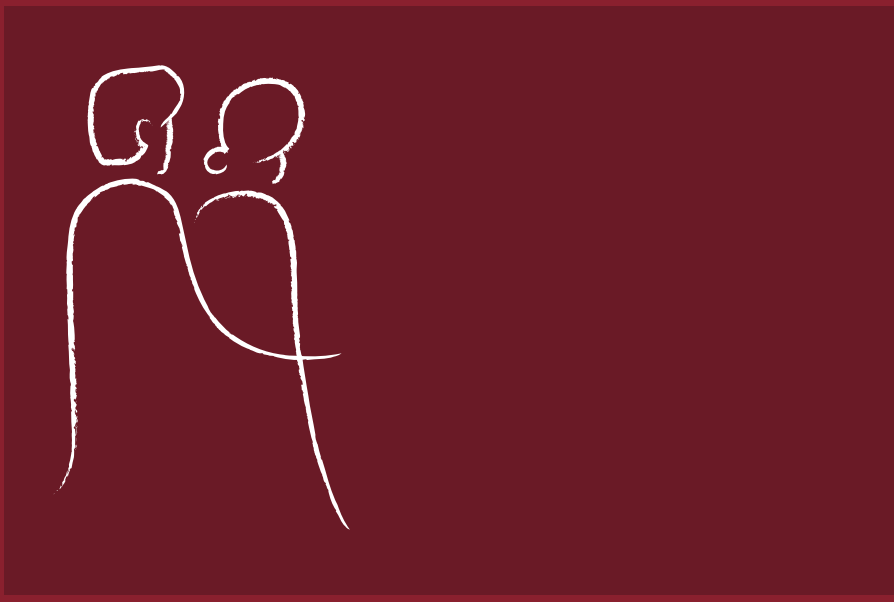
Management of HIV Infection and Antiretroviral Therapy in Adults and Adolescents



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ACRONYMS AND ABBREVIATIONS

3TC	lamivudine
AB	antibody
ABC	abacavir
ACTG	AIDS Clinical Trials Group
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APV	amprenavir
ART	antiretroviral therapy
ARV	antiretroviral (drug)
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the curve
AZT	zidovudine (also known as ZDV)
BMI	body mass index
CD4 count	CD4+ T-lymphocyte count
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CSF	cerebrospinal fluid
CTX	co-trimoxazole
CXR	chest X-ray
d4T	stavudine
ddI	didanosine
DNA	deoxyribonucleic acid
DOT	directly observed treatment
DRV	darunavir
EC	enteric coated
EFV	efavirenz
EPTB	extrapulmonary tuberculosis
FBC	full blood count
FPV	fos-amprenavir

FTC	emtricitabine
GI	gastrointestinal
GGT	gamma glutamyl transpeptidase
HDL	high-density lipoprotein
Hb	haemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health-care provider
HCV	hepatitis C virus
hgc	hard-gel capsule
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
IDV	indinavir
IDU	injecting drug user
IFN	interferon
INH	isoniazid
IRIS	immune reconstitution inflammatory syndrome
JCV	JC virus (virus that causes progressive multifocal leukoencephalopathy [PML]. JC are the two initials of a patient with PML.)
KOH	potassium hydroxide
LDH	lactate dehydrogenase
LPV	lopinavir
MAC	*Mycobacterium avium* complex
MSM	men who have sex with men
MTCT	mother-to-child transmission (of HIV)
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
nPEP	non-occupational post-exposure prophylaxis
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NVP	nevirapine
OHL	oral hairy leukoplakia
OI	opportunistic infection
OST	opioid substitution treatment
Pap	Papanicolaou
PCP	*Pneumocystis jiroveci* pneumonia (earlier known as *Pneumocystis carinii*)

PEP	post-exposure prophylaxis
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
PK	pharmacokinetic
PLHA	people living with HIV/AIDS
PML	progressive multifocal leukoencephalopathy
PMTCT	prevention of mother-to-child transmission (of HIV)
PPE	pruritic papular eruption
PTB	pulmonary tuberculosis
/r	low-dose ritonavir
RBV	ribavirin
REE	resting energy expenditure
RNA	ribonucleic acid
RPR	rapid plasma reagin (test)
RTI	reverse transcriptase inhibitor
RTV	ritonavir
SDN	single-dose nevirapine
SOP	standard operating procedure
SQV	saquinavir
STI	sexually transmitted infection
SW	sex worker
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TLC	total lymphocyte count
TPHA	*Treponema pallidum* haemagglutination (test)
ULN	upper limit of normal
VDRL	Venereal Disease Research Laboratory (test)
WBC	white blood cell count
WHO	World Health Organization
ZN	Ziehl–Neelsen

CONTENTS

Annexes

Introduction

This document updates the World Health Organization, Regional Office for South-East Asia's guideline *The use of antiretroviral therapy: a simplified approach for resource-constrained countries*, published in July 2002. This new document provides a simplified and standardized approach to the clinical management of people living with HIV/AIDS (PLHA) and use of antiretroviral therapy (ART) as part of comprehensive HIV care. The term adult is used for persons 18 years of age and above and the term adolescent for those 10–18 years of age. Whether to treat adolescents following the paediatric guidelines or adult/adolescent guidelines depends on the treating physician.

The objectives of this clinical manual are (i) to guide medical doctors and other health-care providers in the clinical management of HIV and ART; (ii) to serve as a source of reference for AIDS programme managers and health planners in planning HIV care and treatment programmes and in developing national HIV care and treatment guidelines; and (iii) to provide a source of reference for PLHA, caregivers and community-based organizations.

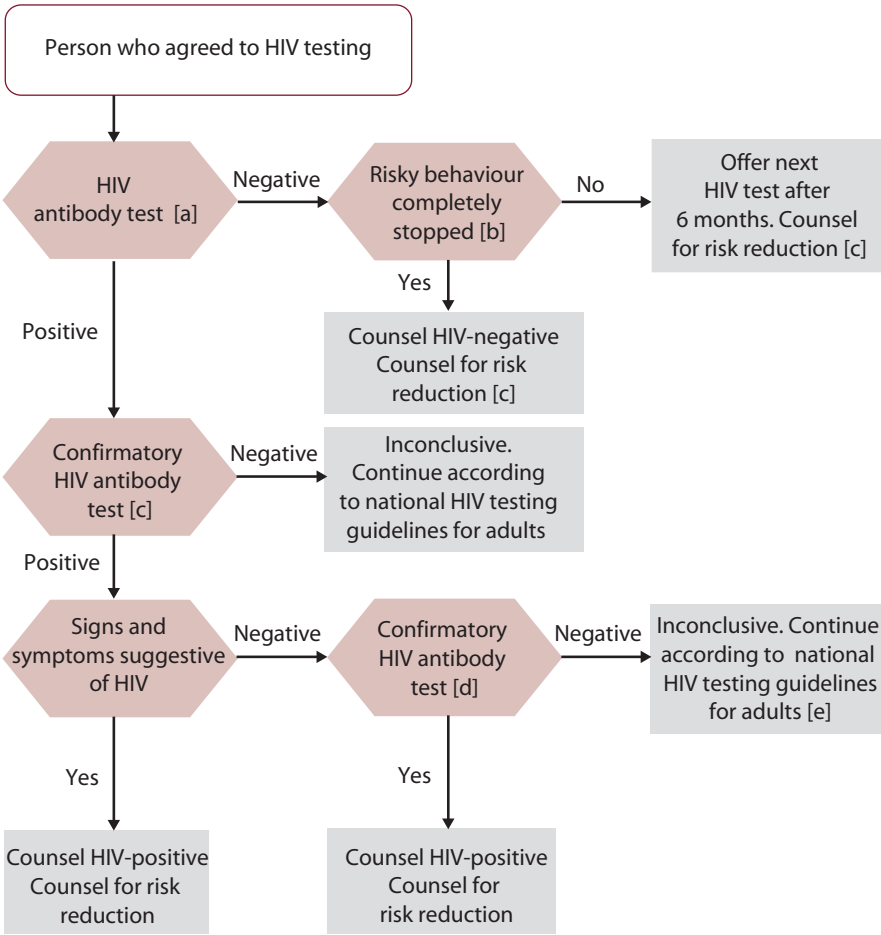
The following related publications from WHO Regional Office for South-East Asia should be consulted in conjunction with this manual:

- *Laboratory guidelines for enumerating CD4 T lymphocytes in the context of HIV/AIDS,* 2007.
- *Antiretrovirals for HIV: a compilation of facts and product information,* 2007.
- *Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: a clinical manual*, 2006.
- *Training toolkit – HIV care and antiretroviral treatment recording and reporting system,* 2006.
- *Guidelines for HIV diagnosis and monitoring of antiretroviral therapy. Revision,* 2005.

The full set of WHO guidelines is available at www.searo.who.int/hiv-aids publications and http://www.who.int/hiv/pub/guidelines/en/index.html.

1 Laboratory Diagnosis of HIV Infection in Adults and Adolescents

Figure 1. HIV testing algorithm



Notes

[a] HIV testing procedures should follow each country's national guidelines. WHO recommends that the HIV tests used should have a sensitivity of at least 99% and a specificity of 98%. The specific test combinations need to be evaluated in the context in which they will be used before wide-scale implementation. Tests selected should be of assured quality, and a number of these are evaluated against standard panels by designated reference laboratories. The introduction of highly sensitive, specific, simple-to-use, rapid antibody tests that do not require sophisticated laboratory services, running water or electricity is recommended in settings where immediate provision of test results is important. Accurate results can be available within a much shorter time than for traditional enzyme-linked immunosorbent assays (ELISA). ELISA may be preferable in settings where large numbers of tests need to be performed, and where immediate provision of test results is less important.[1,2]

[b] Antibodies against HIV appear from 2 weeks to 3 months after first exposure to HIV (97%). This period is called the window period. Therefore, if the initial negative HIV test was conducted within the first 3 months of possible exposure, a repeat test should be considered, in particular, when there is continued risky behaviour such as (i) unprotected sex in persons with a history of sexually transmitted infection (STI), sex workers (SWs) and their clients, men who have sex with men (MSM) and sex partners of people living with HIV/AIDS (PLHA) as well as (ii) sharing of injecting equipment among injecting drug users (IDUs).

[c] WHO recommends serial testing algorithms as shown in Figure 1. If the result of the first test is negative, the HIV antibody test is reported as negative. If the test result is positive, the specimen is tested with a second test using different antigens and/or platform from the first. Tests that are exactly the same but sold under different names should not be used in combination. A second positive test result is considered to indicate a true positive result in populations with an HIV prevalence of 5% or more. WHO and UNAIDS recommend serial testing in most settings because it is cheaper and a second test is only required when the initial test is reactive.

[d] In low-prevalence settings (<5%) where false-positive results are more likely, a third confirmatory test may be required.[1]

[e] If the result remains inconclusive following the initial and confirmatory tests, it is repeated two weeks later. If it is still inconclusive, follow-up testing may be required. Conduct a careful risk assessment and provide counselling on HIV prevention. If the person is at high risk, consider retesting at 6 and 12 months. If the results remain inconclusive after 1 year, the person is considered HIV negative if no HIV exposure has occurred in the previous 12 months.[1]

2 Assessment of Adults and Adolescents with HIV Infection

2.1 Clinical assessment

At entry into care and prior to starting ART, the medical history should be taken and clinical assessment performed (**Tables 1, 2**):

- To determine the clinical stage of HIV infection
- To identify past HIV-related illnesses
- To identify current HIV-related illnesses that require treatment
- To determine the need for ART and prophylaxis for opportunistic infection (OI)
- To identify coexisting medical conditions and treatments that may influence the choice of therapy.

The recognition of HIV-related clinical events facilitates staging of a patient's disease and decisions on when to initiate OI prophylaxis and ART. Annex 1 details those conditions which should alert the physician that the patient may have HIV infection. Many conditions require only a clinical diagnosis.

Conditions that come under WHO stages 1, 2 and 3, with the exception of moderate anaemia, can be readily recognized clinically. For WHO stage 4 conditions, definite diagnostic criteria are recommended for diseases such as lymphoma and cervical cancer where a clinical diagnosis is not possible.[3]

Medical history (Table 1)

Many individuals with HIV infection are unaware of their status (i.e. whether they are HIV-positive or negative). HIV testing should be performed for any patient who requests it following pre-test counselling. Other indications for HIV testing include the presence of sexually transmitted infections (STIs), pregnancy, active tuberculosis (TB) and signs and symptoms suggestive of HIV infection.

Box 1: Risk factors for HIV infection

- Male or female sex worker (SW)
- Present or past injecting drug user (IDU)
- Men who have sex with men (MSM) and transgenders
- Present or past unprotected sex, particularly with a female or male SW
- Present or past STI
- Present or past recipient of blood or blood products
- Injections, tattooing, ear piercing or body piercing using non-sterile instruments.

Table 1: Medical history checklist

HIV testing	HIV risk
▪ Ever tested for HIV in the past? ▪ Date and place of first HIV test ▪ Reason for the test ▪ Documentation of the result ▪ Date of last negative HIV test result ▪ Prior CD4+cell counts (if available) ▪ Prior viral load (if available)	▪ Unprotected sexual contact ▪ Injecting drug use ▪ Men who have sex with men (MSM) ▪ Occupational exposure ▪ Perinatal transmission ▪ Recipient of blood products ▪ Unknown
Systemic review	**Past history of HIV-related illnesses**
▪ Unexplained weight loss ▪ Swollen lymph nodes ▪ Night sweats and fever ▪ Unusual headaches or poor concentration ▪ Changes in appetite ▪ Skin rashes ▪ Sores or white spots in the mouth ▪ Pain on swallowing ▪ Chest pain, cough, shortness of breath ▪ Stomach pain, vomiting, diarrhoea ▪ Numbness or tingling in the hands and feet ▪ Muscle weakness and changes in vision	▪ Oral or osophageal candidiasis ▪ Persistent diarrhoea ▪ Varicella zoster (shingles) ▪ Oral hairy leukoplakia (OHL) ▪ *Pneumocystis jiroveci* pneumonia (PCP) ▪ Recurrent bacterial pneumonia ▪ Cryptococcal meningitis ▪ Toxoplasmosis ▪ Kaposi sarcoma ▪ Disseminated *Mycobacterium avium* complex (MAC) disease ▪ Cytomegalovirus (CMV) infection ▪ TB ▪ Invasive cervical cancer
TB history	**Sexually transmitted infections (STIs)**
▪ Last chest X-ray (CXR) ▪ History of past TB ▪ Treatment given (drugs and duration) ▪ History of exposure to TB	▪ Genital ulcer or other lesion ▪ Genital discharge (abnormal vaginal discharge in women) ▪ Lower abdominal pain

Table 1 *(contd)*: Medical history checklist

Gynaecological history ▪ Last Papanicolaou (Pap) smear ▪ Menstrual irregularities ▪ Pelvic pain or discharge	**General medical history** ▪ Any other past medical condition such as diabetes, hypertension, cardiovascular disease, hepatitis B, hepatitis C
Pregnancy and contraception history ▪ Previous pregnancies and terminations of pregnancy ▪ Children and HIV status of children (living and dead) ▪ Exposure to antiretroviral drugs (ARV) during pregnancy ▪ Drugs taken and duration of ART ▪ Contraception used ▪ Last menstrual period	**Vaccination history** ▪ BCG ▪ Hepatitis A vaccine ▪ Hepatitis B vaccine
Medication ▪ Past drugs and reasons for taking them ▪ Current drugs and reasons for taking them ▪ Traditional remedies taken in the past or currently being taken ▪ Opioid substitution therapy (OST)	**Allergies** ▪ Known allergies to drugs or other substances or materials
ART history ▪ Current and past exposure to ART ▪ Which drugs taken and for how long ▪ Understanding and readiness to commence ART if never taken	**Psychosocial history** ▪ Family history, e.g. other immediate family member with known HIV infection ▪ Social history, e.g. marital status, education, occupation, source of income ▪ Financial and family support status ▪ Disclosure status, readiness to disclose ▪ Care and treatment support available
Substance use ▪ Alcohol, stimulant, opiate and other drug use ▪ Smoking history	**Functional status** ▪ Able to work, go to school, do housework ▪ Ambulatory but not able to work ▪ Bedridden ▪ Amount of day-to-day care needed

History-taking is followed by physical examination.

Table 2: Physical examination checklist	
Record vital signs: body weight, temperature, blood pressure, pulse rate, respiratory rate	
Appearance	▪ Unexplained moderate or severe weight loss, HIV wasting (*see* Annex 1) ▪ Rapid weight loss is suggestive of active OI, especially if associated with fever. ▪ Gradual weight loss (not caused by malnutrition or other obvious illness) is suggestive of HIV infection. ▪ Gradual weight loss, fever and anaemia are common presentations of infection with MAC. ▪ "Track marks" and soft tissue infections are common in IDUs.
Consider conditions other than HIV	▪ Malaria, TB, syphilis, gastrointestinal (GI) infections, bacterial pneumonia, pelvic inflammatory disease, viral hepatitis
Skin	▪ Look for signs of HIV-related and other skin problems. These include diffuse dry skin, typical lesions of pruritic papular eruptions (PPE) especially on the legs, seborrhoeic dermatitis on the face and scalp. ▪ Look for herpes simplex and herpes zoster, or scarring suggestive of previous herpes zoster.
Lymph nodes	▪ Start with the posterior cervical nodes. ▪ Persistent generalized lymphadenopathy (PGL) typically presents as multiple bilateral, soft, non-tender, mobile cervical nodes. Similar nodes may be found in the armpits and groins. ▪ Tuberculous lymph nodes typically present as unilateral, painful, hard, enlarging nodes with constitutional symptoms such as fever, night sweats and weight loss.
Mouth	▪ Look for signs suggestive of HIV infection including white plaques on the tongue, cheeks and roof of the mouth (oral candidiasis), white striped lesions on the side of the tongue (OHL) and cracks at the corners of the mouth (angular cheilitis).
Chest	▪ The most common problems are PCP and TB. ▪ Signs and symptoms are cough, shortness of breath, haemoptysis, weigh loss, fever, congestion or consolidation. ▪ Do a chest X-ray if possible.
Abdomen	▪ Look for hepatosplenomegaly, masses and local tenderness. ▪ Jaundice may indicate viral hepatitis. ▪ Difficulty in swallowing is commonly caused by oesophageal candidiasis.

Table 2 *(contd)*: Physical examination checklist	
Anogenital	▪ Look for herpes simplex and other genital sores/lesions, vaginal or penile discharge. ▪ Perform a Pap smear if possible.
Neurological examination	▪ Focus on the visual fields and look for signs of neuropathy (bilateral, peripheral or localized mononeuropathies). ▪ Assess for focal neurological deficit.

MAC *Mycobacterium avium* complex IDU injecting drug user PPE pruritic papular eruptions PGL persistent generalized lymphadenopathy OHL oral hairy leukoplakia PCP *Pneumocystis jiroveci* pneumonia Pap Papanicolaou TB tuberculosis

2.2 Revised WHO clinical staging of HIV-related disease in adults and adolescents aged 15 years or more

The revised WHO clinical classification of HIV-associated disease is designed to be used in patients with **confirmed HIV infection (Tables 3 and 4)**. Along with measurement of the CD4 count, where available, the staging system is used to guide decisions on when to start OI prophylaxis and when to start and switch ART.

Table 3: Revised WHO clinical staging of HIV-related disease in adults and adolescents aged 15 years or more
Clinical stage 1 (Asymptomatic)
Asymptomatic PGL
Clinical stage 2 (Mild disease)
Unexplained moderate weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulcerations Pruritic papular erruptions (PPE) Seborrhoeic dermatitis Fungal nail infections

Table 3 *(contd)*: Revised WHO clinical staging of HIV-related disease in adults and adolescents aged 15 years or more
Clinical stage 3 (Moderate disease)
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than one month Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia (OHL) Pulmonary TB Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropenia (<0.5 x 10^9/litre) or chronic thrombocytopenia (<50 x 10^9/litre)
Clinical stage 4 (Severe disease)
HIV wasting syndrome *Pneumocystis jiroveci* pneumonia (PCP) Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal, of more than one month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of the trachea, bronchi or lungs) Extrapulmonary TB (EPTB) Kaposi sarcoma Cytomegalovirus (CMV) infection (retinitis or infection of other organs) Toxoplasmosis of the central nervous system (CNS) HIV encephalopathy Extrapulmonary cryptococcosis including meningitis Disseminated non-tuberculous mycobacterial infection Progressive multifocal leukoencephalopathy (PML) Penicilliosis Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis, coccidiodomycosis) Recurrent septicaemia (including due to non-typhoidal *Salmonella*) Lymphoma (cerebral or B-cell, non-Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Table 4: Signs and symptoms suggestive of HIV infection	
General conditions	
▪ Weight loss of >10% of baseline body weight ▪ Fever (continuous or intermittent, oral temperature >37.5ºC) for more than one month ▪ Diarrhoea (continuous or intermittent) for more than one month ▪ Generalized lymphadenopathy	
Skin conditions	
PPE* and diffuse dryness of skin* are strongly suggestive of HIV infection. Some conditions, such as genital warts, folliculitis and psoriasis, are common in HIV-infected patients but are not necessarily HIV related (*see* Annex 8).	
Infections	
Fungal infections	▪ oral candidiasis (thrush)* ▪ seborrhoeic dermatitis* ▪ vaginal candidiasis (recurrent)
Viral infections	▪ herpes zoster (recurrent or involving more than one dermatome)* ▪ genital herpes (recurrent) ▪ molluscum contagiosum ▪ condyloma (genital warts)
Respiratory conditions	▪ cough for more than one month ▪ dyspnoea ▪ TB ▪ recurrent pneumonia ▪ chronic or recurrent sinusutis
Neurological manifestations	▪ worsening headache (continuous and unexplained) ▪ febrile convulsion ▪ declining cognitive function

* These conditions are strongly suggestive of HIV infection.

2.3 Immunological assessment

A CD4 count is the most reliable way of assessing the patient's immune status. The CD4 cell count complements clinical assessment. It can detect immune deficiency requiring intervention with OI prophylaxis and ART before the patient's disease progresses.

CD4 counts vary from day to day and with intercurrent illness. Splenectomy results in falsely raised CD4 counts. In this case, the CD4% should be used to guide decision-making. If possible, CD4 testing should be repeated before a major management decision is taken, such as commencing ART. Better access to CD4 testing is promoted by WHO but the absence of CD4 testing is not a barrier to initiating ART. CD4 counts are also used to monitor response to ART.

2.4 Total lymphocyte count

In the absence of a CD4 cell count, a total lymphocyte count (TLC) may be used as a surrogate marker of immune function. It is not employed in many ART programmes and is useful in only one clinical situation (patients with WHO stage 2 disease when facilities for measuring the CD4 count are not available). Decision-making is otherwise simple. ART is recommended for all patients with WHO stages 3 and 4 disease, and not recommended for asymptomatic patients (stage 1). WHO recommends that TLC be phased out. It is not useful and is not recommended for monitoring the response to ART or for deciding whether ART is failing. There is more evidence for its utility in deciding when to initiate ART in children and has been included in the current WHO paediatric ART guidelines.

3 Assessment and Management after the Diagnosis of HIV Infection is Confirmed

Table 5: Determining eligibility for ART

Visit 1

- Medical history
- Symptom checklist
- Physical and laboratory examination (*see* chapters 5–8)
- CXR if chest symptoms present
- Behavioural/psychosocial assessment
  - Education level, employment history, financial resources
  - Social support, family/household structure
  - Disclosure status, readiness to disclose
  - Understanding of HIV/AIDS, transmission, risk reduction, treatment options
- Nutritional assessment
- Family/household assessment to determine if there are other HIV-infected family members who may need care
- Condom use recommended at every visit

Eligible for ART

Visit 2 (in less than 2 weeks)

- History (new problems)
- Symptom checklist
- Examination
- Co-trimoxazole prophylaxis (*see* chapter 4)
- Psychosocial support
- Adherence counselling; more than one session may be needed prior to commencing ART (*see* chapter 7)

Visit 3 (2 weeks after previous visit)

- Commence ART if stable on co-trimoxazole and patient is ready (*see* chapter 6)
- Commence lead-in dose of nevirapine (NVP) 200 mg once daily (*see* chapter 6.3)
- Clinical evaluation

Not eligible now for ART

Visit 2 (in less than 2 weeks)

- History (new problems)
- Symptom checklist
- Examination
- Psychosocial support

Visit 4 (2 weeks after previous visit)

- History (new problems)
- Clinical evaluation
- Haemoglobin if on zidovudine (AZT)
- If on NVP, any side-effects (rash, fever, signs of liver toxicity)
- Dose escalation of NVP to 200 mg 2 times per day (*see* chapter 6.3)
- Adherence assessment/support (*see* chapter 7)

Visit 5 (2 weeks after previous visit)

- History (new problems)
- Symptom checklist
- Examination
- Adherence assessment/support (*see* chapter 7)

Follow up

- History (new problems)
- Symptom checklist
- Examination
- Adherence assessment/support
- Psychosocial support
- Visits every 1–3 months and more often as needed
- CD4 count every 3–6 months if available
- Assess condom use

- History (new problems)
- Symptom checklist
- Examination
- Psychosocial support

4 Prophylaxis for Opportunistic Infections

4.1 Co-trimoxazole prophylaxis

Randomized clinical trials, studies using historical controls and observational cohort studies have demonstrated the effectiveness of co-trimoxazole prophylaxis in reducing mortality and morbidity across varying levels of background resistance to co-trimoxazole and prevalence of malaria.

It is therefore recommended that all HIV-infected adolescents and adults who fulfil the clinical and immunological criteria for commencing ART should also receive co-trimoxazole prophylaxis to prevent the first episode of PCP and toxoplasmosis (Table 6).

Table 6: Summary of recommendations for co-trimoxazole prophylaxis, 2006[4]

When to commence primary co-trimoxazole prophylaxis	**CD4 count not available**	**CD4 count available**
	WHO clinical stages 2, 3, 4 **(including all patients with TB disease)**	Any WHO clinical stage and **CD4 count <200 cells/mm³** **OR** WHO clinical stage 3 or 4 irrespective of CD4 level*
Secondary co-trimoxazole prophylaxis	Secondary prophylaxis for the prevention of relapse is recommended for all patients who have completed successful treatment for *Pneumocystis jiroveci* pneumonia (PCP).	
Timing the initiation of co-trimoxazole in relation to initiating ART	Start co-trimoxazole prophylaxis first. Start ART two weeks later if the individual tolerates co-trimoxazole and has no symptoms suggestive of allergy (rash, hepatotoxicity).§	
Dosages of co-trimoxazole in adults and adolescents	One double-strength tablet or two single-strength tablets once daily. Total daily dose is 960 mg (800 mg sulfamethoxazole [SMZ] + 160 mg trimethoprim [TMP]).	

Table 6 *(contd)*: Summary of recommendations for co-trimoxazole prophylaxis, 2006[4]	
Co-trimoxazole in pregnant/lactating women	Women who fulfil the criteria for co-trimoxazole prophylaxis should continue on it throughout their pregnancy.[5] If a woman requires co-trimoxazole prophylaxis during pregnancy, it should be started regardless of the stage of pregnancy.[6] Breastfeeding women should continue to receive co-trimoxazole prophylaxis.
Patients allergic to sulfa-based medications	Dapsone 100 mg per day can be given. Co-trimoxazole desensitization may be attempted but not in patients with a previous history of severe reaction to co-trimoxazole or other sulfa-containing drugs.
Monitoring	No specific laboratory monitoring is required for patients receiving co-trimoxazole.
Universal option	Co-trimoxazole prophylaxis may be considered for all patients with active TB and HIV-infected persons from certain high-risk populations such as IDUs and SWs who typically present late with advanced disease and are less likely to have access to facilities for CD4 counts.

* **Option 2:** Any WHO clinical stage and **CD4 count <350 cells/mm³** where the aim of co-trimoxazole prophylaxis is reduction in the morbidity and mortality associated with bacterial infections and malaria, in addition to the prevention of PCP and toxoplasmosis.

§ This will help in differentiating between the similar side-effects caused by co-trimoxazole and ART (especially if starting an NVP-containing regimen).

4.2 Co-trimoxazole desensitization

Co-trimoxazole desensitization has been shown to be successful and safe in approximately 70% of patients with previous mild-to-moderate hypersensitivity.[7,8] Desensitization should not be attempted in individuals with a previous history of severe reaction to co-trimoxazole or other sulfonamides **(Table 7)**. If a reaction occurs, the desensitization regimen should be stopped. Once the patient recovers fully, dapsone 100 mg per day may be tried. Some patients may be allergic to both co-trimoxazole and dapsone. There are no other drug options for prophylaxis in resource-limited settings.

Table 7: Protocol for co-trimoxazole desensitization	
Step	**Dose**
Day 1	80 mg SMX + 16 mg TMP (2 ml oral suspension)
Day 2	160 mg SMX + 32 mg TMP (4 ml oral suspension)
Day 3	240 mg SMX + 48 mg TMP (6 ml oral suspension)
Day 4	320 mg SMX + 64 mg TMP (8 ml oral suspension)
Day 5	One single-strength SMX–TMP tablet (400 mg SMX + 80 mg TMP)
Day 6	Two single-strength SMX–TMP tablets or one double-strength tablet (800 mg SMX + 160 mg TMP)

Source: *Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings: recommendations for a public health approach*. Geneva, World Health Organization, 2006.

Note: Co-trimoxazole oral suspension contains 200 mg SMX + 40 mg TMP per 5 ml.

4.3 Starting and stopping prophylaxis for opportunistic infections

The purpose of prescribing preventive therapy for OIs is to prevent the first-ever episode (primary prophylaxis) or to prevent recurrence (secondary prophylaxis) of an OI (**Table 8**).

Table 8: Criteria for starting and stopping OI prophylaxis				
Opportunistic infection	**Primary prophylaxis indicated when CD4 is [a]**	**Drug of choice**	**Discontinue primary prophylaxis when CD4 is [b]**	**Discontinue secondary prophylaxis when CD4 is [b]**
PCP	<200 cells/mm^3 [a]	TMP–SMX 1 DS tablet once daily	>200 cells/mm^3	>200 cells/mm^3
Toxoplasmosis	<200 cells/mm^3	TMP–SMX 1 DS tablet once daily	>200 cells/mm^3	>200 cells/mm^3
Cryptococcus meningitis	Not indicated in most settings (*see* chapter 4.4)	Fluconazole	>100 cells/mm^3	>100 cells/mm^3
Oral and oesophageal candidiasis	Not indicated	Not applicable	Not applicable	Not applicable

PCP *Pneumocystis jiroveci* pneumonia TMP–SMX trimethoprim–sulfamethoxazole
DS double strength

Note

[a] Co-trimoxazole prophylaxis may be initiated in two different contexts. "Classic" prophylaxis, where the target is the prevention of PCP and toxoplasmosis, is recommended for all HIV-infected adults with WHO stages 2–3 and 4 HIV disease or with a CD4 count <200 cells/mm^3. If the targets of prophylaxis are reduction in the morbidity and mortality associated with bacterial infections and malaria, in addition to the prevention of PCP and toxoplasmosis, co-trimoxazole is recommended for HIV-infected adults with a CD4 count <350 cells/mm^3 or with the same clinical criteria (WHO stages 2–3 or 4).

[b] Discontinue when two consecutive CD4 counts are more than that listed in the table, the patient is on ART for more than 6 months and adherence is good. Reintroduce prophylaxis if the CD4 count falls below the starting level.

4.4 Prophylaxis for cryptococcosis

Primary prophylaxis for cryptococcosis should be considered in countries where cryptococcal meningitis is a common OI and fluconazole is available and affordable. Secondary prophylaxis for prevention of relapse after treatment should be considered for all patients with a previous history of episodes of cryptococcal disease **(Table 9)**.

Table 9: Summary of recommendations for prophylaxis of cryptococcal infection

	When to start	What to start	When to stop
Primary prophylaxis	CD4 count <100 cells/mm^3 **OR** WHO stage IV	Fluconazole 400 mg once weekly	Sustained increase of CD4 count >100 cells/mm^3 after at least 6 months of ART If CD4 count not done continue lifelong secondary prophylaxis
Secondary prophylaxis	After completion of initial treatment for cryptococcosis	Fluconazole 200 mg once daily	

5 When to Start Antiretroviral Therapy in Adults and Adolescents

5.1 CD4 count not available

In the absence of facilities for measuring the CD4 count, all patients with WHO stages 3 and 4 disease should start ART. Those with WHO stages 1 and 2 disease should be monitored carefully, with a minimum of three-monthly clinical reviews, and at any time if new symptoms develop **(Table 10)**.

Table 10: Starting antiretroviral therapy based on clinical staging

WHO clinical stage	Recommendation
1	Do not treat
2*	Do not treat
3	**Treat**
4	**Treat**

* Consider starting treatment in patients with WHO stage 2 disease and TLC <1200 cells/mm^3

5.2 CD4 count available

The optimum time to commence ART is prior to patients becoming unwell or presenting with their first OI. Disease progression is greater in patients who commence ART with a CD4 cell count <200 cells/mm^3 compared with those who start therapy at counts above this level.[9,10,11,12,13,14] If facilities for CD4 count measurement are available, ART should be started before the CD4 count drops below 200 cells/mm^3. The optimum time to initiate ART in patients with a CD4 cell count of 200–350 cells/mm^3 remains unknown, and patients with CD4 counts in this range require regular clinical and immunological evaluation.

Initiation of ART is recommended for all patients with pulmonary TB or severe bacterial infections and CD4 counts <350 cells/mm^3. Initiation of ART is also recommended for all pregnant women with any stage 3 disease and a CD4 count <350 cells/mm^3 **(Table 11)**.

Table 11: Starting antiretroviral therapy by CD4 count	
WHO clinical staging	**CD4 count available**
1	Treat if CD4 count <200 cells/mm^3
2	
3	**General principles** ▪ Consider treatment if CD4 count <350 cells/mm^3 but initiate before CD4 count drops below 200 cells/mm^3 **In the case of pregnancy or TB** ▪ Start ART in all HIV-infected pregnant women with WHO stage 3 disease and **CD4 count <350 cells/mm^3** ▪ Start ART in all HIV-infected patients with **CD4 count <350 cells/mm^3** and pulmonary TB (WHO stage 3) or severe bacterial disease
4	Treat irrespective of CD4 count (extrapulmonary TB is WHO stage 4 disease)

The decision to initiate ART in adults and adolescents is based on clinical and immunological assessment. In many resource-limited settings, clinical staging alone will be available to guide the decision of when to start ART. Measuring viral load (HIV RNA) is **not** recommended to guide decision on when to start ART.

The process of initiating ART involves assessment of patient readiness to commence therapy and an understanding of its implications (lifelong therapy, adherence, toxicities). Access to nutritional and psychosocial support, and family and peer support groups is important when making decisions about initiating ART.

5.3 Commencing ART in the presence of active opportunistic infections

Do not start ART in the presence of an active OI. In general, the OI should be treated or stabilized before commencing ART (*see* **chapters 11 and 17**). An exception is MAC, in which commencing ART may be the preferred option, especially in situations where specific therapy for MAC is not available. Other conditions that may regress after ART is started include candidiasis and cryptosporidiosis.

The OIs and HIV-related illnesses that need treatment or stabilization before ART is started are given in **Table 12**.

5.4 Managing opportunistic infections before starting antiretroviral therapy

Table 12: Managing opportunistic infections before starting antiretroviral therapy

Clinical situation	Action
Any undiagnosed active infection in a patient who has fever and is unwell	Diagnose and treat first; start ART when stable.
TB	Treat TB first; start ART as recommended in the section on TB (*see* section 11 and Annex 6).
PCP	Treat PCP first; start ART when PCP treatment has been completed.
Invasive fungal diseases: oesophageal candidiasis, cryptococcal meningitis, penicilliosis, histoplasmosis	Treat oesophageal candidiasis first; start ART as soon as the patient can swallow comfortably. Treat cryptococcal meningitis, penicilliosis, histoplasmosis first; start ART when treatment has been completed.
Bacterial pneumonia	Treat pneumonia first; start ART when treatment has been completed.
Malaria	Treat malaria first; start ART when treatment has been completed.
Drug reaction	Do not start ART during an acute reaction.
Significant acute diarrhoea which may reduce absorption of ART	Diagnose and treat acute diarrhoea first; start ART when diarrhoea has been stabilized or controlled.
Non-severe anaemia (Hb >8 g/dl)	Start ART if no other cause for anaemia is found (HIV is often the cause of the anaemia); avoid zidovudine (AZT).
Skin conditions such as PPE and seborrhoeic dermatitis, psoriasis, HIV-related exfoliative dermatitis	Start ART (ART may resolve these problems).
Suspected MAC, cryptosporidiosis and microsporidiosis	Start ART (ART may resolve these problems).
CMV infection	Treat if drugs available. If not available, start ART.

6 Recommended First-line Antiretroviral Regimens

6.1 Recommended first-line ARV regimens

Box 2: Principles for selecting the antiretroviral drug

1. Choose lamivudine (3TC), **plus**
2. Choose one nucleoside reverse transcriptase inhibitor (NRTI). Zidovudine (AZT) or tenofovir disoproxil fumarate (TDF) are preferred.

Table 13: Selecting antiretroviral drugs for first-line regimens

Recommendation	Regimen	Comments
Preferred first-line regimen	AZT + 3TC + NVP	AZT may cause anaemia and WHO recommends haemoglobin monitoring, but AZT is preferred to stavudine (d4T) because of d4T toxicity (lipoatrophy, lactic acidosis, peripheral neuropathy). Patients, particularly women with CD4+ cell counts >250 cells/mm^3 at initiation of NVP therapy, are at higher risk for the development of symptomatic hepatic events, often associated with rash. The risk of symptomatic hepatic events regardless of severity is greatest during the first 6 weeks of therapy.[15]
Alternative first-line regimens	AZT + 3TC + EFV	Efavirenz (EFV) is substituted for NVP if there is intolerance and if the patient is receiving rifampicin. EFV should not be used in patients with raised alanine aminotransferase (ALT) levels of grade 4 or higher. Pregnancy should be avoided in women treated with EFV. Women with childbearing potential should undergo pregnancy testing before initiation of therapy with EFV.[15]
	d4T +3TC + (NVP or EFV)	d4T may continue to be used by many programmes because it is available and does not require laboratory monitoring.

Table 13 *(contd)*: Selecting antiretroviral drugs for first-line regimens		
Other options	TDF + 3TC + (NVP or EFV)	Availability of tenofovir disoproxil fumarate (TDF) is limited in most countries. The current cost is high.
	ABC + 3TC + (NVP or EFV)	Abacavir (ABC) is registered in many countries and currently the cost is high.
	FTC can be substituted for 3TC in any first-line regimen	Emtricitabine (FTC) is not available in many countries but this may change. A co-formulation of FTC/TDF is available.

6.2 Choice of nucleoside reverse transcriptase inhibitors (NRTIs)

Table 14: Choice of nucleoside reverse transcriptase inhibitors (NRTIs)		
NRTI	**Advantages**	**Disadvantages**
Lamivudine (3TC)	Good safety profile, non-teratogenic Once-daily regimen Effective against hepatitis B Widely available, including in fixed-dose combinations	Low genetic barrier to resistance
Emtricitabine (FTC)	FTC is an alternative to 3TC Good safety profile Same efficacy against HIV and hepatitis B as 3TC and the same resistance profile[16] Available as a fixed-dose combination with TDF	FTC is not yet on the WHO list of essential medications
Tenofovir disoproxil fumarate (TDF)	Good efficacy and safety profile Once-daily regimen Metabolic complications such as lactic acidosis and lipoatrophy are less common than with d4T	Reports of renal dysfunction[17,18] Safety in pregnancy not established. Adverse effects on fetal growth and bone density reported Limited availability
Zidovudine (AZT)	Generally well tolerated Widely available, including as fixed-dose combinations Metabolic complications less common than with d4T	Initial headache and nausea Severe anaemia and neutropenia Haemoglobin monitoring recommended

Table 14 *(contd)*: Choice of nucleoside reverse transcriptase inhibitors (NRTIs)		
Abacavir (ABC)	Good efficacy profile and once-daily regimen Causes the least lipodystrophy and lactic acidosis compared with other NRTIs	Severe hypersensitivity reaction in 2–5% of adult patients Currently the cost is high
Stavudine (d4T)	Good efficacy profile and cheap No or limited laboratory monitoring needed Widely available as fixed-dose combinations	Consistently associated most often with lactic acidosis, lipoatrophy and peripheral neuropathy

6.3 Starting and stopping non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Table 15: Starting nevirapine (NVP)		
Lead-in NVP dose for the first 2 weeks*	**Morning**	**Evening**
	Fixed-dose combination AZT or d4T + 3TC + NVP	AZT or d4T + 3TC **OR** Fixed-dose combination AZT or d4T +3TC
Escalate to full NVP dose after 2 weeks	Fixed-dose combination AZT or d4T + 3TC + NVP	Fixed-dose combination AZT or d4T + 3TC + NVP

* Start NVP 200 mg once daily for the first 14 days. If there is no rash and there are no signs of hepatic toxicity, increase the dose to 200 mg twice daily. Starting treatment with a reduced dose is necessary because during the first two weeks of treatment NVP induces its own metabolism. The lead-in dose also decreases the risk of rash and early NVP-induced hepatitis.

If NVP is restarted after more than 14 days of treatment interruption, lead-in dosing (200 mg once daily for 2 weeks, then 200 mg twice daily) is again necessary.

Box 3: Stopping either nevirapine (NVP) or efavirenz (EFV)

- Stop NVP or EFV.
- Continue NRTI backbone (2 drugs only) for 7 days then stop all drugs.
- This is done to cover the long half-life of the NNRTI and reduce the risk of NNRTI resistance.

6.4 Triple NRTI-based regimens

Triple NRTI regimens are inferior to NRTI/NNRTI regimens.[19,20,21,22,] AZT+3TC+ABC may be considered in patients with intolerance or resistance to NNRTIs when protease inhibitor (PI)-based regimens are unavailable, to preserve second-line options for the treatment of HIV-2 infection and for the treatment of HIV/TB co-infected patients receiving rifampicin.

6.5 Use of protease inhibitors in initial therapy

PIs are not recommended in first-line regimens because the use of PIs in an initial treatment regimen essentially rules out second-line options in the setting of limited drug availability. PIs may be considered in first-line regimens (with a standard dual NRTI backbone) for the treatment of HIV-2 infection, in women with a CD4 count >250 cells/mm^3 who require ART and who cannot take EFV, or in patients with NNRTI intolerance.

6.6 ARV combinations that are not recommended

Table 16: Antiretroviral (ARV) combinations that are not recommended

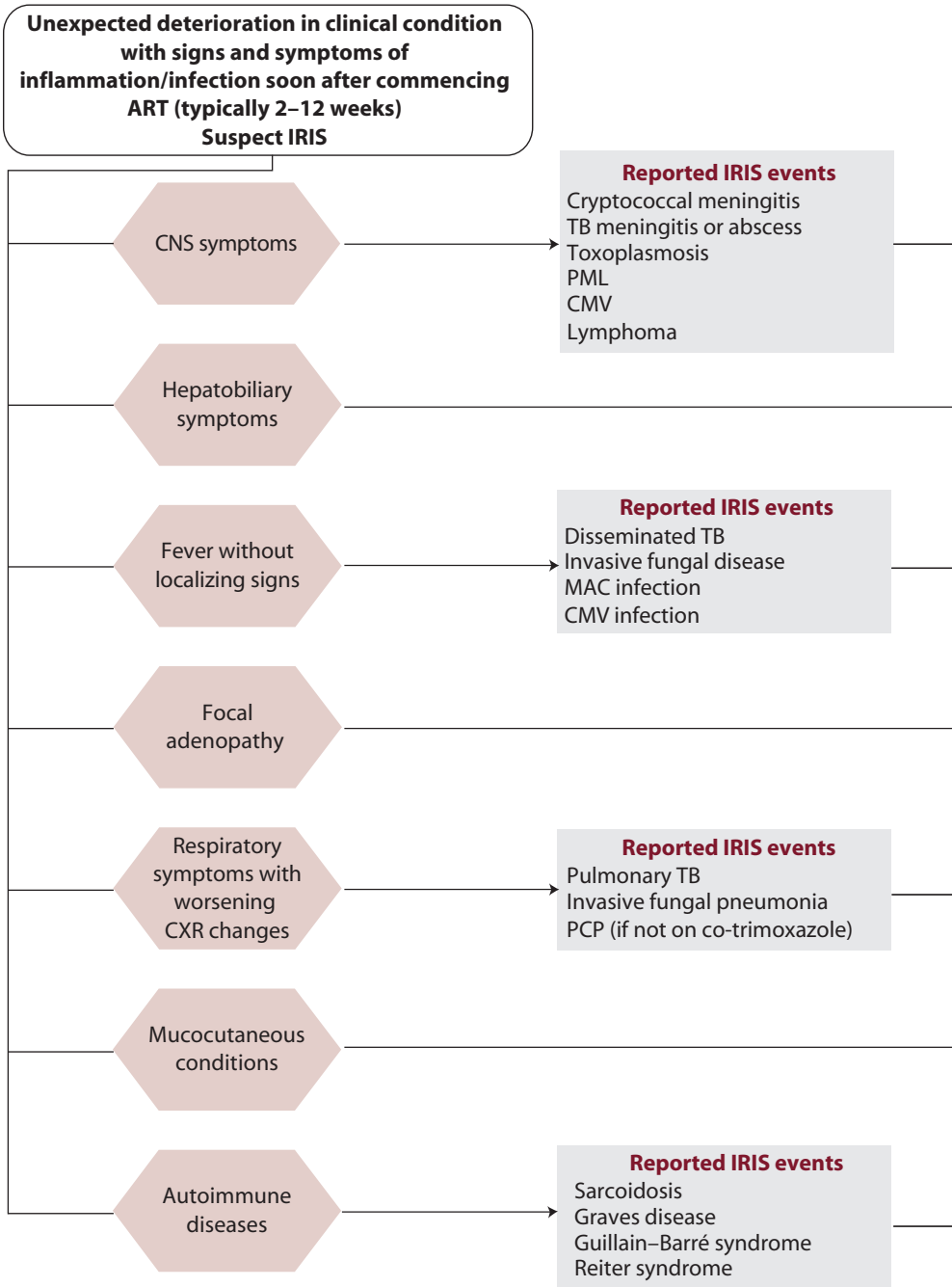
ARV combinations	Reason not to use
Monotherapy or dual therapy to treat chronic HIV infection	Rapid development of resistance
d4T + AZT	Antagonism (reduced levels of both drugs)
d4T + didanosine (ddI)	Overlapping toxicities (pancreatitis, hepatitis, lipoatrophy) Deaths reported in pregnant women
3TC + FTC	Interchangeable, but should not be used together
TDF + 3TC + ABC **or** TDF + 3TC + ddI	These ARV combinations will increase *K65R* mutation and are associated with a high incidence of early virological failure
TDF + ddI + any NNRTI	High incidence of early virological failure

6.7 Immune reconstitution inflammatory syndrome (IRIS)

Table 17: Immune reconstitution inflammatory syndrome (IRIS)	
Definition	A collection of signs and symptoms resulting from the ability to mount an immune response associated with immune recovery while on ART. It is a paradoxical reaction against a foreign antigen (live or dead) in patients who have started ART and have undergone a reconstitution of their immune responses against this antigen. *M. tuberculosis* accounts for approximately one-third of all IRIS events.[23]
Frequency	10% of all patients initiating ART Up to 25% of patients initiating ART with a CD4 cell count <50 cells/mm^3 [24,25]
Timing	Typically within 2–12 weeks of initiation of ART but may present later
Signs and symptoms	Unexpected deterioration in clinical status soon after commencing ART Unmasking of subclinical infections such as TB, which present as new active disease Worsening of co-existing infections such as a flare-up of hepatitis B or C infection
Most common IRIS events	60% of IRIS events are related to infection with *M. tuberculosis*, MAC or *Cryptococcus neoformans* [26]
Management	IRIS may be mild and resolve without treatment. Continue ART if the patient can tolerate it. Treat unmasked active OI, such as TB. This may mean a temporary interruption of ART in patients with severe IRIS until the patient is stable on TB drugs, then reintroduction of ART. If the patient is receiving rifampicin and is on NVP, switch to EFV* if available. ABC is a second alternative. Switching back to the original regimen can be considered once the rifampicin-containing regimen is completed. When switching back from EFV to NVP, no lead-in dose of NVP is required. Switching back should be done with caution if the patient's CD4 count has increased since the last time NVP was taken. If EFV or ABC is not available or contraindicated, continue NVP-based ART with close clinical monitoring and symptom-directed liver function tests. Corticosteroid treatment to suppress exaggerated inflammatory response may be indicated; for example, an acute hepatic flare where coinfection with viral hepatitis is known or suspected. If the patient is taking NVP, clinical hepatitis and/or rising hepatic enzymes in association with rash and fever is more likely to be due to NVP than IRIS and switching to EFV is recommended. Prednisone (or prednisolone) 0.5 mg/kg/day for 5–10 days is suggested in moderate to severe cases of IRIS.[27,28]

* Pregnancy should be avoided in women under treatment with EFV. Women with childbearing potential should undergo pregnancy testing before initiation of therapy with EFV.[15]

Figure 2. Management of immune reconstitution inflammatory syndrome



Reported IRIS events
Flare-up of hepatitis B or C
Visceral leishmaniasis
TB abscess

Reported IRIS events
Extrapulmonary TB
MAC infection
Kaposi sarcoma
Histoplasmosis

Reported IRIS events
Herpes zoster and herpes simplex
HPV infection (warts)
Molluscum contagiosum
Kaposi sarcoma
Psoriasis
Eczema, folliculitis, PPE
Leprosy
Mucocutaneous leishmaniasis

Principles of management

1. Continue ART if possible.
2. Discontinue ART and prioritize treatment of the pathogen in patients who are severely ill.
3. Treat the specific pathogen in order to decrease the antigen load.
4. Consider corticosteroids in moderate-to-severe cases of IRIS (prednisone or prednisolone) at 0.5 mg/kg/day orally or IV for 5–10 days or longer, depending on the severity of the inflammation.
5. Aspirate and drain lymph nodes and abscesses (may need to be repeated several times).
6. Perform emergency surgical decompression in cases of tracheal or intestinal obstruction.

7 Adherence

The most common reason for failure of ART is poor adherence. Adherence should be routinely assessed and reinforced at every clinic visit.

A high degree of adherence to ARV drugs is necessary for optimal virological suppression. Studies indicate that 90–95% of the doses should be taken for optimal suppression; lesser degrees of adherence are more often associated with virological failure.[29] Maintaining this level of adherence is difficult. Imperfect adherence is common and a survey indicated that one-third of patients missed doses within 3 days of the survey.[30]

Factors associated with poor adherence include a poor patient–clinician relationship, high pill burden, forgetfulness, mental depression, lack of patient education, inability of patients to identify their medications, drug toxicity and being too ill.[31]

Prior to starting therapy, the patient's willingness and understanding to take such therapy should be clearly established. A treatment plan should be made which the patient understands and can commit to. The importance of taking medicines on a regular basis and the implications of non-compliance should be explained to the patient. Written instructions should be given to literate patients to help them understand the benefits of the prescribed drugs. Pill pictures and cartoons are useful tools to show patients visually how to take their ART correctly. Possible side-effects should be explained in advance. Educating the patient's family and friends may be helpful. A patient suffering from active substance abuse or mental illness may benefit more from ART if these problems are taken care of prior to starting ART.

The process of offering information, counselling and adherence support must be carried out by staff (counsellors and/or PLHA) who understand the problems in the lives of PLHA. There are three steps in this process. In some cases, all three steps may be carried out during one session.

Step 1: Giving information

Clients are given basic information that enables them to understand the need for a high level of commitment to treatment and adherence. Information can be provided to a group of PLHA if the facilitator has some understanding of group dynamics and is able to stimulate group discussion.

Step 2: Counselling – in one or more individual sessions (Box 4)

Help the client explore his/her feelings. Many clients will be preoccupied with problems related to family, job, relationships, etc. and cannot focus on strict adherence until they have released negative feelings about these problems.

Many have no private place to store their medicines and are not able to take them in secret. Not wanting others to know their HIV status is by far the commonest reason that providers come across for poor adherence. The client needs to be realistic about who needs to know their HIV status and how to tell them.

Step 3: Solving practical problems and creating a treatment plan

- Where will the ARV drugs be stored?
- At what time will they be taken?
- Who will remind the client to take the medication if they forget?
- What will the client do if their normal routine is interrupted?

A time should be arranged to meet or telephone the client within a few days of starting ART to discuss any problems.

A trusting and caring relationship between the patient and health-care provider (HCP) is essential. Regular appointments and follow-up visits help in the continued care of the patient. Provider attitudes that are supportive and non-judgemental will encourage patients to be honest about their adherence. The health-care team should have up-to-date knowledge of ART and adherence, and should undertake training if necessary. New medical problems may influence adherence. Temporary discontinuation of all medicines may be less harmful than uncertain adherence.

Box 4: Elements of counselling for treatment adherence

- Establish a trusting relationship with the patient.
- Provide necessary information and advice.
- Encourage peer participation and help to identify persons for treatment support.
- Develop an individual treatment plan fitting ART into the patient's lifestyle/ daily events and identify treatment reminders.
- Assess the readiness and commitment of patients for ART. Readiness to commence ART may be assessed by:
  – past ability to attend regular clinic visits and not miss appointments
  – past ability to take OI prophylaxis such as co-trimoxazole
  – past ability to complete a full course of TB therapy
  – adequate understanding.
- Ensure strict adherence to treatment. This means that missing >3 doses per month is associated with an increased risk of drug resistance and failure.
- If doses are repeatedly missed or taken late, reinforce adherence counselling. Enlist community outreach teams and peer support groups of PLHA as appropriate.
- Emphasize that treatment has to be continued for life.
- Explain that the timing of drug intake is critical (e.g. drugs taken twice daily must be taken every 12 hours + 1 hour).
- Tell the patient that missed doses can be taken up to 6 hours later in a twice-daily regimen. If >6 hours elapse, the dose should be skipped and the next usual dose taken.
- Explain how the drugs are to be taken (some drugs have to be taken with food, some on an empty stomach, and some require an increased intake of water).
- Explain the side-effects of the drugs and ensure that the patient understandes these before commencing ART.
- Emphasize that people on ART need to continue to use condoms regularly and use safe injecting equipment.
- Inform the patient that other medications, including herbal products, may interact with ART. Patients need careful counselling about which medications are allowed with their ART and which are not.
- Impress on the patient that regular clinic attendance for monitoring of efficacy, side-effects and adherence is essential.
- Make a call or a home visit if a patient cannot keep the clinic appointment.

The treatment regimen should be simplified by reducing the number of pills and frequency of therapy (such as once- or twice-daily dosing), and minimizing side-effects. Simple regimens improve adherence. Adherence may be measured by the patient's self-report, pill count and the report of the primary care provider. During therapy, people taking ART need repeated adherence counselling (**Box 5**).

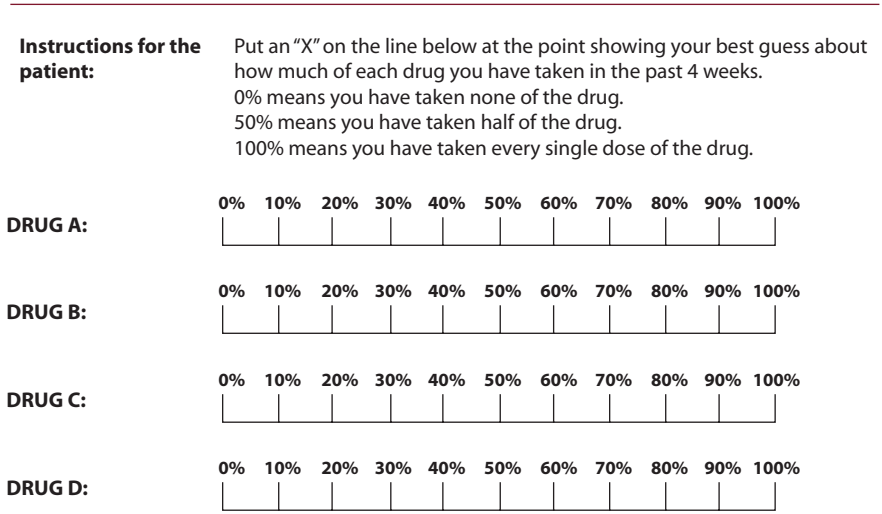
Box 5: Checklist to assess treatment adherence

Ask for

- Number of doses missed in the past 3 days
- Number of doses missed since the last visit
- Whether dose taken at correct time (if no, ask for delay in hours/days)
- If correct dose taken
- Why there was an interruption or modification/failure to take the doses

Another method could include estimating the proportion of doses taken using the visual analogue scale (Figure 3).

Figure 3. Visual analogue scale – Adherence self-assessment instrument



8 Clinical and Laboratory Monitoring Prior to Commencing and on First-line ART

Table 18: Recommended clinical and laboratory monitoring prior to commencing and on first-line ART

Evaluation	Before or at start of ART	Week 2	Week 4	Week 8	Week 12	Week 24	Every 6 months	As needed (symptom directed)
Clinical								
Clinical evaluation	✓	✓	✓	✓	✓	✓	✓	
Weight	✓	✓	✓	✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	
Check ART adherence		✓	✓	✓	✓	✓	✓	
Laboratory								
HIV antibody test [a]	✓							
CD4 count	✓						✓	✓
Haemoglobin [b]	✓		✓	✓	✓			✓
Pregnancy test [c]	✓							
VDRL/RPR	✓							
Serum chemistry								✓
Serum lactate								✓
HIV RNA (viral load) [d]								✓

Notes

[a] A historically documented HIV antibody test is sufficient to commence ART. In the absence of a documented, confirmed HIV antibody test, testing prior to commencing ART is recommended.

[b] For patients receiving AZT: Measurement of haemoglobin is recommended prior to commencing AZT and at weeks 4, 8 and 12, and as required thereafter.

[c] Pregnancy testing for women initiating a first-line regimen containing EFV: Do not commence EFV if the pregnancy test is positive and the woman is in the first trimester.

Pregnancy testing if pregnancy is suspected in a woman who is receiving an EFV-based regimen: Change to a non-EFV based regimen if the pregnancy test is positive and the woman is in the first trimester.

[d] Measurement of viral load (HIV RNA) is currently not recommended for decision-making on initiation or regular monitoring of ART in resource-limited settings. It may be considered to make an early diagnosis of treatment failure or to assess discordant clinical findings and CD4 count results in patients suspected of failing ART.

9 Antiretroviral Drug Toxicities

9.1 Grading of antiretroviral toxicity

Management of ART toxicity is based on the clinician and laboratory toxicity grading scales given in Annex 7.

- **Grade1:** Mild reactions: No change in therapy is required.
- **Grade 2:** Moderate reactions: Consider continuation of ART as long as feasible. If there is no improvement with symptomatic therapy, consider single drug substitution.
- **Grade 3:** Severe reactions: Substitute another drug for the offending one without stopping ART.
- **Grade 4:** Severe life-threatening reactions: Immediately discontinue ART and manage the medical event (symptomatic and supportive therapy) and reintroduce ART using a modified regimen by substituting the offending drug with another one when the patient is stabilized.

9.2 What toxicities to expect after commencing first-line ART

Table 19: Side-effects and toxicities of antiretroviral drugs and when they occur

Time	Side-effects and toxicities	Common causes
Short term (the first few weeks)	GI toxicities including nausea and vomiting, diarrhoea	AZT, TDF, PIs
	Rash Most rashes occur within the first 2–3 weeks	NVP, EFV, ABC, PIs (rarely)
	Hepatoxicity More common if there is coinfection with hepatitis B or C	NVP, EFV, PIs
	Drowsiness, dizziness, confusion and vivid dreams are associated with the use of EFV Normally self-resolving but can take weeks to months	EFV
Medium term (the first few months)	Anaemia and neutropenia Sudden and acute bone marrow suppression due to AZT can occur within the first weeks of therapy or present as slowly progressive anaemia over months	AZT
	Hyperpigmentation of skin, nails and mucous membranes	AZT
	Lactic acidosis can occur at any time More common after the first few months Most commonly associated with d4T	d4T, ddI, AZT
	Peripheral neuropathy can occur at any time More common after the first few months	d4T, ddI
	Pancreatitis can occur at any time	ddI
Long term (after 6–18 months)	Lipodystrophy and lipoatrophy	d4T, ddI, AZT, PIs
	Dyslipidaemia	d4T, EFV, PIs
	Diabetes	Indinavir (IDV)
	Skin, hair and nail abnormalities	PIs, especially IDV

9.3 Symptom-directed toxicity management

Table 20: Management of side-effects and toxicities of antiretroviral drugs

Toxicity	Causative ARVs	Recommendations
Acute pancreatitis	d4T and ddI	Discontinue ART. Provide supportive treatment and laboratory monitoring. Resume ART with an NRTI with a low risk of pancreatic toxicity (AZT, ABC, TDF).
Diarrhoea	ddI (buffered formulation), NVF, lopinavir/ritonavir (LPV/r), saquinavir/ritonavir (SQV/r)	Usually self-limited, without need to discontinue ART. Symptomatic treatment should be offered.
Drug eruptions (mild to severe, including Stevens–Johnson syndrome or toxic epidermal necrolysis)	NVP, EFV (rarely)	In mild cases, give antihistamines. Moderate rash, non-progressive and without mucosal involvement or systemic signs, consider a single NNRTI substitution (i.e. NVP with EFV). In moderate and severe cases, discontinue ART and give supportive treatment. After resolution, resume ART with 3 NRTI or 2 NRTI + PI regimens.
Dyslipidaemia, insulin resistance and hyperglycaemia	PIs EFV	Consider replacing the suspected PI by drugs with a lower risk of metabolic toxicity.
GI intolerance	All ARVs	Usually self-limited, no need to discontinue ART. Symptomatic treatment should be offered.
Haematological toxicities (particularly anaemia and leucopenia)	AZT	If severe (Hb <6.5 g% and/or absolute neutrophil count <500 cells/mm^3) replace by an ARV with minimal or no bone marrow toxicity (e.g. d4T, ABC or TDF) and consider blood transfusion in severely distressed persons.
Hepatitis	All ARVs (particularly NVP and PI/r)	If ALT >5-fold the basal level, discontinue ART and monitor. After resolution, replace the drug most likely to be associated with another one.
Hyperbilirubinaemia (indirect)	Atazanavir (ATV)	Generally asymptomatic, but can cause scleral icterus (without ALT elevation). Replace ATV with another PI.
Hypersensitivity reaction	ABC	Discontinue ABC and **do not restart**. Give symptomatic treatment. Re-exposure may lead to a severe and potentially life-threatening reaction.
Lactic acidosis	All NRTIs (particularly d4T and ddI)	Discontinue ART and give supportive treatment. After clinical resolution, resume ART, replacing the offending NRTI. ABC, TDF and 3TC are less likely to cause this type of toxicity.

Table 20 *(contd)*: Management of side-effects and toxicities of antiretroviral drugs

Toxicity	Causative ARVs	Recommendations
Lipoatrophy and lipodystrophy	All NRTIs (particularly d4T)	Early replacement of the suspected ARV drug (e.g. d4T for TDF or ABC). Consider aesthetic treatment and physical exercises.
Neuropsychiatric changes	EFV	Usually self-limited, without need to discontinue ART.
Renal toxicity (nephrolithiasis)	IDV	If using IDV, interrupt IDV and offer hydration, laboratory monitoring and symptomatic treatment (50% recurrence rate). Consider replacing IDV with another PI.
Renal toxicity (renal tubular dysfunction)	TDF	Discontinue TDF and give supportive treatment. After clinical resolution, resume ART, replacing the offending drug with another.
Peripheral neuropathy	d4T and ddI	Consider replacement by an NRTI with minimal or no neurotoxicity (AZT, TDF or ABC). Symptomatic treatment should be considered.

9.4 Individual drug substitutions for toxicity and intolerance

Table 21: Individual drug substitutions for toxicity and intolerance

ARV drug	Frequently associated toxicity	Suggested substitute
ABC	Hypersensitivity reaction	AZT or TDF or d4T
AZT	Severe anaemia or neutropenia Severe GI intolerance	TDF or d4T or ABC
	Lactic acidosis	TDF or ABC Boosted PI + NNRTI if ABC and TDF are not available (e.g. IDV/r + EFV)
d4T	Lactic acidosis Lipoatrophy/metabolic syndrome	TDF or ABC Boosted PI + NNRTI if ABC and TDF are not available (e.g. IDV/r + EFV)
	Peripheral neuropathy	AZT or TDF or ABC
TDF	Renal toxicity (renal tubular dysfunction)	AZT or ABC or d4T
EFV	Persistent and severe CNS toxicity	NVP or TDF or ABC
	Potential teratogenicity (first trimester of pregnancy or women not using adequate contraception)	NVP or ABC
NVP	Hepatitis	EFV or TDF or ABC
	Non-severe (grade 1 or 2) moderate hypersensitivity reaction	1. Substitute EFV for NVP following a non-severe NVP rash and/or hepatotoxicity; careful monitoring is needed. 2. TDF or ABC 3. PI-based regimen if ABC and TDF not available
	Severe or life-threatening rash (Stevens–Johnson syndrome)	Stop all ARVs until stable. Then start TDF or a PI-based regimen

Notes

The general principle is that single-drug substitution for toxicity should be made within the same ARV class, e.g. substitution of AZT or TDF for d4T for neuropathy, TDF or d4T for AZT for anaemia, or NVP for EFV for CNS toxicity or in pregnancy.

If a life-threatening toxicity occurs, all ARVs should be stopped until the toxicity has resolved. A revised regimen is commenced when the patient has recovered.

9.5 Notes on stavudine (d4T)

d4T is the NRTI most often associated with lactic acidosis, lipoatrophy and peripheral neuropathy **(Box 6)**.[32] Because of its current wide availability as a fixed-dose combination and lower price compared with other ARVs, d4T-containing regimens may be the most accessible option for people in resource-limited settings. Till safer first-line ART choices become available, close monitoring for d4T toxicity is recommended.

After the publication of WHO's 2006 guidelines for HIV therapy in adults and adolescents, the WHO Guidelines Development Group reviewed evidence for the use of d4T at reduced doses. Previously, the preferred d4T dosage was weight-based. The dose recommended for patients >60 kg was 40 mg twice daily; for patients <60 kg it was 30 mg twice daily. A systematic review of nine randomized trials and six observational cohort studies strongly suggests that stavudine-containing regimens maintain clinical and virological efficacy when the dose of stavudine is 30 mg twice daily, and that this reduced dose is associated with lower rates of toxicity, especially peripheral neuropathy, compared with the 40 mg twice daily dose. Complementary studies have also demonstrated a significant reduction of mitochondrial DNA depletion in patients on the 30 mg twice daily dose.[33,34,35]

Some countries (such as Thailand) and some treating physicians have adopted the principle of commencing treatment with a d4T-based regimen and switching to an AZT-based regimen after 6–12 months. The rationale for this is twofold. First, AZT may be contraindicated in patients with anaemia at the time of commencement of ART (common in those with advanced HIV disease). These patients can be started on d4T and then switched to AZT once the anaemia improves on ART. Second, switching from an initial d4T-based regimen to AZT as soon as signs of lipoatrophy or peripheral neuropathy appear is an appropriate way to manage these side-effects. As no clinical trial data are available to support this strategy, such trials are being planned.

Box 6: Lipodystrophy

Features of the lipodystrophy syndrome

- Dyslipidaemia consisting of raised total cholesterol, low high-density lipoprotein (HDL) cholesterol and raised triglyceride (TG) levels
- Insulin resistance with hyperglycaemia
- Central fat accumulation (visceral, breast, neck) and local fat accumulation (lipomas, "buffalo hump")
- Generalized diminution of subcutaneous fat mass (lipoatrophy)

Lipoatrophy is characterized by loss of subcutaneous fat from the face, arms, legs, abdomen and/or buttocks. It is most commonly associated with d4T but occurs with all thymidine NRTIs (d4T >ddI >AZT).[36,37] It is also associated with PI-based regimens alone and in combination with NRTIs.

Figure 4. Lipoatrophy of the face and leg

Fat accumulation can occur within the abdominal cavity, upper back, neck, breasts and subcutaneous tissue and is usually associated with PI-based regimens. It can also occur with non-PI based regimens.

Management

The fat loss is likely to be permanent in most cases. Alert the patient and intervene early with revision of the drug regimen if possible (e.g. switch from d4T to AZT, TDF or ABC). Switching to another drug may result in some recovery and may stop further fat loss.[38,39]

Lactic acidosis

d4T, ddI (and, to a lesser extent, other nucleosides such as AZT, 3TC and ABC) have been associated with life-threatening lactic acidosis due to the mitochondrial toxicity induced by these drugs.[40] After doing well

for six months or more on ART the patient presents with unexpected clinical deterioration characterized by weakness, weight loss, abdominal pain and distension, anorexia, nausea, vomiting and diarrhoea. Blood chemistry is abnormal, and includes raised levels of serum lactate, ALT, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and an abnormal anion gap ([Na + K] – [HCO^3 +Cl]).

Management

Patients must be asked to report any unexpected deterioration in their general health. Stop all ARVs. Recovery is slow (1–2 months). Thiamine or riboflavin (30 mg/day) may be effective. If the patient is unwell, hospitalization may be required for institution of life-support measures. Deaths have been reported. Restart ART after full recovery using a TDF- or ABC-containing regimen. Do not use d4T or AZT again.

Peripheral neuropathy

Peripheral neuropathy is most commonly associated with the use of d4T.[41] It presents over weeks to months in the following sequence of events – numbness followed by tingling and burning and then pain, usually beginning in the lower extremities.

Management

Stop the drug if possible. There may be a short period, typically up to 4 or 8 weeks during which symptoms intensify after drug withdrawal. Analgesics are usually ineffective and drugs used to treat neuropathic pain (amitriptyline 25–50 mg at bedtime) may be of some use.

Dyslipidaemia

Dyslipidaemia is associated with all three classes of ARVs; PIs, NRTIs and NNRTIs. The increase in cholesterol and triglyceride (TG) levels is greater with d4T than with TDF. ABC is more likely to increase cholesterol and TG levels than AZT. NNRTIs cause a rise in total cholesterol and, to a lesser extent, TG levels (EFV >NVP).

Insulin resistance

d4T and some PIs (IDV, RTV, LPV/r) cause insulin resistance and abnormal glucose metabolism. Clinical diabetes may result.

Table 22: Strategies to maximize the safe use of stavudine (d4T)	
Training health-care professionals (HCPs) to recognize the signs and symptoms of lactic acidosis, lipoatrophy and peripheral neuropathy	Adequately **educating patients** in the early recognition of side-effects of d4T and when to expect them
Switching to an alternative NRTI (such as AZT, TDF or ABC) as soon as side-effects occur may reduce the severity of d4T toxicity **Commence** with d4T in patients with anaemia and switch to an alternative NRTI (such as AZT, TDF or ABC) if anaemia improves on ART	WHO recommends that d4T 30 mg is given to everyone irrespective of body weight [34] For details, see the web link: <http://www.who.int/hiv/treatment/en/index.html>

9.6 Choice of NNRTIs

Table 23: Choice of non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
NNRTI	**Advantages**	**Disadvantages**
NVP	Widely available including as fixed-dose combination Less expensive than EFV Preferred NNRTI for women when there is a potential for pregnancy or those in first trimester	Higher incidence of rash than with EFV Rash may be severe and life-threatening, including Stevens–Johnson syndrome Potentially life-threatening risk of hepatotoxicity, especially in women with CD4 count >250 cells/mm^3
EFV	Once daily regimen Generally well tolerated Rash is less common than with NVP and generally self-resolving NNRTI of choice in individuals with TB/HIV coinfection receiving rifampicin	Teratogenic and cannot be used in first trimester Use with caution in women with childbearing potential More expensive than NVP and not always widely available CNS side-effects

10 ART for Pregnant Women and those with Childbearing Potential

10.1 ART for pregnant women and those with childbearing potential

Table 24: Antiretroviral drugs in pregnancy

Clinical situation	Guiding principles	Recommendations
All women	Treatment decisions are based solely on the woman's medical need.	Recommended first-line regimen is NVP plus 2 NRTIs. EFV plus 2 NRTIs may be used if women have access to consistent and reliable barrier methods of contraception or after the first trimester of pregnancy.
Initiating ART in pregnant women	ART is recommended for pregnant women according to the same eligibility criteria as for non-pregnant adults. ART should be initiated in pregnant women with WHO clinical stage 3 or 4 disease, or those with WHO clinical stage 1 or 2 disease before the CD4 count drops below 200 cells/mm^3.	Some experts recommend that all pregnant women with WHO clinical stage 3 disease and CD4 count <350 cells/mm^3 should initiate ART. The recommended regimen is 2 NRTIs plus an NNRTI. The preferred regimen is AZT+3TC+NVP with careful monitoring in women with higher CD4 counts >250 cells/mm^3.
Women who are pregnant, are in the first trimester and are taking EFV	EFV should be discontinued and replaced by another drug.	NVP is substituted for EFV with close monitoring in women with CD4 count >250 cells/mm^3.[15] Alternatively, a PI-based or triple NRTI regimen could be given.
Women who are breastfeeding	ART is recommended for postpartum breastfeeding women who meet the WHO criteria for initiation of therapy for their own health.	The preferred regimen is AZT+3TC+NVP.
Women who received ART as part of prevention of mother-to-child transmission (PMTCT) intervention	Women who have previously received single-dose NVP prophylaxis for PMTCT should be considered eligible for NNRTI-based regimens. Alternatives may be considered for women whose exposure to single-dose NVP was <6 months before ART was initiated.	Single-dose NVP (SDN) >6 months – NNRTI-based regimen SDN <6 months – A triple NRTI regimen or PI-based regimen also can be considered.

Notes on NVP

Women with CD4 counts >250 cells/mm^3 are at increased risk for NVP hypersensitivity with fatal hepatic toxicity. This applies to both pregnant and non-pregnant women. NVP should be used with caution, and with careful clinical and liver function monitoring in this population.

10.2 ART and hormonal contraceptives

NVP, RTV, nelfinavir (NFV), LPV/r and SQV/r cause a reduction in ethinyl-estradiol levels.[42,43] Estrogen levels are slightly increased by ATV, IDV and EFV. Consistent use of condoms is recommended in all HIV-infected women taking ART. The limited data available do not show interaction between medroxyprogesterone acetate and NVP, EFV or NFV.[33]

10.3 Initiating ART in pregnant women

Table 25: Starting antiretroviral therapy in pregnancy

When to start ART in pregnant woman		
WHO stage	**CD4 count not available**	**CD4 count available**
1	Do not treat	Treat if CD4 count <200 cells/mm^3
2*	Do not treat	
3	Treat	**Treat if CD4 count <350 cells/mm^3**
4	Treat	Treat irrespective of CD4 cell count

* Many women with a CD4 count >250 cells/mm^3 will require ART within the first year post partum and the efficacy of NNRTI-based ART initiated <6 months after exposure to SDN viral suppression may be compromised due to NVP resistance.[15]

Close monitoring of aspartate aminotransferase (AST)/ALT levels is recom–mended during the first few months after commencing an NVP-containing regimen in pregnant women. Testing should be done at weeks 0, 2, 4, 6, 8 and then monthly until delivery. NVP should be discontinued if the ALT is >2.5 times the upper limit of normal (ULN), a lower threshold than normally recommended in adults.

The preferred NRTIs for use in pregnant women are AZT and 3TC. The combination of d4T/ddI should not be used. There are no data on the use of FTC in pregnancy. Studies have shown TDF to be associated with decreased fetal growth and bone demineralization.[44,45]

The preferred NNRTI is NVP, due to extensive clinical experience with this drug in pregnant women and its proven efficacy in reducing MTCT. SQV/r and NFV are the preferred PIs in women who cannot tolerate NVP. EFV may be considered after the first trimester.

11 Antiretroviral Therapy in Tuberculosis/HIV Coinfection

11.1 Initiating antiretroviral therapy in patients with active tuberculosis

Table 26: Starting antiretroviral therapy in patients with tuberculosis

CD4 cell count (cells/mm^3)	ART recommendations	Timing of ART in relation to initiation of TB treatment
<200	Recommend ART	Between 2 and 8 weeks
Between 200 and 350	Recommend ART	After 8 weeks
>350	Defer ART	Re-evaluate patient at 8 weeks and at the end of TB treatment
CD4 count not available	Recommend ART	2–8 weeks

Choice of NRTI

This is the same as for all HIV-infected persons.

Choice of NNRTI

EFV is the preferred NNRTI. EFV blood levels are decreased in the presence of rifampicin. There is evidence that the standard EFV dosage of 600 mg/day in patients weighing <60 kg is adequate.[46,47,48,49,50]

NVP levels are also decreased in the presence of rifampicin. However, standard NVP dosing is recommended.[51,52,53,54,55] Due to concerns about hepatotoxicity, NVP-containing regimens should be used only when no alternative is available, particularly for women on rifampicin-containing regimens, with CD4 cell counts >250 cells/mm^3 who need to start ART.[15]

A triple NRTI regimen (AZT+3TC+ABC or AZT+3TC+TDF) can be used with rifampicin. AZT, 3TC and TDF have no or minimal interactions with rifampicin but triple NRTI regimens are less potent than NNRTI-based regimens.

11.2 Recommendations for patients on ART who develop active TB

Table 27: Antiretroviral therapy in patients who develop active tuberculosis

First- or second-line ART	ART regimen at the time TB occurs	ART options
First-line	2 NRTI + EFV	Continue with 2 NRTI + EFV
	2 NRTI + NVP*	Change to EFV **or** Change to triple NRTIs **or** Continue with 2 NRTI + NVP*
	Triple NRTI	Continue triple NRTI
Second-line	2 NRTI + PI	Change to or continue (if already being taken) LPV/r- or SQV/r-containing regimen and adjust dose of RTV

* Due to concerns about hepatotoxicity, NVP-containing regimens should be used only when no alternative is available, particularly for women on rifampicin-containing regimens, with CD4 cell counts >250 cells/mm^3 who need to start on ART.

Switching back to NVP after treatment with rifampicin is completed can be considered. When switching back from EFV to NVP no lead-in dose is required. If a pregnant woman in the second or third trimester develops active TB, an EFV-containing ART regimen can be considered. An alternative in women with active TB in the first trimester is a triple NRTI regimen or an NVP-containing regimen, with careful monitoring in women with CD4 counts >250 cells/mm^3 or when the CD4 count is unknown.

11.3 Second-line ART for patients with TB and indications of first-line ART failure

Unboosted PIs cannot be used with rifampicin-containing regimens because the PI levels are subtherapeutic.[56,57] If a patient needs to switch to or is already on a PI-based regimen, LPV 400 mg/RTV 400 mg twice daily in combination with rifampicin could be considered under close clinical and laboratory supervision for hepatotoxicity. An alternative is SQV 400 mg/RTV 400 mg with close clinical and laboratory monitoring. Recommendations and precautions for the use of PI-based regimens in combination with rifampicin in women with childbearing potential and pregnant women are the same as for other patients with TB.

12 Injecting Drug Users

12.1 Principles of comprehensive care for HIV-infected IDUs

The key components of comprehensive care for IDUs are:

- Assessment and management of physical and psychological co-morbidities including viral hepatitis and psychiatric conditions (such as depression)
- Assessment of the patient's treatment priorities, goals and readiness to start ART if it is medically indicated
- Provision of opioid substitution therapy (OST)
- Provision of clean injecting equipment and condoms
- Management of injecting-related health problems.

Current or former injecting drug use is not a reason to withhold ART.

Links to harm-reduction programmes

The objectives of the *Biregional strategy for harm reduction 2005–2009*[58] are to ensure access to the essential prevention package and to treatment, care and support services for people who inject drugs, and create an enabling environment for harm-reduction interventions.

Harm-reduction programmes have trained staff (social workers, counsellors and outreach workers) with experience in reaching out to and communicating with IDUs, and have established credibility and trust. Harm-reduction programmes should plan HIV treatment for IDUs[59] with a focus on:

- Outreach to potential clients for HIV testing and prevention of transmission of HIV
- Support for adherence to ART
- Follow up of patients who drop out of care
- Implementing OST for suitable patients
- Education and peer support

12.2 Antiretroviral therapy for injecting drug users

Table 28: Initiating antiretroviral therapy in substance-using patients	
Initiating ART	The criteria for initiating ART in substance-using patients are the same as for other patients with HIV. Before starting ART, specific factors that may affect the timing of initiation and choice of ART should be considered. These include social instability, active use of illicit drugs and presence of co-morbidities such as mental problems and coinfection with hepatitis viruses. Unavailability of OST or active use of illicit drugs should not preclude access to ART for those IDUs in need of treatment. Effective links between ART and harm-reduction programmes are essential. Unless the person is severely ill, initiation of ART is not urgent. Adequate time spent on preparing to start ART, understanding treatment goals, adherence and the lifelong nature of ART will maximize treatment outcomes.
Choice of ART	WHO-recommended regimens can be chosen for the majority of IDUs. The choice of specific ARV drugs depends on: ● Co-morbidities (especially hepatitis B/C and psychiatric disorders) ● Drug interactions (methadone) ● Use of fixed-dose combinations and, if available, once-daily ARV regimens are preferable.
Preferred first-line regimen	**AZT + 3TC + (EFV or NVP)** AZT may be replaced by d4T.
Choice of NNRTI	Hepatitis C and B infections are extremely common in IDUs. Monitoring for hepatotoxicity is strongly recommended in IDUs receiving NNRTI-based ART, especially NVP. **EFV** EFV is recommended by some experts due the high prevalence of coinfection with hepatitis B and C in IDUs, and the lower risk of hepatic complications with EFV compared with NVP.[60] EFV is preferred in patients with clinical and/or laboratory evidence of significant (grade 3 or 4) hepatic dysfunction. EFV should be used with caution in patients with depression or other significant psychiatric conditions. **NVP** NVP is recommended in patients with no other significant co-morbidities; specifically, patients with no clinical signs of hepatic dysfunction or increase in hepatic transaminases (grade 3 or 4). If NVP is the only NNRTI available, use with careful clinical and laboratory (liver enzyme) monitoring.
Alternative first-line regimen	**TDF + (3TC or FTC) + (EFV or NVP)** Patients who are HBsAg-positive and TDF is available
Second-line regimen	Recommendations are the same as for all patients with HIV. (ddI or TDF) + ABC+ PI/r **or** TDF + 3TC (± AZT) + PI/r

Table 28 *(contd)*: Initiating antiretroviral therapy in substance-using patients	
Adherence	With experienced staff and adequate support, IDUs can adhere to ART and have clinical outcomes comparable with those of HIV-infected patients who do not use drugs.[61,62]
Methadone	Administration of methadone with EFV, NVP or RTV decreases the plasma levels of methadone, which may precipitate symptoms of opiate withdrawal.[63] Patients receiving methadone and commencing ART may require increased doses of methadone.
DOT	True directly observed therapy (DOT) is possible only with once-daily regimens. Modified DOT with supervised daytime dosing and take-home evening doses may be an option.

Opioid withdrawal symptoms are unspecific and often difficult to diagnose. The most common ones are nausea, muscle aches, abdominal cramps, irritability, loss of appetite, weakness, restlessness, headache, dizziness, sneezing, hot and cold flashes and, most importantly, craving for drugs.[64]

Choice of NNRTI component

Patients, particularly women, with increased CD4+ cell counts at initiation of NVP therapy (>250 cells/mm^3 in women and >400 cells/mm^3 in men) are at higher risk for the development of symptomatic hepatic events, often associated with rash. The risk of symptomatic hepatic events regardless of severity is greatest during the first 6 weeks of therapy. However, hepatic events may occur at any time during treatment. In some cases, patients present with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Patients who have infection with hepatitis B or C and/or abnormal liver function tests at the start of therapy with NVP are at greater risk for later symptomatic events (6 weeks or more after starting NVP) and asymptomatic increases in AST and/or ALT.

Serious psychiatric adverse events have been reported in patients treated with EFV. These include severe depression, suicidal ideation, aggressive behaviour, paranoid reactions and manic reactions.

12.3 Viral hepatitis and chronic liver disease

Coinfection with hepatitis C virus (HCV) is common in HIV-infected IDUs. Chronic, active hepatitis B and alcoholic liver disease are also common.

Hepatotoxicity associated with these conditions complicates the choice of ART. NRTIs with the most hepatotoxicity are AZT, ddI and d4T. Both the available NNRTIs can cause hepatotoxicity. NVP is more commonly associated with severe hepatotoxicity and should be avoided if possible in all patients with chronic liver disease.[65] EFV can be administered in full doses in patients with liver insufficiency. PIs are also associated with hepatotoxicity, and the dosing is complex in patients with hepatic insufficiency.[66]

If drugs are available, the recommended treatment for HIV/hepatitis B virus (HBV) coinfection is TDF alone or in combination with 3TC or FTC as part of the ART regimen. 3TC should not be used alone due to rapid development of resistance by HBV. Fatal cases of an acute flare-up of HBV infection have been documented in HIV/HBV co-infected patients who discontinue 3TC monotherapy.[67,68]

Drugs for treating hepatitis C are often not available in resource-limited settings and pegylated interferon (IFN) and ribavirin (RBV) are used. There is no other treatment for hepatitis C. Patients should be stable on ART with CD4 counts >200 cells/mm^3 before pegylated IFN and RBV are started. AZT levels are increased by RBV and patients should be closely monitored for hepatic toxicity, neutropenia and anaemia.

Other causes of hepatic dysfunction need to be considered in addition to viral hepatitis. Alcohol use/dependency has the same implication for treatment options and monitoring as viral hepatitis. Where possible, the least hepatotoxic ARV should be used and hepatic enzymes monitored in all patients with hepatic dysfunction.

12.4 Opioid substitution therapy

OST is the most effective treatment for opioid dependence, and results in substantially higher retention rates, suppression of drug use and improved psychosocial functioning. Its use in the context of HIV treatment has been associated with improved adherence to and outcomes of treatment. Detoxification and abstinence-based programmes are unlikely to achieve similar levels of clinical effectiveness and may prove counterproductive in the context of ART. If possible, stabilization of substance use with substitution treatment is recommended prior to commencement of ART. Where substitution therapy is available,

consideration should be given to offering HIV care and dispensing HIV medication at the same site where substitution therapy is delivered. This approach can achieve maximal levels of treatment supervision which should enhance efficacy and reduce the risk of HIV drug resistance. In addition, co-location of these services facilitates the management of drug–drug interactions between methadone and ART.

Outcomes of OST in a structured programme include:

- Decreased heroin use and reduced chaotic drug-taking
- Decreased needle-sharing
- Stabilization of clients' lives
- Improved quality of life and the chance to lead a productive life in the community
- Improved ability to commence and adhere to ART

OST programmes generally use either methadone liquid or buprenorphine sublingual tablets.

Methadone and buprenorphine are included in the WHO Essential Drugs List. (http://www.who.int/medicines/publications/essentialmedicines/en/index.html)

Methadone

Methadone, an orally administered long-acting opiate agonist, is the most commonly used pharmacological treatment for opiate addiction. Methadone is inexpensive and widely available.

12.5 ARV dose adjustments in patients receiving methadone

There are two relevant interactions.

Methadone and NNRTIs

Methadone levels are decreased by up to 50% in those receiving EFV and NVP, and clinical signs of opiate withdrawal may be precipitated. Signs and symptoms of opiate withdrawal typically occur 4–8 days after starting NNRTI-based ART. Patients receiving methadone replacement therapy and NNRTI-based ART require a step-wise increase in the daily

dose of methadone by 5–10 mg until they are comfortable (Table 29). Precipitating opiate withdrawal may trigger relapse to heroin use, distrust of medical providers, and unwillingness to take ART. The levels of EFV and NVP are not affected by methadone.

Methadone and NRTIs

ddI concentrations are reduced by approximately 60% when administered with methadone. This may lead to subtherapeutic levels of ddI and the combination should be avoided. The levels of enteric-coated (EC) ddI are not affected by methadone.

Methadone and PIs

PI levels are generally not affected by methadone, except for amprenavir (APV), which is reduced by 30%. Administration of APV, NFV, LPV and RTV

Table 29: Methadone maintenance therapy

Contraindications for methadone use	▪ Known hypersensitivity to methadone ▪ Acute asthma (or other unstable medical condition) ▪ Alcoholism (unstable alcohol use) ▪ Treatment with monoamine oxidase inhibitor (MAOI) antidepressants (or unstable psychiatric condition) ▪ Severe hepatic impairment ▪ History of biliary or renal tract spasm (relative contraindication)
Initial dose	Usually 20–30 mg per day The initial dose should be reduced if there is concomitant benzodiazepine or alcohol use or dependence; the dose should be carefully increased in the first 2 weeks of treatment.
Follow up	Review before the third dose.
Dose escalation	5–10 mg at a time (keep 5 days between each dose increase) if the client has discomfort or requires a higher dose.
Usual maintenance dose	Individualized Doses of 60–120 mg per day are more effective in achieving treatment outcomes (no relapse) than lower doses.
Termination of treatment	The minimum duration of treatment should be one year. Three years or more of treatment are likely to have improved long-term outcomes.

results in a significant decrease in methadone levels and may result in symptoms of opiate withdrawal (*see* Annex 5).

Buprenorphine

Buprenorphine is administered as a single daily dose in the range of 8–34 mg/day. The average dose for most patients is 16 mg/day but doses up to 34 mg/day may be required. Tablets should be placed under the tongue until they are dissolved. Swallowing the tablets reduces the bioavailability of the drug.

There are two sublingual formulations, buprenorphine alone and buprenorphine combined with naloxone. Addition of the opioid antagonist naloxone is intended to deter injecting of the crushed dissolved tablets.

Interactions between ART and buprenorphine are less well researched than with methadone (*see* Annex 5). Emerging evidence indicates that PIs including RTV and ATV inhibit buprenorphine metabolism resulting in a clinically significant effect. The dose of buprenorphine may need to be reduced in this context.[60]

13 HIV and Hepatitis Coinfection

13.1 Hepatitis B infection

Table 30: Principles of therapy for HIV/HBV coinfection	
Choice of ART	Drugs with anti-HBV activity should be included in the first-line ART regimen for HIV-infected patients who are HBsAg-positive and HBeAg-positive if known.
Preferred first-line ART	TDF + (3TC or FTC) + EFV
Alternatives if TDF is unavailable	(AZT or d4T) + (3TC or FTC) + EFV (AZT or d4T) + (3TC or FTC) + NVP (*see* Choice of NNRTI below) In this case, 3TC (or FTC) will be the only drug with activity against HBV.
Choice of NNRTI	▪ EFV is the preferred NNRTI option. ▪ NVP should be used with care and regular monitoring in patients who have known HIV/HBV coinfection and grade 1, 2 or 3 increase in ALT/AST. ▪ NVP is not recommended for patients with grade 4 or greater increase in ALT/AST.
Second-line regimen	3TC should be continued as part of second-line ART following initial ART failure, even if it was used in the first-line regimen.
HBV resistance	▪ Ideally, 3TC should be used either with TDF or not at all. ▪ This may not be feasible in resource-limited settings. ▪ HBV resistance to 3TC will develop in 50% of patients after two years and in 90% after four years of treatment if 3TC is the only active anti-HBV drug in the ART regimen.
Therapy outcomes	HBV seroconversion (loss of HBeAg and development of HBeAb) occurs in 11–22% of HBeAg-positive HIV-infected patients who are treated with 3TC for one year.
Hepatic flares	▪ Starts soon after initiation of ART as part of IRIS ▪ Discontinuation of 3TC may also result in hepatic flares
FTC	FTC has a similar rate of suppression of HBV and a similar safety profile and resistance pattern as 3TC.

Note: ARV programmes in areas of the world with a high seroprevalence of HBV and no capacity to screen for HBV may consider the use of TDF plus either FTC or 3TC as the preferred initial NRTI combination if these drugs are available.

Hepatic flares

Hepatic flares may occur

- Following initiation of ART as part of IRIS
- When ART is stopped.

Flares typically present as an unexpected increase in ALT/AST levels and symptoms of clinical hepatitis (fatigue, nausea, abdominal pain and jaundice) within 6–12 weeks of commencing ART. Flares may be difficult to distinguish from ART-induced hepatic toxicity. Drugs active against HBV should preferably be continued during a suspected flare. If it is not possible to distinguish between a serious hepatitis B flare and grade 4 drug toxicity, all ART should be stopped until the patient stabilizes.

13.2 Hepatitis C infection

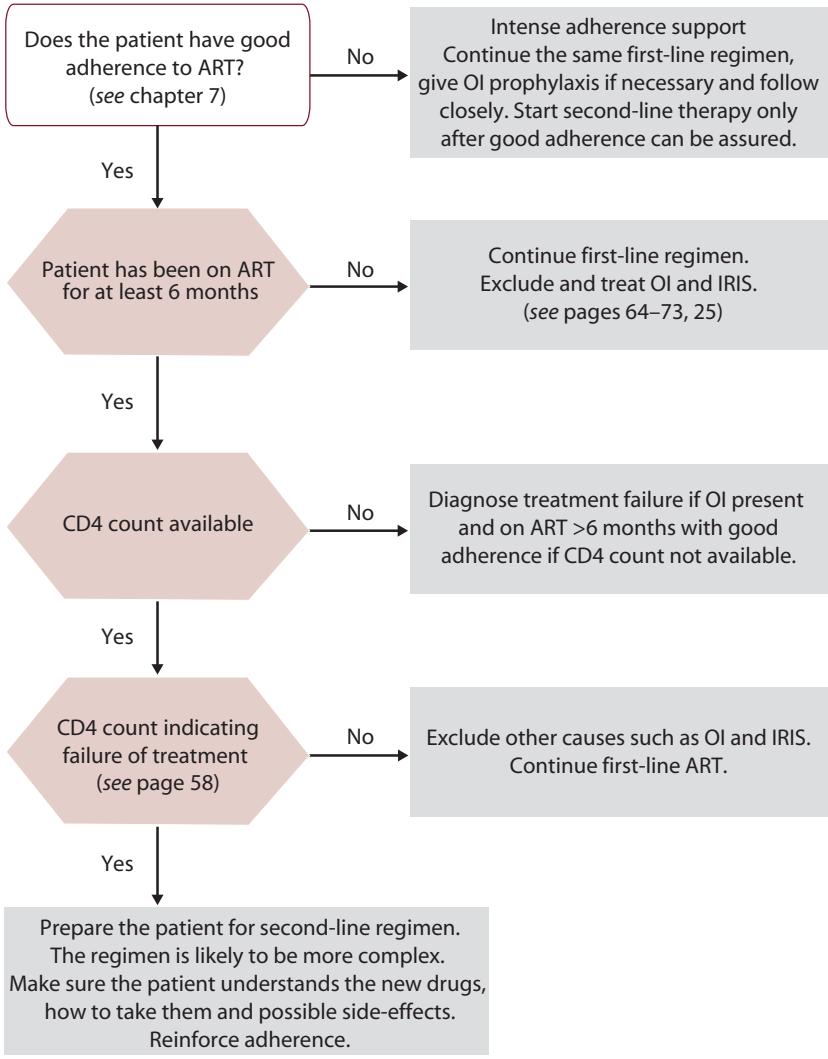
Table 31: Principles of therapy for HIV/HCV coinfection

HCV therapy	No ARVs are directly active against HCV. However, ART has been shown to delay the progression of HCV liver disease in HIV/HCV coinfection. The only effective treatment is pegylated IFN and RBV, which are generally not available in resource-limited settings.[69]
Therapy outcomes	Clinical trial outcomes ▪ HCV genotype 1: 15–28% sustained virological response rates ▪ HCV genotypes 2 and 3: 60–70% virological response rates
Side-effects of IFN	Up to 60% of individuals treated with IFN will experience mental health problems, most commonly depression. Monitor mental health closely.
Timing of HCV therapy	▪ Commence anti-HCV therapy before the CD4 count drops to levels where ART is required. ▪ If ART is required in HCV-positive patients, they should be stable on ART with a CD4 count >200 cells/mm^3 before anti-HCV therapy is considered.[60]
Preferred first-line ART regimen	▪ The choice of NRTI is the same as for HCV-uninfected patients. ▪ EFV is the preferred NNRTI. ▪ NVP should be used with care and regular monitoring in patients who have known HIV/HCV coinfection and grade 1, 2 or 3 increase in ALT/AST. ▪ NVP is not recommended for patients with grade 4 or higher increase in ALT/AST.
Drug interactions	▪ RBV and d4T/ddI – pancreatitis/lactic acidosis ▪ Do not co-administer. ▪ RBV and AZT – anaemia ▪ Monitor closely. ▪ IFN and EFV – depression ▪ Monitor closely.
Hepatic flares	Soon after initiation of ART as part of IRIS

14 ART Failure and when to Switch Therapy

14.1 Determining ART failure

Figure 5. Determining ART failure



Switching to a second-line regimen is not an emergency. Review the patient's OI prophylaxis. Patients on a failing regimen with WHO stage 2, 3 or 4 disease or CD4 count <200 cells/mm^3 need to restart co-trimoxazole. While a failing regimen may retain some anti-HIV activity, the more time that the patient remains on a failing regimen, the more resistance mutations will accumulate, reducing the chances of success of the second-line regimen. The decision to switch is based on clinical, immunological or virological definitions of failure (presented below) and the availability of second-line ARVs.

14.2 Defining failure

Definitions

Clinical failure: New or recurrent WHO stage 4 condition after at least 6 months of ART.

Exceptions are TB, oesophageal candidiasis and severe bacterial infections which may not always represent ART failure.

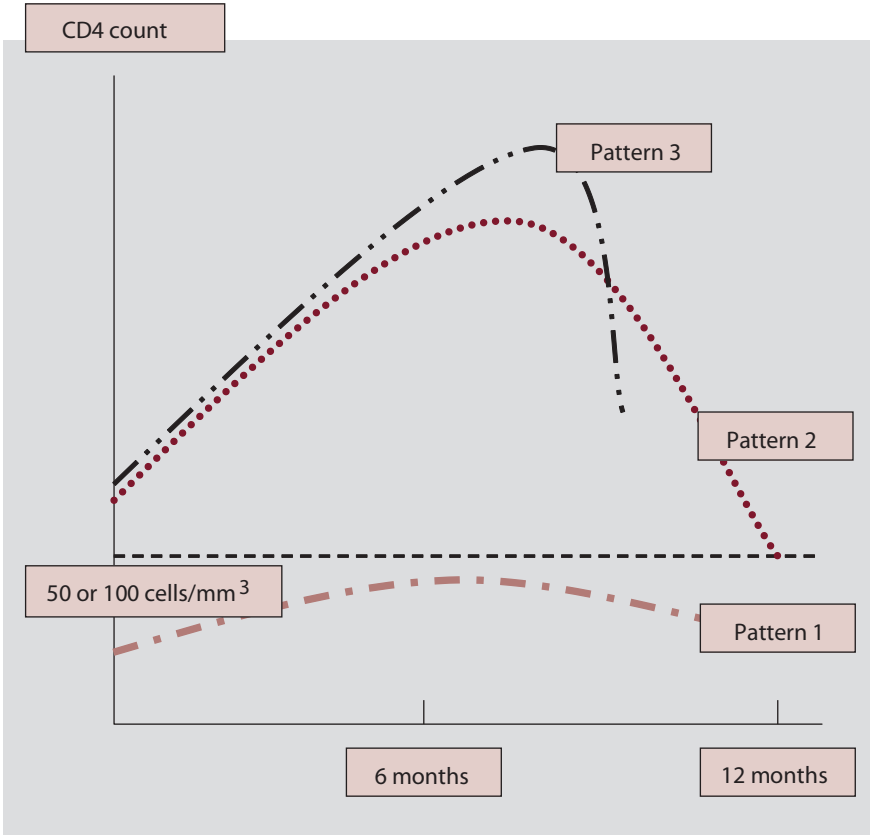
Review the response to therapy first and if the response is good, do not switch.

Virological failure: Viral load >10 000 copies/ml after at least 6 months on ART.

ART failure cannot be diagnosed based on clinical criteria alone in the first 6 months of taking ART. Clinical events that occur during the first 6 months of therapy often represent IRIS and not failure.

14.3 Immunological criteria for failure

Figure 6. Pattern of immunological failure of ART



Pattern 1: CD4 count <100 cells/mm^3 (some experts recommend <50 cells/mm^3) after one year of therapy

Pattern 2: Return to or a fall below the pre-therapy baseline CD4 count after one year of therapy

Pattern 3: 50% decline from the on-treatment peak CD4 value (if known)

CD4 cell count can also be used to determine when not to switch therapy. For example, in a patient with a new clinical stage 3 event for whom a switch is being considered, switching is not recommended if the CD4 cell count is >200 cells/mm^3.

Virological criteria for failure are included here as some countries in the Region (such as India and Thailand) have increasing capacity to perform affordable viral load testing. Viral load remains the most sensitive indicator of ART failure. Recognizing early failure facilitates switching before multiple resistance mutations have developed to drugs in the first-line regimen. The optimal viral load value at which ART should be switched has not been defined. However, values >5000–10 000 copies/ml have been associated with subsequent clinical progression and appreciable CD4 cell count decline.[70,71,72,73]

15 Choice of Second-line Regimens for Treatment Failure

The entire treatment regimen needs be changed in the setting of treatment failure (**Table 32**).

Table 32: Which second-line regimens to choose

First-line regimen		Second-line regimen	
		Reverse transcriptase inhibitor (RTI) component*	**Protease inhibitor (PI) component**
Preferred regimen	AZT or d4T + 3TC + NVP or EFV [§]	ddI + ABC or TDF + ABC or TDF + 3TC (± AZT)	PI/r *
Alternative regimen	AZT or d4T + 3TC + TDF or ABC[¶]	EFV or NVP ± ddI	

* Boosted PI/NRTI combinations: An RTV-boosted PI (PI/r) such as ATV/r, fosamprenavir (FPV)/r, IDV/r, LPV/r or SQV/r is the backbone of all second-line regimens. Unboosted PIs are not recommended with the exception of NFV if RTV is not available. NFV is less potent than a boosted PI. Two unused NRTIs are added to the PI/r; ddI is a preferred NRTI.[76]

§ If AZT or d4T are used in the first-line regimen (as may be the case in many countries), TDF or ABC are included in all preferred second-line regimens. If these drugs are not available, the choices are limited, and ddI + 3TC (± AZT) may be the only option. If preferred NRTIs are not available, some experts recommend supporting the boosted PI component of the second-line regimen with ddI plus retaining 3TC (± AZT), even though it was used in the first-line regimen. The use of 3TC reduces HIV fitness even if there is resistance to 3TC.

The combination of TDF and ddI plus an NNRTI is not recommended due to reports of early virological failure,[77] falling CD4 counts despite an undetectable viral load[78,79] and safety concerns. TDF increases ddI exposure by 60% and intracellular ddI levels twofold.[80]

¶ For those who received a triple NRTI first-line regimen, the recommended combination is a boosted PI plus an NNRTI with the option of adding ddI and/or 3TC to the boosted PI/NNRTI combination.[81,82]

16 Clinical and Laboratory Monitoring Prior to Commencing and on Second-line ART

Table 33: Clinical and laboratory monitoring prior to commencing and on second-line ART

Evaluation	Before or at ART switch	Week 2	Week 4	Week 8	Week 12	Week 24	Every 6 months	As needed (symptom-directed)
Clinical								
Clinical evaluation	✓	✓	✓	✓	✓	✓	✓	
Weight	✓	✓	✓	✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	
Check ART adherence	✓	✓	✓	✓	✓	✓	✓	
Laboratory								
CD4 count	✓						✓	✓
Haemoglobin [a]	✓		✓	✓	✓			✓
Pregnancy test [b]	✓						✓	
Creatinine [c]	✓						✓	
Fasting lipids [d]							✓	
Fasting glucose [e]	✓						✓	
Serum lactate								✓
HIV RNA (viral load) [f]								✓

Notes

[a] For patients receiving AZT, haemoglobin monitoring should be done prior to commencing AZT and at weeks 4, 8 and 12, and as required.

[b] Pregnancy testing should be done for women before switching to a PI-based second-line ART and if pregnancy is suspected in women receiving an EFV-based regimen. Change to a non-EFV based regimen if the pregnancy test is positive and the woman is in the first trimester.

[c] For patients taking TDF, baseline and 6-monthly monitoring of creatinine is recommended.

[d] All PIs can raise levels of cholesterol and triglycerides. Monitor 6-monthly.

[e] Only for patients taking IDV, baseline and 6-monthly fasting glucose should be tested.

[f] HIV RNA measurement is currently not recommended for decision-making on initiation or regular monitoring of ART in resource-limited settings. It may be considered to make an early diagnosis of treatment failure or to assess discordant clinical findings and CD4 counts in patients suspected of failing ART.

Table 34: Symptom-directed management of toxicities of second-line antiretroviral drugs

Toxicity	Causative ARVs	Recommendations
Acute pancreatitis	ddI	Discontinue ART. Provide supportive treatment and laboratory monitoring. Start new regimen replacing ddI with ABC or TDF if available.
Diarrhoea	NVF, ddI (buffered formulation), LPV/r SQV/r	Usually self-limited, without need to discontinue ART. Symptomatic treatment should be offered. NFV is most commonly associated with diarrhoea. Replace NFV with another PI.
Dyslipidaemia	PIs	Cholesterol and TG levels raised to grade 1 or 2: Monitor, diet, exercise Cholesterol and TG levels raised to grade 3 or 4: Treat raised TG with fibrates (fenofibrate 600 mg 1–2 times per day). Treat increased cholesterol with statins. Avoid simvastatin as it interacts with PIs (*see* Annex 4).
Insulin resistance and hyperglycaemia	IDV	Switch to a different PI.
Renal colic and calculi	IDV	Ask the patient to drink 3 litres of fluid per day. Consider switching to another PI.
GI intolerance	All ARVs	Usually self-limited, without need to discontinue ART. Symptomatic treatment should be offered.
Haematological toxicities (particularly anaemia and leucopenia)	AZT	If severe (Hb <6.5 g/dl) stop AZT and consider blood transfusion.
Hepatitic dysfunction	LPV/r and less commonly other PIs	If ALT >5-fold the basal level, discontinue ART and monitor. After resolution, try a different PI.
Hyperbilirubinaemia (indirect)	ATV, IDV	Generally asymptomatic, but can cause scleral icterus (without ALT increase). Replace ATV or IDV with another PI.

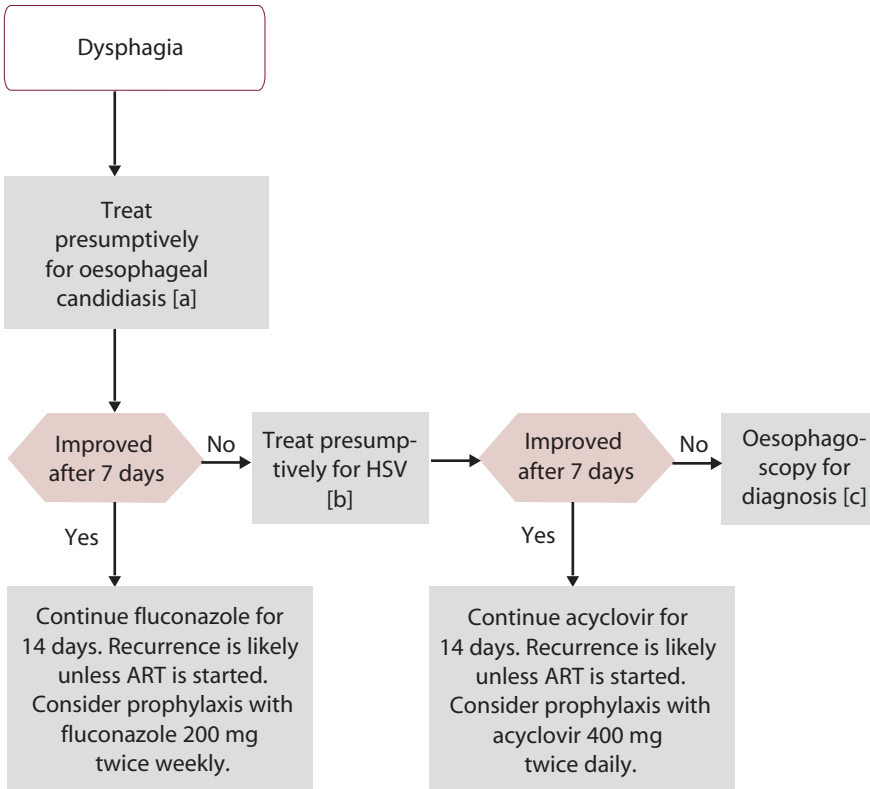
Table 34 *(contd)*: Symptom-directed management of toxicities of second-line antiretroviral drugs

Toxicity	Causative ARVs	Recommendations
Hypersensitivity reaction	ABC	Discontinue ABC and **do not restart**. Give symptomatic treatment. Re-exposure may lead to a severe and potentially life-threatening reaction.
Lactic acidosis	All NRTIs (particularly d4T and ddI)	Discontinue ART and give supportive treatment. After clinical resolution, resume ART, replacing the offending NRTI. ABC, TDF and 3TC are less likely to cause this type of toxicity.
Lipoatrophy and lipodystrophy	All NRTIs (particularly d4T) and PIs	Replace the suspected ARV drug with another. TDF and AZT are less likely to cause lipodystrophy than d4T and ddI. Among the protease inhibitors, atazanavir (ATZ) may cause less lipodystrophy than the other PIs.
Renal toxicity (renal tubular dysfunction)	TDF	Discontinue TDF and give supportive treatment. After clinical resolution, resume ART, replacing the offending drug. AZT, ddI or ABC may be substituted for TDF.

17 Syndromic Approach to The Management of Opportunistic Infections

17.1 Dysphagia

Figure 7. Management of dysphagia



Notes

[a] **Oesophageal candidiasis**

Candidiasis may infect the oesophagus in immune-compromised patients, causing difficulty and pain on swallowing. The diagnosis is based on clinical symptoms and response to systemic antifungal therapy. Endoscopy is not required unless the patient fails to respond to treatment.

Treatment

- Fluconazole 200 mg daily for 14 days **or**
- Itraconazole 400 mg daily for 14 days **or**
- Ketoconazole 200 mg daily for 14 days

[b] Acyclovir 400 mg every 4 hours

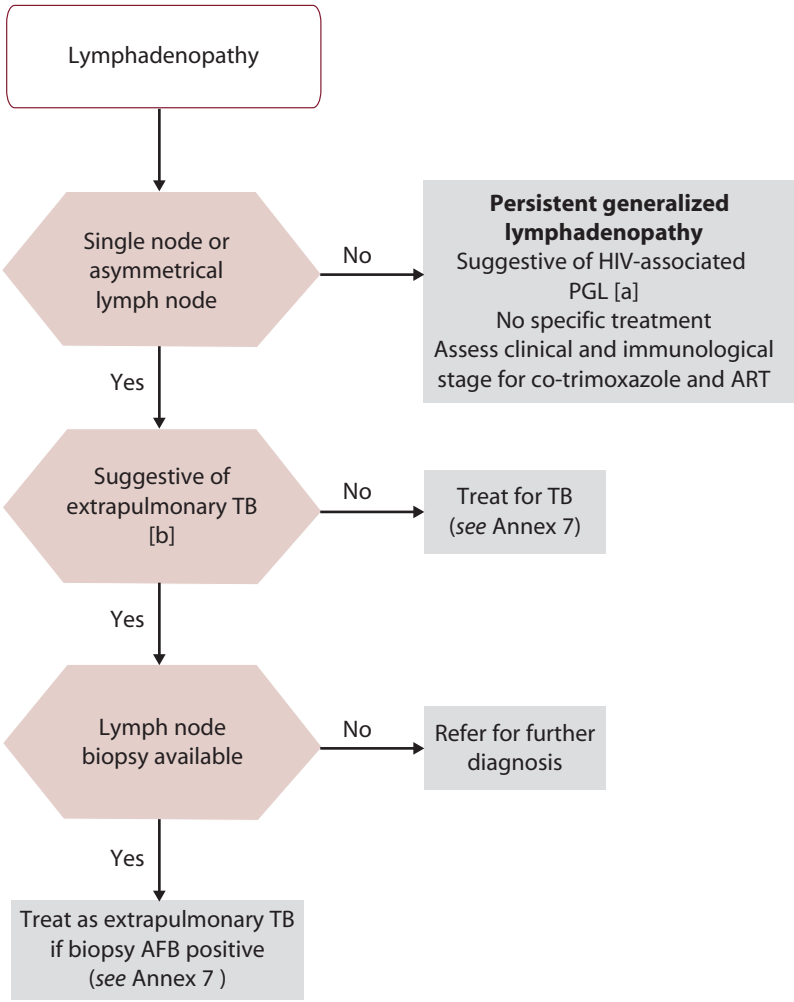
[c] **Failure of treatment**

Other causes of oesophagitis are CMV infection, Kaposi sarcoma and lymphoma.

Non-HIV related causes include acid reflux. Endoscopy is required for diagnosis.

17.2 Lymphadenopathy

Figure 8. Management of lymphadenopathy



AFB acid-fast bacilli

Notes

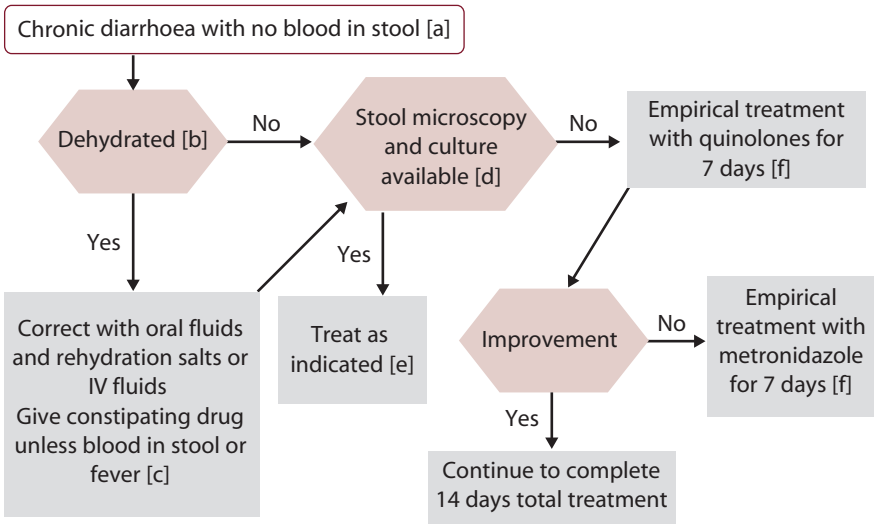
[a] **Persistent generalized lymphadenopathy (PGL)** is common in HIV-infected patients. In an asymptomatic patient no further investigation or treatment is required. However, in patients with recently symptomatic lymphadenopathy, rapidly enlarging nodes, marked nodal asymmetry and constitutional symptoms, further evaluation and treatment is necessary.

Causes of lymphadenopathy (other than HIV) include TB, cryptococcosis, histoplasmosis, lymphoma and Kaposi sarcoma.

[b] **Extrapulmonary TB** (EPTB) is common in HIV-infected patients. Clinical suspicion of TB is raised by the presence of the following signs and symptoms: fever, weight loss, unilateral nodes increasing in size, and matted and fluctuant nodes. Treat according to the national TB guidelines.

17.3 Chronic diarrhoea

Figure 9. Management of chronic diarrhoea without blood



Notes

[a] **Definition of chronic diarrhoea:** liquid stool three or more times a day, continuously or episodically for more than one month

[b] **Assessment of dehydration**

General appearance	Restless, irritable
Pulse	Rapid
Respiration	Deep, may be rapid
Skin elasticity	Pinched skin retracts slowly
Eyes	Sunken
Mucous membranes	Dry
Urine	Reduced in amount and dark in colour

In the case of **moderate dehydration**, correct with oral fluids and oral rehydration salts (ORS), prescribe intravenous fluids in case of severe dehydration. Supplemental feeding should be given slowly with multiple and divided feeding, along with intravenous fluids (minimum 1.5 litres of water a day).

[c] **Symptomatic treatment**

Loperamide, 4 mg initially, followed by a further 2 mg after each unformed stool (maximum daily dosage 16 mg). Constipating agents should not be used in patients with bloody diarrhoea, because of the risk of inducing toxic megacolon.

[d] Multiple stool examinations (each day for 3 days) increase the diagnostic yield.

[e] **Specific treatment for diarrhoea due to common pathogens**

Disease	Drug used	Dosage (per day)	Treatment duration
Salmonellosis and shigellosis	Ciprofloxacin 500 mg	2 times	7–10 days
	Ofloxacin 400 mg	2 times	7–10 days
Campylobacteriosis	Erythromycin 500 mg	4 times	5 days
Giardiasis	Metronidazole 500 mg	3 times	5 days
Amoebiasis	Metronidazole 500 mg	3 times	7–10 days
Isosporiasis	TMP–SMX 860 mg	4 times	7 days
Strongyloidiasis	Thiabendazole 25 mg/kg body weight	3 times	3 days
Mycobacterium avium complex	For treatment, *see* Annex 6		

Cryptosporidiosis: There is currently no established effective treatment except ART. Maintenance of fluid and electrolyte balance is of greatest importance, and agents that aid constipation may also be useful. In HIV-infected patients, salmonellosis, shigellosis, *Campylobacter* infection and isosporiasis often relapse. If relapse occurs after an initial course of antimicrobial therapy, a 6–12-week course of therapy should be administered.

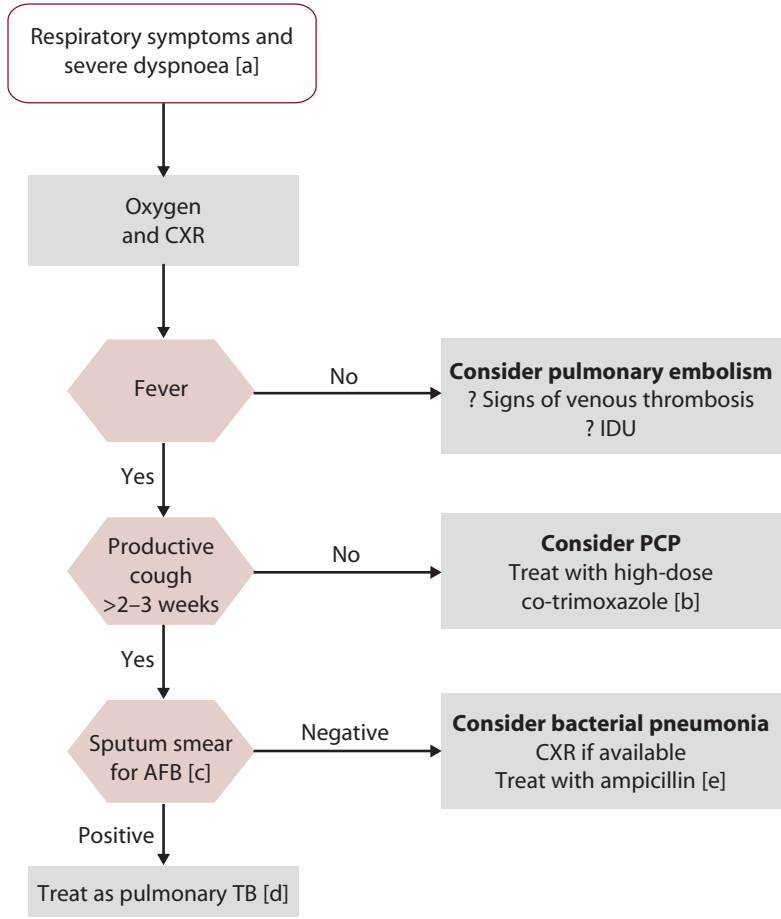
[f] If the patient improves after 7 days of therapy with metronidazole, the drug should be continued for a total of 14 days. If there is no improvement, consider other HIV-associated chronic diarrhoea including the possibility of starting ART (*see* Annex 1).

Empirical treatment for chronic diarrhoea without blood

Option	Drug used	Dosage/day	Treatment duration
1	Ciprofloxacin 500 mg **OR**	2 times	7–10 days
	Ofloxacin 400 mg	2 times	7–10 days
2	Metronidazole 500 mg	3 times	7 days

17.4 Respiratory symptoms

Figure 10. Management of respiratory symptoms



AFB acid-fast bacilli

Notes

[a] Common respiratory symptoms in patients with HIV infection and immunodeficiency are fever, dry cough (typical of PCP), productive cough with sputum and/or haemoptysis (typical of pneumonia and TB), shortness of breath and severe respiratory distress.

Causes of respiratory symptoms

Infections

- *Mycobacterium tuberculosis* (cough for >2–3 weeks)
- *Pneumocystis jiroveci* pneumonia (cough, often for 1–2 months)
- Bacterial pneumonia
- Fungal infection (cryptococcosis, histoplasmosis)
- Atypical mycobacteria (MAC)
- CMV pneumonitis
- Malignancies: lymphoma, Kaposi sarcoma

Others

- Pleural effusion/empyema (TB, bacterial infection or malignancies)
- Pneumothorax (TB or PCP)
- Pulmonary embolism (common among IDUs)
- Pericardial effusion (often associated with TB)

[b] **PCP:** Typically has a slow onset over weeks to months of dry cough, fever and shortness of breath. Clinical diagnosis supported by CXR findings is preferred for the diagnosis of PCP (*see* Annex 6).

[c] **Sputum examination** for acid-fast bacilli (AFB) is indicated in patients with cough for >2–3 weeks. At least two separate sputum smear examinations are recommended.

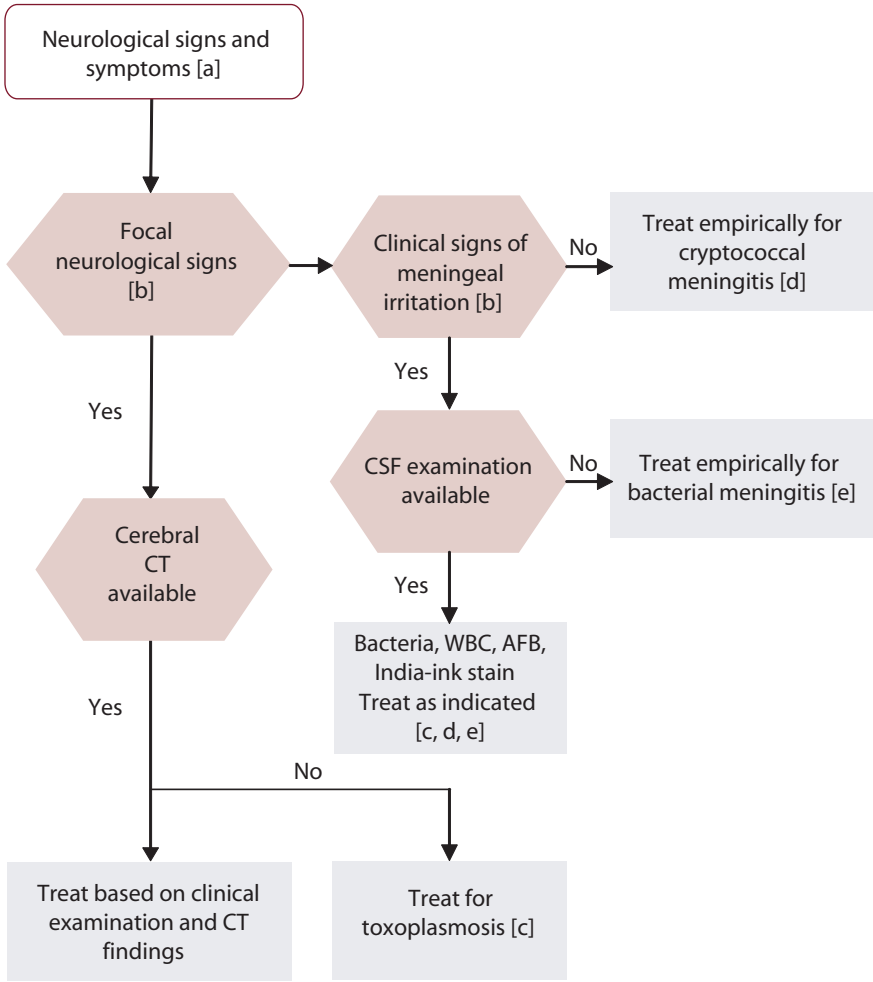
[d] **TB:** No CXR pattern is absolutely typical of pulmonary TB. The classical pattern is more common in HIV-negative patients; the atypical pattern is more common in HIV-positive patients. Pleural effusion is a prominent feature. Pleural tap and microscopic examination of the pleural fluid may be helpful for diagnosis. Treat according to national TB guidelines.

Classical pattern	**Atypical pattern**
Upper lobe infiltrates	Interstitial infiltrates (especially lower zones)
Cavitation	Bilateral infiltrates
Pulmonary fibrosis	No cavitation

[e] **Bacterial pneumonia:** The typical presentation is with productive cough, purulent sputum and fever for 1–2 weeks. PCP presents more slowly and there is normally non-productive cough. The typical CXR finding is lobar consolidation. Gram-positive pyogenic bacteria are the most probable cause of bacterial pneumonia. Amoxycillin 500 mg 3 times per day or erythromycin 500 mg 4 times per day for 7 days can be given if the clinical presentation suggests bacterial pneumonia and not PCP.

17.5 Neurological signs and symptoms

Figure 11. Management of neurological signs and symptoms



Notes

[a] Causes of **headache** include cryptococcal meningitis, tuberculous meningitis, cerebral toxoplasmosis, chronic HIV meningitis, bacterial meningitis and lymphoma.

Causes of headache not related to HIV infection include migraine, syphilis, tension, sinusitis, refractive disorders, dental disease, anaemia and hypertension. Other infectious diseases such as malaria, typhoid fever, dengue fever and rickettsiosis may also cause headache.

[b] **Neurological examination**

- Evidence of meningeal irritation (photophobia, neck stiffness) or raised intracranial pressure (high blood pressure and slow pulse in the presence of fever)
- Changes in mental state
- Focal neurological deficits including paresis, cranial nerve palsies, movement disorders, ataxia, aphasia and seizures

[c] **Toxoplasmosis** (for treatment, refer to Annex 6).

[d] **Cryptococcal meningitis** (for treatment, refer to Annex 6).

[e] **Bacterial meningitis**

Benzyl penicillin 1.2–2.4 million IU daily by IV injection every 4 hours in divided doses.
Treat for a minimum of 7 days or for 4–5 days after the patient becomes afebrile. Ceftriaxone 2–4 g daily by intravenous infusion or by deep intramuscular injection can be used if the patient is allergic to penicillin, ampicillin or chloramphenicol.

18 Nutritional Support

Depending upon the stage of the disease, HIV causes the following:

- Reduction in food intake
- Difficulties related to digestion
- Difficulties related to absorption
- Altered metabolism of nutrients (e.g. metabolism of carbohydrates/ lipids may be altered in HIV-infected persons)
- Altered body functions: inability to produce saliva, other digestive juices
- Improper utilization of fats.

Increased *resting energy expenditure* (REE) is observed in HIV-infected adults.

- Energy requirements are likely to increase by 10% to maintain body weight and physical activity in asymptomatic HIV-infected adults, and maintain growth in asymptomatic children.
- Once HIV infection becomes symptomatic, and subsequently after the development of AIDS, energy requirements increase by approximately 20–30% to maintain adult body weight.

Nutritional counselling must be provided every time PLHA visit the clinic. It is aimed at providing the following necessary practical guidelines on nutrition to PLHA and their caregivers:

1. Simple steps on food handling and safety:
    - Cook food thoroughly.
    - Eat cooked food immediately.
    - Store food carefully.
    - Re-heat cooked food thoroughly.
    - Avoid contact between raw and cooked food.
    - Wash your hands thoroughly before and after cooking.

- Keep kitchen surfaces clean.
- Protect food from rodents, insects and animals.
- Use clean water.

2. Commonly available food items and their nutritional content
3. Recommendations on which food items to avoid:
   - Raw eggs
   - Food that has not been thoroughly cooked, especially meat and chicken
   - Unboiled water or juices made with unboiled water.
   - Alcohol and coffee
   - Stale food
4. Symptom-based nutritional care and support **(Table 35)**
5. Nutrition and ART, including food–drug interactions

Paying greater attention to diet and nutrition may enhance the acceptability and effectiveness of ART, as well as adherence to it. Give counselling on correct nutrition and foods that can enhance the well-being of PLHA. Food can affect the absorption, metabolism, distribution and excretion of medication. Medication too can affect the metabolism of food.

- High-fat meals reduce the absorption of IDV (unboosted).
- High-fat meals increase the bioavailability of TDF.
- RTV causes changes in fat metabolism.
- The side-effects of medication may adversely affect the consumption and absorption of food, e.g. AZT causes nausea, anorexia and vomiting; ddI causes vomiting, diarrhoea and dryness of the mouth.
- The combination of certain medications and alcohol can produce side-effects, e.g. taking ddI together with alcohol may result in pancreatitis.
- Take AZT with low-fat meals.
- Take ddI on an empty stomach.
- Avoid alcohol with any medication.

Table 35: Symptom-based nutritional care

Symptoms	Management
Loss of appetite	▪ Eat small, frequent meals (5–6 meals/day) ▪ Eat nutritious snacks ▪ Drink plenty of liquids ▪ Take walks before meals—the fresh air helps to stimulate appetite ▪ Have family or friends assist with the preparation of food ▪ Take light exercise and do light activity ▪ Add flavour to drinks and food
Mouth ulcer	▪ Avoid citrus fruits, and acidic and spicy foods ▪ Eat food at room temperature ▪ Eat soft and moist food ▪ Avoid caffeine and alcohol
Candidiasis	▪ Eat soft, cool and bland foods (such as rice porridge, oatmeal, mashed vegetables, apple juice, milk) ▪ Add garlic (optional) ▪ Avoid sugar (glucose, cane sugar), yeast, caffeine, spicy food, carbonated drinks and alcohol
Nausea and vomiting	▪ Eat small, frequent meals ▪ Avoid being on an empty stomach as this makes the nausea worse ▪ Eat bland food ▪ Avoid food with strong or unpleasant odours ▪ Drink plenty of liquids ▪ Rest and relax after meals ▪ Avoid lying down immediately after eating ▪ Avoid coffee and alcohol
Constipation	▪ Eat fibre-rich and sprouted food ▪ Take light exercise and do light activity ▪ Drink plenty of water ▪ Take warm drinks
Anaemia	▪ Eat meat and fish ▪ Eat cereals ▪ Eat a variety of green leafy vegetables. The best way for the body to utilize iron from plant sources is to combine food rich in iron with a food rich in vitamin C, such as oranges, lemons, tomatoes and papaya

19 Palliative Care in HIV Infection[83]

19.1 Definition

Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification, and impeccable assessment and treatment of pain and other problems – physical, psychosocial and spiritual. Palliative care extends, if necessary, to support in bereavement.

Palliative care in HIV:

- is family and patient-centred;
- optimizes the quality of life by active participation, prevention and treatment of suffering;
- involves an interdisciplinary team approach throughout the continuum of illness, placing critical importance on the building of respectful and trusting relationships;
- addresses physical, intellectual, emotional, social and spiritual needs.

The availability of ART and palliative care has made HIV a chronic, manageable disease for many. Apart from regular management of pain, nutritional support and management of OIs, palliative care includes giving support for drug failure and severe toxicities due to ART.

Special attention needs to be given to the following HIV-related conditions, which may present as terminal illnesses. These conditions can be managed with proper medical care and support.

1. Severe oral and oesophageal candidiasis, leading to severe pain and weight loss.
2. Cryptococcal meningitis and toxoplasma encephalitis.

19.2 Components of palliative care

The main components of palliative care include the following:

- Pain management
- Symptom management
- Nutritional support
- Psychosocial support
- Spiritual support
- End-of-life care
- Bereavement counselling.

19.3 Management of pain

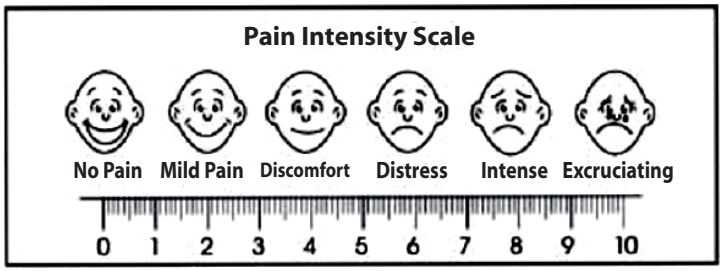
(1) Assess the patient for pain:

- Determine the severity, site and nature of the pain (bone pain, mouth pain, shooting nerve pain, colicky pain, severe muscle spasms).
- If there is infection, prompt management of infection is the main step in controlling the pain (e.g. treating severe oral and oesophageal candidiasis with fluconazole relieves the pain).
- The severity of the pain can be graded with the help of the tool below **(Figure 10)**.

GO BY WHAT THE PATIENT SAYS IS HURTING: Do not disregard the patient's complaint of pain just because there is no apparent physical cause.

Figure 12. Visual scale to assess pain intensity

The following format may be used for assessing pain in any patient.

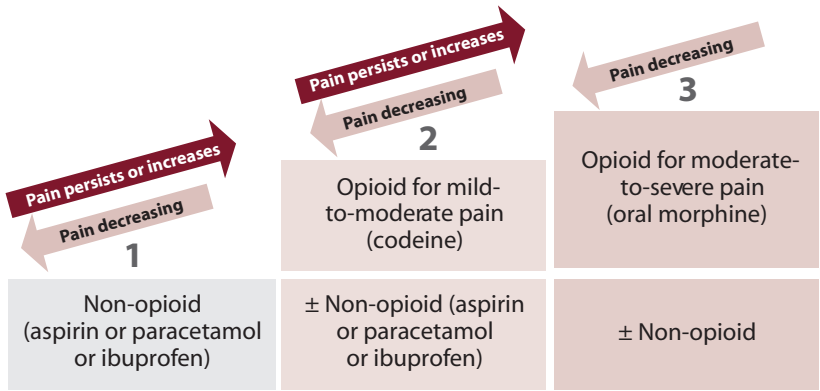


(2) The treatment strategies for pain are shown in Figure 13.

Figure 13. Strategies for treatment of pain

By mouth	By the clock
▪ If possible, administer painkiller by mouth (rectal administration is an alternative – avoid the intramuscular route).	▪ Give painkillers at fixed time intervals (by the clock or radio or sun). ▪ Start with a small dose, and then titrate the dose against the patient's pain until the patient is comfortable. ▪ The next dose should be given before the effect of the previous one wears off. ▪ For breakthrough pain, give an extra "rescue" dose, in addition to the regular schedule.

By the analgesic ladder:



The right dose is the dose that relieves the patient's pain.

Source: *Palliative care: symptom management and end-of-life care. Integrated management of adolescent and adult illness. Interim guidelines for first-level facility health workers.* Geneva, WHO, 2004.

(3) Use opioid and non-opioid analgesics:

Give only one drug from the opioid and non-opioid groups at a time. The exception is codeine – if it cannot be given, use aspirin every four hours combined with paracetamol every four hours – overlap the two so that one is given every two hours.

Table 36: Use of analgesics in pain relief

	Analgesics	Starting dose in adults	Range	Side-effects/ precautions
STEP 1	**Non-opioid**			
	Paracetamol (also lowers fever)	2 tablets of 500 mg every 4–6 hours (skip dose at night or give another analgesic to keep the total to 8 tablets)	Only 1 tablet may be required in the elderly or very ill, or when combined with an opioid. Mild pain may be controlled with 6-hourly dosing.	Do not exceed 8 tablets of 500 mg in 24 hours (more can cause serious liver toxicity).
	Aspirin (acetylsalicylic acid) (also anti-inflammatory and lowers fever)	300 mg (2 tablets) every 4 hours		Avoid use if gastric problems. Stop if epigastric pain, indigestion, black stools, petechiae or bleeding. Avoid if any bleeding is present.
	Ibuprofen (also anti-inflammatory, lowers fever, relieves bone pain)	400 mg every 6 hours		Maximum dose 8 tablets per day
STEP 2	**Opioid for mild-to-moderate pain (give in addition to aspirin or paracetamol)**			
	Codeine (if not available, consider alternating aspirin and paracetamol)	30 mg every 4 hours	30–60 mg every 4–8 hours Maximum daily dose for pain 180–240 mg as it causes constipation – if so, switch to morphine.	Give laxative to avoid constipation unless there is diarrhoea.

Table 36 *(contd)*: Use of analgesics in pain relief

	Analgesics	Starting dose in adults	Range	Side-effects/ precautions
STEP 3	**Opioid for moderate-to-severe pain**			
	Oral morphine 5 mg/5 ml or 50 mg/5 ml. Drop into mouth. Can also be given rectally (by syringe)	2.5–5 mg every 4 hours (dose can be increased by 1.5 mg or doubled after 24 hours if pain persists)	According to need of patient and breathing. There is NO ceiling dose.	Give laxative to avoid constipation unless there is diarrhoea.

Source: *Palliative care: symptom management and end-of-life care. Integrated management of adolescent and adult illness. Interim guidelines for first-level facility health workers.* Geneva, WHO, 2004.

19.4 Medications to control special pain problems

Pain may be due to special conditions, which can be relieved by specific medications **(Table 37)**. Provide specific treatment in combination with drugs from the analgesic ladder.

19.5 Additional methods for pain control

Combine these with pain medications if the patient agrees and it helps:

- Emotional support
- Physical methods: touch (stroking, massage, rocking, vibration); ice or heat; deep breathing
- Cognitive methods: distraction such as playing a radio, music, imagining a pleasant scene
- Prayer (with respect to the patient's practice)
- Traditional practices which are helpful and not harmful – get to know what can help in the local setting.

Table 37: Medications for special types of pain	
Special pain problems	**Medication**
For burning pain; pain due to abnormal sensation; severe, shooting pain with relatively little pain in between; pins and needles	Low-dose amitriptyline (25 mg at night or 12.5 mg twice daily; some start with 12.5 mg daily) – wait 2 weeks for response, then increase gradually to 50 mg at night or 25 mg twice daily.
For painful muscle spasms or paralysis	Diazepam 5 mg orally or rectally 2–3 times per day
Herpes zoster (or the shooting pain following it) Refer patients with ophthalmic zoster	Low-dose amitriptyline Early eruption: acyclovir if available; apply gentian violet if ruptured vesicles
Gastrointestinal pain from colic only after intestinal obstruction has been excluded (i.e. vomiting, no passage of stool and flatus, visible bowel movements)	Codeine 30 mg every 4 hours or antispasmodics such as hyoscine (buscopan) 10 mg three times daily (can increase up to 40 mg three times daily)
Bone pain or renal colic or dysmenorrhoea	Ibuprofen (or other non-steroidal anti-inflammatory drug [NSAID]
Pain from: ▪ Swelling around tumour ▪ Severe oesophageal ulceration and cannot swallow ▪ Nerve or spinal cord compression ▪ Persistent severe headache (likely from increased intracranial pressure)	When giving end-of-life care and referral not desired, can consider use of steroids under careful clinical supervision.

Source: *Palliative care: symptom management and end-of-life care. Integrated management of adolescent and adult illness. Interim guidelines for first-level facility health workers.* Geneva, WHO, 2004.

19.6 Symptom management

Table 38: Management of symptoms with medications and home care

Symptoms	Medications to give	Home care
Nausea and vomiting	Give an antiemetic: metoclopramide (10 mg every 8 hours). Give only for a day at a time or haloperidol (1–2 mg once daily) or chlorpromazine (25–50 mg every 6–12 hours).	The patient should ▪ Eat small, frequent meals. ▪ Avoid an empty stomach as this makes the nausea worse. ▪ Eat bland foods. ▪ Avoid foods with strong or unpleasant odours. ▪ Drink plenty of liquids. ▪ Rest and relax after and between meals. ▪ Avoid lying down immediately after eating. ▪ Avoid coffee and alcohol.
Painful mouth ulcers or pain on swallowing	▪ If *Candida:* give fluconazole, nystatin or miconazole orally Topical anaesthetics can provide some relief. Pain medication may be regulated according to analgesic ladder ▪ For aphthous ulcers: crush one 5 mg prednisone tablet and apply a few grains. ▪ Smelly mouth/breath (halitosis) from oral cancer or other lesions: metronidazole 400 mg twice a day or chlorhexidine gluconate 1% 10 ml mouthwash four times a day or hexetidine 0.1% 10 ml four times a day or benzydamine 0.5% mouthwash or sodium bicarbonate mouthwash (1 tsp in 1 pint warm water) ▪ For herpes simplex: Acyclovir 400 mg every four hours for 5 days	▪ Remove bits of food stuck in the mouth with cotton wool, gauze or soft cloth soaked in salt water. ▪ Rinse the mouth with diluted salt water (a finger pinch of salt or 1/2 teaspoon sodium bicarbonate in a glass of water) after eating and at bedtime. ▪ Mix 2 tablets of aspirin in water and rinse the mouth up to 4 times a day. ▪ Eat a soft diet to decrease discomfort such as rice porridge, oatmeal, depending on what the sick person feels is helpful. ▪ More textured foods and fluids may be easier to swallow than fluids. ▪ Avoid extremely hot or cold or spicy foods.

Table 38 *(contd)*: Management of symptoms with medications and home care

Symptoms	Medications to give	Home care
Bed sores	▪ All patients need skin care to avoid pressure problems. ▪ Check for signs of infection. ▪ For smelly tumours or ulcers, sprinkle metronidazole powder – enough to cover the area and keep dry.	▪ For small sores, clean gently with salt water and allow to dry. ▪ Apply honey to bedsores that are not deep and leave the wound open to the air. ▪ If painful, give painkillers such as paracetamol or aspirin regularly. ▪ For deep or large sores, clean daily gently with diluted salt water, fill the bedsore area with pure honey and cover with a clean light dressing to encourage healing.

Source: *Palliative care: symptom management and end-of-life care. Integrated management of adolescent and adult illness. Interim guidelines for first-level facility health workers.* Geneva, WHO, 2004.

19.7 End-of-life care

"How people die lives on in the memory of those left behind."

The terminal phase is defined as the period when day-to-day deterioration occurs, particularly of strength, appetite and awareness. It is difficult to predict when death will occur and it is better not to do so. The aim of care at this stage should be to ensure the patient's comfort holistically, and a peaceful and dignified death.

Provide psychosocial and spiritual support to the patient:

- Active listening, counselling and social/emotional support
- Spiritual support is very important:
  - Be prepared to discuss any matter the patient would like to.
  - Learn to listen with empathy.
  - Understand reactions to the patient's losses in life (the different stages of grief).
  - Be prepared to "absorb" some reactions, for example, anger projected onto the health-care provider.
  - Do not impose your own views.
  - Share religious beliefs with the appropriate person (e.g. religious leader, spiritual counsellor, etc.) as required.

- Empower the family to provide care:
  - Help the family come to terms with the fact that the patient is leaving them soon: let family members be around to see and talk to the patient.
  - Deal gently with their anxieties and fears.
  - Give information and teach skills.

Table 39: Management of end-of-life care issues

Steps	Actions
Preparing for death	▪ Encourage communication within the family. ▪ Discuss worrying issues such as custody of children, family support, future school fees, old quarrels, funeral costs. ▪ Tell the patient that they are loved and will be remembered. ▪ Talk about death if the person wishes to (keep in mind cultural taboos if not in a close relationship). ▪ Make sure the patient gets help with feelings of guilt or regret. ▪ Connect with a spiritual counsellor or arrange for pastoral care as the patient wishes.
Presence	▪ Approach, be present and compassionate. ▪ Make an outreach visit regularly and offer home-based care. ▪ Someone needs to hold the hand, listen, converse with the patient and family.
Caring	▪ Provide comfort and physical contact by light touch, holding hands (if appropriate).
Comfort measures near the end of life	▪ Moisten lips, mouth, eyes. ▪ Keep the patient clean and dry and prepare for incontinence of the bowel and bladder. ▪ Give only essential medications – pain relief, antidiarrhoeals, and treat fever and pain (e.g. paracetamol round-the-clock), etc. ▪ Control symptoms with medical treatment as needed to relieve suffering (including antibiotics and antifungals). ▪ Eating less is acceptable. Ensure hydration. ▪ Take care of the skin; turn the patient every 2 hours or more frequently to prevent bed sores.
Signs of imminent death	▪ Decreased social interaction – sleeps more, acts confused, coma ▪ Decreased food and fluid intake – no hunger or thirst ▪ Changes in elimination – reduced urine and bowel movements, incontinence ▪ Respiratory changes – irregular breathing, "death rattle" ▪ Circulatory changes – cold and greyish or purple extremities, decreased heart rate and blood pressure
Signs of death	▪ Breathing stops completely ▪ Heart beat and pulse stop ▪ Totally unresponsive to shaking, shouting ▪ Eyes fixed in one direction, eyelids open or closed ▪ Changes in skin tone – white to grey

20 Management of Occupational Exposure Including Post-exposure Prophylaxis[84]

20.1 Introduction

Avoiding occupational exposure to blood is the primary way to prevent transmission of HIV, HBV and HBC in health-care settings. Hepatitis B immunization and appropriate post-exposure management are integral components of a programme to prevent infection following exposure to blood-borne pathogens.

Appropriate post-exposure management guidelines form an important element of workplace safety. These guidelines should describe the risks of infection, preventive measures and procedures to be followed after occupational exposure.

These guidelines should address the following aspects of occupational exposure to blood:

- Who is at risk?
- What is the risk?
- What practices may influence this risk and how can the risk be minimized?
- What is the role of antiretroviral agents in reducing this risk?
- Issues about the safety of drugs for post-exposure prophylaxis (PEP) and their use in pregnancy
- Operational recommendations to develop a comprehensive programme for implementation of PEP with 24-hour access to the needed drugs.

20.2 Definitions

Occupational exposure refers to exposure to potential blood-borne infections (HIV, HBV and HCV) that occurs during the performance of job duties.

Post-exposure prophylaxis refers to the comprehensive management given to minimize the risk of infection following potential exposure to bloodborne pathogens (HIV, HBV, HCV). This includes counselling, risk assessment, relevant laboratory investigations based on informed consent of the source and exposed person, first aid and, depending on the risk assessment, the provision of short-term (4 weeks) ARV drugs, with follow up and support.

The term **health-care personnel (HCP)** includes any person, paid or unpaid, working in health-care settings, who is potentially exposed to infectious materials (e.g. blood, tissue and specific body fluids, and medical supplies, equipment, or environmental surfaces contaminated with these substances). If required, PEP can also be given to public safety workers, including law enforcement personnel, prison staff, fire-fighters, workers in needle-exchange programmes and workers in international HIV programmes.

Exposure that may place an HCP at risk for a bloodborne infection is defined as:

- A percutaneous injury (e.g. needle-stick or cut with a sharp instrument)
- Contact with the mucous membranes of the eye or mouth
- Contact with non-intact skin (particularly when the exposed skin is chapped, abraded, or afflicted with dermatitis), or
- Prolonged contact (e.g. several minutes or more) with intact skin contaminated with blood or other potentially infectious body fluids.

20.3 Principles of providing PEP

Non-discrimination: The decisions about whether to provide PEP should be based only on the clinical consideration of risk. Providers should give information, services and education without discrimination.

Confidentiality: The provision of information regarding PEP should be confidential, including information about HIV testing, PEP provision and the reasons for seeking PEP.

Informed consent: Informed consent for taking PEP needs to be obtained as for any other medical procedure. This should be taken in writing. Consent for HIV testing in the context of HIV exposure and/or taking PEP needs to conform to the national counselling and testing guidelines.

20.4 Who is at risk?

Professionals with frequent exposure to blood:

- Interns and medical students
- Nurses and nursing students
- Physicians
- Surgeons
- Labour and delivery room personnel
- Emergency care providers
- Dentists
- Laboratory technicians
- Pathologists, autopsy staff
- Health facility cleaning staff and clinical waste handlers.

20.5 Infectious body fluids

Not all body fluids are considered to carry a risk for HIV transmission **(Table 40)**.

Table 40: Potentially infectious body fluids

Exposure to body fluid considered *"at risk"*	**Exposure to body fluid considered *"not at risk"***	
Blood	Tears	*unless these secretions contain visible blood*
Semen	Sweat	
Vaginal secretions	Urine and feces	
Cerebrospinal fluid	Saliva	
Synovial, pleural, peritoneal, pericardial fluid		
Amniotic fluid		

Any direct contact (i.e. contact without barrier protection) to concentrated virus in a research laboratory or production facility requires clinical evaluation. For human bites, clinical evaluation must include the possibility that both the person bitten and the person who inflicted the bite were exposed to bloodborne pathogens. Transmission of HIV infection after human bites has rarely been reported.

20.6 What is the average risk of acquiring HIV, HBV or HBC infection after an occupational exposure?

The average risk of acquiring HIV infection after different types of occupational exposure is low compared with the risk of acquiring HBV or HCV infection. In terms of occupational exposure the important routes are needle-stick exposure (0.3% risk for HIV, 9–30% for HBV and 1–10% for HCV) and mucous membrane exposure (0.09% for HIV).

20.7 Practices that influence risk and how to reduce risk (occupational exposure)

Certain work practices increase the risk of needle-stick injury such as:

- Recapping needles (most important)
- Transferring a body fluid from one container to another
- Failing to dispose of used needles properly in puncture-resistant sharps containers
- Poor health-care waste management practices.

Protecting oneself from needle-stick/sharps injuries

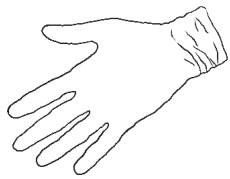
- Avoid the use of needles where safe and effective alternatives are available.
- Avoid recapping needles.
- Plan for safe handling and disposal of needles before using them.
- Promptly dispose of used needles in appropriate sharps disposal containers.
- Report all needle-stick and sharps-related injuries promptly to ensure that you receive appropriate follow-up care.
- Participate in training related to infection prevention.
- Help your institute select and evaluate devices with safety features that reduce the risk of needle-stick injury.
- Use devices with safety features provided by the institute (wherever possible).
- Record and monitor injuries by means of an injury register in each location of health-care setting.

20.8 Preventing exposure to and transmission of HIV and other viruses

Staff information: All categories of HCP within the hospital should be informed about how to protect themselves against HIV and other pathogens transmitted by blood or body fluids. The knowledge must be reinforced on a regular basis. All staff share an individual and collective responsibility in this regard. The medical director/dean/principal/person responsible for hospital policies must constitute a hospital infection control committee which will conduct regular training and monitor hospital infection control including universal standard precautions, and implementation of PEP and quality control. The medical director must ensure that the hospital has a written protocol and standard operating procedure (SOP) for handling occupational exposure and that these are disseminated to all relevant personnel/departments.

Key information:

- The universal standard precautions to be followed in the health services (**Box 7**)
- Use of personal protective equipment
- Other preventive measures to be taken against these viruses (including vaccination)
- SOPs to be followed in case of accidental exposure to blood and body fluids.



Minimize the use of sharps/injections: All medical staff should try to minimize the use of invasive interventions, for example, use oral drugs in place of injections wherever possible. Where the use of sharps is indicated try to use safer alternatives where practical and possible within the limitations of the system.

Protection against HBV: All HCP should be vaccinated against HBV. The schedule comprises three doses; initial dose on day 0, second dose after one month and third dose after six months. Seroconversion after completing the full course is 99% (*see* p. 100).

Box 7: Universal standard precautions

Universal standard precautions are intended to prevent exposure of HCP and patients to bloodborne pathogens. These must be practised with regard to the blood and body fluids of all patients, regardless of their infection status.

Universal standard precautions include:

- Hand-washing before and after all medical procedures.
- Safe handling and immediate safe disposal of sharps: not recapping needles; using special containers for sharps disposal; using a needle cutter/destroyer; using forceps instead of the fingers for guiding sutures; using vacutainers where possible.
- Safe decontamination of instruments.
- Use of protective barriers whenever indicated to prevent direct contact with blood and body fluids such as gloves, masks, goggles, aprons and boots. An HCP who has a cut or abrasion should cover the wound before providing care.
- Safe disposal of contaminated waste.

20.9 Management of the exposed person

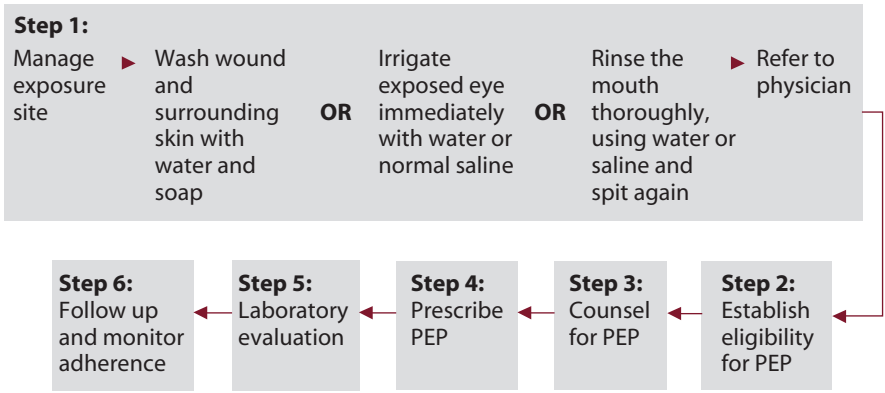
Table 41: Summary of dos and don'ts

Do	Do not
Remove gloves, if appropriate	**Do not** panic
Wash the exposed site thoroughly with running water	**Do not** put the pricked finger in the mouth
Irrigate with water or saline if the eyes or mouth have been exposed	**Do not** squeeze the wound to bleed it
Wash the skin with soap and water	**Do not** use bleach, chlorine, alcohol, betadine, iodine or other antiseptics/ detergents on the wound

Do: Consult the designated physician immediately for management of the occupational exposure as per institutional guidelines.

20.10 Steps for managing occupational exposure

Step 1: Manage the exposure site – First aid



For the skin – if the skin is broken after injury with a needle-stick or sharp instrument:

- Immediately wash the wound and surrounding skin with water and soap, and rinse. Do not scrub.
- Do not use antiseptics or skin washes (bleach, chlorine, alcohol, betadine).

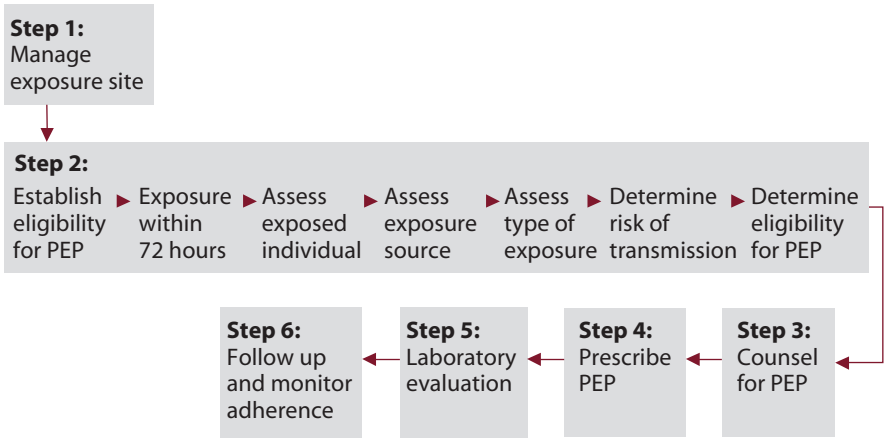
After a splash of blood or body fluids:

- For unbroken skin:
  - Wash the area immediately with water and soap, and rinse. Do not scrub.
  - Do not use antiseptics or skin washes (bleach, chlorine, alcohol, betadine).
- For the eye:
  - Irrigate the exposed eye immediately with water or normal saline.
  - Sit on a chair, tilt the head back and ask a colleague to gently pour water or normal saline over the eye.
  - If wearing a contact lens, leave it in place while irrigating, as it forms a barrier over the eye and will help protect it. Once the eye is cleaned, remove the contact lens and clean it in the normal manner. This will make it safe to wear again.
  - Do not use soap or disinfectant in the eye.

- For the mouth:
  - Spit out fluid immediately.
  - Rinse the mouth thoroughly, using water or saline and spit again. Repeat this process several times.
  - Do not use soap or disinfectant in the mouth.

Consult the designated physician of the institution immediately for management of the exposure.

Step 2: Establish eligibility for PEP



A risk assessment to establish eligibility for PEP should be undertaken by a trained person as soon as possible after every occupational exposure, no matter what time of the day it occurs. The risk assessment is conducted to determine the severity of the exposure and whether any immediate medical action (such as the provision of PEP) is required. An appropriate risk assessment should be performed as close to the workplace as possible, depending on the competency of workplace support.

Local protocols must designate the person or position to be contacted to perform a risk assessment. If there is no one on duty with the necessary skills, this could be performed over the telephone, or radio (or other method of communication over a distance) if a skilled person or service has been identified in the protocol.

The first dose of PEP should be administered within the first 72 hours of exposure and the risk evaluated as soon as possible. If the risk is insignificant, PEP could be discontinued if already commenced.

Even if the exposure is not considered to be significant for HIV transmission, prompt intervention including assessment and communication of risk can significantly reduce the anxiety a worker may experience after an exposure.

Two main factors determine the risk of infection: the status of the source patient and the type of exposure.

Box 8: Eligibility criteria for PEP

1. Exposure less than 72 hours ago, **and**
2. Exposed individual not known to be HIV-infected, **and**
3. Source of exposure HIV-infected or of unknown status, **and**
4. Exposure was to blood, body tissues, visibly blood-stained fluid, concentrated virus, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid or amniotic fluid, **and**
5. Exposure penetrated the skin with spontaneous bleeding or deep puncture, **or** a significant amount of fluid splashed onto a mucous membrane, or there was prolonged contact of at-risk substance with non-intact skin, **and**
6. (If skin penetration) Exposure was from a recently used hollow-bore needle or other sharp object visibly contaminated with blood.

Assess status of the exposed individual

The exposed individual should be assessed for **pre-existing HIV infection** as PEP is intended for people who are HIV-negative at the time of their potential exposure to HIV. Exposed individuals who are known or discovered to be HIV-positive should not start or continue PEP. In the case of unknown HIV status PEP should be started before the test result is known.

Assessing the status of the exposure source

If the source person's HIV infection status is unknown at the time of exposure, use of PEP should be decided on a case-by-case basis, after

considering the type of exposure and the clinical and/or epidemiological likelihood of HIV infection of the source.

Identification and HIV testing of the source of the exposure is only necessary **if the results are likely to change the clinical management of the exposed worker.** If the exposure is assessed as having no or very low risk of HIV transmission, there is no need to test the source.

If the HIV status of the source is not already known or available by rapid testing, the decision to commence PEP should be based on the factors listed above. Waiting for the results of the source's test will jeopardize the timeliness of commencing PEP. Therefore, PEP should be given after a significant exposure if there is a possibility that the source is HIV-positive.

Source testing should be encouraged using standard national HIV testing and counselling protocols. The source could consent to testing but PEP should be started without waiting for the results. Source testing in all workplace settings requires consent. The exposed worker must not be involved in obtaining consent from the source for HIV testing.

If the source can be tested and consents to testing, the test results should be a part of the decision as to whether to continue PEP if commenced. If the source is HIV antibody negative at the time of the incident, assessment should be made as to whether the person could possibly be in the window period before the HCP makes a decision to discontinue PEP if commenced.

In the case of a source who is unknown, or unable or unwilling to be tested, universal standard precautions dictate that all sources should be regarded as potentially HIV-infected and PEP should be initiated if indicated by the severity of the exposure.

If the source is known to be HIV-positive the treating physician should be consulted for the history of and response to ART.

Assessing the nature of exposure and risk of transmission

Table 42: Factors to be considered in a risk assessment

Type of exposure – sharps injury

- The type (solid or hollow-bore) and size of the needle or sharp object
- What the needle or sharp object was used for
- The severity of the injury
- Whether the penetration site bled
- The type of blood or body substance the person was exposed to
- The amount of blood or body substance the person was exposed to
- Whether the injury occurred through gloves or clothing
- When the exposure occurred
- How recently the sharp had been used

Type of exposure – splash

- The type of body fluids the person was exposed to
- Whether the fluid the person was exposed to contained blood
- The amount of blood or body substance the person was exposed to
- Whether non-intact skin or mucous membrane was exposed
- When the exposure occurred

Source (of the blood or body fluid or tissue)

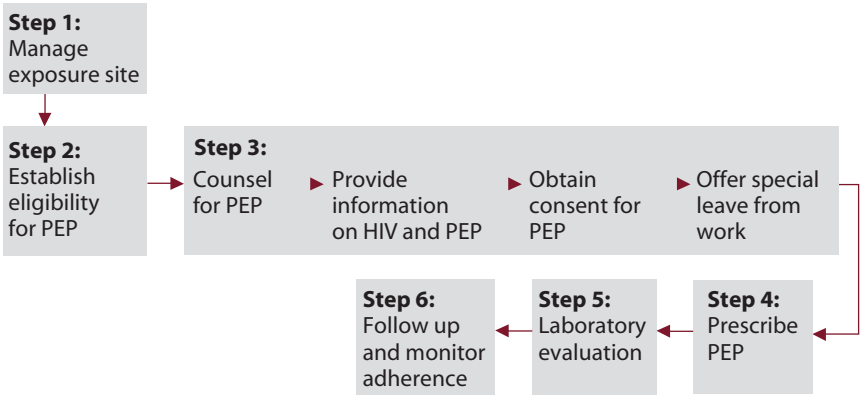
- Known or unknown
- HIV status (if known)
- Stage of HIV infection (if known)
- HIV RNA viral load (if known)
- ART history (if known)
- Estimated population prevalence of HIV (this includes geographical region and country prevalence, and also prevalence within the cultural, ethnic or behavioural group)

Wearing of gloves during any of these accidents constitutes a protective factor.

Note

In case of an accidental exposure to blood with material such as discarded sharps/needles contaminated for over 48 hours, the risk of infection becomes negligible for HIV, but still remains significant for HBV. HBV survives longer than HIV outside the body.

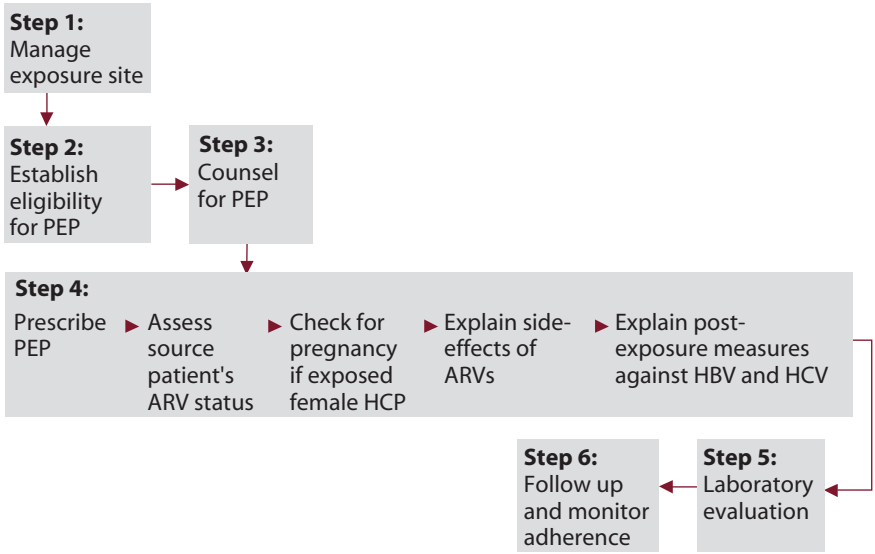
Step 3: Counsel for PEP



Exposed persons should receive appropriate information and counselling about what PEP is and the risks and benefits of PEP in order to provide informed consent. It should be clear that PEP is not mandatory.

Special leave from work should be considered and offered for a period of time, e.g. two weeks (initially), then as required based on an assessment of the exposed person's mental state, side-effects of PEP and other requirements.

Step 4: Prescribe PEP



The drugs used for PEP should be aligned with the formulary adopted in the country. AZT, 3TC and boosted PIs are the most common ARV drugs used in these situations. An alternative NRTI that can be considered is d4T. **NVP is NOT recommended for PEP** due to the risk of severe reactions reported in these situations. EFV should be avoided due to its CNS side-effects and should not be given to pregnant women or women with childbearing potential. There is also no evidence that a three-drug PEP regimen is superior to a two-drug one.

- **A two-drug regimen** is used for all exposures that may have a potential risk of HIV transmission.
- **A three- or more drug regimen** is used for all exposures that may have a potential risk of HIV transmission where the source is known or suspected to have ARV resistance.

Selection of the PEP regimen when the source patient is known to be on ART: The physician should consider the comparative risk represented by the exposure and information about the source of the exposure, including history of and response to ART based on clinical response, CD4 cell counts, viral load measurements (if available), and current disease stage (WHO clinical staging and history). When the source person's virus is known or suspected to be resistant to one or more of the drugs considered for the PEP regimen, it is recommended that drugs to which the source person's virus is unlikely to be resistant be selected. Refer to an expert for opinion.

If this information is not immediately available, **initiation of PEP, if indicated, should not be delayed. Give the two-drug (basic) regimen (Table 43).** Changes in the PEP regimen can be made after PEP has been started, as appropriate. Re-evaluation of the exposed person should be considered within 72 hours post exposure, especially as additional information about the exposure or source person becomes available.

Table 43: PEP regimens

	Preferred	Alternative
Two-drug regimen (basic PEP regimen)	**First choice:** AZT + 3TC	**Second choice:** d4T + 3TC
Three-drug regimen (expanded PEP regimen): consult an expert before starting a third drug, e.g. LPV/r, NFV or IDV.		
Not recommended	ddI + d4T combination NNRTIs such as NVP should not be used for PEP.	

More information on alternative schedules is available in the latest update of the Updated US Public Health Service (USPHS) Guidelines issued on 30 September 2005. (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5409a1.htm) or www.who.int

PEP during pregnancy

If the exposed person is pregnant, the risk of infection and need for PEP should be evaluated as with any other person who has had an exposure to HIV. However, the decision to use any ARV drug during pregnancy should involve a discussion between the woman and her physician regarding the potential benefits and risks to her and the fetus.

Data regarding the potential effects of ARV drugs on the developing fetus or neonate are limited. There is a clear contraindication for EFV (first 3 months of pregnancy) and IDV (prenatal).

In conclusion, for a female HCP considering PEP, a **pregnancy test** is recommended if there is any chance that she may be pregnant. It is recommended that pregnant HCP begin the basic two-drug regimen, and if a third drug is needed, NFV is the drug of choice.

Side-effects and adherence to PEP

Studies of HCP taking PEP have reported more side-effects than PLHA taking ART, most commonly nausea and fatigue. Possible side-effects occur mainly at the beginning of treatment and include nausea, diarrhoea, muscular pain and headache. The person taking the treatment should be informed that these may occur and **should be dissuaded from stopping treatment** as most side-effects are mild and transient, though possibly uncomfortable (*see* **Tables 19, 20**). Anaemia and/or leucopenia and/or thrombocytopenia may occur during the month of treatment. A complete blood count and liver function tests (transaminases) may be performed at the beginning of treatment (as baseline) and after 4 weeks.

In practice and from HCP studies, many HCP do not complete the full course of PEP because of side-effects. Side-effects can be reduced by prescribing regimens that do not include a PI, by giving medications

to reduce nausea and gastritis, and by educating clients about how to reduce side-effects, e.g. taking PEP medications with food. It is important that side-effects should be explained before initiating PEP so that the symptoms are not confused with symptoms of seroconversion to HIV.

Information on adherence and psychological support are essential. More than 95% adherence is important to maximize the efficacy of PEP.

Dispensing PEP

All clients starting on PEP must take four weeks (28 days) of medication. In all cases, the **first dose of PEP** should be offered as soon as possible, once the decision to give PEP has been made. HIV testing can be done later and results of the source's HIV test can follow.

As usage of PEP drugs is not frequent and the shelf-life is 1–1.5 years, it is proposed that **starter packs for 7 days** can be put in the emergency department with instructions to go to a designated clinic/officer within 1–3 days for a complete risk assessment, HIV counselling and testing, and dispensing of medications and management. At least three such kits should be provided in the casualty department.

Post-exposure measures against hepatitis B and C

Hepatitis B

All health staff should be vaccinated against HBV.

Unvaccinated persons or persons known to not have responded to a complete hepatitis B vaccine series should receive both hepatitis B immune globulin (HBIG) and hepatitis B vaccine as soon as possible after exposure (preferably <24 hours) if the exposure source is **known to be HBsAg**-positive. Hepatitis B vaccine may be administered simultaneously with HBIG at a separate injection site.[85]

Schedule for hepatitis B vaccination					
Vaccine	**Age**	**Dose**	**Volume**	**No. of doses**	**Schedule**
Engerix-B	<20 years	10 µg	0.5 ml	3	0, 1–2, 4 months*
	≥20 years	20 µg	1 ml	3	0, 1, 6 months*
Recombivax HB	≥ 20 years	10 µg	1 ml	3	0, 1, 6 months

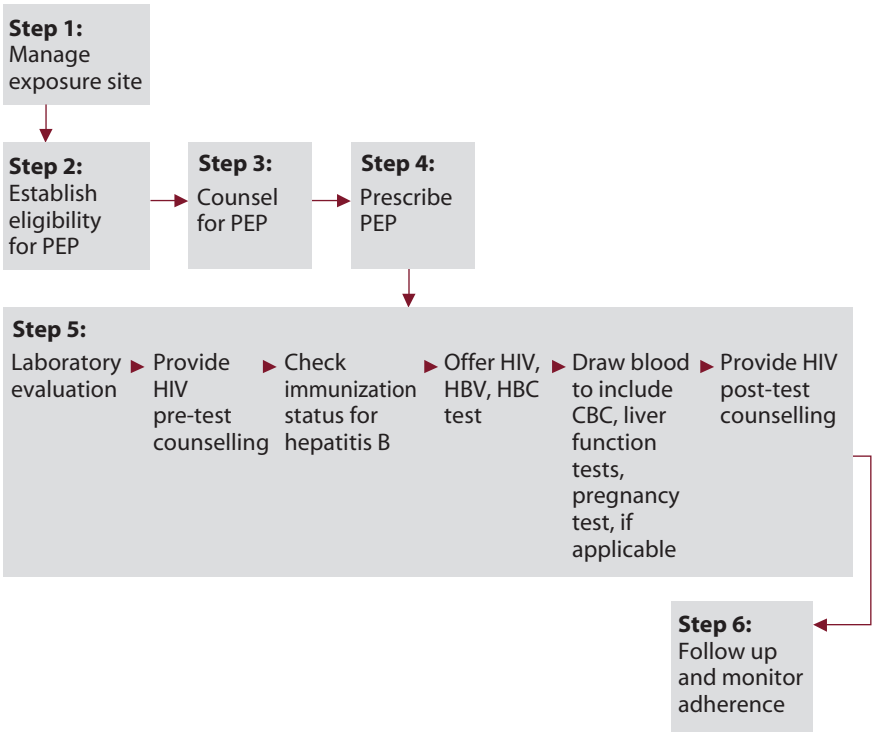
* Double-dose regimen is recommended in the context of HIV infection.

Unvaccinated persons should receive the hepatitis B vaccine series with the first dose initiated as soon as possible after exposure, preferably <24 hours if the exposure source has an **unknown HBsAg status**. The vaccine series should be completed using the age-appropriate dose and schedule.[85]

Hepatitis C

There is presently no vaccine available against hepatitis C. There is no post-exposure prophylaxis for HCV disease.

Step 5: Laboratory evaluation



The reason for HIV testing soon after an occupational exposure is to establish a "baseline" against which to compare future test results (**Table 44**). If the worker is HIV-negative at the baseline test, it is in principle possible to prove that subsequent infection identified by follow-up testing is related to the occupational exposure (depending on the

timing of infection and consideration of other risks or exposures). When offered HIV testing, the exposed person should receive standard pre-test counselling according to the national HIV testing and counselling guidelines, and should give informed consent for testing. Confidentiality of the test result must be assured.

There are different reasons for possibly delaying HIV testing: the HCP may be unable to give informed consent immediately after the exposure due to anxiety, the exposure occurs outside working hours or in settings where HIV testing is not readily available. The HIV test may be done up to several days after the exposure, with assurance and respect for confidentiality, based on informed consent and with pre- and post-test counselling.

Providing PEP should not be delayed if HIV testing is not available.

Table 44: Recommended baseline laboratory evaluation

Timing	In persons taking PEP (standard regimen)	In persons not taking PEP
Baseline (within 8 days after accidental exposure to blood)	Antibodies: HIV, HCV, HBV in unvaccinated HCP Complete blood count Transaminases	Antibodies: HIV, HCV, HBV in unvaccinated HCP

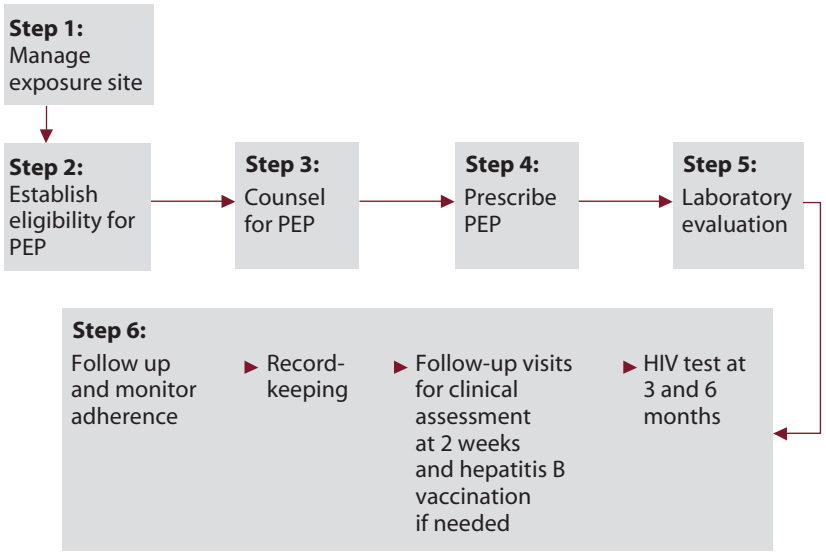
HIV RNA testing by polymerase chain reaction (PCR) during PEP has a very poor positive predictive value and should be strongly discouraged.

Pregnancy testing should also be available, but its unavailability should not prevent the provision of PEP.

Other laboratory testing such as haemoglobin measurement should be available, especially when AZT is used for PEP in areas where anaemia is common. The absence of baseline laboratory testing should not delay the commencement of PEP.

Testing for other bloodborne diseases such as syphilis, malaria and kala-azar may also be useful, depending on the nature of risk, symptoms of the source patient, local prevalence and laboratory capacity.

Step 6: Follow up of an exposed person



The treating physician should document the findings of steps 1–5 in the patient record and findings from follow-up visits.

Whether or not PEP prophylaxis has been started, follow up is indicated to monitor for possible infections and provide psychological support.

The exposed person must be monitored for the eventual appearance of signs indicating HIV seroconversion: acute fever, generalized lymphadenopathy, cutaneous eruptions, pharyngitis, non-specific 'flu-like symptoms and ulcers in the mouth or genital area. These symptoms appear in 50–70% of individuals with primary (acute) HIV infection and almost always within 3–6 weeks after exposure.

An exposed person should be advised to use precautions (e.g. avoid blood or tissue donations, breastfeeding, unprotected sexual relations or pregnancy) to prevent secondary transmission, especially during the first 6–12 weeks following exposure. **Use of condoms is recommended.**

Counselling for adherence and side-effects should be provided and reinforced at every follow-up visit. Psychological support and mental health counselling are often required.

Follow-up HIV testing: Exposed persons should be offered HIV testing following national guidlines. A baseline HIV test and **testing at 3 months and again at 6 months is recommended**. Very few cases of seroconversion after 6 months have been reported. Hence, no further testing is recommended if the HIV test at 6 months is negative.

Psychological support: Many people feel anxious after exposure. Every exposed person needs to be informed about the risks and measures that can be taken. This will help to relieve part of the anxiety, but some may require further specialized psychological support.

21 Management of Non-occupational Exposure Including Post-exposure Prophylaxis

21.1 Definition

Non-occupational exposure refers to exposure to potential blood-borne infections (HIV, HBV, HCV) outside the work setting.

Table 45: Estimated risk for acquisition of HIV by exposure route[86]

Exposure type (sexual exposure assumes no condom use)	Risk per 10 000 exposures to an infected source
Blood transfusion	9000
Needle-sharing injecting drug use	67
Receptive anal intercourse	50
Percutaneous needle-stick injury	30
Receptive penile–vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive penile–vaginal intercourse	5

21.2 Situations where non-occupational post-exposure prophylaxis (nPEP) may be provided

- Unprotected sexual exposure including rape
- Needle-sharing by IDUs (single event);
- Injuries from needles discarded in public places with visible blood on them, and[87]
- Human bite injuries.

21.3 Situations where nPEP should not be provided

nPEP should not be provided in case of persistent potential exposure to HIV such as discordant sex partners who rarely use condoms, repeated unprotected sex with sex workers or other non-regular partners, and IDUs who often share injecting equipment. Persons who engage in frequent, recurrent, high-risk behaviour should be counselled and provided with appropriate risk-reduction interventions.

21.4 Evidence for providing nPEP

In Sao Paulo, Brazil 180 women presenting within 72 hours of assault were treated for 28 days with AZT and 3TC (for those without mucosal trauma) or AZT, 3TC and IDV (for those with mucosal trauma or those subjected to unprotected anal sex). None of the women seroconverted. However, 4/145 women (2.7%) who were not treated seroconverted.[88]

Four hundred eighty HIV-negative rape victims in South Africa received AZT and 3TC and were followed up for at least 6 weeks. A woman who was started on AZT + 3TC 96 hours after the assault was the only one who seroconverted.[86]

In Brazil, nPEP (AZT + 3TC) was offered to 200 homosexual and bisexual men. Among the men who took nPEP, only one seroconverted, while among those who did not, 11 seroconverted.[89,90]

21.5 Evaluation of persons with potential non-occupational exposure to HIV

This evaluation should include:

- HIV status of the person potentially exposed to HIV
- Timing and characteristics of the most recent exposure
- Frequency of potential exposures to HIV
- HIV status of the source if it can be ascertained
- Concomitant STIs.

21.6 Initiating nPEP

The same schedule is recommended as for occupational PEP; commence ARVs as soon as possible after the exposure, within 72 hours, and continue for 28 days. There are no data to support the use of PEP started after 72 hours.

21.7 HIV status of the source

When the HIV status of the source is unknown, determine whether the source is available for HIV testing. If the risk associated with the exposure is considered substantial, nPEP can be started pending determination of

the HIV status of the source and then stopped if the source is determined to be non-infected.

When the source is known to be from a group with a high prevalence of HIV infection (e.g. a homosexual or bisexual man, an IDU, or a sex worker), the risk of transmission is increased. In the case of sexual violence, the source person may not be identifiable. Where the HIV status of the source is unknown and cannot be determined, nPEP should be offered following risk evaluation and counselling of the exposed person by a trained HCP. In case of sexual violence the steps for PEP may differ from those of other other non-occupational exposure and are described elsewhere.[91]

If the source person is known to be HIV-positive, nPEP is indicated and a two-drug regimen should be given unless there is evidence that the source person has a current or past history of ARV use with poor adherence, or is known to have failed first-line ART. A three-drug PEP regimen is recommended in this case.

21.8 ARVs for nPEP

The choice of ARVs is the same for both occupational and non-occupati–onal PEP (**Table 43**).

21.9 Counselling

- Assess the extent, frequency and timing of risk exposure.
- Try to ascertain the HIV status of the source (often unknown).
- Evaluate for STI syndromes.
- Assess the need for and offer emergency contraception ("morning-after" pill).
- Give pre-HIV test counselling.
- Carry out baseline tests for the following:
  - HIV
  - Hepatitis B and C
  - Swabs and cultures for gonorrhoea and chlamydia, if available
  - Syphilis (Venereal Disease Research Laboratory [VDRL] and *Treponema pallidum* haemagglutination [TPHA])
  - Pregnancy test (if available) following appropriate counselling.

- Counsel the individual that they must not give blood and must practise safe sex and safe injecting practices and not breastfeed until the outcome is known.
- Review and give baseline results.
- Offer hepatitis B vaccination if the individual has not been vaccinated, was known not to have responded to a complete hepatitis B vaccine series or has no antibodies against HBV showing past or current infection.
- Offer tetanus toxoid vaccination if there are any tears, cuts or abrasions in case of sexual assault.
- Offer PEP for STIs.

21.10 Emergency contraception[91]

Emergency contraceptive pills can be used for up to 5 days after unprotected intercourse. However, the sooner they are taken, the more effective they are. Several regimens are available, using levonorgestrel or combined oral contraceptive pills.

A second option for emergency contraception is insertion of a copper-bearing IUD within 5 days of the rape. This will prevent more than 99% of pregnancies. The IUD may be removed during the woman's next menstrual period or left in place for continued contraception. If an IUD is inserted, make sure to **give full STI treatment** as recommended below.

If more than 5 days have passed, counsel the woman on the availability of abortion services (in most countries, post-rape abortion is legal). A woman who has been raped should first be offered a pregnancy test to rule out the possibility of a pre-existing pregnancy.

21.11 Presumptive treatment of STIs

Another concrete benefit of early medical intervention following rape is the possibility of treating the person for a number of STIs. STI prophylaxis can be started on the same day as emergency contraception, although the doses should be spread out (and taken with food) to reduce side-effects such as nausea.

The incubation periods of different STIs vary from a few days for gonorrhoea and chancroid to weeks or months for syphilis and HIV. Treatment may thus relieve a source of stress, but the decision regarding whether to provide presumptive treatment or wait for the results of STI tests should be made in consultation with the treating physician.

Table 46 lists treatment options that are effective whether taken soon after exposure or after the appearance of symptoms. (Women often do not develop symptoms.)

Table 46: Treatment of sexually transmitted infections

Coverage	**Option 1** All single dose, highly effective. Choose one from each box (= 3 or 4 drugs)	**Option 2** Effective substitutes – possible resistance in some areas, or require multiple dosage	**If patient is pregnant, breastfeeding** OR **under 16 years of age** Choose one from each box (= 3 or 4 drugs)
Syphilis	**Benzathine penicillin** [a] 2.4 million units by single intramuscular injection	**Doxycycline** [b] 100 mg orally twice a day for 14 days (in case of penicillin allergy only)	**Benzathine penicillin** [a] 2.4 million units by single intramuscular injection
Gonorrhoea/ chancroid	**Cefixime** 400 mg orally as a single dose, or **ceftriaxone** 125 mg by intramuscular injection	**Ciprofloxacin** [c] 500 mg orally as a single dose, or **spectinomycin** 2 g by intramuscular injection	**Cefixime** 400 mg orally as a single dose, or **ceftriaxone** 125 mg by intramuscular injection
Chlamydia/ lymphogranuloma venereum	**Azithromycin** 1 g orally as single dose	**Doxycycline** [b] 100 mg orally twice a day for 7 days, or **tetracycline** 500 mg orally 4 times a day for 7 days	**Erythromycin** 500 mg orally 4 times a day for 7 days
Trichomoniasis	**Metronidazole** [d] 2 g orally as a single dose	**Tinidazole** 2 g [e] orally as a single dose	**Metronidazole** 2 g [d] orally as a single dose, or 400–500 mg 3 times a day for 7 days

Source: Sexually transmitted and other reproductive tract infections. Geneva, WHO, 2005:141–150.

Notes

[a] Benzathine penicillin can be omitted if treatment includes either azithromycin 1 g or 14 days of doxycycline, tetracycline or erythromycin, all of which are effective against incubating syphilis.

[b] These drugs are contraindicated in pregnant or breastfeeding women.

[c] The use of a quinolone should take into consideration the patterns of *Neisseria gonorrhoeae* resistance, such as in the WHO South-East Asia and Western Pacific Regions.

[d] Metronidazole should be avoided in the first trimester of pregnancy. Patients taking metronidazole should be cautioned to avoid alcohol.

[e] Patients taking tinidazole should be cautioned to avoid alcohol.

ANNEX 1 Criteria for HIV-related Clinical Events in Adults and Adolescents

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical stage 1		
Asymptomatic	No HIV-related symptoms reported and no signs on examination	Not applicable
Persistent generalized lymphadenopathy (PGL)	Painless enlarged lymph nodes >1 cm, in two or more non-contiguous sites (excluding inguinal), in absence of known cause and persisting for ? 3 months	Histology
Clinical stage 2		
Moderate unexplained weight loss (<10% of body weight)	Reported unexplained weight loss. In pregnancy failure to gain weight	Documented weight loss <10% of body weight
Recurrent bacterial upper respiratory tract infections (current event plus one or more in the past six-month period)	Symptom complex, e.g. unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media), or tonsillo-pharyngitis without features of viral infection (e.g. coryza, cough)	Laboratory studies where available, e.g. culture of suitable body fluid
Herpes zoster	Painful vesicular rash in dermatomal distribution of a nerve supply; does not cross midline	Clinical diagnosis
Angular cheilitis	Splits or cracks at the angle of the mouth not due to iron or vitamin deficiency, and usually responding to antifungal treatment	Clinical diagnosis
Recurrent oral ulcerations (two or more episodes in the past six months)	Aphthous ulceration, typically painful with a halo of inflammation and a yellow-grey pseudomembrane	Clinical diagnosis
Papular pruritic eruptions (PPE)	Pruritic papular eruptions lesions, often with marked post-inflammatory hyperpigmentation	Clinical diagnosis
Seborrhoeic dermatitis	Itchy, scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin)	Clinical diagnosis

Clinical event	Clinical diagnosis	Definitive diagnosis
Fungal nail infections	Paronychia (painful, red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails (white discoloration – especially involving proximal part of nail plate – with thickening and separation of nail from nail bed)	Fungal culture of nail/nail plate material
Clinical stage 3		
Severe unexplained weight loss (>10% of body weight)	Reported unexplained weight loss (>10% of body weight or body mass index <18.5). In pregnancy weight loss may be masked	Documented loss of >10% of body weight
Unexplained chronic diarrhoea for longer than one month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month	Not required but confirmed if three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens
Unexplained persistent fever (intermittent or constant and lasting for longer than one month)	Reports of fever or night sweats for more than one month, either intermittent or constant with reported lack of response to antibiotics or antimalarials, without other obvious foci of disease reported or found on examination. Malaria must be excluded in malarial areas	Documented fever >37.6 °C with negative blood culture, negative Ziehl–Neelsen (ZN) stain, negative malaria slide, normal or unchanged chest X-ray (CXR) and no other obvious focus of infection
Oral candidiasis	Persistent or recurring creamy-white curd-like plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Clinical diagnosis
Oral hairy leukoplakia (OHL)	Fine white, small, linear or corrugated lesions on lateral borders of the tongue, which do not scrape off	Clinical diagnosis

Clinical event	Clinical diagnosis	Definitive diagnosis
Pulmonary TB (current)	Chronic symptoms: (lasting ≥2–3 weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats, **PLUS** either positive sputum smear **OR** Negative sputum smear **AND** compatible chest radiograph (including but not restricted to upper lobe infiltrates, cavitation, pulmonary fibrosis and shrinkage). No evidence of extrapulmonary disease	Isolation of *M. tuberculosis* on sputum culture or histology of lung biopsy (together with compatible symptoms)
Severe bacterial infection (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease)	Fever accompanied by specific symptoms or signs that localize infection, and response to appropriate antibiotic	Isolation of bacteria from appropriate clinical specimens (i.e. usually sterile sites)
Acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour and rapid loss of bone and/or soft tissue	Clinical diagnosis
Clinical stage 4		
HIV wasting syndrome	Reported unexplained weight loss (>10% body weight), with obvious wasting or body mass index <18.5 **PLUS** EITHER Unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month **OR** Reports of fever or night sweats for more than one month without other cause and lack of response to antibiotics or antimalarials. Malaria must be excluded in malarial areas	Documented weight loss >10% of body weight; **PLUS** Two or more unformed stools negative for pathogens **OR** Documented temperature >37.6^{0}C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged CXR

Clinical event	Clinical diagnosis	Definitive diagnosis
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past 3 months), tachypnoea and fever; **AND** Chest X-ray evidence of diffuse bilateral interstitial infiltrates **AND** No evidence of a bacterial pneumonia. Bilateral crepitations on auscultation with or without reduced air entry	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue
Recurrent bacterial pneumonia (this episode plus one or more episodes in the past 6 months)	Current episode plus one or more previous episodes in the past 6 months. Acute onset (<2 weeks) of symptoms (e.g. fever, cough, dyspnoea and chest pain) **PLUS** new consolidation on clinical examination or CXR. Response to antibiotics	Positive culture or antigen test of a compatible organism
Chronic herpes simplex virus (HSV) infection (orolabial, genital or anorectal) of more than one month's duration	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrent HSV infection and reported for more than one month. History of previous episodes. Visceral HSV requires definitive diagnosis	Positive culture or DNA (by PCR) of HSV or compatible cytology/ histology
Oesophageal candidiasis	Recent onset of retrosternal pain or difficulty in swallowing (food and fluids) together with oral candidiasis	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy/histology
Extrapulmonary TB (EPTB)	Systemic illness (e.g. fever, night sweats, weakness and weight loss). Other evidence of extrapulmonary or disseminated TB varies by site: pleural, pericardial, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy, osteitis Miliary TB: diffuse, uniformly distributed, small miliary shadows or micronodules on CXR Discrete cervical lymph node *M. tuberculosis* infection is usually considered a less severe form of EPTB	*M. tuberculosis* isolation or compatible histology from appropriate site, together with compatible symptoms/signs (if culture/histology is from respiratory specimen then must have other evidence of extrapulmonary disease)
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat patches with a pink or blood-bruise colour, skin lesions that usually develop into violaceous plaques or nodules	Macroscopic appearance at endoscopy or bronchoscopy, or by histology

Clinical event	Clinical diagnosis	Definitive diagnosis
CNS toxoplasmosis	Recent onset of a focal neurological abnormality or reduced level of consciousness **AND** response within 10 days to specific therapy	Positive serum *Toxoplasma* antibody **AND** (if available) single/ multiple intracranial mass lesion on neuro-imaging
HIV encephalopathy	Clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection which might explain the findings	Diagnosis of exclusion: and (if available) neuro-imaging (CT or MRI)
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute fever with increasingly severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Isolation of *Cryptococcus neoformans* from extrapulmonary site or positive cryptococcal antigen test (CRAG) on CSF/blood
Disseminated non-tuberculous mycobacterial infection	No presumptive clinical diagnosis	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding lung
Progressive multifocal leukoencephalopathy (PML)	No presumptive clinical diagnosis	Progressive neurological disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuro-imaging or positive polyomavirus (JCV) PCR on CSF
Cryptosporidiosis (with diarrhoea lasting for more than one month)	No presumptive clinical diagnosis	Cysts identified on modified ZN microscopic examination of unformed stool
Chronic isosporiasis	No presumptive clinical diagnosis	Identification of *Isospora*
Disseminated mycosis (coccidioidomycosis, histoplasmosis)	No presumptive clinical diagnosis	Histology, antigen detection or culture from clinical specimen or blood culture

Clinical event	Clinical diagnosis	Definitive diagnosis
Recurrent non-typhoid *Salmonella* bacteraemia	No presumptive clinical diagnosis	Blood culture
Lymphoma (cerebral or B cell non-Hodgkin) or other solid HIV-associated tumours	No presumptive clinical diagnosis	Histology of relevant specimen or neuroimaging techniques for CNS tumours
Invasive cervical carcinoma	No presumptive clinical diagnosis	Histology or cytology
Visceral leishmaniasis	No presumptive clinical diagnosis	Diagnosed by histology (amastigotes visualized) or culture from any appropriate clinical specimen
HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

Source: *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children.* Geneva, World Health Organization, 2006.

ANNEX 2 Dosages of Antiretroviral Drugs for Adults and Adolescents

Generic name	Dose	
Nucleoside RTIs (NsRTIs)		
Abacavir (ABC)	300 mg twice daily or 600 mg once daily	
Zidovudine (AZT)	250 mg or 300 mg twice daily [a]	
Emtricitabine (FTC)	200 mg once daily	
Didanosine (ddI) [b] buffered tablets or enteric-coated (EC) capsules	>60 kg: 400 mg once daily <60 kg: 250 mg once daily	
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily	
Stavudine (d4T)	30 mg twice daily irrespective of weight	
Nucleotide RTIs (NtRTIs)		
Tenofovir (TDF)	300 mg once daily	
Non-nucleoside RTIs (NNRTIs)		
Efavirenz (EFV)	600 mg once daily	
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily	
Protease inhibitors (PIs)		
Atazanavir/ritonavir (ATV/r) [c]	300 mg/100 mg once daily	
Fos-amprenavir/ritonavir (FPV/r)	700 mg/100 mg twice daily	
Indinavir/ritonavir (IDV/r) [d]	800 mg/100 mg twice daily	
Lopinavir/ritonavir (LPV/r) [e]	Capsule lopinavir 133.3 mg + ritonavir 33.3 mg	Three capsules twice daily (400/100 mg twice daily) four capsules twice daily when combined with EFV or NVP (533/133.33 mg twice daily)
	Tablet (heat-stable formulation) lopinavir 200 mg + ritonavir 50 mg	Two tablets twice daily (400/100 mg twice daily)
		Three tablets twice daily when combined with EFV or NVP (600/150 mg twice daily)
Nelfinavir (NFV)	1250 mg twice daily	
Saquinavir/ritonavir (SQV/r) [e]	1000/100 mg twice daily	
Darunavir (DRV)	600/100 mg twice daily	

Notes

[a] AZT 250 mg 2 times per day is included as an option in the 2006 WHO guidelines for adult ART and is available as the fixed-dose combination of AZT 250 mg/3TC 150 mg/NVP 200 mg (*Gpovir-Z*). New data from Thailand may support a dose of 200 mg 2 times per day in the Thai population.[92]

[b] The dose of ddI should be adjusted when co-administered with TDF. If the weight is >60 kg, the recommended dose is 250 mg once daily. If the weight is <60 kg, there are no data to make a recommendation. (Some preliminary pharmacokinetic [PK] studies suggest 125–200 mg once daily.[93]) Buffered ddI needs to be taken on an empty stomach.

[c] In resource-limited settings, PIs are not recommended in first-line regimens. If for some special reason such as intolerance to all NNRTIs ATV is given to a treatment-naive patient, the dose is 200 mg once daily (without RTV).

[d] Other dosage regimens in clinical use are 600 mg/100 mg,[94] and 400 mg/100 mg.[95]

[e] *See* the section on TB for TB-specific dose modifications of LPV/r and SQV/r.

ANNEX 3 Storage of Antiretroviral Drugs

Generic name	Storage requirements
Nucleoside RTIs (NsRTIs)	
Abacavir (ABC)	Room temperature
Zidovudine (AZT)	Room temperature
Didanosine (ddI)	Room temperature for tablets and capsules Reconstituted buffered powder should be refrigerated; oral solution for children is stable after reconstitution for 30 days if refrigerated.
Emtricatabine (FTC)	Room temperature
Lamivudine (3TC)	Room temperature
Stavudine (d4T)	Room temperature. After reconstitution, oral solution should be kept refrigerated; if so, it is stable for 30 days.
Stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP)	Room temperature
Zidovudine (AZT) + lamivudine (3TC) + abacavir (ABC)	Room temperature
Zidovudine (AZT) + lamivudine (3TC) + nevirapine (NVP)	Room temperature
Nucleotide RTIs (NtRTIs)	
Tenofovir (TDF)	Room temperature
Non-nucleoside RTIs (NNRTIs)	
Efavirenz (EFV)	Room temperature
Nevirapine (NVP)	Room temperature
Protease inhibitors (PIs)	
Atazanavir (ATV)	Room temperature
Indinavir (IDV)	Room temperature
Fos-amprenavir (FPV)	Room temperature
Lopinavir/ritonavir (LPV/r) capsules	Refrigerate for long-term storage At room temperature: stable for 30 days
Lopinavir/ritonavir (LPV/r) heat-stable tablets	Room temperature
Nelfinavir (NFV)	Room temperature

Generic name	Storage requirements
Ritonavir (RTV)	Refrigerate capsules until dispensed Stable at room temperature for 30 days Room temperature for oral solution (do not refrigerate)
Saquinavir – hard gel capsules (SQV_{hgc})	Room temperature
Darunavir (DRV)	Room temperature

Room temperature is defined as 15–30°C. Refrigeration is defined as 2–8°C.

ARV	NVP	EFV	LPV/r	NFV	SQV
Antimycobacterials					
Rifampicin	↓NVP level by 20–58%. Virological consequences are uncertain; the potential for additive hepatotoxicity exists. Careful monitoring is required during co-administration.	↓EFV level by 25% Standard dosing of EFV recommended	↓LPV AUC by 75% Should not be co-administered	↓NFV level by 82% Should not be co-administered	↓SQV level by 84% Severe liver impairment with co-administration reported Should not be co-administered
Rifabutin	↓NVP level by 16% No dose adjustment	EFV level unchanged; rifabutin level ↓ 35% Dose: ↑rifabutin dose to 450–600 mg once daily or 600 mg thrice weekly EFV: Standard	Rifabutin AUC ↑ 3-fold ↓ rifabutin dose to 150 mg once daily or thrice weekly LPV/r: Standard	↓NFV level by 82% Should not be co-administered	Levels: ↓SQV by 40% Contraindicated unless SQV/RTV Dose: Rifabutin 150 mg once daily or thrice weekly

ARV	NVP	EFV	LPV/r	NFV	SQV
Clarithromycin	None	↓Clarithromycin level by 39% Monitor for efficacy or use alternative drugs	↑Clarithromycin AUC by 75%, adjust clarithromycin dose if renal impairment	No data	Without RTV, ↑ clarithromycin level by 45%, ↑SQV level by 177% RTV can ↑ clarithromycin level by 75% No clarithromycin dose adjustment needed for unboosted SQV. For boosted SQV if renal impairment – no data
Antifungals					
Ketoconazole	↑Ketoconazole level by 63% ↑NVP level by 15–30% Co-administration not recommended	No significant changes in ketoconazole or EFV levels	↑LPV AUC ↑Ketoconazole level 3-fold Do not exceed 200 mg/day ketoconazole	No dose adjustment necessary	↑SQV level 3-fold No dose adjustment necessary if given unboosted For RTV-boosted SQV – no data (RTV treatment dose can increase ketoconazole level 3-fold)
Fluconazole	↑NVP C_{max}, AUC, C_{min} by 100% No change in fluconazole level Possible increase in hepatotoxicity with co-administration; requires monitoring of NVP toxicity	No data	No data	No data	No data

ARV	NVP	EFV	LPV/r	NFV	SQV
Itraconazole	No data	No data	↑Itraconazole level Do not exceed 200 mg/day itraconazole	No data but potential for bidirectional inhibition, monitor toxicities	Bidirectional interaction has been observed. May need to decrease itraconazole dose. Consider monitoring SQV level (especially if given unboosted with RTV)
Oral contraceptives					
Ethinylestradiol	↓Ethinylestradiol level by 20% Use alternative or additional methods of contraception	↑Ethinylestradiol level by 37%. Use alternative or additional methods of contraception	↓Ethinylestradiol level by 42% Use alternative or additional methods of contraception	↓Levels of norethindrone by 18% and ethinylestradiol by 47%	No data for unboosted SQV RTV treatment dose can ↓level of ethinylestradiol by 41%
Anticonvulsants					
Carbamazepine Phenytoin	Use with caution. One case report showed low EFV concentrations with phenytoin	Unknown. Use with caution	Many possible interactions: Carbamazepine: ↑ levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels. Phenytoin: ↓levels of LPV, RTV and↓ levels of phenytoin when administered together Avoid concomitant use or monitor LPV level	Unknown, but may decrease NFV levels substantially Monitor anticonvulsant levels and virological response	Unknown, but may markedly ↓ SQV levels Monitor anticonvulsant levels and consider obtaining SQV level

ARV	NVP	EFV	LPV/r	NFV	SQV
Lipid-lowering agents					
Simvastatin, lovastatin	No data	↓ Simvastatin level by 58% EFV level unchanged Adjust simvastatin dose according to lipid response, do not exceed the maximum recommended dose	Potential large ↑ in statin level Avoid concomitant use	↑Simvastatin AUC by 505% Potential large ↑ in lovastatin AUC Avoid concomitant use	Potential large ↑ in statin level Avoid concomitant use
Atorvastatin	No data	↓Atorvastatin AUC by 43% EFV level unchanged Adjust atorvastatin dose according to lipid response, do not exceed maximum recommended dose	↑Atorvastatin AUC 5.88-fold Use lowest possible starting dose with careful monitoring	↑Atorvastatin AUC by 74% Use lowest possible starting dose with careful monitoring	↑Atorvastatin level by 450% when used as SQV/RTV Use lowest possible starting dose with careful monitoring
Pravastatin	No data	No data	↑Pravastatin AUC by 33% No dose adjustment needed	No data	↓Pravastatin level by 50% No dose adjustment needed
Proton-pump inhibitors. All the PIs and EFV can ↑ levels of cisapride and non-sedating antihistamines (astemizole, terfenedine), which can cause cardiac toxicity. Co-administration is not recommended.					

AUC area under the curve C_{max} maximum concentration C_{min} minimum concentration

Note: Concomitant use of fluticasone with RTV results in significant reduction of serum cortisol concentrations. Co-administration of fluticasone with RTV or any RTV-boosted PI regimen is not recommended unless the potential benefit outweighs the risk of systemic corticosteroid side-effects.

(Adapted from *Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents*, 4 May 2006. www.aidsinfo.nih.gov)

ANNEX 5 Drug Interactions between Opiates and Antiretrovirals and other Drugs

Interaction between methadone and antiretroviral drugs

ARV	Effect on methadone	Effect on ARV	Comments
NRTIs			
Didanosine (ddI) Buffered tablet Enteric-coated (EC) capsule	None reported No dosage adjustments necessary	Concentrations decreased by 60% when buffered tablet taken, but not with EC capsule	Avoid use of ddI buffered tablets Use EC capsule if available
NNRTIs			
Efavirenz (EFV)	Decrease in methadone level by up to 60% Symptoms of opiate withdrawal common	Unknown	Observe for symptoms of methadone withdrawal and increase dosage as necessary
Nevirapine (NVP)	Decrease in methadone level by up to 50% Symptoms of opiate withdrawal common	None reported	Considerable increase in methadone dose up to 50% commonly required
PIs			
Lopinavir/ritonavir (LPV/r)	Decrease in methadone level by up to 50%	None reported	May require increase in methadone dose
Ritonavir (RTV)	Decrease in methadone level by 37%	Dose adjustment may be required	Studies limited Observe for signs of methadone withdrawal

Interactions between methadone and other drugs

Drug	Indication	Effect on methadone	Comments
Rifampicin	TB	Decrease in methadone level by 33–68% and may induce symptoms of opiate withdrawal	Increase in methadone dose required if withdrawal symptoms present
Sertraline	Antidepressant	Increase in methadone levels by 26%	Associated with cardiac rhythm disturbances, caution when used with methadone
Carbamazepine and phenytoin	Anticonvulsants	Decrease in methadone levels and may cause symptoms of methadone withdrawal	Increase in methadone dose may be required Consider using sodium valproate as an alternative

Interactions between buprenorphine and antiretroviral drugs

ARV	Effect on buprenorphine	Effect on ARV	Comments
NRTIs/ NNRTIs			
No significant interactions reported			
PIs			
Ritonavir (RTV)	Inhibition of buprenorphine metabolism resulting in a clinically significant increase in buprenorphine levels	None reported	Buprenorphine dose may need to be reduced
Atazanavir (ATV)			

Opportunistic infection	Clinical features	Diagnosis	Treatment
Pneumocystis jiroveci pneumonia (PCP) (previously known as *Pneumocystis carinii* pneumonia)	Dry cough Shortness of breath Fever Night sweats Subacute presentation over 1–2 months	Chest X-ray is abnormal in more than 90% cases of PCP, and typically shows bilateral interstitial infiltrates	**Preferred treatment** Co-trimoxazole (trimethoprim–sulfamethoxazole, TMP 15 mg plus SMZ 75 mg/kg daily) in 4 divided doses, orally or intravenously, for 21 days Co-trimoxazole should be given IV in severely ill patients. Patients can switch to oral co-trimoxazole once they improve clinically Oral doses are 480 mg, 2 tablets 4 times daily (patient <40 kg) and 3 tablets 4 times daily (patient >40 kg) **Alternative treatment** Clindamycin 600 mg IV or 450 mg orally 3 times per day + primaquine 15 mg orally once daily for 21 days if allergy to sulfonamides Prednisolone 20 mg 4 times daily, with slow reduction of the dose over 7–10 days, depending on response to therapy, is recommended for severely ill patients

Opportunistic infection	Clinical features	Diagnosis	Treatment
Candidiasis	Oral candidiasis White mucosal plaques ± erythema in the oral cavity	Typical clinical appearance on physical examination Microscopic demonstration of psuedohyphae in potassium hydroxide (KOH) preparation	Nystatin pessaries 100 000 IU, to be sucked every 4 hours for 7 days **OR** Nystatin oral suspension 100 000 IU, three times a day for 7 days **OR** Amphotericin B oral suspension, 1 spoon three times a day for 7 days **OR** Miconazole 2% oral gel, 2 spoons 3 times daily for 7 days
	Oesophageal candidiasis Dysphagia ± retrosternal chest pain	Typical clinical presentation and response to antifungal therapy Endoscopy should be done if available	Fluconazole 200 mg daily for 14 days **OR** Itraconazole 400 mg daily for 14 days **OR** Ketoconazole 200 mg daily for 14 days
Cryptococcosis	Occipital headache, meningeal irritation, photophobia, neck stiffness or raised intracranial pressure Fever Changes in mental state Disseminated disease with papulonecrotic skin lesions resembling molluscum contagiosum associated with fever and pulmonary infiltrates	Raised intracranial pressure and on lumbar puncture, protein in CSF Organisms demonstrated from CSF or skin lesions with India-ink stain and on light microscopy	**Preferred treatment** IV amphotericin B (0.7 mg/kg/day) for 2 weeks followed by itraconazole 200 mg 2 times daily or fluconazole 400 mg daily for 8 weeks **Alternative treatment** Fluconazole 400 mg daily for 8–12 weeks Maintenance therapy Itraconazole 200 mg/day or fluconazole 200 mg/day

Opportunistic infection	Clinical features	Diagnosis	Treatment
Penicilliosis	Papulonecrotic skin lesions associated with systemic features of fever, lung involvement, cough, weight loss, anaemia and lymphadenopathy 70% of patients with disseminated *Penicillium marneffei* infection will have skin lesions	Microscopy of skin biopsy or lymph node aspirate Organism demonstrated with Wright or Cotton blue stain	**Preferred treatment** IV amphotericin B (0.7mg/kg daily) for 2 weeks followed by itraconazole 400 mg orally daily for 8–10 weeks **Maintenance therapy** Itraconazole 400 mg daily
Cerebral toxoplasmosis	Headache Drowsiness Fever Focal neurological abnormality Seizures	Focal neurological signs Single or multiple ring-enhancing lesions on CT (if available) Response to presumptive treatment can be used to support the diagnosis	**Preferred treatment** Pyrimethamine loading dose 75–100 mg, then 25–50 mg daily plus sulfadiazine, 4 g daily in 4 divided doses Folic acid 15 mg every second day if available Treat for 6 weeks **Maintenance therapy** Pyrimethamine 25 mg daily plus sulfadiazine, 2 g daily in 4 divided doses
Herpes simplex virus (HSV) infection	Clusters of typical blisters, usually in genital area or face Systemic involvement (such as HSV oesophagitis, encephalitis) is possible	Typical clinical appearance	Usually self-limiting and may not require treatment Local care of the lesion, such as with gentian violet and chlorhexidine If indicated, acyclovir 200–400 mg 5 times daily for 7 days can be given

Opportunistic infection	Clinical features	Diagnosis	Treatment
Herpes zoster	Typical painful blisters in clusters along dermatomes Can involve the eye	Clinical appearance	Local care of the lesion, such as with gentian violet and chlorhexidine. Acyclovir 800 mg 5 times daily orally for 7 days, commenced within 72 hours of onset of blisters. Famciclovir and valaciclovir are alternatives. Acyclovir ointment applied in the eye every 4 hours for ophthalmic herpes zoster
Tuberculosis	**Pulmonary TB** Cough, fever, weight loss, fatigue	Sputum examination for AFB Chest X-ray **Classic chest X-ray pattern** Upper lobe infiltrates, cavitation **Atypical pattern** Bilateral interstitial infiltrates Pleural effusion Pleural tap for AFB	Treat according to national TB guidelines. For WHO recommendations *see* Annex 7
	Extrapulmonary TB Enlarged lymph nodes or spleen CNS or GI symptoms	Unilateral nodes increasing in size, matted nodes, fluctuant nodes, fever, weight loss, splenomegaly, diarrhoea and abdominal pain	

Opportunistic infection	Clinical features	Diagnosis	Treatment
Mycobacterium avium complex (MAC) disease	Chronic or recurrent fever Weight loss Fatigue	Isolation of organism from blood or other sites Unexplained anaemia	**Preferred treatment** Azithromycin 500–600 mg once a day, or clarithromycin 500 mg twice a day plus ethambutol 15 mg/kg/day plus rifabutin 300 g once a day The condition may resolve with ART **Maintenance therapy** Clarithromycin 500 mg twice a day or azithromycin 500 mg once a day plus ethambutol 15 mg/kg once a day
Cryptosporidiosis	Chronic diarrhoea Cramps and vomiting Right upper quadrant pain	Stool specimen stained with modified AFB stain	ART is the preferred treatment

ANNEX 7 Tuberculosis Case Definitions and Treatment

1. Case definitions

- **TB suspect.** Any person who presents with symptoms or signs suggestive of TB, in particular, cough of long duration (>2–3 weeks).
- **Case of TB.** A patient in whom TB has been bacteriologically confirmed or diagnosed by a clinician. Any person given treatment for TB should be recorded as a case. Incomplete "trial" TB treatment should not be used as a method for diagnosis.
- **Definite case of TB.** A patient with two sputum smears positive for AFB. In countries where culture is routinely available, a patient with a positive culture for *Mycobacterium tuberculosis* complex is also considered a "definite" case.

2. Site of TB disease (pulmonary and extrapulmonary)

In general, recommended treatment regimens are similar irrespective of site. The importance of defining the site is primarily for recording and reporting purposes.

Pulmonary TB (PTB) refers to disease involving the lung parenchyma. Therefore, tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB (EPTB). A patient with both PTB and EPTB should be classified as a case of PTB.

Extrapulmonary TB (EPTB) refers to TB of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of TB chemotherapy. The definition of a case with EPTB with several sites affected depends on the site representing the most severe form of the disease.

Pulmonary TB, sputum smear-positive (PTB+)

a. Two or more initial sputum smear examinations positive for AFB, **or**
b. One sputum smear examination positive for AFB plus radiographic abnormalities consistent with active PTB as determined by a clinician, **or**
c. One sputum smear positive for AFB plus sputum culture positive for *M. tuberculosis*.

Pulmonary TB, sputum smear-negative (PTB–)

a. At least two negative sputum specimens for AFB, **and**
b. Radiographic abnormalities consistent with active TB, **and**
c. Decision by a clinician to treat with a full course of anti-TB chemotherapy, **or**
d. Sputum smear negative for AFB but culture positive for *M. tuberculosis*.

3. First-line anti-TB drugs

First-line anti-TB drugs	Mode of action	Potency	Recommended dose (mg/kg of body weight)	
			Daily	Intermittent (3 times a week)
Isoniazid (H)	Bactericidal	High	5	10
Rifampicin (R)	Bactericidal	High	10	10
Pyrazinamide (Z)	Bactericidal	Low	25	25
Streptomycin (S)	Bactericidal	Low	15	15
Ethambutol (E)	Bactericidal	Low	15	30

Letters in parentheses are the standard abbreviations of the names of the drugs.

4. Possible alternative treatment regimens for each TB treatment category

TB diagnostic category	Type of TB patient	Alternative treatment regimens	
		Initial phase (daily or 3 times per week) [a]	Continuation phase (daily or 3 times per week)
I	New smear-positive PTB; new smear-negative PTB with extensive parenchymal involvement; severe concomitant HIV disease or severe forms of EPTB	2 HRZE [b]	4 HR **OR** 6 HE daily [c]
II	Previously treated sputum smear-positive PTB: ▪ Relapse ▪ Treatment failure [d] ▪ Treatment after interruption	2 HRZES/1 HRZE	5 HRE
III	New smear-negative PTB (other than in Category I); less severe forms of EPTB	2 HRZE [e]	4 HR or 6 HE daily [c]
IV	Chronic and multidrug-resistant (MDR) TB cases (still sputum-positive after supervised re-treatment) [f]	Specially designed standardized or individualized regimens are suggested for this category	

In the standard code for TB treatment regimens, each anti-TB drug has an abbreviation: streptomycin (S), isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). A regimen consists of two phases.

[a] Direct observation of drug intake is required during the initial phase of treatment in smear-positive cases, and always in treatment that includes rifampicin.

[b] Streptomycin (provided that sterile syringes and needles, and sharps disposal are available) may be used instead of ethambutol. In meningeal TB, ethambutol should be replaced by streptomycin.

[c] This regimen may be associated with a higher rate of treatment failure and relapse compared with the six-month regimen with rifampicin in the continuation phase.

[d] Whenever possible, drug sensitivity testing is recommended before prescribing Category II treatment in failure cases. It is recommended that patients with proven MDR-TB use Category IV regimens.

[e] Ethambutol may be omitted during the initial phase of treatment for patients with non-cavitary, smear-negative PTB who are known to be HIV-negative, patients known to be infected with fully drug-susceptible bacilli, and young children with primary TB.

[f] Contacts of patients with culture-proven MDR-TB should be considered for early culture and sensitivity testing.

Infection	Clinical features	Diagnosis	Treatment
1. Pruritic (itchy) rashes			
Eosinophilic folliculitis	Erythematous, pruritic, follicular papules/pustules on face, upper trunk, upper arms, intense itching; hyperpigmented area after healing	☺ Clinical	Treat mild disease with topical steroids and oral antihistamines.[96] Treat moderate-to-severe disease with oral itraconazole, isotretinoin or phototherapy.
Pruritic papular eruptions (PPE)*	Hyperpigmented, hyperkeratotic papules and nodules which are often symmetrically distributed on the arms, legs, lower back, buttocks	☺ Clinical	Treatment includes mild topical steroids and systemic antihistamines to relieve the itching that often accompanies this condition. If secondary impetigo occurs, topical or systemic antibiotics may be needed. The condition improves with immune recovery on ART but scarring from old lesions may be permanent.
Scabies	Rash and excoriations on torso; burrows in web spaces and wrist; face spared	Microscopy of skin scrapings KOH or mineral oil preparations	Gammabenzene hexachloride once a week for 2–3 weeks or until the lesions have cleared **OR** Permethrin cream 5%: Apply from chin to toes and take a shower 10–12 hours later; repeat after 1 week **OR** 25% benzylbenzoate solution:[97] Apply the lotion from head to toe. The application is left to dry on the skin and then repeated the next day. Treatment should be repeated weekly until all lesions have cleared. Itching can be relieved by taking chlorpheniramine 4 mg 3–4 tablets/day **AND** Clothes and bedding should also be washed and kept separately for 3 days to prevent re-infestation. Household contacts should be treated. After treatment, all the clothes and bed linen should be washed and dried.
Norwegian scabies	Extensive crusting (psoriasis-like lesions) with thick, hyperkeratotic scales on the elbows, knees, palms and soles		

Infection	Clinical features	Diagnosis	Treatment
Scabies (*contd.*)			Household and other close contacts require the same treatment. In severe cases, ivermectin (if available) administered in a single oral dose of 200 µg/kg may be considered.[98]
Xerosis	Dry and rough skin, sometimes with fine cracks	☺ Clinical	A moisturizing skin lotion can be used to relieve dryness and antihistamines for itching (chlorpheniramine 4 mg 3 times per day or hydroxyzine 10 mg 2 times per day). The condition improves with immune restoration on ART.[99]
2. Erythematous rashes			
Primary HIV infection*	Generalized maculopapular rash usually with fever and systemic symptoms	Serology for HIV RNA or HIV DNA May be negative in early primary HIV infection	No specific treatment is indicated for the rash or for primary HIV infection. Patient counselling, education and behaviour modification are necessary.
Drug reaction	Generalized, erythematous, pruritic rash with or without fever and signs of hepatotoxicity. Severe drug reactions (Stevens–Johnson syndrome) result in blistering of skin and/or mucous membranes Typically in the first days to weeks of commencing the new drug	☺ Clinical	Stop the causative drug. Give antihistamines and topical moisturizing creams. Hospitalization with cardiorespiratory support may be needed for patients with Stevens–Johnson syndrome. Most experts recommend the use of short-course systemic steroids in cases of severe drug reactions. Start with prednisone 0.5 mg/kg per day, and reduce the dose over 5–10 days.

Infection	Clinical features	Diagnosis	Treatment
3. Blisters, sores, nodules and pustules			
Herpes zoster*	Typical painful blisters in clusters along dermatomes. Can involve the eye. HIV infection should be suspected if lesions are multidermatomal or episodes are recurrent. Prodromal symptoms include paraesthesiae and/or pain in the dermatome a few days before the rash appears. Fever, malaise and headache may precede the outbreak of blisters.	☺ Clinical	Care of the local lesion with gentian violet and chlorhexidine. Acyclovir 800 mg 5 times daily for 7 days should be started within 72 hours of onset of the blisters. Famciclovir and valaciclovir are alternative drugs. For ophthalmic herpes zoster, acyclovir ointment can be applied in the eye every 4 hours. Pain is managed with paracetamol 1 g 6-hourly; stronger analgesics can be used if necessary. Amitriptyline 25–50 mg before bedtime is useful for the control of the neuropathic pain associated with herpes zoster and for postherpetic neuralgia, which may persist for months after an episode of herpes zoster.
Herpes simplex	Typical blisters, with pain and tingling, usually in genital area or face. Chronic HSV infection presents as progressive, shallow, clean-based ulcers on genitalia, perianal, perioral areas.	☺ Clinical	Care of the local lesion, such as wet compresses for 15 minutes with Burow solution 4–5 times/day or gentian violet or chlorhexidine. If available, give acyclovir 200–400 mg 5 times daily for 7 days. In case of frequent recurrences, long-term suppressive therapy with acyclovir 400 mg 2 times per day may be necessary. Secondary prophylaxis or long-term suppressive therapy with acyclovir 400 mg 2 times per day may be necessary for cases with frequent recurrences. In immunosuppressed patients herpes simplex can be chronic and invasive (e.g. oesophagitis, encephalitis). An alternative is famciclovir 500 mg 2 times per day for 7 days followed by suppressive therapy with 250 mg once daily. In immunosuppressed patients herpes simplex can be chronic and invasive (e.g. oesophagitis, encephalitis).

Infection	Clinical features	Diagnosis	Treatment
Cryptococcosis*	Generalized papulonecrotic skin lesions resembling molluscum contagiosum, associated with fever and other symptoms of disseminated cryptococcosis such as meningitis, lung infection	Microscopic examination of skin biopsy, lymph node aspirate or CSF. India ink, Wright or Cotton blue staining Blood culture CXR	Preferred: IV amphotericin B (0.7 mg/kg daily) + flucytosine (25 mg/kg 4 times a day) for 2 weeks, then fluconazole (400 mg daily) for 8 weeks Alternatives: IV amphotericin B (0.7 mg/kg daily) for 2 weeks, then fluconazole (400 mg daily) for 8 weeks. Secondary prophylaxis is given with fluconazole (200 mg daily) lifelong or until evidence of immune recovery on ART (CD4 cell count >100 cells/mm^3).
Penicilliosis*	Papulonecrotic skin lesions associated with systemic symptoms of fever, lung involvement, cough, weight loss, anaemia, hepatosplenomegaly and lymphadenopathy. 70% of patients with disseminated *Penicillium marneffei* infection will have skin lesions. Endemic in northern Thailand, Southern China, Viet Nam, Indonesia and Hong Kong		IV amphotericin B (0.7 mg/kg daily) for 2 weeks then itraconazole 400 mg orally daily for 10 weeks In mild cases, give itraconazole 400 mg orally daily for 8 weeks. Secondary prophylaxis is given with itraconazole 200 mg per day for life or until immune recovery on ART.
Histoplasmosis*	Pustules, nodules, ulcers and papules in a patient with systemic symptoms including those due to lung, CNS, gastrointestinal and ocular involvement	Tissue biopsy Haematoxylin–eosin staining Blood or tissue culture	Amphotericin B (0.7 mg/kg daily), minimum total dose should be 2 g. Secondary prophylaxis is given with itraconazole 200 mg per day for life or until immune recovery on ART.
Bacillary angiomatosis*	Papules or nodules resembling pyogenic granuloma, nodules or plaques resembling Kaposi sarcoma. Splenomegaly, anaemia	Microscopy of tissue/skin scraping Warthin–Starry silver or Grocott–silver methenamine stain	Erythromycin (500 mg 4 times per day) is the drug of choice. Doxycycline (100 mg) is an alternative. Rifampicin (300 mg 2 times a day) may be added to erythromycin or doxycycline in patients with severe disease who are immunocompromised.

Infection	Clinical features	Diagnosis	Treatment
Mycobacterium avium complex (MAC)*	Papulopustular eruptions on trunk and extremities. Systemic symptoms include fever and pulmonary symptoms, lymphadenopathy, diarrhoea, weight loss, night sweats	AFB on skin biopsy Blood culture	**Preferred therapy** Azithromycin 500–600 mg once a day, or clarithromycin 500 mg twice a day plus ethambutol 15 mg/kg/day plus rifabutin 300 g once a day The condition may resolve with ART. **Maintenance therapy** Clarithromycin 500 mg twice a day or azithromycin 500 mg once a day plus ethambutol 15 mg/kg once a day.
Primary syphilis	Painless, indurated genital ulcer (chancre) with localized lymphadenopathy. Chancres may also be seen in the mouth and anus.	Dark-field microscopy or immunofluor-escent staining RPR, VDRL not positive until 7–10 days after appearance of chancre	**Primary, secondary and early latent syphilis (<1 year's duration)** Single dose of benzathine penicillin G, 2.4 million U IM Alternative treatments (only for non-pregnant, penicillin-allergic patients): 2-week course of doxycycline 100 mg 2 times per day, tetracycline 500 mg 4 times per day, or erythromycin base 500 mg times per day. **Late latent syphilis (>1 year's duration), syphilis of undetermined duration and late syphilis** Benzathine penicillin G, 2.4 million U IM once weekly for 3 consecutive weeks Alternative treatment: doxycycline 100 mg orally 2 times per day or tetracycline 500 mg 4 times per day for 4 weeks **Neurosyphilis** Aqueous crystalline penicillin G, 2–4 million U IV 4-hourly for 10–14 days Alternative treatment: Procaine penicillin, 2.4 million U IM once a day, plus probenecid 500 mg 4 times per day for 10–14 days
Secondary syphilis	Macular, papular or pustular rash on entire body, especially on palms and soles 40% of these patients will have CNS involvement with headache and meningism	RPR, VDRL, TPHA CSF examination Protein and cell count	

Infection	Clinical features	Diagnosis	Treatment
Cutaneous TB	**TB verrucosa cutis**: Asymptomatic, warty papules on hands or extremities often mistaken for verruca vulgaris. Lesions may evolve and persist for years. **Disseminated TB** presents as papulonecrotic lesions (indistinguishable from penicilliosis, histoplasmosis, cryptococcosis)	Tissue/skin scraping Ziehl–Neelsen stain	Treatment should follow the national TB treatment guidelines.
4. Skin rashes with few or no symptoms			
Seborrhoea	Erythematous plaques with greasy scaling on the scalp, face, postauricular area and chest	☺ Clinical	In mild cases, use 1% hydrocortisone cream or 0.1% triamcinolone cream or a similar topical steroid cream. This condition also responds to topical antifungals. Use 2% ketoconazole shampoo to wash the hair and scalp and spread shampoo lather over the face, eyebrows, etc. Leave on for 5 minutes and wash off. Repeat daily until the lesions have cleared and use once weekly to prevent recurrence. Ketoconazole cream can also be used on the face. Alternative option: Whitfield ointment twice a day or gentian violet twice a day or miconazole 2% cream twice daily. For refractory cases, oral ketoconazole 200 mg/day for 7–14 days can be used.
Molluscum contagiosum	Raised, dome-shaped pedunculated lesions usually on face, neck, genital area and armpits	☺ Clinical	Remove by enucleation (with forceps) or cryotherapy; prick the centre and apply phenol.
Condyloma acuminata	Multiple, raised, irregular lesions with a cauliflower-like appearance typically in genital area	☺ Clinical	Remove by cryotherapy, cauterization or application of podophylline 25% solution (2–3 times weekly). Annual Papanicolaou (Pap) smears must be done in women as the risk of invasive cervical cancer is increased.

Infection	Clinical features	Diagnosis	Treatment
HIV-associated skin rash	Itchy, maculopapular and generalized	☺ Clinical	As no specific cause has been identified, treatment is mainly symptomatic such as antihistamines and application of emollient creams. The condition may improve with immune recovery on ART.
5. Severe soft tissue or muscle infection			
Pyomyositis and skin abscess	Abscess or affected area is fluctuant and warm. There may be discharge.	Gram stain or culture	▪ Flucloxacillin 500 mg 4 times per day orally for 10 days or 1–2 g IV 4 times per day for 10 days ▪ Surgical drainage may be necessary for pyomyositis.

☺ Clinical diagnosis preferred. Diagnostic test is normally not required.

*Highly suggestive of HIV infection. HIV counselling and testing should be done if the HIV status is unknown.

ANNEX 9 Severity Grading of Selected Clinical and Laboratory Toxicities

(*Source*: Division of AIDS, National Institute of Allergy and Infectious Diseases [modified])

For abnormalities NOT found in the toxicity table use the scale below to estimate the grade of toxicity:

GRADE 1 Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

GRADE 2 Mild-to-moderate limitation in activity—some assistance may be needed; no or minimal medical intervention/therapy required.

GRADE 3 Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible

GRADE 4 Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care.

HAEMATOLOGY	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Haemoglobin	8.0–9.4 g/dl **OR** 80–94 g/L **OR** 4.93–5.83 mmol/L	7.0–7.9 g/dl **OR** 70–79 g/L **OR** 4.3–4.92 mmol/L	6.5–6.9 g/dl **OR** 65–69 g/L **OR** 4.03–4.30 mmol/L	<6.5 g/dl **OR** <65 g/L **OR** <4.03 mmol/L
Absolute neutrophil count	1000–1500/mm^3 **OR** 1.0–1.5 g/L*	750–999/mm^3 **OR** 0.75–0.99 g/L*	500–749/mm^3 **OR** 0.5–0.749 g/L*	<500/mm^3 **OR** <0.5 g/L*
Platelets	75 000–99 000/mm^3 **OR** 75–99 g/L*	50 000–74 999/mm^3 **OR** 50–74.9 g/L*	20 000–49 999/mm^3 **OR** 20–49.9 g/L*	<20 000/mm^3 **OR** <20 g/L*
CHEMISTRIES	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Sodium				
Hyponatraemia	130–135 mEq/L **OR** 130–135 mmol/L	123–129 mEq/L **OR** 123–129 mmol/L	116–122 mEq/L **OR** 116–122 mmol/L	<116 mEq/L **OR** <116 mmol/L

CHEMISTRIES (*contd.*)	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hypernatraemia	146–150 mEq/L **OR** 146–150 mmol/L	151–157 mEq/L **OR** 151–157 mmol/L	158–165 mEq/L **OR** 158–165 mmol/L	>165 mEq/L **OR** >165 mmol/L
Potassium				
Hyperkalaemia	5.6–6.0 mEq/L **OR** 5.6–6.0 mmol/L	6.1–6.5 mEq/L **OR** 6.1–6.5 mmol/L	6.6–7.0 mEq/L **OR** 6.6–7.0 mmol/L	>7.0 mEq/L **OR** >7.0 mmol/L
Hypokalaemia	3.0–3.4 mEq/L **OR** 3.0–3.4 mmol/L	2.5–2.9 mEq/L **OR** 2.5–2.9 mmol/L	2.0–2.4 mEq/L **OR** 2.0–2.4 mmol/L	<2.0 mEq/L **OR** <2.0 mmol/L
Bilirubin				
Hyperbilirubinaemia	>1.0–1.5 X ULN	1.6–2.5 X ULN	2.6–5 X ULN	>5 X ULN
Glucose				
Hypoglycaemia	55–64 mg/dL **OR** 3.01–3.55 mmol/L	40–54 mg/dl **OR** 2.19–3.00 mmol/L	30–39 mg/dl **OR** 1.67–2.18 mmol/L	<30 mg/dl **OR** <1.67 mmol/L
Hyperglycaemia (non-fasting and no prior diabetes)	116–160 mg/dl **OR** 6.44–8.90 mmol/L	161–250 mg/dl **OR** 8.91–13.88 mmol/L	251–500 mg/dl **OR** 13.89–27.76 mmol/L	>500 mg/dl **OR** >27.76 mmol/L
Triglycerides	—	400–750 mg/dl **OR** 4.52–8.47 mmol/L	751–1200 mg/dl **OR** 8.48–13.55 mmol/L	>1200 mg/dl **OR** >13.55 mmol/L
Creatinine	>1.0–1.5 X ULN	1.6–3.0 X ULN	3.1–6.0 X ULN	>6.0 X ULN
Transaminases				
AST (SGOT)	1.25–2.5 X ULN	2.6–5.0 X ULN	5.1–10.0 X ULN	>10.0 X ULN
ALT (SGPT)	1.25–2.5 X ULN	2.6–5.0 X ULN	5.1–10.0 X ULN	>10.0 X ULN
Gamma glutamyl transpeptidase (GGT)	1.25–2.5 X ULN	2.6–5.0 X ULN	5.1–10.0 X ULN	>10.0 X ULN
Alkaline phosphatase	1.25–2.5 X ULN	2.6–5.0 X ULN	5.1–10.0 X ULN	>10.0 X ULN
Amylase	1.0–1.5 X ULN	1.6–2.0 X ULN	2.1–5.0 X ULN	>5.0 X ULN
Pancreatic amylase	1.0–1.5 X ULN	1.6–2.0 X ULN	2.1–5.0 X ULN	>5.0 X ULN
Lipase	>1.0–1.5 X ULN	1.6–3.0 X ULN	3.1–5.0 X ULN	>5.0 X ULN

Transaminases (*contd.*)				
Lactate	<2.0 X ULN without acidosis	>2.0 X ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
GASTROINTESTINAL	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Nausea	Mild **OR** transient; reasonable intake maintained	Moderate discomfort **OR** intake decreased for <3 days	Severe discomfort **OR** minimal intake for ≥3 days	Hospitalization required
Vomiting	Mild **OR** transient; 2–3 episodes per day **OR** mild vomiting lasting <1 week	Moderate **OR** persistent; 4–5 episodes per day **OR** vomiting lasting ≥ 1 week	Severe vomiting of all food/fluids in 24 hours **OR** orthostatic hypotension **OR** IV treatment required	Hypotensive shock **OR** hospitalization for IV treatment required
Diarrhoea	Mild **OR** transient; 3–4 loose stools per day **OR** mild diarrhoea lasting <1 week	Moderate **OR** persistent; 5–7 loose stools per day **OR** diarrhoea lasting ≥1 week	Bloody diarrhoea **OR** orthostatic hypotension **OR** >7 loose stools/day **OR** IV treatment required	Hypotensive shock **OR** hospitalization required
RESPIRATORY	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Dyspnoea	Dyspnoea on exertion	Dyspnoea with normal activity	Dyspnoea at rest	Dyspnoea requiring O_2 therapy
URINALYSIS	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Proteinuria				
Spot urine	1+	2–3+	4+	Nephrotic syndrome
24-hour urine	200 mg–1 g loss/day **OR** <0.3% **OR** <3 g/L	1–2 g loss/day **OR** 0.3–1.0% **OR** 3–10 g/L	2–3.5 g loss/day **OR** >1.0% **OR** >10 g/L	Nephrotic syndrome **OR** >3.5 g loss/day
Gross haematuria	Microscopic only	Gross, no clots	Gross plus clots	Obstructive

MISCELLANEOUS	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Fever (oral, >12 hours)	37.7–38.5°C	38.6–39.5°C	39.6–40.5°C	>40.5°C for ≥12 continuous hours
Headache	Mild, or does not require treatment	Moderate, which responds to non-narcotic analgesics	Severe, which responds to initial narcotic analgesic	Intractable
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria, angioedema	Anaphylaxis
Rash Hypersensitivity	Erythema, pruritus	Diffuse, maculopapular rash **OR** dry desquamation	Vesiculation **OR** moist desquamation **OR** ulceration	Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis
Fatigue	Normal activity reduced <25%	Normal activity reduced 25–50%	Normal activity reduced >50%; cannot work	Unable to care for self

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Index

Successful scaling-up of antiretroviral therapy requires the rational use of antiretroviral drugs. This manual provides guidance and information in a practical and user-friendly format, using tables and figures, accompanied by limited text and provides recommendations based on evidence from clinical trials, observational cohort data and expert opinion. It comprises eight main sections:

- Laboratory diagnosis of HIV infection in adults and adolescents;
- Assessment of adults and adolescents with HIV infection;
- Prevention of opportunistic infections;
- Management of antiretroviral therapy;
- Management of opportunistic infections;
- Management of nutrition and palliative care;
- Management of post-exposure prophylaxis, and related
- Annexes.

The full set of WHO guidelines is available at www.searo.who.int/hiv-aids publications and http://www.who.int/hiv/pub/guidelines/en/index.html.

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