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Ministry of Health and Social Services

Directorate of Special Programmes



National Guidelines for Antiretroviral Therapy

Second Edition

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Foreword

For the past three years the Ministry of Health and Social Services (MoHSS) has been implementing an antiretroviral (ARV) programme in Namibia's public health facilities. Treatment with highly active antiretroviral therapy (HAART) started with 6 pilot hospitals in 2003. This was rapidly rolled out to involve all 34 state hospitals in Namibia. This was in response to the high demand for HAART services across the country given the high number of HIV-positive Namibians in need of ARV therapy. To date, 93% of patients that have been enrolled in the programme are alive and on treatment. Their health status has improved and many are leading productive lives. As a result of the success of the ARV programme, community acceptability of other related services has been reflected in increased utilisation of these services; there have been more clients seen at VCT and PMTCT facilities and more individuals seeking post-exposure prophylaxis for both occupational and rape exposures. The Ministry of Health and Social Services is providing leadership in HIV prevention and control.

Treatment should not be seen in isolation. It is part of comprehensive care that supports families and communities that are affected by HIV/AIDS. I urge other partners such as those dealing with Orphans and Vulnerable Children, the Network of People Living with HIV, non-governmental organisations, community-based organisations, other Ministries, and the private sector to continue giving support to communities and individuals that have been affected by this disease.

Despite all efforts that have gone into prevention and care, active participation of men in all of these programmes is lagging behind. Only one third of patients in ARV programmes are male. A strong call is made to Namibian men to utilize the available health services.

This Second Edition of the *National Guidelines for Antiretroviral Therapy* has been released so that HIV care in Namibia can keep up with new treatment options and improved monitoring systems. These revised guidelines are based on new scientific evidence from international reports and studies. They are the result of collaborative efforts among our local HIV specialists and other medical experts that make up the Ministry of Health and Social Services' Technical Advisory Committee on ARVs. Additional support has come from our developmental partners and the recently updated WHO guidelines on HIV care in resource limited settings. The Ministry will continue to revise, update and formulate other editions of these guidelines as more information becomes available. The Ministry acknowledges the support that has been received from our development partners and contributed to our success.

Dr. Richard Nchabi Kamwi, MP
Minister

Preface

The first edition of the *National Guidelines for Antiretroviral Therapy* was launched in May 2003. Since then, antiretroviral (ART) services have been rolled out to the entire country, making these services accessible to those who need them. In keeping with the pace of new changes, the first ARV guidelines have been revised in accordance with the latest evidence-based best practices. Realising the current challenges in human resources, we have made the second edition user-friendly for most service providers. The major achievements of the Namibian antiretroviral treatment programme are:

- More than 30% of patients in need of ART are receiving ART*.
- 64% of patients on ART are women.
- 16% of patients on ART are children*.
- Complete nationwide coverage of ART service delivery.
- Regular training of all health workers who are providing ART services in the public sector.
- Introduction of training for private healthcare providers.
- Introduction of the Integrated Management of Adolescent and Adult Illnesses (IMAI) strategy by MoHSS.

The availability of highly active antiretroviral therapy (HAART) has increased the survival rate of Namibians living with HIV and improved the quality of their lives. The latest ARV regimen has fewer side-effects, a better toxicity profile, less medication interactions, and a lower pill burden. These new, safe, and more effective medicines, changes in WHO guidelines, and observations from ARV clinics in the last 3 years have necessitated the modification of second line regimen options. While the cost of treatment is considerable, simplified regimens result in savings to the healthcare system through reduced need for hospitalisation and clinic visits.

In order to achieve good results from the ART treatment provided, it is imperative that patients adhere to treatment as per doctor instructions. Knowing that HAART is a lifelong commitment, it is the duty of all stakeholders – including family, friends, employers and other partners – to render support to HIV/AIDS patients to comply with treatment. Failing to do so will result in the development of ARV resistant HIV strains with dire consequences to our nation. Therefore, to promote 95% adherence, which is acceptable for patients on treatment, new cadres called 'community counsellors' have been introduced into the health delivery system. The monitoring of patients has been simplified and is likely to reduce the cost of laboratory monitoring for patients on treatment. Viral load monitoring will be utilised to prevent patients from failing at an earlier state of care.

This second edition of the ART guidelines is more comprehensive. It offers more guidance on management and prevention of co-morbidities such as TB and hepatitis co-infection, and updates the WHO Clinical Staging System. Additional information on non-communicable disorders, such as diabetes mellitus, renal failure, and hypertension that commonly affect Namibians, and second line therapy modifications, is incorporated.

Development of such a challenging document for antiretroviral therapy in the context of Namibia required the collaboration of numerous individuals, agencies, and organisations. As such, the Ministry of Health and Social Services wishes to recognise the contributions of the Directorate of Special Programmes, Tertiary Health Care Services, Departments of Medicine and Paediatrics, Windhoek Central Hospital, the Directorate of Primary Health Care, the Medical Association of Namibia, the HIV Clinicians' Society, the International Education and Training Center on HIV, and the United States Centers for Disease Control and Prevention. I urge all doctors, nurses, and other healthcare professionals to familiarise themselves with the content of these guidelines in order to provide quality care to fellow Namibians.

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List of Abbreviations

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
ANC	Antenatal care
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
AZT	Zidovudine
AZT+3TC	Zidovudine + lamivudine
BD	Twice per day
CD4	Cluster designation 4
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
CXR	Chest x-ray
D4T	Stavudine
ddI	Didanosine
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
EFV	Efavirenz
ELISA	Enzyme-linked immunosorbent assay
FBC	Full blood count
GMP	Growth monitoring and promotion
HAART	Highly active antiretroviral therapy
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human Immunodeficiency Virus
ICU	Intensive care unit
IDV	Indinavir
IDV/r	Indinavir + ritonavir
IM	Intramuscular
INH	Isoniazid
IRIS	Immune Reconstitution Inflammatory Syndrome
IUCD	Intrauterine contraceptive device
IV	Intravenous
IVI	Intravenous injection
LFT	Liver function test
LPV/r	Lopinavir + ritonavir
MAC	<i>Mycobacterium avium</i> complex
MOTT	Mycobacterium other than tuberculosis
NVP	Nevirapine
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
od or OD	Once daily
OIs	Opportunistic infections
PCP	<i>Pneumocystis jirovecii (carinii)</i> pneumonia

List of Abbreviations, continued

PCR	Polymerase chain reaction
PI	Protease Inhibitor
PLWHA or PLWHAs	Person or People living with HIV/AIDS
PML	Progressive multifocal leukoencephalopathy
PO	By mouth
RNA	Ribonucleic acid
RTV	Ritonavir
SMZ	Sulfamethoxazole
STAT	Immediately
STIs	Sexually transmitted infections
TB	Tuberculosis
TDF	Tenofovir
tds or TDS	Three times per day
TEN	Toxic epidermo-necrolysis
TMP	Trimethoprim
ULN	Upper limit of normal
VZV	<i>Varicella zoster virus</i>
WBC	White blood count
WHO	World Health Organization

Introduction

More than ten years after the introduction of highly active antiretroviral therapy (HAART), new advances in the diagnosis and treatment of HIV/AIDS continue to emerge. The First Edition of the *National Guidelines for Antiretroviral Therapy*, developed in 2003, have been revised to keep abreast with the latest evidence based practices.

Research in industrialised and developing countries acknowledged by WHO has shown that only a limited number of regimens ensure optimal viral suppression and long-term adherence to therapy. These regimens are recommended in these guidelines. To promote early diagnosis of HIV infection and facilitate lifelong adherence to therapy, a favourable environment is essential. The following prerequisites remain essential before the provision of HAART:

- Easy access to counselling and testing for early diagnosis of HIV infection to ensure timely access to therapy.
- Identification of sufficient resources to pay for HAART on a long-term basis through the private sector.
- Counselling for the patient and his/her treatment supporter to ensure full understanding of HAART, the importance of treatment compliance, timing of medication intake in relation to meals, and possible side-effects of HAART.
- Follow-up counselling of the patient and review of his/her environment to ensure continued psychosocial support and to enhance adherence to treatment.
- Capacity to recognise and appropriately manage common HIV-related illnesses, opportunistic infections and adverse reactions to antiretroviral medications (ARVs).
- Reliable laboratory monitoring services including routine haematological and biochemical tests for the detection of medication toxicity and response to therapy.
- Assurance of an adequate supply of quality medications, including medicines for treatment of opportunistic infections and other HIV-related illnesses.
- Availability of trained interdisciplinary healthcare teams, including doctors, pharmacists, nurses, social workers, and counsellors. These teams should, where possible, closely collaborate with support groups and community-based organisations (CBOs) for persons with HIV and their caregivers.
- Availability of a system for training, continuous education, monitoring and feedback on safe and effective management of HIV-related disease and HAART.
- Availability of appropriate care, support services and referral mechanisms in case of treatment failure.

The cost of ARVs has continued to decrease over the last years through initiatives of producers of original medications and under pressure of generic substitutes. In addition to public health services, increasing numbers of persons with HIV-related diseases have access to treatment through medical aid schemes or other private sector initiatives.

These guidelines have enabled healthcare providers to provide standardised national management to HIV/AIDS patients over the last three years and will continue to do so with the revised edition. The guidelines will continue to be regularly updated to reflect new developments as they occur.

HAART is not a cure, but it has converted a potentially fatal disease into a chronic manageable condition. The most important emphasis in curbing the pandemic remains the prevention of primary HIV infection.

Implementation of the Second Edition of the National Guidelines for Antiretroviral Therapy

This Second Edition of the *National Guidelines for Antiretroviral Therapy* includes several significant changes from the First Edition. In order for these revised guidelines to be implemented with minimum disruption to patient care, a smooth transition from the first edition to the second edition of the guidelines is essential. This is also important to ensure that the supply of medications through the central medial store all the way to the patient is uninterrupted and wastage of ARVs due to expiry is minimised.

Experience garnered from changes in other treatment guidelines shows that prescribers are eager to change to using newer regimens, even when the necessary medicines may not yet be freely available. This causes disruption to patient care as well as the pharmacy supply system and can easily result in loss of medicines due to wastage of the previously recommended supplies.

In order to prevent such problems in the very delicate and costly area of ART it is essential that the following basic principles are adhered to by all prescribers and dispensers;

1. Just because a new regimen is mentioned in the guidelines it does not mean that patients must be transferred onto this regimen immediately.
2. The general rule is that if a patient is stabilised on the current ART regimen and not suffering from significant adverse side effects, then **that patient's medication should not be changed.**
 - One exception to the general rule is for patients who have been on stavudine containing regimens **for more than 2 years**. These patients should, if possible, be transferred on to AZT based regimens. This is to minimise their risk of stavudine related toxicities, which occur more frequently after a patient has been on stavudine for 2 years or longer. (Please refer to Section 1.9.3 for further information)
 - Therefore many patients who have currently been receiving first line therapy of d4T/3TC/NVP will continue on this regimen and NOT automatically be transferred onto AZT/3TC/NVP, even though this is the first line therapy mentioned in these guidelines.
 - However if a patient new to ART presents at the clinic then they should be started on AZT/3TC/NVP unless there are contra-indications to this regimen.

Abacavir (ABC) has been introduced in these second edition guidelines, despite the high cost of this medicine. It therefore has only been included to be used in certain limited clinical situations where other options have been ruled out. For this reason ABC will not be stocked in all Districts. Regional Pharmacists will be able to stock a small amount that is to be used for named patients in their region. Before a patient is initiated on ABC then a specialist must be consulted to discuss the treatment. If the specialist advises that the patient should be initiated on ABC then the District must notify the Regional Pharmacist of the patient's details, (including why this patient requires ABC) and who is the advising specialist. The Regional Pharmacist will issue a supply of ABC to the District specifically for this patient. The pharmacy will then be responsible to ensure that this supply of ABC is used solely for the named patient. Please see Section 1.10.1 for further information.

A consequence of ABC only being issued on a named patient basis will be that a prescriber must plan the patient's medication change. The change can only be implemented once the ABC has been received at the relevant pharmacy.

Another major change in the treatments recommended in this second edition of the guidelines is the use of a triple Fixed Dose Combination (FDC) ARV for paediatric patients. Please refer to section 3.5.2 of the guidelines for details of how to manage changing paediatric patients onto FDCs. Please note that regimens being well tolerated and clinically effective should not be switched simply because FDCs are available.

PART 1: Antiretroviral Therapy of Adults and Adolescents

1.1 Assessment of HIV-infected adults and adolescents

Namibians who receive a positive HIV test result, wherever and whenever the test is done, shall be evaluated for the need to begin highly active antiretroviral therapy (HAART). In the public sector, HIV-positive individuals should be referred to the nearest communicable disease clinic (CDC) or, in cases of pregnancy, to the nearest antenatal clinic (ANC) providing HAART, as a matter of urgency. At this clinic, the HIV-positive person will be evaluated for eligibility to begin ARVs. This assessment includes a complete medical history and HIV disease directed physical examination to determine WHO Clinical Staging (see Appendix 1), a CD4 cell count, and a review of social eligibility criteria (see page 5). At this first visit, all patients will be registered into the Antiretroviral Management Information System (ARV MIS) to assist with follow-up tracking and record-keeping for overall programme management. In the private sector, HIV-positive individuals should be assessed similarly by their healthcare providers and started on HAART per these guidelines, preferably by an HIV-experienced clinician.

1.2 When to start antiretroviral therapy in adults and adolescents

Adolescents and adults should start HAART when they have:

- WHO Clinical Stage 3 or 4 HIV disease, irrespective of CD4 cell count, *or*
- CD4 cell counts ≤ 200 cells/mm³ (≤ 250 cells/mm³ for pregnant women), irrespective of WHO Clinical Stage, *and*
- Met social eligibility criteria.

Accurate assessment of the clinical stage of each HIV patient, at diagnosis and at every 6 months thereafter, is a critical and required step in assuring that eligible Namibians are referred for antiretroviral therapy. Persons who have been ill or hospitalised in the preceding year should be carefully and rapidly assessed. CD4 count should be determined in order that HIV-infected persons with few or no symptoms (Stages 1 and 2), but who have CD4 cell counts below the appropriate cut off point, are also offered HAART.

Considering the variability of CD4 cell determination, this test should be repeated in asymptomatic patients (WHO Stage 1) before starting HAART. An assessment of baseline viral load is not considered essential before starting ART.

1.3 Adherence

1.3.1 Importance of adherence

ARV medication adherence is absolutely vital for the success of HAART. Very high levels of adherence, taking at least 95% of prescribed doses, are required to achieve sustained suppression of HIV growth over time (Table 1). Levels of adherence just slightly lower (e.g., taking 70-90% of HAART doses) provide temporary clinical benefit along with a very high risk of development of ARV resistance and treatment failure within 1 year. Adherence is promoted by simplified, well-tolerated regimens involving as few pills as possible, administered no more than two times per day.

Table 1. Correlation between adherence and virologic response to HAART

Adherence to HAART*	Viral load <400 c/ml
>95% adherence	78%
90% to 95% adherence	45%
80% to 90% adherence	33%
70% to 80% adherence	29%
<70% adherence	18%
*Number of doses taken/number prescribed	

(Source: Paterson et al., *Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection*. Ann Intern Med, July 2000; 133:21-30.)

1.3.2 Methods to achieve readiness to start HAART and maintain adherence

HAART should not be started at the first clinic visit. A period of education and preparation to try to maximise future adherence is important. The preparation of the patient for ART should include a review of expected benefits and potential side-effects of the regimen chosen, a review of possible medication interactions (such as with oral contraceptives), commitment to lifelong therapy, the critical need to maintain safer sexual practices to prevent HIV transmission, the importance of medication adherence to a successful outcome, and the need to report any perceived, or real, side-effects of the medications. This is typically a coordinated effort involving the patient, physicians, pharmacists, nurses, other healthcare providers and persons within the immediate environment of the patient. If the patient is not fully committed to adhering to therapy, therapy should be delayed while all the shortcomings are being addressed. Some methods for ensuring maximum adherence are presented in Figure 1.

Once therapy has begun, continued monitoring of adherence and ongoing patient education is essential. In some settings, introduction of directly observed antiretroviral therapy (DART) with caregivers' or family members' assistance may be considered. Successful tuberculosis treatment programmes may particularly wish to consider such an approach. At any rate, ongoing attention to, and reinforcement of, adherence throughout the entire course of HAART is an essential part of any successful therapy programme. Patients should receive care at the communicable disease clinic nearest their home, but should not be denied care or medication refills if they are away from home and need to attend another clinic.

Figure 1. Methods to achieve readiness to start HAART and maintain adherence

<p>Patient-related:</p> <ul style="list-style-type: none"> • Negotiate a plan or regimen that the patient understands and to which he/she commits himself/herself. • Take time needed, >2 visits at least 2 - 4 weeks apart, to ensure readiness before 1st HAART prescription. • Recruit a family member, a friend, peer and community support for treatment supervision. • Use memory aids: timers/alarm clock/cell phone, written schedule, pill boxes. • Plan ahead: keep extra medications in key locations, plan for trips out of town, obtain refills. • Active drug and alcohol use and untreated mental illness are associated with poor adherence.
<p>Provider-related:</p> <ul style="list-style-type: none"> • Educate patient regarding goals of therapy, proper dosing, medication interactions, food effects and side-effects. • Assess adherence potential before HAART. Monitor at each visit. • Treat side-effects. • Ensure access at off-hours and weekends for questions or addressing problems. • Utilise entire healthcare team. • Consider effect of new diagnoses and events on adherence.
<p>Regimen-related:</p> <ul style="list-style-type: none"> • Avoid adverse medicine interactions. • Simplify regimen regarding: dose frequency, pill burden, pill storage, and food requirements. • Inform patient of anticipated side-effects.
<p>Health team-related:</p> <ul style="list-style-type: none"> • Provide training updates on adherence for all team members and utilise entire team to reinforce adherence. • Monitor adherence and intensify management in periods of low adherence. • Educate volunteers, organisations of people living with HIV/AIDS (PLWHA) and community representatives.

1.4 Social Eligibility Criteria for starting HAART in Namibia

The Ministry of Health and Social Services has established social criteria, in addition to clinical and immunologic criteria, which must be met before an individual can start on HAART. The intention of these criteria is to maximise adherence and reduce the risk of failure of HAART and the development of resistance.

In order to start HAART, the patient must:

- Have lived at a fixed address for the past 3 months.
- Have ready access to a designated treatment centre for follow-up.
- Not drink alcohol.
- Have no untreated underlying psychiatric disorders.
- Be committed to:
 - Lifelong treatment with HAART.
 - Strict adherence to treatment.
 - Practising safer sex.
 - Allowing home visits if indicated.

1.4.1 Treatment supporters

Since the beginning of the antiretroviral programme in Namibia, the Social Eligibility Criteria have included that each patient must have a designated treatment supporter before starting HAART. This should be someone at home, in the community, or at the workplace, who can accompany the patient to visits and assist with daily adherence to HAART. Experience has shown that this is a very difficult criterion for some patients to meet. The MoHSS maintains that it is desirable for all patients to have a treatment supporter. Absence of a treatment supporter, however, should not be a reason to deny treatment to a patient. Where possible, patients who are unable to name a treatment supporter on their own may benefit from connection with a community-based organisation or a home-based care agency to assist with treatment support. Each case should be evaluated on its own merit.

1.4.2 Defaulters

Any patient who misses two consecutive clinic visits resulting in a break in ARV treatment due to an insufficient supply of medications, is a defaulter. Such a patient should have his/her HAART discontinued. He/she should be interviewed to uncover and understand the reasons behind the missed visits. Each case of defaulting should be carefully evaluated by a doctor before discontinuing treatment in any patient. If the patient still desires to be treated with HAART, he/she must be counselled again regarding the importance of adherence. Efforts should be made to correct the circumstances leading to the lapse in treatment. Once this has been accomplished, a trial period of usually three months must be scheduled, during which time the patient must demonstrate adherence to a regimen of daily cotrimoxazole prophylaxis and multivitamins with regular monthly visits for medication refills and further adherence counselling. If at the end of this time, the healthcare team is convinced that the patient will be able to adhere to HAART, the treatment can be restarted. In most cases this will mean restarting the patient's prior treatment regimen. If, however, the prior regimen was intolerable to the patient, resulting in the lapse in adherence, an alternative regimen should be prescribed. As with patients who are initiating HAART for the first time, patients reinitiating HAART after defaulting should have their viral load checked after a 6 month interval.

1.5 Antiretroviral medications

There are four classes of antiretroviral agents*:

1. **Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)**. These medications inhibit the transcription of viral RNA into DNA, which is necessary for reproduction of the virus. The class includes zidovudine (AZT), lamivudine (3TC), didanosine (ddI), stavudine (D4T), abacavir (ABC) and emtricitabine (FTC). The nucleotide analogue tenofovir (TDF) is also included in this class.
2. **Non-Nucleoside Analogue Transcriptase Inhibitors (NNRTIs)**. These medications are of a chemically different class from NRTIs, but also inhibit transcription of viral RNA into DNA. The class includes nevirapine (NVP), efavirenz (EFV) and delavirdine (DLV).
3. **Protease inhibitors (PIs)**: act on the viral enzyme that cuts long chains of virally produced amino acids into smaller proteins. The class includes lopinavir (LPV), indinavir (IDV), nelfinavir (NFV), saquinavir (SQV), ritonavir (RTV), atazanavir (ATV), fosamprenavir (FPV), tipranavir (TPV) and darunavir (DRV).
4. **Fusion inhibitors**: block the virus from being able to merge with the host cell (i.e. CD4 cell) after binding. The only currently available fusion inhibitor is enfuvirtide (T-20).

*Not all of these medications are currently available in Namibia. The comprehensive list at the time of this printing is given here for completeness.

1.6 HAART regimens

Recommended HAART regimens consist of a combination of 2 NRTIs plus an NNRTI or PI. Considerations in the selection of ARV regimens include potency, side-effect profile, the potential for maintenance of future treatment options, convenience of the regimen (pill burden, frequency of intake, absorption), coexistent conditions (e.g., TB and hepatitis B), pregnancy or the risk thereof, the use of other medications and potential medication interactions, costs, and required conditions for storage. Based on all of these variables, specific first and second line ARV regimens to be used in Namibia have been selected and will be presented in these guidelines. Individuals who cannot tolerate – or who experience failure on – the first and second line regimens should be referred for individualised care by specialist physicians.

Recommended basic HAART combinations:

- 2 NRTIs + 1 NNRTI, *or*
- 2 NRTIs + 1 PI or 'boosted' PI, *or*
- 3 NRTIs (recommended only for special situations)

Examples and explanations of regimens which are NOT recommended:

- Monotherapy – ineffective, early resistance.
- Dual therapy – ineffective, early resistance.
- Regimens containing both ddl and D4T – increased toxicities.
- Regimens containing both AZT and D4T – antagonism.
- Regimens containing both ddl and TDF – interactions and poor CD4 responses.
- Regimens containing both NVP and EFV – antagonism.
- Regimens containing AZT after D4T failure and vice versa – cross resistance.
- Regimens containing EFV after NVP failure and vice versa – cross resistance.

1.7 Recommended HAART regimens in Namibia

The first line regimen for HAART in adults and adolescents in Namibia is:

AZT 300 mg + 3TC 150mg + NVP* 200mg twice daily

****Due to metabolism issues and increased risks of hypersensitivity reactions, nevirapine treatment is always initiated as once daily therapy for the first 14 days. If it is well tolerated, then it is increased to twice daily dosing.***

Note that the recommended first line regimen in Namibia has changed from D4T/3TC/NVP, which becomes an alternate first line regimen (see below). This change was made in keeping with the 2006 WHO Guidelines which were based on the growing body of evidence that D4T based regimens are associated with more long term serious side effects than AZT based regimens. **Please note, however, that stable patients on D4T/3TC/NVP for less than 2 years, and who are suffering no have no adverse effects, should be continued on this regimen.** Refer to section 1.9.3 for more information.

Because some patients will not tolerate or cannot take the recommended first line regimen, alternative first line therapies have also been reviewed and included in these guidelines. These alternative regimens, along with second line regimens and salvage regimens, are included in Table 2. *The discussion of second line regimens begins on page 11.*

These alternative regimens are recommended for a number of reasons:

- Multiple studies show equivalent efficacies of these regimens.
- Significant toxic side-effects are associated with D4T:
 - Peripheral neuropathy.
 - Lactic acidosis.
 - Lipoatrophy.
- Similar pill burden as the first line regimen.
- Similar time to resistance as the first line regimen.
- Minimal increase in cost to the public system.
- Consistent with 2006 WHO recommendations.

Table 2. Recommended HAART regimens in Namibia – see Appendix 2 for doses

Designation	Regimen	Comments	Major toxicities
FIRST LINE	AZT+3TC+NVP	Preferred first line regimen for adults and adolescents of both sexes. Safe in pregnancy	<ul style="list-style-type: none"> • AZT-associated anaemia and neutropaenia • NVP-associated hepatotoxicity and severe rash • NRTI-associated metabolic side-effects
ALTERNATIVES TO FIRST LINE	D4T+3TC+NVP AZT+3TC+ EFV D4T+3TC+EFV	To be used in patients who cannot tolerate first line. EFV is contra-indicated in the 1 st trimester of pregnancy. Effective contraception should therefore be provided for women with reproductive potential before initiation of EFV therapy	<ul style="list-style-type: none"> • AZT-related anaemia and neutropaenia • D4T-related neuropathy and lipodystrophy • EFV-associated CNS (mood and sleep disorders) • NVP-associated hepatotoxicity and severe rash • Possible teratogenicity of EFV. • NRTI-associated metabolic side-effects
SECOND LINE OPTIONS	TDF+AZT+3TC+LPV/r AZT+3TC+ddl +LPV/r ABC+ddl+LPV/r * * ABC only to be used after consultation with HIV Specialist	Second line regimens are only to be used in the event of documented clinical, immunologic or virologic failure LPV/r is available as fixed dose combination heat stable tablets with LPV 200mg+RTV 50mg	<ul style="list-style-type: none"> • AZT-related anaemia • D4T-related neuropathy and lipodystrophy • ddl-associated pancreatitis and peripheral neuropathy • PI-associated lipid and glucose abnormalities • NRTI-associated metabolic side-effects • TDF-associated proteinuria
SALVAGE THERAPY	ddl+3TC+IDV+LPV/r TDF+3TC+IDV+LPV/r	Dual PI regimens to be used in extreme cases only. Expert consultation with a specialist is required	<ul style="list-style-type: none"> • ddl-associated pancreatitis and peripheral neuropathy • TDF-associated proteinuria • IDV-associated nephrolithiasis and skin changes • PI-associated lipid and glucose abnormalities • NRTI-associated metabolic side-effects

Both nevirapine (NVP) and efavirenz (EFV) are included in first line regimens options for HAART. They have similar potency. Nevirapine is preferred due to its safety in pregnancy and its significantly lower cost as a generic product. The advantages of efavirenz are the ability to use it in combination with TB treatment, lower overall side-effect profile, and the ability to administer it once per day.

Efavirenz (EFV) may be teratogenic and should not be used in pregnancy during the first trimester. Women of childbearing potential should only receive efavirenz (EFV) in combination with effective contraceptive methods as described below.

The most common toxicities experienced with nevirapine are rash and liver toxicity. The most common toxicities experienced with efavirenz are central nervous system/psychiatric effects and rash. These toxicities usually occur during the first few weeks of treatment. Nevirapine hepato-toxicity is more common in women who initiate nevirapine with CD4 counts > 250 cells/ml (11% in women with CD4 > 250 cells/ml vs 0.9% in women with CD4 < 250 cells/ml), and in men with CD4 counts > 400 cells/ml. Consequently, nevirapine should not be used for initial therapy in individuals with CD4 counts above these levels. It can be safely continued in patients whose CD4 counts have risen above these levels due to responses to HAART.

Second line options consisting of dual nucleoside plus protease inhibitor (PI) regimens have been selected because of their proven potency in reducing viral loads following NNRTI-based regimen failures. Disadvantages include higher cost, higher pill counts, significant interactions with other medications that preclude or complicate their use during standard TB treatment, and metabolic abnormalities. On the basis of efficacy, costs, and side-effects, lopinavir-ritonavir (LPV/r) is the boosted PI of choice.

The salvage regimens presented in Table 2 include dual boosted PIs. These regimens are complicated and should only be implemented following the recommendation of an HIV specialist.

Patients successfully treated on any of the above mentioned HAART regimens should continue their treatments, unless there are specific indications to change their regimens (see Section 1.9, page 11).

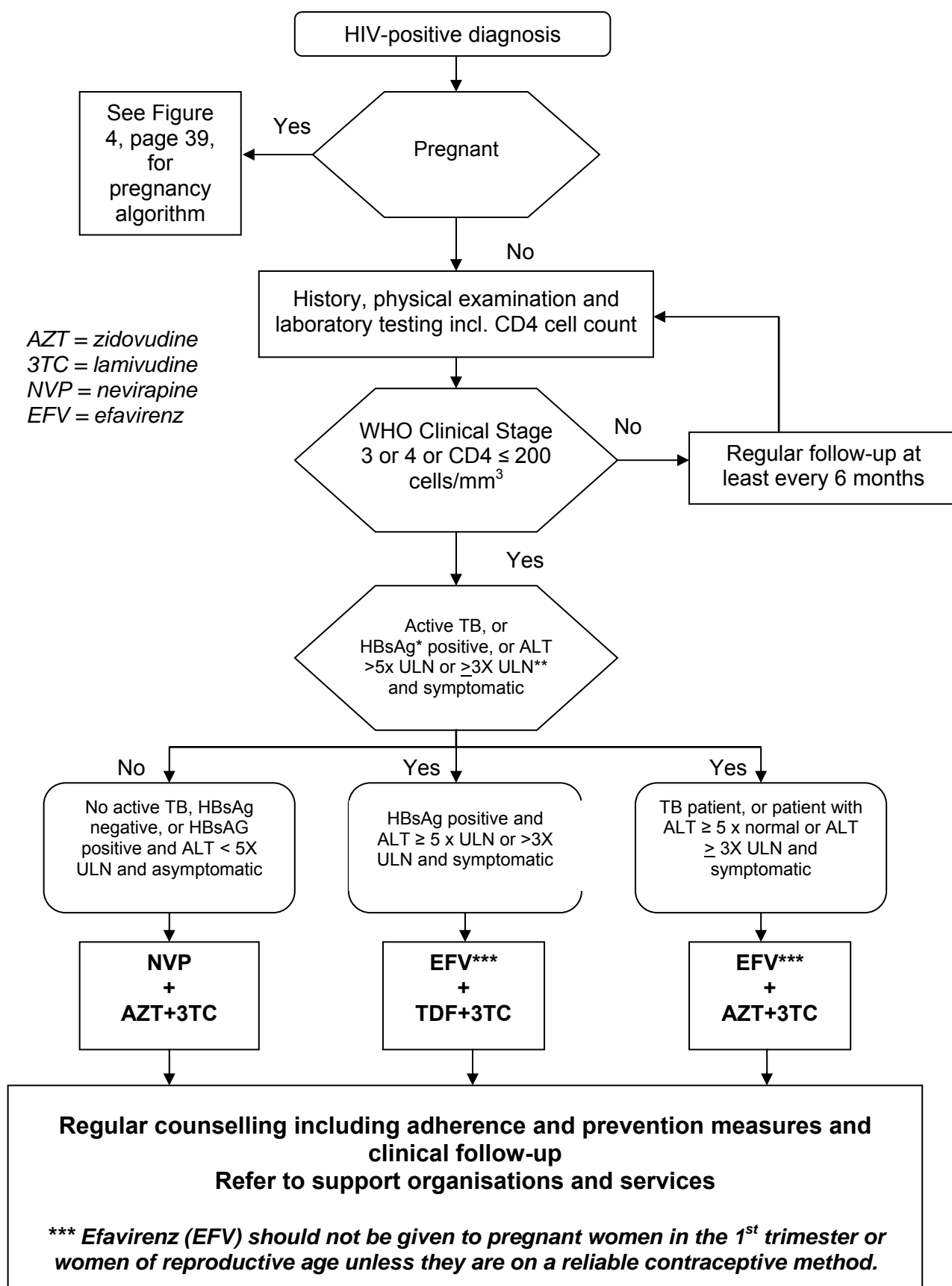
The algorithm for prescribing HAART in Namibia is summarised in Figure 2.

1.8 HAART in women of childbearing age

Many ARVs are safe to use during pregnancy, while others should be avoided. Efavirenz (EFV) cannot be used in the first trimester due to teratogenicity, and tenofovir (TDF) is not recommended due to the risk of bone demineralization in the foetus.

The use of barrier contraception methods is recommended for all male and female patients receiving HAART in order to reduce the risk of transmission of STIs and HIV, even when both partners are HIV-positive (it is possible for a person with a resistant strain of HIV to infect his/her partner with the resistant strain). To minimise the risk of unintended pregnancies, an additional highly effective contraceptive method, such as an intrauterine contraceptive device (IUCD), injectable progesterone-based contraceptives (depo-medroxyprogesterone acetate, DMPA), or sterilisation, is recommended for all women of childbearing age. Nevirapine, efavirenz, nelfinavir and all the ritonavir boosted PIs affect blood concentrations of oral contraceptives and women receiving these medications should use alternative methods. Contraception and planning of pregnancies should be adequately addressed in all female patients receiving HAART at each clinic visit.

Figure 2. Algorithm for prescribing HAART in adults and adolescents



*Hepatitis B surface antigen
 ** Upper limit of normal

1.9 Reasons for changing antiretroviral therapy

Studies have shown that first line regimens give patients the best chance of long-term treatment success. Therefore, changing therapy is to be avoided wherever possible. HAART may need to be changed due to therapy failure or medication toxicity, but there must be a very good reason for doing so.

1.9.1 Changing due to toxicity

If a change in a regimen is needed because of toxicity and the toxicity is related to an identifiable medication in the regimen, the offending medicine can be replaced with another medicine that does not have the same side-effects (Tables 8 and 10). When it is not possible to identify the offending medication, an entirely new second line regimen should be prescribed. Before any change is made due to failure, the circumstances contributing to the failure (e.g., poor adherence, medication interactions, malabsorption) should be thoroughly investigated and corrected before a new regimen can be started. Each case should be discussed with a specialist physician.

1.9.2 Changing due to treatment failure

Treatment failure can be established clinically by history and physical examination, immunologically by following CD4 counts, and virologically by measuring viral loads. Clinical evidence of failure is indicated by HIV disease progression (e.g., new opportunistic infections) in a patient who had been clinically stable. A useful marker of failure by immunological evaluation is a fall in the CD4 count by >50% from its peak, or a return to the pre-therapy baseline count. Virologic failure is defined as a viral load >1,000 copies/ml 24 weeks after starting HAART or viral rebound to >1,000 copies/ml on two consecutive measurements after a period of viral suppression. If a change in regimen is indicated because of treatment failure, a new second line regimen will need to be used. Again, consultation with an HIV specialist is indicated.

1.9.3 Switching patients from D4T based regimens

Long term side effects from D4T are well-documented and patients exhibiting these side effects may be switched from D4T containing regimens. Patients with signs of mitochondrial toxicity such as peripheral neuropathy, lipoatrophy and/or lipodystrophy, and/or consistently elevated liver transaminases (>3 X the upper limit of normal on two blood draws 6 weeks apart) should be changed to a non-D4T containing regimen. Usually this means simply substituting AZT for D4T, as long as there are no contraindications to using AZT. Additionally, in order to minimise the risk of developing side effects, patients who have been on D4T for longer than 24 months may be considered for changing to a non-D4T containing regimen. **No patient should be switched from a D4T containing regimen which is clinically effective and being well tolerated without good reason.**

1.10 Second line HAART regimens

Sequencing HAART regimens, particularly in the absence of resistance testing, is difficult. Cross-resistance within the same ARV class is common. For example, zidovudine resistance implies stavudine resistance, and nevirapine resistance implies efavirenz resistance. In the absence of ARV resistance testing, the WHO recommends that the entire regimen be changed from a first to a second line combination regimen in the case of treatment failure.

The new regimen will ideally include at least two new ARVs, with one from at least one new class of antiretrovirals. When zidovudine-lamivudine-nevirapine (AZT/3TC/NVP) is used in the first line regimen, the second line regimen could contain tenofovir-zidovudine-lamivudine (TDF/AZT/3TC) plus lopinavir/ritonavir (LPV/rvt). The TDF and LPV/rvt are both new and the LPV/rvt, a protease inhibitor, is from a new class.

The number of second line regimen options is limited and these are usually less effective than first line therapy. Moreover, there may be serious cost implications. For many patients on HAART, the second line regimen is their last option for durable viral suppression. It is therefore important to ensure that all possible causes for failure of the first line therapy are identified and properly addressed.

The second line regimen choices for HAART in adults and adolescents in Namibia are:

Tenofovir-zidovudine-lamivudine (TDF/AZT/3TC) plus lopinavir/ritonavir (LPV/rvt)*

or

**zidovudine-lamivudine-didanosine (AZT/3TC/ddl)
plus LPV/rvt***

or

abacavir-didanosine (ABC/ddl) plus LPV/rvt*
(only after consultation with an HIV Specialist Consultant)

*See Appendix 2 for correct weight-based dosing.

Table 3. Recommendations for second line regimens after first line regimen fails

First line regimen	Recommended second line regimen
Zidovudine-lamivudine-nevirapine (AZT/3TC/NVP)	Tenofovir-zidovudine-lamivudine (TDF/AZT/3TC)* <i>OR</i> zidovudine-lamivudine-didanosine (AZT/3TC/ddl)
Zidovudine-lamivudine-efavirenz (AZT/3TC/EFV)	<i>OR</i> abacavir-didanosine (ABC/ddl) <i>PLUS</i> Lopinavir/ritonavir (LPV/rvt)
Stavudine-lamivudine-nevirapine (D4T/3TC/NVP)	Tenofovir-zidovudine-lamivudine (TDF/3TC)* <i>OR</i> abacavir-didanosine (ABC/ddl)
Stavudine-lamivudine-efavirenz (D4T/3TC/EFV)	<i>PLUS</i> Lopinavir-ritonavir (LPV/rvt)
Tenofovir-lamivudine-efavirenz (TDF/3TC/EFV) – in HBsAg positive patients	Tenofovir-zidovudine-lamivudine (TDF/AZT/3TC)** <i>PLUS</i> Lopinavir-ritonavir (LPV/rvt)

*TDF/AZT/3TC should retain some activity after an AZT or D4T first line regimen fails. Studies show failing thymidine/3TC/NNRTI regimens develop resistance to 3TC or the NNRTI before the thymidine analogue.

** In this case, TDF and 3TC are continued to prevent an HBV flare upon withdrawal of treatment.

1.10.1 Abacavir (ABC) containing regimens

Due to the high cost of abacavir (ABC) this ARV is only to be used in certain limited controlled circumstances where its benefits outweigh the cost implications. No patient can be started on

ABC unless recommended by an HIV specialist consultant. Detailed below are the situations where the use of ABC can be considered, as well as the control mechanisms to be used to prevent the inappropriate use of ABC.

Situations where use of ABC can be considered:

- In a pregnant woman on TB treatment (use AZT + 3TC + ABC)
- In a patient who has a life threatening intolerance to AZT or history of lactic acidosis
- As second line in a paediatric patient.

Control Mechanisms for ABC:

- Regional Pharmacists may order a small stock of ABC to be held at the pharmacy in the regional centre and issued to the districts on a name patient basis.
- HIV specialist consultant must give verbal prescription for any ABC containing regimen following consultation with treating medical officer.
- Treating Medical Officer must document the following details in the patient's ART card and health passport;
 - Reason for change to ABC containing regimen
 - Name of HIV Specialist consulted; date of consultation
 - Planned start date for ABC (giving time for stock to be received from the medical stores).
- Pharmacy to order supply of ABC for this name patient from the Regional Pharmacist.
- Pharmacy to inform treating medical officer when stock of ABC received.
- Pharmacy to ensure that the stock of ABC is used solely for the name patient and not for other patients.
 - The only exception to this would be an emergency supply to a patient who is in transit through a district and has already been initiated on ABC by their treating medical officer.
- Patients who are taking ABC should be counselled that the medicine they are taking will not be freely available from other MoHSS hospitals and that they need to plan their medications very carefully before travelling from their normal place of residence.
- Regional Pharmacist to keep records of all patients receiving ABC.

1.11 Monitoring of antiretroviral therapy: Clinical monitoring

1.11.1 Baseline clinical assessment

The baseline medical history should be recorded in a standardised patient file and should include essential demographic characteristics; the past medical history including major illnesses (e.g., tuberculosis), hospitalisations and surgeries; the length of time since the diagnosis of HIV infection; current medications; and any active symptoms. In the case of women, current or planned pregnancy and access to contraceptive services should be reviewed.

The baseline physical examination should also be recorded in the patient's file, including vital signs, weight, and detailing of any abnormalities of the eyes (including fundi, if possible), oropharynx, lymph nodes, lungs, heart, abdomen, extremities, skin, genital tract and nervous system.

Once HAART has started, a reasonable schedule for clinical monitoring includes follow-up visits two and six weeks after initiation (which will also be useful to evaluate and reinforce adherence to antiretroviral therapy), and a minimum of every three months thereafter (including clinical and laboratory monitoring). Monthly visits with trained nursing staff, which can be combined with medication dispensing, are encouraged to monitor and reinforce adherence and identify problems requiring referral. At each visit, inquiries should be made with respect to the following 3 aspects of HAART:

1. Is HAART adherence excellent? If not, why not and what steps can be taken to improve adherence?
2. Are there any new symptoms that may be related to medication side-effects?
3. Are there any new symptoms that may be related to HIV disease progression or opportunistic infections? The development of significant opportunistic infections (OIs) while on HAART may indicate clinical failure, but early on in treatment may also be attributable to Immune Reconstitution Inflammatory Syndrome (IRIS) (see page 28).

1.11.2 Clinical monitoring for toxicities and effectiveness of ARVs

Patients should be informed about the symptoms of ARV toxicities and when to seek care. Clinical evaluation of the effectiveness of HAART is important. The long-term basic parameters examined and documented should include:

- The patient's perception of how he/she is doing on therapy.
- Changes in body weight over the course of therapy.
- Changes in the frequency or severity of HIV-associated symptoms (fevers, diarrhoea).
- Physical findings, such as signs of Immune Reconstitution Inflammatory Syndrome (e.g., lymph node swelling), signs of immune improvement (e.g., regression of Kaposi's sarcoma lesions or molluscum contagiosum), signs of HIV-related disease progression (e.g., oropharyngeal and/or vulvovaginal candidiasis, etc.), or signs of medication toxicities (rash, lipodystrophy).

1.12 Monitoring of antiretroviral therapy: Laboratory monitoring

1.12.1 Basic laboratory monitoring for toxicity and effectiveness of HAART

Specific laboratory investigations are recommended as the basic level of care that is necessary to safely start HAART. Such tests are needed to monitor response to treatment and to identify potential toxic reactions which might trigger changes in ARV regimens according to the national guidelines. These tests should be performed at baseline, before the initiation of ART, and at follow-up as indicated (see below).

The recommended minimum laboratory tests before initiating ART are:

- An HIV antibody test, confirming HIV infection.
- Full blood count to monitor for anaemia and thrombocytopenia.
- Serum alanine aminotransferase (ALT) level to assess the possibility of hepatitis and to monitor for hepatotoxicity.
- Serum creatinine to assess baseline renal function.
- Serum RPR
- Hepatitis B surface antigen
- Pregnancy tests for all women of childbearing age.

CD4 levels are important markers of immune function. CD4 testing is recommended at baseline to determine eligibility for HAART and for monitoring response to treatment. CD4 tests are available to all Namibians receiving HAART. Unavailability of CD4 testing or results should not delay the onset of ARV therapy for those who need it on clinical grounds

Additional baseline and routine laboratory monitoring is recommended for patients on second line regimens, including serum lipid and glucose levels for patients with other cardiovascular risk factors. Other tests may be indicated based on the suspicion of a medication toxicity (such as ddl-induced pancreatitis) or clinical disease progression.

Table 4. Baseline laboratory assessment for HAART

Required tests	Frequency
At VCT centre, ANC-PMTCT site, OPD, primary care clinic, or hospital	
ELISA or rapid HIV testing	Baseline
At primary care clinic, OPD, or hospital	
CD4 cell count	Baseline
At communicable disease clinic or ANC-HAART clinic	
Full blood count	Baseline
Hb	Follow-up per schedule
Creatinine	Baseline and as indicated
ALT	Baseline and follow-up per schedule
Blood glucose	Only as indicated (especially for patients receiving PIs)
RPR test	Baseline
Hep B surface antigen (HBsAg)	Baseline
Pregnancy test	Baseline (where indicated)
CD4 cell count	Baseline, at 1 year, and then every 6 months
Serum lipids	Yearly (for patients on EFV, PIs, or with cardiovascular risk factors)
Amylase	For patients with pancreatitis symptoms, especially on didanosine or stavudine
Urine dipstick	Baseline and every 6 months for patients on tenofovir and indinavir
Viral load (recommended)	Not at baseline. To be done 6 months after initiating HAART. Useful for programme monitoring and in case of suspected treatment failure in individual patients
Optional tests	Frequency
ARV genotypic resistance (not available in Namibia)	In case of treatment failure. Prohibitively expensive. For purposes of surveillance for ARV resistant HIV in Namibia

1.12.2 CD4 lymphocyte counts

CD4 lymphocyte counts are one of the most useful and reliable ways of assessing whether an HIV-positive patient should start ART and are also extremely important in the assessment of the effectiveness of ART. An increase of >100 CD4 cells/mm³ in the first 6-12 months is typically seen in an ARV naïve, adherent patient. Higher elevations can be seen and the response often continues in subsequent years in individuals who are maximally virologically suppressed. Immunologic failure on therapy can also be assessed by CD4 cell counts.

1.12.3 Plasma HIV-RNA levels (viral load)

Although desirable, viral load assay has not been used routinely for monitoring patients on HAART. This is due to the high cost of viral load assay and the lack of availability in most facilities that are offering ARV therapy. Viral load levels are likely to reach undetectable levels of less than 50 copies per ml by 6 months of therapy in fully adherent patients. With the introduction of this Second Edition of the ART guidelines, all patients initiating therapy will routinely have a viral load assay done 6 months after beginning therapy. The aim is to earlier identify patients who are having suboptimal responses to ARV therapy and whose immunologic and clinical responses have not yet deteriorated at this stage. These patients have viral loads > 1,000 copies per ml. Such patients must undergo intensive adherence counseling and support to avoid further failure, to achieve viral suppression and to prevent the emergency of ARV resistance virus and the necessity to switch to second line treatment.

Viral load assays are also recommended for patients already on treatment who are showing evidence of immunologic and or clinical failure. The test has to be repeated in this category of patients 4 months after changing therapy, to evaluate response to the new regimen and to

evaluate the level of adherence in this group of patients. The tests to be monitored and the frequency of testing will vary depending on whether the patient is on a first or second line regimen, as summarised in Tables 5 and 6. Table 7 lists possible actions to be taken in the case of abnormal results.

Table 5. First line regimens: clinical and laboratory monitoring by regimen

Zidovudine-lamivudine- nevirapine (AZT/3TC/NVP)	M 0.5	M 1	M 1.5	M 2	M 2.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	As clinically indicated
History and targeted physical exam	X		X			X	X	X	X	X		
HB	X		X			X	X		X		X	
ALT	X		X			X	X		X		X	
Creatinine							X		X		X	
CD4 count									X		X	
HIV-1 RNA viral load							X					X
Amylase												X
Labs to assess lactic acidosis												X
Pregnancy test												X

Stavudine-lamivudine- nevirapine (D4T/3TC/NVP)	M 0.5	M 1	M 1.5	M 2	M 2.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	As clinically indicated
History and targeted physical exam	X		X			X	X	X	X	X		
HB						X	X		X		X	
ALT	X		X			X	X		X		X	
Creatinine							X		X		X	
CD4 count									X		X	
HIV-1 RNA viral load							X					X
Amylase												X
Labs to assess lactic acidosis												X
Pregnancy test												X

Zidovudine-lamivudine- efavirenz (AZT/3TC/EFV)	M 0.5	M 1	M 1.5	M 2	M 2.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	As clinically indicated
History and targeted physical exam	X		X			X	X	X	X	X		
HB	X		X			X	X		X		X	
ALT							X		X		X	
Creatinine							X		X		X	
CD4 count									X		X	
HIV-1RNA viral load							X					X
Amylase												X
Labs to assess lactic acidosis												X
Pregnancy test												X

M = month

Q = every

Stavudine-lamivudine-efavirenz (D4T/3TC/EFV)	M 0.5	M 1	M 1.5	M 2	M 2.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	As clinically indicated
History and targeted physical exam	X		X			X	X	X	X	X		
HB							X		X		X	
ALT							X		X		X	
Creatinine							X		X		X	
CD4 count									X		X	
HIV-1 RNA viral load							X					X
Amylase												X
Labs to assess lactic acidosis												X
Pregnancy test												X

Tenofovir-lamivudine-efavirenz (TDF/3TC/EFV)	M 0.5	M 1	M 1.5	M 2	M 2.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	As clinically indicated
History and targeted physical exam	X		X			X	X	X	X	X		
HB							X		X		X	
ALT							X		X		X	
Creatinine							X		X		X	
Urine dipstick for protein						X	X		X		X	
CD4 count									X		X	
HIV-1 RNA viral load							X					X
Amylase												X
Labs to assess lactic acidosis												X
Pregnancy test												X

Table 6. Second line regimens: clinical and laboratory monitoring for by regimen

Tenofovir-zidovudine-lamivudine-lopinavir-ritonavir (TDF/AZT/3TC/LPV/rty)	M 0.5	M 1	M 1.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	Q 12M	As clinically indicated
History and targeted physical exam	X		X	X	X	X	X	X			
HB	X		X	X	X		X		X		
ALT				X	X		X		X		
Creatinine					X		X		X		
Urine dipstick for protein				X	X		X		X		
CD4 count							X		X		
Cholesterol/triglycerides							X			X	
HIV 1 RNA Viral load					X						X
Amylase											X
Labs to assess lactic acidosis											X
Pregnancy test											X

Abacavir-didanosine- lopinavir-ritonavir (ABC/ddi/LPV/rvt)	M 0.5	M 1	M 1.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	Q 12M	As clinically indicated
History and targeted physical exam	X		X	X	X	X	X	X			
HB					X		X		X		
ALT				X	X		X		X		
Creatinine					X		X		X		
CD4 count							X		X		
Cholesterol triglycerides							X			X	
HIV1 RNA Viral load					X						X
Amylase											X
Labs to assess lactic acidosis											X
Pregnancy test											X

Table 7. Actions to take in case of abnormalities in laboratory monitoring

ARV	Lab test	Result	Recommendation
Zidovudine (AZT)	HB	< 7.0 grams	Switch ZDV to D4T
	WBC	< 1,250 cells/mL	Switch ZDV to D4T
	Neutrophils	< 750 cells/mL	Switch ZDV to D4T
Nevirapine (NVP)	ALT	> 3x ULN with rash, hepatitis symptoms or jaundice	Switch NPV to EFV
	ALT	> 5 - 10x ULN without symptoms	Switch NVP to EFV
Stavudine (D4T) Zidovudine (AZT) Lamivudine (3TC) Didanosine (ddI)	Creatinine	> 150 micromols/L	Calculate creatinine clearance (p. 31) and adjust dose if needed (Appendix 2).
Tenofovir (TDF)	Creatinine	> 150 micromols/L	Substitute another NRTI for calculated creatinine clearance (p.31) < 50 ml/min.
	Urine protein	≥2+ on dipstick	Substitute another NRTI, i.e., D4T or AZT.

See also discussion of hepatitis B virus and management of ALT abnormalities, page 29.

1.13 Antiretroviral toxicity

Antiretroviral toxicities can occur in a wide range – from mild and self-limiting (AZT-associated headaches) to long-term and disabling (D4T-associated peripheral neuropathy) and even to potentially fatal (NRTI-associated lactic acidosis). Some toxicities are class related; others are related to one particular ARV. The frequency and severity of class-related toxicities also vary among the medicines within the same class. Clinicians working with patients on HAART should be aware of the common and serious side-effects associated with these medications. Patients must be made aware of these potential toxicities and when to report them to their healthcare providers. These steps can prevent unnecessary morbidity and can help to improve adherence to HAART, thereby increasing therapeutic success and decreasing the risk of ARV resistance. The more serious HAART-related toxicities are listed here in Table 8. Other common toxicities of ARVs are categorised Appendix 2.

Table 8. ARV-associated toxicities

Potentially fatal	Associated agents	Clinical response
Pancreatitis	Didanosine (ddI), Stavudine (D4T) Lamivudine (3TC)(paeds)	Stop immediately
Hypersensitivity reactions	Abacavir (ABC)	Stop immediately Never re-challenge
	Nevirapine (NVP)	Stop immediately Never re-challenge
Toxic epidermo-necrolysis (TEN) or Stevens-Johnson Syndrome	Nevirapine (NVP)	Stop immediately
Lactic Acidosis	All NRTIs	Stop immediately
Hepatotoxicity	Nevirapine (NVP) Lopinavir (LPV) Ritonavir (RTV)	Stop according to criteria (see text)
Haematological toxicity Anaemia, leucocytopenia	Zidovudine (AZT)	Stop according to criteria (see text)
Disabling	Associated agents	Clinical response
Peripheral neuropathy	Didanosine (ddI), Stavudine (D4T), Lamivudine (3TC)	Change therapy
Osteonecrosis / osteoporosis	Origin uncertain (PIs?)	Unknown
Hepatotoxicity	NNRTIs PIs	Stop according to criteria (see text)
Long term	Associated agents	Clinical response
Lipoatrophy	NRTIs	Explain side-effects Monitor patient Consider changing therapy
Fat accumulation	PIs	
Hyperlipidaemia	Efavirenz (EFV) PIs	
Lactic acidosis	All NRTIs	
Insulin resistance	NRTIs and PIs	Stop therapy, refer Discuss with specialist

(Compiled from: Pham et al., (2005). *Antiretroviral Drug Interactions: A Practical Approach*. Baltimore, Johns Hopkins University.)

1.14 Management of HAART-associated toxicities

1.14.1 Rash

Minor, self-limited rashes are common occurrences when starting patients on HAART. Such minor rashes are associated with zidovudine (AZT), and efavirenz (EFV). Rash is also commonly seen in patients taking cotrimoxazole and other non-ARV medicines used in conditions related to HIV disease. Management of most of these rashes can simply be observation until they resolve or may include short courses of antihistamines.

Any rash associated with nevirapine, however, could indicate a hypersensitivity reaction which may also involve the liver. Any patient with NVP-induced rash needs an ALT level checked immediately. If the ALT is normal, the patient can be closely followed on NVP. If the ALT is more than three times the upper limit of normal ($\geq 3x$ UNL), nevirapine should be stopped and substituted with either efavirenz or a PI.

A severe rash associated with nevirapine, especially if it is accompanied by fever, mucositis, and/or blisters, may be life-threatening and all medications must be stopped immediately (see 'Considerations when stopping or changing HAART', below). The patient should be hospitalised and given supportive care appropriate for Stevens-Johnson Syndrome. Nevirapine (many sources would include all NNRTIs) may never be used in the patient again as this hypersensitivity reaction is likely to recur.

Any rash in a patient on abacavir (ABC) could be part of a life-threatening hypersensitivity reaction seen in approximately 5% of patients starting ABC. Patients with rashes on ABC need immediate careful evaluation.

Any rash in a patient taking nevirapine requires immediate clinical evaluation and immediate measurement of ALT.

Any rash in a patient on abacavir requires immediate clinical evaluation.

1.14.2 Haematologic toxicity

Anaemia, leucopaenia, lymphopaenia and thrombocytopaenia are found in 30% to 40% of patients with HIV. Therefore, it is necessary to have a baseline FBC, differential, and platelet count prior to starting ART. Zidovudine (AZT) can be bone marrow toxic, resulting in anaemia, neutropaenia, or both. If the baseline Hb is below 7.0 gm/dl, a patient should not be started on AZT and an alternative first line regimen should be used. Patients on AZT should be monitored with Hb at two weeks, six weeks, twelve weeks and then every six months on therapy (see tables regarding laboratory monitoring of specific regimens). Hb should be repeated monthly in patients with Hb levels below 9 gm/dl. AZT should be substituted immediately if Hb falls below 7.0 gm/dl. See the notes on changing and stopping HAART below.

1.14.3 Hepatotoxicity

Patients with pre-existing liver dysfunction should be monitored closely, especially if started on nevirapine. For HBV and HIV co-infection see page 29. Patients taking nevirapine may experience increases in liver enzymes and, rarely, severe hepatitis leading to hepatic failure. This can occur in the absence of the rash discussed above. After measuring transaminase (ALT) at baseline, ALT should be monitored at two weeks, six weeks, twelve weeks and every six months thereafter. This patient follow-up schedule is critical and HAART should not be started if the patient can not commit to follow-up visits. Other medicines commonly used in HIV-infected patients, notably TB treatment (including prophylactic isoniazid), may also cause hepatitis. Patients taking protease inhibitors, especially indinavir, may develop unconjugated hyperbiliribinaemia with normal ALT levels. This resembles Gilbert's Syndrome and generally does not require treatment.

Stop or substitute relevant hepatotoxic medications in asymptomatic patients if transaminases are more than 5 times the upper limit of normal, and consult a specialist physician for further management. If transaminases are more than 10 times the upper limit of normal in asymptomatic patients, stop all medications immediately. Hepatotoxic medicines should be discontinued for moderate or greater elevations of transaminases. Nevirapine should be discontinued if a rash is accompanied by elevated transaminases. See the notes on changing and stopping HAART below.

NOTE: Fluconazole can double blood levels of nevirapine when these medications are taken together, increasing the risk of nevirapine hepatotoxicity. For patients on nevirapine, use topical treatment rather than fluconazole for skin, oral and vaginal fungal infections whenever possible. When fluconazole must be used, for example in treating oesophageal candidiasis or cryptococcal meningitis, close monitoring of ALT is essential.

1.14.4 Lactic acidosis

This life-threatening (mortality approaching 50% in early studies) complication of HAART is caused by mitochondrial dysfunction and a resulting disruption in normal cellular metabolism. It can be difficult to recognise given its presentation with non-specific symptoms. Clinicians must have a high index of suspicion for lactic acidosis, especially in patients who have been on NRTIs for a prolonged period (>6 months). It has been particularly associated with D4T

use; although it has been reported with most NRTIs (abacavir and tenofovir are possible exceptions). Patients taking a combination of D4T and ddI, especially pregnant women, are at even greater risk for developing lactic acidosis. Additional risk factors include female gender and obesity. Patients with lactic acidosis often have had excellent virological and immunological response to their ARVs. Clinical symptoms of lactic acidosis are non-specific.

Table 9. Clinical symptoms of lactic acidosis

Abdominal pain	Hyperventilation	Liver dysfunction
Weight loss	Nausea and vomiting	Arrhythmias
Malaise	Cold extremities	Cyanosis
Lethargy	Hypotension	Stupor or coma

The most common presenting symptoms are in bold type.

In addition to the symptoms of metabolic acidosis, lactic acidosis is distinguished by hyperlactataemia:

- PH < 7.25 (normal arterial blood pH ranges from 7.38 to 7.42).
- HCO₃⁻ < 21 mEq/L.
- Plasma lactate 2 to 5 mmol/L (moderate).
- Plasma lactate > 5 mmol/L or greater than 2 times the upper limit of normal (severe).

Lactic acidosis should be suspected in any patient having an unexplained acidosis (no evidence of diabetic ketoacidosis, renal failure, dehydration, etc.). Early intervention can lead to resolution of lactic acidosis. Treatment must include immediate discontinuation of HAART. Supportive management within an ICU setting may be lifesaving:

- Hydration.
- Respiratory and/or haemodynamic support to improve tissue perfusion.
- Maintenance of airway patency.
- Delivery of oxygen.
- Monitoring of cardiac rhythm.
- Bicarbonate replacement is controversial and should be avoided.

Recovery from an episode of lactic acidosis can be slow. Continuation of HAART following lactic acidosis can only occur after complete resolution and recovery from the acidosis. NRTIs generally cannot be restarted in these patients, and modified HAART regimens will be required. Consultation with a specialist is essential. See the notes on changing and stopping HAART below.

1.14.5 Pancreatitis

Toxicity resulting in pancreatitis is most commonly associated with the use of didanosine (ddI). It also can be seen with the use of other NRTIs, especially stavudine (D4T), and an increased incidence has been seen with the combined use of ddI and D4T. Patients taking ddI must be cautioned to report the development of abdominal or epigastric pain as soon as possible. These patients should have serum amylase levels measured urgently. Consultation with a specialist physician is recommended if amylase levels are repeatedly above the upper limit of normal (ULN). Didanosine or other potentially offending medicines (D4T) should immediately be stopped if amylase levels are more than 2.5 times ULN. Patients who experience ddI/D4T-related pancreatitis should never receive these ARVs again. See the section on changing and stopping HAART below.

1.14.6 Lipodystrophy and lipid abnormalities

Some patients receiving HAART can, after several months or even years, develop body changes resulting from the loss of subcutaneous fat in some areas and the abnormal deposition of fat in other areas. Some patients will also develop elevations in cholesterol and or triglyceride levels. These changes are most commonly associated with protease inhibitor-containing HAART regimens, but have been seen in patients on all regimens. For most patients, these changes will be minor, but for some, the cosmetic changes can be extreme – especially when fat is lost from the face resulting in sunken cheeks and temples. For others, the changes can be physically uncomfortable (such as fat loss in the buttocks making sitting uncomfortable, or fat deposition around the neck and upper back making lying down uncomfortable). Currently there are no recommended treatments for these fat changes other than cosmetic surgery. With respect to lipid changes, patients on protease inhibitors with other risk factors for cardiovascular disease should have their lipids monitored on an annual basis and should be counselled to reduce all possible cardiovascular risks (e.g., smoking). If these fat and lipid changes become intolerable, consideration can be given to changing regimens, although this has had variable results in trials. Stopping ARV treatment can usually halt the process and will sometimes result in a decrease in the fat deposits, but does little to correct fat losses. Patients should be informed of these potential side-effects, with careful emphasis on HIV disease progression if HAART is discontinued or delayed.

1.15 Considerations when changing or stopping HAART

When an ARV must be stopped due to intolerance or mild to moderate toxicity, and the offending agent can be easily identified, simple substitution with another ARV in the same class may be done without stopping treatment. For example, a patient taking a zidovudine-containing regimen who develops anaemia can have the zidovudine replaced by stavudine. Similarly, a patient on nevirapine who develops a non-life threatening rash can have efavirenz substituted for nevirapine. See Table 10.

When antiretrovirals must be stopped, as in cases of severe or life-threatening toxicity, care must be taken so that resistance is avoided. HIV develops resistance quickly when there are insufficient blood and tissue levels of enough antiretroviral medications. Traditionally, this meant all medications in a HAART regimen were stopped at the same time, even if only one medication was the source of the problem. This approach still holds true for HAART regimens that combine NRTIs with PIs. Nevirapine and efavirenz (the NNRTIs), however, both have very long half lives, so blood and tissue levels persist for some time after the last dose is taken. In this situation, stopping both NRTIs and an NNRTI together leaves the virus exposed to slowly falling levels of the NNRTI over days or weeks, with a risk of emergence of resistance to the NNRTI class of medications. Research is underway to define the best way to manage discontinuing NRTI-NNRTI HAART combinations. When an NNRTI (nevirapine or efavirenz) must be stopped, the recommended option at this time is to continue the 2 NRTI medications (e.g. AZT-3TC or D4T-3TC) at their usual dosing for 7 days. This will decrease the risk of developing NNRTI resistance.

In situations where the toxicity is not severe, an immediate substitution can be made. Patients with moderate toxicity (grade 1 or 2) on nevirapine can switch immediately to efavirenz, continuing their 2 NRTI medications with close clinical monitoring. Patients with life-threatening toxicity on nevirapine, such as symptomatic hepatitis, Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis, should stop all medications immediately. When the toxicity has resolved and the patient has recovered, HAART can be restarted without using an NNRTI, to avoid recurrence of the toxic event.

Table 10. Changing first line antiretrovirals in case of toxicity

Regimen	Toxicity	ARV substitution
AZT/3TC/NVP	<ol style="list-style-type: none"> 1. AZT-related persistent GI intolerance or severe haematological toxicity 2. NVP-related severe hepatotoxicity 3. NVP-related moderate rash (but not life threatening) 4. NVP-related life-threatening rash (Stevens-Johnson Syndrome) 	<ol style="list-style-type: none"> 1. Switch AZT → D4T 2. Switch NVP → EFV [not in pregnancy (**)] 3. Switch NVP → EFV [not in pregnancy (**)] 4. Switch NVP → PI(***)
D4T/3TC/NVP	<ol style="list-style-type: none"> 1. D4T-related neuropathy or pancreatitis 2. D4T-related lipoatrophy 3. NVP-related severe hepatotoxicity 4. NVP-related severe rash (not life-threatening) 5. NVP-related life-threatening rash (Stevens-Johnson Syndrome) 	<ol style="list-style-type: none"> 1. Switch D4T → AZT 2. Switch D4T → TDF 3. Switch NVP → EFV [not in pregnancy (**)] 4. Switch NVP → EFV [not in pregnancy (**)] 5. Switch NVP → PI (***)
AZT/3TC/EFV	<ol style="list-style-type: none"> 1. AZT-related persistent GI intolerance or severe haematological toxicity 2. EFV-related persistent CNS toxicity 	<ol style="list-style-type: none"> 1. Switch AZT → D4T 2. Switch EFV → NVP
D4T/3TC/EFV	<ol style="list-style-type: none"> 1. D4T-related neuropathy or pancreatitis 2. D4T-related lipoatrophy 3. EFV-related persistent CNS toxicity 	<ol style="list-style-type: none"> 1. Switch D4T → AZT 2. Switch D4T → TDF 3. Switch EFV → NVP

(*) Switching off D4T typically does not reverse lipoatrophy but may slow its progression. TDF can be considered as an alternative but availability is currently limited. In the absence of TDF availability, ddI or AZT are additional alternatives to consider.

(**) In first trimester pregnancy switch to LPV/r or possibly ABC.

(***) PI can be LPV/r or IDV/r.

(Adapted from WHO: *Scaling Up Antiretroviral Therapy in Resource Poor Settings*, 2006 revision.)

1.16 Food and medication interactions

Due to HIV's impact on the body's immune system, persons infected with HIV are more prone to opportunistic infections than healthy individuals. Furthermore, a low CD4 count and/or high viral load greatly increases one's chances for infections. While antiretroviral therapy (ART) provides the body with tremendous benefit in increasing CD4 levels, decreasing viral load, and reducing the number of infections, special nutrition considerations must be taken when prescribing ART to clients.

In addition, PLWHAs may take other medications with ART, such as antibiotics to treat opportunistic infections, anti-malarial, anti-helminthic (worm) or anti-fungal medications to treat other conditions such as malaria, intestinal parasites, and thrush. Many of these medications may interact with each other, or with specific nutrients or types of foods. These

interactions can reduce the effectiveness of the medication, or cause adverse reactions (side-effects) that cause individuals to stop taking them or become sicker.

To minimise the negative effects of food-medication interactions and to maximise the benefits of available medications and nutrients, it is important to know about food and medication interactions and how to manage them to improve the health of the client.

Foods and medications can interact in a number of ways that result in both positive and negative health and nutritional outcomes in people living with HIV/AIDS. Interactions between medications and food are as follows:

- The effect of certain foods on how medicine works in the body.
- The effect of certain medicine on how food is used in the body.
- The side-effects of a medication, which, in turn, can affect food intake and nutrient absorption.
- Unhealthy side-effects caused by combinations of certain medications and foods.

Proper nutrition management interventions can help alleviate some of these negative effects and can help people living with HIV/AIDS maintain adequate food and nutrient intake.

1.16.1 The effects of food on how medications work

Food can enhance or inhibit the absorption, metabolism, distribution, and excretion of medication and, therefore, affect the medication's efficacy and the overall health of the individual. For example, food decreases the absorption of didanosine (ddl). Medications such as isoniazid may interfere with the metabolism of vitamin B6, and sulfadoxine may interfere with the metabolism of folic acid. In addition to interactions, proper food intake can simply help medications work better in the body and prevent debilitating side-effects, such as nausea, diarrhoea, and mouth sores. Nutrition management may require micronutrient supplements or increased food intake, especially if there is a need to compensate for a depleted nutrient.

1.16.2 Side-effects of medications and food

Medications may cause side-effects that affect food intake and nutrient absorption in the following ways:

- Side-effects of medication, such as taste changes, loss of appetite (i.e., anorexia), nausea, bloating, heartburn, constipation, vomiting and diarrhoea reduce food intake or nutrient absorption.
- Reduced food intake and poor nutrient absorption can lead to weight loss.
- Weight loss leads to further weakening of the immune system.
- A weakened immune system allows HIV to progress to AIDS more rapidly.

Proper nutrition management can help maintain food intake, compensate for nutrient losses, prevent weight loss and improve the condition of the patient. Proper nutritional management can also improve adherence to the regimen. When not properly managed, side-effects often lead to the interruption of treatment and contribute to poor adherence. For these reasons, nutrition counselling should be provided to all clients on ART from the start of therapy. Health workers and counsellors should provide clients with dietary guidance that is specific to the patient's situation.

1.16.3 Multiple medications taken in combination

Treatment of AIDS may require taking many pills on a daily basis, which can make it difficult to maintain food intake. If medications make it difficult to eat, a person is less likely to strictly adhere to the medication regimen, and this can lead to resistance to the medicine, especially in the case of ART. Furthermore, multiple medications have multiple food-medicine and medicine-medicine interactions. The resultant side-effects may require setting specific timings

for taking ARVs, and identifying recommended foods and foods to be avoided, for each medicine. Health workers should spend enough time with the patient to provide advice on all the medicines taken and counsel on the nutrition management of the side-effects and the interactions with food.

Medication interactions need to be managed adequately in order to ensure that the prescribed medicine combination does not reduce the efficacy of the medication or increase the side-effects and affect nutritional status.

To provide counselling for clients on antiretroviral therapy, health workers should:

- Always promote and encourage optimal nutrition intake with a variety of foods every day.
- Discuss ART and food interactions with the client before they begin treatment.
- Ask the client about food availability and access at the household level. Address such issues with referrals to community-based projects, or other assistance.
- Use the Food and Medication Intake Form to assist in counselling the client on the importance of food intake with ART.
- Identify medications that have special food interactions – such as didanosine (ddl), which must be taken either 1 hour before or 2 hours after a meal.
- Identify potential nutrition-related side-effects with ART and provide counselling on management of side-effects.

1.17 Traditional therapies and supplements

Traditional therapies and supplements for PLWHA should be used with caution and guidance from health workers. Some traditional herbs can help enhance the flavour of foods, but when taken in large quantities and with less balanced meals, can potentially interact poorly with medications.

Considerations when discussing traditional therapies and supplements with clients:

- Multi-mineral supplements (multivitamins) as prescribed by a health worker are acceptable for PLWHA to take on a daily basis to prevent micronutrient deficiencies.
- Other supplements in pill form that claim to boost the immune system or cure diseases should be discouraged as these are often very expensive and tend to replace nutritious foods.
- Traditional herbs and remedies are acceptable to use, but should always be used with caution when taking multiple medications. Always use herbs and remedies in their natural form, not in pill form or in high quantities relative to other foods.
- Herbs and supplements (even if prescribed by a doctor) should never replace nutritious foods.

1.18 Prophylaxis of opportunistic infections

1.18.1 Cotrimoxazole prophylaxis

- Daily cotrimoxazole reduces the risk of death and hospitalisation of persons with HIV. In several African countries, different studies have shown that it has reduced overall mortality, hospitalisations, cases of pneumocystis pneumonia, cases of toxoplasmic encephalitis, malaria episodes, bacterial infections including bacterial pneumonia, bacterial diarrhoea and bacteraemia, and it may reduce diarrhoea from *Isospora* sp. Cotrimoxazole also reduces morbidity and mortality in TB patients who are co-infected with HIV. Cotrimoxazole prophylaxis (two x 400/80mg tablets - 800/160mg total - daily) is recommended for persons with HIV and either WHO Clinical Stage 3 or 4 disease (see Appendix 1) or a CD4 cell count ≤ 300 (Table 11).

1.18.2 Isoniazid (INH) preventive treatment of tuberculosis (TB-IPT)

TB-IPT is very effective in preventing TB disease in individuals who have latent TB infection. Persons who qualify for TB-IPT include:

- HIV-positive persons in whom active TB disease has been excluded.
- 0 to 5 years old children who are close contacts of patients with infectious TB.
- Close contacts of a smear positive TB patient who have medical conditions that suppress the immune system, such as Hodgkin's disease, leukaemia, or diabetes mellitus, or who have been on immunosuppressive therapy like chronic steroids or cancer chemotherapy.

Individuals with both HIV infection and latent TB infection have a 5-10% risk of developing active TB disease each year, compared to HIV-negative individuals, whose lifetime risk is 10%. The combination of HIV and TB is one of the major causes of death in Namibia. Six months of daily isoniazid (INH) reduces the risk of TB disease in HIV-infected patients by at least 60%. The safety of TB-IPT has been well established in pregnancy and in children. Risks of TB-IPT include INH-induced hepatitis, inadequate treatment of persons with active TB, with the potential development of INH resistance in such persons. Following the strict criteria for TB-IPT eligibility, along with proper monitoring and follow-up, will minimise these risks. Patients who have signs and symptoms of active TB, however, should never be started on TB-IPT due to the potential risk of selecting for INH resistant TB. Patients with active TB need to be treated with the appropriate regimen of directly-observed TB treatment.

To qualify for TB-IPT the HIV-positive individual must:

- Be healthy.
- Have no symptoms or signs of TB – cough, fever, weight loss, night sweats, fatigue, blood in sputum, chest pain, diarrhoea, shortness of breath, chronically enlarged lymph nodes, loss of appetite.
- Have no history of alcoholism.
- Have no history of active liver disease, liver insufficiency, or jaundice.
- Have no history of INH hypersensitivity.
- Have no history of exfoliative dermatitis.
- Be motivated for TB-IPT after being educated about the benefits and possible side-effects and risks.

Precautions:

- Persons starting TB-IPT must be warned about the possible side-effects of TB-IPT. INH-induced hepatitis will present with nausea and vomiting accompanied by passing dark urine and/or generalised itching. If these symptoms develop, the patient must stop taking INH and report immediately to the nearest health facility for assessment and management.
- Health workers should always check clients for signs and symptoms of hepatitis and skin itching when they come to collect isoniazid.

Treatment:

- Isoniazid is given daily for a period of 6 months at a dosage of 5mg/kg bodyweight up to a maximum of 300mg/per day.
- Pyridoxine 10mg/day is administered with the INH to decrease the risk of neuropathy. The risk of developing neuropathy increases in patients also on D4T.
- Temporary TB treatment interruption, although not ideal, is acceptable, as long as the patient completes 6 months of treatment within 9 months.

Recording and reporting:

All details of the person receiving TB-IPT must be recorded as required on:

- Client TB-IPT identity card:
 - Personal details, registration number and attendance for isoniazid collection.

- TB-IPT clinic register.

Only one 6-month course of TB-IPT is given to an individual patient. Its efficacy lasts for approximately two years, after which a PLWHA has the same risk of developing TB disease as before the TB-IPT. High risks of reinfection and high susceptibility for TB infection and disease in HIV-positive persons are the cause of this limited efficacy. Currently, there is no recommendation to repeat TB-IPT after two years.

1.18.3 Malaria intermittent presumptive treatment during pregnancy (IPT)

Pregnant women without HIV should take two doses of sulfadoxine-pyrimethamine, one month apart, during pregnancy to reduce their burden of malaria and reduce the chance of a low birth weight infant. Pregnant HIV-positive women at WHO Clinical Stage 1 or 2 and CD4 counts > 300, and who are therefore not on cotrimoxazole, should take three doses of sulfadoxine-pyrimethamine, one month apart. Pregnant HIV-positive women on cotrimoxazole, however, should not take sulfadoxine-pyrimethamine as the cotrimoxazole already is a form of malaria prophylaxis.

Table 11. Prevention of opportunistic infections in adults and adolescents

Pathogen	Indication	Medicine and dose	Discontinuation
Pneumocystis pneumonia and toxoplasmosis	<ul style="list-style-type: none"> • CD4 ≤ 300 • WHO Clinical Stage 3 or 4 (AIDS) 	Cotrimoxazole 2 SS (or 1 DS) tab/d (800/160 mg)	CD4 increases to >300 for > 3 months on HAART
TB*	<ul style="list-style-type: none"> • Healthy, no terminal AIDS, no evidence of active TB, no TB treatment in past 2 years, no jaundice or liver insufficiency, no alcoholism, no history of reactions to INH or exfoliative dermatitis 	INH 300 mg/d plus pyridoxine 10 mg/d for 6 months	

*TB prophylaxis should only be considered if active TB has been excluded after thorough clinical evaluation (a chest x-ray [CXR] is not recommended) and adherence can be ensured. Patients should be highly motivated or live under conditions where supervised prophylaxis can be provided (workplaces, prisons, health workers, etc.).

In non-compliant patients, prophylaxis should be discontinued and no further efforts should be made to restart prophylaxis.

1.19 Immune reconstitution

Improvement in a patient's response to antiretroviral therapy (immune reconstitution) is quantitative (CD4 response) and qualitative (antigen/microbe-specific). The clinical impact of immune reconstitution has been demonstrated by:

- The safety of discontinuing prophylaxis for selected OIs.
- The control of several chronic, untreatable opportunistic infections.
- An impressive decline in virtually all HIV-associated complications except lymphomas and liver disease.
- An inflammatory response ascribed to immunologic reactions to selected microbial antigens.

Chronic, relatively untreatable infections that can be controlled with immune reconstitution include molluscum contagiosum, progressive multifocal leukoencephalopathy (PML), cytomegalovirus infections (CMV), cryptosporidiosis, and microsporidiosis. Secondary prophylaxis (suppressive therapy after disease) for opportunistic infections (OIs) may be suspended with adequate criteria for immune reconstitution for virtually all OIs (see Table 12).

1.19.1 Immune Reconstitution Inflammatory Syndrome (IRIS)

This relatively common syndrome results from a dramatic increase in the inflammatory response to antigens from previous, partially treated or latent infections in HIV patients shortly after initiating HAART. It usually occurs in the first few weeks after a patient starts therapy. Patients will present with symptoms that suggest worsening of previously diagnosed opportunistic infections or the development of new infections. Although patients with IRIS appear as though HAART is failing, these patients are actually undergoing robust improvements in their immune systems. Infections which have been associated with IRIS include focal MAC, cryptococcal meningitis with a marked increase in CSF WBCs, mild herpes zoster, PML, CMV vitritis, and progression of TB lesions with sparse organisms. Recommendations for management vary by pathogen and clinical expression, but most involve medications directed against the pathogen with or without anti-inflammatory agents. Common examples are given in Table 12.

Table 12. Immune Reconstitution Inflammatory Syndromes

Opportunistic infection	Clinical features	Treatment
MAC (one form of MOTT)	Focal adenitis, granulomatous masses	MAC therapy: azithromycin 600mg/d plus ethambutol 15mg/kg/day plus steroids Stop treatment when CD4 counts > 100
CMV	Vitritis	CMV therapy: intraocular ganciclovir implant (<i>Vitrasert</i>) + oral valganciclovir 900 mg/day plus local steroids. Stop treatment when CD4 counts > 100
TB	Pneumonitis, lymphadenitis, sparse acid-fast bacillus (AFB)	TB treatment \pm steroids
Cryptococcosis	Meningitis with high CSF WBC	Antifungal therapy: amphotericin B IV 0.7-1 mg/kg for 2 weeks, followed by fluconazole 400 mg/d for 8 weeks. Maintenance: fluconazole 200 mg/d Stop treatment if CD4 > 100 for 6 mo
HBV	Active hepatitis, cirrhosis	Lamivudine plus tenofovir
Herpes zoster	Mild disease	Symptomatic treatment. (oral acyclovir where indicated)
Progressive multifocal leukoencephalopathy (PML)	Neurologic deficits, MRI with peripheral enhancement	Continue HAART

1.20 Special populations

1.20.1 People with tuberculosis and HIV co-infection

The close association between TB and HIV/AIDS is well-established. According to the World Health Organization, in 2005 the case notification rate of new and relapsed cases of TB in Namibia was 735 per 100,000 persons. Of the new adult TB cases (aged 15-49 years), 56% tested HIV-positive. (Source: http://www.who.int/GlobalAtlas/predefinedReports/TB/PDF_Files/nam.pdf.) In Namibia, TB is the most common opportunistic infection in individuals who are HIV-positive. Therefore, HIV/AIDS and TB care need to be integrated at the service provision level to ensure comprehensive care. In addition, health workers caring for TB

patients must have a good working knowledge of the care of HIV/AIDS patients and likewise, health workers caring for PLWHAs must have knowledge of TB.

In March of 2006, the Ministry of Health and Social Services released the second edition of *The National Guidelines for the Management of Tuberculosis*. This important document contains comprehensive sections on the management of TB/HIV co-infection. Clinicians are strongly urged to familiarise themselves with this document and to follow the National TB guidelines when caring for co-infected patients.

Pulmonary tuberculosis is a WHO Clinical Stage 3 disease, while extra-pulmonary TB is Clinical Stage 4. Individuals with either diagnosis are eligible for HAART, regardless of CD4 count. Standard TB treatment is used for patients with HIV. In order to reduce the risk of toxicity and to maximise adherence, it is recommended, whenever possible, to postpone HAART until the initial intensive phase of TB treatment with four medications is completed. At that time, when TB treatment is reduced to INH plus rifampicin, it should be easier and safer for the patient to begin HAART. Because severe illness from TB can also lower CD4 cell counts, some patients will have an increase in their CD4 cell counts from treatment of TB even without HAART. Patients with a CD4 cell count >350 after 2 months of TB treatment may elect to postpone HAART and instead have follow-up CD4 counts every 6 months.

Rifampicin, an important component of TB treatment, interacts with many medications, including many ARVs. Therefore, only certain HAART regimens can be used in combination with TB therapy. Rifampicin decreases blood levels of protease inhibitors by approximately 80%, nevirapine by 30-50%, and efavirenz by 25%. This effect on efavirenz is not clinically significant and efavirenz can be used with rifampicin. At standard doses, efavirenz (EFV) in combination with zidovudine-lamivudine (AZT/3TC) or stavudine/lamivudine (D4T/3TC) is effective. Once treatment with rifampicin has ended, the less expensive nevirapine can be substituted for efavirenz (using the usual 2-week 200 mg once daily induction phase of nevirapine while continuing the NRTIs). Caution must be taken, however, in those patients who have had a robust response in their immune systems, as switching to NVP in men with CD4 counts >400 and in women with CD4 counts >250 increases their risks of developing severe hepatotoxicity, and switching to NVP is not recommended.

For patients on rifampicin, alternatives to efavirenz are:

1. Triple nucleoside regimens:
 - tenofovir (TDF) + lamivudine (3TC) + zidovudine (AZT) or stavudine (D4T)
 - abacavir (ABC) + lamivudine (3TC) + zidovudine (AZT) or stavudine (D4T)
2. A lopinavir based regimen with high dose ritonavir:
 - AZT +3TC or D4T + 3TC with lopinavir 400mg PLUS ritonavir 400 mg BD (very poorly tolerated).

1.20.2 People with hepatitis B virus (HBV) and HIV co-infection

Namibia has a high prevalence of HBV infection. According to a 1997 study of 1,074 first-time blood donors to the Namibian National Blood Transfusion Service, 14.8% tested positive for markers of current HBV infection and 53 % showed markers for past exposure to HBV (Seidel et al.). Although the prevalence of HIV/HBV co-infection is not known in Namibia, studies in other sub-Saharan African countries have shown that HBV sero-prevalence in HIV positive individuals is at least as high as it is in the general population, suggesting that nearly 15% of all HIV infected persons in Namibia can be expected to be co-infected with HBV (Burnett et al). In addition to the liver damage caused by chronic HBV co-infection, patients on HAART are also at risk for hepatotoxicity associated with many HAART regimens. Patients may also experience accelerated liver damage following immune reconstitution (HBV-associated IRIS). Patients eligible for HAART should be assessed at baseline for hepatitis B surface antigen and ALT. Two ARVs, lamivudine (3TC) and tenofovir (TDF), also have antiviral effects on

HBV. Used together these medications can effectively suppress HBV replication. The combination also decreases the risk of HBV developing resistance to these medications. HBV resistance to lamivudine develops within two years in 50% of HIV/HBV co-infected patients on lamivudine-containing HAART without tenofovir.

Table 13. Recommended first line regimen based on HBsAg and ALT testing

Hepatitis B surface antigen	ALT level	Recommended first line regimen
Negative	< 3x ULN	Zidovudine-lamivudine-nevirapine (AZT/3TC/NVP)
Negative	≥ 3 x UNL	Zidovudine-lamivudine-efavirenz (AZT/3TC/EFV)
Positive	< 3x ULN	Tenofovir-lamivudine-nevirapine (TDF/3TC/NVP)
Positive	≥ 3 x UNL	Tenofovir-lamivudine-efavirenz (TDF/3TC/EFV)

Patients with HIV/HBV co-infection on HAART require close monitoring for clinical signs and symptoms of hepatotoxicity and laboratory monitoring of ALT. Elevated ALT arising during therapy may have many causes, and needs to be carefully evaluated.

Table 14. Common causes of liver disease among HIV-positive persons in Namibia

Category of liver disease	General etiology	Specific etiology	Notes
Hepatocellular disease (↑ALT or ↑AST)	Medication toxicity	ARVs: NVP>>RTV>EFV	See Table 8
	Lactic acidosis with steatohepatitis	NRTIs: D4T>ddI>AZT	See pages 20 -21
	Acute viral hepatitis	Hepatitis A, B	Self-limited
	Chronic viral hepatitis	Hepatitis B, C	ALT may ↑early in effective hepatitis B therapy, with abrupt withdrawal of TDF or 3TC, or with development of resistance to anti-hepatitis B medicines
	Immune Reconstitution Inflammatory Syndrome	Immunologic response to hepatitis B	If severe may have to stop HAART temporarily
	Alcoholic liver disease	Alcoholic steatosis or acute alcoholic hepatitis	Reduce or eliminate alcohol use
Jaundice (↑Bilirubin)	Medication effect	Indinavir	↑ indirect bilirubin with nl ALT and no haemolysis; can continue indinavir
	Severe liver insufficiency	Any cause	↑ direct bilirubin, ↑ ALT/AST, low albumin, prolonged prothrombin time, may have ascites, encephalopathy, GI bleeding
	Severe malaria	Haemolysis rather than hepatitis	↑ indirect bilirubin with anaemia and positive malaria smear
	Biliary tract obstruction	Common bile duct stones, pancreatic cancer, mass in porta hepatis	↑ direct bilirubin, ↑ alkaline phosphatase, nl ALT/AST, sonogram helpful
Infiltrative liver disease	Infections	Extra-pulmonary or disseminated TB, MOTT	↑ alkaline phosphatase, other LFTs nearly normal, hepatomegaly
	Immune Reconstitution Inflammatory Syndrome	Immune response to TB or MOTT	See Table 12
	Malignancies	Hepatoma, lymphoma, liver metastases	Sonogram helpful, liver biopsy diagnostic

1.20.3 People with renal disease

In patients with renal insufficiency or renal failure, ARV dosages need to be adjusted for some medicines on the basis of creatinine clearance (see Appendix 2). Consult with a specialist physician before starting HAART in a patient with renal failure or when renal failure develops in a patient on HAART.

The formula to calculate the creatinine clearance in men is as follows:

$$\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.22}{\text{Serum creatinine in micromoles/L}} = \text{creatinine clearance ml/min}$$

Multiply the above by 0.85 for creatinine clearance in women.

1.21 Non-communicable HIV-associated diseases in Namibia

1.21.1 Common cardiovascular conditions

Non-communicable diseases also affect HIV-infected patients. These diseases include hypertension, diabetes mellitus, and ischaemic and rheumatic valvular heart disease. Generally, cardiovascular conditions – particularly pericarditis and dilated cardiomyopathies – may be HIV-, OI-, or medication-related. Pericarditis may be constrictive or effusive, and is predominately caused by TB. In few cases, it is due to Kaposi's sarcoma and lymphoma. In the cases of dilated cardiomyopathies, it can be following previous myocarditis. Important differential diagnoses consist of:

- Large pericardial effusion.
- Rheumatic valvular heart disease.

The differential is based on new clinical, ECG and chest X-ray features. During the management of large pericardial effusion, pericardiocentesis is performed if there is cardiovascular compromise. Otherwise, TB treatment and steroids are prescribed. In case of dilated cardiomyopathy and conventional cardiac failure, treatment is provided with diuretics, digoxin, ACE-inhibitors, and carvedilol.

Though ischaemic heart disease is rare among black populations, some ARVs, especially PIs, may cause hypercholesterolemia and in the long term could result in premature onset of coronary artery disease or stroke. Therefore, there should be constant screening of such complications with treatment as indicated.

Increased vasculitic events have been noted in HIV/AIDS patients leading to strokes, peripheral arterial occlusions and other vaso-occlusive events.

1.21.2 Haematological conditions

Common problems may present as anaemia, leukopaenia, thrombocytopenia, and pancytopenia. Possible causes are:

- HIV-related bone marrow suppression.
- Medication (ARV, cotrimoxazole, AZT).
- Nutritional.
- Myeloproliferative conditions (leukaemia, lymphoma, KS).
- Infections (TB, CMV, toxoplasmosis).

Necessary investigations:

- Bone marrow biopsy.
- Peripheral blood smear.
- FBC.
- Fe studies, B12, and folate levels, as directed.

Treatments for ITP include steroids and HAART. There is an increased risk of thrombotic events – such as deep vein thrombosis (DVT) – in HIV/AIDS patients, especially with CD4 <200.

1.21.3 Central nervous system conditions

Increased incidents of multipathogenic meningitis:

- Viral meningitis.
- Bacterial meningitis.
- TB.
- Cryptococcus meningitis.
- Neuro-syphilis.
- Aseptic meningitis.
- HIV-specific meningitis – Primary HIV Infection Syndrome.

All unexplained headache and fever symptoms should be investigated for meningitis with lumbar puncture (LP), followed by empiric STAT dose of ceftriaxone (2 grams ivi).

Treatment of neuro-syphilis is benzathine penicillin 2 - 4 million units given IV every 4 hours together with probenecid (500 grams orally 6 hourly) for 10 – 14 days.

Alternative treatments for neuro-syphilis are doxycycline (200 mg BD) for 21 days. Amoxicillin (2g 8 hourly) should be taken with probenecid (500mg 6 hourly for 28 days).

1.21.4 Seizures

Look for space-occupying lesions (SOL) such as those caused by toxoplasmosis. The following may cause seizures:

- Meningitis.
- Metabolic disturbances such as sodium and magnesium.
- Any organ failure (liver, kidney).
- Stroke (haemorrhagic or intact).
- Progressive multifocal leucoencephalopathy (PML).

NOTE: Most anti-epileptic medicines interfere with the plasma levels of ARVs.

Single contrast-enhanced CNS lesions in HIV/AIDS patients could suggest:

- Toxoplasmosis.
- Cryptococcus meningitis.
- Tuberculoma.
- Brain abscess.
- Lymphoma.

If CD4 count is < 200 and toxoseroLOGY is positive, then treat for toxoplasmosis.

If toxoplasmosis is negative and the patient does not respond to empiric toxoplasmosis treatment, then one should treat for tuberculosis meningitis (TBM).

Spinal cord conditions may present as weakness of the limbs in HIV patients:

- Myelopathy, due to TB, *Varicella zoster virus* (VZV), syphilis, or HIV, amongst others.
- Spinal cord compression.
- Spinal root pathologies/radiculopathy/poliomyelitis.
- Neuropathy: Guillain Barre, acute inflammatory demyelinating polyneuropathy (AIDP), or chronic inflammatory demyelinating polyneuropathy (CIDP) – which is steroid responsive, unlike AIDP which does not respond to steroids. Other causes of neuropathies are:
 - HIV-related.
 - Medication-related (INH, cotrimoxazole, D4T, ddl).
 - The use of amitriptyline is preferable to anti-epileptic medicines because of ARV medication interactions.
- Myopathy:
 - HIV-related.
 - Toxoplasmosis.
 - Cytomegalovirus.
 - Cryptococcus.
 - Mycobacterium other than tuberculosis (MOTT).
 - Lymphoma.
 - Medications (esp. AZT).
- Bell's palsy is common among HIV patients and may be VZV-associated: if the patient presents within 48 hours of the onset of symptoms give prednisolone of 50 mg for 5 days.

1.21.5 Confusion/delirium in HIV/AIDS patients

Always suspect and rule out organic causes, such as:

- Primary HIV Infection Syndrome.
- Sepsis.
- Meningitis.
- Metabolic abnormalities including electrolyte disorders.
- Endocrinologic disorders (hypo or hyperglycaemia, hypo or hyperthyroid, and others).
- Organ failure (liver, kidney, stroke).
- Drug withdrawal (ethanol, sleeping tablets, recreational drugs).

1.21.6 Rheumatologic conditions

May present as arthritis, neuritis, or myopathies. Possible causes of arthritis:

- HIV-associated arthritis.
- Septic arthritis.
- Syphilitic arthritis.
- Reactive arthritis.
- Osteoarticular TB.
- Sero-negative reactive arthritis (Reiter's Syndrome).
- Psoriatic arthritis.
- Osteomyelitis (TB, bacterial).
- ARV-related.

1.22 When to consult a specialist

Good collaboration between general practitioners and clinical specialists is essential for the establishment of successful and durable antiretroviral therapy. In the following circumstances consultation with a specialist is recommended:

- Co-morbid pathologies (hepatitis, renal failure, diabetes, neoplasia, etc.).
- Severe medication toxicities.
- Failure of, or severe toxicity with, first line therapy and consideration of second line therapy.
- Discordant couples considering having children.
- Pregnant women receiving any other treatment than the recommended regimens: zidovudine-lamivudine-nevirapine (AZT/3TC/NVP), or stavudine-lamivudine-nevirapine (D4T/3TC/NVP) for women with anaemia.

PART 2: Prevention of Mother-to-Child Transmission (PMTCT)

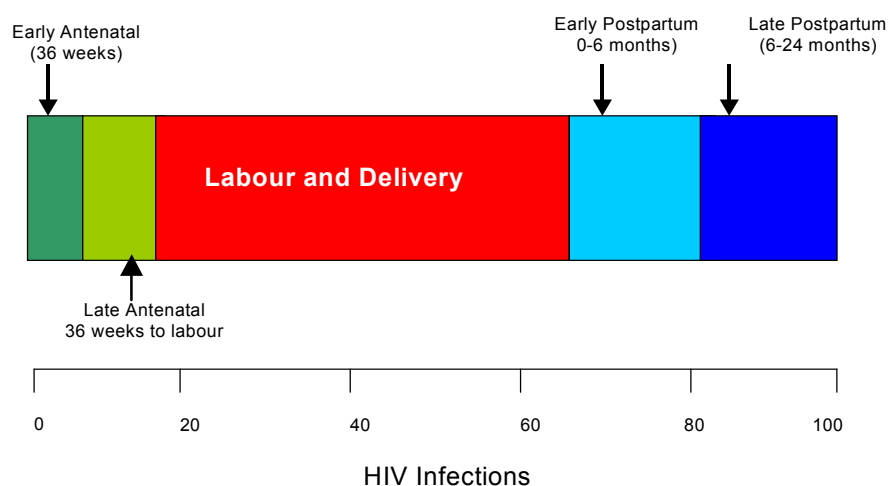
2.1 General considerations

PMTCT includes 3 main strategies:

1. Primary prevention of HIV in women of reproductive age.
2. Prevention of unintended pregnancy in HIV-infected women.
3. Provision of ARV medications to pregnant, HIV-infected women. This strategy is covered in this chapter. Adjustments in obstetrical and infant feeding practices are also important for PMTCT and are briefly described.

In the absence of antiretroviral medicines and with breastfeeding, published estimated rates of mother-to-child transmission (MTCT) of HIV range from 21% to 43% in various African settings. When it occurs, most transmission takes place during labour and delivery, followed by transmission in the uterus and through breastfeeding, depending on duration. The longer the child is breastfed, the greater the risk of HIV transmission.

Figure 3. Timing of mother-to-child transmission with breastfeeding and no ARVs



(Adapted from Bertolli et al., *Estimating the timing of mother-to-child transmission of human immunodeficiency virus in a breast-feeding population in Kinshasa, Zaire*. J Infect Dis. 1996 Oct. 174(4): 722-6.)

The main factors that increase the risk of mother-to-child transmission include:

- High viral load in the mother, although transmission can occur at any level.
- Advanced HIV/AIDS, as measured by low CD4 count, although transmission can occur at any level.
- Invasive obstetrical practices, such as episiotomy, prolonged rupture of the membranes (>4 hrs), and mode of delivery (vaginal delivery is associated with a higher risk of MTCT than a scheduled Caesarean section before the onset of labour).
- Duration of breastfeeding and conditions of the breast (e.g., mastitis, cracked nipples).
- Presence of other genital tract infections (STIs).

Numerous clinical trials have demonstrated that the appropriate use of ARVs can be highly efficacious in reducing the risk of MTCT. All pregnant women should undergo voluntary counselling and testing at their first antenatal visit and further counselling and clinical care during at least three follow-up visits in order to optimise antenatal care, provide an appropriate antiretroviral regimen, and promote safe feeding practices.

2.2 Management of ARVs in pregnancy according to clinical scenarios

This following section is adapted from the MoHSS *Guidelines on Prevention of Mother to Child Transmission of HIV*.

Scenario 1: HIV-infected pregnant women already on HAART during current pregnancy

HAART regimens in pregnant women achieve efficacy for PMTCT through significant reductions in maternal viral load. For women already receiving HAART and who become pregnant, continuation of HAART with a recommended regimen for pregnant women is the best option for mother and child. Not all HAART regimens, however, are safe or recommended in pregnant women.

All recommended regimens consist of two nucleosides and a potent third medicine to complement it. Because some patients will not tolerate the recommended first line therapy, clinicians providing HAART should be familiar with the various regimens.

The most widely used ARV therapy regimens in pregnant women include zidovudine-lamivudine (AZT/3TC), in combination with nevirapine (NVP), or lopinavir/ritonavir (LPV/r). These combinations are recommended by WHO.

Note:

- *Although the combination of stavudine-didanosine (D4T/ddI) should NEVER be used, it is even more important that this combination is avoided in pregnant women due to the increased risk of lactic acidosis.*
- *Efavirenz (EFV) should not be used in the first trimester of pregnancy due to the potential teratogenic effects on the foetus.*
- *Women who cannot tolerate nevirapine (NVP) should be given lopinavir/ritonavir (LPV/r).*
- *Women on HAART should be counselled about potential risks and benefits of continuing therapy during the first trimester. If therapy is discontinued during the first trimester, stop the ARVs per protocol (section 1.15, page 22) and restart the same ARVs regimen in the second trimester as long as the medicines are not contraindicated in pregnancy. If the pregnancy is identified after the first trimester, continue with treatment.*

Consult a specialist physician if HAART in a pregnant woman needs to be switched or interrupted.

Scenario 2: HIV-positive pregnant women who have not received prior antiretroviral therapy but need it for their own health

For HIV-positive pregnant women who have not received ARV therapy, follow Figure 3 to determine if she qualifies for ARV therapy. The use of ARV therapy during pregnancy, when indicated, will improve the health of the mother and substantially decrease the risk of transmission of HIV to the infant. If she does not qualify for ARV therapy, she should receive a short course ARV regimen for PMTCT.

Pregnant women should be started on ARV therapy if they meet the following criteria:

- WHO Stage 3 or 4 HIV disease irrespective of CD4 cell count.
- WHO Stages 1 or 2, with a CD4 cell count below 250/mm³.
- Social criteria, which include the following:
 - Lived in a stable residence for the past 3 months.
 - Are not acutely abusing alcohol or other substances.
 - Have access to the ART clinics for follow-up.
 - Patient is committed to long-term ARV therapy, adherence to treatment, practising safe sex, and allowing home visits if indicated.
 - Patient has identified someone at home, in the community, or at the workplace to serve as a therapy supporter.

**The first line regimen for HIV-positive pregnant women who do not have active TB and meet the eligibility criteria for HAART is:
zidovudine-lamivudine-nevirapine (AZT-3TC-NVP).**

The dosages for the first line HAART regimen in pregnant women are:

- i. Zidovudine (AZT) 300 mg twice daily. Monitor haemoglobin levels.
- ii. Lamivudine (3TC) 150 mg twice daily.
- iii. Nevirapine (NVP) 200 mg daily x 14 days, then 200mg twice daily. Monitor alanine amino transferase (ALT) levels.

HAART should be started in the second trimester unless the patient is severely ill with advanced HIV disease, in which case HAART should be started as soon as possible. Prior to initiation of therapy, assessment must be done for medical contraindications to the regimen.

ARVs should be continued as usual during labour and the postpartum period. Special attention should be made to watch for the following side-effects:

- Nevirapine-related liver toxicity and skin rash.
- Zidovudine (AZT) should not be used in women with Hb ≤ 7 g/dl. They should receive stavudine (D4T 30mg) twice daily as well as appropriate management of underlying causes of anaemia.

Scenario 3: HIV-infected pregnant women who do not qualify for HAART but present at ANC

HIV-positive pregnant women who are not yet eligible for HAART on the basis of their disease status should be offered a short course ARV regimen for PMTCT.

Antepartum: AZT from 28 weeks or as soon as possible thereafter.

- Only pregnant women living with HIV with Hb >7 g/dl will receive the AZT regimen.
- If the Hb is ≤ 7 g/dl, then focus on identifying the cause of anaemia and treat. Once the Hb is corrected AZT can be started.
- Women on the AZT regimen will be seen at the ANC every two weeks and will receive their supply during these visits.
- Hb will be monitored at the clinic at each visit. If the Hb falls below 7g/dl AZT will be stopped.
- AZT tablets will be monitored at each visit (pill count method).

Intrapartum: AZT/3TC+single dose nevirapine at the onset of labour.
If AZT is contra-indicated, then administer single dose nevirapine alone.

Postpartum: AZT/3TC for 7 days for the mother.
If mother's Hb ≤ 7 g/dl before delivery then do not administer AZT/3TC postpartum.

Infant: Single dose nevirapine 2mg/kg within 12-72 hours + AZT 4mg/kg + 3TC 2mg/kg BD for 7 days.

See Figure 5 below for guidance on use of AZT antepartum in HIV-positive pregnant women with anaemia.

Scenario 4: HIV-infected pregnant women who present at maternity ward and have received no ARVs during their pregnancy

Intrapartum: AZT/3TC + single dose nevirapine at the onset of labour.

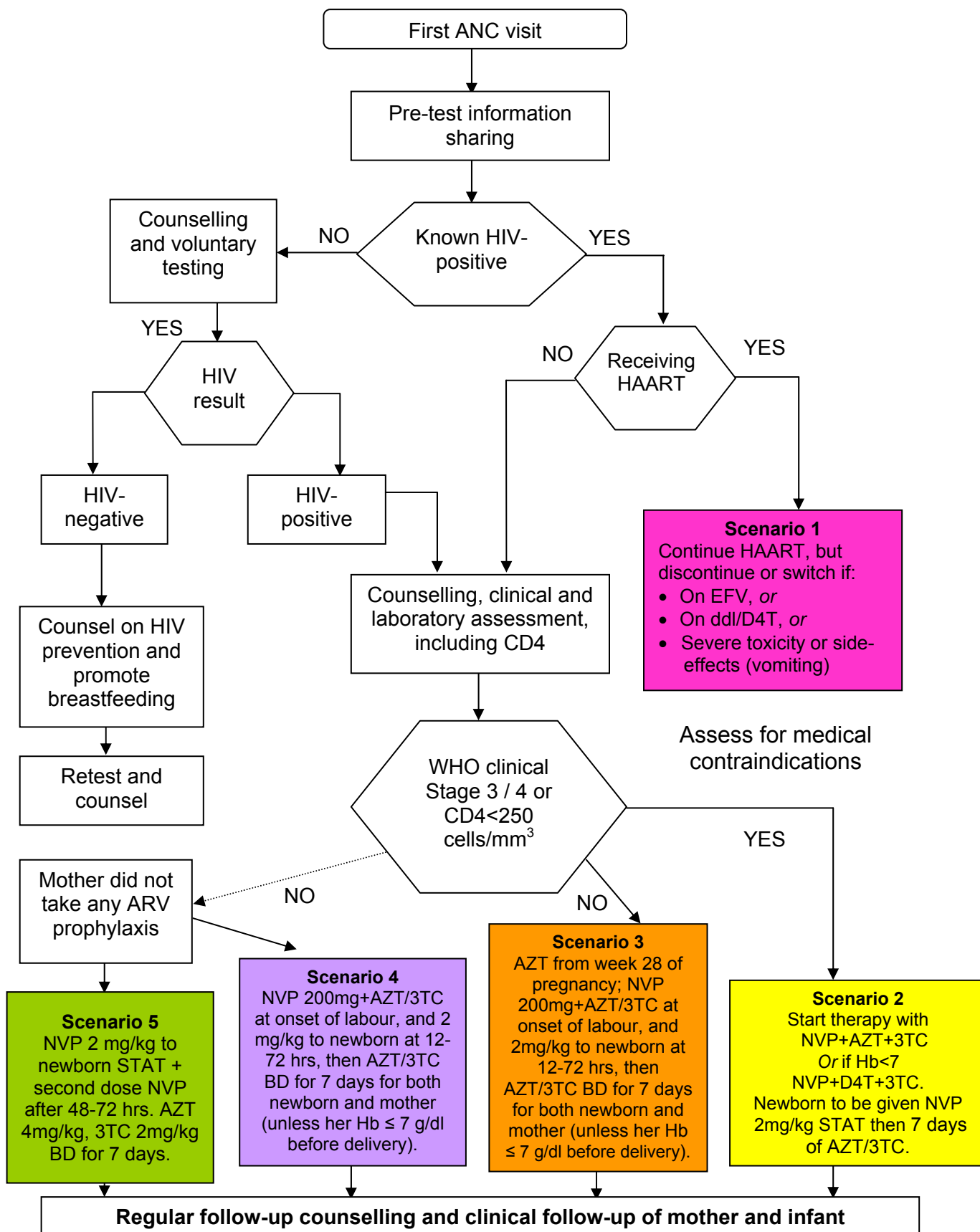
Postpartum: AZT/3TC BD for 7 days for the mother.
If mother's Hb \leq 7g/dl before delivery then do not administer AZT/3TC postpartum.

Infant: Single dose nevirapine 2mg/kg within 12-72 hours + AZT 4mg/kg + 3TC 2mg/kg BD for 7 days.

Scenario 5: Infants born to HIV-infected mothers who received no ARV medicines during pregnancy or labour

- Newborns who present at less than 24 hrs of age should receive a STAT dose of nevirapine 2mg/kg and a second dose 2mg/kg at 48-72 hrs. In addition, the infant should be given AZT/3TC for 7 days (AZT 4mg/kg + 3TC 2mg/kg every 12 hours).
- Newborns who present at more than 24 hrs of age but less than 72 hours of age should receive a single dose of nevirapine 2mg/kg plus AZT/3TC for 7 days (AZT 4mg/kg + 3TC 2mg/kg every 12 hours).
- Newborns who present more than 72 hours after birth do not benefit from PMTCT prophylaxis and should not receive any ARVs.

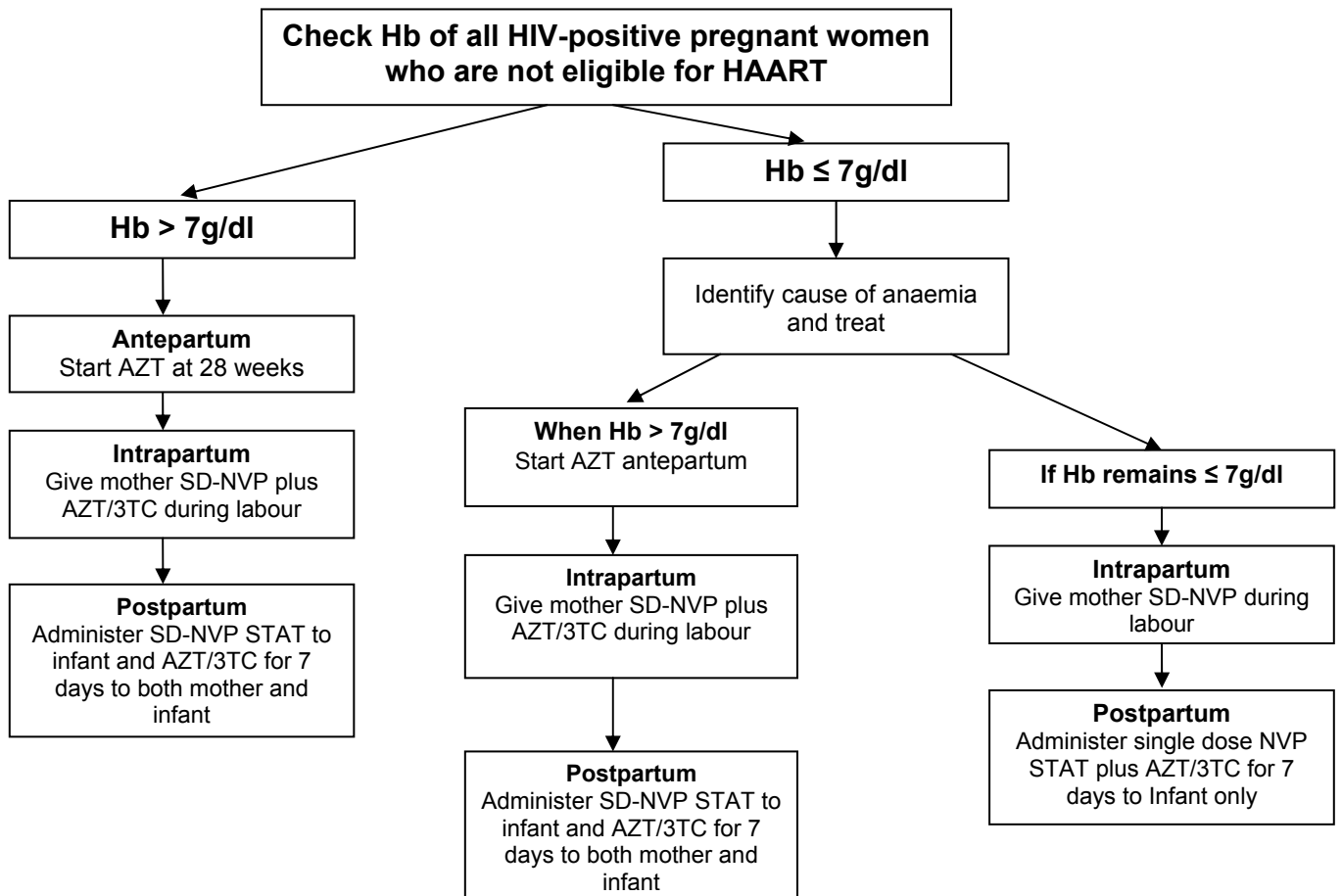
Figure 4. Algorithm for the use of ARVs for HAART or PMTCT in pregnant women



EFV = efavirenz AZT = zidovudine
 D4T = stavudine NVP = nevirapine
 3TC=lamivudine

For those on TB treatment, a special regimen is required. See text.

Figure 5. Algorithm for use of ANC AZT in HIV-positive women not eligible for HAART



2.3 Clinical monitoring for pregnant women placed on HAART

2.3.1 Baseline clinical assessment

The baseline medical history should include:

- Essential demographic characteristics.
- The past medical history including major illnesses, hospitalisations and surgeries.
- The length of time since the diagnosis of HIV infection.
- Current medications.
- Review of symptoms.

The baseline physical examination should include:

- Vital signs
- Weight
- Height, and detailing any abnormalities of the:

– Eyes	– Lymph nodes
– Abdomen	– Nervous system
– Oropharynx	– Lungs
– Extremities	– Genital tract
	– Heart

Once HAART has commenced, clinical monitoring must include follow-up visits at two, four, and six weeks after initiation and a minimum of every three months thereafter for clinical and laboratory monitoring.

Patients should be assessed by a trained member of staff every month – this visit should include medicine dispensing, monitoring and reinforcement of adherence, and identifying problems requiring referral. At each visit the health worker must assess adherence to treatment, and note any new symptoms that may be related to medicine side-effects, HIV disease progression, or opportunistic infections.

2.3.2 Clinical monitoring for toxicities and effectiveness of ARVs in pregnant women

Patients should be informed about the symptoms of ARV medicines side-effects/toxicities and should be educated regarding the need to seek care. Clinical evaluation of the effectiveness of ART is important. The basic parameters examined and documented should include:

- The patient's perception of how she is doing on therapy.
- Changes in body weight over the course of therapy/pregnancy.
- Signs of immune reconstitution inflammatory syndromes.
- HIV-related disease progression.
- Signs of medicine toxicities.
- Decrease in symptoms of HIV disease and an improved quality of life.

2.3.3 Baseline laboratory assessment

Baseline laboratory assessment for HIV-infected pregnant women prior to starting ARV therapy:

- HIV antibody
- HBsAg (hepatitis B surface antigen)
- CD4 count
- ALT
- FBC
- Creatinine
- RPR
- Blood glucose

Refer to pages 14-18 for the detailed schedule of laboratory tests to be performed for each different HAART regimen.

2.4 Management of pregnant HIV-positive women with concurrent diseases

2.4.1 Tuberculosis

It is preferable that pregnant women should complete their TB treatment before they start on HAART. One of the major problems with treating TB and HAART are the high number of interactions and side-effects from the medicines, as well as the very high pill burden.

Pregnant women with TB disease should if possible complete their TB therapy prior to beginning HAART.

1. CD4 >350mm³

- Treat TB.
- Monitor CD4 counts and reassess need for HAART after completion of TB treatment.

2. CD4 200-350mm³ or pulmonary TB

- Treat TB.
- Postpone HAART until after TB treatment.

3. CD4 50-200/mm³ or extra-pulmonary TB

- Start TB treatment.
- Start HAART after 2 months of TB therapy.
- If in 2nd trimester of pregnancy use AZT/3TC + efavirenz.
- Before 2nd trimester, consider a triple NRTI regimen such as AZT/3TC + ABC. Consult a specialist.

4. CD4 <50/mm³

- Start TB therapy.
- Evaluation at 2 weeks.
- Start HAART as soon as TB therapy is tolerated.
- If in 2nd trimester of pregnancy use AZT/3TC + efavirenz.
- Before 2nd trimester, consider a triple NRTI regimen such as AZT/3TC + ABC. Consult a specialist.

2.4.2 Hepatitis B

Limited studies have shown that there is a high prevalence of HBV among Namibians with HIV (see section 1.20.2, page 29). Among patients on effective HAART, liver disease is one of the most common complications due to the hepatotoxicity of many HAART regimens, as well as accelerated liver damage following immune reconstitution.

Lamivudine and tenofovir have an antiviral effect on HBV. The combination of these medicines reduces the development of viral resistance of HBV. All ARV medicines are potentially hepatotoxic. Among the NNRTIs, efavirenz is the best tolerated in patients with HBV. The use of tenofovir (TDF) is generally not recommended in pregnancy due to the risk of bone demineralization in the foetus. If a pregnant woman is already on a TDF/3TC based regimen, however, then it is preferable to continue this regimen to prevent flaring up of the hepatitis B during pregnancy.

1st trimester:

First line: AZT/3TC/ABC

If the patient can't tolerate ABC due to hypersensitivity, and provided ALT is < 3 times the upper limit of normal (ULN) and there is no clinical evidence of active hepatitis, then use AZT/3TC/LPV/r.

If the woman is still in the first trimester, can't tolerate ABC, and has active hepatitis or ALT is $\geq 3 \times$ ULN, then consult with a specialist.

After 1st trimester:

First line: AZT/3TC/Efavirenz

2.4.3 Renal failure

In patients with renal failure, dosages need to be adjusted for some medicines on the basis of creatinine clearance.

Table 15. Use of ARVs in patients with renal failure

Dose adjustment needed	No dose adjustment needed
Lamivudine	Abacavir
Didanosine	Efavirenz
Stavudine	Nevirapine
Tenofovir	Indinavir
Zidovudine	Lopinavir/ritonavir
	Ritonvir

Consult with a specialist physician before starting HAART in a patient with renal failure or when renal failure develops in a patient on HAART. Tenofovir can cause a Fanconi-like syndrome. This is asymptomatic and can be monitored by checking for proteinuria and elevated creatinine.

Refer to section 1.20, page 28, for more detailed coverage regarding the use of ARVs in "Special Populations".

2.5 When to consult a specialist

In the following circumstance, consult a specialist:

- Failure of first line therapy.
- Discordant couples considering having children.
- Combined pathologies (TB, hepatitis, renal failure, diabetes, neoplasia, etc.).
- Severe medicine toxicities.
- Pregnant women receiving any other treatment than the recommended ones.

PART 3: Children

3.1 The natural course of HIV disease in children

Children may be infected with HIV during pregnancy, during delivery, or postnatally (through breastfeeding). Left untreated, the mortality rate from HIV/AIDS is approximately 30% by age 1 year, 50% by age 2, and 60% by age 3. The mortality rate from untreated HIV/AIDS is highest at < 18 months of age, when the diagnosis is most difficult due to transplacental transfer of maternal antibodies to the infant.

HIV RNA levels in perinatally infected infants are generally low at birth (i.e., <10,000 copies/ml), increase to high values by age 2 months and then decrease slowly after the first year over the next few years of life. This pattern probably reflects the lower efficiency of an immature but developing immune system in containing viral replication and possibly a greater number of HIV-susceptible cells (see Table 16).

CD4 T-lymphocyte counts and percentage values in healthy infants who are not infected with HIV are considerably higher than those observed in uninfected adults and slowly decline to adult values by age 6 years. A paediatric clinical and immunologic staging system for HIV infection has been developed that includes age-related definitions of immune suppression. Although the CD4 absolute number that identifies a specific level of immune suppression changes with age, the CD4 percentage that defines each immunologic category does not. Thus, a change in CD4 percentage, not number, should be used to monitor disease progression in children.

Table 16. HIV Paediatric classification: immune categories

Classification of HIV-associated immunodeficiency	Age-related CD4 values			
	≤ 11 months (%)	12 - 35 months (%)	36 - 59 months (%)	≥ 5 years (cells/mm ³)
Not significant	≥ 35	> 30	> 25	> 500
Mild	30-35	25-30	20-25	350-499
Advanced	25-29	20-24	15-19	200-349
Severe	< 25	< 20	< 15	< 200 or < 15%

NOTE: CD4 cell values can be associated with considerable variation due to minor infections and immunisations, and are therefore best measured when patients are clinically stable.

Table 17. WHO Clinical Staging of HIV in infants and children

<p>Clinical Stage 1 (Asymptomatic)</p> <ul style="list-style-type: none"> – Asymptomatic – Persistent generalised lymphadenopathy
<p>Clinical Stage 2 (Mild)</p> <ul style="list-style-type: none"> – Unexplained persistent hepatosplenomegaly – Papular pruritic eruptions – Extensive wart virus infection – Extensive molluscum contagiosum – Recurrent oral ulcerations – Unexplained persistent parotid enlargement – Lineal gingival erythema – Herpes zoster – Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) – Fungal nail infections
<p>Clinical Stage 3 (Advanced)</p> <ul style="list-style-type: none"> – Unexplained moderate malnutrition not adequately responding to standard therapy – Unexplained persistent diarrhoea (14 days or more) – Unexplained persistent fever (above 37.5 °C, intermittent or constant, for longer than one month) – Persistent oral candidiasis (after first 6 weeks of life) – Oral hairy leukoplakia – Acute necrotizing ulcerative gingivitis/periodontitis – Lymph node TB – Pulmonary TB – Severe recurrent bacterial pneumonia – Symptomatic lymphoid interstitial pneumonitis – Chronic HIV-associated lung disease including bronchiectasis – Unexplained anaemia (< 8.0 g/dl), neutropenia (< 0.5 x 10⁹/L³) or chronic thrombocytopenia (< 50 x 10⁹/L³)
<p>Clinical Stage 4 (Severe)</p> <ul style="list-style-type: none"> – Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy – Pneumocystis pneumonia – Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) – Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration, or visceral at any site) – Extrapulmonary TB – Kaposi's sarcoma – Oesophageal candidiasis (or candida of trachea, bronchi or lungs) – Central nervous system toxoplasmosis (after the neonatal period) – HIV encephalopathy – Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month – Extrapulmonary cryptococcosis (including meningitis) – Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis) – Chronic cryptosporidiosis (with diarrhoea) – Chronic isosporiasis – Disseminated non-tuberculous mycobacteria infection – Cerebral or B cell non-Hodgkin lymphoma – Progressive multifocal leukoencephalopathy – HIV-associated cardiomyopathy or nephropathy

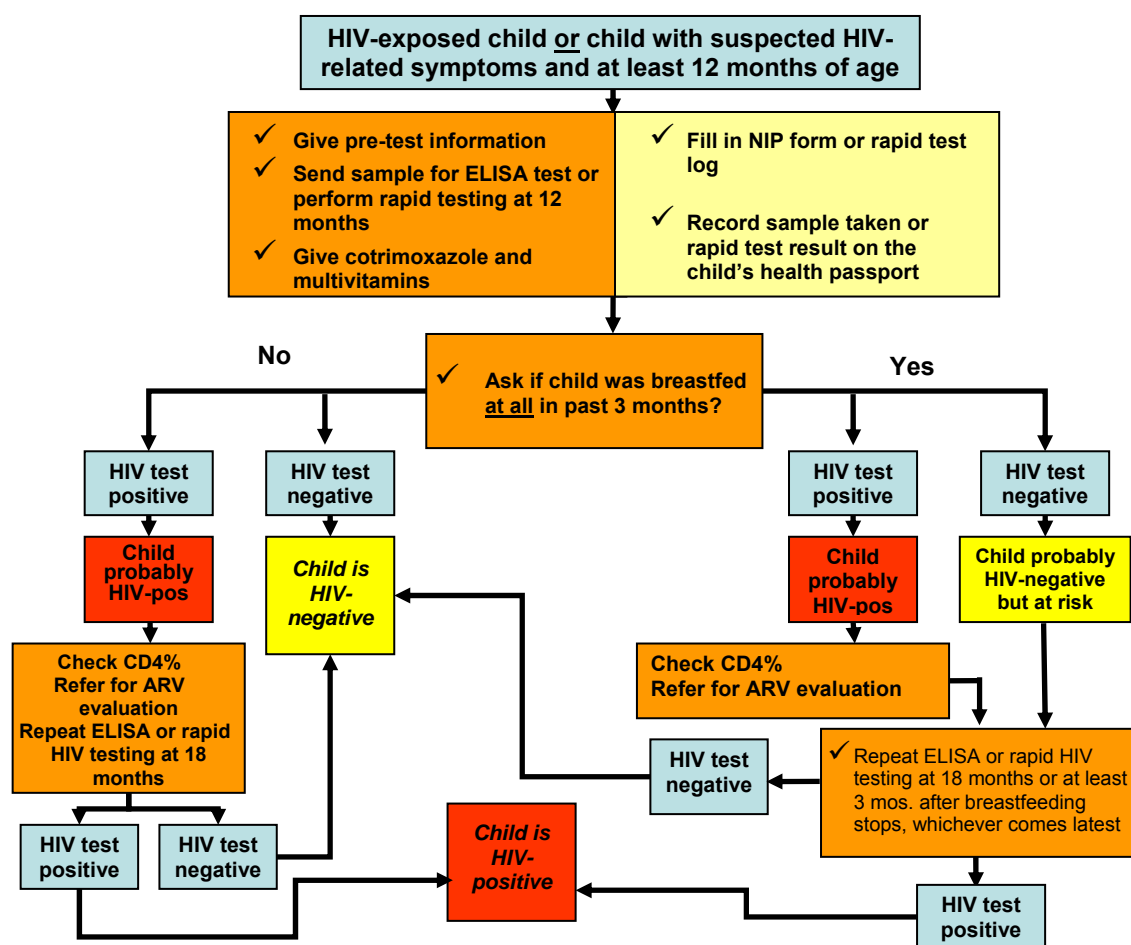
3.2 Diagnosis of HIV infection in children

3.2.1 ELISA or rapid HIV testing

At present, the majority of children are diagnosed on the basis of symptomatic HIV disease and a positive HIV test of the mother or the child. As with adults, either ELISA (enzyme-linked immunosorbent assay) or rapid HIV testing can be used in children. Passively transferred maternal anti-HIV antibodies, however, may persist in a child for up to 18 months. Therefore, to establish a definitive serological diagnosis of HIV infection in a child, an anti-HIV antibody test should be repeated at the age of 18 months. Children > 18 months old who have had prolonged breastfeeding would need to have a negative HIV test result at least 3 months after breastfeeding is discontinued to exclude HIV infection.

The algorithm for HIV diagnosis using ELISA or rapid testing is outlined in Figure 5. In summary: using either ELISA or rapid HIV testing at 12 months of age or older, diagnosis of HIV infection may be excluded if the child's test is negative and there has been no breastfeeding for the past 3 months. If the child tests positive before 18 months, the test needs to be repeated at 18 months to exclude the possibility of persisting maternal antibodies. If ELISA or rapid testing is negative at 18 months, then the child is HIV-negative as long as there has been no breastfeeding during the previous 3 months. ELISA or rapid HIV testing is the recommended testing approach for the diagnosis of, or exclusion of, HIV in children older than 18 months.

Figure 6. Ministry of Health and Social Services algorithm for diagnosis of HIV in children using ELISA or rapid testing



3.2.2 Early infant diagnosis of HIV using diagnostic PCR testing

As a result of the programme for the prevention of mother-to-child transmission (PMTCT), a large number of HIV-exposed infants are being identified who require follow-up care and HIV diagnosis. It is important to identify young infants with HIV infection and in need of ART because of the high mortality from untreated HIV/AIDS in this age group. It is also important to promptly identify young infants who are not HIV-infected in order to reassure their parent(s), discharge them from costly follow-up, and to measure the overall effectiveness of the PMTCT programme.

The polymerase chain reaction (PCR) test can reliably and accurately detect HIV DNA or RNA from serum or from a dried blood spot (DBS) specimen at an early age. This test detects the genetic material of HIV instead of anti-HIV antibodies, and therefore is not affected by the transplacental transfer of maternal anti-HIV antibodies, unlike the standard HIV tests. A positive PCR test confirms true HIV infection in the child. A negative PCR test in a child who has not breast fed for the previous 2 months, confirms that the child is truly HIV-negative. The algorithm for diagnostic PCR testing is summarised in Figure 7, page 49.

Parent(s) can be counselled and a child should be clinically managed as being HIV-positive if:

- HIV ELISA or rapid testing is positive at \geq 18 months, regardless of symptoms, *or*
- HIV ELISA or rapid testing is positive at an earlier age, e.g. 12 months, and there are signs and symptoms suggestive of HIV/AIDS. The child still needs to be re-tested at 18 months to document their HIV status, *or*
- Diagnostic PCR testing is positive at any age

Children who test positive by PCR, ELISA, or rapid testing at an early age should be evaluated for ART as soon as possible due the high mortality rate in young children. It is recommended that children who test positive by ELISA, rapid, or PCR testing in early infancy should have repeated ELISA or rapid testing at 18 months of age.

The parent(s) can be counselled that their child is HIV-negative and the child can be discharged from HIV follow-up if:

- HIV ELISA or rapid testing is negative at age 12 months or later and the child has not been breastfed for the preceding 3 months, *or*
- Diagnostic PCR testing is negative and the child has not been breastfed for the preceding 2 months.

Until further notice, children who test negative by ELISA, rapid, or PCR testing should repeat ELISA or rapid testing at 18 months of age.

3.3 Prevention of opportunistic infections in children

3.3.1 Cotrimoxazole for PCP prevention

Pneumocystis pneumonia (PCP) prophylaxis with cotrimoxazole (sulfamethoxazole plus trimethoprim or SMZ/TMP) is recommended for all exposed children in the first year of life, from the age of 6 weeks. From the age of 1 year prophylaxis can be discontinued if the HIV test of the child is negative. Cotrimoxazole has also been shown to have protective effects against some bacterial and parasitic infections, including malaria.

Table 18. Recommended doses of cotrimoxazole for PCP prophylaxis

Age	Cotrimoxazole dosage
Six weeks to five months	2.5 ml once daily
Six months to six years	5 ml once daily
Six years and older	10 ml, or 1 400mg/80mg tablet daily

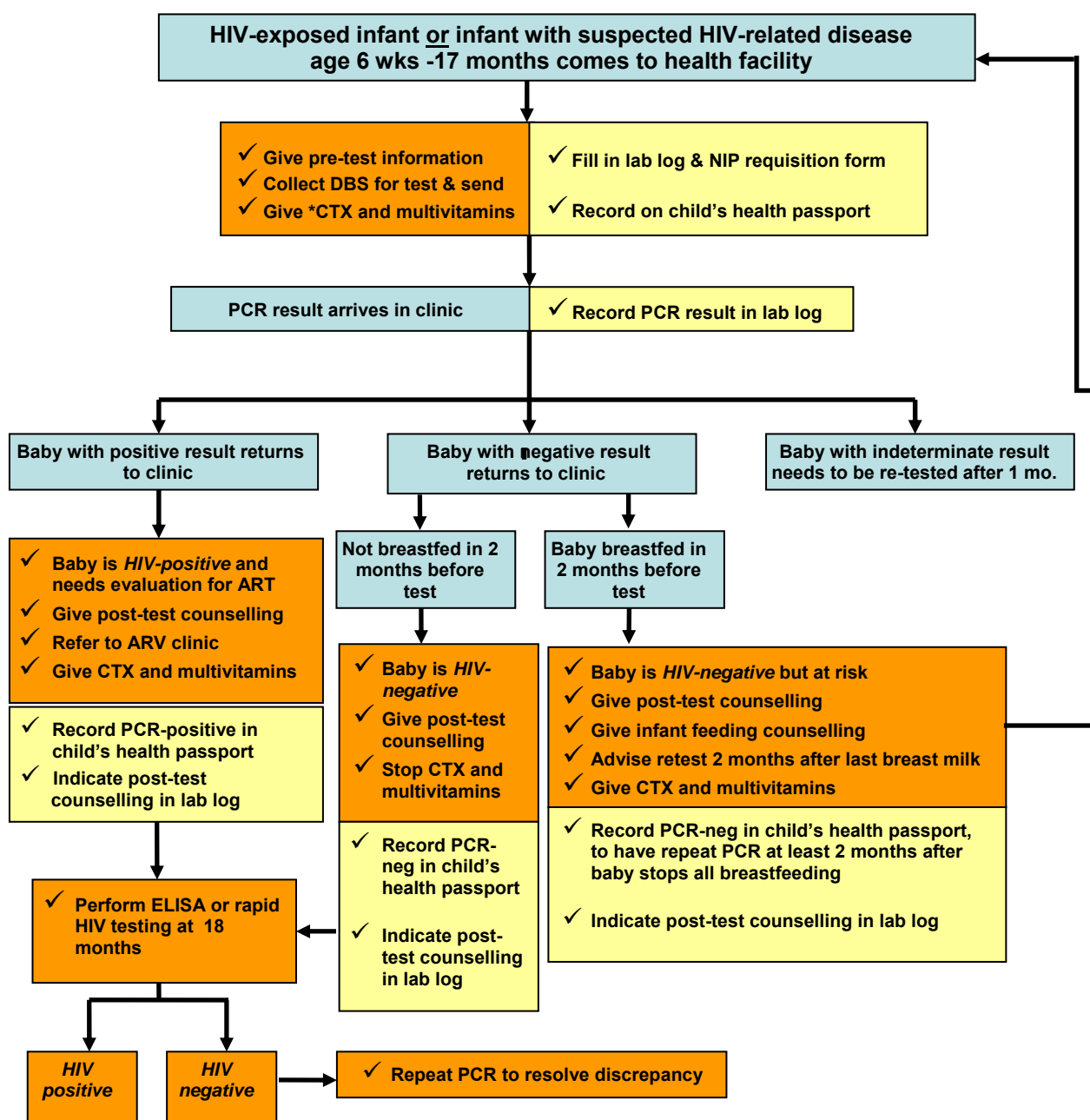
*Using a paediatric cotrimoxazole suspension of SMZ/TMP 200 mg/40 mg per 5 ml.

3.3.2 Isoniazid (INH) for TB prevention – TB-IPT for children

In all children who have had contact with sputum positive TB patients (especially those children under 5 years), and infants born to mothers with TB disease, supervised INH prophylaxis should be considered once active TB disease has been excluded. The dosage for INH is 5mg per kg daily for 6 months.

Pyridoxine may be dosed along with INH due to the high frequency of INH associated peripheral neuropathy. A dose of pyridoxine 5mg/day is suggested for children. As the Namibian public sector only has 25mg tablets available at the time of this publication, one-quarter of a 25mg tablet (approximately 6.25mg) is the suggested dose.

Figure 7. Ministry of Health and Social Services algorithm for early infant diagnosis of HIV using diagnostic PCR



* CTX = cotrimoxazole prophylaxis
ART = antiretroviral therapy

3.4 HAART in children and when to start

The response to HAART is different in children than in adults.

- The immunological response in children is better than in adults. Children restore their CD4 T cell counts better and more rapidly than adults, even in a late stage of HIV-1 infection. Moreover, normalisation of CD4 T cell count in HIV-1-infected children taking HAART is age independent, suggesting that thymic function allows children in all age groups to meet their widely different CD4 T cell production demands.
- Virological success, with viral load levels of <50/ml may be more difficult to achieve in children. Remarkably, HAART has a beneficial effect on immune reconstitution regardless of virological success.

When to start ART in Infants <18 months of age:

- If an infant has been proven to have HIV infection (defined as a positive HIV DNA PCR test), start ART if:
 - WHO Paediatric Stage 3 or 4, regardless of CD4%.
 - WHO Paediatric Stage 1 or 2, only if CD4 <25%.
- If an infant is HIV-exposed, but DNA PCR test not available (HIV infection not confirmed), start ART* if:
 - WHO Paediatric Stage 3 or 4, regardless of CD4%.
 - WHO Paediatric Stage 2, only if CD4 <20%.
 - WHO Paediatric Stage 1 – do not treat in infant <18 months if virological tests are not available.

*If starting ART, repeat antibody test at 18 months for definitive diagnosis of HIV and only continue ART if infection is confirmed.

When to start ART in children >18 months of age:

- If infant has proven HIV infection, start ART if:
 - WHO Paediatric Stage 3 or 4, regardless of CD4%.
 - WHO Paediatric Stage 1 or 2, only if CD4 <20%.

3.5 The choice of ARVs for children

Most ARV medications available for adults are also available for children, but not all formulations are suitable for children. Large volumes and numbers of bottles of suspensions are often required, leading to confusion and impracticality with dosage administration. Therefore, crushed or swallowed tablets or capsules may be used. Several manufacturers have developed paediatric versions of Fixed Dose Combination tablets (FDCs) which can be dosed more accurately in children than split adult FDCs and which are easier to prescribe and administer than individual single drug formulations. The tablets are scored, crushable and dispersible in water and may be dosed in children of all weights including infants as small as 3kg. The currently available paediatric FDCs contain d4T, 3TC and NVP, but unlike similar adult formulations, paediatric FDCs have a higher proportion of NVP which makes them better suited for dosing in children who metabolize nevirapine more rapidly than adults. Different manufacturers' formulations have different concentrations of the three components and are therefore not interchangeable and must be dosed according to their respective dosing schedules. These dosing schedules were developed by the WHO in light of recent data which suggest that the paediatric daily dose of NVP must be between 300 and 400 mg/m². This range is higher than the previously recommended range and as a result, WHO dosing may differ from the manufacturers' recommendation.

Table 19 shows the composition of paediatric dual (d4T and 3TC) and triple (d4T, 3TC and NVP) FDCs that are available in Namibia. The recent availability of d4T based paediatric fixed dose combinations (FDCs) may facilitate an easier way to prescribe and administer

paediatric ARVs than individual single drug formulations. Stavudine (D4T) solution is difficult to use due to the need of refrigeration. FDCs may lead to better adherence and therefore better outcomes with paediatric ART. Adult strength FDCs (i.e. combined tablets of zidovudine-lamivudine (AZT/3TC)) can be split into halves for dosing in children. Additionally Abacavir is available in a paediatric formulation. Consult an HIV specialist paediatrician if its use is considered. See tables 19, 20, and 23 for dosing of ARVs in children.

**The first line HAART regimen for children in Namibia is:
stavudine-lamivudine-nevirapine (D4T/3TC/NVP).**

3.5.1 Initiating children on HAART

All patients who are receiving NVP for the first time should be dosed at half of the standard dose for the first 2 weeks of treatment while metabolic enzymes are being induced. Induction dosing is associated with a lower incidence of NVP rash. Children who are being initiated on d4T, 3TC and NVP with FDCs, should be given a combination of triple and dual FDCs for the first two weeks and dosed with a triple FDC in the morning and a dual FDC in the evening. After 2 weeks, if there is no evidence of rash, the NVP dose should be escalated and the child should be dosed with a triple FDC twice a day. Dual FDCs may also be used for children who need to take d4T, 3TC and efavirenz (EFV). In this case dual FDCs must be dosed twice daily and combined with EFV taken in the evening.

3.5.2 Switching children over to paediatric FDCs

Children already on treatment with paediatric single drug formulations or adult split FDCs may benefit from switching to paediatric FDC tablets, especially in settings where adherence is a concern. Children who are receiving a regimen of d4T, 3TC and NVP can be switched over to paediatric FDCs easily, using the recommendations for maintenance doses (see Table 19). A switch to paediatric FDCs may also be considered for children who are on treatment with AZT/3TC/NVP if there is evidence of toxicity (see below) or if adherence is at risk (e.g. due to difficulty managing large volumes of liquid formulations). Treatment failure must be ruled out (no evidence of disease progression or falling CD4 percentages or counts) before switching to FDCs. Regimens being well tolerated and clinically effective should not be switched simply because FDCs are available. (See section 3.5.4)

Table 19 : Dosing of Fixed Dose Combination (FDCs) Tablets by weight in children

WHO Abbreviation	Stavudine (D4T) dose/tablet (mg)	Lamivudine (3TC) dose/tablet (mg)	Nevirapine (NVP) dose/tablet (mg)
Paediatric FDC 6 dual	6	30	-
Paediatric FDC 6 triple	6	30	50
Paediatric FDC 12 dual	12	60	-
Paediatric FDC 12 triple	12	60	100

Weight Band	FDC 6 or 12	D4T 3TC NVP regimen				D4T 3TC EFV regimen		
		Initiation of Treatment Day 1 to 14		Maintenance dose after 2 week induction period		D4T 3TC		EFV
		Triple tabs am	Dual tabs pm	Triple tabs am	Triple tabs pm	Dual tabs am	Dual tabs pm	EFV capsules at night
3 – 3.9 kg	FDC 6	1	1	1	1			EFV should not to be given to children under 10kg
4 – 4.9 kg	FDC 6	1	1	1	1			
5 – 5.9 kg	FDC 6	1	1	1	1			
6 – 6.9 kg	FDC 6	1.5	1.5	1.5	1.5			
7 – 7.9 kg	FDC 6	1.5	1.5	1.5	1.5			
8 – 8.9 kg	FDC 6	1.5	1.5	1.5	1.5			
9 – 9.9 kg	FDC 6	1.5	1.5	1.5	1.5			
10 – 10.9 kg	FDC 6	2	2	2	2	2	2	200 mg
11 – 11.9 kg	FDC 6	2	2	2	2	2	2	200 mg
12 – 13.9 kg	FDC 6	2	2	2	2	2	2	200 mg
14 – 16.9 kg	FDC 12	1.5	1	1.5	1	1.5	1	200 mg plus 50 mg
17 – 19.9 kg	FDC 12	1.5	1	1.5	1	1.5	1	200 mg plus 50 mg
20 – 24.9 kg	FDC 12	1.5	1.5	1.5	1.5	1.5	1.5	200 mg plus 2 x 50 mg
25 – 29.9 kg	FDC 12	2	2	2	2	2	2	200 mg plus 3 x 50 mg

Table 20. Paediatric non-FDC antiretroviral dosage charts for use in resource-constrained settings. (Modified for Namibia from the WHO 2006 paediatric dosing chart)

First line therapy

Weight	Stavudine (D4T)	Lamivudine (3TC)		Zidovudine (ZDV, AZT)		Nevirapine (NVP)						Efavirenz (EFV)		
						Induction dose: 4 mg/kg once daily for first 14 days, then give maintenance dose→	Maintenance dose							
1 mg/kg twice daily	4 mg/kg twice daily		240 mg/m ² twice daily				< 8 yrs 7 mg/kg twice daily	≥ 8 yrs 4 mg/kg twice daily		Dose as shown once daily				
kg	Capsules 15, 20, 30 mg	Liquid 10 mg/ml	Tablet 150 mg	Liquid 10 mg/ml	Capsule 100 mg, Tab 300 mg	Liquid 10 mg/ml	Tablet 200 mg	Liquid 10 mg/ml	Tablet 200 mg	Liquid 10 mg/ml	Tablet 200 mg	Liquid 30 mg/ml	Capsules 50, 100, 200 mg	
5 - 6.9		2 ml		7 ml		2 ml		4 ml						
7 - 9.9	15 mg	3 ml		9 ml	100 mg	3 ml		6 ml						
10 - 11.9	15 mg	4 ml		12 ml	100 mg	4 ml		8 ml	100 mg			9 ml	200 mg	
12 - 14.9	15 mg	5 ml		14 ml	100 mg	5 ml		9 ml	100 mg			9 ml	200 mg	
15 - 16.9	15 mg or (20 mg)	6 ml	75 mg	15 ml	200 mg	6 ml		10 ml	100 mg			10 ml	200 mg + 50 mg	
17 - 19.9	20 mg	7 ml	75 mg	17 ml	200 mg	7 ml		13 ml	200 mg AM + 100 mg PM			10 ml	200 mg + 50 mg	
20 - 24.9	20 mg	9 ml	75 mg	20 ml	200 mg	9 ml	100 mg	16 ml	200 mg AM + 100 mg PM	9 ml	100 mg	12 ml	200 mg + 100 mg	
25 - 29.9	30 mg	11 ml	150 mg	24 ml	300 mg	11 ml	100 mg	20 ml	200 mg	11 ml	100 mg	15 ml	200 mg + 100 mg +50 mg	
30 - 34.9	30 mg	13 ml	150 mg	27 ml	300 mg	13 ml	200 mg			13 ml	200 mg AM + 100 mg PM	30 – 32.5 kg	15 ml	200 mg + 100 mg + 50 mg
												32.5 – 34.9 kg	17 ml	200 mg + 200 mg
35 - 40	30 mg	15 ml	150 mg	30 ml	300 mg	15 ml	200 mg			15 ml	200 mg AM + 100 mg PM	17 ml	200 mg + 200 mg	

3.5.3 Substitution within first line HAART regimen in infants and children due to ARV toxicities

If toxicity is related to an identifiable medication in a regimen, the offending ARV can be replaced with another ARV from the same class that does not have the same adverse effect, e.g. substitution of D4T for AZT in the case of anaemia, or NVP for EFV in the case of CNS toxicity or pregnancy in an adolescent girl. (See Table 21.)

Table 21. Severe toxicities in infants and children associated with specific first line antiretrovirals and potential first line substitutions

First line ARV medication	Most frequent significant toxicity for the ARV	Suggested first line ARV substitution
ABC	Hypersensitivity reaction	AZT
AZT	Severe anaemia (a) or neutropenia (b)	D4T
	Lactic acidosis	ABC (d)
	Severe gastrointestinal intolerance (c)	D4T
D4T	Lactic acidosis	ABC (d)
	Peripheral neuropathy	AZT (f)
	Pancreatitis	
	Lipoatrophy/metabolic syndrome (e)	ABC
EFV	Persistent and severe central nervous system toxicity (g)	NVP
	Potential teratogenicity (adolescent girl in first trimester of pregnancy, or of childbearing potential and not receiving adequate contraception)	
NVP	Acute symptomatic hepatitis (h)	EFV (i)
	Hypersensitivity reaction	Preferred substitution of NVP to: <ul style="list-style-type: none"> • a third NRTI (disadvantage: maybe less potent) or <ul style="list-style-type: none"> • PI (disadvantage: premature start of class usually reserved for second line) (k)
	Severe or life-threatening rash (Stevens-Johnson Syndrome) (j)	

NOTE: 3TC-associated pancreatitis has been described in adults but is considered very rare in children.

- a. Exclude malaria in areas of endemic malaria. Severe anaemia is defined as Hb < 7.5g/dl.
- b. Defined as neutrophil count < 500/mm³.
- c. Defined as severe, refractory gastrointestinal intolerance that prevents ingestion of ARV regimen (e.g. persistent nausea and vomiting).
- d. Reinitiation of ART should not include D4T or AZT if possible, therefore ABC is preferred.
- e. Substitution of D4T typically may not reverse lipoatrophy.
- f. In children, ABC or AZT can be considered as an alternative.
- g. E.g. persistent hallucinations or psychosis.
- h. Or asymptomatic hepatitis with ALT > 5 x ULN.
- i. EFV may also cause hepatitis but much rarer than NVP.
- j. Hospitalisation usually required.
- k. Cannot use EFV in the face of Stevens-Johnson Syndrome from NVP due to the possibility of cross reactivity.

3.5.4 When to change therapy in children

How to determine a regimen has failed and when to consider switching regimens:

- In the absence of routine viral load testing, judgments regarding treatment failure should be based on:
 - Disease progression and CD4 decline as defined in Table 22 below.
 - Generally, a patient should have received 6 months or more of ART, and adherence problems must be ruled out before treatment failure and switching ARV regimens is considered.

Table 22. Clinical and CD4 definition of ARV treatment failure in children (after 6 months or more of ARV)

Clinical criteria*	CD4 criteria**
<ul style="list-style-type: none">• Lack or decline in growth among children with initial growth response to ARV.• Loss of neurodevelopmental milestones or onset of encephalopathy.• New or recurrent WHO Paediatric Stage 4 condition.	<ul style="list-style-type: none">• Return of CD4% (if age <6 years) and CD4 count or % (if age >6 years) to pre- therapy baseline or below without other causative factor.• >50% fall from peak CD4% (if age <6 years) or CD4 count or % (if age >6 years) without other causative factor.

* Whenever possible, a CD4 assay should be done and CD4 criteria should also be met.

** CD4 abnormalities should be confirmed by second tests.

Deterioration in any clinical criteria may be an indication to investigate for possible failure. Immunological failure is confirmed by a rapid and substantial decrease in CD4 percentage. Virological failure alone is not an indication for changing therapy. It is recommended to consult with a paediatrician experienced in HAART before starting a second line therapy regimen.

**The second line HAART therapy for children in Namibia is:
abacavir- didanosine -lopinavir/ritonavir (ABC + ddi + LPV/r).**

Second line therapy**Table 23. Dosage chart for second line paediatric ARVs**

Weight in kg	Abacavir (ABC)		Didanosine (ddl)	Lopinavir/ritonavir (LPV-r)	
	8 mg/kg twice daily		120 mg/m ² twice daily <i>(Always give two of the chewable tablets!)</i>	5-7.9 kg: 16mg/4mg per kg LPV/RTV 8 -15 kg: 12mg/3mg per kg LPV/RTV 15-40kg: 10mg/2.5mg per kg LPV/RTV twice daily	
	Liquid 20 mg/ml	Tablet 300 mg	Chewable tablets 25, 50, 100mg	Liquid 80 mg LVP/ml	Tablet 200/50 mg LVP/r
5 – 6.9	2 ml				
7 – 9.9	3 ml		25mg + 25mg	1.5 ml	
10 – 11.9	4 ml		25mg + 25mg	2 ml	
12 – 14.9	5 ml		50mg + 25mg	2 ml	1 tab
15 – 16.9	6 ml	150 mg	50mg + 25mg	2.5 ml	1 tab
17 – 19.9	7 ml	150 mg	50mg + 50mg	2.5 ml	1 tab
20 – 24.9	9 ml	150 mg	100mg + 25mg	3 ml	1 tab
25 – 29.9	12 ml	300 mg	50mg + 50mg	3.5 ml	2 tabs AM + 1 tab PM
30 – 34.9	13 ml	300 mg	100mg + 25mg	4 ml	2 tabs
35 – 40	15 ml	300 mg	100mg + 25mg	5 ml	2 tabs

3.6 Children with tuberculosis and HIV co-infection

HIV-infected children with pulmonary tuberculosis have WHO Stage 3 disease and those with extra-pulmonary TB have WHO Stage 4 disease. Both groups are eligible for HAART. In order to reduce the risk of toxicity and to maximise adherence, it is recommended to postpone HAART until the intensive phase of TB treatment (usually the first two months) is completed. At that time – when TB treatment is reduced to INH and rifampicin (plus the vitamin pyridoxine) – it should be easier and safer for the patient to begin HAART.

If a child has clinical Stage 4 disease, begin ART regardless of CD4 count following the 2 month intensive phase of TB treatment. If there is clinical deterioration whilst on TB treatment, then start ART earlier. For clinical Stage 3 disease, initiation of ART will depend on CD4 %:

- <18 months, CD4 % <25
- ≥18 months, CD4 % <20

Refer to the *National Guidelines for the Management of Tuberculosis* for help with diagnosing TB in children.

3.6.1 HAART regimens for children with TB

Only certain HAART regimens can be used in combination with rifampicin. Rifampicin lowers the blood levels of protease inhibitors approximately by 80%, of nevirapine by 30-50%, and of efavirenz by 25%. Nevirapine (NVP) is probably not effective when rifampicin is also used. At standard doses, efavirenz (EFV) in combination with zidovudine-lamivudine (AZT/3TC) or

stavudine/lamivudine (D4T/3TC) remains effective in the presence of rifampicin.

If a child presents with TB before commencing ARV therapy and develops the need for HAART, the following regimens should be used:

- >3 years old and weight above 10 kg
 - AZT + 3TC + EFV
- <3 years old or weight below 10 kg
 - AZT + 3TC + ABC
 - (or AZT + 3TC + RTV)

Consultation with a paediatrician is recommended.

If a child is on first line ART and is diagnosed with TB:

- >3 years old and weight above 10 kg and on AZT + 3TC + EFV, leave unchanged.
- >3 years old and weight above 10 kg and on AZT + 3TC + NVP, change to AZT + 3TC + EFV.
- <3 years old or weight below 10 kg and on AZT + 3TC + NVP, then change to AZT + 3TC + ABC or RTV.

If a child is diagnosed with TB on second line ART (ABC + ddI + LPV/r), increase the dose of RTV to the same dose in mg as LPV. For example, a 10 kg child receiving 2 ml of LPV/rtv suspension (containing 80mg LPV and 20mg RTV per ml) is getting 120 mg of LPV and 40 mg of RTV. Such a child on TB treatment would need an additional 80mg of RTV to reach the proper dose.

The use of D4T with INH in TB therapy may result in a greater incidence of peripheral neuropathy.

3.7 Immune Reconstitution Inflammatory Syndrome (IRIS) in children

IRIS has been observed in children who have initiated HAART, especially those children receiving anti-TB treatments. IRIS is characterised by worsening of disease after initial clinical improvement and can manifest with:

- New onset of systematic symptoms such as fever.
- Worsening of pulmonary infiltrates.
- Peripheral or mediastinal adenopathy.
- Expanding CNS lesions.

It usually occurs during the first three months of HAART treatment. Generally, IRIS is self-limiting – lasting 10-14 days – but may, however, require a short course of glucocorticosteroid treatment for symptom management. Close monitoring of the child is essential.

3.8 Monitoring of antiretroviral therapy in children

3.8.1 Nutrition and growth monitoring

Increased energy needs

HIV-infected children have greater energy needs compared to healthy non-HIV-infected children. The energy requirements of HIV-infected children with no symptoms are increased by 10%. During the symptomatic phase without weight loss, energy requirements increase by 20 to 30% over the level of energy intake recommended for healthy non-HIV-infected children of the same age. When the child is both symptomatic and losing weight, energy requirements

increase by 50 to 100% (FANTA, 2004).

Protein needs

Protein and micronutrient requirements remain the same for children of the same age, sex and physical activity, regardless of HIV status. With an increase in calorie intake, protein intake tends to naturally increase, as long as the diet is balanced and complete. If, however, children have pre-existing micronutrient deficiencies or inadequate protein intake, these need to be addressed and may require micronutrient supplementation and/or increased protein intake.

Micronutrient needs

Micronutrient needs for children are the same as for adults; modification of some fruits and vegetables, however, may be needed for easier chewing and swallowing. As with adults, micronutrients found in fruits and vegetables will help the child fight off infections by boosting the immune system. Iron, vitamin A, and vitamin C-rich foods are important in the development of children and in the prevention of childhood diseases. An infant's iron stores from the mother begin to deplete after the first year; therefore it is critical to make sure the child gets enough iron from meats, beans, and vegetables such as spinach to prevent anaemia. Vitamin C-rich foods – such as oranges, mangoes, pawpaw, guava, baobab, and tomatoes – help iron absorb faster and more effectively into the body. Under the guidance of a health worker, the child should take a multivitamin/mineral supplement daily. Vitamin A supplementation should be done community-wide for all children in conjunction with the Expanded Programme on Immunization (EPI) Policy.

Growth monitoring

Malnutrition is most effectively detected and monitored through regular growth monitoring and promotion (GMP) and watching for clinical signs of protein-energy malnutrition. HIV and other opportunistic infections can impact optimal growth for a child, leading to poor brain development, growth failure, and severe malnutrition. Initially, growth failure may present as only a slight decline in normal growth; however if not adequately addressed this could lead to static (unchanging) growth or weight loss. Therefore, charting height, weight and head circumference can strongly predict HIV disease progression and child survival. Additionally, GMP can be used as an indication of ART effectiveness and tolerance.

3.8.2 Clinical monitoring

Careful clinical follow-up is essential to manage HIV-infected children and to monitor the effectiveness of HAART. The basic parameters examined and documented should include weight, length, developmental milestones, neurological development, head circumference, infections, toxicity and intolerance of the current regimen. The child's growth chart should be used to document these parameters. Listed below are criteria for baseline clinical assessment following confirmation of HIV infection.

1. Clinical staging.
2. Identification of concomitant conditions (i.e., TB, pregnancy in adolescent girls).
3. Detailing of concomitant medications (i.e., cotrimoxazole, traditional medications).
4. Immunisation status.
5. Weight, height, and head circumference. Plot on growth chart.
6. Nutritional status (i.e., assessment of quality and quantity of intake).
7. For those eligible for ART, assessment of children's and caretakers' preparedness for therapy.

3.8.3 Laboratory monitoring

Table 24. Laboratory monitoring for HAART in children

Required tests	Frequency
HIV test	Baseline
Full blood count	Baseline
CD4 cell count, percentage	Baseline, every 3 months for infants up to 18 months, every 6 months after 18 months
Hb (or Ht)	Baseline and follow-up as per schedule
Creatinine	Baseline and as clinically indicated
ALT	Baseline and follow-up as per schedule
HbsAg (Hep B surface antigen)	Baseline only
Serum cholesterol, triglycerides, and glucose	Annually only for patients on protease inhibitors

Table 25. Laboratory monitoring by regimen in children

When on first line regimen – D4T/3TC/NVP	M 0.5	M 1	M 1.5	M 2.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	As clinically indicated
History, physical exam, wt	X		X		X	X	X	X	X	X	
FBC											X
HB						X		X		X	
ALT	X		X		X	X		X		X	
Creatinine											X
CD4 count								X		X	
Viral load						X					X
Amylase for suspected pancreatitis											X
Labs to assess lactic acidosis											X

When on alternate first line regimen – (AZT/3TC/NVP)	M 0.5	M 1	M 1.5	M 2.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	As clinically indicated
History, physical exam, wt	X		X		X	X	X	X	X	X	
FBC											
HB	X		X		X	X		X		X	
ALT	X		X		X	X		X		X	
Creatinine											X
CD4 count								X		X	
Viral load						X					X
Amylase for suspected pancreatitis											X
Labs to assess lactic acidosis											X

M = month

Q = every

When on alternate first line regimen – (D4T/3TC/EFV)	M 0.5	M 1	M 1.5	M 2.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	As clinically indicated
History, physical exam, wt	X		X		X	X	X	X	X	X	
FBC											X
HB						X		X		X	
ALT					X	X		X		X	
Creatinine											X
CD4 count								X		X	
Viral load						X					X
Amylase for suspected pancreatitis											X
Labs to assess lactic acidosis											X

When on alternate first line regimen – (AZT/3TC/EFV)	M 0.5	M 1	M 1.5	M 2.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	As clinically indicated
History, physical exam, wt	X		X		X	X	X	X	X		
FBC											X
HB	X		X		X	X		X		X	
ALT						X		X		X	
Creatinine											X
CD4 count								X		X	
Viral load						X					X
Amylase for suspected pancreatitis											X
Labs to assess lactic acidosis											X

When on second line regimen – (ABC/ddI/LPV/r)	M 0.5	M 1	M 1.5	M 2.5	M 3	M 6	M 9	M 12	Q 3M	Q 6M	As clinically indicated
History, physical exam, wt	X		X		X	X	X	X	X		
FBC											
HB						X		X		X	
ALT					X	X		X		X	
Creatinine											X
CD4 count								X		X	
Cholesterol triglycerides, and glucose											X
Viral load						X					X
Amylase for suspected pancreatitis											X
Labs to assess lactic acidosis											X

M = month

Q = every

The criteria for baseline laboratory assessment are:

1. Confirmation of HIV status:
 - <18 months = HIV DNA PCR.
 - >18 months = HIV antibody test.
2. CD4 count and percentage.
3. Full blood count.
4. Liver enzymes.
5. Screening for:
 - Hep B.
 - TB (See MoHSS *National Guidelines for the Management of Tuberculosis* for how to diagnose TB in children. X ray chest and skin testing are done only if indicated).
6. Pregnancy test for adolescent girls.

Routine monitoring of children, who are not yet eligible for ART consists of:

1. Clinical evaluation every 3 to 6 months:
 - As for baseline - clinical evaluation.
2. CD4 count every 3 to 6 months.
3. Laboratory tests as required or symptom-directed.
4. Frequent clinical evaluation and CD4 measurements as clinical and immunological threshold for initiating ART approaches, and in infants and young children because of the rapid rate of disease progression.

Routine monitoring of children on ART includes:

1. Use of all parameters in clinical baseline evaluation.
2. Evaluation of adherence to therapy.
3. Observation of potential medicine toxicity signs and symptoms.
4. Observation of treatment failure signs and symptoms (e.g., poor growth progression, development of neurological symptoms or poor development, and development of new infections).
5. Frequent clinical and laboratory monitoring (see Tables 24 and 25).

3.9 Vaccinations

All vaccinations should be given according to the regular vaccination scheme. In addition, hepatitis B vaccine should be given to all children of HIV-positive mothers at birth, 6 weeks, and 14 weeks simultaneously with BCG, DPT1 and DPT3.

It is anticipated that hepatitis B vaccine will be made available in the future to all children as part of the national immunisation schedule.

3.10 When to consult a specialist paediatrician

Good collaboration between general practitioners and specialist paediatricians is essential for the establishment of successful and durable antiretroviral therapy in children. In the following circumstances it is recommended to consult a specialist:

- Combined pathologies (hepatitis, renal failure, diabetes, tuberculosis, etc.).
- Severe medication toxicities.
- Insufficient clinical response to therapy (as identified by growth and development parameters).
- Immunological failure of first line therapy.
- Lack of clinical response to treatment or worsening clinical condition.

PART 4: Post-Exposure Prophylaxis (PEP)

4.1 Prophylaxis after occupational exposure to HIV

4.1.1 Introduction

Healthcare workers have a low but measurable risk of HIV infection after accidental exposure to infected blood or body fluids. Based on over 3,000 incidents, the average risk of HIV infection after a single percutaneous exposure is 0.3%. As a result, HIV attributable to occupational exposure is an uncommon, but definite risk.

Compliance with infection control recommendations in handling sharps is the mainstay of prevention of occupational HIV infection. Additional prevention strategies now include post-exposure prophylaxis with antiretroviral therapy. The biological rationale for prophylaxis with antiretroviral therapy is that initial virus uptake and antigen processing after inoculation may take several hours, or even days. This presents a window for therapeutic intervention before virus propagation occurs. A case-controlled study of healthcare workers indicated that zidovudine (AZT) given soon after exposure reduced sero-conversion by 79%.

4.1.2 Risk of infection

Factors that increase the risk of sero-conversion include exposures to large inoculums of infected blood (indicated by a deep injury, visible blood on the device, and procedures involving needles placed directly in arteries or veins) and a source patient with advanced HIV infection. If the source patient is unavailable or refuses to be tested, then, considering the high prevalence of HIV in Namibia, PEP is recommended.

Table 26. Risk factors for HIV infection in healthcare workers after percutaneous exposure to HIV-infected blood

Risk factors	Adjusted odds ratio (95% confidence interval)
Deep injury	16.1 (6.1 – 44.6)
Visible blood on device	5.2 (1.8 – 17.7)
Procedure involving needle placed directly in a vein or artery	5.1 (1.9 – 14.8)
Terminal illness in source patient	6.4 (2.2 – 18.9)
Post-exposure use of zidovudine	0.2 (0.1 – 0.6)

Table 27. Assessment of exposure risk

Low risk exposure (EC1)	High risk exposure (EC2 and EC3)
<ul style="list-style-type: none"> Exposure to a small volume of blood An injury with a solid needle Any superficial injury or mucocutaneous exposure 	<ul style="list-style-type: none"> Exposure to large volume of blood or potentially infectious fluids e.g., contaminated blood transfusion Injury with a hollow bore needle Deep and extensive injury Suspected ARV resistance in source patient
Source Code (SC1)	Source Code (SC2)
<ul style="list-style-type: none"> Exposure to blood contaminated fluids from asymptomatic HIV-positive patients 	<ul style="list-style-type: none"> Exposure to blood or blood contaminated fluids from a patient with advanced HIV disease (Stage 3 or 4) or early sero-conversion phase of HIV

4.1.3 Recommendations for post-exposure prophylaxis

1. Draw baseline laboratory tests: HIV testing (with consent), HBsAb, FBC, ALT, and creatinine. Drawing these tests and waiting for the results must not delay starting PEP.
2. AZT 300mg plus 3TC 150mg BD for 28 days is the recommended ARV regimen for PEP in Namibia. This treatment is usually well tolerated. Short-term toxicity associated with

higher doses of AZT primarily includes gastro-intestinal symptoms, fatigue, and headache. For exposed persons who cannot tolerate AZT, an alternate regimen of TDF 300mg daily plus 3TC 150mg BD for 28 days can be used.

3. In cases of high risk exposure, such as contaminated blood transfusion or injection of a substantial volume of contaminated blood, it is recommended to add a third ARV (such as efavirenz) or a ritonavir-boosted protease inhibitor (such as lopinavir or indinavir) to the prophylaxis regimen.
4. PEP should be recommended to exposed workers after occupational exposures (percutaneous or trans-mucous membrane) to blood. For exposures with negligible risk (intact skin contact with blood), PEP is not justified. The exposed health worker has the right to decline PEP without risk of losing eventual compensations if infection develops.
5. PEP should be initiated promptly, preferably within 1 - 2 hours post-exposure. PEP is probably not effective when started later than 24 - 36 hours post-exposure. PEP is not offered at more than 72 hours after exposure.
6. Considering the importance of early initiation of PEP and the high prevalence of HIV among hospitalised patients, it is recommended to initiate PEP immediately if the source patient is HIV-positive or the patient's HIV status is unknown. If results of the HIV sero-status of the source patient later become available, decisions about discontinuation of PEP can be made on a case-by-case basis.
7. Workers with occupational exposures to HIV should be offered, and should undergo, baseline testing for HIV and receive follow-up counselling and medical evaluation. HIV-positive workers should discontinue PEP immediately, once their positive sero-status is confirmed (as prolonged exposure to AZT+3TC may induce resistance development). Workers who are HIV-positive at baseline should be referred for appropriate medical care. Workers who are HIV-negative at baseline should repeat HIV-antibody tests at 6 weeks, 12 weeks, and 6 months. Viral load, p24 antigen, and DNA PCR testing cannot be used to determine sero-status due to the possibility of false results. Exposed workers should be counselled to observe precautions to prevent possible secondary transmission (for example to their sexual partner or from mother to child) until they are found to be HIV-negative 6 months following the exposure.
8. Monitoring for medication toxicities should include a complete blood count, liver transaminase (ALT) level, and creatinine testing at baseline and 2 weeks after starting PEP. If subjective or objective toxicity is noted, ARV substitution should be considered with expert consultation, and further diagnostic studies may be indicated.
9. Relative contraindications to the use of PEP include significant renal or liver impairment, severe anaemia, and severely ill workers. When in doubt about the use of PEP, urgent consultation from a specialised physician or referral centre can be sought, but care must be taken that this consult not unduly delay the initiation of treatment when indicated. It may be necessary to begin PEP while awaiting this consultation.
10. Health workers who become infected with HIV should receive appropriate medical care.

4.1.4 PEP regimens

Prophylaxis is always given for 28 days.

Recommended basic regimen:

- AZT 300 mg + 3TC 150 mg twice daily for 28 days.
- TDF 300 mg daily + 3TC 150 mg twice daily for 28 days may be used for exposed workers who cannot tolerate AZT.

Expanded regimens include the basic regimen (AZT+3TC) plus one of the following for 28 days:

- Efavirenz 600 mg once nightly (not to be used in first trimester pregnancies)
- Lopinavir 400mg plus ritonavir 100mg twice daily.
- Indinavir 800 mg plus ritonavir 100mg twice daily.
- Nelfinavir 1,250 mg BD. (**N.B.** not available in public sector)

NOTE: Nevirapine is contraindicated for PEP due to a high risk of hepatotoxicity in immunocompetent persons.

PEP regimens when the source patient has been on HAART:

If the source patient has been on HAART and there is reason to believe the regimen is failing (i.e., clinical progression, falling CD4 level, documented elevated viral load), viral resistance should be suspected. In this instance, consideration must be given to the source patient's HAART regimen, and ARVs with a different resistance profile should be used for PEP. For example, if the source patient is (or was) on first line therapy with AZT+3TC+NVP, a basic PEP regimen could include ABC+TDF or ABC+ddI. If an expanded PEP regimen is indicated for the exposure, ABC+3TC or TDF+3TC in addition to one of the protease inhibitor-containing options above should be used. Efavirenz should not be used for PEP if there is a possibility the source patient may be resistant to nevirapine due to issues of cross-resistance.

Table 28. Summary of PEP recommendations

Exposure	PEP recommendation	Basic regimen	Expanded regimen
High risk exposure (EC2 or EC3)	Recommend	In case of low risk source (SC1)	In case of high risk source (SC2)
Low risk exposure (EC1)	Offer	In case of high risk source (SC2) Consider for low risk source (SC1)	
Intact skin Low risk fluids HIV-negative source	Do not offer		

4.1.5 Accompanying measures

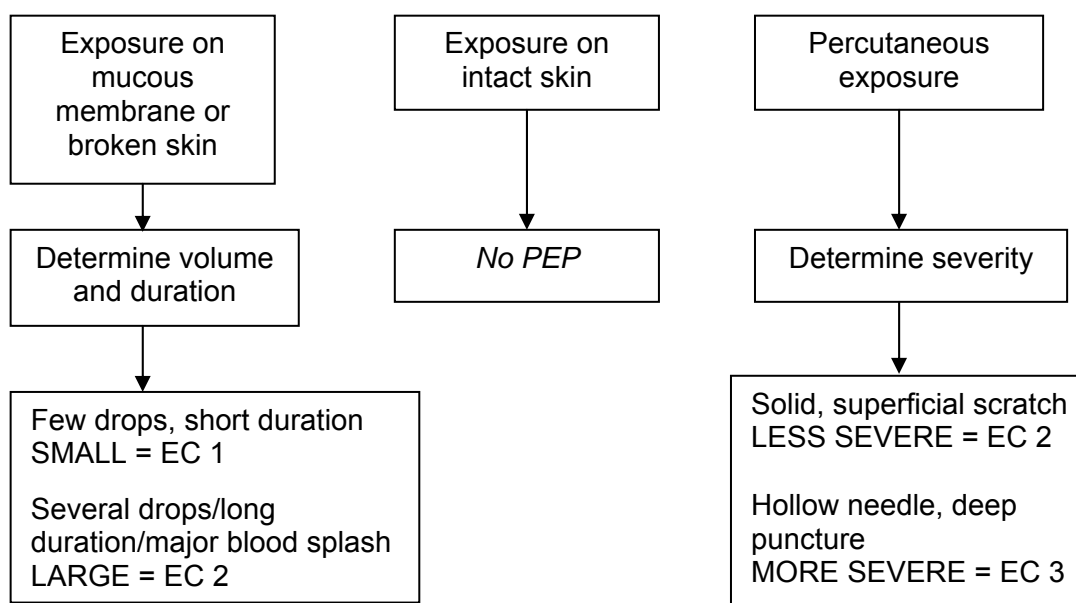
To ensure that the risk for occupational exposure is minimised and PEP is administered according to the guidelines, it is recommended that the following measures be taken:

1. Infection control committees should be put in place to cover all health facilities throughout the country.
2. Strict attention should be given to the correct handling of sharps and all infected materials through standard precautions (e.g., no recapping or bending of needles, disposal of all sharps in solid containers, etc.).
3. Staff should be fully informed about the measures to be taken following an exposure to a potentially infectious body fluid. Each health facility should establish and disseminate clear procedures to ensure appropriate management following an occupational exposure.
4. Monitoring of all potential exposures. For each incident, the facility supervisors should investigate the circumstances and report the findings and measures proposed to avoid reoccurrence to the infection control committee. Risks for support staff (cleaners, porters, etc.) should be minimised. Registration of accidents should be standardised and they should be regularly reported by all relevant health facilities.
5. Antiretroviral medications for PEP should be made available on a 24-hour basis (for example through casualty services). In addition, access to private pharmacies should be standardised and facilitated.
6. All employees of health facilities should be vaccinated against HBV and tetanus. Hepatitis B PEP with hepatitis B immunoglobulin should also be provided for all healthcare workers following sharps injuries or exposure to infected materials. The risk of transmission of hepatitis B infection following a needle stick injury ranges from 6-30%. Thus, the risk of transmission of hepatitis B from an occupational exposure is significantly greater than the risk for transmission of HIV.

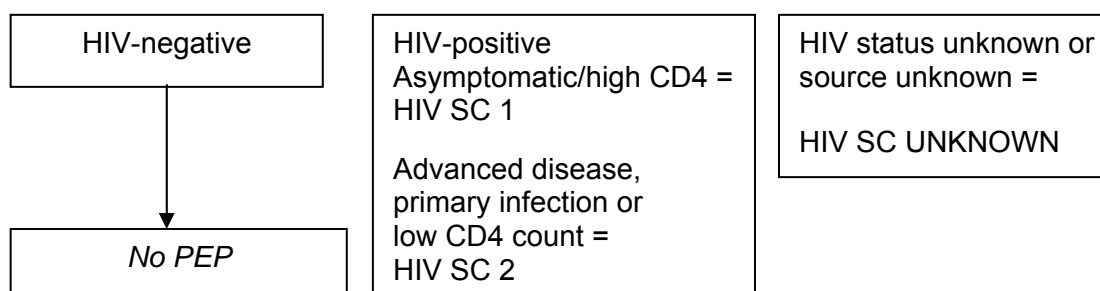
Figure 8. Algorithm for PEP after occupational exposure

Step 1: First Aid. Immediately clean the wound with soap and water or flush mucous membranes with water.

Step 2: Type of exposure – determine the Exposure Code (EC)



Step 3: Determine HIV Status Code of source (HIV SC)



Step 4: Determine PEP recommendation from EC and HIV SC

HIV SC	EC	PEP recommendation
1	1	PEP may not be warranted
2	1	Consider basic regimen
1	2	Recommend basic regimen
2	2	Expanded regimen recommended
1 or 2	3	Expanded regimen recommended
Unknown		Where EC is 2 or 3 and a risk exists consider PEP basic regimen

Step 5: Test the exposed person for HIV and hepatitis B. Administer tetanus immunisation and HBV immunoglobulin as indicated

NOTE: Basic regime: AZT + 3TC.

Expanded regimen: AZT + 3TC + EFV or LPV/r or IDV/r or NFV.

4.2 Prophylaxis after rape

4.2.1 Introduction

All women, men and children presenting to a health facility after being raped should be counselled by the examining healthcare worker about the potential risks of HIV transmission post-rape. If the rape survivor presents within 72 hours of being raped, post-exposure prophylaxis (PEP) should be offered to prevent HIV transmission.

4.2.2 Issues to be addressed during counselling

The following issues should be addressed during counselling:

- The risk of HIV transmission is not known, but it exists.
- It is important for the survivor to know her/his HIV status prior to starting PEP.
- It is important to start PEP as soon as possible.
- It is the survivor's choice to receive PEP and to have HIV testing.
- For each rape survivor, blood and urine will be taken routinely to screen for syphilis, HIV (unless refused), and existing pregnancy.
- If the possible risk for HIV transmission has been established, the rape has occurred within a period of 72 hours, and the rape survivor is HIV-negative or results are not immediately available, PEP will be offered.
- The efficacy of PEP in preventing HIV sero-conversion in cases of sexual assault is not known.
- The common side-effects of the medicines should be explained, with particular reference to feelings of fatigue, nausea, headache, and flu-like symptoms.
- PEP should be discontinued immediately if the baseline HIV test of the survivor is confirmed to be positive. Even in the absence of on-the-spot rapid testing, this should not take more than 3 days.
- The importance of adherence to treatment should be emphasised.
- Survivors should be counselled to observe precautions to prevent possible secondary transmission (for example to their sexual partner or from mother to child) until they are found to be HIV-negative 6 months following the exposure.

All women who choose to use PEP should undergo pregnancy testing to ensure that pregnant women are identified and then receive appropriate antenatal care. The use of AZT+3TC+LPV/r in pregnancy has not been shown to be teratogenic. The possibility of HIV transmission to the unborn baby should the woman sero-convert should be discussed.

Survivors presenting more than 72 hours after the rape should be counselled about the possible risk of HIV transmission. For those who request PEP, it should be explained that there is good evidence that the use of PEP so long after the rape will have no impact on preventing HIV sero-conversion. This patient will therefore not be given ARVs. If a rape survivor becomes pregnant as a result of the rape, she should be counselled on the option of termination of the pregnancy as per provisions of the Abortion and Sterilization Act, 1975 (Act No. 2 of 1975).

4.2.3 Laboratory tests

Voluntary HIV testing – using rapid testing, if possible – should be made available and should be done for all rape survivors, whether or not they are choosing to use PEP. Additionally, tests for syphilis, pregnancy, and hepatitis B antibody should be done.

It may be difficult to obtain informed consent for HIV testing shortly after the rape. The importance of an HIV test should be explained. All rape survivors who present within 72 hours should be offered a 3-day course of AZT/3TC/LPV/r and be given a return appointment at the ARV clinic within three days, during which time either their HIV test results will become available, or they will have been given time to think further about consenting to testing.

Monitoring for toxicities due to PEP should include a complete blood count, liver transaminase (ALT) and creatinine at baseline, and repeated 2 weeks after starting PEP or when symptoms occur. If subjective or objective toxicity is noted, ARV substitution should be considered with expert consultation, and further diagnostic studies may be indicated.

HIV serology should be done at 6 weeks, 12 weeks and 6 months. Rape survivors who become infected with HIV should receive appropriate medical care.

4.2.4 PEP regimen after rape

**The recommended antiretroviral regimen following rape is:
AZT 300mg plus 3TC 150mg plus lopinavir 400mg/ritonavir 100mg BD for 28 days.**

If the survivor cannot tolerate AZT and pregnancy has been ruled out, TDF may be substituted for AZT.

Survivors should be given a three day supply of PEP and a date to return to the ARV clinic for reassessment within 3 days for further counselling and evaluation. The remainder of the 28 day PEP regimen should be given at this visit.

The next visits should be at 6 weeks, then 3 months, and 6 months after the rape. HIV antibody testing should be performed at each of these visits.

Survivors who are either known to be HIV-positive or found to be HIV-positive at baseline should be appropriately counselled and referred to an appropriate health facility for long-term management of HIV infection.

Relative contraindications to the use of PEP include significant renal or liver impairment and severe anaemia. When in doubt about the use of PEP, urgent consultation from a specialised physician or referral centre can be sought, but care must be taken that this consult not unduly delay the initiation of treatment when indicated. It may be necessary to begin PEP while awaiting this consultation.

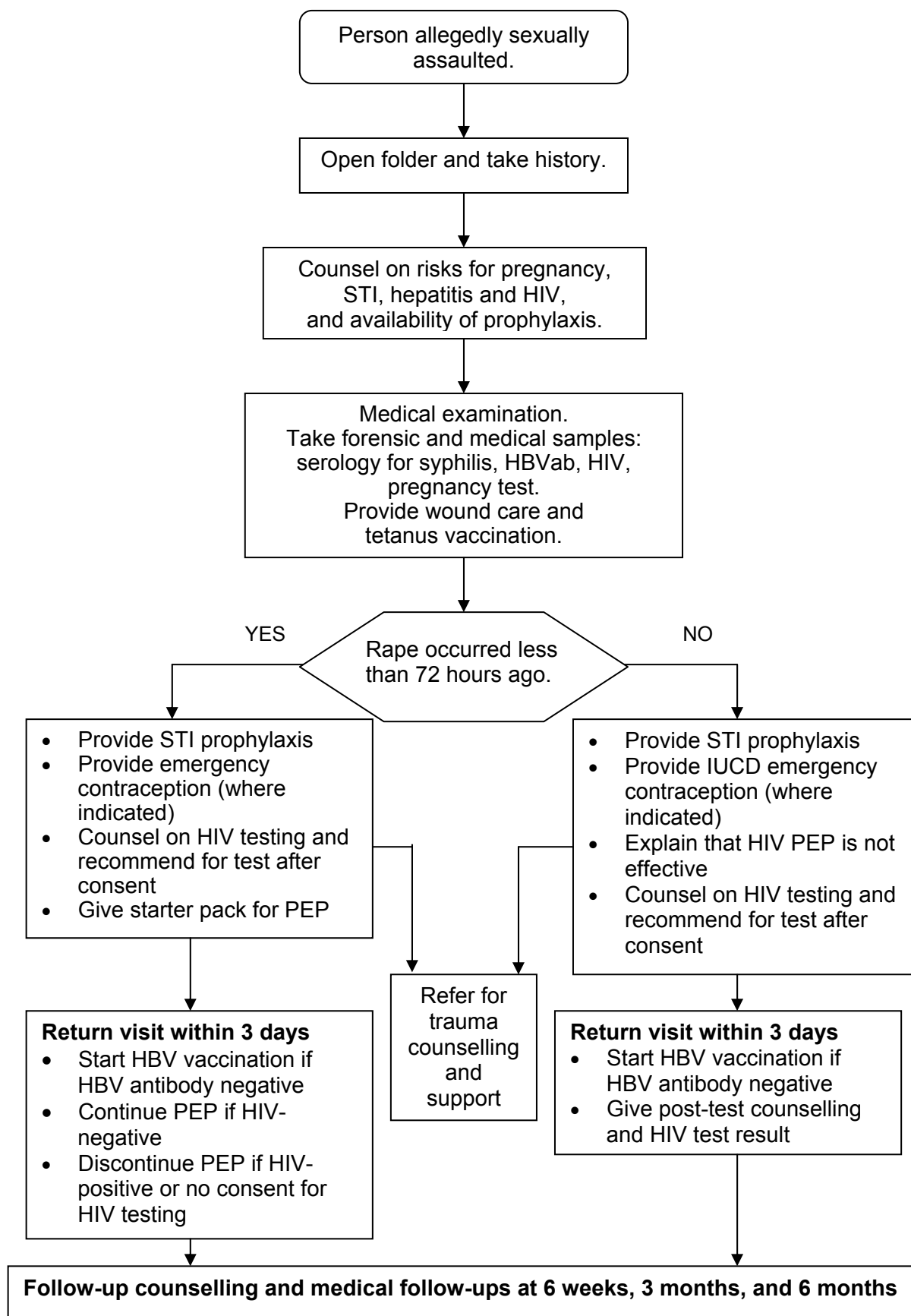
4.2.5 Comprehensive management

It is strongly suggested that PEP be administered only in the context of a comprehensive support programme for rape survivors. This should encompass the following:

1. STI prophylaxis: presumptive prophylaxis should be given in the form of ciprofloxacin 500mg (STAT) plus azithromycin 1g (STAT) or doxycycline 100mg BD for 7 days. Azithromycin is preferred as it is a single dose and covers chancroid, chlamydia and incubating syphilis.
2. Emergency contraception within 72 hours: norgestrel 0.5mg (500 mcg) and ethynyl oestradiol 0.05mg (50 mcg) (*Ovral*): 2 tablets STAT and 2 tablets 12 hours later. Another regimen is levonorgestrel 2 tablets (or 0.75 mg) STAT and 2 tablets (or 0.75 mg) 12 hours later. A copper T IUCD can be inserted up to 5 days after the first unprotected intercourse, or up to 5 days after the calculated earliest day of ovulation.
3. Hepatitis B immunoglobulin and hepatitis B vaccination should be started as soon as possible, and no later than 21 days after the incident. Vaccinate at 0, 1, and 3 to 6 months.
4. A tetanus booster should be given.
5. Counselling of the rape survivor, identification of support needs, and necessary referrals should be done.

6. In cases where rape survivors have severe bleeding, the issue of proper nutrition with regards to foods that are high in iron, folate, riboflavin, vitamin A and vitamin B12 to avoid developing anaemia should be emphasised.
7. In subsequent visits, issues relating to stress management should be discussed as part of the support programme. The survivor should be made aware of the indicators that point to stress such as general irritability, trembling, pain in the neck and/or lower back, changes in appetite or sleep pattern etc., as stress may eventually cause exhaustion and illness, either physical or psychological.
8. Medico-legal assessment of injuries.
9. Completion of appropriate registers.

Figure 9. Algorithm for PEP for rape survivors



Appendix 1. WHO clinical staging of HIV disease in adults and adolescents

Clinical Stage 1

- Asymptomatic
- Persistent generalised lymphadenopathy

Clinical Stage 2

- Unexplained^(a) moderate weight loss (under 10% of presumed or measured body weight)^(b)
- Recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infection

Clinical Stage 3

- Unexplained^(a) severe weight loss (over 10% of presumed or measured body weight)^(b)
- Unexplained^(a) chronic diarrhoea for longer than one month
- Unexplained^(a) persistent fever (intermittent or constant for longer than one month)
- Persistent oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia, severe pelvic inflammatory disease)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained^(a) anaemia (below 8 g/dl), neutropenia (below $0.5 \times 10^9/L$) and/or chronic thrombocytopenia (below $50 \times 10^9/L$)

Clinical Stage 4^(c)

- HIV wasting syndrome
- *Pneumocystis* pneumonia
- Recurrent bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary tuberculosis
- Kaposi's sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated mycosis (coccidiomycosis or histoplasmosis)
- Recurrent septicaemia (including non-typhoidal *Salmonella*)
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

(a) Unexplained refers to where the condition is not explained by other conditions.

(b) Assessment of body weight among pregnant woman needs to take into consideration the expected weight gain of pregnancy.

(c) Some additional specific conditions can also be included in regional classifications, such as the reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in the WHO Region of the Americas, and penicilliosis in Asia.

Source: Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance.2006 (in press).

Appendix 2. Antiretroviral medication dosages and toxicities

Medicine name	Form	Usual adult dose	Renal failure dosing				Liver failure dosing	Toxicity
			CrCl 30 - 50 ml/min	CrCl 10 - 29 ml/min	CrCl <10 ml/min	Dialysis		
Abacavir (ABC)	300 mg tablet	300 mg BD	Dosing adjustment not necessary				Usual dose Avoid in severe cases	Hypersensitivity reaction, lactic acidosis
Didanosine (ddI)	25,50,100,200 mg tablets 250mg, 400mg EC tablets	< 60 kg: 250 mg od	125 mg od	125 mg od	125 mg od	125 mg od	Usual dose Monitor for toxicity	Peripheral neuropathy, pancreatitis, hyperlipidaemia, lactic acidosis, lipoatrophy
		> 60 kg: 400 mg od	200 mg od	125 mg od	125 mg od	125 mg od		
Lamivudine (3TC)	150 mg tab	150 mg BD	150 mg od	150 mg 1 st dose, then 100 mg od	150 mg 1 st dose then 50 mg od	150 mg 1 st dose then 50 mg od	Usual dose	<i>All rare</i> Lactic acidosis, lipoatrophy, pancreatitis, peripheral neuropathy
Stavudine (D4T)	15, 20, 30, 40 mg tab	30 mg BD*	15 mg BD	15 mg od	15 mg od	15 mg od	Usual dose	Peripheral neuropathy, lactic acidosis, pancreatitis, lipoatrophy
Zidovudine (AZT)	100 mg cap, 300 mg tab	300 mg BD	Usual dose	Usual dose	(<15 ml/min) 100 mg tds	100 mg tds	Reduction in daily dose or extension of dosing interval may be needed; 50% decrease in dose or doubling of the dosage interval has been recommended (<i>limited data</i>)	Haematological toxicity, lactic acidosis, lipoatrophy, myopathy
Tenofovir (TDF)	300 mg tab	300 mg od	300 mg q48h	300 mg twice per week	300 mg weekly	300 mg weekly	Usual dose	Renal insufficiency, Lactic acidosis, lipoatrophy, GI (diarrhoea, Nausea, vomiting), asthenia
Efavirenz (EFV)	200, 600 mg tab	600 mg nocte	Dosing adjustment not necessary				Use with caution. Avoid in severe cases	Rash, rarely Stevens Johnson syndrome, Hyperlipidemia, CNS/Neurologic toxicity (Dizziness, Insomnia, somnolence, abnormal dreams, suicidal ideation)
Nevirapine (NVP)	200 mg tab	200 mg od for 14 days, then 200 mg BD	Dosing adjustment not necessary				Use with caution. Avoid in severe cases	Hypersensitivity reactions, hepatotoxicity, Stevens-Johnson Syndrome, TEN
Indinavir (IDV)	400 mg cap	800 mg + 100 mg RTV BD	Dosing adjustment not necessary				Use with caution. Watch for nephrolithiasis	Hyperbilirubin-aemia, nephrolithiasis, hyperlipidaemia, lipodystrophy, hepatotoxicity, insulin resistance
Lopinavir/ritonavir (LVP/r)	200/50 mg tab	400/100 mg BD	Dosing adjustment not necessary				Use with caution. Avoid in severe cases	Hepatotoxicity, hyperlipidaemia, lipodystrophy, insulin resistance
Ritonavir (RTV)	100 mg cap	Used only as a booster for other PIs	Dosing adjustment not necessary				Use with caution. Avoid in severe cases	Hepatotoxicity, perioral parasthesia hyperlipidaemia, lipodystrophy, insulin resistance, hyperuricaemia

***In accordance with the WHO guidelines and international standards, D4T 40 mg tablets will be phased out. Patients on D4T who are tolerating it well should be continued as long as the 40 mg tablets are available. All adults newly initiating treatment with D4T will be started on 30 mg BD. Patients on 40 mg BD will transition to 30 mg BD as current pharmaceutical stock is depleted of D4T 40mg tablets.**

Appendix 3. ARV medicines interactions table

Medicine name	Interactions
Nucleoside Reverse Transcriptase Inhibitors	
Abacavir (ABC)	<ul style="list-style-type: none"> Plasma concentration of ABC potentially reduced by phenobarbital, phenytoin and rifampicin Alcohol increases ABC levels by 41%
Didanosine (ddl)	<ul style="list-style-type: none"> Food – decreases ddl bioavailability. <i>Take on an empty stomach.</i> Allopurinol increases plasma concentration. <i>Monitor</i> Isoniazid – peripheral neuropathy. <i>Monitor.</i> D4T, hydroxyurea – pancreatitis, lactic acidosis, peripheral neuropathy. Do not use together. TDF increases plasma concentrations. Do not use together. Hydralazine – Peripheral neuropathy. <i>Avoid long term use.</i> Quinolones, tetracyclines, ketoconazole – decreases bioavailability of antimicrobials. <i>Give ddl 6 hrs before or 2 hrs after antimicrobial.</i>
Lamivudine (3TC)	<ul style="list-style-type: none"> plasma concentration of lamivudine increased by trimethoprim (as cotrimoxazole)—avoid concomitant use of high-dose cotrimoxazole
Stavudine (D4T)	<ul style="list-style-type: none"> Isoniazid, vincristine, hydralazine – peripheral neuropathy. <i>Monitor.</i> ddl, hydroxyurea – pancreatitis, lactic acidosis, peripheral neuropathy. <i>Do not use together.</i>
Zidovudine (AZT)	<ul style="list-style-type: none"> Sulfadiazine, antineoplastics – bone marrow suppression. <i>Monitor.</i>
Nucleotide Reverse Transcriptase Inhibitors	
Tenofovir (TDF)	<ul style="list-style-type: none"> TDF increases plasma concentrations of Didanosine (and increases risk of toxicity)— Do not use together Use with caution in lactose intolerant patients. Plasma concentrations of TDF increased by Lopinavir
Non- Nucleoside Reverse Transcriptase Inhibitors	
Efavirenz (EFV)	<ul style="list-style-type: none"> Food – fatty meals increase bioavailability. <i>Avoid fatty meals.</i> Clarithromycin – decreases bioavailability of clarithromycin. <i>Use azithromycin.</i> Carbamazepine, phenobarbital, phenytoin – levels of anticonvulsants decreased. <i>Use valproic acid.</i> Oral contraceptives – efficacy of OC may be reduced. <i>Use barrier method.</i> Artemether, warfarin, mefloquine, statins – serum levels decreased by EFV. <i>Monitor closely.</i> St. John’s Wort, echinacea – may decrease EFV levels. <i>Do not use together.</i> Ergot alkaloids – ergotamine levels significantly increased. <i>Do not use together. Use sumatriptan.</i> Benzodiazepines – may increase levels of BDZ. <i>Use lorazepam.</i> Sertraline – decreases bioavailability of sertraline. <i>Titrate sertraline to effect.</i> Pioglitazone – levels of pioglitazone may be decreased. <i>Use rosiglitazone.</i>

Medicine name	Interactions
Nevirapine (NVP)	<ul style="list-style-type: none"> • Rifampicin – decreases NVP levels. <i>Do not use together.</i> • Carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin – levels of anticonvulsants decreased. <i>Use valproic acid.</i> • Fluconazole – risk of hepatitis because NVP levels are increased. <i>Monitor.</i> • Artemether, mefloquine, amiodarone, calcium channel blockers – serum levels of other medicines decreased. <i>Monitor closely.</i> • Warfarin – serum levels of warfarin increased. <i>Monitor.</i> • Echinachea, St. John’s Wort – may decrease NVP levels. <i>Avoid.</i> • Pioglitazone – may decrease pioglitazone levels. <i>Use rosiglitazone.</i> • Ergot alkaloids – clinical significance unknown. <i>Consider sumatriptan.</i> • Oral contraceptives – efficacy of OC may be reduced. <i>Use barrier method or depo-medroxyprogesterone acetate.</i>
Protease Inhibitors	
Indinavir (IDV)	<ul style="list-style-type: none"> • Food – presence of food decreases the absorption of IDV. <i>Take on an empty stomach.</i> • Rifampicin – levels of IDV decreased. <i>Do not use together.</i> • Carbamazepine, ethosuximide, phenobarbital, phenytoin – levels of anticonvulsants decreased. <i>Use valproic acid.</i> • Anti-neoplastics – may increase or decrease serum levels on antineoplastics. <i>Use with caution.</i> • Artemether, warfarin, mefloquine – may increase levels of other medicines. <i>Monitor closely.</i> • Calcium channel blockers – may increase levels of calcium channel blocker. <i>Start at lowest dose and titrate slowly.</i> • Amiodarone – amiodarone levels increased. <i>Contraindicated.</i> • Erectile dysfunction agents – increased levels of erectile dysfunction meds. <i>Preferably use sildenafil. Do not exceed 25 mg in 48 hours.</i> • Echinachea, milk thistle, St. John’s Wort – may decrease IDV levels. <i>Avoid.</i> • Pioglitazone – may increase pioglitazone levels. <i>Use rosiglitazone.</i> • Statins – IDV may increase other statin levels. <i>Use prava, rosuva, and fluvastatin only.</i> • Ergot alkaloids – ergotamine levels significantly increased. <i>Do not use together. Use sumatriptan.</i> • Contraceptives – increased levels of OC. <i>Barrier method preferred.</i> • Benzodiazepines – may increase levels of BDZ. <i>Use lorazepam.</i> • Pimozide – Increased levels of pimozide. <i>Use planzapine.</i>

Medicine name	Interactions
Lopinavir/ritonavir (LPV/r)	<ul style="list-style-type: none"> • Food – food increases GI tolerance of LPV/r. <i>Take with food.</i> • Clarithromycin – increased clarithromycin levels. <i>Preferably use azithromycin.</i> • Rifampicin – decreases levels of LPV/r. <i>Use with caution, increase RTV dose to 400mg BD.</i> • Carbamazepine, ethosuximide, phenobarbital, phenytoin – levels of anticonvulsants increased. <i>Use valproic acid.</i> • Anti-neoplastics – may increase serum levels on antineoplastics. <i>Use with caution.</i> • Artemether, warfarin, mefloquine, amiodarone – may increase levels of these medicines. <i>Monitor closely.</i> • Quinidine – may increase quinidine levels. <i>Contraindicated.</i> • Calcium channel blockers – may increase levels of calcium channel blockers. <i>Start at lowest dose and titrate slowly.</i> • Erectile dysfunction agents – increased levels of erectile dysfunction medicines. <i>Preferably use sildenafil. Do not exceed 25 mg in 48 hours.</i> • Echinacea, St. John’s Wort – may decrease LPV/r levels. <i>Avoid.</i> • Pioglitazone – may increase pioglitazone levels. <i>Use rosiglitazone.</i> • Statins – <i>Use prava, rosuva, and fluvastatin only.</i> LPV/r may increase other statin levels. • Ergot alkaloids – ergotamine levels significantly increased. <i>Use sumatriptan.</i> • Contraceptives – levels of ethiny estradiol decrease. <i>Use of barrier method or injectable progesterone preferred.</i> • Benzodiazepines – may increase levels of BD. <i>Use lorazepam.</i> • Pimozide – increased levels of pimozide. <i>Use olanzapine.</i>
Ritonavir (RTV)	<ul style="list-style-type: none"> • As above: Lopinavir/ritonavir

Appendix 4. Summary of ARV formulations and doses

Name of medicine	Formulations	Age (weight) dose and frequency	Side-effects and toxicity	Other comments
NRTIs				
Abacavir (ABC)	Liquid: 20 mg/ml Tablet: 300 mg	< 37.5 kg or < 16 years: 8 mg/kg BD > 37.5 kg or < 16 years: 300 mg BD Recommended for children over 3 months old.	Hypersensitivity syndrome (rash occurs in about half of the cases. Symptoms progressively worsen with each subsequent dose). Rash, headache, nausea, vomiting and diarrhoea.	No food restrictions. Should be stopped permanently if hypersensitivity occurs. Store between 20 and 25 °C. Tablets can be crushed and mixed with small amount of water or food for immediate use.
Zidovudine (AZT)	Syrup: 10mg/ml Capsules: 100mg Tablets: 300mg	< 4 weeks: 4mg/kg BD 4wks-13 yrs: 180-240 mg/m ² BD 13 yrs and older: 300mg BD	Anaemia, granulocytopenia, fatigue, malaise, headache, myopathy, nausea, vomiting, myositis, liver toxicity, lactic acidosis, myopathy.	Syrup should be stored in away from light. Can give with food. Tablets can be crushed and combined with small amounts of water. Capsules can be opened and dispersed in water of small amount of food for immediate use.
Lamivudine (3TC)	Oral solution 10mg/ml Tablet 150 mg	< 4 wks: 2 mg/kg BD > 4wks, 4mg/kg BD	Headache, fatigue, nausea, diarrhoea, skin rash, abdominal pain, pancreatitis, peripheral neuropathy, Decreased neutrophils, increased liver enzymes.	Usually well tolerated. Can give with food. Use solution within one month of opening.
Stavudine (D4T)	Capsules 15,20,30, and 40mg	1mg per kg of body weight every 12 hours (up to weight of 30kg)	Peripheral neuropathy, pancreatitis and diarrhoea	Capsules can be opened and mixed with food. Capsules can also be dissolved in small quantities of water for immediate use.
Didanosine (ddI)	Chewable tablets with buffers: 25, 50, 100, 150mg, 200mg. Enteric-coated beadlets in capsules: 125, 200, 250, and 400mg.	< 3 months: 50 mg/m ² BD 3 months to 13 years: 90 - 120 mg/m ² BD or 240mg per m ² once daily Max. dose for children >60 kg: 200 mg BD or 400 mg once daily	Diarrhoea, abdominal pain, nausea, vomiting, peripheral neuropathy (dose-related), electrolyte anomalies, hyperuricemia, lactic acidosis and severe hepatomegaly, pancreatitis, increased transaminase tests, retinal depigmentation.	Food decreases absorption so give 1 hr before or 3 hrs after meals. Use at least 2 chewable tablets to improve buffering capacity. Capsules with enteric-coated beadlets can be opened and sprinkled on small amount of food.
NNRTIs				
Nevirapine (NVP)	Suspension: 10mg/ml Tablets: 200mg	Induction: Daily dose for 14 days at 4mg/kg po daily Maintenance: < 8 yrs: 7 mg/kg po BD ≥ 8 yrs: 4 mg/kg po BD PMTCT: 2mg/kg/dose within 72 hours of birth.	Skin rash (can be severe, SJS), TEN. Fever, nausea, headache, diarrhoea raised liver enzymes, liver toxicity can be severe. Hypersensitivity reactions.	No food restrictions. Rifampicin significantly reduces nevirapine levels and should not be used concurrently.

Guidelines for Antiretroviral Therapy

Name of medicine	Formulations	Age (weight) dose and frequency	Side-effects and toxicity	Other comments	
Efavirenz (EFV)	Capsules: 50, 100, 200mg	Administered once daily:		Skin rash, SJS, TEN CNS (somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, etc., more so in adults), raised liver enzymes, impaired concentration, hyperlipidemia.	Can be taken with or without food. High fat meals increase absorption by 50 % – advise patient to avoid. Capsules can be opened and added to liquids or food but has peppery taste – fruit jelly hides taste. Bedtime dosing recommended to improve tolerability of CNS side-effects. <i>Not recommended for children under 3 years of age.</i> NB Oral liquid is to be used ONLY in patients who can not swallow solids, and should be ordered by Regional Pharmacist for specific patients
		10 to < 14kg: 200mg OD			
		14 to < 20kg: 250mg OD			
		20 to < 25kg: 300mg OD			
	Oral Liquid 30mg/ml (180mls)	Wt band	Syrup		
		10-15kg	270mg		
		15-<20kg	300mg		
20-<25kg	360mg				
25-<32.5kg	450mg				
32.5kg-<40kg	510mg				
>40kg	Max dose 600mg				
Pls					
Lopinavir/ritonavir (LPV/r)	Paediatric oral solution: 80mg/ml lopinavir and 20mg/ml ritonavir Tablets: 200mg LVP and 50mg RTV	5-7.9 kg: 16mg/kg LVP <i>plus</i> 4mg/kg RTV BD with food 8 to 15kg: 12mg/kg LVP <i>plus</i> 3mg /kg RTV BD with food 15 to 40kg: 10mg/kg LPV <i>plus</i> 2.5mg/kg RTV BD with food > 40kg: 400mg LPV/100mg RTV BD with food.	Diarrhoea, headache, asthenia, nausea, vomiting. Elevated lipids, rash, pancreatitis, hyperglycemia, ketoacidosis, diabetes hepatitis.	Oral solution should be kept refrigerated (stable for 2 months at less than 25° C). Liquid has bitter taste. <i>Tablets cannot be split, crushed or opened. They must be swallowed whole.</i> Recommended for children above 6 months. Tablets have no food restrictions and are heat stable.	

NOTE: Metre² body surface area calculation: square root of (height in centimetres multiplied by weight in kilograms divided by 3,600).

Body Surface Area in M² =

$$\sqrt{\frac{\text{Height in cm} \times \text{Weight in kg}}{3,600}}$$

The nomogram on the inside back cover may also be used for determining body surface areas.

References

<http://www.who.int/hiv/events/paediatricmeetingreport.pdf>

<http://www.who.int/hiv/paediatric/generictool/en/index.html>

[List of drug interactions: British National Formularyh](#)

(<http://www.bnf.org/bnf/bnf/53/53178.htm>)

Bartlett, J. G., (2003). *Pocket Guide to Adult HIV/AIDS Treatment*. Baltimore, AETC National Resource Centre, The Johns Hopkins University. Available at: <http://www.hopkins-aids.edu/publications>

Bartlett, J. G. and Gallant J. E., (2004). *Medical Management of HIV Infection*. Baltimore, The Johns Hopkins University.

Bartlett J.G, and Gallant J.E., (2005). *2005-2006 Medical Management of HIV infection*. Baltimore, The Johns Hopkins University.

Bertolli et al., (1996). *Estimating the timing of mother-to-child transmission of human immunodeficiency virus in a breast-feeding population in Kinshasa, Zaire*. J Infect Dis. 1996 Oct; 174(4):722-6.

British Medical Association and Royal Pharmaceutical Society of Great Britain, (September 2003). *British National Formulary* (46 Ed.) London, William Clowes, Beccles, Suffolk.

Burnett, R.J., François, G., Kew, M.C., Leroux-Roels, G., Meheus, A., Hoosen, A. A. and Mphahlele, M.J., (2005). *Hepatitis B virus and human immunodeficiency virus co-infection in sub-Saharan Africa: a call for further investigation*. Liver International 25 (2), 201–213.

CDC Morbidity and Mortality Weekly Reports (MMWR), (June 2001). *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV and HIV, and Recommendations for Post-Exposure Prophylaxis*. Vol. 50, RR-11. Available at: <http://www.aidsinfo.nih.gov>

Food and Nutrition Technical Assistance (FANTA) Project, (2004). *HIV/AIDs: A Guide for Nutritional Care and Support* (2nd Ed.). Academy for Educational Development, Washington D.C.

McNicholl, I.R. and Rodriguez, R.A., (2006). *Dosing of Antiretroviral Drugs in Adults with Renal Insufficiency and Haemodialysis*. Developed by HIV InSite in collaboration with the AETC National Resource Centre. Available at: <http://hivinsite.ucsf.edu/tables>

Ministry of Health and Social Services, Directorate of Primary Health Care, (publication pending, 2006). *Nutrition Management for People Living with HIV/AIDS: a resource guideline for clinical health workers*. Windhoek, MoHSS.

Ministry of Health and Social Services, (2006). *National Guidelines for the Management of Tuberculosis* (2nd Ed), Windhoek, MoHSS.

Ministry of Health and Social Services, (2004). *Guidelines for the Prevention of Mother to Child Transmission of HIV* (1st Ed.). Windhoek, MoHSS.

Ministry of Health and Social Services, (2003). *National Guidelines on Clinical Management of HIV Disease and AIDS*. Windhoek, MoHSS.

O'Brien, D.P., Sauvageot, D., Zachariah, R. and Humblet, P., (2006). 'In resource limited settings good early outcomes can be achieved in children using adult fixed-dose combination antiretroviral therapy' in *AIDS*, 20: 1955-1960.

Paterson et al., (2000). *Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection*, Ann Intern Med, July 2000; 133: 21-30.

Perinatal HIV Guidelines Working Group, (2004). *Public Health Service Task Force Recommendations for the Use of Antiretroviral Medicines in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*. Available at: <http://www.aidsinfo.nih.gov>

Pham, A. P. and Flexner, C. W., (2005). *Antiretroviral Drug Interactions: A Practical Approach*, Baltimore, Johns Hopkins University.

Seidel, K. et al., (unpublished document, 1997). *The prevalence of serological markers for hepatitis B amongst first-time blood donors in Namibia – Baseline studies for immunisation*. Namibian Blood Transfusion Service and Department of Community Health, University of the Witwatersrand.

Shankar G et al. *Comparative bioavailability study of a novel pediatric fixed dose dispersible tablet (FDDT) of lamivudine, stavudine and nevirapine versus individual marketed liquid formulations*. Sixteenth International AIDS Conference, Toronto, abstract WeAb0304, 2006.

South African Medical Association, (2005). *South African Medicines Formulary* (6th Ed.) Cape Town, South African Medical Association, Health & Medical Publishing Group.
The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, (2004). *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*. Convened by the National Pediatric and Family HIV Resource Centre (NPHRC), The Health Resources and Services Administration (HRSA), and The National Institutes of Health (NIH). Available at: <http://www.aidsinfo.nih.gov>

Thomson Micromedex 2007. *Micromedex Healthcare series Vol. 133 exp 9/2007*

US Department of Health and Human Resources (DHHS), (2004). *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the US Department of Health and Human Resources (DHHS). Available at: <http://www.aidsinfo.nih.gov>

USPHS/IDSA, (2001). *Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus*. Available at: <http://www.aidsinfo.nih.gov>

WHO, (2004). *Antiretroviral Medicines for Treating Pregnant Women and Preventing HIV Infection in Infants. Guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings*. Geneva, WHO. Available at: <http://www.who.int/hiv/pub/mtct/guidelines/en/>

WHO, (2006). *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants in resource-limited settings. Towards universal access. Recommendations for a public health approach*. Geneva, WHO.

WHO, (2006). *Antiretroviral therapy for HIV infection in adults and adolescents in resource limited settings: Towards Universal Access. Recommendations for a public health approach*. Geneva, WHO.

WHO, (2006). *Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Recommendations for a public health approach*. Geneva, WHO.

WHO, (2006). *Guidelines on cotrimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings. Recommendations for a public health approach*. Geneva, WHO.

WHO/RHR/02.08 *Clinical Management of Survivors of Rape*. Available at:
www.rhrc.org/pdf/cmrs1.pdf