REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Directorate of Special Programmes

National Guidelines for Antiretroviral Therapy

Third Edition

July 2010

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Foreword

For the past seven 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 Third 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 that has contributed to our success.

Dr. Richard Nchabi Kamwi, MP

Minister

Preface

The second edition of the National Guidelines for Antiretroviral Therapy was launched in April 2007. 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 second edition of the ART guidelines have been revised in accordance with the latest evidence-based best practices. Realising the current challenges in human resources, we have made the third edition user-friendly for most service providers. The major achievements of the Namibian antiretroviral treatment programme are:

- More than 80% of patients in need of ART are receiving ART*.
- 64% of patients on ART are women.
- 16% of patients on ART are children*.
- Complete nation wide 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 health care providers.
- Introduction of the Integrated Management of Adolescent and Adult Illnesses (IMAI) strategy by MoHSS.
- Introduction of the quality management program (HIVQUAL) to continuously assess and improve the quality of HIV care in public health facilities.

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 ART clinics in the last seven years have necessitated the modification of second line regimen options. While the cost of treatment is considerable, simplified regimens result in savings to the health care 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. Viral load monitoring will be utilised to detect patients who are failing at an earlier stage of care. This third 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 are incorporated as are common interactions with non-ARV medications.

The unprecedented rapid scale-up of HIV treatment in Namibia faced the challenge of ensuring that high quality care standards are maintained. The MOHSS established the Namibia HIVQUAL program to monitor the quality of HIV care and support quality improvement (QI) processes in HIV care and treatment within the public health sector.Through this program, I urge all health care providers to consistently ensure that the quality of HIV care provided in all our facilities is maintained at high levels or improved where necessary in order to assure improved quality of life for all people living with HIV and AIDS in Namibia.

Development of this kind of 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 for Health, and the United States Centers for Disease Control and Prevention. I urge all doctors, nurses, and other health care professionals to familiarise themselves with the content of these guidelines in order to provide quality care to fellow Namibians.

Mr. Kahijoro S. M. Kahuure

Permanent Secretary

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Abreviations

3TC	Lamivudine
ABC	Abacavir
AIDS	Aquired Immune deficiency Syndrome
ALT	Alanine aminotransferase
ANC	Ante natal care
ART	Anti retroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
AZT	Zidovudine
AZT + 3TC	Zidovudine & lamivudine
BD	Twice Per Day
CD4	Cluster of Differentiation 4
CMV	Cytomegalovirus
CSF	Cerebrospinal Fluid
CXR	Chest X Ray
D4T	Stavudine
Ddl	Didanosine
DNA	Deoxyribonucleic acid
DVT	Deep Vein Thrombosis
EFV	Efavirenz
ELISA	Enzyme-linked immunosorbent assay
ENF	Enfurvitide
ETV	Etravirine
FBC	Full Blood Count
GMP	Groth 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
IPT	Isoniazid Preventive Therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
IUCD	Intra Uterine Contraceptive device
IV	Intra venous
IVI	Intra venous injection
LFT	Liver function test
LPV/r	Lopinavir + ritonavir
MAC	Mycobacterium avium complex
MOTT	Mycobacterium other that tuberculoses
MVC	Maraviroc
NIP	Namibia Institute of Pathology
NVP	Nevirapine
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-Nucleoside reverse transcriptase inhibitor
OD or od	Once daily
OIs	Opportunistic infections
PCP	Pneumocystis jiroveci (carinii) pneumonia
PCR	Polymerase chain reaction
PI	Protease Inhibitor
PLHIV	People living with HIV
PML	Progressive multifocal leukoencephalopathy
PO	Per os (by mouth)
RAL	Raltegravir
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 epidermal-necrolysis
TMP	Trimethoprim
ULN	Upper limit of normal
VZV	Varicella zoster virus
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 was developed in 2003, a second edition was published in 2007 and this has 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 counseling 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 public sector.
- Counseling for the patient and his/her treatment supporter to ensure full understanding of HAART, the importance of treatment adherence, timing of medication intake in relation to meals, and possible side-effects of HAART.
- Follow-up counseling 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 health care teams, including doctors, pharmacists, nurses, social workers, and counselors. 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 health care providers to provide standardised national management to HIV/AIDS patients over the last four 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 Third Edition of the National Guidelines for Antiretroviral Therapy

This Third Edition of the National Guidelines for Antiretroviral Therapy includes several significant changes from the Second Edition. In order for these revised guidelines to be implemented with minimum disruption to patient care, a smooth transition from the second edition to the third edition of the guidelines is essential. This is also important to ensure that the supply of medications through the central medical 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, this does not mean that patients must be transferred onto that regimen immediately.

2. The general rule is that if a patient is stable 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 TDF based regimens. This is to minimise their risk of stavudine related toxicities, which occur more frequently after a patient has been on D4T for 2 years or longer. (Please refer to Section 1.9.3 for further information)
- Many patients who have currently been receiving first line therapy of D4T/3TC/NVP will automatically be transferred onto TDF/3TC/NVP.
- If a patient new to ART presents at the clinic then they should be started on TDF/3TC/NVP unless there are contra-indications to this regimen.

Abacavir (ABC) has been introduced in these third 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. 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.

PART 1: Antiretroviral Therapy for Adults

1.1 Assessment of HIV-infected adults

A patient/client who receives 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, physical examination to determine WHO Clinical Staging (see Appendix 1) and other co-morbidities, a CD4 cell count, Hepatitis B Surface Antigen and a review of social eligibility criteria (see also section 1.4). 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 health care providers and started on HAART according to these guidelines, preferably by a trained HIV clinician. For more detailed guidelines for management of HIV Infected adolescents, refer to Paeditaric guidelines (Part 3)

1.2 When to start antiretroviral therapy in adults

Adults should start HAART when they have:

- WHO Clinical Stage 3 or 4 HIV disease, irrespective of CD4 cell count, or
- CD4 cell counts $\leq$ 350 cells/mm^3 including pregnant women irrespective of WHO Clinical Stage, and
- Fulfilled social eligibility criteria.
- Patients who are HBsAg positive do ALT
  - If >2 x ULN: treat with HAART
  - If <2 x ULN: do HBeAg
    - If positive: treat with HAART
    - If negative, monitor with CD4 count 6-month until either ALT>2 x ULN or eligible for HAART by clinical stage or CD4

N.B. Adherence counselling must be strengthened: intensify counselling especially for those with CD4 counts between 250 – 350 as they may not feel ill and hence may not fully understand the consequences of non-adherence.

Accurate assessment of the clinical stage of each HIV patient, at diagnosis and at every 3 to 6 months thereafter, is a critical and required step in assuring that eligible patients/clients are referred for antiretroviral therapy. Persons who have been ill or hospitalised in the preceding year should be promptly and carefully 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 threshhold, are also offered HAART.

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. Adherence is promoted by proper ongoing support and counseling.

Adherence is also promoted by simplified, well-tolerated regimens involving as few pills as possible, administered no more than two times per day.

If a patient misses a dose of antiretrovirals, he/she should **take the missed dose as soon as it is remembered**. If it more than 2 hours until the next dose is due, take the next dose at the usual time and continue with the normal schedule. If it is less than 2 hours until the next dose is due, take the missed dose, omit the next dose and then continue with the normal schedule. For example, if a patient was due for tablets at 8 AM and remembers at 4 PM that the dose was not taken, he/she should take that dose immediately and still take the 8 PM dose on time. If the patient was due for tablets at 8 AM and remembers at 7PM, then he/she should take the forgotten dose at 7 PM but should omit the 8 PM dose, and then go back to the normal 8 AM/8 PM schedule.

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. In order to achieve maximum readiness for HAART, there should be a coordinated effort involving the patient, physicians, pharmacy staff, nurses, other health care providers and persons within the immediate environment of the patient. If the patient is not fully committed to adhering to therapy, ART should be delayed while all the shortcomings are being addressed. Some methods for ensuring maximum adherence are presented in Figure 1.1.

Once therapy has begun, continued monitoring of adherence and ongoing patient education is essential. 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.

Figure1.1 *Methods to achieve readiness to start HAART and maintain adherence*

Patient-related:
· Take time needed, >2 visits at least 1-2 weeks apart, to ensure readiness before 1st HAART prescription (readiness check list). · Where possible recruit a family member, a friend, peer and community support for treatment supervision. · Negotiate a plan or regimen that the patient understands and to which he/she commits himself/herself · 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, and obtain refills. NB: Look out for active drug/alcohol use and untreated mental illnesses because they are associated with poor adherence.
Provider-related:
· Educate patient regarding goals of therapy, proper dosing, medication interactions, food effects and side-effects. · Assess adherence potential before HAART. Monitor at each visit. · Manage side-effects. · Monitor adherence and intensify management in periods of low adherence. · Ensure access at off-hours and weekends for questions or addressing problems. · Utilise entire health care team. · Consider effect of new diagnoses and events on adherence.
Regimen-related:
· Consider patient's current medications and prevent adverse medicine interactions and reactions. · Simplify regimen regarding: dose frequency, pill burden, pill storage, and food requirements. · Inform patient of anticipated side-effects.
Health team-related:
· Provide training updates on adherence for all team members and utilise entire team to reinforce adherence. · Educate volunteers, organisations of people living with HIV/AIDS (PLHIV) and community representatives on importance of adherence.

1.4 Social Considerations for starting HAART in Namibia

The Ministry of Health and Social Services has established social criteria, in addition to clinical and immunologic criteria. Meeting the social eligibility is necessary but should not be an obstacle for accessing HAART. The intention of these criteria is to maximise adherence and reduce the risk of failure of HAART and the development of resistance.

The social considerations that support better adherence to treatment includes the following:

- Having a fixed address for the past 3 months.
- Having ready access to a designated treatment centre for follow-up.
- Not abusing alcohol or ready to stop alcohol abuse.
- Not having unstable 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. 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, social worker and the Sister in charge of the treatment centre and sometimes the hospital ARV committee before discontinuing treatment. 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 may 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 the patient is deteriorating rapidly or CD4 count is extremely low, however, interrupting ART for three months may be omitted. If at the end of this time, the health care 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 six 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 tenofovir (TDF), zidovudine (AZT), lamivudine (3TC), didanosine (ddI), stavudine (D4T), abacavir (ABC) and emtricitabine (FTC).
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 Etravirine (ETV)
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 (ENF).
5 **Intergrase inhibitors**: Raltegravir (RAL)
6 **CCR5 entry inhibitors**: Maraviroc (MVR)*

**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 can not tolerate or who experience failure on the first and second line regimens should be referred for individualised care by an HIV specialist.

Recommended basic HAART combinations:

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

Examples and explanations of regimens which are NOT recommended:

- Regimens containing both ddI and D4T – increased toxicities.
- Regimens containing both AZT and D4T – antagonism.
- Regimens containing both ddI 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 in Namibia is:

TDF 300 mg + 3TC 300mg daily Plus 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, and then it is increased to twice daily.

**NVP should not be given to women with a CD4 count of >350 or men with a CD4 count of > 400.*

For women with a CD4 count of < 350, NVP can be used as the NNRTI of choice, however for women with a CD4 count of greater than 350, Efavirenz should be used instead unless contra indicated. When using EFV in women, ensure that the woman is prepared to use contraception – ideally injectable. In cases where both NVP and EFV are contra indicated, Lopinavir/ritonavir (LPV/r) should be used instead.

For all men with a CD4 count of < 400, NVP can be used as drug of choice, but if the CD4 is above 400 and the man is classified as either stage 3 or 4, NVP should be avoided and EFV should be used instead.

Note that the recommended first line regimen in Namibia has changed from AZT/3TC/NVP, which becomes an alternate first line regimen (see below). This change was made in keeping with the 2009 WHO Guidelines which were based on the growing body of evidence that AZT based regimens are associated with anemia and limitation of future treatment options compared with TDF based regimens. **Please note that stable patients on AZT/3TC/NVP, and who have no adverse effects, should be continued on this regimen. Clients who do not tolerate TDF or AZT, should be started on D4T.** 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 third line regimens, are included in Table 1.1

Table 1.1. *Recommended HAART regimens in Namibia* ***(see Appendix 4 for doses)***

What ART to start – First Line		
Target population	**2010 ART guidelines**	**Remarks**
HIV+ARV-naïve adults	TDF/3TC/NVP (preferred first line)	AZT/3TC/NVP (alternative to preferred first line). Use EFV if CD4>350
HIV+ARV-naïve pregnant women	TDF/3TC/NVP	EFV included as a NNRTI option where CD4>350 after first trimester. Benefits of NVP outweigh risks where CD4 count is 250 to 350 cells
HIV/TB co-infection	TDF/3TC/EFV	ART should be initiated as soon as possible in all HIV/TB co-infected patients with active TB (as soon as TB Rx is tolerated and within 8 weeks of commencement)
HIV/HBV co-infection	TDF/3TC/NVP if ALT <5 TDF/3TC/EFV if ALT >5	HBSAg positive clients with CD4>350 whose ALT is >2x ULN or ALT<2x ULN but with HBeAg+ are eligible for Rx regardless of WHO clinical stage. NNRTI regimens that contain both TDF/3TC are required *(see section 1.2)*
Second -Line ART		
Target population	**2010 ART guidelines**	**Remarks**
HIV+ adults	AZT/TDF/3TC/LPV/r	Where standard first line regimes were used
HIV+pregnant women	As above (adults)	
HIV/TB co-infection	As above (adults)	Adjust dose of RTV: i.e., LPV/r 400mg/400mg *
HIV/HBV co-infection	AZT/TDF/3TC/LPV/r	
Third Line (Salvage)		
Refer to HIV specialist		

Note that ABC and ddI can be considered as backup options in case of AZT or TDF toxicity or contraindication.

*This regimen is poorly tolerated and some patients may have to complete TB treatment before restarting ARV due to unacceptable gastrointestinal side effects.

Both nevirapine (NVP) and efavirenz (EFV) are included in first line regimen 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 daily.

Efavirenz (EFV) may be teratogenic and should be avoided 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 > 350 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 however be safely continued in patients whose CD4 counts have risen above these levels during the course of treatment.

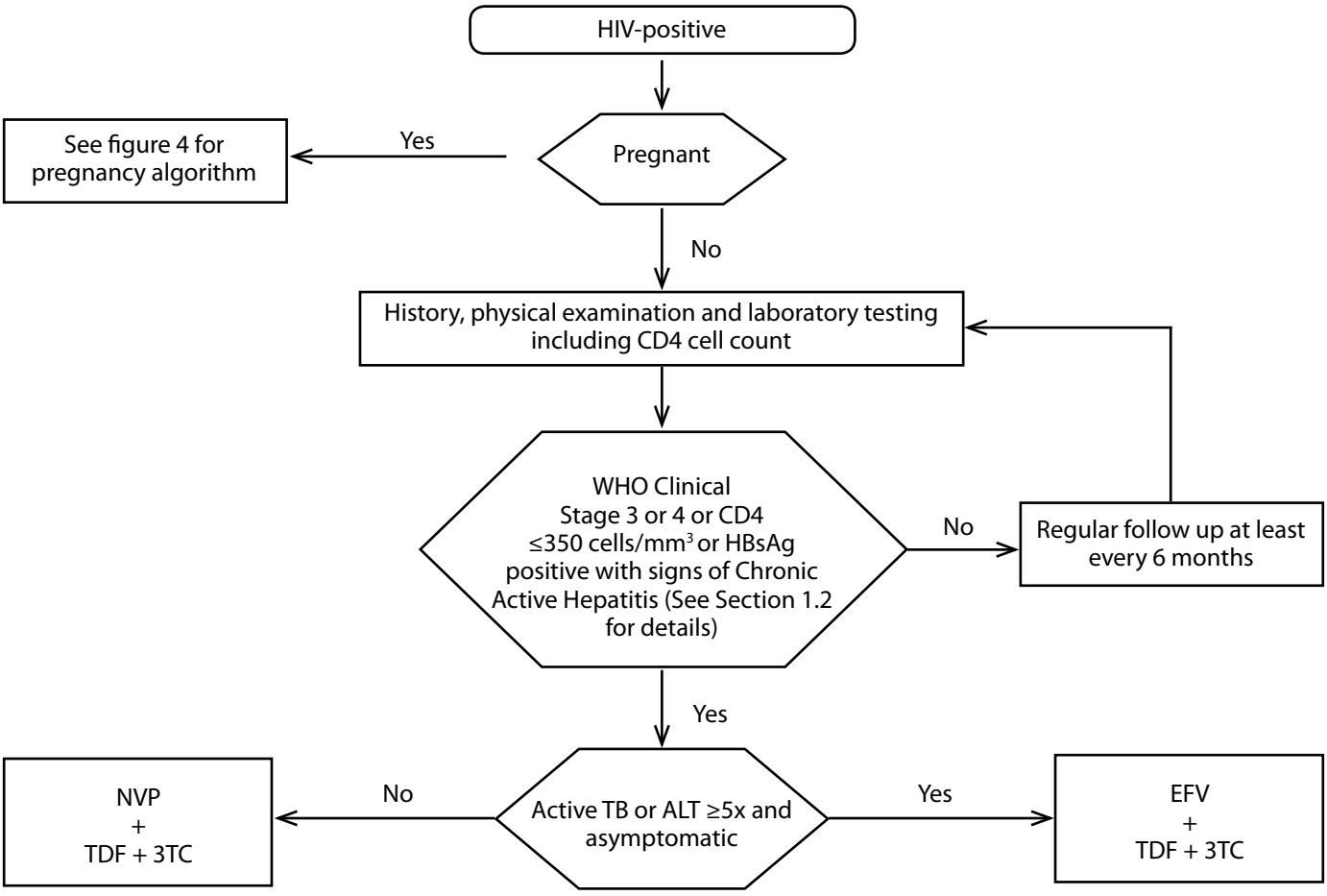
Second line options consisting of dual nucleoside plus protease inhibitor (PI) regimens have been selected because of their proven potency in reducing viral loads following NNRTI-based regimen failures. Disadvantages include higher cost, higher pill counts, significant interactions with other medications 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 3rd Line regimens are complicated and should only be implemented following the recommendation and close supervision of an HIV specialist.

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

The algorithm for prescribing HAART in Namibia is summarised in Figure 1.2.

Figure 1.2 *Algorithm for prescribing HAART in adults*



1.8 HAART in women of childbearing age

Many ARVs are safe to use during pregnancy, whilst others should be avoided. Efavirenz (EFV) cannot be used in the first month and is generally avoided in the first trimester due to a slight risk of teratogenicity.

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 Bilateral tubal ligation or vasectomy (for partners), is recommended for all women of childbearing age with clients' informed consent. Nevirapine, efavirenz and all the ritonavir boosted PIs affect blood concentrations of oral contraceptives and women receiving these medications should use additional contraceptive methods. Dual protection (use of condom + any other contraceptive method) and planning of pregnancies should be adequately addressed in all couples with both or one of them receiving HAART.

1.9 Reasons for changing antiretroviral therapy

Studies have shown that first line regimens give patients the best chance of long-term treatment success. Thus, 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 1.4 and 1.6). When it is not possible to identify the offending medication, discussion with an HIV specialist is recommended. It may be possible to re-introduce medications one at a time after short intervals.

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. Before any change is made due to failure, the circumstances contributing to the failure (e.g., poor adherence, medication interactions, malabsorbtion) should be thoroughly investigated and corrected before a new regimen can be started. Each case should be discussed with colleagues or a specialist physician.

1.9.3 Starting patients on TDF based regimens

The most important side effect of TDF is nephrotoxicity and declining renal function, although the incidence of these complications is rare. Where possible it is better to avoid TDF in patients at risk of renal failure from other causes such as hypertension, or diabetes mellitus. TDF can however still be used in specific patients with renal insuffiency (e.g. hepatitis B co-infection) if it is the only one available but should be carefully monitored and the dosage should be according to the recommendations concerning use of TDF in renal failure. (See Table 1.2 below)

The creatinine clearance must be calculated for each patient before starting TDF and regularly during therapy.

Table 1.2 *Recommendations for Tenofovir Dose Adjustment in Patients with Altered Creatinine Clearance*.*

Creatinine Clearance (mL/min)	Recommend Dosing of TDF 300 mg[30]
≥50	Every 24 hours
30-49	Every 48 hours
10-29	Twice a week
≤10	No recommendation available owing to a lack of pharmacokinetic data in this population
Hemodialysis patients	Every 7 days or after a total of 12 hours of dialysis (administer following completion of dialysis)

**Joel E. Gallant, MD, MPH (2005).Tenofovir and Renal Function: A Guide for Clinicians*

1.9.4 Changing patients from D4T based regimens

Long term side effects from D4T are well-documented and patients exhibiting these side effects should be switched from D4T containing regimens. Patients with signs of mitochondrial toxicity such as peripheral neuropathy, lipoatrophy and/ or lipodystrophy, lactic acidosis and/or consistently elevated liver transaminases (>5 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 TDF for D4T, as long as there are no contraindications to using TDF. Additionally, in order to minimise the risk of developing side effects, in patients who have been on a D4T-contaning regimen for longer than 24 months, the regimen should be changed to a TDF containing first line regimen. **Before 24 months, no patient should be changed from a D4T containing regimen which is clinically effective and being well tolerated unless they meet the above criteria. NB: when changing a patient to TDF remember to monitor CrCl at baseline, 3 and 6 months, then every six months.**

For patients who are stable on AZT based regimens; AZT should not be replaced by TDF

1.10 Second line HAART regimens

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 second line HAART regimen will ideally include at least two new ARVs, with one from at least one new class of antiretrovirals.

The number of second line regimen options is limited. Cross-resistance within the same ARV class is common. For example, zidovudine resistance implies stavudine resistance, and nevirapine resistance implies efavirenz resistance. 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 choice for HAART in adults in Namibia is:

Tenofovir-lamivudine-Zidovudine plus lopinavir/ritonavir

Although management of patients would be easier if resistance testing was done prior to selection of a second line regimen, this is costly and should not be done routinely. However resistance testing may be essential for patient who has failed a second line regimen and a third line regimen is needed. An HIV specialist must give approval for this on an individual patient basis, and in any case should be consulted for further management of the patient.

Ordering an HIV genotype resistance test should be done using the specific form for that purpose. On this form, patient medication history, the indications for doing the test and which of the authorized HIV specialists has been consulted should be specified. Without a fully completed form, the Namibia Institute of Pathology (NIP) laboratory will not accept the sample for testing.

Interpreting results of resistance testing is complex and should be analysed in conjunction with the ART history of the patient, noting that it may only provide information about resistance to the current regime the patient is on.

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 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 in the first trimester. Preferred treatment would be TDF-3TC-AZT but if either AZT or TDF is contraindicated abacavir can be substituted.
- In a patient with renal failure who has a life threatening intolerance to AZT, unable to tolerate D4T(or has already used D4T for >2 years) or history of lactic acidosis
- Second line treatment will sometimes require use of ABC where there is a complex treatment history, or toxicities to the usual second line regime.

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 named patient basis.
- HIV specialist 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 named patient from the Regional Pharmacist.
- Pharmacy to inform treating medical officer when stock of ABC is received.
- Pharmacy to ensure that the stock of ABC is used solely for the named 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 PLHIV: 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 section 1.19.1)

Cervical Cancer and HIV

Globally and in Namibia, cervical cancer is the second most common cancer (after breast cancer) among women. HIV infected women are at higher risk of:

- Infection with Human Papilloma Virus (HPV), the causative agent for cervical cancer.
- Having pre-cancerous lesions (2-6 times) depending on degree of immune suppression
- Developing cervical cancer from HPV
- Early progression to invasive cancer
- Presenting with late disease with poor prognosis

As part of clinical monitoring of PLHIV, annual screening using PAP smear is therefore now recommended for all women with HIV infection. All women with a positive PAP smear should be referred for colposcopy.

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. WHO clinical T-staging should be done and recorded for patients on treatment using the standard WHO clinical staging list. 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 (e.g., 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 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).Experience in some sites has shown that laboratory results are often not available at the time patients are seen for their follow-up visits, causing delays in evaluation of results of lab tests. Sites should therefore find a way for nurses to draw blood for laboratory tests a few days or a week prior to the outpatient visit so results will be available when patients seen for routine assessment.

RPR and Hepatitis B Surface Antigen will be done at the same time as CD4 soon after a patient has been diagnosed with HIV.

The recommended minimum laboratory tests before initiating ART are:

1. HbSAg if patient was hepatitis B negative at HIV diagnosis (in case new infection has occurred)
2. ALT
3. FBC
4. Creatinine clearance (CrCl) i.e. NOT simply a Creatinine.
5. Urine dipstick (looking for pre-existing renal disease, diabetes mellitus, etc)
6. Ask women about last normal menstrual period (pregnancy test if indicated)
7. (RPR and CD4 if not yet done)

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.

Routine monitoring after starting HAART (see also appendix 3)

1. If on TDF: creatinine clearance at 3, 6 months and 6-monthly thereafter
2. If on AZT: Hb at 2, 6 and 12 weeks, 6 months and 6 monthly thereafter
3. If HbSAg (+) OR on NVP: ALT at 2, 6 and 12 weeks, 6 months and 6 monthly thereafter
4. If on EFV and HbSAg (-): ALT at 12 weeks , 6 months, 1 year and 6 monthly thereafter.
5. If on EFV or PI, FASTING cholesterol and triglyceride at 12 months and yearly thereafter
6. Viral load at 6 months. If VL is >1000, do CD4, do intensive adherence counselling and repeat VL in 3 months. If not improving, consider changing to second line if adherence issues are resolved.
7. CD4 at 12 months and 6-monthly thereafter.
8. Additional VLs and CD4s will be done as indicated clinically (development of OI for example)
9. Due to high laboratory costs, a very limited number of resistance tests will be done in the public sector, where indicated **only after consultation and approval from designated specialist physicians.**

N.B. *Regions and districts must be made aware that to ensure validity of viral load (VL) results; viral load specimens must reach NIP laboratories within 6 hours. Due to reduced validity of results from old specimens, specimens reaching the laboratory after 6hours will be rejected. For districts and facilities which do not have easy access to an NIP lab, alternative arrangements will have to be made such as sending the patient to a district hospital with an NIP lab or NIP visiting sites on specified days. NIP will write SOPs for processing of samples at facility level. Facilities will determine the time that specimens will be drawn (e.g. 8-12 am) to ensure that samples get to the lab within 6 hours.*

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 ddI-induced pancreatitis) or clinical disease progression.

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. 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 emergence of ARV resistant 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 appendix 3.

***Table 1.3**. Baseline laboratory assessment for HAART*

Required Tests	Frequency
At VCT Centres, ANC-PMTCT site, OPD, Primary care clinic or hospital	
ELISA or rapid HIV Testing	diagnosis
At primary care clinic, OPD or Hospital	
CD4 cell count	immediately after diagnosis
RPR test	immediately after diagnosis
Hep B surface antigen (HBsAg)	immediately after diagnosis and when eligible for HAART
At communicable disease clinic or ANC-HAART clinic	
Full blood count	Baseline assessment when patient eligible for HAART
Hb	Follow-up per schedule
Creatinine Clearance	Baseline assessment when patient eligible for HAART and as indicated
ALT	Baseline assessment when patient eligible for HAART OR all patients with HBsAG positive soon after HIV diagnosis. Follow up per schedule
Blood Glucose	Only as indicated (especially for patients receiving PIs)
Pregnancy Test	Baseline (Where indicated)
CD4 cell Count	For preART patients: every 3 months For ART patients Baseline, at 1st year, and then every 6 months
Fasting Cholesterol and Triglycerides	Yearly (For patients on EFV, PIs or with cardiovascular risk factors)
Amylase	For patients with pancreatitis symptoms, especially on didanosine or stavudine
Urine Dipstick	Immediately after diagnosis
Viral load	To be done 6 months after initiating HAART. Useful for programme monitoring and in case of suspected treatment failure in individual. If VL is >1000, do CD4 and intensive adherence counseling and repeat VL in 3 months. If not improving, consider changing to 2nd line if adherence issues resolved
ARV genotypic resistance	Restricted to consultation with HIV specialists

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 health care providers. **Clinicians should immediately report any medicine adverse reactions to the Therapeutics Information and Pharmocovigilance Center (TIPC) using the appropriate form. See Appendix 9.** 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 1.4.

***Table 1.4**. 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 epidermal necrolysis (TEN) or Steven's Johnsons Syndrome	Nevirapine (NVP)	Stop immediately Never re-challenge
Lactic Acidosis	All NRTIs	Stop Immediately
Hepatotoxicity	NNRTIs 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	Didasone (ddI), Stavudine (D4T), Lamivudine (3TC)	Change therapy
Osteonecrosis/osteoporosis	Origin uncertain (PIs?)	Unknown
Long Term	**Associated Agents**	**Clinical response**
Lipoatrophy	NRTIs	Explain side effects Monitor patients Consider changing therapy
Fat accumulation	PIs	
Hyperlipidaemia	Efavirenz (EFV), PIs	
Lactic Acidosis	All NRTIs	Stop therapy, refer
Insulin Resistance	NRTIs PIs	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 with nevirapine, efavirenz and occasionally NRTIs . 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.

Nevirapine, however, may also provoke a serious 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 (≥ 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 may never be used in the patient again as this hypersensitivity reaction is likely to recur, and efavirenz should be avoided.

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 8.0 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). If Hb drops at all, refer to doctor for evaluation; (1) Doctor to investigate for any other causes of anaemia, (2) If drops is >10% but <25%, repeat Hb in one week. AZT should be substituted immediately if Hb falls below 8.0 gm/dl or drops by more than 25%.

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 section 1.20.2. 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, six months 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 symptomatic 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. 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 complication of HAART (mortality approaching 50% in early studies) is caused by mitochondrial dysfunction and a resulting disruption in normal cellular metabolism. Lactic acidosis can be difficult to recognise as clinical symptoms are non- specific.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 exceptions). Patients should not be taking a combination of D4T and ddI, especially pregnant women, because of the high 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.

***Table 1.5**. 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

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).
- HCO_3< 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 symptomatic patient having an unexplained acidosis (no evidence of diabetic ketoacidosis, renal failure, dehydration, etc.). Asymptomatic hyperlactataemia is common anong patients on HAART and requires no treatment. 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. Modified HAART regimens will be required hence 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. High Amylase is common in asymptomatic HIV patients and is usually not due to pancreatitis but to sialoadenitis.

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 or substituting 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 TDF. Similarly, a patient on nevirapine who develops a non-life threatening rash can have efavirenz substituted for nevirapine. (See Table 1.6)

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 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. 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) at their usual dosing for 7 days. This will decrease the risk of developing NNRTI resistance. For HAART regimens that combine NRTIs with PIs, all medications may be stopped at the same time.**

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 1.6**. Changing first line antiretrovirals in case of toxicity*

Medicine	Toxicity	ARV Substitution
TDF	1. TDF related Renal insufficiency	1. Switch TDF to AZT
AZT	2. AZT related severe haematological toxicity	2. Switch AZT to TDF
NVP	3. NVP related severe hepatotoxicity and NVP related moderate rash (but not life threatening) 4. NVP related life threatening rash (Stevens Johnsons Syndrome)	3. Switch NVP to EFV 4. Switch NVP to PI
D4T	5. D4T related neuropathy or pancreatitis or D4T related lipoatrophy/lypedydtrophy	5. Switch D4T to TDF
(Adapted from WHO: Scaling Up Antoretroviral Therapy in Resource Poor settings, 2006 version)		

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.

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.

Some of the interactions may be specific to some ARVs;

- Grapefruit juice may inhibit intestinal enzymes that metabolize ARVs especially PIs resulting in poor bioavailability and slow detoxification.
- Garlic may reduce the efficacy of Saquinavir.
- A high-fat meal increases the bioavailability of Tenofovir but lowers absorption of Amprenavir
- High protein foods reduce absorption of Indinavir but increases that of Nelfinavir

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 (ddI). Medications such as PIs are absorbed better with fatty meals.

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, 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.

However most patients recover quickly and do well on ARV medications.

Nutritional related side effects of ARV's

While ARVs contribute to improved nutritional status, they occasionally create nutritional problems, which require nutritional interventions.

High blood cholesterol: Nutritional counseling to reduce dietary fat intake and limiting saturated and trans fat intake, increase daily vegetable and fruit intake, and regular exercise should be promoted.

High triglycerides: Nutritional counseling to limit saturated and trans fats intake (low density lipoproteins), moderation in carbohydrate intake and an increase in intake of whole grain cereals, fruits, and vegetables. Regular exercise is a vital supportive measure.

Peripheral neuropathy: This is a condition that is felt as numbness, tingling, burning sensation in the toes, feet, fingers or hands and may be caused by ARVs. Supplementation with B vitamins is only useful where nutritional deficiency is considered likely.

Liver damage: ARVs such as protease inhibitors can damage the liver.

Kidney stones: Condition manifests as severe pain in the lower back and side as well as difficult and painful urination. Kidney stones may be caused by ARV's such as Indinavir and can be prevented by drinking plenty of clean safe water (extra 1.5L per day).

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 HIV 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.

In addition, PLHIVs may take other medications with ART, such as antibiotics to treat opportunistic infections, anti-malaria, anti-helminthic (worm) or anti-fungal medications to treat other conditions such as malaria, intestinal parasites and thrush respectively. 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 that cause individuals to stop taking them or become sicker.

Drug-drug interactions are often a serious complication of taking multiple medications and account for 3% to 5% of all in-hospital medication errors. The consequences of drug interactions vary, ranging from drug toxicities to therapeutic failures.

These consequences can result in suboptimal treatment of the targeted disease states, damage to vital organ systems, or death. Drug interactions are of particular concern in patients infected with HIV who are receiving highly active antiretroviral therapy (HAART).

ARVs used in the treatment of HIV are often prone to drug interactions because many of them are metabolized through the CYP450 system., Since NRTIs, fusion inhibitors, and integrase inhibitors do not undergo hepatic metabolism through the CYP450 system, their drug interaction profile is minimal. Conversely, NNRTIs, PIs, and maraviroc (a CCR5 antagonist), are extensively metabolized by the CYP450 system; thus, they are highly susceptible to drug interactions. Furthermore, NNRTIs and PIs can inhibit and/or induce some of the CYP450 isoforms.

The pharmacokinetic properties of NNRTIs and PIs can lead to sub- or supratherapeutic levels of concomitant drugs that are metabolized by the same CYP450 isoenzymes. Alternatively, if the concomitant drug acts as an inhibitor or inducer of the CYP450 isoenzymes that the NNRTIs and PIs are metabolized through, the ARV levels will change accordingly, possibly resulting in a reduced antivirologic response or ARV-related toxicities to the patient.

Understanding the mechanisms of the CYP450-system mediated drug interactions between ARVs and commonly prescribed medications in the HIV patient population is important in order to determine if dosing modifications, close monitoring for adverse effects of drugs, or careful monitoring of a patient's viral load for virologic failure are necessary

These guidelines will discuss major drug interactions that occur with NNRTIs and PIs, focusing on the following classes of drugs: antiepileptic drugs (AEDs), antidepressants, antidepressants, calcium channel blockers and acid-suppressive agents.

1.16.3.1 Antiepileptics

The first-generation AEDs (i.e., carbamazepine, phenytoin, Phenobarbital) are substrates as well as inducers of the CYP450 system. There is a decreased metabolism and subsequent toxicity of carbamazepine when concomitantly administered with PIs, particularly ritonavir (including low doses of ritonavir utilized for boosting other PIs). Therefore, in patients receiving carbamazepine concurrently with a ritonavir-containing HAART regimen, it may be appropriate to choose an alternative AED such as Sodium Valproate or the newer AEDs.

Induction of certain CYP450 isoenzymes (i.e., 2C9/19 by lopinavir/ritonavir and nelfinavir) has been reported and can lead to an increase in the metabolism of AEDs like phenytoin, a narrow therapeutic index drug. Consequently, this reduction in the anticonvulsant serum concentrations can lead to seizures. Likewise, ritonavir-based HAART regimens have been shown to decrease valproic acid concentrations. This interaction is likely due to ritonavir's ability to induce valproic acid metabolism via glucuronidation.

Both NNRTIs (efavirenz and nevirapine) have been shown to decrease carbamazepine levels. This reduction in carbamazepine levels occurs as a result of the induction of the CYP3A4 isoenzyme by efavirenz and nevirapine.

Furthermore, carbamazepine, phenytoin, and phenobarbital all have the potential to induce PI, efavirenz, and etravirine metabolism and thus reduce serum concentrations of these drugs, which can lead to ARV resistance and treatment failure. Formal recommendations regarding dosing adjustments of PIs, efavirenz, or etravirine are lacking. Therefore, careful monitoring for virologic resistance and failure is essential.

Some of the newer, second-generation AEDs may have pharmacokinetic advantages over traditional agents, including decreased drug interactions. However, there are limited clinical data to support their use in combination with ARVs. Gabapentin, levetiracetam, and lamotrigine are minimally metabolized by the CYP450 system and may be considered when the potential for significant drug interactions limits the use of first-generation AEDs. Use of other second-generation AEDs (e.g., topiramate, tiagabine, oxcarbazepine, felbamate) may be limited due to their induction/inhibition of CYP450 isoenzymes and/or their adverse-effect profiles.

Due to the difficulty in predicting the potential interactions between first-generation AEDs and ARVs, strict monitoring of serum concentrations of these AEDs are necessary in order to avoid drug toxicity or inadequate control of seizures/disease states. Dosing adjustments should be made according to serum AED concentrations, control of the patient's disease state, and adverse effects. Moreover, it is important to also monitor the patient's virologic response to HAART since some AEDs have the potential to accelerate the clearance of some ARVs, resulting in a likely decrease in efficacy.

Alternatively, other second-generation AEDs that are minimally metabolized by the CYP450 system may be suitable alternatives if deemed appropriate for the patient.

1.16.3.2 Antidepressants

Depression is a frequent disorder among HIV patients, with a reported incidence of up to 47.8% in some studies. Patients are often treated with a variety of antidepressants, including selective serotonin reuptake inhibitors (SSRIs). The majority of ARVs (PIs and NNRTIs) and antidepressants are substrates for, and can inhibit or induce, the CYP450 system, and they have the potential to cause clinically significant drug interactions including serotonin syndrome, a potentially fatal complication.

Ritonavir has been shown to augment levels of a variety of SSRIs, including fluoxetine, citalopram, paroxetine, and sertraline. Monitoring for antidepressant side effects when initiating ritonavir in patients receiving concurrent SSRI therapy is recommended. The dosing of antidepressants should be reduced when administered with concomitant ritonavir based regimen or ritonavir should be discontinued. Other ARVs are anticipated to affect SSRIs to a lesser extent, and initial dose adjustments may not be necessary.

Fluvoxamine, a potent inhibitor of CYP1A2 along with fluoxetine and paroxetine (both potent inhibitors of CYP2D6), may also cause PI toxicity by increasing their concentrations. Sertraline, citalopram, and escitalopram appear to have little effect on the major CYP isoforms and are not expected to affect levels of the ARVs.

When coadministering antidepressants and either a PI- or NNRTI-based HAART regimen, antidepressants should be initiated at a low dose and titrated over several weeks. Patients should also be closely monitored for adverse effects.

1.16.3.3 Anticoagulants

The PIs and NNRTIs have varaiable effects on CYP: induction, inhibition, or mixed. When administering warfarin with concomitant PIs or NNRTI, high warfarin doses are required to maintain therapeutic international normalized ratios (INRs). INR should be monitored regularly and carefully.

1.16.3.4 Acid reducing agents

Studies suggest that some of the interactions between protease inhibitors and acid-reducing agents may be mitigated by temporal separation of dose administration. Acid-reducing agents reduce the absorption of PIs. Proton pump inhibitors such as Omeprazole reduce the blood concentration levels of PIs. There have not been many reports of adverse interactions with H2 receptor blockers (ranitidine). Educating patients about the importance of reporting the use of any acid-reducing agents, whether prescription or over-the-counter, is essential to optimizing the treatment of HIV disease, as is the need for care providers and patients to agree upon strategies for managing gastric symptoms and HIV disease simultaneously. Clinicians should be aware of the potential drug-drug interactions between some protease inhibitors and acid-reducing agents.

1.16.3.5 Calcium channel blockers (CCBs)

Ischemic cardiovascular disease and hypertension occur in persons with HIV infection, and the incidence and prevalence may increase over time as the infected population ages. Standard pharmacologic interventions for these illnesses often include calcium channel blockers (CCBs).

Many of the calcium channel blockers are metabolized by cytochrome P450 3A4 (CYP 3A4), which is inhibited by some protease inhibitors (PIs). Thus, there is potential for clinically significant interactions between CCBs and PIs. The presence of significant drug-drug interactions may influence the dosing, monitoring, and choice of CCBs and/or PIs when used in persons with HIV infection

1.16.4 Nutrient requirements of people living with HIV/AIDS

To provide counseling 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 counseling the client on the importance of food intake with ART.
- Identify medications that have special food interactions – such as didanosine (ddI), which must be taken either 1 hour before or 2 hours after a meal.
- Identify potential nutrition-related side-effects with ART and provide counseling on management of side-effects.

Malnutrition among PLHIV manifests most commonly as weight loss and wasting in adults. Weight loss among PLHIV occurs due to reduced intake (starvation), malabsorption and sudden increase in energy expenditure, problems with utilization or a combination of these factors. Therefore, a key objective of nutrition, care and support for PLWHA is to prevent weight loss and maintain nutritional status within the normal range.

Good 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. For these reasons, nutrition counselling should be provided to all clients on ART from the start of therapy.

Increased energy needs

Asymptomatic adult PLHIV require an additional 10% while symptomatic adult PLHIV require an additional 20-50% depending on disease stage. To achieve the additional energy needs, PLHIV should be counselled and educated on consumption of a variety of foods.

Strategies to meet increased energy requirements of PLHIV include

- Dietary adjustments and meal plans of regular energy giving foods such as mahangu, maize, rice, potatoes, cassava, wheat
- Adoption of food preparation methods that add value for example sweetening porridge or adding nuts, and frying potato chips raises their energy values several folds.
- Consumption of snacks between meal

Protein needs

According to WHO, there is insufficient evidence to support increased protein requirements for PLHIV. However, the quality of protein with respect to adequacy of essential amino acids is important. PLHIV should therefore be encouraged to consume foods rich in both animal protein (dried small fish, chicken, Mopani worms, fillet and beef) and plants source protein (soya, lentil seeds, beans, groundnuts and peas).

Micronutrient needs

Adequate micronutrient intake is achievable through consumption of a healthy balanced diet including plenty of fruits and vegetables. Current evidence does not support increased micronutrient needs above 1 Recommended Daily Allowance (RDA) for PLHIV compared to non-HIV infected individuals. Therefore, PLHIV should be encouraged to consume plenty of fruits (such as oranges, mangoes, pawpaw, guava, apples, and baobab) and vegetables (such as spinach, amaranthus, cauliflower). Health workers should however consider supplementation in cases of identified deficiencies.

Water requirement

Water consumption is an integral part of good nutritional practices. A daily fluid intake of 2 litres, equivalent to 8 glasses of about 250 ml is required. PLHIV must take adequate amount of clean and safe water to avoid dehydration aid transport of nutrients, removal of wastes (such as medication by-products), assist metabolic activities, provide lubrication to moving parts and helps regulate body temperature. In the absence of clean safe water, point-of-use water treatment should be provided to the patients.

Severe acute malnutrition in HIV positive adults

PLHIV are at greater risk of malnutrition (under-nutrition) than non-HIV-infected adults. This manifests as wasting, weight loss and/or reduced immunity and is usually as a result of deficiency in macro- and micronutrients. Prevention or treatment of moderate and malnutrition is essential in HIV infected adults. All HIV infected adults attending the ART clinic should regularly undergo nutrition assessment (weight, height, BMI or MUAC) for categorization of their nutritional status.

Furthermore they should be adequately counselled/educated on nutrition using appropriate guidelines. For the management of moderate/severe malnutrition in HIV positive adults refer to Appendix 7.

1.17 Traditional therapies and supplements

Traditional therapies and supplements for PLHIV 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 PLHIV 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 Preventive Therapy (CPT)

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 (800/160mg total -daily) is recommended for persons with HIV and either WHO Clinical Stage 3 or 4 disease (see Appendix 1) or any WHO clinical stage with a CD4 cell count ≤ 350 (Table 1.7). However, CPT may be discontinued when CD4 increases to > 350 for two consecutive CD 4 measurements at least 6 months apart.

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 other 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, peripheral neuropathy, 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, 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 (TB-IPT should not be given to patients who are unwell and where there is no explanation of the illness).
- Have no symptoms or signs of TB – cough, fever, weight loss, night sweats, fatigue, blood in sputum, chest pain, diarrhoea, shortness of breath, 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, possible side-effects and risks.
- Have not had TB within the last 2 years and not had previous IPT

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. Peripheral neuropathy manifests as burning, numbness or tingling in feet and/or hands.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, neuropathy and skin itching when patient come to collect INH.

Treatment:

- Isoniazid is given daily for a period of 6 months at a dosage of 10 mg/kg bodyweight up to a maximum of 300mg/per day.
- Pyridoxine 25 mg daily is administered with the INH to decrease the risk of neuropathy. The risk of developing neuropathy increases in patients also on D4T.
- Temporary TB - IPT interruption, although not ideal, is acceptable, as long as the patient completes a total of 6 months of treatment within a 9 month period. In non-adherent patients, prophylaxis should be discontinued and no further efforts should be made to restart TB - IPT.

Recording and reporting:

All details of the person receiving TB-IPT must be recorded as required in TB-IPT clinic register, and either TB-IPT identity card or any other form used by individual clinics which remains in the patients passport. IPT status should also be recorded in the patient care booklet:

Only one 6-month course of TB-IPT is given to an individual patient. Its efficacy lasts for approximately two years, after which a PLHIV 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 Fluconazole prophylaxis

If a patient has suffered from cryptococcal meningitis, they should remain on fluconazole 200mg daily for life as secondary prophylaxis (i.e. to prevent recurrence). This can be discontinued if CD4 remains above 200 for more than 6 months on 2 consecutive occasions and the patient is on HAART

1.18.4 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 > 350, 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 1.7**. Prevention of opportunistic infections in adults*

Pathogen	Indication	Medicine and dose	Discontinuation
Pneumocystis pneumonia and toxoplasmosis	· CD4 < 350 · WHO Clinical stage 3 or 4 (AIDS)	Cotrimoxazole 2SS (or 1 DS) tab/d (800/160mg)	CD4 increases to > 350 for two consecutive CD 4 measurements at least 6 months apart
TB*	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	Isoniazid 300mg/d plus pyridoxine 25mg/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 in asymptomatic patients) 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.).*

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.

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.

Recommendations for management vary by pathogen and clinical expression, but most involve continuation of HAART and medications directed against the pathogen, with or without anti-inflammatory agents. Common examples are given in Table 1.8.

***Table 1.8**. Immune Reconstitution Inflammatory Syndromes*

Opportunistic Infection	Clinical features	Treatment
MAC (One form of MOTT)	Focal adenitis, granulomatous masses	MAC Therapy: Azithromycin 500mg/d plus Ethambutol 15mg/kg/day plus steroids_ For patients with CD4 < 50, add either a quinolone* or Amikacin 10-15 mg/kg daily Stop treatment when CD4 count > 100 two consecutive readings 6 months apart
CMV	Vitritis	CMV therapy: Intra ocular ganciclovir implant (Vitrasert) + oral valganciclovir 900mg/day plus local steroids. Stop treatment when CD4 > 100 two consecutive readings 6 months apart
TB	Pneumonitis, lymphadenitis, sparse acid-fast bacillus (AFB)	TB treatment + steroids
Cryptococcis	Meningitis with high CSF WBC	Antifungal therapy: amphotericin B IV 0.7-1mg/kg for 2 weeks, followed by fluconazole 400mg/d for 8 weeks. Maintenance: fluconazole 200mg/d Stop treatment if CD4 > 200 for 6 months two consecutive readings 6 months apart
HBV	Active hepatitis	HAART which should include Lamivudine plus Tenofovir
Herpes Zoster	Mild disease	Symtomatic treatment (oral acyclovir where indicated)
Progressive multifocal leukoencephalopathy (PML)	Neurologic deficits, MRI with peripheral enhancement	Continue HAART - no additional specific therapy

** Available quinolones in the state are levofloxacin and ciprofloxacin*

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 2008 the case notification rate of new and relapsed cases of TB in Namibia was 717 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 PLHIV must have knowledge of TB. Clinicians are strongly urged to familiarise themselves with the National Guidelines for the Management of TB and Leprosy 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. ART should be initiated as soon as possible in all HIV/TB coinfected patients with active TB (within 8 weeks after the commencement of TB treatment)

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 2NRTIs such as tenofovir-lamivudine (TDF/3TC) is effective.

For patients on rifampicin, alternatives to efavirenz are:

1. Triple nucleoside regimens:
   - e.g. tenofovir (TDF) + lamivudine (3TC) + zidovudine (AZT)
     N.B. These combinations are short term and the patient should be switched to a NNRTI containing regimen two weeks after completing Rifampicin.
2. A lopinavir based regimen super boosted with ritonavir:
   TDF or AZT+3TC with LPV/r 400mg+ritonavir 400 mg BD (poorly tolerated).

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

WHO in 2010 recommended that all patients with chronic **Active** Hepatitis B should be started on HAART regardless of CD4 and clinical staging. Diagnosing Chronic Active Hepatitis without histology is difficult and Namibia recommends that all patients who are HBsAg positive should have an ALT done and if the ALT is > 2x ULN then active hepatitis B is very likely to be present. However HBsAg positive patients with ALT <2 ULN but HBeAg positive should also be considered as likely to be having chronic active hepatitis. Both types of patients should be commenced on HAART regardless of CD4 or clinical stage. 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 enrolment 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 coinfected patients on lamivudine-containing HAART without tenofovir. Patients with HIV/HBV co-infection on HAART require close monitoring for clinical signs and symptoms of hepatotoxicity and laboratory monitoring of ALT.

All patients in whom HbSAg is positive shall have ALT at 2, 6, 12 weeks, 6 months and 6-monthly thereafter. Elevated ALT arising during therapy may have many causes, and needs to be carefully evaluated.

Table 1.9. *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	ARV's: NVP>>RTV>EFV	
	Lactic acidosis with steatohepatitis	NRTIs:D4T>ddI>AZT	
	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 resistence 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, acute alcoholic hepatitis	Reduce or eliminate alcohol use
Jaundice ↑ Bilirubin	Medication effect	Indinavir	↑ indirect bilirubin with normal ALT and no haemolysis; can continue indinavir
	Severe liver insufficiency	Any cause	↑ direct bilirubin, ↑ ALT/AST, low albumin, prolonged prothrombin time, may have ascitis, encephalopathy, GI bleeding
	Severe malaria	Haemolysis rather than hepatitis	↑ indirect bilirubin with anaemia and positive malaria smear
	Biliary tract obstruction	Common bile duct stones, pancreatitic cancer, mass in prota hepatis	↑ direct bilirubin, ↑ alkaline phosphatase, normal ALT/AST, sonogram helpful
Infiltrative liver disease	Infections	Extra-pulmonary or disseminated TB, MOTT	↑ alkaline phosphastase, other LFTs nearly normal, hepatomegaly
	Immune reconstitution Inflammatory syndrome	Immune response to TB or MOTT	See table 1.8
	Malignancies	Hepatoma, lymphoma, liver metastasis	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). Discuss with colleagues or where possible consult with an HIV specialist 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:

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

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. Dilated cardiomyopathies can follow previous myocarditis. Important differential diagnoses include:

- Large pericardial effusion.
- Rheumatic valvular heart disease.

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

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 regular screening of such complications of 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

Haematological conditions may present as anaemia, leukopaenia, thrombocytopaenia, and pancytopaenia. Possible causes are:

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

Necessary investigations:

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

Treatment for Immune Thrombocytopaenic Purpura (ITP) includes 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 incidence of multipathogenic meningitis:

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

All unexplained headache and fever symptoms should be investigated lumbar puncture (LP), followed by empiric STAT dose of ceftriaxone (2 grams iv). Refer to MoHSS Standard Treatment Guidelines (STGs).

- Treatment of neuro-syphilis is benzyl penicillin (penicillin G) 2 to 4 million units given IV every 4 to 6 hours 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 also 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. However valproic acid is less likely to interact with 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 toxoplasma serology is positive, then treat for toxoplasmosis. If toxoplasma serology 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, D4T, ddI).
- Myopathy: -HIV-related. -Toxoplasmosis. -Cytomegalovirus. -Cryptoccocus. -Mycobacterium other than tuberculosis (MOTT). -Lymphoma. -Medications (esp. AZT).
- Bell's palsy is common among HIV patients and may be HSV or VZV-associated: if the patient presents within 48 hours of the onset of symptoms give prednisolone 50 mg for 5 days as well as specific treatment

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).
- Psoariatic arthritis.
- Osteomyelitis (TB, bacterial).
- Avascular necrosis

1.22 When to consult an HIV specialist

Good collaboration between general practitioners and HIV 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.

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

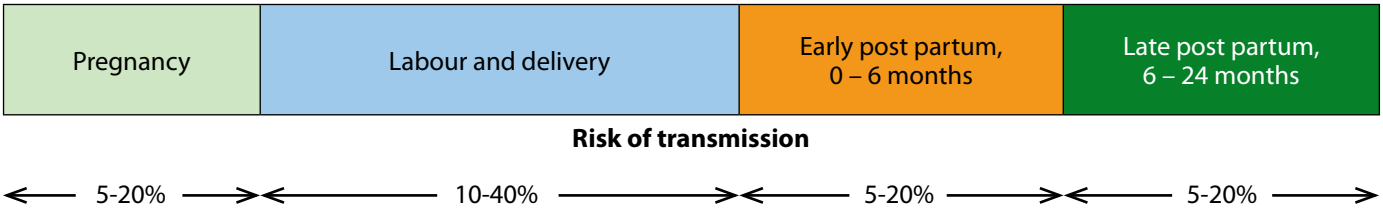
2.1 General considerations

PMTCT includes 4 main strategies:

1. Primary prevention of HIV infection.
2. Prevention of unintended pregnancy in HIV-infected women.
3. Prevention of HIV transmission from HIV-infected women to their infants.
4. Provision of comprehensive care to mothers living with HIV, their children and families.

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 2.1 *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:

Table 2.1 *Factors that increase the risk of mother-to-child transmission*

Obtetrical	Maternal	Foetus/New Born	Viral
· Episiotomy · Invasive monitoring resistance · Instrumental delivery · Rupture of membranes (ROM) >4 hours · Antepartum and intra partum haemorrhage · Amniocentesis	· High viral load · Low CD4 count · Advanced disease · Poor nutrition · Breast conditions · STIs · New HIV infection · Maternal TB	· Prematurity · Multiple birth · Breast feeding · Mixed feeding · Immature gastrointestinal tract · Genetic factors · Immature immune system	· Viral type · Viral resistance

Numerous clinical trials have demonstrated that appropriate use of ARVs can be highly efficacious in reducing the risk of MTCT. All pregnant women should be offered HIV testing and counselling at their first antenatal visit or other visits if not already tested. All women should receive further counselling and clinical care during follow-up for the pregnancy in order to optimize antenatal care, provide an appropriate antiretroviral regimen and promote safe feeding practices.

Pregnant women who initially test HIV-negative should be re-tested for HIV at 36 weeks or later.

2.2 Management of ARVs in pregnancy according to clinical scenarios

The following section is adapted from the WHO Rapid advice 2009

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

HAART regimens in pregnant women reduce HIV transmission by significant reductions in maternal viral load. All recommended HAART 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 pregnant woman should remain on her current HAART regimen unless there is a reason to change it such as side effects or failure. This includes maintaining TDF in women who were already taking TDF as previous concerns about use of TDF in pregnancy have been largely relieved by a volume of accumulated pregnancy data.

Where a woman presents in the first month of pregnancy and is using efavirenz, the woman should be switched on to nevirapine unless there is a contraindication. It is recognized that women very rarely present in the first month of pregnancy, however.

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

Infant: Both breastfeeding and non breastfeeding infants receive daily nevirapine from birth until 6 weeks of age.

Extended simplified infant NVP dosing recommendations based on the dosing required to sustain sufficient serum exposure of > 100 ng/ml with least dose changes.

Table: 2.2 *Simplified infant NVP dosing recommendations*

Infant age	NVP daily dosing
Birth -6 weeks	
• Birth Weight < 2,500 gram	10 mg/daily
• Birth Weight >2,500 gram	15 mg/daily
>6 weeks to 6 months	20 mg/daily
>6 to 9 months	30 mg/daily
>9 months to end of BF	40 mg/daily

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

For an HIV-positive pregnant woman who has not received ARV therapy, eligibility for ARV therapy must be determined. Where eligible, the use of ARV therapy during pregnancy will improve the health of the mother and substantially decrease the risk of transmission of HIV to the infant.

Pregnant women should be started on HAART 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 350/mm^3.
- Social eligibility criteria should be met as described in section 1.4.

Where possible (and CD4 >200 with no symptoms), it may be better to delay HAART until the end of first trimester to avoid the period of morning sickness. If the patient is severely ill with advanced HIV disease, HAART should be started as soon as possible.

What to start in pregnant women needing treatment for their own health with previous NVP exposure

I. If the woman has previously received sdNVP (+/- antepartum AZT) **without** AZT/3TC tail in last 12 months: initiate non-NNRTI regimen (PI)

II. If the woman has previously received sdNVP (+/- antepartum AZT) **with** AZT/3TC tail in last 12 months: initiate NNRTI regimen, check VL at 6 months

III. If the woman has previously received sdNVP (+/- antepartum AZT) **with or without** AZT/3TC tail more than 12 months ago: initiate NNRTI regimen, check VL at 6 months

The first line regimen for HIV-positive pregnant women who do not have active TB and meet the eligibility criteria for HAART is:

If CD4<350: -tenofovir lamivudine-nevirapine (TDF+3TC+NVP)

Alternative regimens include TDF+3TC+EFV (after the first trimester)

AZT+3TC+NVP

AZT + 3TC + EFV(after first trimester)

If CD4> 350: TDF+3TC+EFV

Alternative: AZT+3TC+EFV

The dosages for the first line HAART regimen in pregnant women are the same as in other adults. ARVs should be continued as usual during labour and the postpartum period. Particular care should be taken to screen for the following side effects

- Nevirapine-related liver toxicity and skin rash.
- Tenofovir –induced impairment of creatinine clearance
- Zidovudine (AZT) induced anaemia. AZT should not be used in women with Hb ≤8g/dl.

Infant: daily nevirapine from birth until 6 weeks of age.

Scenario 3: HIV Infected pregnant woman who do not qualify for HAART but present at ANC

All HIV-infected pregnant women who are not in need of ART for their own health require an effective ARV prophylaxis strategy to prevent HIV transmission to the infant. ARV prophylaxis should be started from as early as 14 weeks gestation (second trimester) or as soon as possible when women present late in labour or delivery. For all those HIV-infected pregnant women who are not in need of ART for their own health, ARV prophylaxis will be as shown in the text box below.

Namibia PMTCT regimen for pregnant mothers who do not qualify for HAART

Mother

- Antepartum AZT daily from 14 weeks gestation (N.B. ***not 28 weeks as was previously recommended***).
- sd-NVP at onset of labour*
- AZT + 3TC stat then 12 hourly during labour & delivery*
- AZT + 3TC twice daily for 7 days postpartum*

** sd-NVP and AZT+3TC can be omitted if mother receives > 4 wks AZT antepartum*

- *N.B AZT must not be used unless Hb >8g/dl*
- *If woman is on AZT, Hb will be monitored at the clinic every 2 weeks. If the Hb falls below 8g/dl or falls >25% from the baseline level, AZT should be stopped.*

Infant

Breastfeeding population
- Daily NVP (from birth until 4 weeks after all exposure to breast milk has ended)

Non-breastfeeding population
- Daily NVP from birth until 6 weeks of age

Laboratory monitoring is as per schedule in Appendix 3.

Scenario 4: HIV Infected pregnant woman who present during labour and have received no ARVs during pregnancy

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

Post partum: AZT/3TC BD for 7 days for the mother, If mother's HB ≤7g/dl before delivery then do not administer AZT/3TC postpartum

Infant:

Breastfeeding population
- Daily NVP (from birth until 4 weeks after all exposure to breast milk has ended)

Non-breastfeeding population
- Daily NVP from birth until 6 weeks of age

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

Infant:

Breastfeeding population
- Daily NVP (from birth until 4 weeks after all exposure to breast milk has ended)

Non-breastfeeding population
- Daily NVP from birth until 6 weeks of age

2.3 Infant feeding recommendations

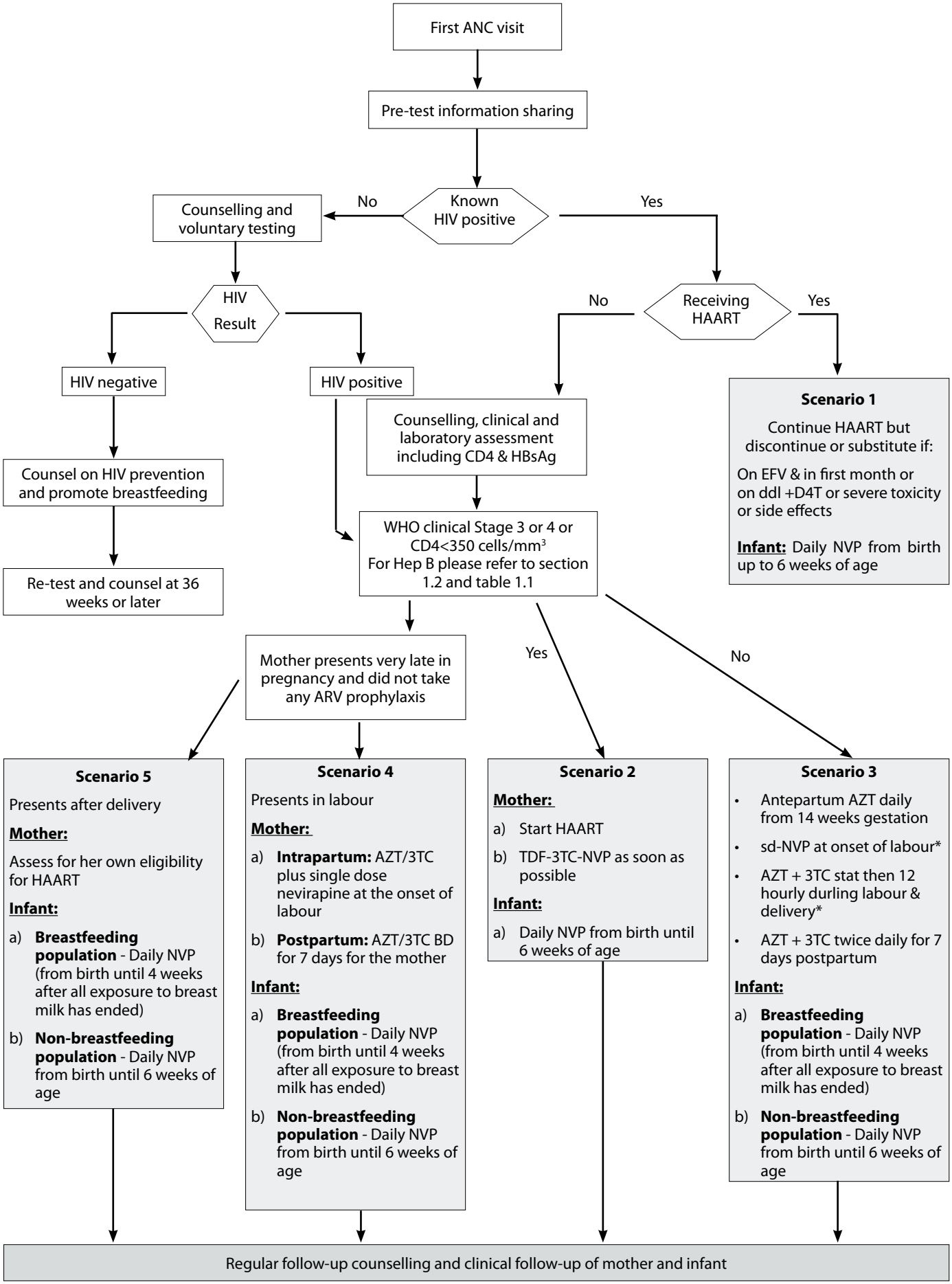
1 **Mothers who are known to be HIV uninfected or whose HIV status is unknown** should breastfeed their infants for the first six months of life and then introduce appropriate complementary foods while continuing to breastfeed for 24 months or beyond.

2 **Mothers known to be HIV-infected and whose infants are HIV uninfected or of unknown HIV status** should breastfeed their infants exclusively for the first six months of life, introduce appropriate complementary foods thereafter and continue breastfeeding for the first twelve months of life, with ARVs up to 4 weeks after all breastfeeding has stopped . However for those mothers on HAART for their own health, the infant only takes NVP for 6 weeks. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided

3 **When infants and young children are known to be HIV infected**, mothers should breastfeed exclusively for the first six months of life and then introduce appropriate complementary foods while continuing to breastfeed for 24 months or beyond. These babies should however all be put on HAART as per the guidelines.

	Mothers who are known to be HIV uninfected or whose HIV status is unknown	Mothers known to be HIV-infected and whose infants are HIV uninfected or of unknown HIV status	Infants and young children known to be HIV infected
< 6 months	Exclusive breastfeeding from birth until six months.	Exclusive breastfeeding from birth until six months, with ARVs.	Exclusive breastfeeding from birth until six months.
≥ 6 months	Introduce appropriate complementary foods at six months and continue to breastfeed up to 24 months or beyond.	Introduce appropriate complementary foods at six months and continue to breastfeed up to 12 months, with ARVs up to 4 weeks after all breastfeeding has stopped. **Breastfeeding should only stop once a nutritionally adequate and safe diet without breast milk can be provided**.	Introduce appropriate complementary foods at six months and continue to breastfeed up to 24 months or beyond.

Figure 2.2 *Algorithm for the use of HAART or ARV prophylaxis in PMTCT*



** sd-NVP and AZT+3TC can be omitted if mother receives >4 weeks AZT antepartum*

2.4 Clinical Monitoring for pregnant women placed on HAART

2.4.1 Baseline Clinical Assessment

The Baseline medical history should include:

- Essential demographic characteristics
- Gestational age
- Past medical history including major illnesses, hospitalisations and surgery
- Length of time since the diagnosis of HIV infection and if already on HAART
- Current medications
- Review of symptoms

The baseline physical examination should include: vital signs, weight, gestational age and height, and should detail any abnormalities of the:

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

Once HAART has commenced, clinical monitoring must include follow-up visits at two, four, and six weeks after initiation and monthly thereafter for clinical and/or laboratory monitoring.

Patients should be assessed by a trained member of staff every month – this visit should include medicine dispensing, performing lab tests as per schedule ,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.

2.4.2 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 syndrome.
- HIV-related disease progression.
- Signs of medicine toxicities.
- Decrease in symptoms of HIV disease and an improvement in the quality of life.

2.4.3 Baseline laboratory assessment

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

- HBsAg (Hepatitis B surface antigen)
- CD4 count
- ALT
- FBC
- Creatinine clearance
- RPR

Refer to Appendix 3 at then back pages of this book for the detailed schedule of laboratory tests to be performed for each different HAART regimen.

2.5 Management of pregnant HIV-positive women with concurrent diseases

2.5.1 Tuberculosis

New WHO recommendations from 2009 clearly indicate that all HIV infected individuals with active TB should start HAART regardless of CD4 count. This equally applies to pregnant women.TB treatment is started first. ART should be started between 2 and 8 weeks later depending on tolerance of medications.Efavirenz is the preferred NNRTI for these patients. NVP should NOT be used.

2.5.2 Hepatitis B

Limited studies have shown that there is a high prevalence of HBV in Namibia (see section 1.20.2). 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. ALT should be checked according to the schedule on Appendix 3.Pregnant women with Hepatitis B should be commenced or continued on:

TDF + 3TC + EFV if **ALT <5** x ULN and CD4 <350

TDF + 3TC + EFV if **ALT >5** x ULN or CD4 >350 or cannot tolerate NVP

2.5.3 Renal failure

In patients with renal failure, dosages need to be adjusted for some medicines on the basis of creatinine clearance. (see appendix 11)

Table 2.3 *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
	Ritonavir

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

2.6 When to consult a specialist

In the following circumstances, 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 regimen than the recommended ones.

PART 3: Antiretroviral Therapy for Infants and Children including Adolescents

Many of the goals of ART in children are similar to those in adults and are listed below:

- Durable suppression of HIV replication
- Restoration and/or preservation of immune function
- Reduction of HIV related morbidity and mortality
- Preservation of normal growth and development
- Improvement in quality of life for child and family

It is the preservation of normal growth and development that is peculiar to pediatrics. In order for ART to be considered a success, growth and development must be monitored carefully and taken into consideration when managing such patients.

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.

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 in younger children.

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 5 years. A paediatric immunological classification system for HIV infection has been developed that includes age-related definitions of immune suppression. (see Table 3.1). Although the CD4 absolute number that identifies a specific level of immune suppression changes with age, the CD4 percentage that defines each immunologic category is less variable. Thus, a change in CD4 percentage, not absolute count, should be used to monitor disease progression in children aged less than 5 years.

Table 3.1. *HIV Paediatric immunological classification*

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 vary considerably with minor infections and immunizations, and are therefore best measured when patients are stable.

As with adults, progression of clinical HIV disease is determined through classification of associated illnesses and conditions into 4 clinical stages (See Appendix 2). These are similar to adult staging classifications, however they include some conditions specifically targeting children such as stunting, unexplained parotid enlargement, symptomatic lymphoid interstitial pneumonitis, and others. As with adults, clinical staging is one of the criteria used to determine whether or not a child ≥2 years old is eligible for HAART. Therefore it is important for all clinicians to become familiar with the conditions listed in the different clinical stages.

3.2 Diagnosis of HIV infection in children

3.2.1 Early infant diagnosis of HIV using diagnostic DNA PCR testing

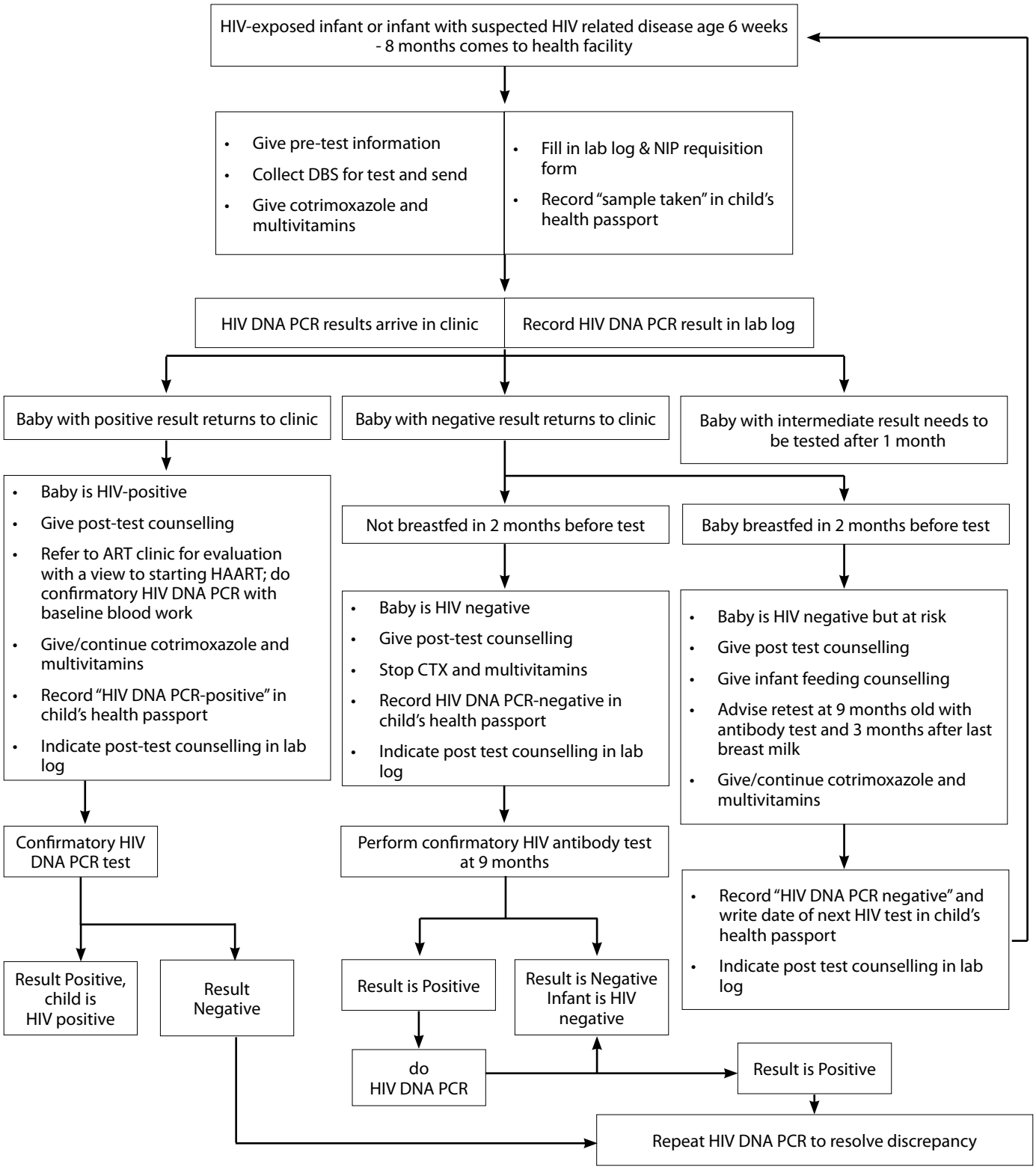
As a result of the programme for prevention of mother-to-child transmission (PMTCT), a large number of HIV-exposed infants are being identified who require follow-up care and HIV diagnosis. It is important to identify young infants with HIV infection and enrol them in HIV care early because of the high mortality from untreated HIV 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 from whole blood or from a dried blood spot (DBS) specimen at an early age. This test detects the genetic material of HIV rather than of anti-HIV antibodies, and therefore is not affected by the transplacental transfer of maternal anti-HIV antibodies, unlike the HIV antibody tests. **A positive HIV DNA PCR test confirms true HIV infection in the child.**

An HIV-exposed infant who did not breastfeed and who tests HIV DNA PCR negative at 6 weeks should have a HIV rapid test done at 9 months of age to co-incide with a routine visit for measles immunisation. If the RT result is negative, this confirms HIV negative status. If the RT result is positive, an HIV DNA PCR should be done to determine if the infant is truly HIV positive. Breastfeeding HIV-exposed infants who initially tested HIV negative at 6 weeks of age should have a rapid test done at 9 months of age. If the result is positive a HIV DNA PCR test should be done to confirm if the infant is truly HIV positive. If the results of the RT or the HIV DNA PCR are negative, a repeat RT should be done 3 months after the last exposure to breast milk. The infant should remain on cotrimoxazole until confirmed HIV negative.

The algorithm for diagnostic HIV DNA PCR testing is summarised in Figure 3.1

Figure 3.1. *Ministry of Health and Social Services algorithm for early infant diagnosis of HIV using diagnostic DNA PCR*



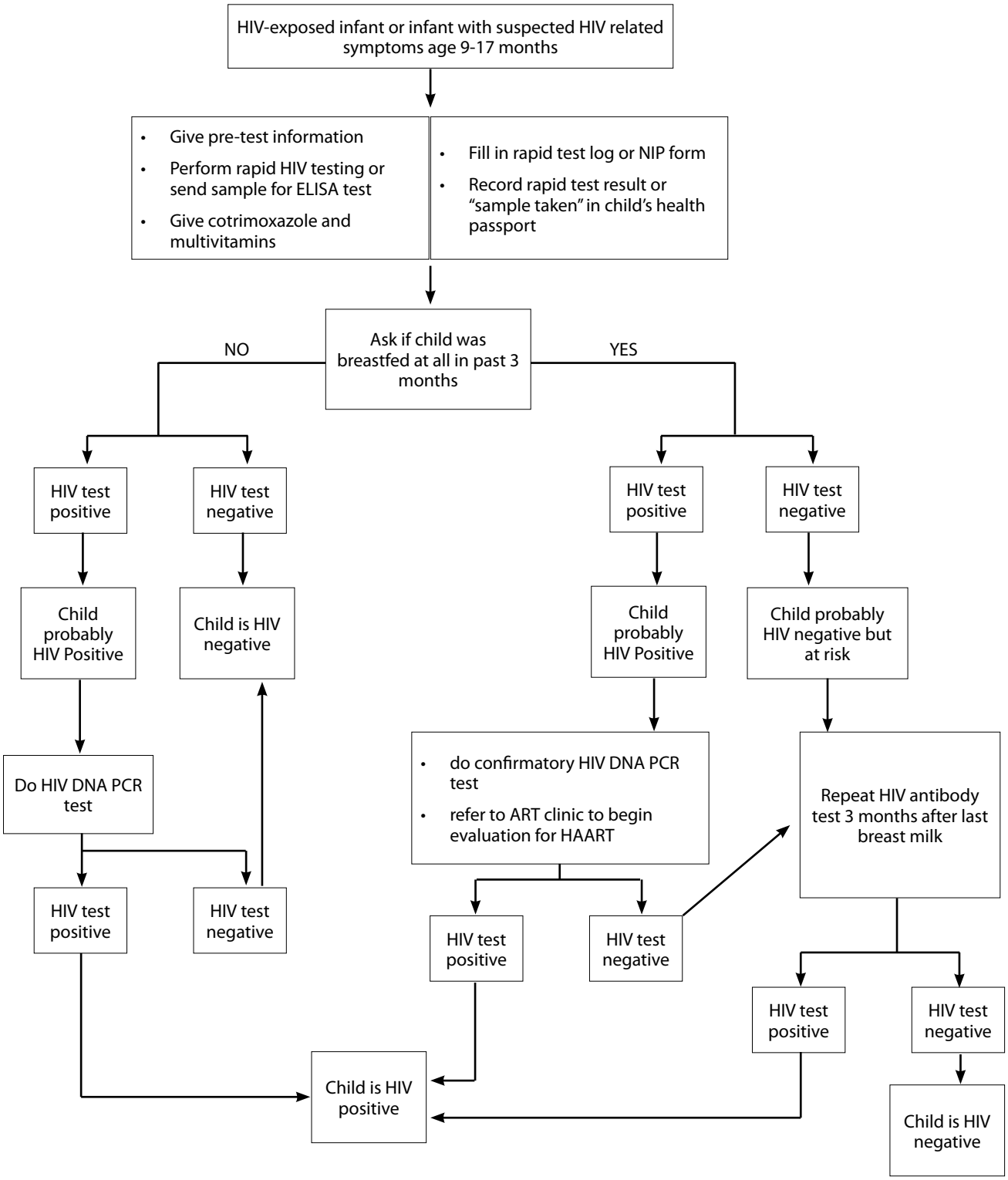
3.2.2 HIV antibody testing

As with adults, HIV antibody testing gives definitive results for diagnosis of HIV infection in children ≥18 months old. Either rapid HIV testing or ELISA (enzyme-linked immunosorbent assay) can be used. As such this is the recommended testing approach for the diagnosis or exclusion of HIV in this age group. It is important to remember that HIV-exposed children ≥18 months old who have had prolonged breastfeeding would need to have a negative HIV antibody test result at least 3 months after breastfeeding is discontinued to exclude HIV infection.

Antibody testing for HIV diagnosis is less useful in infants because passively transferred maternal anti-HIV antibodies may persist and be detected in a child for up to 18 months of age.

The algorithm for HIV diagnosis using ELISA or rapid testing is outlined in Figure 3.2. In summary: following HIV antibody testing at 9 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, an HIV DNA PCR test should be performed to confirm HIV infection.

Figure 3.2. *Ministry of Health and Social Services algorithm for diagnosis of HIV in children using HIV antibody testing*



3.2.3 Criteria for diagnosis or exclusion of HIV

3.2.3.1 HIV-positive children

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

- HIV DNA PCR test is positive at any age, or
- HIV antibody test is positive at ≥ 18 months, regardless of symptoms, or
- HIV antibody testing is positive at an earlier age, e.g. 14 months, and there are signs and symptoms suggestive of HIV-infection. In this case the infant should have an HIV DNA PCR test for confirmation, but counseling and baseline blood testing can be done while awaiting the result.

Children who are confirmed HIV positive by HIV DNA PCR or HIV antibody testing at an early age should be evaluated for ART as soon as possible due to the high mortality rate in young children (see Section 3.4). **Indeed, all children <24 months are medically eligible to start HAART once HIV infection is confirmed by HIV DNA PCR irrespective of immune status or clinical stage.** Counseling of parents and/or caregivers should begin as soon as a child is confirmed HIV positive with a view to actually starting HAART within 2 weeks. It is important that the main parent/caregiver select a treatment supporter in case he/she becomes ill, for example, and another person needs to give medication to, and care for, the child.

WHO recommends that children who test HIV positive in early infancy with HIV DNA PCR should have a confirmatory HIV test done, because otherwise lifelong treatment will be given on the basis of one blood test. A repeat confirmatory HIV DNA PCR should therefore be done for HIV-positive infants <18 months old at the same time as the baseline blood tests are taken, however HAART should be commenced based on the first result – do not wait for the results of the confirmatory HIV DNA PCR.

Note:

- Occasional lab errors might account for any discrepancy found.
- Very occasionally in infants who initiate HAART early and have rapid maximal viral suppression, the antibody test can actually be negative. A repeat HIV DNA PCR test would be positive in such cases, and should be done.

3.2.3.2 HIV-negative children

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

- Diagnostic HIV DNA PCR test is negative and the child has not been breastfed for the preceding 2 months or
- HIV antibody test is negative and the child has not been breastfed for the preceding 3 months

HIV-exposed children in whom HIV infection has been excluded by one HIV DNA PCR test, should have a confirmatory antibody test (preferably rapid test) at 9 months of age. Health workers should therefore make a note in the child's health passport to that effect. The child should then conveniently be tested when the child attends any clinic doing rapid HIV antibody testing at 9 months ideally co-inciding with the measles immunisation.

3.3 Prevention of opportunistic infections in children

3.3.1 Cotrimoxazole preventive treatment

Cotrimoxazole (sulfamethoxazole (SMZ) plus trimethoprim (TMP)) preventive treatment is recommended for all HIV-exposed children from the age of 6 weeks. Cotrimoxazole has been shown to have protective effects against pneumocystis pneumonia, and other bacterial and parasitic infections, including malaria.

Prophylaxis should be discontinued if the child is proven to be HIV negative according to the criteria mentioned in section 3.2.3.2 above. For HIV positive children, WHO guidelines recommend that cotrimoxazole preventive treatment, should continue up to the age of 5 years at which point it may be reassessed.

Table 3.2 below gives the recommended doses of cotrimoxazole to be given as preventive treatment to children.

Table 3.2. *Recommended doses of cotrimoxazole for preventive treatment*

Age	Cotrimoxazole dosage*
Six weeks to 5 months	2.5 ml once daily
Six months to 5 years	5 ml once daily
Six to 14 years	10 ml, or one 400mg/80mg tablet daily
>14 years	two x 400mg/80mg tablets daily

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

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

In all children <5 years old (whether HIV positive or negative) who have had contact with sputum positive TB patients, and infants born to mothers with pulmonary TB disease, supervised isoniazid prophylaxis should be given once active TB disease has been excluded. In addition any HIV-positive child in whom active TB has been excluded and who has not been on TB treatment for the previous 2 years is eligible for TB-IPT, whether there has been exposure to active TB or not. The dosage for isoniazid is 10-15 mg per kg (maximum 300mg) daily for 6 months. This increase from the previous dosage was required because studies have shown that children metabolise isoniazid more quickly than adults. See table 3.3 for simplified weight-based dosing for children.

Table 3.3. *Simplified paediatric weight-based dosing for isoniazid*

Weight (kg)	Dose (mg)	Number of 100mg isoniazid tablets per dose
<5	50	½ tablet
5.5 - 9.9	100	1 tablet
10 - 13.9	150	1½ tablets
14 - 19.9	200	2 tablets
20-24.9	250	2½ tablets
≥ 25	300	3 tablets or one adult 300mg tablet

Pyridoxine may be given along with isoniazid to prevent isoniazid associated neuropathy. A dose of pyridoxine of 5mg/day is suggested for children ≥5 years of age. 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.

3.4 HAART in children and when to start

3.4.1 Response to HAART in children

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

- The immunological response in children with HIV is better than in adults. Children restore their CD4 T cell counts and percentages better and more rapidly than adults, even in late stages of HIV-1 infection. Moreover, normalisation of CD4 T cell count in HIV-1-infected children taking HAART is age independent.
- Early studies suggested that virological success with undetectable viral loads may be more difficult to achieve in children. However recent reports have demonstrated that viral suppression was initially achieved in >80% of treatment-naïve children in resource poor settings, similar to the responses seen in adults.

3.4.2 Counseling prior to starting ART

Children are dependent on their parents / caregivers for managing their ARV administration and for overall care and support. Therefore careful discussion about the illness and adherence counseling for the primary caregiver and at least one other treatment supporter should be done from the outset. Some parents may themselves be infected with HIV or may have other health or social challenges which might put maintenance of the child's care at risk, so there needs to be a "back-up" system in place. It is important for children to initiate treatment as soon as possible after diagnosis of HIV, ideally within 2 weeks, therefore counseling sessions need to be scheduled immediately upon diagnosis.

3.4.3 When to start ART in infants <24 months of age:

Data emerging from recent studies in resource constrained settings confirm that for infants acquiring HIV from maternal transmission, disease progression occurs very rapidly, often leading to death. The majority of deaths in children with HIV occur within the first 2 years. For this reason, in 2010 WHO recommended antiretroviral treatment for all HIV infected infants under the age of 2. Therefore:

All infants under 24 months of age with confirmed HIV infection are eligible for and should be started on antiretroviral therapy, irrespective of clinical stage or immunological classification.

3.4.4 When to start ART in children 24-59 months of age:

- A child 24-59 months with proven HIV infection is eligible for ART if:
  - WHO Paediatric Stage 3 or 4, regardless of CD4%.
  - WHO Paediatric Stage 1 or 2, only if CD4 ≤25%.

3.4.5 When to start ART in children ≥ 5 years of age:

• Similar to adult criteria:

- WHO Paediatric Stage 3 or 4, regardless of CD4 count
- WHO Paediatric Stage 1 or 2, only if CD4 ≤350 cells/mm^3

3.5 The choice of ARVs for children

3.5.1 Formulations Available

Many antiretrovirals have liquid formulations available for use in children. Although sometimes essential for comprehensive paediatric HIV care, there are some limitations to liquid formulations. They generally require prescription of several bottles and administration of large volumes to the child, sometimes leading to confusion. Care must be taken to mark syringes with a blade or permanent marker at the correct dose for the child. At times the "permanent" mark and the ml scale marks wear off by the end of a month, leading to errors in dosing. Liquid formulations may also have an unpalatable after-taste. In addition some solutions are impractical to use, e.g., stavudine (d4T) needs refrigeration and is unstable in solution making it unsuitable for the pharmacy to mix in advance.

Several manufacturers have developed paediatric versions of Fixed Dose Combination tablets (FDCs) which are much easier to administer than liquid formulations while still allowing the more accurate dosage required for small children. The pediatric tablets are scored, crushable and dispersible in water and may be given in appropriate doses to 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 use in young 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 given according to their respective dosing schedules. Table 3.4 shows the composition of paediatric dual (d4T and 3TC) and triple (d4T, 3TC and NVP) FDCs that are available in Namibia. These d4T-based paediatric fixed dose combinations (FDCs) facilitate an easier way to prescribe and administer paediatric ARVs than individual single medicine formulations. FDCs may thus lead to better adherence and therefore better patient outcomes.

Table 3.4: *Doses of Paediatric Fixed Dose Combination (FDC) d4T containing tablets by weight*

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

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

Children can be taught to swallow tablets and capsules from an early age, practicing with small sweets. This helps to make adult formulations more available for use by children. In addition, most 'adult' formulation tablets are crushable and capsules can be opened, mixed with a small amount of food and given immediately. One exception to this is LPV/r tablets which must be swallowed whole.

The currently available adult strength FDCs (e.g. combined tablets of zidovudine-lamivudine (AZT/3TC)) can be split into halves to facilitate dosing in children. See tables 3.5 and 3.6 for paediatric dosages of single medicine formulations, including adult preparations and one adult FDC. Table 3.5 is for NRTIs, and the dosage for AZT in younger children has increased in line with the currently accepted dosage being 240mg/m^2. Table 3.6 is for NNRTIs and PIs.

Table 3.5 *Paediatric Dosage Chart for NRTIs*

Weight	Stavudine (D4T)	Lamivudine (3TC)		Zidovudine (AZT, ZDV)		AZT/3TC FDC	Abacavir (ABC)		Didanosine (ddI)
	1 mg/kg **Twice daily** **Max: 30mg**	4 mg/kg **Twice daily** **Max: 150mg**		240 mg/m^2 **Twice daily** **Max: 300mg**		Max: 1 tablet / dose **Twice daily**	**<16 years or <37.5kg** 8 mg/kg/dose **>16 years or ≥37.5kg** 300mg / dose **Twice daily**		**<3 months** 50 mg / m^2 / dose **3 months to <13 years** 90-120 mg/ m^2 / dose **≥13 years *and* >60 kg:** **Max dose 200 mg** **Twice daily** *Always give two of the chewable tablets!* *Should give on an empty stomach*
Kg	Capsules 15, 20, 30mg	Oral solution 10 mg/ ml	Tablet 150mg	Syrup 10 mg/ml	Capsule 100mg, Tab 300mg	Tablet AZT (300mg) / 3TC (150mg)	Oral solution 20mg/ml	Tablets 300mg	Chewable tablets 25, 50, 100 mg
3 - 3.9		3ml		5ml			3ml		
4 - 4.9		3ml		6ml			3ml		
5 - 5.9		3ml		7ml			3ml		25mg + 25mg
6 - 6.9		3ml		8ml			3ml		50mg + 25mg AM 25mg + 25mg PM
7 - 7.9		4ml		9ml			4ml		50mg + 25mg AM 25mg + 25mg PM
8 - 8.9		4ml		10ml	100mg		4ml		50mg + 25mg AM 25mg + 25mg PM
9 - 9.9		4ml		11ml	100mg		4ml		50mg + 25mg AM 25mg + 25mg PM
10 - 10.9	15mg	5ml		12ml	100mg		5ml		50mg + 25mg
11 - 11.9	15mg	5ml			100mg		5ml		50mg + 25mg
12 - 13.9	15mg	6ml			100mg		6ml		50mg + 25mg
14 - 16.9	20mg		75mg		150mg	0.5 tab		150mg	50mg + 50mg AM 50mg + 25mg PM
17 - 19.9	20mg		75mg		150mg	0.5 tab		150mg	50mg + 50mg AM 50mg + 25mg PM
20 - 24.9	20mg		150mg AM 75mg PM		200mg	1 tab AM 0.5 tab PM		300mg AM 150mg PM	50mg + 50mg
25 - 29.9	30mg		150mg		300mg AM 150mg PM	1 tab AM 0.5 tab PM		300mg	100mg + 25mg
30 - 34.9	30mg		150mg		300mg	1 tab		300mg	100mg + 25mg
35 - 39.9	30mg		150mg		300mg	1 tab		300mg	100mg + 25mg

Table 3.6 *Paediatric Dosage Chart for NNRTI's and PI*

Weight	Nevirapine (NVP)				Efavirenz (EFV)		Lopinavir/ritonavir (LPV/r)	
	Induction dose: 160-200 mg/m² **Once daily** for first 14 days, then give maintenance dose		**Maintenance dose:** 160-200 mg/m² **Max: 200mg** **Twice daily**		**Capsule:** 15mg / kg/ day **Syrup:** 19.5 mg / kg / day **≥40 kg and max dose: 600 mg** **Once daily**		230-350 mg/m² **Max. dose:** 400mg/100mg LPV/r **Twice daily**	
Kg	**Oral suspension 10 mg/ml**	**Tablet 200mg**	**Oral suspension 10 mg/ml**	**Tablet 200mg**	**Syrup 30 mg/ml**	**Capsules 50, 100, 200 mg**	**Liquid 80 mg LPV/ml**	**Tablet 200/50 mg LPV/r**
3 – 3.9	5 ml		5ml				1ml	
4 – 4.9	5ml		5ml				1.5ml	
5 - 5.9	6ml		6ml				1.5ml	
6 - 6.9	7ml		7ml				1.5ml	
7 - 7.9	8ml		8ml				1.5ml	
8 - 8.9	8ml		8ml				1.5ml	
9 - 9.9	9ml		9ml				1.5ml	
10 - 10.9	10ml	100mg	10ml	100mg	7ml	200mg	2ml	
11 - 11.9	10ml	100mg	10ml	100mg	8ml	200mg	2ml	
12 - 13.9	10ml	100mg	10ml	100mg	9ml	200mg	2ml	1 tab
14 - 16.9		100mg		200mg AM 100mg PM		200mg + 100mg	2.5ml	1 tab
17 - 19.9		200mg		200mg AM 100mg PM		200mg + 100mg	2.5ml	1 tab
20 - 24.9		200mg		200mg AM 100mg PM		200mg + 100mg	3ml	1 tab
25 - 29.9		200mg		200mg		200mg + 200mg	3.5ml	2 tabs AM 1 tab PM
30 - 34.9		200mg		200mg		200mg + 200mg	4ml	2 tabs
35 - 39.9		200mg		200mg		200mg + 200mg	5ml	2 tabs

3.5.2 First line HAART regimens for children

3.5.2.1 Initiating treatment

The initial choice of HAART regimen in children depends upon age, prior nevirapine exposure and appropriate formulation choices.

- **Infants <24 months old with known prior exposure to NVP or to maternal NVP-containing HAART or PMTCT prophylaxis should start on a regimen including d4T/3TC as paediatric FDC dispersible tablets plus LPV/r liquid.** *NB: Although d4T would not otherwise be a preferred NRTI first line choice, its availability in an easy-to-use paediatric FDC formulation makes it so. If for any reason the pediatric FDC d4T/3TC is not available, AZT and 3TC as liquids should be given. In addition, if pediatric FDCs containing AZT and 3TC become available, this should be used in preference.*
- **Infants <24 months old without (or with unknown) prior exposure to NVP, and children ≥24 months old but <14 kg should start on d4T/3TC/NVP as paediatric FDCs** due to its ease of administration.
- For **children ≥ 24 months and ≥14 kg**, sexual maturity needs to be taken into consideration in order to select between using AZT or TDF as part of the first line regimen, as it is currently thought unsafe to use TDF in growing children due to concerns related to bone demineralisation.

Sexual maturity rating, also called Tanner staging, divides sexual development into 5 stages from pre-adolescent to adult. Charts showing the 5 stages have been developed for girls and boys and are shown respectively in Tables 3.7 and 3.8:

Table 3.7: *Sexual Maturity Rating (Tanner Staging) in FEMALE adolescents*

Stage	Breast Growth	Pubic Hair Growth	Other Changes	Age Range (years)
I	Pre-adolescent	None	Pre-adolescent	0-15
II	Breast budding; areolar hyperplasia with small amount of breast tissue	Long, downy pubic hair near the labia, often appearing with breast budding or several weeks or months later	Peak growth velocity often occurs soon after stage II	8 – 15
III	Further enlargement of breast tissue and areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 25% of girls late in stage III	10-15
IV	Separation of contour; areola and nipple form secondary mound above breast tissue	Adult in type but not in distribution	Menarche occurs in most girls in stage IV, 1-3 years after breast budding	10-17
V	Large breast with single contour	Adult in distribution	Menarche occurs in 10% of girls in stage V	12½ - 18

Table 3.8*: Sexual Maturity Rating (Tanner Staging) in MALE adolescents*

Stage	Testes Growth	Penis Growth	Pubic Hair Growth	Other Changes	Age Range (years)
I	Pre-adolescent ≤2.5 cm	Pre-adolescent	None	Pre-adolescent	0-15
II	Enlargement of testes; pigmentation of scrotal sac	Minimal or no enlargement	Long, downy hair, often appearing several months after testicular growth; variable pattern noted with pubarche	-	10 – 15
III	Further enlargement	Significant enlargement, especially in diameter	Increase in amount, curling	-	10½ -16½
IV	Further enlargement	Further enlargement, especially in diameter	Adult in type but not in distribution	Axillary hair and some facial hair develops	Variable (12-17)
V	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs; linea alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity	13-18

- **Children ≥24 months ≥14 kg and sexual maturity rating Tanner Stage I-III should be started on AZT/3TC/NVP** utilizing adult formulation tablets or capsules as appropriate for weight.
- **For children who have reached sexual maturity rating Tanner Stage IV or above, the preferred first line is the same as for adults: TDF/3TC/NVP.** Tenofovir is considered safe for children who have reached Tanner Stage IV in development and therefore is preferred as an NRTI over AZT.

The box below summarises the preferred first line HAART regimens for children in Namibia:

Preferred first line HAART regimens for children are:

Infants <24 months who are nevirapine-exposed
stavudine-lamivudine-lopinavir/ritonavir (D4T/3TC as paediatric FDC plus LPV/r suspension)

Infants <24 months who have no or unknown nevirapine exposure and children ≥24 months but <14 kg
stavudine-lamivudine-nevirapine (D4T/3TC/NVP as pediatric FDCs)

Children ≥ 24 months, ≥14 kg and Tanner Stage I-III
zidovudine-lamivudine-nevirapine (AZT/3TC/NVP)

Tanner Stage IV or post-pubertal adolescents:
tenofovir-lamivudine-nevirapine (TDF/3TC/NVP)

All patients who are receiving NVP for the first time should have half of the daily maintenance dose given once daily for the first 2 weeks of treatment while metabolic enzymes are being induced. Induction dosing is associated with a lower incidence of NVP rash and hepatotoxicity. Children who are being initiated on d4T, 3TC and NVP with FDCs, should have both triple and dual FDCs dispensed for the first two weeks: triple FDCs for the morning dose and dual FDCs for the evening dose. After 2 weeks, if there is no evidence of rash or hepatotoxicity, the NVP dose should be increased and the child should be given triple FDCs twice a day. If a child develops a MILD RASH with nevirapine, check for nausea & hepatic tenderness, send blood for ALT and continue induction dose for a further week. Counsel caregiver to bring the child back if rash gets worse, and reassess the child in one week. Dual FDCs may also be used for children who need to take d4T, 3TC and efavirenz (EFV). In this case dual FDCs must be given twice daily with EFV taken only in the evening.

3.5.2.2 Changing children from D4T to another NRTI

Stavudine has been found to be a potent cause of lipoatrophy in children. In addition d4T may cause lipohypertrophy and dyslipidaemia. Therefore in children, as in adults, it is important to change from d4T once a child has been taking d4T for ≥2 years in order to try to avoid these complications. If the child is still Tanner Stage I-III in sexual maturity, the appropriate change would be to AZT (unless there was previous AZT toxicity), and if Tanner Stage IV or V, to TDF. Children <14 kg and therefore not eligible for adult formulation tablets/capsules, should continue on the d4T FDC until they reach 14 kg.

3.5.2.3 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 with D4T for AZT in the case of anaemia, or with NVP for EFV in the case of CNS toxicity or pregnancy in an adolescent girl. (See Table 3.9)

Table 3.9. *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 severe neutropenia (b)	D4T
	Lactic acidosis	ABC (d)
	Severe gastrointestinal intolerance (c)	D4T
D4T	Lactic acidosis	ABC (d)
	Peripheral neuropathy	AZT (e)
	Pancreatitis	
	Lipoatrophy/metabolic syndrome (f)	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 or asymptomatic hepatitis with ALT>5x ULN	EFV, unless severe hepatitis (h)
	Hypersensitivity reaction	*NOT* EFV (j)
	Severe or life threatening rash (Stevens Johnsons Syndrome) (i)	Substitute with LPV/r

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/mm^3.
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 or TDF if Tanner stage IV or V is preferred.
e. In children, ABC or AZT can be considered as an alternative, or TDF if Tanner stage IV or V.
f. Substitution of D4T may not reverse lipoatrophy however it may prevent it from getting worse; may use TDF if Tanner stage IV or V
g. e.g. persistent hallucinations or psychosis.
h. EFV may also cause hepatitis but much rarer than NVP. If NVP-induced hepatitis is severe, avoid EFV as well.
i. Hospitalisation required.
j. Cannot use EFV in the face of Stevens - Johnson syndrome from NVP due to the possibility of cross reactivity.

3.5.3 Second Line HAART

3.5.3.1 When to switch therapy in children

The term "switching" regimens is usually reserved for changing a regimen due to virologic failure rather than for toxicity or other reasons.

Deterioration or lack of improvement in either clinical or immunological criteria are indications to investigate for possible failure.

Viral load should be done in cases of suspected failure, however a non-suppressed viral load is not necessarily an indication for switching therapy.

The most common cause of virologic failure is non-adherence to therapy. Children who have non-suppressed viral loads need urgent attention paid to adherence to help determine any factors that negatively impact on adherence. ART administration should be reviewed in detail, including pill counts, discussion about who administers the medicine routinely and on holidays, when and where, as well as how medication times fit into the family schedule. There are other causes of failure which need to be considered as well such as intercurrent OI (e.g. TB), incorrect dosage of ARVs, adverse drug-drug interactions, poor absorption of medication and incorrect storage of medication.

A viral load result >1000 cells/ml after at least 6 months of therapy in a patient whose adherence is good and who has no other explanation for failure (see above) should have a repeat viral load done 2 – 3 months after intensive adherence counseling. A persistently high viral load despite good adherence is a reason to consider switching therapy to second line. A switch should only be made if adherence problems are solved and it is anticipated that adherence to second line will be good.

In the rare event that viral load testing is not available, judgments regarding suspected treatment failure could be based on disease progression and CD4 decline as defined in Table 3.10 below in a patient on ART for at least 6 months. However it is possible to have clinical and immunological failure in the face of viral suppression, and in those cases, switching antiretroviral therapy to second line would not be warranted. Therefore before switching to second line based on clinical or immunological failure, consult an HIV specialist.

Table 3.10: *Clinical and immunologic criteria for treatment failure in children where viral load testing is not available*

Clinical Criteria	*CD4 Criteria
• Lack of or decline in growth among children with initial growth response to ART • Loss of neurodevelopmental milestones or onset of encephalopathy. • New or recurrent WHO Paediatric Stage 4 condition	• Return of CD4% (if age <5 years) and CD4 count or % (if age ≥ 5 years) to pre-therapy baseline or below without causative factor. • >50% fall from peak CD4% (if <5 years) or CD4 count or % (if age ≥5 years) without other causative factor

* CD4 results should be confirmed by a repeat test.

3.5.3.2 Second line regimens

As a general rule, when considering switching to second line therapy in children, a second opinion from an HIV expert should be sought to thoroughly review all aspects of the patient's case. Children who are Sexual maturity rating Tanner stage IV or V (see Tables 3.7 and 3.8) should have tenofovir in the second line regimen instead abacavir.

The preferred second line regimens for children are listed in the box below.

The second line HAART regimen for children Tanner stages I-III who had NNRTI-based first line is:

abacavir-zidovudine-lamivudine-lopinavir/ritonavir (ABC + AZT + 3TC + LPV/r)

The second line HAART regimen for children Tanner stages I-III who had PI-based first line is:

abacavir-zidovudine-lamivudine-[nevirapine or efavirenz] (ABC + AZT + 3TC + [NVP or EFV])

The second line HAART regimen for children who are Tanner stage IV or V:

Replace abacavir in the regimens above with tenofovir

NB: if the first line regimen included tenofovir, seek advice of an HIV specialist

Note: Didanosine is no longer recommended as a preferred second line option largely due to its food restrictions. It must be taken on an empty stomach while the other medications should be taken with food. This requirement is difficult to adhere to with small children. In addition some older children object to the taste of ddI and feel nauseated, which could compromise their adherence. If any patient is already on ddI or needs it for any reason, food restriction and palatability issues should be thoroughly discussed to ensure efficacy of the medication.

3.5.3.3 Resistance testing

Although management of patients would be easier if resistance testing was done prior to selection of a second line regimen, this is costly and should not be done routinely. However resistance testing may be essential for a child who has failed a second line regimen and a third line regimen is needed. An HIV specialist can give approval for this on an individual patient basis, and in any case should be consulted for further management of this child.

Ordering an HIV genotype resistance test should be done using the specific "HIV Genotype Resistance Test" form for that purpose. On this form, patient medication history, the indications for doing the test and which of the authorized HIV specialists has been consulted should be specified. Without a fully completed form, NIP will not accept the sample for testing.

Interpreting results of resistance testing is complex and should be analysed in conjunction with the ART history of the child, noting that it may only provide information about resistance to the current regime the child is on.

3.6 Children with Tuberculosis (TB) and HIV co-infection

As with adults, tuberculosis occurs more commonly in children with HIV infection than in those without HIV. Please refer to the National Guidelines for the Management of Tuberculosis for help with diagnosing TB in children.

3.6.1 When to start HAART in HIV/TB co-infected children

HIV-infected children with pulmonary tuberculosis have WHO Clinical Stage 3 disease and those with extra-pulmonary TB, WHO Clinical Stage 4 disease. Both groups are eligible for HAART. The previous recommendation was to postpone starting HAART until the intensive phase of TB treatment (usually the first two months) was completed in order to reduce the risk of drug toxicity or Immune Reconstitution Inflammatory Syndrome (IRIS) and to maximize adherence to a multi-medication regimen.

There is now significant evidence, however, that mortality from delaying the start of HAART in TB co-infected children greatly outweighs the risk. Therefore Namibia has adopted the WHO November 2009 Rapid Advice guidelines recommending:

- Start ART in all HIV-infected individuals with active TB irrespective of CD4 cell count
- Start TB treatment first, followed by ART as soon as possible within 8 weeks after starting TB treatment

3.6.2 HAART regimens for children with TB

Not all antiretrovirals should be used in combination with rifampicin. Rifampicin lowers the blood levels of protease inhibitors by approximately 80%, of nevirapine by 30-50%, and of efavirenz by 25%.

- Given concurrently with rifampicin, nevirapine is probably not as effective and nerivapine resistance can be selected, which may compromise future ARV choices.

- At standard doses, efavirenz remains effective in the presence of rifampicin and is the preferred regimen.
- LPV/r can only be used if "super-boosted". This means adding RTV at 0.75 x the amount of LPV to achieve an equivalent total dose of LPV and ritonavir (RTV). For example, 7 kg child receiving 1.5 ml of LPV/r suspension (containing 80mg LPV and 20mg RTV per ml) is getting 120 mg of LPV and 30 mg of RTV. Such a child on TB treatment would need an additional 90mg of RTV to reach the proper dose. When this guideline went to print RTV liquid was not yet available in Namibia, and adult strength capsules (100mg RTV) are difficult to sub-divide into appropriate pediatric doses.

If a child presents with TB before commencing ARV therapy and need to start HAART, the following regimens are recommended, however ***consultation with a pediatric HIV specialist should be done before final selection of ARVs for any individual child, especially those already on ART:***

- ≥3 years old and weight ≥10 kg
  - AZT + 3TC + EFV if sexual maturity *Tanner Stage I-III
  - TDF + 3TC + EFV if sexual maturity *Tanner stage IV or V

  *see Tables 3.7 and 3.8 in section 3.5.2.1 for explanation of Tanner staging

- <3 years old or weight <10 kg, give either:
  - D4T (as part of pediatric FDC) or AZT + 3TC + ABC or
  - D4T (as part of pediatric FDC) or AZT + 3TC + "super-boosted" LPV/r

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

- ≥3 years old and weight ≥10 kg
  - already on 2NRTIs + EFV: leave unchanged.
  - already on 2NRTIs + NVP: change NVP to EFV.

- <3 years old or weight <10 kg
  - already on 2NRTIs + NVP, change NVP to either:
    - ABC or
    - "super-boosted" LPV/r

- Child of any age
  - already on 2NRTIs + LPV/r as first line:
    - add additional RTV to LPV/r to achieve "super-boosted" LPV/r or
    - change LPV/r to ABC or
    - change LPV/r to EFV if child ≥ 3 years old and ≥10kg

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

- already on 2-3 NRTIs + LPV/r: add additional RTV to LPV/r to achieve "super-boosted" LPV/r. *NB: this child on 2nd line has already failed treatment on NNRTIs, hence it would not be safe to change to EFV or to give triple NRTIs only*.
- already on 2-3 NRTIs + EFV: leave unchanged
- already on 2-3 NRTIs + NVP and
  - ≥3 years old and ≥10 kg: change NVP to EFV
  - <3 years old or <10 kg: consult paediatric HIV specialist

Remember: two weeks after TB treatment with rifampicin is completed, the child should change to the usual first line regimen, or to the regimen he/she was taking before starting TB treatment, particularly if the child has been given a triple NRTI regimen or "super-boosted" LPV/r.

The use of D4T with isoniazid in TB therapy may result in a greater incidence of peripheral neuropathy. If D4T cannot be avoided, monitor for neuropathy and give pyridoxine 5mg/day for children ≥5 years of age. 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.

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 treatment. IRIS is characterised by worsening clinical condition after initial improvement and can manifest with:

- new onset of systemic symptoms such as fever
- worsening of pulmonary infiltrates
- peripheral or mediastinal adenopathy
- expanding CNS lesions

IRIS usually occurs during the first three months of HAART treatment. Generally, IRIS is self-limiting, lasting 10-14 days, but may require a short course of steroid treatment for symptom management. Close monitoring of the child is essential. Please refer to the National Guidelines for the Management of Tuberculosis for discussion on the management of TB IRIS.

3.8 Monitoring in HIV-infected children, before and after HAART initiation

3.8.1 Growth monitoring and nutrition considerations

Malnutrition is common in HIV-infected children and is a major contributor to mortality in both HIV-uninfected and HIV-infected children. In HIV-infected children, wasting (i.e. low weight for height/length) has been associated with reduced length of survival, while weight loss has resulted in increased infectious complications in children with HIV. Conversely, HIV has been associated with nutritional disorders and impaired immune function. HIV-infected children require more energy and nutrients than non-infected. They are at higher risk for acute malnutrition and take longer to recover when they become malnourished. It is important that nutritional support is given early in the onset of malnutrition in order to give these children the best chance of recovery. Early nutritional intervention (i.e. nutritional assessment, counseling and support) is recommended as an integral part of the care plan of HIV infected children (WHO, 2009).

3.8.1.1 Growth monitoring

Monitoring of growth, nutritional status, diet and nutrition-related symptoms, are critical in the early identification of malnutrition and poor growth. Growth failure may present as only a slight decline in normal growth rate, however if not adequately addressed this could lead to static (unchanging) growth or weight loss. Height (or length in infants), weight and head circumference (in children <3 years old) should be routinely measured, recorded and charted on the appropriate growth charts at every visit the child makes to the clinic. This is essential to ensure that doses of medication are escalated along with weight gain and to evaluate whether or not the child is growing and gaining weight normally.

In addition to lack of appropriate diet, HIV and other opportunistic infections can impact optimal growth for a child, leading to poor brain development, growth failure, and severe malnutrition. Other causes of growth failure such as superimposed infection (e.g. TB) and medicine intolerance need also to be considered.

3.8.1.2 Neurological and cognitive develoment

HIV can interfere with the normal neurological and cognitive development in a child. Therefore it is very important that achievement of developmental milestones be monitored and recorded in every child's patient care booklet. A child who is not achieving normal developmental milestones, or indeed who shows signs of regression after having achieved some, should be further assessed and may need initiation of HAART (if not already on it), referral to a physiotherapist / occupational therapist (physical delay) or a social worker (cognitive delay) as appropriate. Screening for normal neurological development need not take much time. A tool such as the one shown in Table 3.11 below offers a quick screen for assessing achievement of developmental milestones.

Table 3.11: *Developmental Screening Checklist*

Age	Developmental milestone
1 month	Raises head, makes crawling movements, alert to sound
2 months	Holds head at midline, lifts chest off table, smiles socially
4 months	Rolls front to back, laughs
6 months	Sits unsupported, babbles
9 months	Pulls to stand
12 months	Walks alone, uses single words
18 months	Can remove garment, scribbles, uses 6 words, runs
24 months	Can wash hands, jump up, combine words
36 months	Can put shirt on, speech is understandable, can balance on one foot
48 months	Can dress alone, draw a person, use complex speech, hop

3.8.1.3 Nutrient requirements of HIV-infected children

3.8.1.3.1 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; WHO Nutrition 2009).

Strategies to meet increased energy requirements include:

- Dietary adjustments and meal plans of available energy giving foods such as mahangu, maize, rice, potatoes, cassava, wheat
- Increased frequency of meal intake in a day
- Adoption of food preparation methods that add value for example sweetening porridge or adding nuts, and frying potato chips raises their energy values several folds.
- Consumption of snacks between meals

3.8.1.3.2 Protein needs

Protein 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 inadequate protein intake, this needs to be addressed and may require increased protein intake.

3.8.1.3.3 Micronutrient needs

Micronutrient needs are the same as for children with or without HIV. Micronutrients found in fruits and vegetables will help the child fight infections by boosting the immune system. Iron, vitamin A, and vitamin C-rich foods are important in the child's development and in the prevention of childhood diseases. Children require adequate iron from meat, 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. In cases of deficiency, the child should take a multivitamin/ mineral supplement daily with the guidance of a health provider. Vitamin A supplementation should be done community-wide for all children in conjunction with the Expanded Programme on Immunization (EPI) Policy.

3.8.1.4 Severe acute malnutrition in HIV-infected children

Severe wasting is a common clinical presentation and life threatening condition in HIV infected children. Special attention must be given to these children during the medical assessment when attending weekly out-patient sessions and follow-up visits. WHO suggests that HIV-infected children with severe malnutrition should be treated according to national guidelines before decisions are made on the initiation of ART.

- When complications are found during the assessment of acute malnutrition in HIV infected children, the treatment of malnutrition complications should be started at least one week before the introduction of anti-retroviral medicines to diminish the risk of serious side effects from the medication.
- The initial treatment of severe malnutrition lasts until the children have stabilized on this treatment and have regained appetite.
- A non-responding child should receive a home visit from a community health care provider prior to discharge, and should be referred to a doctor for further assessment if there is no improvement after three months.

Prevention or treatment of malnutrition is essential in HIV infected children. All HIV infected children attending the clinic should undergo nutrition assessment of weight-for-height (WFH), weight-for-age (WFA), height-for-age (HFA) and mid-upper arm circumference (MUAC) to categorize their nutritional status. Parents/care givers should be counseled/educated using appropriate guidelines. All children with severe malnutrition are at risk for a number of life-threatening problems and urgently require therapeutic feeding (WHO Nutrition 2009). For the management of moderate/severe malnutrition in HIV positive children, refer to Appendix 8.

3.8.2 Adherence and missed doses

Adherence to medication is the single most important factor predicting success of antiretroviral therapy. It should therefore be addressed at each visit to the clinic and in all encounters with health care workers. Pill (and liquid) counts should be routinely done as well as discussions specifically targeting any possible barriers to adherence.

If a child misses a dose of antiretrovirals, he/she should **take the missed dose as soon as it is remembered**.

- If it is more than 2 hours before the next dose is due, take the next dose at the usual time and continue with the normal schedule.
- If it is less than 2 hours before the next dose is due, omit the next dose and then continue with the normal schedule.

For example, if a child was due for tablets at 6AM and remembers at 11AM that the dose was not taken, he/she should take that dose immediately and still take the 6PM dose on time. If the child was due for tablets at 6AM and remembers at 5PM, then he/she should take the forgotten dose at 5PM but should omit the 6PM dose, and then go back to the normal 6AM/6PM schedule.

3.8.3 Disclosure of HIV status

Disclosure of HIV status to children is challenging for caregivers (including parents) and health workers alike. However age-appropriate partial or full disclosure is essential if sustained adherence to medication is to be achieved, especially as children grow into young adolescence.

Before disclosure of HIV status to a child, it is essential that the caregiver(s) are ready for disclosure to take place. There may be concerns about the effect disclosure will have on the child and family, and these concerns need to be discussed and resolved

in advance. Caregivers need to be prepared for any questions that may come from the child at home as they are the ones who will live with the child. The whole family may be worried about possible consequences of stigma or ostracism in the community if the family secret emerges, so caregivers need to work through how they will handle or prevent this.

Some caregivers are comfortable disclosing HIV status to their children, and health workers should support them in their efforts, helping them to anticipate issues and questions that will arise. Other caregivers prefer for disclosure to be done by clinic staff and in that case the health worker should ensure that the caregiver is present and agrees in advance with what the child will be told.

Disclosure is a process rather than a single event. It starts with a relationship of trust that caregivers and/or health workers build with the child in which the child is always told the truth, in a positive and supportive way. At every clinic visit routine age-appropriate discussions with the child should be done concerning their experiences at school, their future plans and why they are taking their medicines. This gives ample opportunity to ensure correct understanding and to detect any problems that may arise.

- Young children should learn that they take their medicines so that they can remain healthy, or so that their "body soldiers" can be strong and can help them to stay healthy. This can be understood by children as young as 5-6 years old.
- Children should know that the health worker's expectation is that if they continue taking their medicines correctly, they can achieve the life goals they set for themselves. This can be re-inforced by asking the child what he/she would like to do when he/she grows up.
- Slightly older children usually understand an allegory of a "bad guy" who attacks "body soldiers" making them weak and fewer in number, such that they can no longer fight off infections. The medicines they take, when taken correctly, keep the "bad guy" asleep so it cannot attack the "body soldiers", thus allowing them to be strong and numerous and to keep the body healthy.
- For the child who fully understands the allegory above, the next step would be to introduce adult terminology, referring to the interactions between HIV, antiretroviral medicines and CD4 cells. Before using the word "HIV", however, it is important to check with the caregiver(s) once again to ensure that they are ready for this.
- Older children and young adolescents should learn the names of their antiretrovirals and should play a major role in remembering to take their medicines on time, still supervised by a care-giver.
- Health workers need to ensure that adolescents are equipped with the information they need about the modes of HIV transmission and prevention before they enter into possible sexual relationships.
- Messages should be positive, and the child's understanding should be assessed and re-enforced at every visit.

3.8.4 Adolescents – special concerns

WHO defines adolescents as children between 10-18 years of age. Older adolescents are in transition from childhood and adulthood – a difficult period even for those without HIV. HIV is an added burden and adolescents who have previously adhered to therapy often start to rebel against taking their medicines in their adolescence. It is important to anticipate this and discuss it with the caregiver.

Possible ways to minimise the risk of non-adherence and subsequent treatment failure include:

- Schedule more frequent visits to allow more interactive discussion and counseling
- Congratulate the adolescent for any success in adherence to the visit and/or to medications
- Ensure that HIV disclosure is done and positive re-enforcement given (see section 3.8.3)
- Ensure that adolescents understand the modes of transmission of HIV and are able to describe them.
- Continue adult supervision of treatment, including watching the adolescent swallow the medication
- If possible, promote adolescent-friendly services in the clinic with activities such as:
  - Grouping adolescent appointments on the same day where this is feasible
  - Providing some group activities for adolescents as they wait to see the HCW
  - Starting adolescent peer support groups
  - Providing family planning counseling and methods.

3.8.5 Clinical assessment and monitoring

Careful clinical assessment and follow-up is essential to managing HIV-infected children and monitoring the effectiveness of HAART.

Baseline clinical assessment following confirmation of HIV infection includes:

1. Weight, length or height, and head circumference (for <3 year olds). Plot on growth chart.
2. Assessment of developmental milestones achieved.
3. WHO Clinical Staging.
4. Identification of concomitant conditions (e.g., TB, other OIs, pregnancy in adolescent girls).
5. Tanner sexual maturity stage for adolescents (refer to Tanner Staging Charts, Tables 3.7 and 3.8)
6. Screening for isoniazid preventive therapy (IPT) eligibility
7. Immunisation status.
8. Nutritional status including assessment of quality and quantity of intake.
9. Detailing of concomitant medications (e.g., cotrimoxazole, traditional medications).
10. For those eligible for ART, assessment of child's and caretakers' preparedness for therapy.

Routine monitoring of children, who are **not yet on HAART** consists of:

1. Clinical evaluation **as for baseline assessment above** every 3 month for young children because of rapid rate of disease progression. Older children or adolescents with high CD4 counts may be seen every 6 months
2. CD4 count and % every 6 months if CD4 count is still high. *NB: all infants <24 months of age are eligible for HAART once confirmed HIV positive irrespective of clinical stage or CD4 count.*
3. Other labouratory tests as required or symptom-directed.

Routine monitoring of children on HAART includes:

1. Clinical evaluation as for baseline assessment above every 3 months
   a. WHO clinical staging done at each visit is termed, and should be recorded in the patient care booklet as, "T-stage" after the child has started on HAART
2. Evaluation of adherence to therapy.
3. Discussion about understanding of the disease process and disclosure as appropriate (see section 3.8.3)
4. Discussion of symptoms and observation for signs of medicine toxicity or intolerance.
5. Discussion of symptoms and observation for signs of treatment failure (e.g., poor growth progression, development of neurological symptoms or poor development, development of new infections).
6. Laboratory monitoring as per Table 3.12
7. Appendix 3 gives details of the laboratory monitoring required depending on the ART regimen the child is on.

3.8.6 Laboratory monitoring

***Table 3.12**. Baseline and monitoring laboratory tests for children prior to and after starting HAART respectively*

Required Tests	Frequency
HIV Test	Baseline: · Repeat HIV DNA PCR if child<18 months for confirmation of diagnosis. DO NOT wait for result before starting HAART · In child ≥18 months, confirm that the antibody test was done; there is no need to re-confirm the result with another test
Full Blood count	Baseline
Hb	Follow up as per schedule (more frequently initially if on AZT)
CD4 cell count, percentage	Baseline; every 6 months after age 2 years if not yet on HAART; at 12 months and 6 monthly thereafter when on HAART NB: This assumes children <2 years old will be starting HAART
*Creatinine Clearance (CrCl)	Baseline and as clinically indicated; at 3 months, 6 months and 6-monthly thereafter if on TDF
ALT	Baseline and follow up as per schedule; if HBsAg positive: 2,6,12 weeks, 6 months and 6 monthly thereafter
HBsAg (Hep B surface antigen)	Baseline only
Viral Load	6-monthly from the start of HAART and as clinically indicated – for all children up to the age of 18 years. This is a change from the previous guidelines
HIV genotypic resistance testing	As clinically indicated after approval from an HIV expert
Fasting serum cholesterol and triglycerides	At 12 months and annually for patients on protease inhibitors or EFV
Fasting glucose	As indicated, especially for patients on PIs

*NOTE: the creatinine clearance calculation for adults is not applicable to children ≤ 18 years old.

The following equation should be used to estimate creatinine clearance (CrCl) in children from 1 week – 18 years of age:

SCHWARTZ equation:

CrCl (ml/min/1.73m^2) ≈ [length (cm) x k x 88.4] / serum creatinine (mmol/l)

k = 0.45 for infants 1 – 52 weeks
k = 0.55 for children 1 – 13 years old
k = 0.55 for adolescent females 13 – 18 years old
k = 0.7 for adolescent males 13 – 18 years old

Ref: Schwartz, GL et. al. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976, 58:259-263

Table 3.13 below gives normal GFR values for children and young adults:

Table 3.13. *Normal GFR in children and young adults*

Age (gender)	Mean GFR ± SD (ml/min/1.73m^3
> 8 weeks and <2 years (males and females)	95.7 ± 21.7
2 - 12 years (males and females)	133 ± 27.0
13 - 21 years (males)	140 ± 30.0
13 - 21 years (females)	126 ± 22.0

Ref: National Kidney Foundation / KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification (2002), National Kidney Foundation, Inc.

3.9 Vaccinations

All vaccinations provided by the MoHSS should be given according to the national vaccination schedule. This includes BCG after birth unless the infant already has signs of immunodeficiency or tuberculosis. Please refer to the Namibian National Guidelines for the Management of Tuberculosis and Leprosy (2010) for further information about BCG and HIV.

3.10 When to consult an HIV specialist

Good collabouration between general practitioners and HIV specialists is essential for the establishment of successful and durable antiretroviral therapy in children. In the following circumstances it is recommended to consult a specialist, ideally a pediatric HIV 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 or virologic failure of first or second 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

Health care 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 medicines. 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.

4.1.2 Risk of infection

Factors that increase the risk of sero-conversion include exposure 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 4.1 *Risk factors for HIV infection in health care 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 – 17.1)
Procedures 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 4.2 *Assessment of exposure risk*

Low risk exposure	High risk exposure
Exposure to a small volume of blood An injury with a solid needle Any superficial injury or mucocutaneous exposure	Exposure to large volume of blood or potentially infectious fluids eg. Contaminated blood transfusion Injury with a hollow bore needle Deep and intensive injury

4.1.3 Recommendations for post-exposure prophylaxis

1. Draw baseline laboratory tests: HIV testing (with consent), HBsAg and Hb, ALT, and creatinine. Drawing these tests and waiting for the results must not delay starting PEP.
2. TDF 300mg plus 3TC 300mg fixed dose combination for 28 days is the recommended ARV regimen for PEP in Namibia.
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 although it is not proven that this confers any additional benefit. In Namibia the preferred ARV is Lopinavir/ritonavir. If the client cannot tolerate the possible gastro-intestinal side effects (nausea, vomiting, diarrhea) then efavirenz can be used instead.
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 antiretrovirals may lead to development of resistance). 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.. 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 ALT level, and Creatinine clearance (Crcl) 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 of PEP include significant renal or liver impairment 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:

- Tenofovir 300 mg daily + lamivudine 300 mg fixed dose combination once daily for 28 days

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

- Lopinavir 400mg plus ritonavir 100mg twice daily.(preferred)
- Efavirenz 600 mg once nightly (not to be used in first trimester pregnancies)

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.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. Where possible, discussion of such cases with an HIV specialist is recommended

Table 4.3 *Summary of PEP recommendations*

Exposure	PEP recommendation	Regimen
High risk exposure	recommended	TDFplus 3TC plus LPV/r
Low risk exposure	offer	TDF plus 3TC
Intact skin Low risk fluids HIV- negative source	Do not offer	

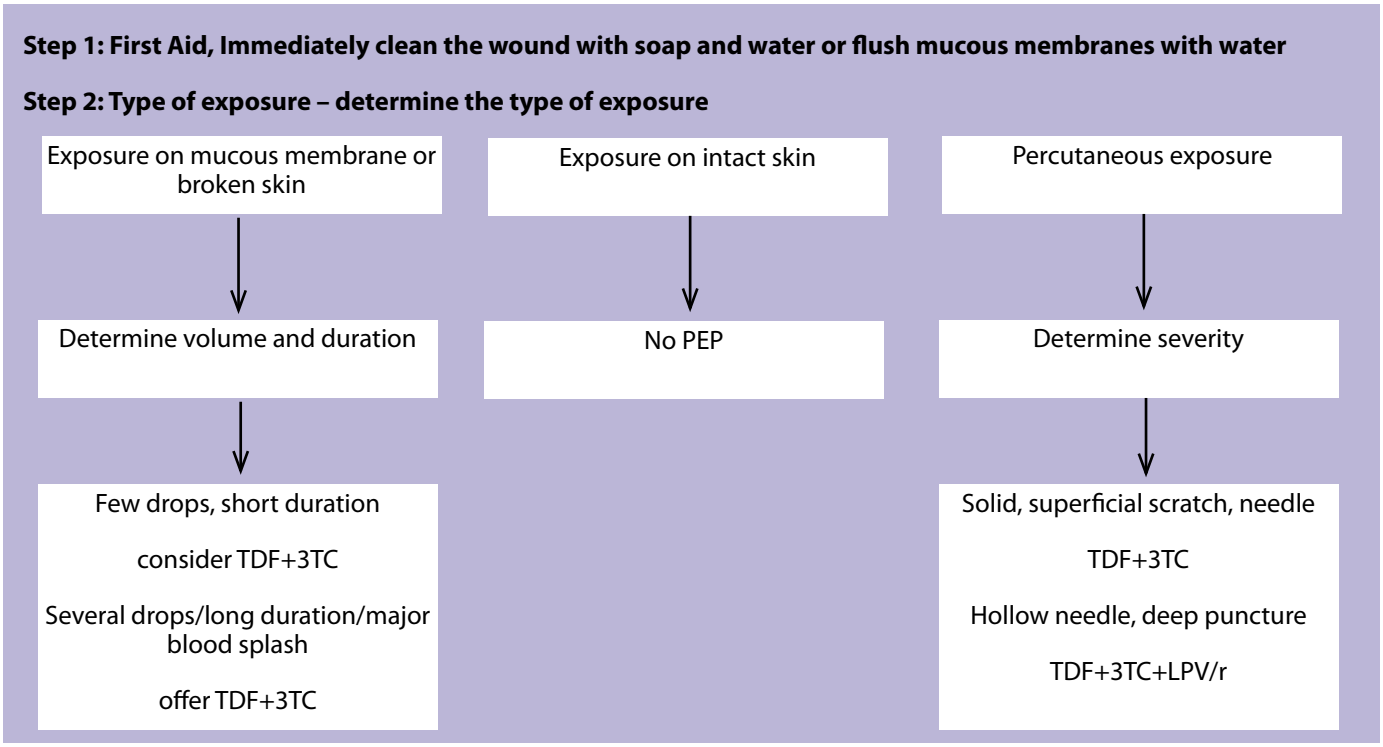
4.1.5 Accompanying measures

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:

- Infection control committees should be put in place to cover all health facilities throughout the country.
- 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.).
- 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.
- 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.
- Antiretroviral medications for PEP should be made available on a 24-hour basis (for example through casualty services).
- All employees of health facilities should be vaccinated against HBV and tetanus. Hepatitis B vaccination series with hepatitis B immunoglobulin (HBIG) should also be provided for all unvaccinated, non-immune health care 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 4.1. *Algorithm for PEP after occupational exposure*



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 health care 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 counseling

The following issues should be addressed during counseling:

- 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 TDF+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 evidence that starting PEP >72 hours after the rape will have no impact on preventing HIV infection. 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 performed for all rape survivors, whether or not they are choosing to use PEP. Additionally, tests for syphilis, pregnancy, and hepatitis B surface Antigen should be performed.

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 TDF+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. The remainder of the 28 day PEP regimen should be given at this visit if the survivor is HIV negative.

Monitoring for toxicities due to PEP should include liver transaminase (ALT) and creatinine clearance 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.

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

HIV serology should be done at 6 weeks, 12 weeks and 6 months. Rape survivors who are found to be HIV positive or who become infected with HIV should receive appropriate medical care at an ART clinic

4.2.4 PEP regimen after rape

The recommended antiretroviral regimen following rape is: Tenofovir 300mg plus lamivudine 300mg (fixed dose combination) plus lopinavir 400mg/ritonavir 100mg BD for 28 days.

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

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:

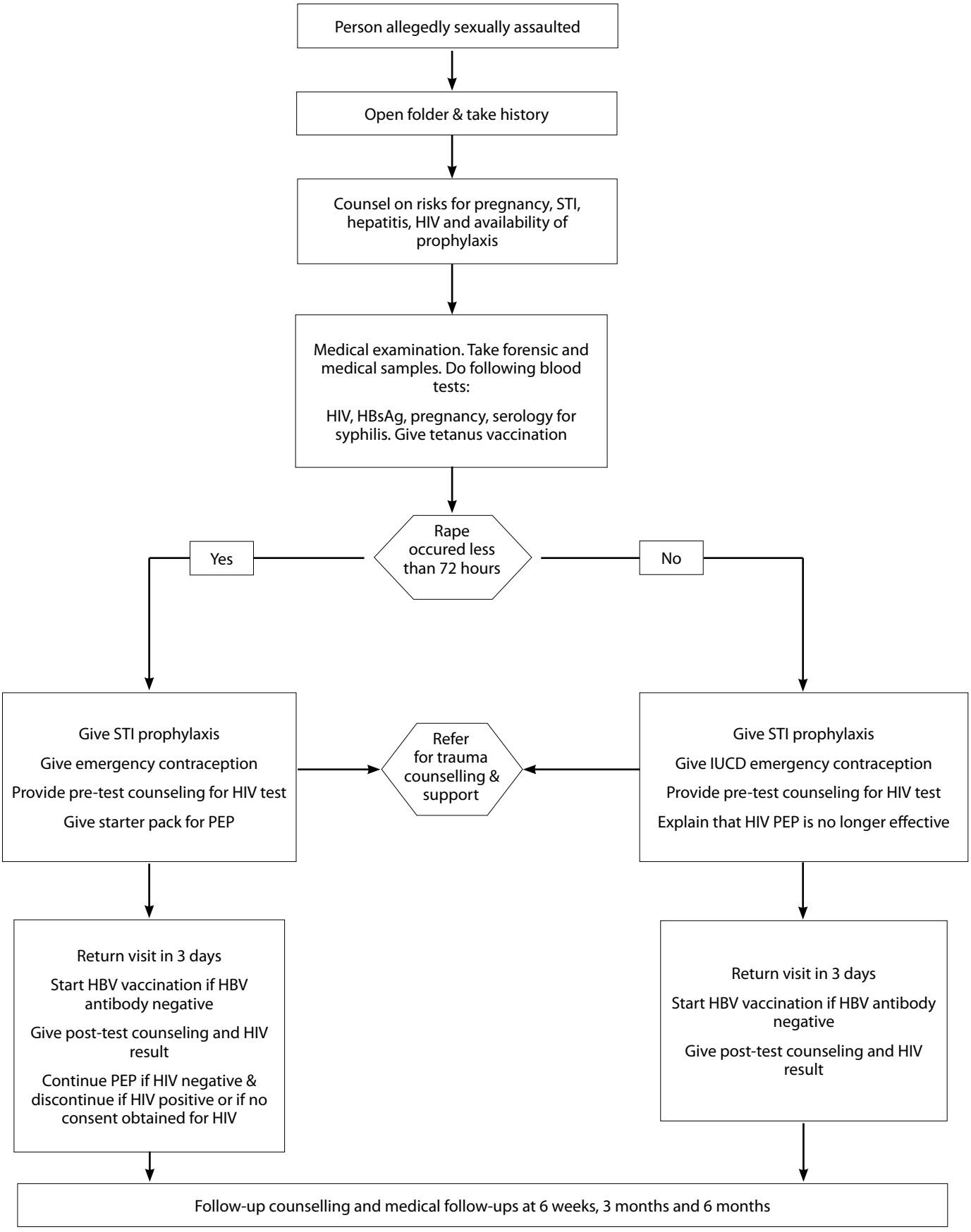
1 STI prophylaxis: presumptive prophylaxis should be given in the form of cefixime 400 mg or ceftriaxone 250 mg IM STAT plus metronidazole 2 gram STAT plus azithromycin 1g STAT .
2 Emergency contraception within 72 hours: norgestrel 0.5mg (500 mcg) and ethynyl oestradiol 0.05mg (50 mcg) (Ovral) given 2 tablets STAT and 2 tablets 12 hours after the first dose. Another regimen available in the private sector is levonorgestel 2 tablets (or 0.75 mg) STAT and 2 tablets (or 0.75 mg) 12 hours after the first dose. A copper T IUCD can be inserted up to 5 days after the rape.
3 Hepatitis B immunoglobulin and hepatitis B vaccination should be started as soon as possible if the patient is not already immune, and no later than 21 days after the incident. If the results of the HBsAb test is non-reactive 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. Since stress may cause illness related to physical and mental exhaustion, the survivor should be made aware of stress indicators such as general irritability, trembling, pain in the neck or back and changes in appetite or sleeping patterns.
8 Medico-legal assessment of injuries.
9 Completion of appropriate registers.

It is recognized that children who experience rape have the need of ongoing, comprehensive support. Where there is any suggestion that a child has been raped, the case should be referred to an experienced paediatrician. Full assessment of physical injuries must be performed, STI prophylaxis will need to be adjusted using paediatric doses, and psychological and emotional support must be initiated systematically.

4.2.6 Post-exposure prophlyaxis in other situations

1. Accidental sexual exposure.
   It is recognized that clients sometimes present to health facilities after having had unprotected sex (or 'burst condom') with a partner of known HIV positive status or unknown serostatus. If the client presents within 72 hours, clinicians may use their judgement as to whether PEP is warranted, but counseling concerning correct condom use and risky behavior is essential. PEP regimen is the same as detailed above.
2. Accidents.Where there is exposure to blood or body fluids such as at the scene of a motor vehicle accident or injuries caused by human bites, clinicians should assess the level of exposure risk as detailed in Table 4.1 and provide the appropriate counseling and PEP regimen.

Figure 4.2 *Algorithm for PEP for rape survivors*



APPENDICES

Appendix 1: WHO Clinical staging of HIV disease in adults and adolescents (2007)

Clinical Stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy

Clinical Stage 2

- Unexplained[1] moderate weight loss (under 10% of presumed or measured body weight)[2]
- Recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent pruritic ulcerations
- Seborrhoeic dermatitis
- Fungal nail infection

Clinical Stage 3

- Unexplained[1] severe weight loss (over 10% of presumed or measured body weight)[2]
- Unexplained[1] chronic diarrhoea for longer than one month
- Unexplained[1] persistent fever above 37.6°C (intermittent or constant, for longer than one month)
- Persistent oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe bacterial infections (e.g. pneumonia, empyema, pyomysitis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained[1] anaemia (below 8 g/dl), neutropenia (below 0.5 x 10^9/L) or chronic thrombocytopenia (below 50 x 10^9/L)

Clinical Stage 4[3]

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital, or anorectal of more than one month's duration or visceral at any site)
- Oesophageal candidiasis (or candidiasis of 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 (with diarrhoea)
- Chronic isosporiasis
- Disseminated mycosis (coccidiomycosis or histoplasmosis)
- Recurrent non-typhoidal Salmonella bacteraemia
- Lymphoma (cerebral or B cell non-Hodgkin) or other solid HIV-associated tumours
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

[1] Unexplained refers to where the condition is not explained by other conditions.
[2] Assessment of body weight among pregnant woman needs to take into consideration the expected weight gain of pregnancy.
[3] 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

Appendix 2: WHO Clinical Staging of HIV in infants and children (2007)

Clinical Stage 1 (Asymptomatic)

- Asymptomatic
- Persistent generalised lymphadenopathy

Clinical Stage 2 (Mild)

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Angular cheilitis
- 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

Clinical Stage 3 (Advanced)

- Unexplained moderate malnutrition or wasting not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5 ºC, intermittent or constant, for longer than one month)
- Persistent oral candidiasis (after first 6-8 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), neutropaenia (< 0.5 x 10^9/L) or chronic thrombocytopaenia (< 50 x 10^9/L)

Clinical Stage 4 (Severe)

- 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 sarcoma
- Oesophageal candidiasis (or candida of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after one month of life)
- 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 (histoplasmosis, coccidiomycosis)
- Chronic cryptosporidiosis (with diarrhoea)
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacteria infection
- Cerebral or B cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV-associated cardiomyopathy or nephropathy

Appendix 3. Routine Laboratory monitoring by regimen

Regimen	2 weeks	6 weeks	3 months	6 months	12 months and every 6 months thereafter	12 months and every year thereafter
TDF/3TC/NVP	ALT	ALT	ALT CrCl	Hb ALT VL CrCl	Hb ALT CD4 CrCl	
TDF/3TC/EFV			ALT CrCl	Hb ALT VL CrCl	Hb ALT CD4 CrCl	Fasting cholesterol and triglyceride
AZT/3TC/NVP	Hb ALT	Hb ALT	Hb ALT	Hb ALT VL CrCl	Hb ALT CD4 CrCl	
AZT/3TC/EFV	Hb	Hb	Hb ALT	Hb ALT VL CrCl	Hb ALT CD4 CrCl	Fasting cholesterol and triglyceride
D4T/3TC/NVP	ALT	ALT	ALT	Hb ALT VL CrCl	Hb ALT CD4 CrCl	
D4T/3TC/EFV			ALT	Hb ALT VL CrCl	Hb ALT CD4 CrCl	Fasting cholesterol and triglyceride
TDF/AZT/3TC/LPV/r	ALT	ALT	ALT CrCl	Hb ALT VL CrCl	Hb ALT CD4 CrCl	Fasting cholesterol, triglyceride and glucose
AZT/DDI/3TC/LPV/r	Hb ALT	Hb ALT	ALT CrCl	Hb ALT VL CrCl	Hb ALT CD4 CrCl	Fasting cholesterol, triglyceride and glucose
AZT/3TC/TDF/LPV/r	Hb if no previous AZT	Hb if no previous AZT	Hb if no previous AZT CrCl	Hb ALT VL CrCl	Hb ALT CD4 CrCl	Fasting cholesterol, triglyceride and glucose

NB: Children up to 18 years of age should have routine 6-monthly viral load tests from the start of HAART

Appendix 4. Summary of ARV formulation and doses

Name of medicine	Formulations	Age (weight) dose and frequency	Side-effects and toxicity	Other comments
NRTIs				
Abacavir (ABC)	Tablet: 300 mg	>37.5 kg or >16 years: 300 mg BD	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 - 25°C. Tablets can be crushed and mixed with small amount of water of food for immediate use.
Zidovudine (AZT)	Capsules: 100mg Tablets: 300mg	300mg BD	Anaemia, granulocytopenia, Fatigue, malaise,headache, myopathy, nausea, vomiting, myositis, liver toxicity,lactic acidosis.	Can give with food. Tablets can be crushed and combined with small amounts of water and taken immediately. Capsules can be opened and dispersed in water or on a small amount of food for immediate use.
Lamivudine (3TC)	Tablet 150 mg	150mg 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. Tablets can be crushed and contents mixed with small amount of food or water and given immediately.
Stavudine (D4T)	Capsules 15,20,and 30 mg	30 mg BD	Peripheral neuropathy, pancreatitis and diarrhoea	Capsules can be opened and mixed with small amount of food or water for immediate use.

Name of medicine	Formulations	Age (weight) dose and frequency	Side-effects and toxicity	Other comments
Didanosine (ddI)	Chewable tablets with buffer: 25, 50,100, 150mg, 200mg. Enteric-coated beadlets in capsules: 125,200,250, and 400mg.	Max. dose for ≥13 years and <60 kg:250 mg once daily and for those > 60kg 200mg BD or 400 mg once daily · 20 to <25kg: 200mg once daily · 25 to <60kg: 250mg once daily · 60kg and above: 400mg once daily[1]	Diarrhoea, abdominal pain, nausea, vomiting, peripheral neuropathy (dose-related), electrolyte abnormalities, hyperuricemia, lactic acidosis and severe hepatomegaly, pancreatitis, increased transaminases, retinal depigmentation.	Food decreases absorption so give 1hr before or 2 hrs after meals. Use at least 2 chewable tablets to improve buffering capacity. Tablets should be chewed or crushed and dispersed in water or clear juice before they are taken. Capsules with enteric coated beadlets (not currently available in the state sector) can be opened and sprinkled on a small amount of food

Name of medicine	Formulations	Age (weight) dose and frequency	Side-effects and toxicity	Other comments
NNRTI				
Nevirapine (NVP)	Tablets: 200mg	Induction: 200 mg once daily for 14 days Maintenance: 200mg BD	Skin rash can be severe, (SJS, TEN). Fever, nausea, headache, diarrhoea, raised liver enzymes, liver toxicity can be severe. Hypersentivity reactions.	No food restrictions. Rifampicin significantly reduces Nevirapine levels and should not be used concurrently. Oral suspension must be well shaken. Tablets can be crushed and combined with small amount of water or food and taken immediately.
Efavirenz (EFV)	Capsules: 50, 100, 200mg Tablet: 600mg	Administered once daily at night ≥40kg: 600mg OD	Skin rash, SJS, TEN CNS (somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, etc., more so in adults), raised liver enzymes, 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 or sweet foods hide taste. Bedtime dosing recommended to improve tolerability of CNS side-effects. Not recommended for children < 3 years of age or < 10 kg.

Name of medicine	Formulations	Age (weight) dose and frequency	Side-effects and toxicity	Other comments
PIs				
Lopinavir/ Ritonavir (LPV/r)	Tablets: LVP 200mg and RTV 50mg Tablets: LPV 100mg and RTV 25mg	Administered twice daily with food: 400mg/100mg LPV/r BD	Diarrhoea, headache, asthenia, nausea, vomiting. Elevated lipids, rash, pancreatitis, hyperglycemia, ketoacidosis, diabetes hepatitis.	Should be taken with food. Oral solution should be kept refrigerated (stable for 2 months at less than 25 °C). Liquid has bitter taste. Tablets cannot be split or crushed. They must be swallowed whole. Tablets have no food restrictions and are heat stable.

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

$$\text{Body Surface Area in } M^2 = \sqrt{\frac{\text{Height in cm X weight in kg}}{3{,}600}}$$

The Nomogram on Appendix 10 may also be used for determining body surface area.

Appendix 5: Dietary Management of Common HIV-Related Symptoms

Illness	Diet	Care and nutrition practices
Anorexia (appetite loss)	· Stimulate appetite by eating favourite foods. · Eat small amounts of food more often. · Eat more energy-dense foods. · Avoid strong-smelling foods.	If appetite loss is a result of illness, seek medical treatment.
Diarrhoea	· Drink a lot of fluids (soups, diluted fruit juices, boiled water and light herbal teas) to avoid dehydration. · Avoid strong citrus fruits (orange, lemon) because they irritate the stomach. · Eat foods rich in soluble fibre (millet, banana, peas, and lentils) to help retain fluids. · Eat fermented foods such as porridges and yoghurt. · Eat easily digestible foods such as rice, bread, millet, maize porridge, potato, sweet potato, and crackers. · Eat small amounts of food frequently. · Continue to eat after illness to recover weight and nutrient loss. · Eat soft fruits and vegetables such as bananas, mashed sweet potato, and mashed carrots. · Drink non-fat milk if there is no problem with lactose. · Boil or steam foods if diarrhoea is associated with fat mal-absorption. · Avoid or reduce intake of some dairy products such as milk, caffeine (coffee and teas) and alcohol, fatty foods, fried foods and extra oil, lard or butter, and gas-forming foods such as cabbage, onions, and carbonated soft drinks.	**Prevention** · Drink clean boiled water. · Wash hands with water and soap before handling, preparing, serving, or storing food. · Wash hands with water and soap after using a toilet or latrine or cleaning a child after defecation. **Treatment** · Drink more fluids to prevent dehydration. Prepare rehydration solutions using oral rehydration salt sachets or a homemade solution from cereals. · Go to a health facility if symptoms such as severe dehydration, fainting, dizziness, shortness of breath, bloody stools, high fever, vomiting, severe abdominal pain, or diarrhoea persist for more than 3 days.
Fever	· Eat soups rich in foods that give energy and nutrients, such as maize, potatoes, and carrots. · Drink plenty of fluids. · Drink teas from lemon, guava, and gum tree. · Continue to eat small, frequent meals as tolerated.	· Drink fluids to prevent dehydration, particularly clean boiled water. · Bathe in cool water. · Take two paracetamol tablets if available, with a meal three times a day (morning, afternoon, and evening). · Go to the health facility if you have fever that lasts several days and is not relieved with aspirin, loss of consciousness, severe body pain, yellow eyes, severe diarrhoea, or convulsions and seizures.

Illness	Diet	Care and nutrition practices
Nausea and vomiting	· Eat small frequent meals. · Eat soups, unsweetened porridge, and fruits such as bananas. · Eat lightly salty and dry foods such as crackers to calm the stomach. · Drink herbal teas and lemon juice in hot water. · Avoid spicy and fatty foods. · Avoid caffeine (coffee and tea) and alcohol. · Drink liquids such as clean boiled water.	· Avoid an empty stomach; nausea is worse if nothing is in the stomach. · Avoid lying down immediately after eating—wait at least 20 minutes. · Avoid vomiting. · Rest between meals.
Thrush	· Eat soft, mashed foods such as carrots, scrambled eggs, mashed potatoes, bananas, soups, and porridge. · Eat cold or room-temperature foods. · Avoid spicy, salty, or sticky foods that may irritate mouth sores. · Avoid sugary foods that cause yeast to grow. · Avoid strong citrus fruits and juices that may irritate mouth sores. · Avoid alcohol and drink plenty of fluids.	· Seek medical treatment. · Use a spoon or cup to eat small amounts of foods. · Tilt your head back when eating to help with swallowing. · Rinse your mouth with boiled warm, salty water after eating to reduce irritation and keep infected areas clean so yeast cannot grow.
Constipation	· Eat more high-fibre foods such as maize, whole wheat bread, green vegetables, and washed fruits with the peel. · Drink plenty of liquids. · Avoid processed or refined foods.	· Avoid cleansing practices such as enemas and medications. · Drink plenty of fluids, including boiled water.
Loss of taste or abnormal taste	· Use flavour enhancers such as salt, spices, herbs, and lemon.	· Eat small frequent meals · Chew food well and move it around the mouth to stimulate receptors

Reverse transcriptase inhibitors

Drug name	Food recommendation	Avoid	Possible side-effects
Efavirenz (EFZ)	· Can be taken without regard to meals. · Do not take a high fat meal (it increases absorption to potentially harmful levels).	· Alcohol · St John's wort	· Elevated blood cholesterol and triglyceride levels. · Rash, dizziness, drowsiness, anorexia, nausea, vomiting, diarrhea, mouth sores, fatigue, sleep disturbances. · Dyspepsia, abdominal pain, flatulence.
Nevirapine (NVP)	· Can be taken without regard to food.	· St John's wort	· Nausea, vomiting, rash, fever, headache, fatigue, stomatitis, abdominal pain, drowsiness. · High hepatotoxicity.
Abacavir (ABC)	· Can be taken without regard to food. · Take with or without food.	· Alcohol	· Nausea, vomiting, fever, allergic reactions, anorexia, diarrhea, anaemia, rash, cough, headache, dizziness. · Hypotension, pancreatitis.
Didanosine (ddI)	· Take on empty stomach (30 minutes before or 2 hours after eating. · Take with water only (food reduces its absorption).	· Alcohol · Grape fruit juice · Antacids containing aluminium or magnesium	· Nausea, headache, dizziness, diarrhea, insomnia, anorexia, vomiting, dry mouth, loss of taste, constipation, anaemia, stomatitis, fever, pancreatitis.
Lamivudine (3TC)	· Can be taken without regard to food.	· Alcohol	· Nausea, headache, dizziness, diarrhea, insomnia, vomiting, anaemia, stomatitis, fever, pancreatitis, muscle pain, nasal symptoms, abdominal pain, peripheral neuropathy.
Stavudine (d4T)	· Can be taken without regard to food.	· Limit the consumption of alcohol	· Nausea, headache, dizziness, diarrhea, insomnia, anorexia, anaemia, stomatitis, fever, pancreatitis, chills and fever, peripheral neuropathy, bone marrow suppression · May increase the risk of lipodystrophy.
Tenofovir (TDF)	· Take with a meal.	· Alcohol	· Abdominal pain, headache, fatigue, dizziness.
Zidovudine (ZDV/AZT)	· Take without food but if it causes nausea or stomach problems, take with a low fat meal. · May require zinc and copper supplementation.	· Alcohol	· Anorexia, anaemia, nausea, vomiting, bone marrow suppression, headache, fatigue, constipation, mouth sores, dyspepsia, fever, dizziness, dyspnoea, insomnia, muscle pain, rash.

Protease Inhibitors

Drug name	Food recommendation	Avoid	Possible side-effects
Indinavir (IDV)	· Take on empty stomach (1 hour before or 2 hours after a meal or with a light non fat meal. · Take with plenty of water to avoid kidney problems - at least 1.5 litres of fluids daily to prevent kidney stones.	· Grape fruits · St John's wort	· Nausea, headache, dizziness, diarrhoea, insomnia, vomiting, ascites, stomatitis, fever, pancreatitis, muscle pain, nasal symptoms, abdominal pain, regurgitation. · May increase the risk of lipodystrophy (increased blood fats).
Lopinavir (LPV)	· Can be taken without regard to food. · May be taken with a high fat meal for better absorption.	· St John's wort	· Abdominal pain, diarrhoea, headache, weakness, nausea, rash, change in taste, anorexia, high blood sugar. · May increase the risk of lipodystrophy (increased blood fats).
Nelfinavir (NFV)	· Take with a meal or light snack. · To increase absorption, take with meal containing <15 g fat.	· St John's wort	· Diarrhoea, flatulence, nausea, abdominal pain, rash. · May increase the risk of lipodystrophy.
Ritonavir (RTV)	· Take within 2 hours after a full meal with high calories and fat for better absorption	· St John's wort	· Nausea, headache, dizziness, diarrhoea, insomnia, anorexia, vomiting, weakness, insomnia, diabetes, fever, numbness around the mouth. · May increase risk of lipodystrophy, pancreatitis and hepatitis.
Saquinavir (SQV)	· Take with a meal or light snack. · Take within 2 hours of a high fat and calcium meal.	· St John's wort · Garlic supplements	· Mouth ulceration, taste changes, nausea, vomiting, abdominal pain, diarrhoea, constipation, flatulence, rash, weakness, headache, insomnia, hepatic impairment. · May increase risk of lipodystrophy, high blood sugars.

<table>
<tr><th colspan="2">ASSESS</th><th rowspan="2">CRITERIA</th><th rowspan="2">CLASSIFICATION</th><th rowspan="2">TREATMENT/CARE</th></tr>
<tr><th>HISTORY</th><th>LOOK FEEL AND MEASURE</th></tr>
<tr>
<td rowspan="4">Ask the client or refer to records:

1. Has the client lost weight in the past month/since the last visit?
2. Has the client had:
– Active TB (on treatment)?
– Another chronic opportunistic infection (OI) or malignancy (e.g., oesophageal infections)?
– Mouth sores/oral thrush?
3. Has the client's body composition/fat distribution changed noticeably?
– Thinning of limbs and face?
– Fat distribution on limbs, breasts, stomach, back?
4. Has the client had:
– Nausea and vomiting?
– Persistent fatigue?
– Poor appetite?</td>
<td rowspan="4">Prevention
· Drink clean boiled water.
· Wash hands with water and soap before handling, preparing, serving, or storing food.
· Wash hands with water and soap after using a toilet or latrine or cleaning a child after defecation.
Treatment
· Drink more fluids to prevent dehydration. Prepare rehydration solutions using oral rehydration salt sachets or a homemade solution from cereals.
1. Go to a health facility if symptoms such as severe dehydration, fainting, dizziness, shortness of breath, bloody stools, high fever, vomiting, severe If the client has oedema on both legs or base of the spine:
– Rule out pre-eclampsia, kidney problems, elephantiasis, heart failure, and wet beriberi (vitamin B1 deficiency with oedema).
2. Measure the client's weight (kg) and height (cm).
3. Compute body mass index (BMI).
4. Measure mid-upper arm circumference (MUAC) for all pregnant women, all women up to 6 months post-partum, and adults who cannot stand straight.
5. Examine the client for conditions that cause secondary malnutrition (e.g., injuries, burns, surgical procedures, pregnancy, diarrhoea, or disease of the gastrointestinal tract, thyroid, kidney, liver, or pancreas).
6. Look for medical complications and danger signs (e.g., anaemia, severe dehydration, active TB, severe bilateral oedema).
7. If the client has no medical complications, give an appetite test using ready-to-use therapeutic food (RUTF).</td>
<td>Adults (non-pregnant and non-post-partum)
BMI < 16 kg/m² (If can't measure BMI, MUAC < 19 cm)
OR
Bilateral pitting oedema (both feet or legs are swollen, and the skin remains indented when pressed with a finger)

Pregnant women and women up to 6 months post-partum
MUAC < 19 cm</td>
<td>Severe acute malnutrition (SAM) with complication (fever, hypothermia, severe anaemia or dehydration, vomiting, bilateral oedema +++) or no appetite</td>
<td><u>Inpatient treatment</u>

Refer to therapeutic feeding programmes</td>
</tr>
<tr>
<td>SAM with appetite and no complication</td>
<td><u>Outpatient treatment</u>
Refer to therapeutic feeding programmes</td>
</tr>
<tr>
<td>Adults (non-pregnant and non-post-partum)
BMI ≥ 16.0–< 18.5 kg/m²
(If can't measure BMI, MUAC ≥ 19–< 22 cm)
Pregnant women and women up to 6 months post-partum
Weight loss or no weight gain
MUAC ≥ 19–< 22 cm</td>
<td>Moderate/mild malnutrition

Significant weight loss</td>
<td rowspan="2">Refer to supplementary feeding programmes</td>
</tr>
<tr>
<td>Severe lung disease

Active TB (first 3 months of treatment)
Chronic diarrhoea
Difficulty swallowing</td>
<td>Signs of symptomatic disease</td>
</tr>
<tr>
<td>Adults (non-pregnant and non-post-partum)
BMI ≥ 18.5 kg/m²
(If can't measure BMI, MUAC ≥ 22 cm)
Pregnant and post-partum women
MUAC ≥ 23 cm</td>
<td>Normal</td>
<td>Nutrition counselling</td>
</tr>
</table>

Appendix 8: Algorithm for classification of Malnutrition in Children 6 months–14 years old

ASK	LOOK,FEEL and MEASURE	CRITERIA	CLASSIFICATION	TREATMENT/CARE
Ask mother or caregiver or refer to records: 1. Has the child lost weight in the past month/since the last visit? 2. Has the child had: a. A cough for more than 21 days? (This may be a result of HIV-related chronic lung disease such as lymphocytic interstitial pneumonia [LIP] or bronchiectasis.) b. Active tuberculosis (TB) (on treatment)? c. Diarrhoea for more than 14 days? d. Another chronic opportunistic infection (OI) or malignancy?	**1. Look for severe visible wasting:** – Loss of muscle bulk on arms, shoulders, buttocks, and thighs, with visible rib outlines – Sagging skin on buttocks **2. Check for oedema** (swelling) in both feet or base of spine. **3. Measure child's weight (kg) and height (cm)** and find weight for height (WFH) using 2006 WHO child growth standards. **4. Measure mid-upper arm circumference (MUAC).** **5. Look at the shape of the curve on the growth chart.** – Has the child lost weight since the last visit? (Measure again to confirm current weight.) – Is the growth curve flattening? – Is the child gaining weight? Weight loss  Growth curve flattening  Weight gain 	**Bilateral pitting oedema** +++ (both feet and/or legs are swollen, and the skin remains indented when pressed with the thumb) **OR** WFH < –3 z-scores (WHO 2006) **OR** BMI for age 10–14 years: ≤ –3 z-score **OR** MUAC 6–59 months: < 11.5 cm 5–9 years: < 13.5 cm 10–14 years: < 16.0 cm **AND** Does not pass an appetite test	**Severe acute malnutrition (SAM)** **With medical complication** (WFH < -4 z-scores, shock, anorexia, intractable vomiting, convulsions, lethargy, lower respiratory tract infection, high fever, severe anaemia or dehydration, hypoglycaemia, hypothermia, pneumonia, TB) or **no appetite** **Without medical complication and with appetite** Clinical wellness Alertness Caregiver able/willing to manage SAM at home and return to clinic every 14 days	**Inpatient treatment** **Refer to therapeutic feeding programmes** **Outpatient treatment** **Refer to therapeutic feeding programmes**
		6–59 months: WFH or BMI for age between –3 and –2 z-scores **OR** MUAC 6–59 months: ≥ 11.5–< 12.5 cm 5–9 years: ≥ 13.5–< 14.5 cm 10–14 years: ≥ 16.0–< 18.5 cm	**Moderate/mild malnutrition (MAM)** **Poor weight gain**	**Refer to supplementary feeding programmes**
		Weight gain parallel to or higher than median growth curve WFH ≥ -2 z-score **OR** MUAC ≥ 12.5 cm	**Normal** **Growing appropriately**	**Nutrition counselling**
		Chronic lung disease, TB, persistent diarrhoea, or other chronic opportunistic infection or malignancy	**Condition with increased nutritional needs**	**Refer to supplementary feeding programmes**

Appendix 9 Safety Yellow Form

Republic of Namibia

Ministry of Health and Social Services

Safety Yellow Form

For reporting ADRs(Adverse Drug Reactions) and medicine use /product problems

TIPC Form

A. Patient Information			
Patient identifier(initials/code)		*Sex*	*M*_____ *F*_____
Age at the time of event		*Weight in kgs*	

B. Adverse Event/Product problem/Error (tick where appropriate)

1. Event/Reaction		**2.Type of Event/Reaction**	
Event/Reaction to ARV/TB/ACT/New medicines/Product		*Adverse Event*	
Serious events with other medicines/Products		*Product problem (e.g. defects/malfunctions)*	
		Product use error (e.g. medication error)	
3. Outcomes attributed to adverse event (tick where appropriate)			
Death (Date: ____/____/____)		*Disability or Permanent damage*	
Life-threatening		*Congenital anomaly/ Birth defect*	
Hospitalization/prolonged hospital stay		*Other serious (important medical events)*	
Required intervention to prevent permanent impairment/damage e.g. use of devices		***4. Date of the Event***	
		5. Date of this report	

6. Describe the Event, Product problem or Product use error and Actions taken

7. Relevant tests/Laboratory investigations done (include dates)

8. Other relevant history, including pre-existing medical conditions (allergies, pregnancy, smoking, alcohol use, liver, kidney problems, race etc)

C. Suspect Product (obtain as much information as possible from product label/packaging)

Name		*Dose/amount*	
Strength		*Frequency*	
Manufacturer		*Route*	
Date of use (From/to or best estimate of duration):			
Event stopped after stopping use? (Yes/No)		*Event stopped after dose was reduced?(Yes/No)*	
Event reappeared after reintroduction (Yes/No)			
Lot number	*Expiry date*		

D. Other products taken by the patient within the last 3 months prior to the reaction

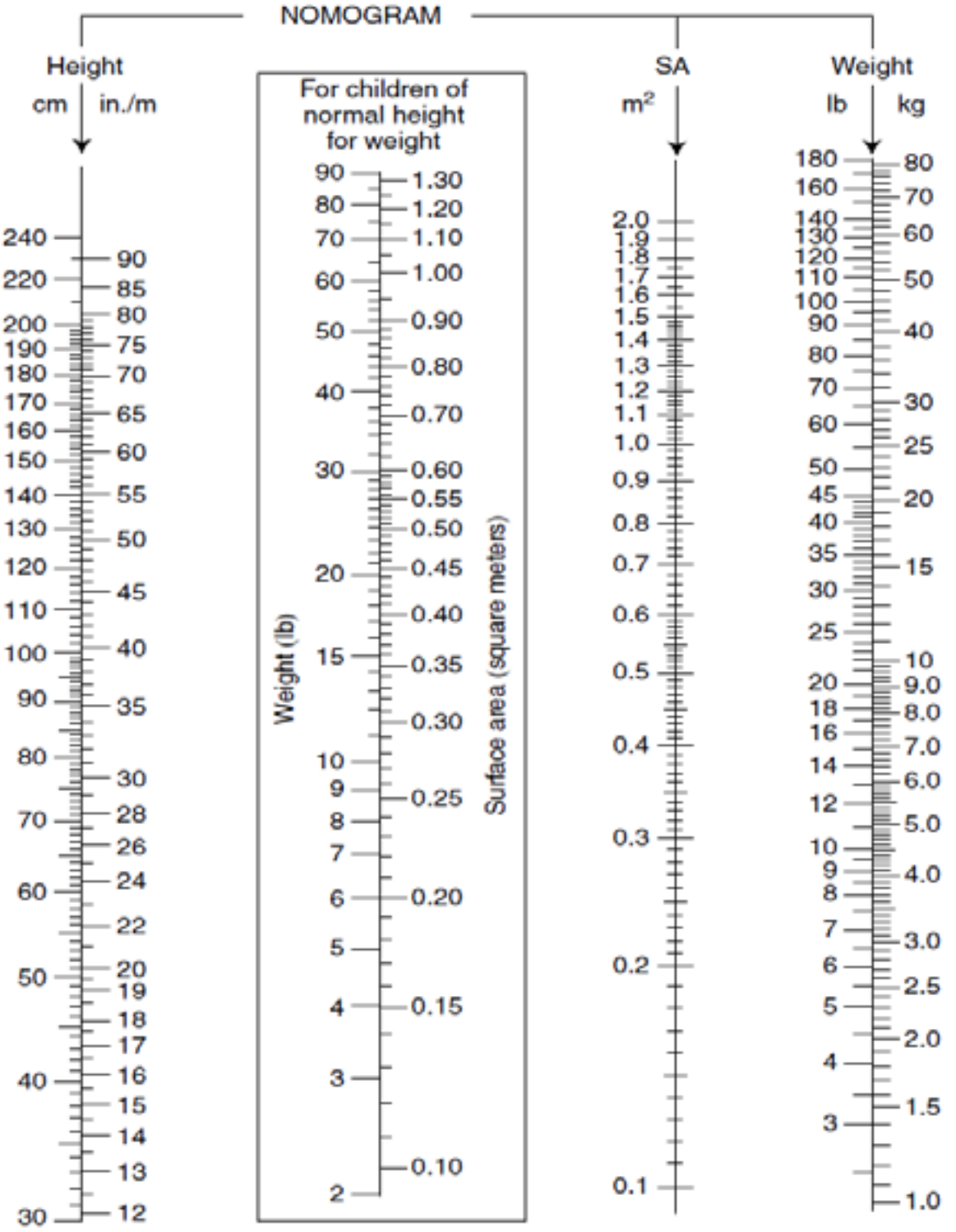
Product name 1		*Product name 3*	
Dosage and dates		*Dosage and dates*	
Product name 2		*Product name 4*	
Dosage and dates		*Dosage and dates*	

E. Information about the reporter

Names		*Profession*	
Telephone		*Fax*	
Region		*Email*	
Health Facility			

Send/ Fax to the Therapeutics Information and Pharmacovigilance Centre: Room 21, Basement Area, Windhoek Central Hospital; Tel: 061 203 2312 Fax: 061 22 66 31

Appendix 10: The West Nomogram-Body Surface Area



Note: Nomogram modified from data of E. Boyd by C.D. West; from Behrman, R.E., Kliegman, R.M., & Jenson, H.B. (eds.). (2000). Nelson textbook of pediatrics (16th ed.). Philadelphia: W.B. Saunders.

Appendix 11: Antiretroviral medication dosage adjustments for renal and hepatic failure

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)	300mg tablet	300mg BD	Dosing adjustment not necessary				Usual dose Avoid in severe cases	Hypersensitivity reaction, lactic acidosis
Didonasine (ddI)	25, 50, 100, 200mg tablets 250mg, 400mg EC tablets	<60kg: 250mg od	125mg od	125mg od	125mg od	125mg od	Usual dose Monitor for toxicity	Peripheral neuropathy, pancreatitis, hyplipidaemia, lactic acidosis, lipoatrophy
		>60kg: 400mg od	200mg od	125mg od	125mg od	125mg od		
Lamivudine (3TC)	150mg tablet	150 mg BD	150mg od	150mg 1st dose, then 100mg od	150mg 1st dose, then 50mg od	150mg 1st dose, then 50mg od	Usual dose	All rare. Lactic acidosis, lipoatrophy, pancreatitis, peripheral neuropathy
Stavudine (D4T)	15, 20, 30, 40mg tablet	30mg BD*	15mg BD	15mg od	15mg od	15mg od	Usual dose	Peripheral neuropathy, lactic acidosis, pancreatitis, lipoatrophy
Zidovudine (AZT)	100mg capsule, 300mg tablet	300mg BD	Usual dose	Usual dose	(<15 ml/min) 100mg tds	100mg 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 (limited data)	Haemotological toxicity, lactic acidosis, lipoatrophy, myopathy
Tenofovir (TDF)	300mg tablet	300mg od	300mg q48h	300 mg twice per week	300mg weekly	300mg weekly	Usual dose	Renal insufficiency, lactic acidosis, lipoatrophy, GI (diarrhoea, nausea, vomiting), asthenia

Medicine Name	Form	Usual adult dose	Renal failure dosing	Liver failure dosing	Toxicity
Efavirenz	200mg, 600mg tablet	600mg nocte	Dosing adjustment not necessary	Use with caution. Avoid in severe cases	Rash, rarely Stevens Johnson Syndrome, Hyperlipidaemia, CNS/ neurologic toxicity (dizziness, insomnia, somnolence, abnormal dreams, suicidal ideation)
Nevirapine (NVP)	200mg tablet	200mg od for 14 days, then 200mg BD	Dosing adjustment not necessary	Use with caution. Avoid in severe cases	Hypersensitivity reactions, hepatotoxicity, Steven Johnson Syndrome, TEN
Indinavir (IDV)	400mg capsules	800mg + 100mg RTV BD	Dosing adjustment not necessary	Use with caution. Avoid in severe cases	Hyperbilirubaenemia, nephrolithiasis, hyperlipidaemia, lipodystrophy, hepatotoxicity, insulin resistence
Lopinavir / ritonavir (LVP/r)	200/50 mg tablets	400/100 mg BD	Dosing adjustment not necessary	Use with caution. Avoid in severe cases	Hepatotoxicity, hyperlipidaemia, lipodystrophy, insulin resistence
Ritonavir (RTV)	100mg tablets	Used only as a booster for other PIs	Dosing adjustment not necessary	Use with caution. Avoid in severe cases	Hepatotoxicity, periol parasthesia, hyperlipidaemia, lipodystrophy, insulin resistence, hyperuricaemia

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(Footnotes)
1 Videx Prescribing Information (Revised in January 2010)
2 Sustiva Prescribing Information