



Ministry of Health and Social Welfare
Kingdom of Swaziland

**NATIONAL GUIDELINES FOR
ANTIRETROVIRAL TREATMENT
AND POST-EXPOSURE
PROPHYLAXIS**

For Adults and Adolescents

MOHSW



**World Health
Organization**

REGIONAL OFFICE FOR

Africa

November 2006



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FOREWORD

Swaziland, is one of the countries that have been hard hit by the HIV/AIDS epidemic. The HIV prevalence rate has been continuing to rise since the first case of HIV was diagnosed in 1986. Currently 220,000 people are estimated to be living with HIV and AIDS and out of these, about 30,000 are in need of ARV drugs.

The country has established the National ART Program in order to offer treatment, care and support services to the people living with HIV and AIDS. Swaziland has been providing free antiretroviral drugs since December 2003 and more than 20,000 PLWHAs have benefited from the program since its launch, out of which, more than 15000 were still on treatment by the end of September 2006. In 2003 the first National HIV treatment guidelines were developed and have been in use up until 2006. The steep increase in the number of people benefiting from the treatment and the lessons learnt from the time the treatment program was launched, has necessitated the review of the previous guidelines to suit the needs of the country, using an evidence-based approach.

These guidelines serve to assist the clinical team in the management of patients on antiretroviral drugs. ART is now considered an integral part of a comprehensive response to HIV prevention, care and support. The approach adopted is to strive for a continuum of care, a holistic focus on the patient in an integrated health system, from the ART clinic to the community and from pre-diagnosis to palliation as appropriate. The focus is at the hospital level within the context of the regional health system with the aim to further decentralise care to the local clinic level. These guidelines have been reviewed in light of new evidence, programmatic experience and the latest revision of the WHO guidelines. In the future, they will again be revised as necessary to reflect the changing world of the treatment of HIV to ensure the highest possible standard of care for all people of Swaziland.

The antiretroviral drugs recommended for the country in these guidelines have been selected based on evidence of their effectiveness in slowing down the multiplication of HIV in the body and improving the quality of life for the person infected with HIV and AIDS. In addition, these drugs provide the patient with a wide spectrum of choices for treatment in case of drug resistant strains of HIV emerge in the future. Proper adherence to these drugs will ensure that the patient has a longer period of survival, while also ensuring that the newer drugs are used for those patients who for some reason have not

responded well to the first-line treatment.

It is therefore very important that all people living with HIV and AIDS commit themselves to improve the quality of their life by ensuring that they prevent getting new infections, live positively when diagnosed HIV positive and take their ARVs properly as advised by the health worker.

ACKNOWLEDGEMENTS

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The valuable contributions made by the health workers from the different health facilities in the country cannot go unnoticed. It is through their experience in ART service delivery that the guidelines have been reviewed to be more practical for each of the different levels of the health care delivery system in the country.

ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AFB	Acid Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
AZT	Zidovudine
BBP	Blood Borne Pathogens
d4T	Stavudine
ddC	Zalcitabine
ddI	Didanosine
DLV	Delavirdine
DNA	Deoxyribonucleic acid
EFV	Efavirenz
ELISA	Enzyme Linked Immunosorbent Assay
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
Hb	Haemoglobin
HCW	Health Care Worker
HIV	Human Immunodeficiency Virus
HTC	HIV Testing and Counselling
IDV	Indinavir
IRIS	Immune Reconstitution Inflammatory Syndrome
KS	Kaposi's Sarcoma
LDH	Lactate Dehydrogenase
LDL	Low density lipoprotein
LFT	Liver function tests
LPV/r	Lopinavir/ritonavir (Kaletra)
NFV	Nelfinavir
NNRTIs	Non Nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
OI	Opportunistic Infections
OPD	Outpatients Department

PCR	Polymerase Chain Reaction
PEP	Post Exposure Prophylaxis
PIs	Protease Inhibitors
PLWHAs	People Living with HIV/AIDS
PMTCT	Prevention of Mother-to-Child Transmission
RBC	Red Blood Cell
RHM	Rural Health Motivators
RTV	Ritonavir
SQV	Saquinavir
STI	Sexually Transmitted Infections
TB	Tuberculosis
TDF	Tenofovir
VCT	Voluntary Counselling and Testing
WHO	World Health Organization

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Section 1

USE OF ANTIRETROVIRAL DRUGS IN ADULTS AND ADOLESCENTS

1. INTRODUCTION

1.1 Background Information

These guidelines have been devised within the framework of a public health approach. Standardised first and second line regimens have been agreed upon, taking into account the ease of dosing, toxicity profiles and laboratory monitoring requirements. These standardised regimens allow for simpler, easier and more effective ART initiation and follow-up in situations where most patients will not be managed by a physician specialised in HIV medicine and require the management of a patient using the health care team approach.

One of the major keys to a successful ART programme lies in **optimal adherence** among people taking the ARVs. Many factors influence adherence to the medication and these need to be key considerations when assessing each individual patient's readiness to be initiated on ART. The guidelines provide information on strategies to ensure good adherence to ART and the practical steps which the health care team can take to ensure optimal adherence, including the involvement of community workers and PLWHA support groups.

It is hoped that with good patient management by the clinicians, optimal adherence by the patient and good linkages between the health workers and the community workers in supporting adherence, the full benefits of ART can be experienced by most of the patients in the country.

1.2. Diagnosis of HIV infection

Laboratory diagnosis of HIV infection is the starting point towards the provision of treatment care and support services to PLWHAs. When considering initiating ART using ARV drugs, it is very important that the diagnosis of HIV infection in the patient is confirmed. For those who do not know their HIV serostatus but have signs and symptoms suggestive of HIV infection, testing and counselling services should be offered to them in the context of provider-initiated testing and counselling. Those patients who may not want to know their HIV status immediately should be informed that they can utilize the VCT centres (client-initiated approach).

HIV diagnosis is done using antibody tests and virological tests.

1. Antibody tests:

- Simple/rapid tests (in Swaziland: Unigold® and Determine® tests)
- ELISA

2. Virological tests (limited availability in Swaziland)

- DNA PCR
- RNA PCR
- P24 antigen

1.3. HIV Testing and Counselling (HTC)

It is recommended that all health care providers routinely offer HIV testing and counselling to patients who present at all levels of health care, more especially to those who present with an illness that is suspected to be due to HIV infection. This can be done in settings of OPD, hospital wards, and other specialized clinics for TB, STI and skin diseases. The benefits of HIV testing and counselling for the individual include:

- Early knowledge of HIV status and acquisition of knowledge on HIV transmission
- Motivation to initiate or maintain safer sexual practices
- Early access to care (including ART) and prevention of opportunistic infection
- Improved health through education and nutritional advice
- Emotional support and better ability to cope with HIV-related anxiety.

IMPORTANT

Health workers are reminded that routine offer of HIV testing and counselling should follow the principle of the 3 "C"s, that is Counselling, Confidentiality and Consent.

2. ART - GOALS, ASSESSMENT AND INDICATIONS

2.1 Goals of ART

The **primary goal** of antiretroviral therapy is to decrease HIV related morbidity and mortality, and thereby:

- the patient should experience fewer HIV related illnesses resulting in an improvement in quality of life.
- immunologic function should be restored and the patient's CD4 count should rise and remain above the baseline count.
- the viral load should become undetectable (< 400 copies/ml) and remain undetectable on ARV therapy – although this test is not yet widely available in Swaziland.

The **secondary goal** is to decrease the incidence of HIV through;

- The increased uptake in voluntary testing and counselling resulting in more people knowing their status and practicing safer sex,
- The reduction of transmission in discordant couples, mother to child and with new partners.
- Changing the perception of the community about HIV and AIDS to a manageable chronic disease.
- Reducing the stigma and discrimination and ensuring enhanced participation of the community and PLWHA in HIV/AIDS control and prevention

2.2 Assessment of HIV infected patients for ART

The process of initiating ART involves both clinical and laboratory assessment of a patient. It also requires assessment of the patient's readiness to commence therapy and understanding of the implications of ART. (lifelong therapy, adherence, and possible toxicities of the drugs.)

Access to nutritional and psychosocial support (in the form of peer support groups and family members) is also important when making decisions regarding initiation of ART.

2.2.1. Clinical staging

It is intended for use where HIV infection has been confirmed by HIV antibody testing. It should form part of baseline and follow up assessments,

and should be used to guide decisions on when to start cotrimoxazole prophylaxis, when to start ART and when to change ARV regimens and should be used in conjunction with results of CD4 testing.

Table 1. WHO classification of HIV-associated clinical disease*

Classification of HIV-associated clinical disease	WHO Clinical Stage
Asymptomatic	1
Mild	2
Advanced	3
Severe	4
* See Annex 1 for latest WHO Clinical Staging.	

2.2.2. Immunological assessment (CD4 testing)

The optimum time to commence ART is prior to patients becoming unwell or presenting with their first opportunistic infection. An absolute CD4 value of 200 cells/mm³ is regarded as the threshold at which there is a substantially increased risk of clinical disease progression. At CD4 values well below 100 cells/mm³ there may also be much slower and less favourable response even to optimal ART and morbidity and mortality is substantially increased.

Routine testing of CD4 cell count is the ideal way to monitor this situation. Ideally patients who have tested early in their disease and have CD4 counts way above 200 cells/mm³ should have CD4 counts done every 6 months, and be monitored to ensure that ART is started before the CD4 drops too far below 200 cells/mm³. A baseline CD4 cell count not only guides the decision on when to initiate ART, but is also used to monitor ART. A baseline CD4 cell count is therefore necessary even if a patient qualifies for ART on clinical grounds.

CD4 testing should be done at the earliest available opportunity when dealing with an HIV infected patient. It should preferably only be done once any inter-current infections have been stabilised. Absolute CD4 cell counts vary, and if possible should be repeated if a major management decision rests

IMPORTANT

The absence of CD4 count should not be used as a deterrent to initiating ART, however for purposes of monitoring, the CD4 count should be done as soon as it is available, preferably within the first month of starting ART.

on the value.

2.3 Indications for ART

Initiation of antiretroviral therapy depends on three factors:

- a. **CD4 cell counts**
- b. **WHO clinical staging**
- c. **Patient readiness/expressed willingness to start ART**

A patient with a **CD4 cell count below 200 cells/mm³** should be started on ART regardless of the clinical status. Patients presenting with disease classified within **WHO clinical stage III with a CD4 cell count below 350 cells/mm³** should be initiated on ART. All patients presenting with **WHO stage IV** disease should be started on ART, regardless of the CD4 cell counts. In addition to all the above, **every patient must be assessed and be found ready to start ART** before any treatment is initiated as this markedly improves the chances of good adherence to the medication.

Table 2. Criteria for initiation of ART in adults and adolescents

CD4 count <200 cells/mm ³ irrespective of WHO clinical stage
OR
WHO clinical stage IV regardless of CD4 cell counts
OR
WHO clinical stage III with a CD4 count <350 cells/mm ³
AND
Patient expresses willingness and readiness to take ART adherently

2.4. Psychosocial considerations (not exclusion criteria):

- Demonstrated reliability, i.e. to honour appointments as scheduled by the health care worker.
- No active alcohol or other substance abuse.
- No untreated active depression.
- Disclosure: It is strongly recommended that clients have disclosed their HIV status to at least one friend or family member (treatment supporter) OR have joined a support group.
- Insight: Clients need to have accepted their HIV positive status, and have insight into the consequences of HIV infection and the role of ARV treatment before commencing ARV therapy.
- Able to attend the antiretroviral centre on a regular basis (outreaches may need to be arranged for patients in rural areas or for those remote from the treatment site) or have access to services able to maintain follow up.

3. INITIATION OF ART

3.1 Process of initiation of ART

ARV THERAPY IS NOT AN EMERGENCY INTERVENTION - it is therefore important that full patient assessment is done and all opportunistic infections are treated or stabilized before ART can be initiated. In addition, adherence counselling must be done prior to initiation of treatment and patients must be encouraged to disclose their status to a trusted individual, who will be the treatment supporter.

The process of ART initiation will involve a number of visits to the ART clinic during which a number of activities will be carried out and this must be clearly explained to the patient. It is very important that all patients coming to the ART clinic are registered, undergo adherence counselling sessions and have laboratory investigations done. Only after a satisfactory attendance of adherence sessions, willingness to start ART, normal laboratory tests and identification of a treatment supporter can a patient be given ART.

Patients who do not fulfil part of the criteria for ART initiation should be given more appointments for further assessment and should not be rushed into starting ART as this has an effect on the level of adherence. This delay in starting ART should be explained to the patient by the health worker.

The initiation of ART should be preceded by an individual adherence counselling session, in which the following is covered:

- Detailed description of the drugs (treatment education)
- Explain drug dosing details and anticipated adverse effects
- Provide instructions on what to do and how to access medical help in case of moderate or severe adverse effects
- Ensure that instructions are clearly written on the container with a permanent marker.

IMPORTANT

The health care team should put great effort in ensuring that they obtain full collaboration from the patient before starting ART.

Determine patient readiness by confirming:

1-Medical eligibility criteria have been met

2-Patient has accepted his/her HIV status and is ready to start ART

- Open the containers and show the drugs to the patient.
- Provide enough medication to last until the next appointment date.
- Reinforce drug dosing details and methods for side effect management before the patient leaves the clinic
- Provide information leaflets in both Siswati and English.

Discuss the social and economic status of the patient to identify probable barriers to adherence and how to overcome them.

Table 3. Types and dosages of ARVs

ARV class	Generic name (Abbreviation)	Brand name	Dosage for adults and adolescents
NRTIs	Zidovudine (AZT)	Retrovir	300 mg twice daily
	Didanosine (ddI)	Videx	400 mg once daily (250 mg once daily if <60 kg)
	Zalcitabine (ddC)	Hivid	0.75 mg three times daily
	Stavudine (d4T)	Zerit	40 mg twice daily (30 mg twice daily if <60 kg)
	Lamivudine (3TC)	Epivir	150 mg twice daily
	Abacavir (ABC)	Ziagen	300 mg twice daily
	Tenofovir (TDF)	Viread	300 mg once daily
NNRTIs	Nevirapine (NVP)	Viramune	200 mg once daily x 14 days, then 200 mg twice daily
	Efavirenz (EFV)	Sustiva	600 mg once daily (in the evening)
	Delavirdine (DLV)	Rescriptor	400 mg three times daily
PIs	Indinavir (IDV)	Crixivan	800 mg twice daily with ritonavir 100 mg
	Ritonavir (RTV)	Norvir	100 mg twice daily in combination with other PIs
	Nelfinavir (NFV)	Viracept	1250 mg twice daily
	Saquinavir (SQV)	Fortovase / Inivase	1000 mg twice daily with ritonavir 100 mg
	Lopinavir/r (LPV/r)	Kaletra	400/100mg twice daily

3.2 First line ARV regimens

Swaziland has been using d4T/3TC/NVP (Triomune®/ Triviro®) fixed dose combination (FDC) as the first line treatment regimen for most patients.

WHO recommendations have now changed to the use of **AZT (Zidovudine) in preference** to d4T (Stavudine) for patients being initiated on ART, following a wide range of studies that have been done in African patients on the life-threatening and sometimes irreversible adverse effects of Stavudine.

TDF (Tenofovir) and ABC (Abacavir) have also been included as possible first line agents in treating HIV infection in patients who may have contra-

REMEMBER:

INITIATION OF ART IS NOT AN EMERGENCY!

indications to using the standard first line regimen. However, these drugs are not yet widely available in Swaziland.

At this time, we are continuing to recommend the use of AZT or d4T containing regimen initially, but this may soon change in accordance with WHO guidelines. When TDF and ABC become readily available in Swaziland, their use can be considered in first line regimen.

Triple nucleoside regimen (consisting of 3 NRTIs) will also become available in the near future as alternative first line agents in a few select patients. (e.g. those unable to tolerate NNRTIs when PI-based regimen are unavailable, women with higher CD4 counts who have a high risk of pregnancy who wish to commence ART, and in some patients with TB requiring ART. The only acceptable combinations of 3 NRTIs are AZT+3TC+ABC or AZT+3TC+TDF.

The following regimen are based on 2 NRTI's and 1 NNRTI. Protease Inhibitors are reserved for second line use.

3.2.1. Recommended first line ARV regimen

AZT/ 3TC/ NVP

3.2.2. Alternative first line ARV regimen

AZT/ 3TC/ EFV	In cases of poor tolerability to NVP or on TB treatment
d4T/ 3TC/ NVP	In cases where AZT is contraindicated, e.g. anaemia
d4T/ 3TC/ EFV	In cases where AZT and NVP are contraindicated

3.2.3. Dosages of ARV drugs in the first line regimen (see also Table 3)

1. Zidovudine (AZT) 300mg every 12 hours
2. Lamivudine (3TC) 150 mg every 12 hours
3. Nevirapine (NVP) 200 mg daily for the first 2 weeks, then increasing to 200 mg every 12 hours if ALT not more than 3x baseline value)*. Evaluate for rash**.
4. Efavirenz (EFV) 600 mg (or 400 mg if < 40 kg) same time in evening before

going to bed

5. Stavudine (d4T) (30 mg every 12 hours)

*If ALT is more than 2.5x (two and a half times) the baseline value at two weeks, it is not advisable to increase NVP, rather continue at once daily and monitor ALT on a weekly basis. Once ALT is stable, the dose can be increased to 12 hourly. If ALT increases 5x the baseline value, NVP should be replaced by EFV.

**NVP may cause a transient rash (less common in EFV) and this should be carefully monitored and the patient adequately counselled. Severe forms of skin eruptions presenting with fever and mucosal involvement (Stevens-Johnson Syndrome) warrant immediate cessation of ART and patient should be restarted with another alternative 1st line regimen after symptoms have subsided and patient has returned to good clinical condition.

3.2.4. Newer ARV drugs that can be included in first line regimen:

Tenofovir (TDF) 300mg once daily

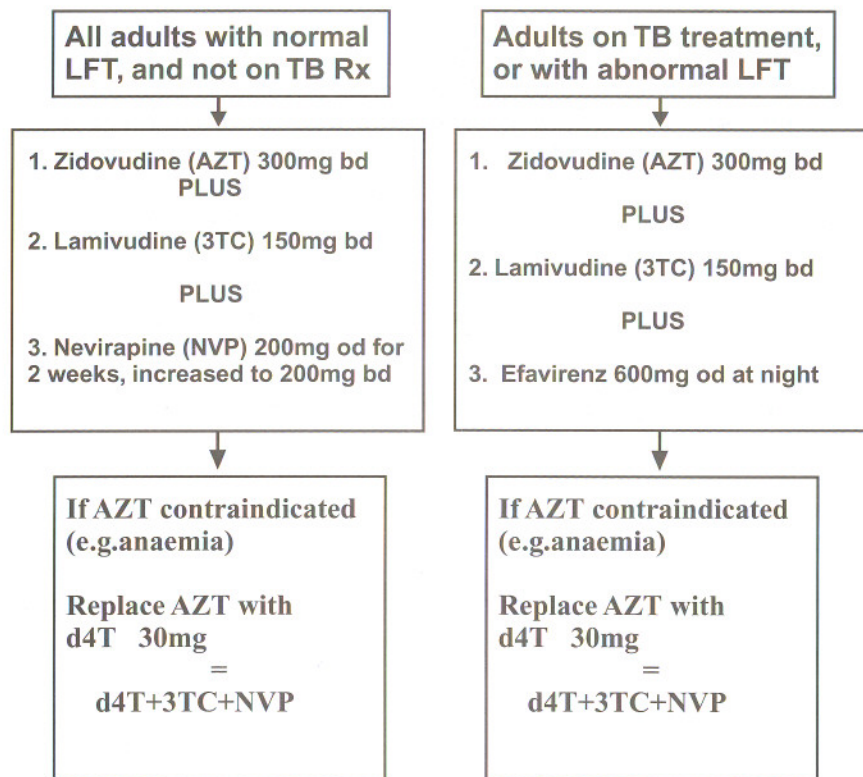
Abacavir (ABC) 300mg every 12 hours or 600mg daily***

*** ABC hypersensitivity – patients may develop hypersensitivity in which case ABC should be stopped immediately and NOT restarted.

3.3 Algorithm for the use of first line ARV regimen

Please note:

Patients who have been exposed to ARVs in the past need to be assessed by the ART doctor BEFORE a treatment regimen is commenced



3.4 Basic principles of ART

- Combination of at least three ARV drugs must be given (HAART).
- Mono- and dual- therapy are not acceptable.
- LPV/r is not dual therapy but mono therapy and should be combined with other classes of drugs.
- Combination of AZT and d4T is contraindicated.
- Combination of ddI and d4T should be avoided especially during pregnancy
- Efavirenz is not recommended for use in the first trimester of pregnancy.

Nevirapine should not be used in the presence of liver dysfunction or concomitantly with drugs metabolised by the liver – e.g. Rifampicin

3.5. Table 4 Factors influencing the choice of ARV Regimen

Anaemia (Hb < 10g/dl)	avoid AZT and use d4T
Severe peripheral neuropathy	avoid d4T and use AZT
TB treatment	avoid NVP and use EFV
Pregnancy or childbearing potential	avoid EFV and use NVP unless the woman can guarantee use of effective contraception such as hormonal combined with barrier methods
Liver disease or deranged LFTs	avoid NVP and use EFV or PI
Women with CD4>250	have increased incidence of hepatitis with NVP NVP may be used but ALT must be monitored at weeks 2, 4, 8 and 12

IMPORTANT

Drug substitutions should only be made after careful consideration and preferably by a doctor trained in ART.

Patients already on d4T containing regimens (e.g. Triomune/Triviro) should be continued on these regimens unless a drug substitution is indicated for clinical reasons.

4. MONITORING OF PATIENTS ON ART.

The first six months on ART is a critical period for the close monitoring of the patients for adverse effects as well as clinical and laboratory monitoring. It is at this time that there should be continuous reinforcement of adherence counselling. It is expected that patients should improve clinically and immunologically during this time, but this is not always the case.

It is therefore not advisable to transfer-out a patient within the first six months of ART initiation.

Notably patients started with advanced clinical disease and lower CD4 cell counts e.g. CD4<50 are more at risk of poorer outcomes. This may not necessarily reflect a poor response to ART, but can also be due to prolonged time to recovery of the immune system or reversal of the catabolism associated with HIV infection, immune reconstitution inflammatory syndrome (IRIS) or the occurrence of new and serious opportunistic infections.

During the first year, visits to the ART clinic must be scheduled monthly for the review of the clinical condition of the patient and for refill of ARV drugs. For the second year of ART, patients who have shown satisfactory adherence and clinical and immunological improvement can be given 3 monthly visits to collect their ARVs.

Patients who are not well, or those who fall in the category of pregnant, child, prolonged low CD4 count that are at high risk may need to be seen more frequently than the regular scheduled visits.

4.1 Clinical and Laboratory monitoring of patients on first line ARV regimen

4.1.1. First Visit Post ART initiation – 2nd week after starting ART

During this visit, the patient **must** be seen by the doctor. This visit follows the ART initiation visit. During this visit, the following activities should take place:

- ✍ Review patient for new signs and symptoms of opportunistic infections
- ✍ Chart weight, functional status and vital signs
- ✍ Check for adverse events of the ARVs, especially if on NVP
- ✍ Ensure the patient is taking the correct dosage of all drugs
- ✍ Reinforce adherence to ART and OIs prophylaxis

- ✍ Perform necessary blood tests e.g. (ALT – see section above) for patients on NVP before dose escalation.

4.1.2. Follow up visits - at 4th week after starting ART and monthly for the first year

During this visit, the patient can be seen by the doctor or ART trained nurse. Patient needs to attend on a monthly basis when collecting medication. They can be seen by a doctor or a nurse depending on their clinical response to treatment. The following must be done:

- ✍ Review patient for new signs and symptoms of OIs
- ✍ Chart weight, functional status and vital signs – important for clinical monitoring.
- ✍ Check for adverse events of the drugs
- ✍ Ensure the correct dosage of ARV's and OIs prophylaxis as necessary (consider weight gain).
- ✍ Reinforce adherence
- ✍ Consider any change in WHO staging on treatment (T staging). See **Annex 1**
- ✍ Perform necessary blood tests e.g. Hb for patients on AZT or ALT for patients on NVP
- ✍ CD4 to be monitored at 3 and 6 months after initiation of treatment, and if adequate improvement, 6 monthly thereafter.

After one year

Once a patient is stable on treatment for one year with adequate improvement in both clinical and laboratory parameters, they may be allowed to collect treatment on a 3-monthly basis (refill every 3 months). Routine blood investigations (CD4, Hb, ALT) should be done every 6 months as directed by the regimen.

4.2 Schedule of Routine Laboratory Monitoring for Patients on ART

4.2.1. Baseline

If possible baseline tests should be complete in order to exclude concurrent diseases (e.g. diabetes, liver disease, etc.). The following tests are recommended:

Full haemogram, Liver and kidney function tests, cholesterol, glucose, triglycerides, amylase, LDH, Urinalysis, CD4 cell count.

4.2.2. Table 5 Follow up (minimum set of laboratory monitoring)

	Week 2	Month 1	Month 2	Month 3	Month 6 and every 6 months
Hb (AZT)		X		X	X
ALT/AST (NVP)	X			X	X
CD4				X	X
Viral load					X If no improvement in CD4 count

IMPORTANT

- *Viral load can be done in special circumstances where clinically indicated or where CD4 counts have decreased or are not increasing adequately. This is to confirm treatment failure in order to change to second line regimens.*
- *CD4 counts to be done at month 3 and 6, then at 6 monthly intervals. It may be necessary to repeat CD4 earlier if clinically indicated – usually after 2 weeks.*
- *Haemoglobin may need to be checked more often if clinically indicated.*
- *ALT/AST should be monitored more frequently (wk 2, 4, 8 and 12) in female patients with baseline CD4 counts >250, or with abnormal liver functions or on concomitant hepatotoxic medications.*
- *ALT/AST results at 2 weeks should be taken into consideration before NVP dose escalation. If elevated >2.5x baseline value, do not increase dose of NVP but repeat test 1 week later.*
- *Females must have pap smears as per national protocol. These may need to be repeated more often depending on the cytological findings.*
- *Tenofovir (TDF) containing regimens should be monitored with renal function tests at baseline and every 6 months on therapy.*
- *Clinical evaluation and specific drug regimens will determine further investigations that may be necessary. e.g lactate, glucose and cholesterol levels.*

5. TREATMENT FAILURE AND SWITCH TO SECOND LINE ARV REGIMEN.

Many factors need to be taken into account when considering a patient's response to ART. The timing of the decision to switch from first line to second line therapy is critical and should not be made prematurely. Conversely, it should not, as far as possible, be delayed as this can lead to further mutations of resistant virus thus jeopardising the patient's chances of success in the future. In Swaziland where viral load monitoring is not routinely available, careful consideration of clinical parameters and CD4 count need to be taken into account.

5.1 Treatment Failure (see also Annex 3)

Treatment failure can be defined:

- clinically
- immunologically
- virologically

5.1.1. Clinical Failure:

New or recurrent WHO stage 4* or some stage 3** conditions

* some stage 4 conditions (lymph node TB, TB pleural disease, Oesophageal candidiasis, recurrent bacterial pneumonia) may not be related to treatment failure

**pulmonary TB, severe bacterial infections

Failure of an ARV regimen on the basis of clinical criteria should only be concluded once:

- Reasonable trial of first line therapy. Usually at least 6-12 months
- Adherence has been assessed and optimised
- Intercurrent opportunistic infections have been treated and resolved

Immune reconstitution inflammatory syndrome (IRIS), clinical events that occur during the first 6 months of therapy, are excluded (*See special considerations section*)

The development of a new or recurrent WHO stage III or IV condition on treatment (but after the first 6 months of ART) is considered functional evidence of HIV disease progression. This is being referred to as "**T staging**" - where the T refers to the staging event on treatment. The assumption is that

with immune restoration on ART, and the subsequent progressive immunodeficiency with a failing ART regimen, the clinical events signalling immune failure will be the same as those which herald advanced then severe immunodeficiency without ART. **Annex 1** indicates how clinical staging on ART (T staging) can be used as an indicator of failure and prompts consideration of the need to switch therapy.

5.1.2. Immunological Failure

- Fall of the CD4 count to pre-therapy baseline or
- Failure to increase CD4 count by 25 -50 cells/mm³ above the baseline during the first year of therapy or
- 50% fall from the on-treatment peak value (if known) or
- Persistent CD4 levels below 100cell/mm³

Cd4 cell count remains the strongest predictor of HIV related complications, even after the initiation of therapy. Measurement of CD4 is readily available in Swaziland and the trend of baseline and subsequent measurements should be considered.

Ideally any values which may indicate the need to consider switching treatment should be repeated and the value confirmed (usually at least 2 weeks after the initial result).

5.1.3. Virological Failure

Although at the moment Viral Load is not routinely available in Swaziland, according to WHO guidelines it can be defined as:

- Plasma HIV1-RNA level above 10,000 copies/ml in a person who has been on a regimen for more than 6 months and in whom drug adherence is determined to be sufficient and preferably once intercurrent infections have been stabilised

5.2. Poor adherence a major contributor to treatment failure

It is the major underlying factor which predisposes to treatment failure. Problems with adherence must be fully addressed before considering a switch to second line therapy. (See also chapter 8)

Good response to ARV therapy with adequate immune reconstitution should lead to better overall health of the patient with fewer HIV related

complications and opportunistic infections. Conversely, poor response to an ARV regimen or the development of resistance may be evident with new onset or recurrence of HIV related conditions and opportunistic infections.

5.3. Second line ARV Regimen - in the event of Treatment Failure.

It is important for clinicians to ensure that the majority of their patients are started and encouraged to remain on the first line ARV regimen. This is because this is the regimen that has the best chance of success and failure to adhere to the first line regimen results in a similar failure to adhere to and respond to second line regimen.. It is therefore recommended that a minimum of two ART trained clinicians make the decision to switch a patient from first line to second line regimen.

When switching to a second line regimen it is recommended to introduce a minimum of 2 new drugs and to include at least one new class.

5.3.1. Recommended Second line ARV Regimen

In case of proved failure of first line treatments (see chapter 3.2.) the recommended second line regimen is:

ddI+ABC+LPV/r

The alternative second line regimen is:

TDF/ABC/LPV/r

Patients who were treated with regimens other than the standard first line regimens will have to be considered carefully before switching to second line regimen.

IMPORTANT

In Swaziland, Protease inhibitors are reserved for second line treatment, ideally supported by two new NRTI's.

5.3.2 Dosing (see also Table 3)

- 1) ABC: 300mg 12 hourly or 600mg once daily
- 2) ddI: >60kg 400mg once daily
<60kg 250mg once daily ~1
- 3) TDF: 300mg once daily
- 4) LPV/r: 400/100mg twice daily (3 capsules Kaletra)

5.3.3 Monitoring of patients on second line ARV regimen

As with initiation of first line regimen, patients should be seen at 2 weeks after switching to second line ARV regimen, 1 month later and monthly thereafter.

- . Advise on new possible side effects with the new regimens (see section on adverse effects).
- . Additional laboratory monitoring includes 6 monthly renal functions for TDF.
- . Consider lipid abnormalities and monitoring fasting glucose in patients on protease inhibitors.

For other drug combinations see Annex 4

6. MANAGEMENT OF ADVERSE EVENTS ON ART

The number of available ARV drugs are limited, therefore it is important to minimise premature switching of ARV regimens.

Adequately informing patients of expected side effects will assist them in recognising and managing problems early.

Most adverse effects can be managed with advice, reassurance and simple medication. Usually adverse effects will not require a drug substitution.

ARV drug toxicity can be divided into **early** and **late** events.

- Early events present within the first few weeks to <6 months of therapy.
- Late events usually present after 6 months of ARV therapy.

Routine clinical and laboratory monitoring is aimed at detecting toxicities as early as possible. (See specific tables in the annexes.)

6.1. Toxicity Grading

Toxicity can be graded as shown below (**refer to Annex 2 for specifics**).

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; minimal medical intervention/therapy may be 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.

4 steps should be followed when managing ARV drug adverse effects:

- Step 1** Establish whether the adverse event is due to antiretroviral agents, other medication or illness.
- Step 2** Try to identify the responsible ARV drug.
- Step 3** Assess the degree/severity of the adverse event using the table below
- Step 4** Decide whether to substitute the particular drug or discontinue all

Table 6: Toxicities of first line ARV Regimen and recommended substitutions

ARV drug	Common associated toxicity	Suggested substitute
AZT	Severe anaemia ^a or neutropaenia ^b Severe gastrointestinal intolerance ^c	TDF or d4T or ABC
	Lactic acidosis	TDF or ABC ^d
d4T	Lactic acidosis Lipoatrophy / metabolic syndrome ^e	TDF or ABC ^d
	Peripheral neuropathy	AZT or TDF or ABC
ABC	Hypersensitivity reaction	AZT or TDF or d4T
TDF	Renal toxicity (renal tubular dysfunction)	AZT or ABC or d4T
EFV	Persistent and severe central nervous system toxicity ^f	NVP or TDF or ABC (or any PI ^h)
	Potential teratogenicity (first trimester of pregnancy or women not using adequate contraception)	NVP or ABC (or any PI ^h)
NVP	Hepatitis	EFV or TDF or ABC (or any PI ^h)
	Hypersensitivity reaction	TDF or ABC (or any PI ^h)
	Severe or life threatening rash (Stevens - Johnson syndrome) ^g	

^a Defined as Hb <6.5g/dl.^b Defined as neutrophil cell count < 500 /mm³ (grade 4).^c Defined as severe, refractory gastrointestinal intolerance that prevents ingestion of ARV drug regimen (e.g. persistent nausea and vomiting).^d Re-initiation of ART should not include d4T or AZT in this situation. TDF or ABC is preferred.^e Substitution of d4T may not reverse lipoatrophy.^f e.g. persistent hallucinations or psychosis.^g Severe rash is defined as extensive rash with desquamation, angioedema, or a reaction resembling serum sickness; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema or conjunctivitis; Stevens-Johnson syndrome can be life-threatening. For life-threatening rash, substitution with EFV is not recommended.^h PI class should be preferentially reserved for second-line therapy as no potent regimen have been identified for recommendation following initial PI failure

6.2 Management of specific adverse reactions

Stop all therapy if there is severe hepatitis, pancreatitis, lactic acidosis or Stevens-Johnson syndrome suspected.

6.2.1. Nausea and vomiting

Nausea and vomiting due to antiretroviral medication must be actively managed, or adherence to ART will be compromised.
Anti-emetics taken half an hour before the antiretroviral dose up to 3 times daily, may be helpful.

6.2.2 Diarrhea

May be associated with the use of ddI and PIs
Differentiate from other causes such as infections (blood or mucus in stool, fever)
If due to ARVs, administer antimotility agents

6.2.3. Rash

Both NVP and EFV may cause skin reactions. This usually occurs within the first 2 months of treatment
Do a clinical assessment to rule out any other causes of the rash.
Enquire about systemic symptoms, and check the temperature in any patient presenting with a rash.
Do a grading of the rash, and refer to tables for management.
If fever, eye discomfort, skin blisters, mouth sores – stop all ARV drugs and refer to hospital immediately, give antihistamine drug and treat rash.
Concomitant (simultaneous) TB therapy may confuse the situation as these drugs can cause similar adverse events.

6.2.4. Peripheral neuropathy

May be due to the use of d4T and ddI

Mild symptoms – reduce dose of d4T by 10mg or substitute with AZT, treat pain with amitriptylline or carbamazepine

Moderate to severe symptoms – discontinue d4T or ddI, substitute with AZT, treat pain as above

6.2.5. Abdominal pain

Abdominal pain in a patient on ART can be caused by a number of serious problems, and should never be ignored.

Important causes include lactic acidosis, pancreatitis, hepatitis, hyperlactataemia (increased serum lactate) and disseminated tuberculosis. Recommended investigations: liver function test, lipase and serum lactate and electrolytes

Abdominal tenderness and jaundice – stop ARVs and refer to hospital

Elevated amylase – stop ARVs and refer to hospital

6.2.6. Hyperlactataemia and lactic acidosis

Asymptomatic elevation of lactate is common in patients taking antiretroviral drugs (up to 20% per year).

Routine monitoring of lactate is not recommended if the patient is asymptomatic.

Patients on ART can occasionally develop symptomatic hyperlactataemia (1-2% per year), and, more rarely, lactic acidosis (0.1-0.2% per year).

Risk factors for lactic acidosis include: female gender, obesity, pregnancy, prolonged ART, chronic renal failure.

A-Symptoms are non-specific:

-unwellness, generalised fatigue, weakness,

-gastro-intestinal symptoms (nausea, vomiting, abdominal pain, abdominal distension)

-shortness of breath, dyspnoea, tachypnoea,

-neurologic symptoms (disequilibrium, motor weakness) Lactate 2-5 mmol/L: monitor monthly, and be alert for clinical symptoms and signs described above.

B-Management:

-Lactate 2-5 mmol/L: monitor monthly and be alerted for clinical symptoms and signs described above

-Lactate >5 mmol/L: STOP all ARV drugs immediately (30% mortality in case series). Other causes of raised lactate must be excluded, such as sepsis, renal failure, diabetic ketoacidosis.

-Metabolic acidosis with raised lactate: STOP all ART. Patient needs urgent admission. Treatment is supportive including carefully monitored intravenous fluids. Patients may require respiratory support.

-After recovery, once lactate is back to normal consider recommencing ART.

-Stavudine and didanosine should be avoided.

6.2.7. Lipodystrophy

HIV-associated lipodystrophy includes fat loss and/or fat accumulation in distinct areas of the body. This includes increased fat around abdomen, buffalo hump, breast hypertrophy, and fat loss from limbs, buttocks and face.

Association with antiretrovirals: lipodystrophy more common in individuals taking NRTIs or PIs.

Management: There are no established methods for treating lipodystrophy, but the following are recommended:

-encourage exercise and dietary adjustments to reduce fat accumulation,

-some patients improve if switched from a protease inhibitor to an NNRTI,

-fibrates are effective at lowering cholesterol and triglycerides levels,

-insulin resistance can be improved with anti-diabetic agents.

6.2.8. Hyperlipidaemia

Patients on lopinavir/ritonavir who develop hyperlipidaemia should be counselled about lifestyle modification:

-weight loss if obese,

-increasing exercise,

-stopping smoking,

-reducing cholesterol and saturated fat intake

Refer to a dietician, if available, for dietary advice

Severe hyperlipidaemia may require drug management.
If triglycerides >5.6 mmol/L after dietary changes or LDL >4.9 mmol/L or LDL > 3.4 mmol/L with 2 more other ischaemic heart disease risk factors, commence fibrates (or atorvastatin).

6.2.9. Lipodystrophy

If the patient develops a Grade III or IV anaemia or neutropenia on zidovudine, the dose can be reduced to 200 mg 12 hourly.
If the anaemia or neutropenia does not improve after dose adjustment, then zidovudine may have to be replaced with stavudine.

7. SPECIAL CONSIDERATIONS WITH ART

7.1 TB and ART

Patients who are candidates for ART may also have active TB. Approximately 70% of the patients with TB are co-infected with HIV. Patients already receiving ART may also develop TB.

All patients being worked up for ARV therapy should be screened for TB before the commencement of ART to avoid IRIS.

Suspect TB if one or more of the following are present:

- Cough > 2 weeks
- Fever / malaise / night sweats / loss of weight
- TB contact

Any patient with suspected TB should be screened for TB with three sputum tests for AFB. For patients presenting with enlarged cervical lymph nodes, fine needle aspiration of lymph nodes and chest X-Ray should be done as indicated.

In TB patients there are 2 scenarios to consider:

7.1.1. Patients who develop TB while on ART

Continue ART with changes to regimens and monitoring as follows:

- A change to EFV is recommended for patients on NVP whenever possible.
- If this is not possible (e.g. intolerance of EFV or significant risk of pregnancy), NVP may be continued in selected cases, with close clinical and laboratory monitoring (i.e. monthly ALT).

7.1.2. Patients who present with TB before starting ART

Major issues with ART and TB treatment include when to start ART and which drugs to use to avoid drug interactions and hepatotoxicity. In all cases, where indicated, TB treatment should be initiated first and once stable on TB treatment, ART can then be initiated. (see Table 7)

Table 7: ART initiation in relation to starting anti-TB therapy.

Initiating first line ART in relation to starting anti-TB therapy		
CD4 Cell Count	ART recommendations	Timing of ART in relation to the start of TB treatment
CD4 < 50 cells/mm ³	Recommend ART	As soon as stable on TB treatment – usually 2 weeks (monitor clinically and with ALT)
CD4 50 - 200 cells/mm ³	Recommend ART *	Usually once intensive phase completed at 2 months
CD4 between 200 - 350 cells/mm ³	Recommend ART	After completion of TB treatment
CD4 ≥ 350 cells/mm ³	Defer ART **	Re-evaluate patient at 8 weeks and at the end of TB treatment
CD4 not available	Recommend ART ***	Between 2 - 8 weeks depending on the clinical condition.

* an EFV-containing regimen is the preferred first line regimen. Alternative first line treatment regimens to the EFV include NVP and triple NRTI (TDF or ABC-based) regimens. For NVP-containing regimens ALT should be checked at 4, 8 and 12 weeks directed by symptom thereafter.

**If other non-TB stage 3 or 4 events are present, start ART.

***For some TB diagnoses that generally respond well to anti-TB therapy (i.e. lymph node TB, uncomplicated pleural effusion) consider defer ART.

7.1.3. Choice of ART with concomitant TB

ART regimens safe for concomitant use with combination anti-TB treatment include:

AZT + 3TC + EFV

D4T + 3TC + EFV

AZT + ddI + LPV/r

Hepatotoxicity occurs with both Rifampicin and NVP. Use of these drugs simultaneously should be avoided.

It is recommended that an EFV based regimen be used. If this is not possible, and NVP is used then ALT should be monitored very carefully (at weeks 2, 4, 8, 12).

Rifampicin increases the metabolism of LPV/r resulting in lower drug levels.

Rifampicin has been shown to reduce the level of EFV in the blood, but this is not thought to be clinically relevant, and it is not necessary to increase the dose of EFV.

7.1.4. Table 8 Shared side effects of anti-TB drugs and ARVs

Side effects	Antiretroviral treatment	Tuberculosis treatment
Nausea	ddI, AZT, RTV, SQV	Pyrazinamide
Hepatitis	NVP, EFV	Rifampicin, Isoniazid, Pyrazinamide
Peripheral neuropathy	d4T, ddI	Isoniazid
Rash	NVP, EFV	Rifampicin, Isoniazid, Pyrazinamide

7.2. Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS includes a spectrum of clinical signs and symptoms resulting from restored ability to mount an immune response that is associated with immune recovery.

Typically IRIS presents within 2 – 12 weeks of initiation of ART. The incidence is about 10% amongst all patients, but up to 25% in patients with Cd4 < 50 cells/mm³.

Mostly a reaction to latent untreated TB and cryptococcal infection.

Treatment is to identify and treat the pathogen. Continue ART and consider adding steroids in severe cases (prednisone 0.5mg/kg/day for 5- 10 days).

Where it is not possible to continue ART, stop the treatment temporarily and resume initial regimen once patient is stabilised.

IMPORTANT

Patients should be pre-emptively counselled about the following: Treatment for TB together with ARV therapy involves taking a large number of tablets and they may struggle with adherence.

7.3. Kaposi Sarcoma (KS)

KS is a WHO Stage 4 disease and its appearance is a clinical indication for initiation of ART. KS presents with skin, mucosal or systemic lesions.

Treatment - ART alone is effective for mild disease i.e. disease limited to the skin. For more severe disease with systemic or visceral involvement, treatment is with a combination of chemotherapy and ART.

Standard ART regimens should be initiated. NNRTI containing regimens have been found to have comparable efficacy to PI containing regimens.

7.4. Viral Hepatitis

Patients often present with co-infection of Hepatitis B and C viruses and HIV. HIV worsens the natural history of chronic viral Hepatitis, with increased cirrhosis and liver cancer.

3TC, FTC (emtricitabine) and TDF have activity specifically against Hepatitis B. The preferred combination is 3TC + TDF + EFV, but it must be stressed that standard regimens must be initiated as the rule.

Use NVP with care if co-infected with hepatitis B and with abnormal ALT. Careful regular monitoring and continued monitoring if grade 3 or less elevation on ALT. Do not start NVP if grade 4 ALT. EFV should rather be used in cases of ALT elevation.

7.5. Pregnancy and ART

All patients attending Antenatal clinic should be tested for HIV as soon as they present for antenatal care.

- HIV negative women - counsel adequately. Retest after 3 months to exclude recent infection.

HIV positive women - assess clinically and take blood for CD4 count as soon as possible

With regard to ART and pregnancy there are 3 clinical scenarios:

IMPORTANT

To prevent IRIS, careful examination and exclusion of latent infections prior to starting ART should be carried out.

7.5.1 Women who become pregnant while on ART

Women who are enrolled on ART should be counselled to use contraception reliably to prevent re-infection with other strains of HIV and to allow their bodies to recover adequately. Some women will fall pregnant on ART and the aim of the clinician is to ensure that therapy is not harmful to the mother or her foetus.

- Women who fall pregnant on NVP can continue with monthly monitoring.
- Women on AZT will need monthly check of Haemoglobin.
- Women on EFV based regimens need to be counselled about the possible risk of teratogenicity in the first trimester. Women on EFV who present in the early stages of the first trimester should be given NVP instead of EFV. Women who present beyond the first trimester can continue with EFV, but need to be adequately counselled about the possibility of congenital abnormalities. It is not an indication for termination of pregnancy.
- All the other drugs have been shown to be safe in pregnancy and benefits to the mother outweigh any risks to the baby.

7.5.2 Women who qualify for ART during pregnancy

The earlier the ART is initiated, the more substantial the protection offered to the foetus. It is recommended that HAART be initiated during pregnancy once the CD4 count is <350 cells/mm³. Once the decision has been made that a mother is eligible for ART, every effort should be made to start the treatment as soon as the mother is ready for maximum suppression of viral load. The following should be considered for pregnant women who qualify for ART:

- It is never too late to start ART in pregnancy.
- Cotrimoxazole prophylaxis must be initiated as for non-pregnant

IMPORTANT

ART fulfils two roles in pregnant women:

Treating the mother's HIV infection with prevention of disease progression.

Preventing the transmission of HIV to their child at birth (PMTCT)

patients. All patients in clinical stage III and IV, or CD4 <350. Benefits to the mother outweigh any risk to the foetus.

- Almost all ARV's are safe in pregnancy, but EFV should be avoided in the first trimester. Exposure to EFV in the first trimester is not an indication for termination of pregnancy. In addition, the combination of d4T and ddI should not be prescribed because of its toxicity.

7.5.3 Pregnant women who require ART for PMTCT only

- Women who do not qualify for long term ART (CD4 >350) should be managed according to the protocol in the national PMTCT guidelines .

7.6. Contraception and ART

Patients need to be counselled on the importance of using **dual method** contraception including both barrier and hormonal contraceptives.

Condoms and other reliable barrier methods protect against pregnancy as well as contracting STIs and HIV. They also offer additional protection against pregnancy where drug interactions between ART and hormonal contraceptives may lead to sub-optimal levels of the contraceptives in the blood.

From available evidence on drug to drug interactions and blood hormone levels it is safest to recommend injectable medroxyprogesterone acetate depot injection as the hormonal method of choice in patients on ART. This should be used in conjunction with barrier methods such as the condom.

8. ADHERENCE AND FOLLOW UP OF PATIENTS ON ART

8.1. Introduction

Adherence refers to the ability to follow the instructions on how to take medication and this means taking the drugs at the same time, the correct dosage and consistently (without missing a dose). Adherence to the HAART regimen is essential as it determines the success of the treatment through sustained viral control/suppression and therefore reduces illness due to HIV and AIDS. Sub-optimal adherence leads to viral resistance and therefore limits the effectiveness of the therapy.

Predictors of optimal adherence to HIV medications and hence optimal viral suppression include:

- availability of emotional and socioeconomic supports
- a patient's ability to fit the medications into his/her daily routine
- understanding that suboptimal adherence leads to resistance
- recognizing that taking all medication doses is critical
- feeling comfortable taking medications in front of others
- keeping clinic appointments

Measurement of adherence can be difficult and patient self-reporting is an unreliable predictor of adherence, however a patient who reports sub-optimal adherence should be taken through intensive adherence counselling.

Adherence rates of more than 95% are necessary in order to maximize the benefits of ART. This means that patients should not miss more than 3 ARV doses in one month.

Adherence is the responsibility of every healthcare worker who comes into contact with a person on ART. It is also the responsibility of the healthcare worker to discuss adherence strategies that will work for the patient in their particular situation and to assist him/her to overcome barriers to adherence.

The key to any successful adherence strategy is the education of patients before the initiation of ART. It is important to assess their understanding of and readiness to undertake the lifelong commitment to ART.

Continued ongoing adherence support is essential, both in the early stages and once the patient has stabilized and improved on ART.

It is also important to remember that the first line regimen is the easiest to take with only twice daily dosing available in fixed dose combinations and no meal restrictions.

8.2. Table 9 Factors affecting adherence to ART (positive or negative)

Socio-economic-related factors	• income • social and family support
Health system-related factors	• instructions from the health worker • implementation of educational interventions • relationship between health worker and patient • support of nurses and pharmacists
Condition-related factors	• asymptomatic vs symptomatic patients
Therapy-related factors	• type of treatment regimes • monitoring • lifestyle alterations • adverse effects of treatment • instructions on how to take the medication • drugs dosing • number of pills per day • dietary restrictions • fitting medication to individual's lifestyle • belief that medication is effective
Patient-related factors	• forgetfulness • life stress and depression • alcohol and drug use • hopelessness and negative feeling • belief in the effectiveness of the ARV drugs

8.3 Adherence strategies

8.3.1. Patient-related strategies

The first principle of patient-related strategies is to negotiate a treatment plan which the patient fully understands and fully commits to. Before the first prescription can be written, the clinician should assess the patient's readiness to take the medications, which might take two or three office visits and patience.

Patient education should cover:

- the goals of ARV therapy, including the increase in the CD4 counts and viral suppression
- the reason for adherence and the plan for and mechanisms for achieving adherence
- the importance of adhering to the first line regimen, which has the best chance of long term success
- the timing of medication in relation to meals and daily routines

- the possible side effects and when they are likely to occur
- instructions on appropriate steps to take in case of side effects and when to contact the clinician
- assess patient's literacy levels before relying on written information and adherence information should be tailored to each patient, e.g. use of visual aids and audio or video information

Education of family or friends and their recruitment as adherence supporters can be useful. Community adherence support groups can also assist adherence. Temporary postponement of HAART initiation has been proposed for patients with identified risks of suboptimal adherence e.g. a patient with active substance abuse or mental illness, and a severely ill or sub-conscious patient. In these situations, the patient may benefit more from the treatment of the opportunistic infection, of the mental illness and undergoes counselling and detoxification (if available) for the drug and substance abuse. No patient should be excluded from ART simply because he/she exhibits a behaviour or characteristic judged by the clinician to indicate a likelihood of non-adherence.

8.3.2. Clinician and health-team related strategies

It is important that the clinicians and health-teams develop trusting relationships with their patients on ART. The patient should understand that he/she is free to communicate with the clinician and health team in-between clinic visits, in case of adverse events and intercurrent illness. Patients should be made to understand that they are being cared for by a team and not just an individual and that it will happen that the clinician takes leave or the staff is rotated to other hospital departments. Supportive and non-judgemental attitudes and behaviours will encourage patient honesty regarding adherence and problems. It may also be useful to provide ART re-fills during the clinicians outreach visits to the community. Clinicians should be aware that adherence reduces as time progresses and treatment fatigue is often seen. Thus it is very important to monitor treatment adherence at every visit. Some strategies to address suboptimal adherence:

8.3.3. Regimen-related strategies

Adherence to ART can be improved by simplifying the treatment regimen as much as possible through:

- reducing the number of pills
- reducing the frequency of pills intake
- minimize adverse effects and drug interactions

Regimens should be chosen after a review of specific food requirements and patient's understanding and agreement to such restrictions.

8.4. Adherence package

IMPORTANT

Encourage disclosure to family members or friends who can provide support

Encourage the patient to identify a specific treatment supporter (preferably a family member or trusted friend).

Spend time with the patient. Explain the goals of therapy and the need for good adherence as many times as is necessary.

Negotiate a treatment plan that the patient can understand and to which he/she commits.

Inform the patient of potential side-effects – severity, duration and coping mechanisms.

Encourage the patient to disclose any over-the-counter and traditional medicines. Other medications as well as some traditional medicines cannot be taken concurrently with ART because they may cancel each other out or may lead to unacceptable side effects

Consider monitoring of medications such as co-trimoxazole or by an alternative method prior to ART initiation.

Provide adherence tools where available – written diary, pill boxes. Ask the patient directly how many pills they may have missed.

Encourage the use of watch alarms, cell phones (sms) or other mechanical aids.

Develop and encourage links with community-based organizations to support adherence.

8.4.1 Basic adherence package at initiation of ART

A-Pre-treatment

- Patient is encouraged to attend a group session on adherence to ART, and subsequently to attend two more individual adherence counselling sessions preferably accompanied by a treatment supporter.
- Cotrimoxazole prophylaxis is initiated for those eligible patients and the count is undertaken during the one month while waiting to commence therapy. This is not to be used to exclude people from ART. It is meant to reinforce daily medication-taking behaviour from the beginning. It is also meant to identify potential adherence problems before starting ART.

B-On treatment

At each visit the following needs to be done:

- Request patients to bring in the containers of their medicines and do the ARV pill- count. Adherence goal is >95% doses taken.
- Tablet count may be done before the patient sees the doctor.
- The count should be reviewed by the doctor during the early/initial visits to evaluate adherence.
- This does take up time and might not be possible at all sites all the time.
- Missed/late clinic visits should trigger concerns about adherence.
- Routine adherence discussion (education) with counsellor is of value. This should be an open-ended discussion, with time for questions
- Feedback from therapeutic counsellors to the rest of team is important to get a better profile of the patient and their environment.
- Encourage participation in a support group.
- Continue monthly visit with therapeutic counsellors for the first three months and quarterly thereafter.
- Arrange regular community visits by patient advocates.

8.4.2. Step-up adherence package for people with reduced adherence

This is necessary when the adherence assessment is <80% at any visit, with or without viral or clinical failure.

The therapeutic counsellor/nurse or doctor needs to re-educate the patient (and their treatment supporter where available) about the importance of adherence. The long-term benefits need to be re-emphasised.

Evaluate the support structures in place

- Are they appropriate?
- How can they be improved?
- What alternatives are there?

Consider the use of pillboxes and/or daily dosing diary.

Insist on participation in a support group or link with a patient advocate.

Consider doing a psychological profile.

Check the family situation (through social worker and therapeutic counsellor).

Redo the case Assessment for alcohol abuse and other abused drugs.

Home visits where possible (spot pill counts to be done at home).

Consider directly-observe therapy for an agreed period.

8.5 Follow up of patients on ART

Patients on ART require vigilant monitoring and follow up by the clinical team to determine treatment outcomes. The follow up of patients on ART includes a mechanism to track down those patients who have failed to honour their appointments (missed appointments), those who have defaulted, stopped treatment, died or just lost from the programme. The definitions are outlined below:

8.5.1. Missed Appointment

A patient who has missed their appointment can be defined as one who has failed to honour his/her clinic appointment from day 1 after the appointment to day 7. It is assumed that these patients still have their extra pills and are still organizing resources (bus fares) to come for their refill. Such

patients should be given their normal refill when they come but the reasons for not honouring their appointment should be sought out and recorded. Studies have shown that patients who miss their appointments are likely to have sub-optimal adherence levels, so these patients should be taken through a 'Step-up adherence session' before the drugs are re-filled. The health care team should initiate measures to track down the patient in their community.

8.5.2. Defaulter

A patient who is a defaulter is one who has not appeared to collect their ARVs on the appointment date and continues to be absent for more than 7 days up to 90 days. It is assumed that such a patient has exhausted all the medication and has therefore a high chance of multiple missed doses. A patient in this category should be tracked down and if found, the reasons for the defaulting should be discussed and the patient taken through a step-up adherence session. Depending on the period of stoppage of treatment, the clinician should take a decision to re-start the patient on ART, either on the same regimen or on an alternative regimen.

8.5.3. Lost to follow up

A patient is classified as 'lost to follow-up' when he/she has failed to show up for drug re-fill for a period lasting over 90 days (3 months) from the appointment date. It is important to note that some of these patients may have worsened clinically and are ill at hospital or home and may have stopped treatment, or they may have died while on treatment. Some may have decided on their own to stop the medication and try other 'alternative' medicines without informing the health care team. In this case, the health care team should make it a priority to trace the patient in their community and if information about their condition is found, it should be recorded in their files as the ART facility. Those who have stopped treatment should receive step up adherence counselling in a manner that is non-judgemental and with the aim of coming up with the best possible treatment plan for the patient.

8.5.4. Tracking lost patients

Methods that can be used to track down lost patients include:

- link directly with the patient or supporter or close relative by phone
- visit the home of the patient

- link up with the community carers such as the RHMs, PLWHAs, Caregivers

Each ART centre should establish a follow up team of health workers. At the end of each clinic day, the team should review the names of those who have honoured their appointments and tick them off in the appointments register. Those who have not honoured their appointment may show up in the next 7 days, so should be ticked off as they show up and should be counseled about the importance of honouring their appointment days. Patients who do not show up after the 7th day should ideally be tracked down using any of the methods mentioned above. Once the information on the patient is obtained, it should be recorded in the suggested follow up register and later transferred to the master ART register. This same information will then be computerized to enable easy analysis.

9. CHRONIC CARE OF PATIENTS WITH HIV AND AIDS

9.1. Introduction

In most resource-limited settings, patients are treated for acute conditions and are rarely followed up over time, as a result, there are no mechanisms to capture patient information that can be used to follow up their medical history over time. Provision of quality care and treatment for HIV and AIDS patients requires the ability to establish continuity of care from the point of diagnosis of HIV to the diagnosis and treatment of various opportunistic infections and when appropriate and available, the initiation of long term opportunistic infections prophylaxis and antiretroviral treatment.

HIV/AIDS is a chronic disease that requires a lifetime of care and treatment activities. A comprehensive chronic care model integrates community resources and policies with the health care system to produce an informed, motivated patient who actively interacts with a prepared, proactive practice team.

9.2. Pre-ART patient follow up

Individuals who test HIV positive and are referred to the ART clinic should have a CD4 count done during their first visit and if found to be above 200 cells/mm³ and are not eligible for ART by clinical stage, should be registered as "Pre-ART patients". These do not yet qualify for ART (unless they are classified under WHO Clinical stage 3 and 4) and should benefit from a pre-ART care package that includes:

- Prompt diagnosis and treatment of opportunistic infections, especially TB
- Provision of medications for prophylaxis of opportunistic infections
- Provision of nutrition supplements and food packages
- A 6-monthly check of CD4 counts and clinical staging
- On-going supportive counselling on condom use, PMTCT, disclosure to partners, testing of partners and children
- Yearly Pap smears and fertility counselling in women on every contact with the health worker.
- Advice on prevention and screening for new opportunistic infections.

- Advice on nutrition and hygiene.

Patients seen in the pre-ART clinic should always be reminded that their visit is not strictly limited to the 6-month interval but that they are expected to see the health care worker any time that they experience symptoms of illness, so that they can be assessed as soon as possible for the need to start ART. Statistics has shown that patients who are started earlier on ART (i.e. when their CD4 count is just below 200cells/mm³), have a better response to ART than those who wait until their CD4 count is very low (such as below 50cells/mm³), so a good pre-ART care would enable the patient to experience the maximum benefits of ART.

10. MONITORING AND EVALUATION OF THE ART PROGRAMME

Patient Monitoring is the practice of capturing the medical history of an individual patient over time and includes a system of following up patients when they are referred for special services or from one facility to another. This information is initially written in files and then transferred into a computerized system, or can be fed directly into the computer as the patient is being seen.

Patient management refers to a one-to-one short or long term relationship between the health care provider and the patient, assisted by written records.

Programme monitoring, on the other hand, refers to the routine tracking of priority information or specific indicators about a programme and its intended outcomes. The data elements for programme monitoring are aggregated from individual patient records, such as the patient manuals and registers. This data is then entered into the computer and analysed for clinic and programme needs and for research.

The collection of data, if not simple and kept to a minimum, may be an impediment to effective service delivery.

Indicators for the National ART Programme:

- Percentage of people with advanced HIV infection receiving antiretroviral combination therapy (UNGASS)
- Continuation of first-line regimen at 6, 12 and 24 months after initiating treatment (this is also a Drug Resistance Early Warning Indicator)
- Survival at 6, 12, 24 and 36 months after initiation of treatment (UNGASS and Drug Resistance Early Warning Indicator)
- Percentage of adults starting first-line ART who are prescribed a standard first-line regimen (Drug Resistance Early Warning Indicator)
- Percentage of patients who started ART 6 or 12 months ago and picked up ARV medications at 6 out of 6 months and 12 out of 12 months (Drug Resistance Early Warning Indicator)
- Existence of national policies, strategies and guidelines for antiretroviral therapy.
- Percentage of health facilities providing antiretroviral therapy services for adults and children disaggregated by facility.
- Number of health workers trained on antiretroviral therapy delivery

in accordance with national guidelines.

- Number of persons on antiretroviral treatment who are receiving nutritional support from health care facilities in the last 12 months.

10.1. Rationale for patient monitoring

Patient monitoring is important in order to:

- Assess the effectiveness of the ARV drug regimen, i.e. success or failure of treatment
- Assess the safety of the treatment regimen, how toxic it is and if the patient tolerates it well
- Assess adherence of the patient to the given regimen

10.2. Patient monitoring tools

In Swaziland, the current recommended ART patient monitoring tools include:

- Patient follow up manual (Patient File)
- Appointments booklet
- Daily attendance register
- Appointments register

10.2.1. The follow up manual/Patient file

Is the patient's file that is kept at the health care facility and has been designed to collect an agreed minimum set of data elements necessary for patient monitoring. The data enables the clinician to track individual patient data over time.

The patient's manual is used to record information on the patient during enrolment for ART and every month during drug refills.

10.2.2. The appointments booklet

Is similar to a take home patient card and is designed to capture key data that will help the health care worker to follow up a patient either at the facility that the patient is being cared for or if an emergency arises and the patient has to be seen in another facility. On initiation of ART, the patient is given a number and issued with an appointment booklet in which the following are recorded:

Names, date, CD4 counts, ARV drug combination and next appointment. The booklet also has a chart to help patient record whether they took all their medication or not, in order to check adherence.

10.2.3. The daily attendance register

Is used to record all patients who have attended the clinic that day and records demographic information of the patient and reason for clinic attendance e.g. for drug refill, for CD4 counts or for on-going adherence counseling. It is helpful in determining the patient load per clinic day at the facility.

10.2.4. The appointments register

Is used to keep a record of the dates of appointment of a group of patients attending the clinic on a particular day and is kept at the dispensing point. Usually, patients who have come on one day are given the same date of their next appointment, which makes it easier for the facility to plan for the amount of drugs needed for a particular clinic day and to check for the level of adherence to keeping appointments.

10.3 Programme monitoring tools

The following tools are used for programme monitoring:

1. The pre-ART register
2. The ART register

The registers are designed to record specific data that is necessary for monitoring of the programme and such information can be shared with international partners and donors.

10.3.1. The Pre-ART Register

Is a master record for all HIV positive patients who are being cared for at the facility. The register records the monthly health status of the patient using specific agreed on parameters such as weight, CD4 count, functional status and presence or absence of opportunistic infections. The information entered into the pre-ART register includes:

- Patient's demographic data and file number
- Baseline information on patient at registration such as

functional status, weight, WHO clinical stage, CD4 cell counts

Information on use of prophylaxis medication such as cotrimoxazole, isoniazid

Information on TB treatment and pregnancy status

Information on ART eligibility and date of initiation of ART

The patient's follow up status is recorded monthly and the outcome reviewed every 6 months (weight, CD4 count, functional status and opportunistic infections).

Once the patient starts ART, their information is transferred to the ART register and subsequently followed up there.

10.3.2. The ART Register

Is a master record of all the patients who are on ART at the facility. The information recorded includes:

1. Demographic information of the patient (can be transferred from the pre-ART register)
2. Baseline information at the start of ART
3. Prophylaxis medication used and dates started
4. TB treatment and pregnancy status
5. ART drug regimen prescribed and when started. Substitutions and switches are also recorded, including the dates of the events.
6. The follow up status of the patient is recorded as in the pre-ART register

10.3.3. Computerized records

The tools mentioned above are currently being used as the longitudinal medical record of the patient on ART, which is designed to record information about individual patients over an indefinite period of time. The usefulness of the longitudinal medical record can be increased with computer software known as the electronic medical record, whose primary advantages are the ability to:

- Easily view and summarize an entire patient record
- Aggregate patient records for analysis at the facility level
- Conduct ad-hoc analysis for different strata of patients

The electronic medical record system becomes very important as the number of patients on ART increases and the volume of patients managed at each facility grows. In particular, the increased demand for reports on patient clinical outcomes, patient patterns of adherence, trend analysis of disease progression, accurate forecasting of drug supplies are made more feasible by an electronic format.

The database system is still undergoing improvement to suit the ever changing needs of the National ART programme.

Section 2

POST - EXPOSURE PROPHYLAXIS

Definition

PEP or Post exposure prophylaxis refers to the immediate provision of medication following an exposure to potentially infected blood or other body fluids in order to minimize the risk of acquiring infection. PEP is an intervention that is meant to minimize the risk of the health worker, victim of sexual abuse and other public worker getting infected with Blood Borne Pathogens (BBP) (especially HIV) in their different situations, i.e. work or rape.

1. RATIONALE FOR PEP

Swaziland has high HIV prevalence (42.6% among ANC mothers in 2004 and 39.2% in 2006).

It has been estimated that more than 60% of hospital admissions are due to HIV-related illnesses.

In addition, the severe short staffing in facilities, coupled with the large numbers of patients requiring medical attention, result in health care workers (HCW) being often fatigued and may not observing precaution adequately.

This therefore puts the HCW at risk of exposure to HIV and other blood-borne pathogens, and makes PEP an important intervention in the efforts to improve the well-being of the health worker.

Other public workers such as Police or Firemen can be exposed accidentally to HIV and may need PEP.

The failure to provide PEP to the HCW and other at risk individuals could understandably reduce their willingness to care for the individuals.

Moreover, society has a moral obligation to protect those who assume even limited risks associated with their job.

In the case of rape, even if the risk of acquiring HIV infection from a single exposure may be small, this type of exposure often causes genital tract trauma and more likely to result in the transmission of HIV if the source person is infected.

The use of ARV drugs for post exposure treatment to prevent HIV infection only makes sense if it is included in a workplace programme where prevention of exposures to blood, blood products and body fluids is the primary goal. Therefore universal precautions should be emphasized to all workers at risk of

exposure and efforts should be put in place to provide the necessary equipment that will ensure protection of the workers.

There is biological probability that infection with HIV within a specific time period can be prevented by using efficacious ARV drugs.

2. PEP FOR HEALTH CARE WORKERS

HCW are defined as those whose activities involve contact with patients or with blood or other body fluids from patients in health care, laboratory or public safety settings.

2.1. Categories of HCW exposed to BBP in health care settings

Doctors, Nurses, Paramedics (e.g. Laboratory personnel, Radiology personnel), Counsellors, medical, laboratory and nursing students
Ambulance Drivers, Orderlies, Cleaners,
Volunteers Home carers and "lodgers"

2.2.Types of exposure for the HCW

Needle stick injury (small, medium or large bore needle)
Cuts with a scalpel blade
Splashes with blood or blood products on non-intact skin
Splashes on mucous membranes

2.3. Post exposure management

The following are important components of post exposure management:

A- Clear policies/procedures

- Ensure confidentiality of exposed and source persons
- Management of exposures
- Procedures posted in visible place

B-Training of HCW in post exposure management

C-Rapid access to:

- Clinical care
- Post exposure prophylaxis drugs
- Rapid testing of source patients/exposed persons

D-Injury prevention assessment

E-Wound management

F-Exposure reporting

G-Assessment of infection risk

- Type and severity of exposure
- Blood-borne infection status of source person

H-Appropriate treatment, follow up and counseling of exposed person

Table 10. Phases in Post Exposure management

PHASE 1
First aid Triage Crisis management
PHASE 2
Exposure risk assessment Source patient evaluation Counselling and testing PEP decision Initiating PEP
PHASE 3
Post Exposure follow up Source patient follow up ARV toxicity monitoring

2.4. Conduct of the HCW following exposure

2.4.1. Immediate conduct after exposure

- Wash skin wounds with soap and water, mucous membranes should be flushed with water only
- Topical antiseptics may be used, although there is no evidence of further risk reduction
- The application of caustic agents such as bleach (jik) are not recommended
- There is no evidence that squeezing the wound will reduce the risk of HIV transmission

2.4.2. Reporting the incident

A HCW that has had an exposure to blood and body fluids should report the incident immediately to his/her supervisor on duty, as per the protocol for the particular institution.

The HCW can then be referred to a PEP centre if services are not available in

the same institution.

2.4.3. Counseling and Testing the HCW

All exposed HCW should undergo pre-test and post-test counseling, with a trained counselor, immediately after reporting the incident.

This should be done in a room separated from HTC centre.

If he/she allows to have a test done, a consent form should be signed by the health worker.

HIV Testing should be done according to the recommended guidelines for HIV testing and counseling in Swaziland

The HIV test should be done preferably in the same counseling room. During the counseling session, all exposed HCWs should be informed on:

- The ARVs used for PEP (the benefits of taking the ARVs for PEP, the duration of PEP drugs, the possible side effects of the ARV drugs, the importance of adherence to PEP drugs)
- The possibility of becoming infected despite the PEP intervention
- The follow up laboratory tests recommended
- Prevention of new HIV infection during the follow up period (sexual abstinence or use of condoms)
- Advise on discontinuation of breastfeeding for an exposed mother
- The legal consequences of delaying to report the exposure incident
- The legal consequences of refusing to be tested or refusal to access PEP services following exposure.

2.4.4. Counseling and testing the source person (the person whose blood has contaminated the HCW)

Counseling and testing should be offered to the source person, with the implications for the risk of HIV transmission to the HCW explained clearly. Information on the history of use of antiretroviral drugs should be sought from the source person, as this has implications on the PEP drug combinations to be offered to the health worker.

HIV testing and counseling guidelines should be adhered to at all times when dealing with the source person.

2.4.5. Implications of the HCW HIV test result.

A **Negative HIV test** for the HCW means that they should be offered PEP drugs, regardless of the HIV status of the source (there is still the risk of HIV transmission during the window period).

A HCW who tests **positive for HIV** should not be offered PEP drugs as this may encourage the development of resistant HIV strains. In this case, clinical assessment and referral for care is needed.

If the source person refuses to be tested, PEP should be offered to the HCW

If the source person cannot be traced or absconds from the facility before testing, PEP should be offered to the HCW

If the HCW refuses to be tested for HIV, then PEP should not be offered to him/her. This is done in the interest of the health worker, should he/she be already HIV positive by the time of the exposure.

As stated before, there is no benefit in giving prophylaxis to such and individual.

PEP should only be offered to the health care worker after thorough risk assessment (see chapter 2.6)

2.5 Other tests that should be done for the HCW, regardless of HIV status

Pregnancy test

Hepatitis test

Hepatitis test

Further information for the management of Hepatitis B and C exposures can be found in other documents

2.6 Risk Assessment and recommended PEP drugs

Health personnel should be made aware that although blood secretions from patients may be infectious, simple contamination of unbroken skin does not comprise a significant risk, but contamination of intact mucous surfaces of the mouth and eye does.

The exposure should be classified as "low risk" or "high risk" for HIV infection as described in the table 11.

Table 11. Risk assessment

Risk Classification	Examples of exposure
Low Risk	Solid needle injury Splash of body fluid on intact skin Drops (small volume) on mucous membrane Drops on non-intact skin Asymptomatic source or viral load <1500c/ml
High Risk	Large bore needle injury Deep needle prick injury Visible blood on device Drops on non-intact skin Needle from patient artery or vein Large volume splash on mucous membranes on non-intact skin Symptomatic source, acute seroconversion, high viral load Defaulter from ARV drugs (possibility of resistance to the recommended PEP drugs)

The risk of exposure to HIV should be assessed by a health worker trained in PEP and the individual should be given PEP drugs according to the assumed risk.

Those of low risk should take 2-drug combination and the high risk a 3-drug combination. Where the risk cannot be ascertained, a 2-drug combination should be used.

The tables below are a summary of the risk of exposure and PEP drugs offered:

Table 12. Recommended PEP drugs for percutaneous injuries

Exposure type	HIV status of source person				
	HIV +ve asymptomatic	HIV +ve Symptomatic AIDS	Unknown HIV status	Unknown source	HIV +ve
Less severe - solid needle or superficial injury	2 ARV drugs	3 ARV drugs	2 ARV drugs	2 ARV drugs	2 ARV drugs
More severe - large bore hollow needle, deep puncture, visible blood on device, needle used in patient's artery or vein	3 ARV drugs	3 ARV drugs	2 ARV drugs	2 ARV drugs	2 ARV drugs

Table 13. Recommended PEP drugs for mucous membranes and non-intact skin exposure

Exposure type	HIV status of source person				
	HIV +ve asymptomatic	HIV +ve Symptomatic AIDS	Unknown HIV status	Unknown source	HIV -ve
Small volume (few drops)	2 ARV drugs	2 ARV drugs	2 ARV drugs	2 ARV drugs	2 ARV drugs
Large volume (blood splash)	2 ARV drugs	3 ARV drugs	2 ARV drugs	2 ARV drugs	2 ARV drugs

2.7 Administration of ARV Drugs for PEP

Administration of PEP drugs should be initiated as soon as possible after the counseling and testing. The optimal delay between time of exposure and time of administration of PEP drugs is **2 to 4 hours**. According to severity of exposure, it is still acceptable to start prophylaxis within **72 hours** (3 days) from time of exposure to contaminated fluids. The optimal duration for PEP drug administration is **4 weeks (1 month)**.

A two drug regimen is recommended for PEP; a triple drug regimen can be used in case of highest risk, such as source person with signs and symptoms of AIDS although its benefit can not be higher.

2.7.1. Basic PEP Regimen

Zidovudine (AZT) 300mg bd
plus
Lamivudine (3CT) 150mg bd



IMPORTANT

Monotherapy is not recommended for PEP

2.7.2. Alternate Basic PEP Regimen

Stavudine (d4T)
>60kg = 40mg bd
<60kg = 30mg bd
plus
Lamivudine (3CT) 150mg bd

2.7.3. Expanded PEP Regimen

Basic regimen
Plus
Lopinavir/ritonavir (133mg/33mg)
Or plus
Efavirenz (600mg od nocte)
Or plus
Indinavir (IDV) 800mg tds

In addition, the total body burden of HIV is substantially lower among exposed HCWs than among persons with established HIV infection.

The recommendation is to use the risk assessment as a guide to the use of a 2 or 3 (or more) drug regimen for PEP.

2.8. ARV drugs for PEP during pregnancy

There is limited data regarding the potential effects of antiretroviral drugs on the developing foetus or neonate. However, the benefits of PEP should be weighed against the risks of potential harm to the foetus and the administration of PEP in this case should be done by a doctor experienced in dealing with HIV in pregnancy. PEP should not be denied solely on the basis of pregnancy status.



IMPORTANT

A 2-drug regimen is a viable option for PEP primarily because the benefit of completing a full course of this regimen exceeds the benefit of adding the third drug.

Drugs that should be avoided in pregnancy

Efavirenz - due to possible occurrence of abnormalities in the foetus
Stavudine and Didanosine combination should be avoided due to lactic acidosis and mitochondrial malfunction in the newborn

2.9. Situations for which PEP is rarely, if ever, warranted:

Intact skin contact with blood and potentially infectious body fluids
Exposure to unknown source in populations where HIV prevalence is low
Low-risk exposure to unknown source

2.10. Toxicity of ARV drugs for PEP

About 74% of health workers who receive PEP experience side effects, primarily Nausea (58%), fatigue (37%), headache (16%), vomiting (16%), diarrhea (14%).

About 53% discontinue the treatment before completing the 4 week course, due to multiple factors including side effects of the drugs.

2.10.1. Mild side effects

Do not require discontinuation of drugs
Nausea and vomiting
Malaise
Headache
Anorexia

2.10.2. Moderate side effects

Do not require discontinuation of drugs, but medical attention must be sought
Muscle pain
Body rashes
Anaemia

2.10.3. Severe side effects

May require discontinuation of drugs after careful clinical and laboratory review

- Pancreatitis
- Kidney stones

2.11. Follow up of the HCW who is on PEP

Follow up is a very important component of care for the exposed health worker. During this period, the health worker should be advised:

- To abstain from sexual intercourse or use condoms to prevent sexual transmission of HIV during the PEP period
- To avoid unwanted pregnancy during the PEP period
- To avoid donating blood
- To discontinue breastfeeding during PEP period
- To seek medical evaluation for any acute illness that occurs during the follow up period
- To repeat HIV testing at 4 weeks, 3 months and 6 months
- To return for clinical and laboratory evaluation for adverse effects of drugs at 2 weeks and 4 weeks

Table 14. Summary of the clinical and laboratory follow up for PEP

Lab test	Baseline	2 weeks	1 month	3 months	6 months
Haematology	X	X	X		
Chemistry	X	X	X		
Pregnancy test	X				
HIV test	X			X	X
Hepatitis screening	X				



IMPORTANT

Nevirapine should never be used for PEP due to severe hepatotoxicity and Steven-Johnson Syndrome.

3. PEP FOR THE PUBLIC WORKER

3.1. Definition of the Public Worker

The public workers who should benefit from PEP are those whose occupation involves direct contact with human blood or body fluids in settings such as motor vehicle accident rescue, city council refuse collection, fire fighters and those involved in violent crime situations.

In these occupations, efforts should be put in place to ensure prevention of exposure through:

- Provision of equipment and supplies necessary for prevention and control of infections, such as gloves, aprons, face masks, goggles and gum boots.
- Training of all workers in handling and disposal of infectious materials
- Provision of guidelines for safe handling of infectious materials

3.2. Categories of public workers at risk of occupationally exposed to HIV:

- Road safety workers
- Police officers (traffic, crime section)
- Fire and emergency service personnel
- Prison guards (violence)
- City council refuse collectors

Only exposure to blood and blood products through percutaneous injury or contact with non-intact skin or mucosae should be considered as potentially dangerous.

3.3. Accessing PEP services

3.3.1. Immediate conduct after the exposure

- Wounds and skin that have been in contact with blood or body fluids should be washed with soap and water
- Splashes on mucous membranes should be rinsed thoroughly with plenty of clean water
- Antiseptics such as Dettol, methylated spirit may be used on the skin, although there is no evidence to suggest further risk reduction

- The use of caustic agents such as “jik” on the skin is not recommended as this may cause damage to the skin
- There is no evidence that squeezing the wound will reduce the risk

3.3.2. Reporting the incident and referral

- The worker exposed to blood and blood products should report the incident to the officer in charge
- The officer in charge should arrange for the worker to be referred to the nearest PEP facility

3.3.3. Intervention at the PEP centre

- The nurse on duty in OPD should attend to the client and should inform the doctor on call
- Counseling and testing should be done according to the HTC guidelines and the doctor or counselor can perform this task as per the protocol for that facility
- The assessment of risk should be done by the doctor on call for PEP and relevant prescriptions made following assessment of risk of exposure

3.3.4. ARV Drugs for PEP

The choice of drugs to be offered will depend on the risk assessment by the doctor prescribing the medication and should be of the same dosage as that offered the exposed HCW (see chapters 2.6 and 2.7) and for the same duration of time.

3.3.5. Follow up

The PEP focal person should arrange for follow up tests for the individual using the same recommended time frames as for the exposed health worker (see chapter 2.11.).

4. SURVIVORS OF SEXUAL ABUSE (RAPE VICTIMS)

In a country with high HIV prevalence in its sexually active population, and a noticeable rape incidence, PEP should be advised for survivors of sexual abuse.

There is a higher risk of acquiring HIV from a single exposure due to the fact that rape causes genital tract trauma, which is an easy route for the HIV to gain access.

4.1. Immediate conduct after the rape incident

- The individual should immediately be accompanied to a health facility for a clinical evaluation even before taking a bath or questioning by the police.
- If the victim is found by the police at the first instance, he/she should be taken to the nearest health facility before recording a statement.

4.2. Clinical evaluation of individual

- A doctor should examine the individual to check his/her clinical status and to determine the extent of violence
- The doctor should also carefully assess the risk of transmission of HIV, e.g. known HIV positive perpetrator, use of condoms

4.3. Counseling and Testing

Pre and post-test counseling and psychosocial support should be offered in a confidential and non-judgemental manner (i.e. ensure privacy). If possible, the perpetrator should be traced and tested for HIV, if he/she refuses to be tested, or cannot be traced, the victim should be offered PEP after being submitted to HIV testing.

4.3.1. Individuals below 18yrs

- Pre and post-test counseling should be offered to the individual and the parents or guardians
- HIV testing should be done when informed consent is signed by the parent/guardian
- Consent can also be given by the following persons:
 - social worker,
 - senior medical officer,
 - police officer in charge
- If the individual is already HIV positive, no PEP should be offered

and referral for HIV care should be done

- If the individual is HIV negative, PEP should be offered
- If the parents/guardians refuse to have the test done on the victim, no PEP will be offered
- In the event of an emergency and non-availability of any of the above persons to give consent, the medical practitioner shall be guided by the best interest of the child/victim and their duty to use discretion in giving treatment, for example, the doctor may give PEP drugs for 2 days while information is being sent to the parents/guardians and the victim will be advised to return as soon as possible for medical test to be done.

4.3.2. Individuals above 18 years

- Counseling and testing will be offered to the individual according to the national HIV Testing and Counselling Guidelines
- The results of the HIV test shall guide the counselor in decision making in a similar way to the situation of the exposed health worker and public worker

4.4. Administration of PEP drugs

The choice of drugs to be offered will depend on the risk assessment by the doctor prescribing the medication and should be of the same dosage as that offered the exposed HCW (see chapters 2.6 and 2.7) and for the same duration of time.

4.5 Follow up

Follow up monitoring tests should be carried out in a similar time frame as that of the exposed health care worker (see chapter 2.11.)

The victim of sexual abuse should be offered on-going counseling and psychological support

Annex 1

WHO Clinical Staging for HIV disease in adults and adolescents (>13 years)

List of Clinical Conditions by Clinical Stage
Clinical stage I - Asymptomatic infection - Persistent generalized lymphadenopathy - Acute retroviral infection
Clinical stage II - Unintentional weight loss, < 10% of body weight - Minor mucocutaneous manifestations (e.g. seborrheic dermatitis, prurigo, fungal nail infections, oropharyngeal ulcerations, angular cheilitis) - Herpes zoster within the past 5 years - Recurrent upper respiratory tract infections (e.g. bacterial sinusitis)
Clinical stage III - Unintentional weight loss, > 10% body weight - Chronic diarrhoea for > 1 month - Prolonged fever (intermittent or constant) for > 1 month - Oral candidiasis (erythematous or pseudomembranous) - Oral hairy leukoplakia - Pulmonary tuberculosis (typical or atypical) within the previous year - Severe bacterial infections (e.g. pneumonia, pyomyositis) - Vulvovaginal candidiasis, chronic (i.e. > 1 month) or poorly responsive to therapy
Clinical stage IV - HIV wasting syndrome <i>Pneumocystis carinii</i> pneumonia - Toxoplasmosis of the brain - Cryptosporidiosis with diarrhoea, > 1 month - Isosporiasis with diarrhoea, > 1 month - Cryptococcosis, extrapulmonary - Cytomegalovirus disease of an organ other than the liver, spleen or lymph nodes - Herpes simplex virus infection, mucocutaneous (>1 month) or visceral (any duration) - Progressive multifocal leukoencephalopathy - Any disseminated endemic mycosis (e.g. histoplasmosis) - Candidiasis of the oesophagus, trachea, bronchi, or lungs - Atypical mycobacteriosis, disseminated - Extrapulmonary tuberculosis - Non typhoid salmonella septicaemia - Lymphoma - Kaposi's sarcoma - HIV encephalopathy

Annex 2

Toxicities of first line ARV Regimen and recommended substitutions

ARV drug	Common associated toxicity	Suggested substitute
AZT	Severe anaemia ^a or neutropaenia ^b Severe gastrointestinal intolerance ^c	TDF or d4T or ABC
	Lactic acidosis	TDF or ABC ^d
d4T	Lactic acidosis Lipoatrophy / metabolic syndrome ^e	TDF or ABC ^d
	Peripheral neuropathy	AZT or TDF or ABC
ABC	Hypersensitivity reaction	AZT or TDF or d4T
TDF	Renal toxicity (renal tubular dysfunction)	AZT or ABC or d4T
EFV	Persistent and severe central nervous system toxicity ^f	NVP or TDF or ABC (or any PI ^h)
	Potential teratogenicity (first trimester of pregnancy or women not using adequate contraception)	NVP or ABC (or any PI ^h)
NVP	Hepatitis	EFV or TDF or ABC (or any PI ^h)
	Hypersensitivity reaction	TDF or ABC (or any PI ^h)
	Severe or life-threatening rash (Stevens - Johnson syndrome) ^g	

^a Defined as Hb <6.5g/dl.

^b Defined as neutrophil cell count < 500 /mm³ (grade 4).

^c Defined as severe, refractory gastrointestinal intolerance that prevents ingestion of ARV drug regimen (e.g. persistent nausea and vomiting).

^d Re-initiation of ART should not include d4T or AZT in this situation. TDF or ABC is preferred.

^e Substitution of d4T may not reverse lipoatrophy.

^f e.g. persistent hallucinations or psychosis.

^g Severe rash is defined as extensive rash with desquamation, angioedema, or a reaction resembling serum sickness; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema or conjunctivitis; Stevens-Johnson syndrome can be life-threatening. For life-threatening rash, substitution with EFV is not recommended.

^h PI class should be preferentially reserved for second-line therapy as no potent regimen have been identified for recommendation following initial PI failure

Clinical, CD4 cell count and virological definitions of treatment failure for patients on first-line ARV regimen.

Clinical failure^a	New or recurrent WHO stage 4 condition ^{b,c}
Immunological failure^d	- Fall of CD4 count to pre-therapy baseline (or below) or 50% fall from the on-treatment peak value (if known) or - Persistent CD4 levels < 100 cells/mm³^e
Virological failure	Plasma viral load >10,000 copies/ml ^f
- Current event must be differentiated from the immune reconstitution inflammatory syndrome (IRIS) - Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections), may be an indication of treatment failure and thus require consideration of second-line therapy. - Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, esophageal candidiasis, recurrent bacterial pneumonia) may not be an indicator of treatment failure and thus not require consideration of second-line therapy. - Without concomitant infection to cause transient CD4 cell decrease. - Some experts consider that a persistent CD4 cell count <50/mm³ after 12 months on ART may be more appropriate - The optimal viral load value at which ART should be switched has not been defined. However, values of more than 10,000 copies/ml have been associated with subsequent clinical progression and appreciable CD4 cell count decline	

Other possible drug combinations (2 NRTIs + 1 or 2 NNRTIs)

Drug regimen	Comment
AZT + 3TC + NVP	Reduced risk of peripheral neuropathy but increased incidence of nausea and vomiting. Efavirenz (EFV) can replace Nevirapine (NVP) in the initial regimen but it is more expensive and associated with increased risk of minor side effects which can decrease adherence. Efavirenz (EFV) might also have teratogenic effects if used during pregnancy. Concurrent use of Lamivudine (3TC) and Zalcitabine (ddC) is contraindicated. <i>This drug combination has been widely used during pregnancy. ARV therapy should be initiated after the first trimester.</i>
AZT + ddI + NVP	Same as above. Didanosine (ddI) must be taken on empty stomach, which may decrease adherence. The regimen must include at least two tablets. Concurrent use of Zidovudine (AZT) and Stavudine (d4T) is contraindicated.
D4T + ddI + NVP	Less nausea and vomiting but increased likelihood of peripheral neuropathy. <i>This combination should only be used during pregnancy when no other alternatives exist due to increased risk of lactic acidosis</i>
AZT + 3TC + LPV/r*	Reduced risk of peripheral neuropathy but increased incidence of nausea and vomiting. IDV/r combination offers improved pharmacokinetic profile, reduces pill burden and side effects, and obviates the need for administration on an empty stomach. Indinavir can be used alone but requires three-times day dosing instead of twice daily for IDV/r, and must be taken on empty stomach. Nelfinavir (NFV) is the best tolerated PI but its cost is prohibitive. Saquinavir (SQV) can also be used in combination with Ritonavir (RTV) but it is expensive and requires a high fat meal. <i>The combination AZT + 3TC + NFV or SQV/r has also been widely used during pregnancy. ARV therapy should be initiated after the first trimester.</i>
AZT + ddI + IDV + RTV	Same as above.
D4T + ddI + IDV + RTV	Same as above. Less nausea and vomiting but increased likelihood of peripheral neuropathy.

ANNEX 5

ANTIRETROVIRAL DRUGS AVAILABLE AT THE CENTRAL MEDICAL STORES, MATSAPHA

1. Zidovudine (AZT)
2. Stavudine (d4T)
3. Lamivudine (3TC)
4. Nevirapine (NVP)
5. Efavirenz (EFV)
6. Stavudine-Lamivudine-Nevirapine
(Triviro/Triommune-30 and 40)
7. Zidovudine-Lamivudine (AZT-3TC)
8. Abacavir (ABC)
9. Lopinavir/ritonavir (LPV/r)
10. Saquinavir (SQV)
11. Ritonavir (RTV)
12. Indinavir (IDV)
13. Tenofovir (TDF)



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