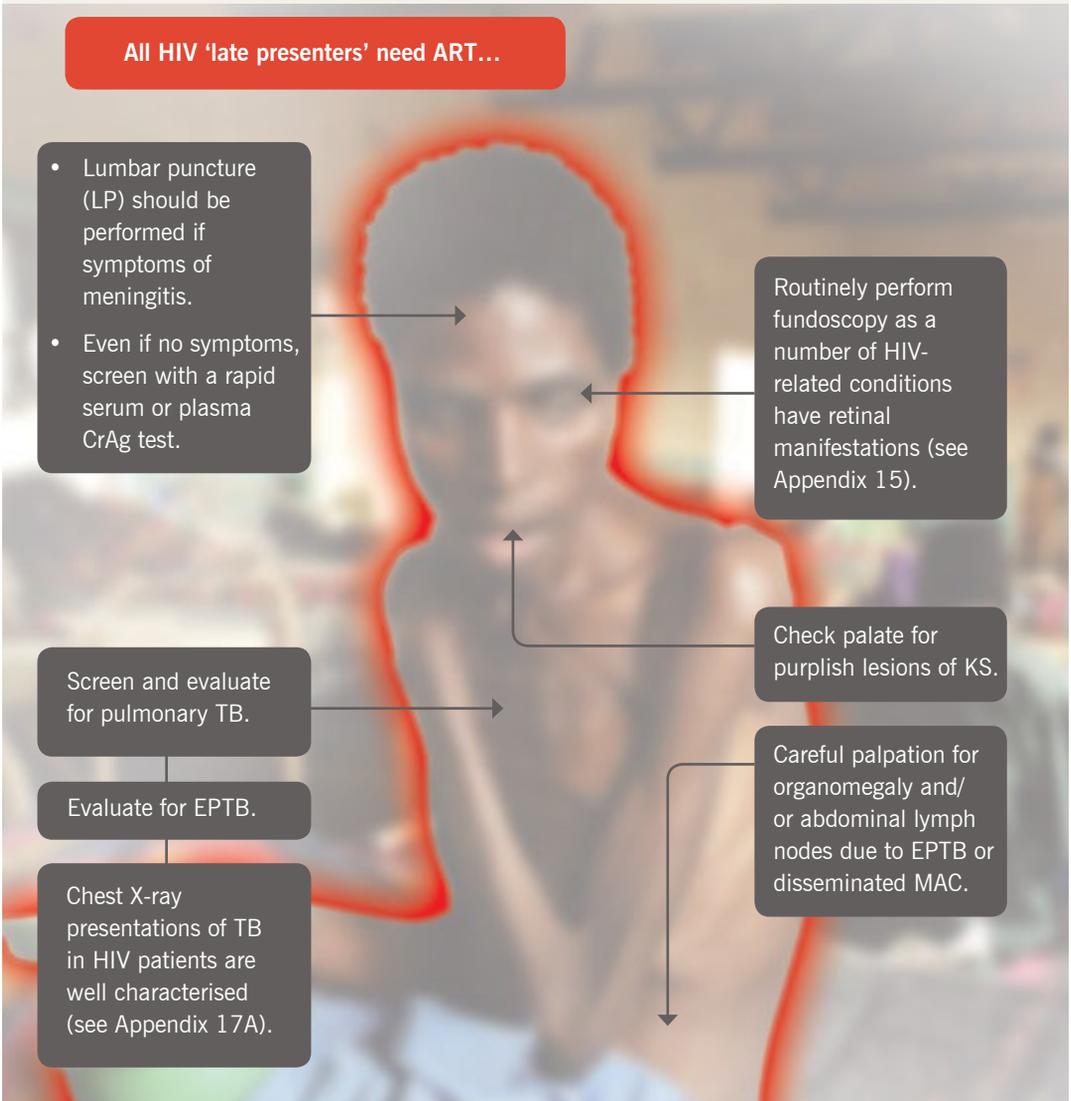
Check palate for purplish lesions of KS.

Careful palpation for organomegaly and/or abdominal lymph nodes due to EPTB or disseminated MAC.

Screen and evaluate for pulmonary TB.

Evaluate for EPTB.

Chest X-ray presentations of TB in HIV patients are well characterised (see Appendix 17A).



Appendix 17A: Chest x-ray presentations of TB in PLHIV

Chest x-ray presentations of TB in PLHIV 'are now well characterised and should no longer be considered atypical for TB in HIV prevalent settings'. (WHO. 2007. *Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary TB among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings*. http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.379_eng.pdf)



Figure 1: This image shows a **right-sided pleural effusion**, which is highly suggestive of tuberculosis in a person having cough, fever, night sweats, and/or weight loss. If straw-coloured fluid is found during pleuracentesis (i.e. 'pleural tap'), this helps to confirm the diagnosis. TB treatment should be initiated immediately.

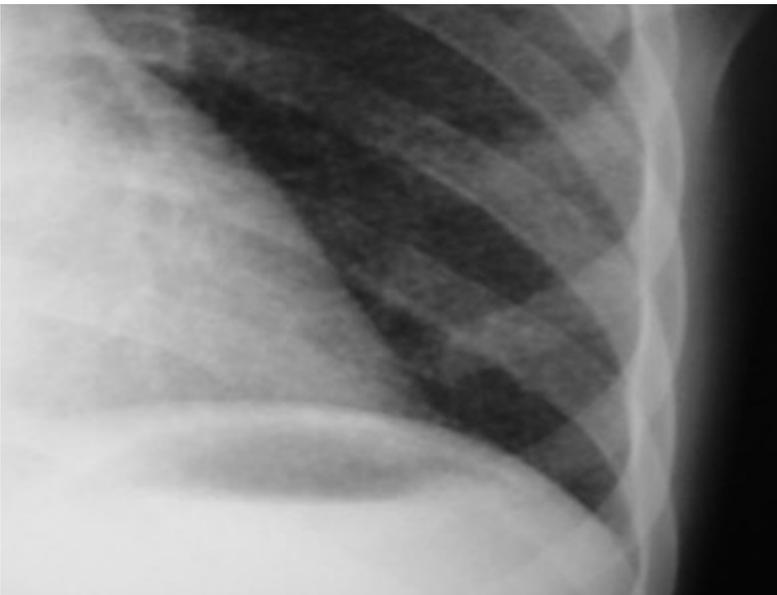


Figure 2: This image demonstrates a **miliary pattern** in a section of the left lung. The hundreds of tiny 'seeds' seen here represent haematogenous spread of TB. Treatment with TB medication should be initiated immediately.

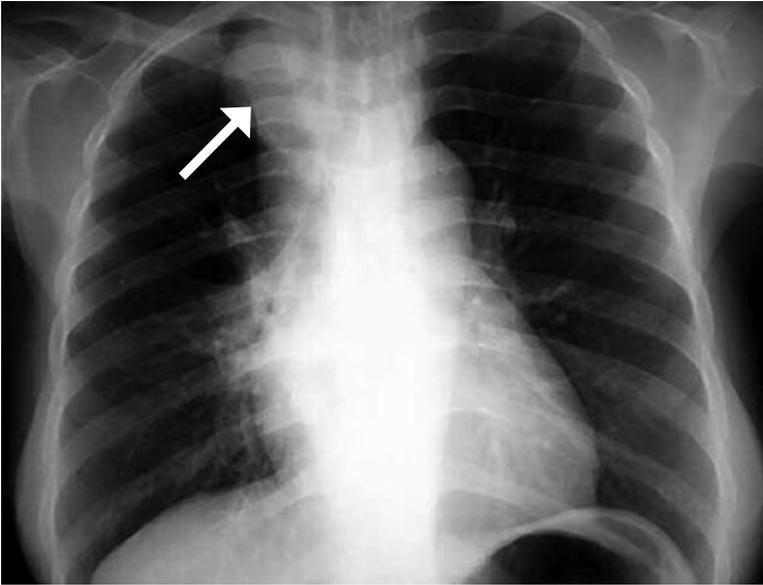


Figure 3: Enlarged lymph nodes are seen in the right mediastinum of this woman with severe immunodeficiency (CD4 count = 20 cells/ μ l). Although acid-fast bacilli (AFB) were not seen in her sputum specimens, she was started on TB treatment on the basis of her clinical condition and this x-ray result.



Figure 4: If a grossly enlarged heart such as this is seen in a person with TB symptoms (especially if the heart is symmetrical and rounded), then TB treatment should be initiated for a provisional diagnosis of TB pericarditis.



Appendix 17B: Paediatric chest x-ray tick sheet

(Courtesy of Savvas Andronikou, MB BCh, FCRad, FRCR, PhD, Department of Radiology, Stellenbosch University, South Africa.)

Note: This tick sheet is meant to assist non-radiologists in the interpretation of chest x-rays through systematic review and recording, particularly with respect to findings suggestive of active TB disease.

<p>Instructions to tick-sheet:</p> <p>A) Mark only one of the tick boxes for each image: <input type="checkbox"/> Yes, <input type="checkbox"/> No, <input type="checkbox"/> Maybe, or <input type="checkbox"/> Not visible (Record only the most positive grading under each section. That means if there is one 'definite' node and 3 'possible' nodes, you must tick 'yes' and not 'maybe') B) Please also cross any number of locations of disease on the appropriate circled number</p>	<p>Grading:</p> <p><input type="checkbox"/> Yes = positive ↑</p> <p><input type="checkbox"/> Maybe</p> <p><input type="checkbox"/> No = negative ↓</p>
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	Airway compressed and tracheal displacement	Soft tissue density = nodal mass	Post process: Overall
Lymphadenopathy			<p>Lymphadenopathy</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Maybe</p> <p><input type="checkbox"/> Not visible</p>
	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Maybe <input type="checkbox"/> Not visible	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Maybe <input type="checkbox"/> Not visible	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Maybe <input type="checkbox"/> Not visible

	Nodular = Miliary or larger widespread and bilateral	Airspace consolidation	Post process: Overall
			<p>Lung disease</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Maybe</p> <p><input type="checkbox"/> Not visible</p>
	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Maybe <input type="checkbox"/> Not visible	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Maybe <input type="checkbox"/> Not visible	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Maybe <input type="checkbox"/> Not visible

	Pleural effusion/thickening	Cavities	Post process: Overall
			<p>Pleura</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Maybe</p> <p><input type="checkbox"/> Not visible</p>
	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Maybe <input type="checkbox"/> Not visible	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Maybe <input type="checkbox"/> Not visible	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Maybe <input type="checkbox"/> Not visible

TB Decision	<input type="checkbox"/> Lymphadenopathy or Miliary = Yes	<input type="checkbox"/> No lymphadenopathy/miliary but positive = Maybe	<input type="checkbox"/> Normal = NO	<input type="checkbox"/> Bad quality = Unreadable
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Appendix 18: South African special considerations for TB patients co-infected with HIV



HIV-positive patients are at higher risk of developing TB compared to the general population, especially during the period immediately after initiating ART, therefore all HIV-positive patients should be screened for TB. If an HIV-positive patient has symptoms suggestive of TB, investigate appropriately using sputum/ GeneXpert and TB culture as per guidelines. It is very important to investigate patients for TB before starting ART and to routinely screen patients on ART. The guidelines remain the same for pregnant women.

Diagnosis of TB

Suspect TB if one or more of the following are present:

1. Cough of duration
2. Sputum production which may occasionally be blood stained
3. Fever
4. Drenching night sweats
5. Unexplained weight loss
6. Loss of appetite, malaise, tiredness
7. Shortness of breath, chest pains
8. New palpable lymphadenopathy

In children the presence of any three or more of the following features is suggestive of TB:

- TB symptoms (cough, fever, failure to thrive, weight loss)
- Physical signs suggestive of TB
- Positive TST
- Chest x-ray findings suggestive of TB

TB treatment in HIV

ART for adults with concomitant TB	
TB develops while on ART	TB diagnosed before starting ART
<p>Continue ARV therapy throughout TB treatment</p> <p>First-line regimen:</p> <p>Patient can remain on the regimen they are taking (unless they are on NVP)</p> <p>Second-line regimen:</p> <p>The Lopinavir/Ritonavir (LPv/r) dose should be doubled (increase gradually from 2 tablets 12 hourly to 4 tablets 12 hourly) while the patient is on Rifampicin-based TB treatment</p> <p>Monitor ALT monthly</p> <p>Reduce Lopinavir/Ritonavir to standard dose 2 weeks after TB treatment is completed</p>	<p>In TB/HIV co-infection not on ART</p> <p>Start with TB treatment first, followed by ART as soon as possible and within 8 weeks</p> <p>If CD4 <50 cells/μl initiate ART within 2 weeks of starting TB treatment, when the patient's symptoms are improving and TB treatment is tolerated</p> <p>If CD4 >50 cells/μl initiate ART within 2-8 weeks of starting TB treatment</p> <p>First line ART regimen:</p> <ul style="list-style-type: none"> • Tenofovir 300mg daily • Lamivudine 300mg or Emtricitabine 200mg daily • Efavirenz 600mg at night

NOTE: HIV positive TB patients qualify for lifelong ART regardless of CD4 cell count.

Complete 2 to 8 weeks maximum, of TB therapy before commencing ART (**and as soon as possible if CD4 count is less than 50 cells/ μ l**). In general, ART should be initiated as soon as the patient is tolerating their TB therapy; this is usually within 2-4 weeks.

EFV-based regimens are generally preferred in patients with active TB; however, other regimens are also effective. Dose adjustment of PI may be required. Patients on Lopinavir/Ritonavir should have their dose doubled slowly over two weeks (to 800/200 mg twice a day); all other regimens can be continued unmodified. Monitor and investigate appropriately for hepatotoxicity symptoms. Continue these changes to Lopinavir/Ritonavir until two weeks after completion of TB treatment.

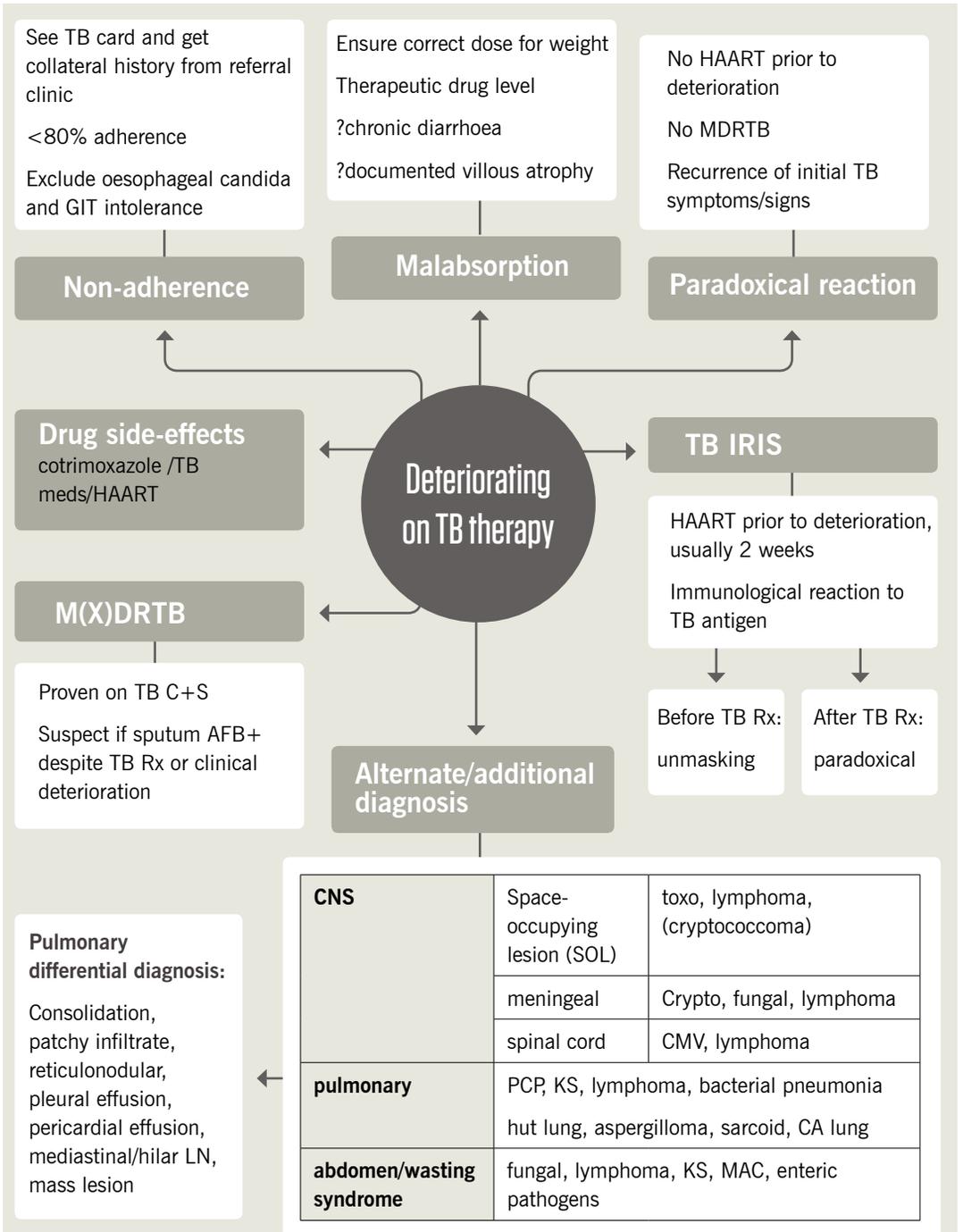
Patient developing TB while on ART:

ART should be continued throughout TB treatment.

Cotrimoxazole can cause erythema multiforme and Stevens-Johnson syndrome. If this occurs, stop the Cotrimoxazole.

Dapsone should be used in Cotrimoxazole intolerant patients. The recommended dose is 2 mg/kg/day or 4 mg/kg/week. The maximum daily dose is 100 mg (1 tablet).

Appendix 19: What to do when a patient deteriorates on TB therapy



Appendix 20: Dosages of DR-TB drugs

Patient weight	Drug	Dosage
<33 kg	Kanamycin (OD)	15–20 mg/kg
	Ethionamide (OD)	15–20 mg/kg
	Pyrazinamide (OD)	30–40 mg/kg
	Levofloxacin (in 2 doses)	15–20 mg/kg
	PAS* (in 2 doses)	150 mg/kg /daily
	Terizidone (in 2 doses)	15–20 mg/kg
	Cycloserine** (in 2 doses)	15–20 mg/kg
33–50 kg	Kanamycin (OD)	500–750 mg
	Ethionamide (OD)	500 mg
	Pyrazinamide (OD)	1000–1750mg
	Levofloxacin (in 2 doses)	750 mg
	PAS* (in 2 doses)	8 g
	Terizidone (in 2 doses)	500–750 mg
	Cycloserine** (in 2 doses)	500–750 mg
51–70 kg	Kanamycin (OD)	1000 mg
	Ethionamide (OD)	750 mg
	Pyrazinamide (OD)	1750–2000 mg
	Levofloxacin (in 2 doses)	1000 mg
	PAS* (in 2 doses)	8 g
	Terizidone (in 2 doses)	750 mg
	Cycloserine** (in 2 doses)	750 mg
> 70 kg	Kanamycin (OD)	1000 mg
	Ethionamide (OD)	750–1000 mg
	Pyrazinamide (OD)	2000–2500 mg
	Levofloxacin (in 2 doses)	1000 mg
	PAS* (in 2 doses)	12 g
	Terizidone (in 2 doses)	1000 mg
	Cycloserine** (in 2 doses)	750–1000 mg

* Note that the dose of sodium PAS is different – check recommendations by manufacturer.

**Pyridoxine (B6) 150 mg to be given daily to patients on cycloserine.

Dose escalation

For ethionamide and cycloserine, consider dose escalation (= dose ramping) over 2 weeks in order to reduce the likelihood of adverse events. For example, a DR-TB patient weighing between 51–70 kg would receive doses according to the following schedule:

Prothionamide/ethionamide

Initial dose: 250 mg OD

After 1 week: 250 mg BD

After 2 weeks: 750 mg OD

Cycloserine

Initial dose: 250 mg OD

After 1 week: 250 mg BD

After 2 weeks: 250 mg AM – 500 mg PM

Appendix 21A: MDR-TB monitoring schedule

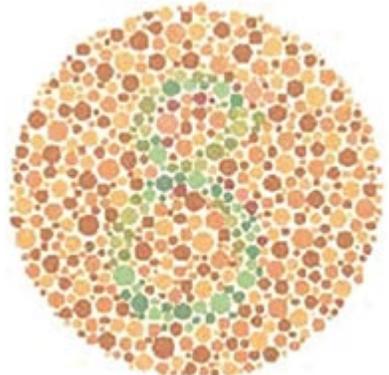
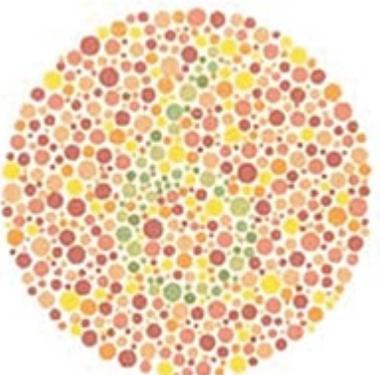
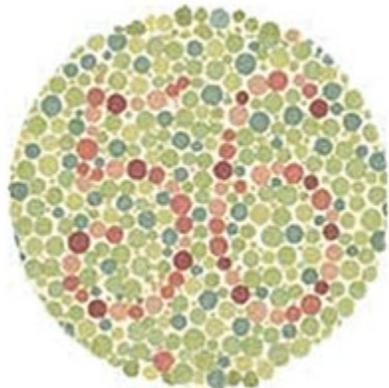
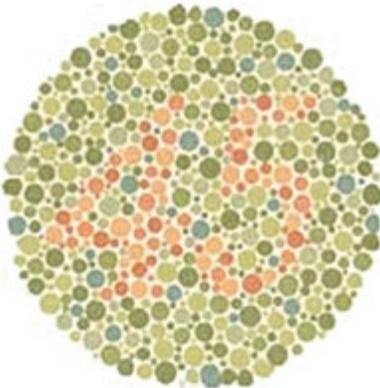
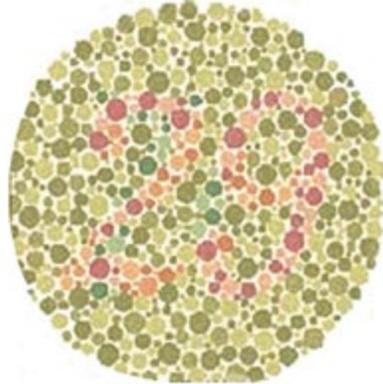
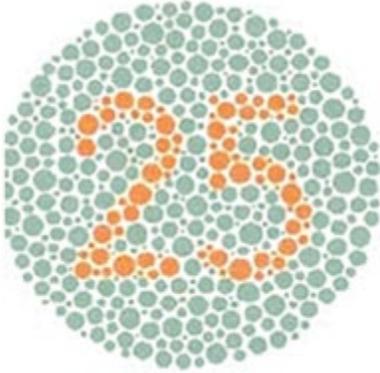
MONTH	Baseline		Intensive phase (IP)								Continuation phase (CP)								
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18-24
Smear	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly
TB Culture	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly
DST first-line	X	Repeat if clinically deteriorating	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	If TB culture becomes positive at any time, or patient is clinically deteriorating, repeat first-line DST and second-line DST (since the TB strain may now be resistant to more drugs)
DST second-line	X																		
CXR	X						X												
HIV screening	X																		
CD4 (if HIV positive)	X						X						X						18 & 24
Audiometry	X	X	X	X	X	X	X	X	X										
Evaluation by clinician	X	Weekly during 1st month, then every 2 weeks if patient is stable	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly
Weight (and BMI)	X						Weekly												Monthly
Urinalysis	X																		
Contraception	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly
Creatinine*	X	X	X	X	X	X	X	X	X										
Potassium	X																		
TSH	X						X											X	18 & 24
ALT	X																		
Haemoglobin	X	X	X	X	X	X	X	X											
Fasting glucose	X																		
Pregnancy test	X																		
Colour vision	X																		

* While receiving an injectable (Km, Am, Cm), use creatinine result to calculate creatinine clearance (see formula on page 221).

Appendix 21B: Ishihara testing

Both ethambutol and linezolid may cause optic neuritis, which can result in irreversible vision loss. Since colour blindness precedes the vision loss, screening with this Ishihara test can allow for early detection and management of eye toxicity and prevent vision loss.

Screen those taking ethambutol or linezolid by asking which numbers they can see in the six patterns of dots below. If the person is unable to visualise the numbers 29, 45, 6, and 8, then a full ophthalmological assessment is necessary.



Appendix 22: Management of common adverse events related to DS-TB and DR-TB treatment in adults

(Adapted from: World Health Organisation. 2008. *Guidelines for the Programmatic Management of Drug-resistant Tuberculosis*. WHO/HTM/TB/2005.361)

Note: It is very important to exclude an underlying medical condition as the cause for the symptoms and to not automatically blame the drugs for the symptoms.

Adverse event	Suspected drug(s)	Suggested management strategies	Comments
Seizures	Cs/Trd FQs H	<p>Rule out other likely causes.</p> <p>Treat any suspected causes.</p> <p>Initiate anticonvulsant therapy (e.g. valproic acid phenytoin; carbamazepine; phenobarbital).</p> <p>Increase pyridoxine up to 300mg daily.</p> <p>Lower dose of suspected drug.</p> <p>Replace or discontinue suspected drug.</p>	<p>Investigate as necessary if suspicion high for infectious, malignant, vascular or metabolic causes.</p> <p>Anticonvulsant generally continued until DR-TB treatment completed (or suspected drug discontinued).</p> <p>History of prior seizure disorder not a contraindication to the use of drugs listed here if patient's seizures are well controlled and/or patient is receiving anticonvulsant therapy.</p> <p>Patients with history of prior seizures may be at increased risk for development of seizures during DR-TB therapy.</p> <p>Seizures are not a permanent sequela of DR-TB treatment.</p>
Peripheral neuropathy (PN)	Cs/Trd Lzd S Km/Am Cm Eto/Pto H E	<p>Increase pyridoxine to 300 mg daily.</p> <p>Begin exercise regimen, focusing on affected regions.</p> <p>Consider initiating therapy with a tricyclic antidepressant drug (e.g. amitriptyline).</p> <p>Lower dose of suspected drug.</p> <p>Replace or discontinue suspected drug.</p>	<p>Patients with co-morbid disease (e.g. diabetes, HIV, alcoholism) are more likely to develop PN, but these conditions are not contraindications to the use of the drugs listed here.</p> <p>PN is generally not reversible, although only a minority (approximately 10%) of patients require continued intervention to keep symptoms controlled once DR-TB treatment is completed.</p>

Adverse event	Suspected drug(s)	Suggested management strategies	Comments
Hearing loss	S Km/Am Cm	Consider reduced frequency of administration (e.g. 5 times or even 3 times per week). Lower dose of suspected drug. Replace or discontinue suspected drug.	Patients with prior exposure to streptomycin may have baseline hearing loss. Hearing loss is generally not reversible.
Psychosis N.B. Rule out underlying medical cause.	Cs/Trd FQs Eto/Pto	Initiate anti-psychotic drugs (e.g. haloperidol). Stop suspected drug for short period of time (1–4 weeks) while psychotic symptoms are brought under control. Lower dose of suspected drug. Replace or discontinue suspected drug.	Some patients will need to continue anti-psychotic treatment throughout DR-TB therapy. Prior history of psychiatric disease is not a contraindication to the use of drugs listed here but may increase the likelihood of development of psychotic symptoms. Psychotic symptoms are generally reversible upon DR-TB treatment completion or discontinuation of offending drug.
Depression	Cs/Trd FQs Cm Eto/Pto H	Rule out contribution of concomitant medications (e.g. amoxicillin-clavulanate, penicillin, benzodiazepines). Institute psychological therapy. Group or individual supportive counselling. Initiate antidepressant drugs, e.g. amitriptyline (preferable if patient on ARVs), nortriptyline, fluoxetine, or sertraline, but use with caution when history of convulsions. Lower dose of suspected drug. Replace or discontinue suspected drug.	Importance of socioeconomic conditions (or chronic disease) should not be underestimated as a contributing factor to depression. Depression and depressive symptoms may fluctuate during therapy. History of prior depression is not a contraindication to the use of the drugs listed here; however, such patients may be at increased risk for developing depression during DR-TB treatment.

Adverse event	Suspected drug(s)	Suggested management strategies	Comments
Nausea and vomiting	Eto/Pto PAS Cm H E Z R	<p>Rehydration.</p> <p>Give an anti-emetic 30 minutes prior to DR-TB drugs.</p> <ul style="list-style-type: none"> • Metoclopramide 10 to 20 mg QID. • In severe cases, consider giving ondansetron 8 mg 30 minutes before DR-TB drugs +/- 8 hours afterwards. <p>Administer Eto in 3 separate doses.</p> <p>Administer Eto at night together with a short-acting benzodiazepine.</p> <p>Lower dose of suspected drug.</p> <p>Replace/discontinue suspected drug.</p>	<p>Nausea and vomiting ubiquitous in early weeks of DR-TB therapy and usually abate with supportive therapy.</p> <p>They are reversible upon discontinuation of the suspected agent.</p> <p>Electrolytes should be monitored and repleted if vomiting is severe.</p>
Gastritis	PAS Eto/Pto E Z	<p>Administer DR-TB medications with small amount of food.</p> <p>Avoid caffeine, cigarettes.</p> <p>Consider proton-pump inhibitors (e.g. omeprazole).</p> <p>Hold suspected drug(s) for short periods of time (e.g. 1–7 days).</p> <p>Lower dose of suspected drug.</p> <p>Replace/discontinue suspected drug.</p>	<p>Severe gastritis is possible, which manifests as hematemesis or rectal bleeding.</p> <p>Dosing of antacids should be carefully timed so as not to interfere with the absorption of DR-TB drugs. Take fluoroquinolones at least 3 hours apart from antacids.</p> <p>Reversible upon discontinuation of suspected drug(s).</p>
Hepatitis	Z H R E FQs Eto/Pto PAS Cm	<p>Stop therapy if hepatitis is severe.</p> <p>Rule out other potential causes of hepatitis.</p> <p>Re-introduce drugs individually while monitoring liver function closely, with least likely drug introduced first.</p> <p>Monitor liver function closely thereafter.</p>	<p>History of prior hepatitis should be carefully analysed to determine most likely causative drug(s); these should be avoided in future regimens.</p> <p>Generally reversible upon discontinuation of suspected agent.</p>

Adverse event	Suspected drug(s)	Suggested management strategies	Comments
Nephro-toxicity and renal failure	Km/Am Cm S	Follow creatinine clearance (CrCl). Treat symptoms. Reduce doses of all renally-excreted medications according to CrCl. Replace/discontinue suspected drug. If on TDF, replace by AZT.	History of diabetes or renal disease not a contraindication to the use of the drugs listed here, although patients with co-morbidities may be at increased risk for developing renal failure. Renal impairment may be permanent.
Optic neuritis	E Lzd Eto/Pto	Replace/discontinue drug.	If detected and managed early, permanent vision loss can be prevented.
Arthralgias	Z FQs	Initiate therapy with non-steroidal anti-inflammatory drugs. Initiate exercise regimen. Lower dose of suspected drug. Replace/discontinue suspected drug.	Symptoms of arthralgia generally diminish over time, even without intervention. Uric acid levels may be elevated in some patients but are of little therapeutic relevance and anti-gout therapy (e.g. allopurinol, colchicine) is of no proven benefit in these patients.
Electrolyte disturbances (hypokalaemia and hypomagnesaemia)	Cm Km/Am S	Replete potassium orally or IV. Treat any associated vomiting or diarrhoea. If hypokalaemia present, check magnesium levels (+/- calcium). Discontinue aminoglycosides if severe.	Hypokalaemia can occur without clinical signs and symptoms and may be life-threatening. If severe hypokalaemia is present, consider hospitalisation.

Appendix 23: The WHO analgesic ladder



WHO has developed a three-step 'ladder' for cancer pain relief in adults.

The WHO pain ladder is a framework for providing symptomatic pain relief. The three-step approach is inexpensive and 80–90% effective.

- By mouth** The oral route is preferred for all steps of the pain ladder.
- By the clock** When pain is continuous – analgesics should be given at regular intervals (according to the individual drug prescribing recommendations), not on demand.
- Adjuvants** To help calm fears and anxiety or where the cause of the pain is specifically neuropathic, adjuvant analgesics may be added at any step of the ladder.

Pain controlled

Step 3

Strong opioid

for moderate to severe pain (e.g. morphine)

± non-opioid

± adjuvant

Pain persisting or increasing

Step 2

Weak opioid

for mild to moderate pain (e.g. codeine)

± non-opioid

± adjuvant

Pain persisting or increasing

Step 1

Non-opioid

(e.g. aspirin, paracetamol or NSAID)

± adjuvant

- The ladder has no 'top rung' as there is no maximum dose for strong opioids.
- If pain is still a problem with high doses of morphine (e.g. greater than 300 mg every 24 hours), or if there are severe side effects, reconsider the cause of pain (e.g. bone pain may be better helped by NSAIDs) and/or seek specialist advice.

Major classes of adjuvant analgesics:

For neuropathic pain	anticonvulsants	sodium valproate, gabapentin levetiracetam
	antidepressants	amitriptyline
	local anaesthetics	lidocaine
For bone pain (consider a NSAID first in the analgesic ladder)	corticosteroids	prednisolone, dexamethasone
For musculoskeletal pain	muscle relaxants	baclofen, diazepam

Appendix 24: Substance abuse and mental illness symptoms screener (SAMISS)

1. How often do you have a drink containing alcohol?

Never 0 Monthly or less 1 2–4 times/mo 2 2–3 times/wk 3 4+ times/wk 4

2. How many drinks do you have on a typical day when you are drinking?

None 0 1 or 2 1 3 or 4 2 5 or 6 3 7–9 4 10 or more 5

3. How often do you have 4 or more drinks on 1 occasion?

Never 0 Less than monthly 1 Monthly 2 Weekly 3 Daily or almost daily 4

Total for Q1–3: _____ (Note: score of 5+ indicates positive screen)

4. In the past year, how often did you use nonprescription drugs to get high or to change the way you feel?

Never 0 Less than monthly 1 Monthly 2 Weekly 3 Daily or almost daily 4

Total for Q4: _____ (Note score of 3+ indicates positive screen)

5. In the past year, how often did you use drugs prescribed to you or to someone else to get high or change the way you feel?

Never 0 Less than monthly 1 Monthly 2 Weekly 3 Daily or almost daily 4

Total for Q5: _____ (Note score of 3+ indicates positive screen)

6. In the past year, how often did you drink or use drugs more than you meant to?

Never 0 Less than monthly 1 Monthly 2 Weekly 3 Daily or almost daily 4

Total for Q6: _____ (Note: score of 1+ indicates positive screen)

15. During your lifetime, as a child or adult, have you experienced or witnessed traumatic event(s) that involved harm to yourself or to others?

Yes No

If yes: In the past year, have you been troubled by flashbacks, nightmares, or thoughts of the trauma?

Yes No

16. In the past 3 months, have you experienced any event(s) or received information that was so upsetting it affected how you cope with everyday life?

Yes No

The substance abuse and mental illness symptoms screener (SAMISS) – Key

Substance abuse:

Respondent screens positive if sum of responses to questions 1–3 is equal to or greater than 5, response to question 4 or 5 is equal to or greater than 3, or response to question 6 or 7 is equal to or greater than 1.

Q 1–3 look at alcohol use.

Q 4–5 look at substances other than alcohol.

Q 6–7 look at the effects of substance use on daily living.

Mental Illness:

Respondent screens positive if response to any question is ‘Yes’.

Q 8 looks at the manic side of bipolar disorder.

Q 9–11 look at depression.

Q 12–14 look at anxiety.

Q 15 looks at PTSD like symptoms.

Q 16 could be a few things, PTSD or depression.

Appendix 25: Drug dosing adjustments in patients with renal impairment

Table A Recommended dose and frequency for patients with CrCl <50 ml/min

Drug	creatinine clearance (CrCl, in ml/min) or eGFR				
ARVs					
3TC	Clearance >50	Clearance 30–49	Clearance 15–29	Clearance 5–14	Clearance <5
	150 mg bd or 300 daily	150 mg daily	150 mg stat then 100 mg daily	150 mg stat then 50 mg daily	50 mg stat then 25 mg daily
d4T	Clearance >50		Clearance 25–50		Clearance 10–25
	30 mg bd		15 mg bd		15 mg daily
Drug	Cr clearance/eGFR >50 Give usual dose		Cr clearance/eGFR 10–50 Dose or % of usual dose		Cr clearance/eGFR <10 Dose or % of usual dose
AZT	300 mg bd		No adjustment needed		300 mg daily
TDF	300 mg nocte		AVOID		AVOID
abacavir	No adjustment needed		No adjustment needed		No adjustment needed
nevirapine	No adjustment needed		No adjustment needed		No adjustment needed
efavirenz	No adjustment needed		No adjustment needed		No adjustment needed
PIs	No adjustment needed		No adjustment needed		No adjustment needed
Anti-hypertensives					
enalapril	2.5–10 mg bd		75–100%		50%
atenolol	25–50 mg daily		50%		25%
HCTZ	12.5–25mg daily		100%		avoid
amlodipine	5–10 mg daily		No adjustment needed		No adjustment needed
doxazosin	2–4 mg daily		No adjustment needed		No adjustment needed
Diabetic meds					
gliclazide.	40–80 mg bd		AVOID		AVOID
gliben- clamide	2.5–5 mg bd		AVOID		AVOID
metformin	500–1000 mg bd		25%		AVOID

Anti-fungals			
fluconazole	200–400 daily	50%	50%
itraconazole	100–200 bd	100%	50% IV form contraindicated
Anti-virals			
acyclovir	200–800mg 4–12 hourly	100%	200 mg bd
Drug	Creatinine clearance or eGFR		
	>50 Give usual dose	10-50 Dose or % of usual dose	<10 Dose or % of usual dose
Antibiotics			
amoxicillin	250–1000 mg tds	Every 8–12 hours	Every 24 hours
azithromycin	500 mg daily	No adjustment needed	No adjustment needed
ceftriaxone	1–2 g daily	No adjustment needed	No adjustment needed
clarithromycin	250–500 mg bd	50%–100%	50%
ciprofloxacin	250–750 mg bd	50%–75%	50%
clindamycin		No adjustment needed	No adjustment needed
co-trimoxazole prophylaxis	2 tabs daily (480 mg tabs)	No adjustment needed	No adjustment needed
co-trimoxazole treatment	2 bd–4 qid (480 mg tabs)	50%	Seek advice
erythromycin		No adjustment needed	No adjustment needed
linezolid		No adjustment needed	No adjustment needed
moxifloxacin	400 mg daily	No adjustment needed	No adjustment needed
ofloxacin	200–400 mg bd	Daily dose	Daily dose
penicillin g	0.5–4 MU 4–6 hourly	75%	25%
TB drugs see separate document below			
Miscellaneous			
NSAIDs	AVOID	AVOID	AVOID
metoclopramide	10 mg tds	75%	50%
omeprazole	20–40 mg daily	No adjustment needed	No adjustment needed
ranitidine	150–300 mg nocte	50%	25%

DR-TB drugs in renal impairment

Monitor creatinine clearance regularly for all DR-TB patients, especially for those at high risk of renal impairment (diabetic, >60 years of age)

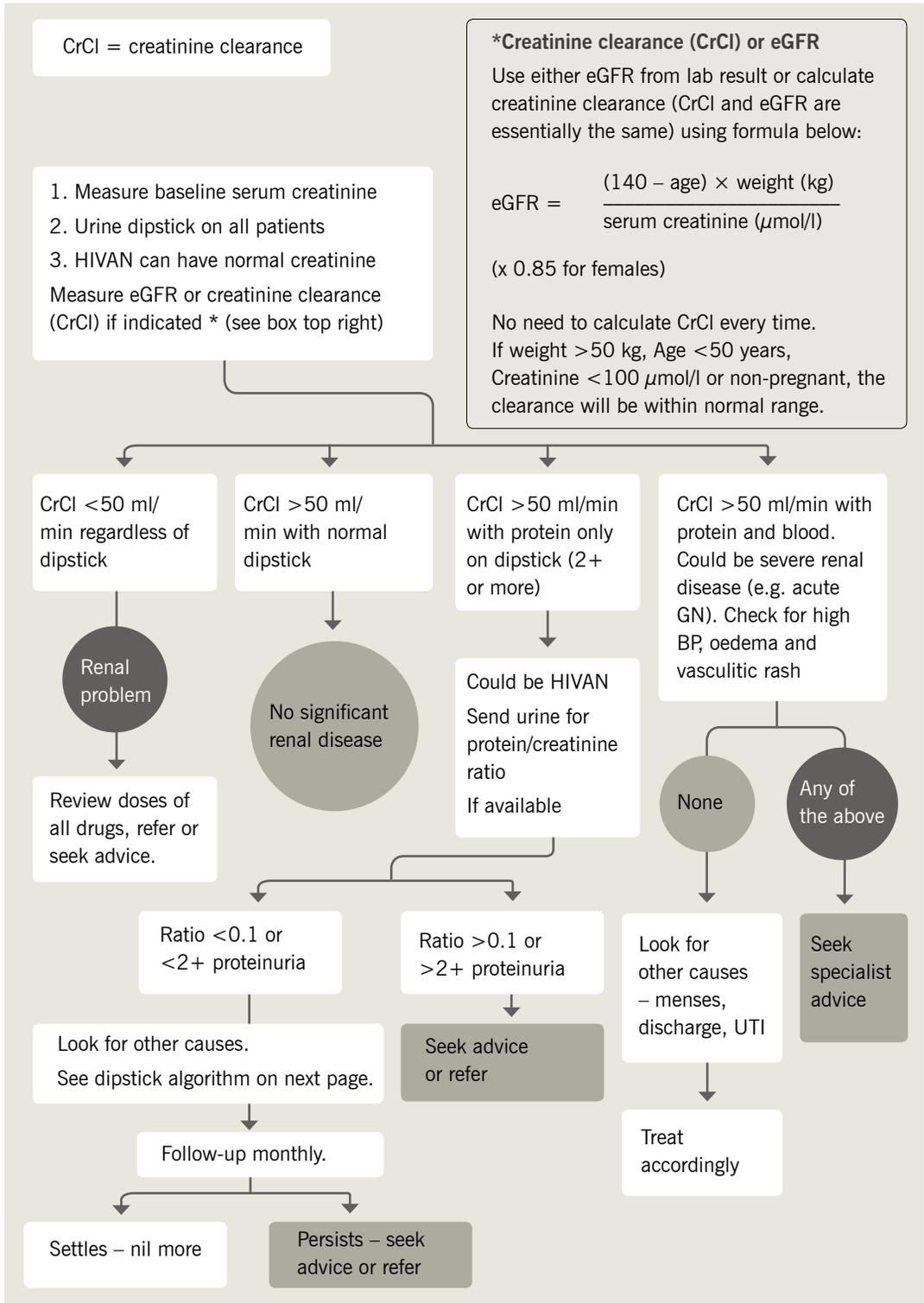
If patient has renal impairment with **creatinine clearance <30 ml/min**, they will need some of their DR-TB meds to be adjusted as follows:

Table B Recommended dose and frequency for patients with CrCl <30 ml/min (or for patients receiving hemodialysis)

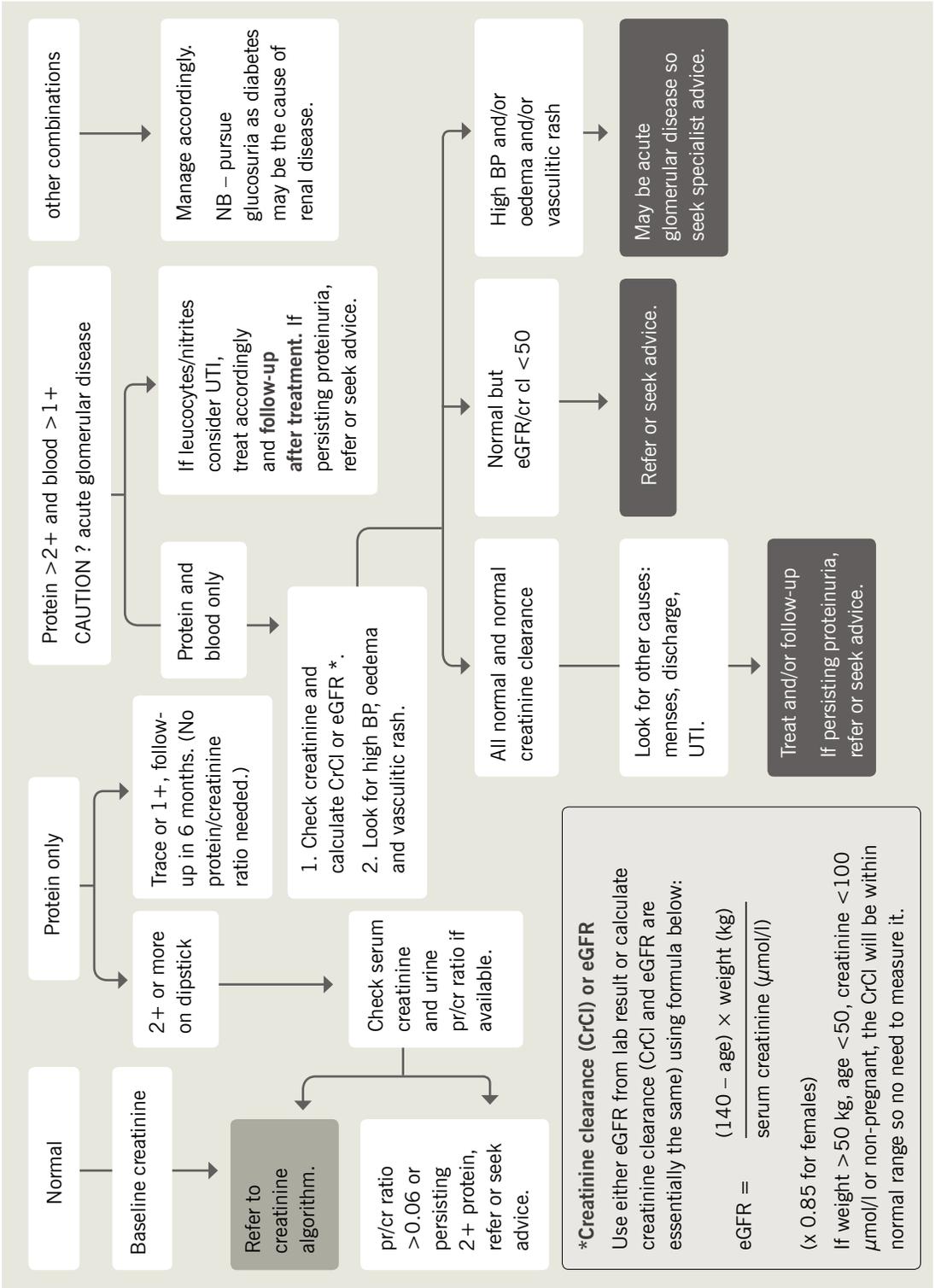
Drug frequency	Change in frequency when CrCl <30 ml/min	Recommended dose and frequency for patients with creatinine
isoniazid	No change	300 mg once daily, or 900 mg 3 x week
rifampicin	No change	600 mg once daily, or 600 mg 3 x week
pyrazinamide	Yes	25–35 mg/kg/dose 3 x week
ethambutol	Yes	15–25 mg/kg/dose 3 x week
ofloxacin	Yes	600–800 mg/kg/dose 3 x week
moxifloxacin	No change	400 mg once daily
terizidone	Yes	250 mg once daily, or 500 mg 3 x week
ethionamide	No change	250–500 mg/dose daily
PAS	No change	4 g/dose, twice daily
streptomycin	Yes	12–15 mg/kg/dose 2 or 3 x week
capreomycin	Yes	12–15 mg/kg/dose 2 or 3 x week
kanamycin	Yes	12–15 mg/kg/dose 2 or 3 x week

(Adapted from American Thoracic Society/Centers for Disease Control and Prevention /Infectious Disease Society of America. 'Treatment of Tuberculosis'. *Am J Respir Crit Care Med* 2003; 167)

Appendix 26A: Creatinine evaluation algorithm



Appendix 26B: Urine dipstick algorithm



Appendix 26C: Creatinine clearance estimation tables (in ml/min)

N.B Creatinine must be measured in $\mu\text{mol/l}$ to use these tables. These tables are provided to assist with manual calculation. Ideally this calculation should be done automatically from the laboratory.

Table 1: Female, age 15–40 years

Cr in $\mu\text{mol/liter}$	30-35 kg	36-40 kg	41-45 kg	46-50 kg	51-55 kg	56-60 kg	61-65 kg	66-70 kg
60	52-76	62-87	71-98	80-108	88-119	97-130	106-141	114-152
70	45-65	53-74	61-84	68-93	76-102	83-111	91-121	98-130
80	39-57	47-65	53-73	60-81	66-89	73-98	79-106	86-114
90	35-51	42-58	48-65	53-72	59-79	65-87	70-94	76-101
100	31-46	37-52	43-59	48-65	53-72	58-78	63-85	69-91
110	28-41	34-47	39-53	43-59	48-65	53-71	58-77	62-83
120	26-38	31-43	36-49	40-54	44-60	49-65	53-70	57-76
130	24-35	29-40	33-45	37-50	41-55	45-60	49-65	53-70
140	22-33	27-37	31-42	34-46	38-51	42-56	45-60	49-65
290	11-16	11-18	15-20	16-22	18-25	20-27	22-29	24-31
300	10-15	16-17	14-20	16-22	18-24	19-26	21-28	23-30
350	9-13	13-15	12-17	14-19	15-20	17-22	18-24	20-26
400	8-11	12-13	11-15	12-16	13-18	15-20	16-21	17-23
450	7-10	10-12	10-13	11-14	12-16	13-17	14-19	15-20
500	6-9	9-10	9-12	10-13	11-14	12-16	13-17	14-18
550	6-8	9-9	8-11	9-12	10-13	11-14	12-15	12-17
600	5-8	8-9	7-10	8-11	9-12	10-13	11-14	11-15
650	5-7	7-8	7-9	7-10	8-11	9-12	10-13	11-14
700	7-12	10-14	9-8	7-9	8-10	8-11	9-12	10-13

Table 2: Female, age 41–65 years

Cr in $\mu\text{mol/liter}$	30-35 kg	36-40 kg	41-45 kg	46-50 kg	51-55 kg	56-60 kg	61-65 kg	66-70 kg
40	59-90	70-103	80-116	90-129	99-142	109-154	119-167	129-180
50	47-72	56-82	64-93	72-103	80-113	87-124	95-134	103-144
60	39-60	47-69	53-77	60-86	66-94	73-103	79-112	86-120
70	33-51	40-59	46-66	51-74	57-81	62-88	68-96	83-103
80	29-45	35-51	40-58	45-64	50-71	55-77	59-84	73-90
90	26-40	31-46	36-51	40-57	44-63	49-69	53-74	65-80
100	23-36	28-41	32-46	36-51	40-57	44-62	48-67	58-72
110	21-33	26-37	29-42	33-47	36-51	40-56	43-61	53-66
120	20-30	23-34	27-39	30-43	33-47	36-51	40-56	49-60
220	11-16	13-19	15-21	16-23	18-26	20-28	22-30	27-33
230	10-16	12-18	14-20	16-22	17-25	19-27	21-29	25-31
300	8-12	9-14	11-15	12-17	13-19	15-21	16-22	19-24
350	7-10	8-12	9-13	10-15	11-16	12-18	14-19	17-21
400	6-9	7-10	8-12	9-13	10-14	11-15	12-17	15-18
450	5-8	6-9	7-10	8-11	9-13	10-14	11-15	13-16
500	5-7	6-8	6-9	7-10	8-11	9-12	10-13	12-14
550	4-7	5-7	6-8	7-9	7-10	8-11	9-12	11-13
600	4-6	5-7	5-8	6-9	7-9	7-10	8-11	10-12

Table 3: Male, age 15–40 years

Cr in $\mu\text{mol/liter}$	30-35 kg	36-40 kg	41-45 kg	46-50 kg	51-55 kg	56-60 kg	61-65 kg	66-70 kg
70	53-77	63-88	72-99	81-110	90-121	98-132	107-143	116-154
80	46-67	55-77	63-86	71-96	78-106	86-115	94-125	101-135
90	41-60	49-68	56-77	63-85	70-94	77-103	83-111	90-120
100	37-54	44-62	50-69	57-77	63-85	69-92	75-100	81-108
110	34-49	40-56	46-63	51-70	57-77	63-84	68-91	74-98
120	31-45	37-51	42-58	47-64	52-70	57-77	63-83	68-90
130	28-41	34-47	39-53	44-59	48-65	53-71	58-77	62-83
140	26-38	32-44	36-49	40-55	45-60	49-66	54-71	58-77
150	25-36	30-41	34-46	38-51	42-56	46-62	50-67	54-72
160	23-34	28-38	32-43	35-48	39-53	43-58	47-62	51-67
170	22-32	26-36	30-41	33-45	37-50	41-54	44-59	48-63
350	11-15	13-18	14-20	16-22	18-24	20-26	21-29	23-31
400	9-13	11-15	13-17	14-19	16-21	17-23	19-25	20-27
450	8-12	10-14	11-15	13-17	14-19	15-21	17-22	18-24
500	7-11	9-12	10-14	11-15	13-17	14-18	15-20	16-22
550	7-10	8-11	9-13	10-14	11-15	13-17	14-18	15-20
600	6-9	7-10	8-12	9-13	10-14	11-15	13-17	14-18
650	6-8	7-9	8-11	9-12	10-13	11-14	12-15	12-17
700	5-8	6-9	7-10	8-11	9-12	10-13	11-14	12-15
750	5-7	6-8	7-9	8-10	8-11	9-12	10-13	11-14
800	5-7	6-8	6-9	7-10	8-11	9-12	9-12	10-13

Table 4: Male, age 41–65 years

Cr in $\mu\text{mol/liter}$	30-35 kg	36-40 kg	41-45 kg	46-50 kg	51-55 kg	56-60 kg	61-65 kg	66-70 kg
50	55-85	66-97	76-110	85-122	94-134	103-146	113-158	122-170
60	46-71	55-81	63-91	71-101	78-112	86-122	94-132	101-142
70	40-61	47-70	54-78	61-87	67-96	74-104	80-113	87-122
80	35-53	42-61	47-68	53-76	59-84	65-91	70-99	76-107
90	31-47	37-54	42-61	47-68	52-74	57-81	63-88	68-95
100	28-43	33-49	38-55	42-61	47-67	52-73	56-79	61-85
110	25-39	30-44	34-50	39-55	43-61	47-66	51-72	55-77
120	23-36	28-41	32-46	35-51	39-56	43-61	47-66	51-71
130	21-33	26-37	29-42	33-47	36-52	40-56	43-61	47-66
260	11-16	13-19	15-21	16-23	18-26	20-28	22-30	23-33
300	9-14	11-16	13-18	14-20	16-22	17-24	19-26	20-28
350	8-12	9-14	11-16	12-17	13-19	15-21	16-23	17-24
400	7-11	8-12	9-14	11-15	12-17	13-18	14-20	15-21
450	6-9	7-11	8-12	9-14	10-15	11-16	13-18	14-19
500	6-9	7-10	8-11	8-12	9-13	10-15	11-16	12-17
550	5-8	6-9	7-10	8-11	9-12	9-13	10-14	11-15
600	5-7	6-8	6-9	7-10	8-11	9-12	9-13	10-14

Appendix 27: Recommended growth monitoring and nutrition support for HIV-exposed or HIV-infected children



AT EACH VISIT

Weigh the child and document in the file.
Plot weight-for-age (W/A) on the growth chart.
In young children, head circumference should also be measured and plotted on the growth chart.

The WHO Global Database on Child Growth and Malnutrition uses a Z-score cut-off point of <-2 SD to classify low weight-for-age, low height-for-age and low weight-for-height as moderate and severe undernutrition, and <-3 SD to define severe undernutrition. The cut-off point of $>+2$ SD classifies high weight-for-height as overweight in children.

W/A is >-2 Z score and
Child is gaining weight.

Child is doing well.
Routine nutritional education.
Nutritional supplements may be given for programmatic reasons.

W/A is <-2 Z score or
Child is failing to gain or losing weight.

Evaluate medically for illness and/or opportunistic infection.
Evaluate family social situation.

<6 months of age

Refer to Therapeutic Feeding Protocol.
REPEAT HIV TESTING.*

>6 months of age

Measure length and calculate weight/height index, or measure MUAC.

W/H >-2 Z-score or
MUAC >125 mm and if
 <12 months old:
Supplement with a RUSF:
300 kcal/day – until infant reaches 12 months.

At discharge
*Repeat HIV testing for exposed children whose status is not already known

$-2 > W/H \geq -3$ Z-score or
 $125 \text{ mm} > \text{MUAC} \geq 115 \text{ mm}$
Supplement with a RUSF.
 ≤ 12 M: 500 kcal/day
 > 12 M: 1000 kcal/day
Supplement until W/H >-2 Z-score or MUAC >125 mm at 2 consecutive visits.
REPEAT HIV TESTING.*

W/H <-3 Z-score
or MUAC <115 mm
Refer to Therapeutic Feeding Protocol.
REPEAT HIV TESTING*

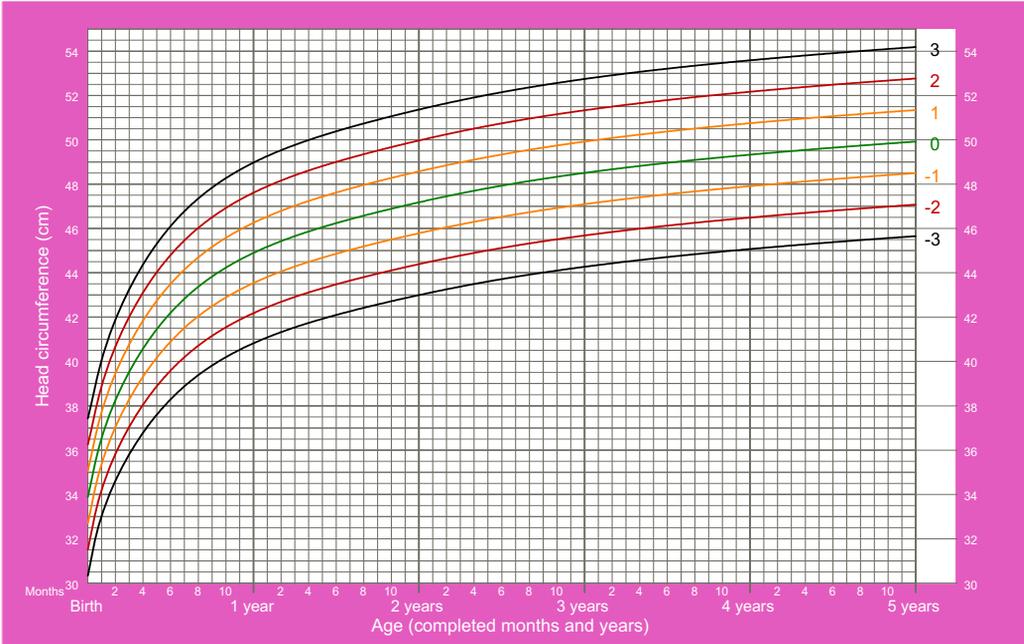
MUAC = mid-upper arm circumference
RUSF = ready-to-use supplementary food

Appendix 28: WHO growth charts



Head circumference-for-age **GIRLS**

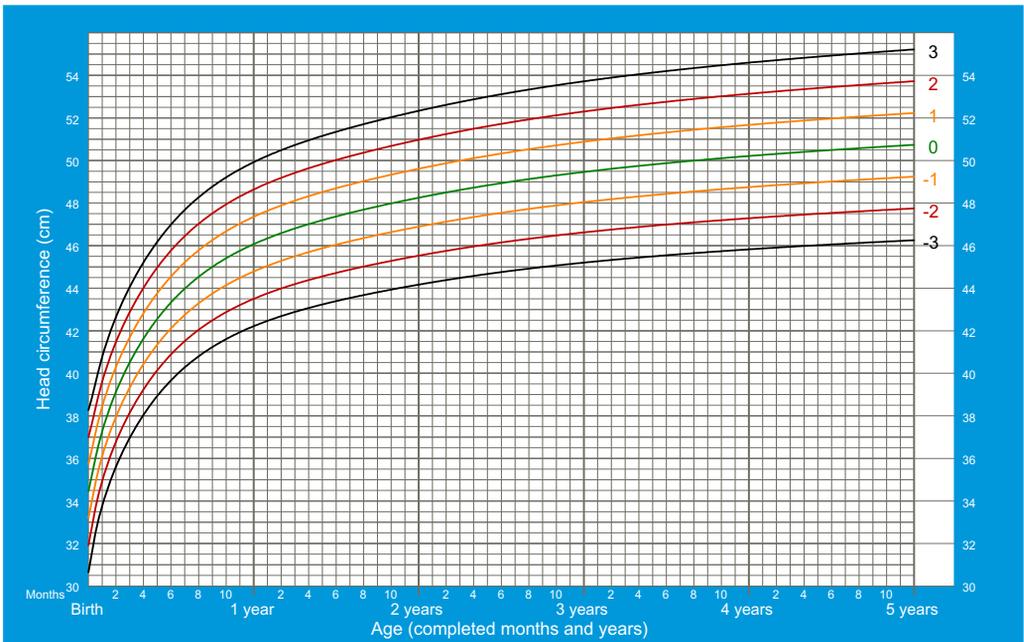
Birth to 5 years (z-scores)



WHO Child Growth Standards

Head circumference-for-age **BOYS**

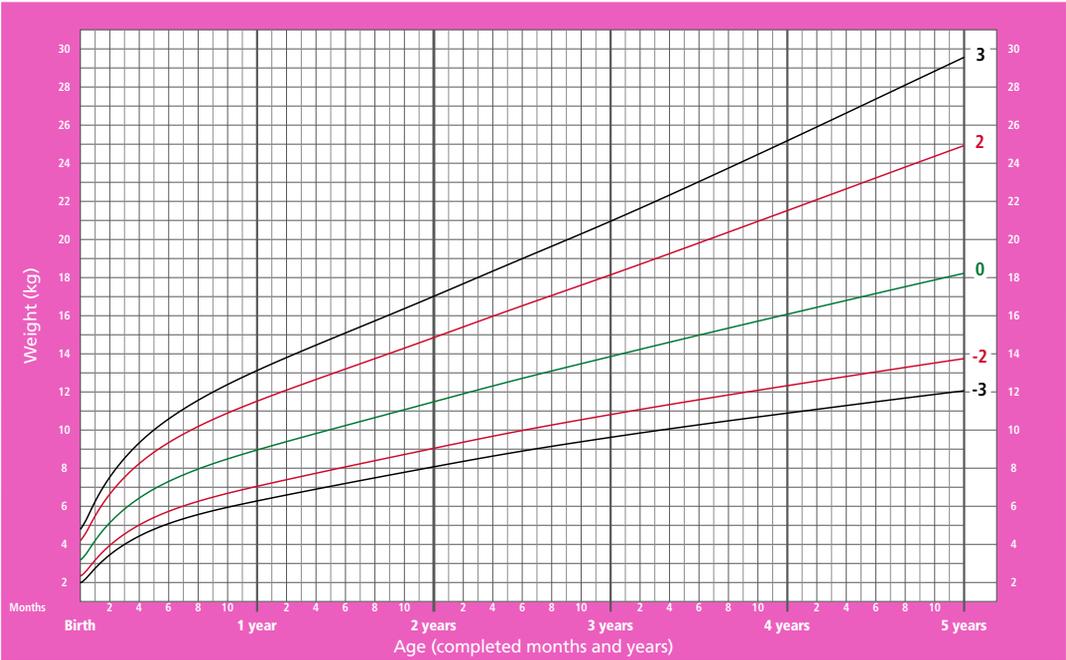
Birth to 5 years (z-scores)



WHO Child Growth Standards

Weight-for-age GIRLS

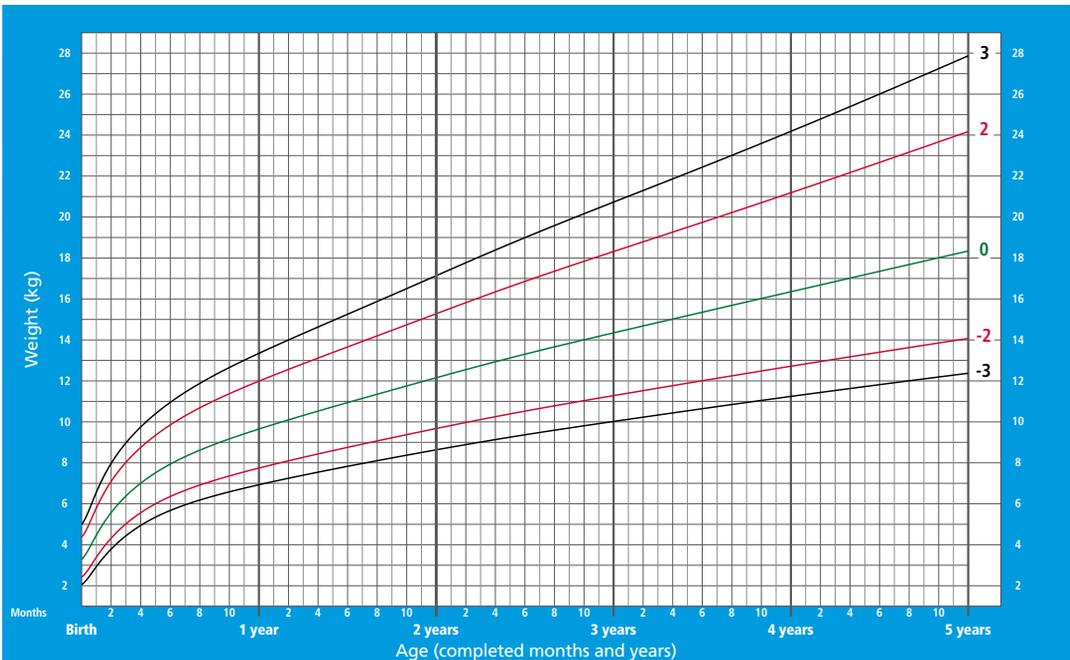
Birth to 5 years (z-scores)



WHO Child Growth Standards

Weight-for-age BOYS

Birth to 5 years (z-scores)

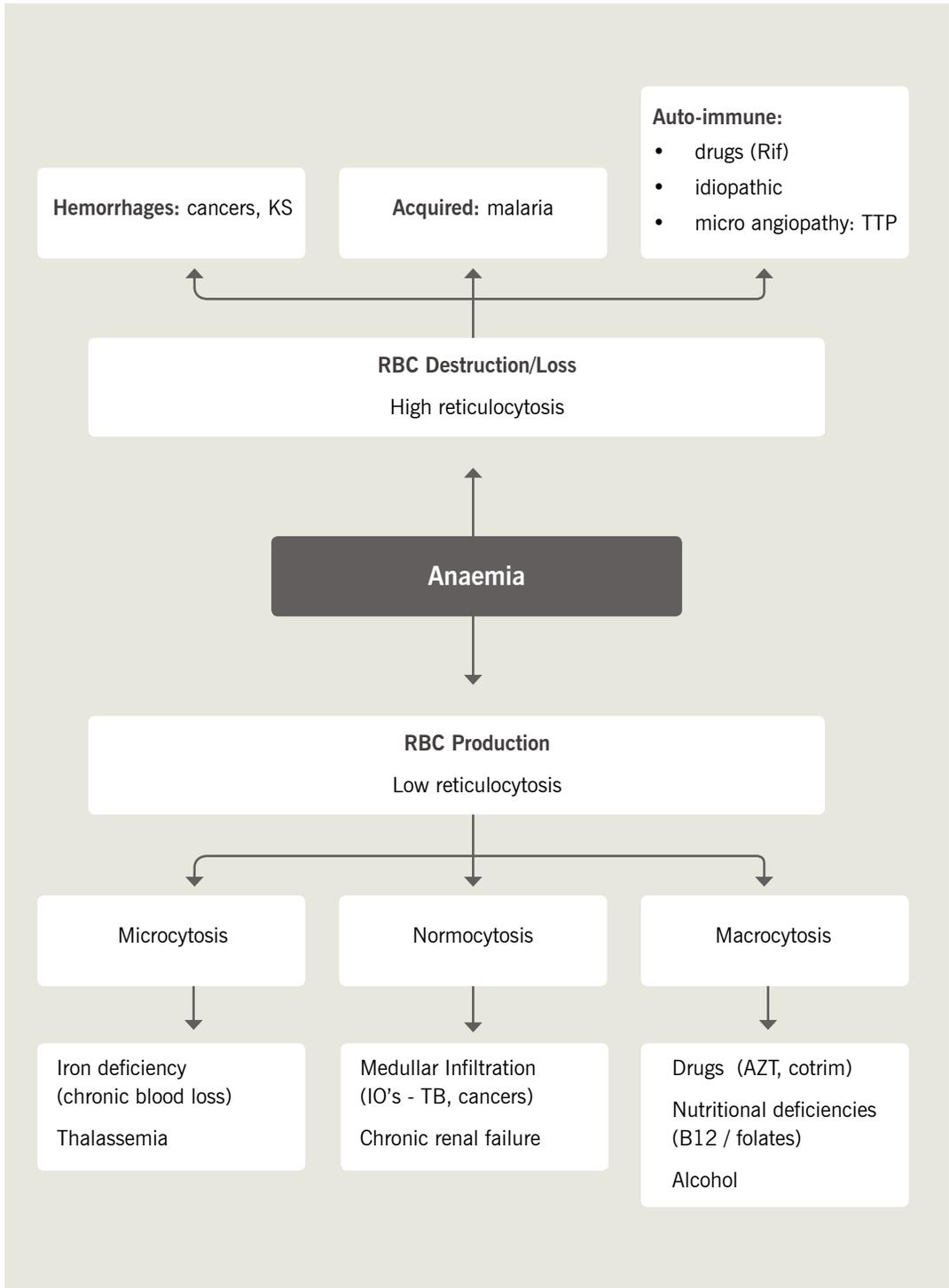


WHO Child Growth Standards

Appendix 29: Normal vital parameters in children

Normal parameters	Heart rate	Mean respiratory rate
Infants <1 year	120–170	40
Toddler 1–2 years	80–110	35
Pre-school 3–4 years	70–110	31
School 5–11 years	70–110	27

Appendix 30: Approach to Anaemia algorithm



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