Republic of Namibia

Ministry of Health and Social Services
Directorate of Special Programmes

National Guidelines for Antiretroviral Therapy

Fourth Edition
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FOREWORD

Namibia continues to be one of the countries with the highest HIV prevalence in the world with 13.1% of the adult population living with HIV in 2013. The HIV burden is much higher among pregnant women with prevalence of 18.2% in 2012. That is why, the Government of Namibia has vowed to progressively provide access, on a sustained and equal basis, to affordable, quality antiretroviral treatment and prophylaxis to prevent opportunistic infections, to all persons who need it as stipulated in the National HIV policy of 2007.

Furthermore, the government is also committed to ensuring that treatment guidelines are continuously updated and brought in line with the latest international recommendations which will ensure quality of treatment and care. The perpetual search for more efficient, safe and easy to administer treatment regimens for both adults and children will greatly contribute to the achievement of health for all Namibians and thus making the vision 2030 a reality.

It is worth mentioning that the treatment successes made to date by Namibia are enormous. About 93% of patients who have been enrolled in the programme are alive their health status has improved and are leading productive lives. As a result of the success of the ART programme, community acceptability of 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 exposure to HIV. The Ministry of Health and Social Services (MoHSS) is providing leadership in HIV prevention and control.

Antiretroviral treatment is part of the comprehensive care that supports families and communities that are affected by HIV /AIDS and should not be dealt with in isolation. 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 providing support to communities and individuals that have been affected by this disease.

Since the beginning of the treatment program, active participation of men remains very poor, with only one third of patients in HIV care and treatment programmes being male. Therefore, once again, I would like to appeal and make a strong call to Namibian men to utilize the available health services for themselves as well as their families, friends and colleagues.

The MoHSS will continue to revise and update these guidelines as more information becomes available. The MoHSS acknowledges the support that has been received from our development partners and all stakeholders that have contributed to our success .

Dr. Richard Nchabi Kamwi
Minister for Health

PREFACE

The Ministry of Health and Social Services, as stipulated in the National Policy on HIV/AIDS 2007, is offering continuum of HIV care to people living with HIV and their families, which is a comprehensive package of HIV prevention, diagnostic, treatment and support services. This comprehensive package includes initial diagnosis and linkage to care, management of opportunistic infections and other comorbid conditions, provision of antiretroviral therapy (ART), and palliative care.

In order to provide quality continuum of care to those in need, standardised ART guidelines were developed in 2003 and this is the fourth edition of the National Guidelines for Antiretroviral Therapy. To date, ART roll out has been very successful, achieving more than 84% coverage against a national target of 90%.

Tremendous efforts have been made to bring HIV treatment closer to where people live so that they do not have to travel long distances in order to access ART services. Presently ART services have been rolled out countywide and are available at all 35 district hospitals as well as at all health centers and most clinics. Outreach services have also been established to cater for smaller clinics where there are no ART services. The availability of ART has increased the survival rate of many Namibians living with HIV and improved the quality of their lives.

In order to achieve good results from the ART, it is imperative that patients adhere to treatment. Knowing that ART 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.

This fourth edition of the National Guidelines for Antiretroviral Therapy expands eligibility for ART significantly. The CD4 cut-off for eligibility has increased from 350 to 500 cells/mm^2 ' for adults and adolescents. In addition, all pregnant women, all children under 15 years old, all HBV/HIV co-infected patients and HIV-positive persons whose partners are HIV-negative are eligible for ART irrespective of CD4 count. Another major advance is the provision of a single tablet given once daily as standard first line ART for adults and adolescents. The guideline offers revised guidance on management and prevention of co-morbidities such as TB and hepatitis B.

I wish to acknowledge all those who participated in the development of these guidelines, in particular the contributions made by the Directorates of Special Programmes, Treatment Technical Advisory Committee, Primary Health Care and Tertiary Health Care & Clinical Support Services, as well as the Departments of Medicine and Paediatrics at Windhoek Central Hospital. A special appreciation goes to our development partners especially the United States Centers for Disease Control and Prevention (CDC); the International Training and Education Center for Health (I-TECH); the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) and the Supply Chain Management System (SCMS) projects funded through the United States Agency for International Development (USAID) and implemented by Management Sciences for Health (MSH); and the World Health Organization (WHO). I urge all doctors, nurses, and other health care professionals as well as community health care workers to famili . Ives with these guidelines in order to provide quality care to our people.

PERMANENT SECRETARY

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Mr A. Ndishishi
28 JAN 2014
Permanent Secretary
Republic of Namibia

MINISTRY OF HEALTH AND SOCIAL SERVICES

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LIST OF ABBREVIATIONS

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
BD	Twice Per Day
CD4	Cluster of Differentiation 4
CMV	Cytomegalovirus
CPT	Cotrimoxazole Preventive Therapy
CrAg	Cryptoccal Antigen
CrCl	Creatinine Clearance
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
ETR	Etravirine
ePMS	ElectronicPatient Monitoring System
FBC	Full Blood Count
GMP	Growth Monitoring and promotion
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCWs	Health Care Workers
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
ICU	Intensive Care Unit
IDV	Indinavir
IM	Intramuscular
H	Isoniazid (INH)
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 boosted with ritonavir
LPV/RTV	Equal doses of LPV and RTV
MAC	Mycobacterium avium complex
MOTT	Mycobacterium other than 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
SJS	Steven Johnson's Sydrome
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
VL	(HIV) Viral Load
VZV	Varicella zoster virus
WBC	White Blood Count
WHO	World Health Organization

INTRODUCTION

Since the diagnosis of first cases of HIV in the early 1980s, new advances in the diagnosis and treatment of HIV/AIDS continue to emerge and hence the need for perpetual revision of treatment guidelines. The First Edition of the National Guidelines for Antiretroviral Therapy was developed in 2003 and this is the Fourth Edition which was newly revised in order to include the most recent scientific evidences and best practices as well as guidance from WHO. The standardized guidelines address clinical, operational and programmatic aspects of using ARV medicines for HIV treatment as well as for prevention. Some of the major operational areas are: adherence to ART; retention in to care; human resources, models of service delivery especially decentralizing of ART to primary health care services and integrating ART with TB treatment, antenatal care and maternal and child programs; laboratory services and medicine supply. Treatment guidelines are intended for use by national HIV program managers, clinicians and other health service providers, managers of laboratory services, people living with HIV and community based organisations, national HIV treatment and prevention advisory bodies as well as international and bilateral agencies that provide financial and technical support.

Major changes in these guidelines include the use of fixed dose triple-ARVcombination as first line for adults and adolescents, routine viral load monitoring and substantially expanded eligibility criteria for ART: for adults and adolescents with a CD4 of500 cells/$mm^3$and below, all HIV infected pregnant and breastfeeding women, all children under 15 years of age, HIV/HBV co-infected persons, and HIV-positive persons whose partner is HIV-negative. The new ARV regimens provided for all ages have proven to be effective, withfewer side effects and most aresimpler in administration.

To promote early diagnosis of HIV infection and facilitate lifelong adherence to therapy, a favorable environment is essential. The following considerationsstill remain essential for the provision of ART:

- Easy access, including mobile, to counseling and testing for early diagnosis of HIV infection to ensure timely access to therapy.
- Understanding of the epidemic in general and HIV in particular.
- Identification of sufficient resources for treatment and care on a long-term basis through the public sector.
- Continuous patient counseling in order to ensure full understanding of ART, the importance of treatment adherence, timing of medication intake in relation to meals, and possible side-effects of ART as well as medicine resistance.
- 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.
- Community involvement through awareness creation, mobilization, referral linkages and other collaborations.
- Availability of a system for training, continuous education, monitoring and feedback on safe and effective management of HIV-related disease and ART.
- Availability of appropriate care, support services and referral mechanisms in case of treatment failure.
- Keeping up with new scientific evidence on treatment and best practices as well as with the updates of WHO guidelines.

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 of HIV/AIDS patients over the last ten years and will continue to do so with the revised editions. The guidelines will continue to be regularly updated to reflect new developments as they occur.

ART does not provide 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 FOURTH EDITION OF THE NATIONAL GUIDELINES FOR ANTIRETROVIRAL THERAPY

This Fourth Edition of the National Guidelines for Antiretroviral Therapy includes several significant changes from the First Edition. In order for these revised guidelines to be implemented with minimum disruption to patient care, a smooth transition from the third edition to the fourth 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 transition patients to newer regimens, even when the necessary supply of medicines may not yet be freely available. This causes disruption to patient care as well as the pharmacy supply system and can result in loss of medicines due to wastage of the previously recommended supplies. In addition, in some patients a change to a new regimen may not be appropriate.

In order to prevent such implementation challenges, the following basic principles are to be adhered to by all prescribers and dispensers;

1. All ART-naïve patients eligible for ART should start on the new preferred ARV first line regimens (unless there are specific contraindications).

2. If a patient is stable on a current ART regimen and has no significant adverse side effects, that patient's medication should only be changed under the specific conditions listed below:

- Patients currently on stavudine should, if possible, transition to to TDF (adults and adolescents)- or ABC (children)-based regimens. This is to minimise risk of stavudine-related toxicities. Adults and adolescents who are currently receiving first line therapy with d4T/3TC/NVP will have virological suppression assessed, and will be transition to TDF/FTC(or 3TC)/EFV if the viral load is <20 copies/ml. Children on d4T-containing regimens should also have viral load assessed and transfer as appropriate to ABC-containing regimens. See tables 1.5 and 3.7 for further details.
- Patients currently on AZT should, if possible, also transition to TDF (adults and adolescents)- or ABC (children)-based regimens following similar assessments of virological suppression. See tables 1.5 and 3.7.
- Pregnant women who are stable on an ART regimen with no adverse effects and whose viral load is suppressed should not change ART regimens during the pregnancy or breast-feeding period. After that period they can transition to new regimens as applicable.

Implementation of the 4th edition of the National Guidelines for Antiretroviral Therapy will entail an increase in storage and dispensing of ARVs as ART services continue to be decentralized to PHC level. Standardisation of dispensing practices at the different service points allows predictable consumption and demand which leads to an uninterrupted ARV supply. This will also allow monitoring of critical adherence-related indicators such as on-time pill pick up of ARVs.

The following standard practices are recommended for dispensing of ARVs:

Routine ARV refills
Unless there are special circumstances, health care workers involved in dispensing of should dispense no more than 3 months' supply of ARVs to stable patients. This is in order to reduce wastages due to expiry and rupture as well as disruptions in the supply chain. Special circumstances may include patients who will be at sea or abroad for more than three months.

In transit patients
All in transit patients that visit ART sites should be supplied with ARVs ideally for no more than two months at the sites they are visiting.

A patient who is planning to be in-transit at another facility for more than two months should obtain a transfer out letter at the original facility and get officially transferred in at the new facility. This recommendation applies to seasonal workers who stay in an area for several months every year e.g. during the harvesting or planting season.

Dispensing of extra ARV pills
It has been noted that when patients are given too many extra tablets, they are prone to being dumped, which also complicates monitoring of adherence by pill count. It is therefore recommended that patients be given extra ARV pills for only 2 extra days.

Other recommendations

- Pill counts should be done routinely for all patients and the number of remaining pills should be entered in the appropriate data capturing tool and health passport.
- Left over medicines should be discarded if they are soiled, broken or expired; this should also be recorded in the data capturing tool

PART 1: ANTIRETROVIRAL THERAPY FOR ADULTS

1.1 Assessment of HIV-positive adults

A patient/client who receives a positive HIV test result, wherever and whenever the test is done, shall be enrolled in HIV care and assessed for the need to begin antiretroviral therapy (ART). In the public sector, HIV-positive individuals should be referred to the nearest ART clinics (or, in cases of pregnancy, to the nearest antenatal clinic (ANC) providing ARTas 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, appropriate baseline laboratory tests and a review of social eligibility criteria (see also section 1.4). At this first visit, clinic staff will register all patients,at the clinic, assign a unique number, and open a patient care booklet. Patients eligible for ART will be identified and prepared for ART initiation.

Those not yet eligible will be given follow-up visits to ensure timely re-assessment for eligibility and to provide ongoing counseling and isoniazid preventive therapy if applicable. Data for all patients will be entered into the Electronic Patient Monitoring System (ePMS), an information system used for pateint enrolled in HIV care 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 ART according to these guidelines, preferably by a trained HIV clinician. For more detailed guidelines for management of HIV-positive adolescents, refer to Paediatric section (Part 3).

1.2 When to start antiretroviral therapy in adults

HIV-positive adults eligible to initiate ART are listed in Table 1.1 below.

Table 1.1. Adult PLHIV eligible to initiate ART

Target Population	Recommendation
WHO Clinical stage 1 or 2	Initiate ART if CD4 ≤500 cells/mm^3
WHO Clinical stage 3 or 4	Initiate ART in all individuals regardless of CD4 cellcount
Active TB Disease	
Pregnant and breastfeeding women	Initiate ART in all individuals regardless of CD4 cell count or WHO Clinical Stage.
Hepatitis B virus Co-infection	
HIV-serodiscordant couples	Provide ART to all HIV-positive individuals in a sero discordant sexual partnership[1]regardless of CD4 cell count or WHO Clinical Stage (to reduce the risk of HIV transmission to the negative partner).
HIV-positive concordant couples currently intending to conceive a child	Provide ART to both partners irrespective of CD4 cell count or WHO clinical stage

NB. Some patients who initiate ART with CD4 counts >350 cells/mm^{3}may not feel ill and hence may not fully understand the consequences of non-adherence. Adherence counselling must address this.

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 ensuring that eligible patients/clients are initiated on antiretroviral therapy in a timely manner. 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 threshold, are also offered ART.

1.3 Adherence

1.3.1 Importance of adherence

ARV medication adherence is absolutely vital for the success of ART. Very high levels of adherence, taking at least 95% of prescribed doses, are required to achieve sustained suppression of HIV replication over time. Adherence is promoted by proper ongoing support and counseling. Adherence is also promoted by prescribing simplified, well-tolerated regimens involving as few pills as possible, administered no more than two times per day.

Remembering to take medication correctly every day is the goal of ART therapy however patients may forget occasionally. They need to be be counseled in advance about what to do should this happen, as part of their pre-initiation counseling. The advice should be as follows:

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, after taking 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 8AM/8PM schedule.

1.3.2 Methods to achieve readiness to start ART and maintain adherence

With the exception of PMTCT and PEP, ART should not be started at the first clinic visit. Before people start ART, it is important to have detailed discussions with them about their willingness and readiness to initiate ART, the ARV regimen, dosage and scheduling, the likely benefits and possible adverse effects and the required follow-up and monitoring visits. For children with HIV, this conversation should directly involve the carer and include discussion about disclosing their HIV status. Initiation of ART should always consider nutritional status, any comorbidities and potentially interacting medications for possible contraindications or dose adjustment.

[1]*Serodiscordant couples are couples in which one partner is living with HIV and the other is HIV-negative. A couple refers to two people in an ongoing sexual relationship; each of these is referred to as a partner in the relationship. How individuals define their relationships varies considerably according to cultural and social context.*

The choice to accept or decline ART ultimately lies with the individual person or his or her caretaker, and if they choose to defer initiation, ART can be offered again at subsequent visits. If there are mental health, substance use or other problems that are major barriers to adherence, appropriate support should provided, and readiness to initiate ART should be reassessed at regular intervals. A wide range of patient information materials as well as community and peer support can help the person's readiness and decision to start therapy. People starting treatment and carers should understand that the first ART regimen offers the best opportunity for effective viral suppression and immune recovery, and that successful .ART requires them to take the medications exactly as prescribed. They should be advised that many adverse effects are temporary or may be treated, or that substitutions can often be made for problematic ARV drugs. People receiving ART and carers should also be asked regularly about any other medications they take, including herbal remedies and nutritional supplements.

People receiving ART should understand that while the ARV medicinesreduce the risk of HIV transmission, they cannot be relied upon to prevent other people from acquiring infection. They should be given advice on safer sex (including condom use) and avoidance of other high-risk activities, such as sharing of injecting equipment, to prevent transmitting HIV to other people. In order to achieve maximum readiness for ART, 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. 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 ART is an essential part of any successful therapy programme. Patients should receive care at the ART clinic nearest their home, but should not be denied care or medication refills if they are away from home and need to attend another clinic.

Figure 1.1 Methods to achieve readiness to start ART and maintain adherence

Patient-related:

- Two visits at least 1-2 weeks apart, to ensure readiness before 1st ART prescription (readiness check list); this is not be applicable to PMTCT and PEP.
- Where possible recruit a family member, a friend, peer orcommunity membersfor treatment support.
- 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: plan for any trips away from homeand ensure you carry enough medication with you and carry your health passport. Obtain refills if necessary.

Provider-related:

- Educate patient regarding goals of therapy, proper dosing, medication interactions, food effects and side-effects.
- Educate patients about the importance of laboratory monitoring and the meaning of their test results.
- Assess adherence potential before ART. Monitor at each visit.
- Look out for active drug/alcohol use and untreated mental illnesses because they are associated with poor adherence.
- Anticipate and 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 minimiseadverse medicine interactions and reactions.
- Simplify regimen as much as possible regarding: dose frequency, pill burden, pill storage, and food requirements.
- Inform patient of potentialside-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 (PLHIV) and community representatives on importance of adherence.
- Develop systems to improve referral linkages and interactions between health facilities and community-based organizations

1.3.3 Re-starting ART in patients Lost and Lost to Follow up.

Interruption of ART may result in viral load rebound and clinical progression of HIV. Any patient who interrupts treatment for 30 consecutive days is defined as “lost” .Any patient who interrupts treatment for 90 consecutive days is defined as “lost to follow up”. He/she should be interviewed to uncover and understand the reasons behind the treatment interruption and a to determine if the interruption was intentional or unintentional. Each case of lost or lost to follow up, once returning to care, should be carefully evaluated by an ART team before discontinuing treatment. If the patient still desires to be treated with ARThe/she must be counselled again regarding the importance of adherence. Efforts should be made to correct the circumstances leading to the lapse in treatment.

For those patients who intentionally interrupted treatment, a trial period of usually three months may be scheduled during which time the patient must be closely monitored and demonstrate adherence to a regimen of daily cotrimoxazole prophylaxis and multivitamins with regular monthly visits for medication refills and further adherence counselling. If at the end of this time, the health care team is convinced that the patient will be able to adhere to ART, 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 considered. As with patients who are initiating ART for the first time, patients reinitiating ART after loss to follow up should have their viral load checked after a 6 month interval.

Patients who return after being lost to follow-up and who are clinicallyunwellshould be assessed andmanaged for any co-infections.

Facilities should print out on a weekly basis a list of patients who missed their appointments and contact the individuals. Health facilities should collaborate with Community organisations operating in their catchment areas to facilitate tracing of lost and lost to follow-up patients.

1.4 Social Considerations for starting ART in Namibia

In addition to clinical and immunologic criteria, the Ministry of Health and Social Services has established social considerations. Meeting social eligibility is necessary but should not be an obstacle for accessing ART. The intention of these considerations is to maximise adherence and reduce the risk of failure of ART and the development of resistance. Social considerations should not be used to deny a person treatment.

The social considerationsthat support better adherence to treatment include the following:

- Having a fixed address
- 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.
- Being committed to:
    - Lifelong treatment with ART.
    - Strict adherence to treatment.
    - Practicing safer sex.
    - Allowing home visits if indicated.

1.4.1 Treatment supporters

A treatment supporter is someone at home, in the community, or at the workplace, who can accompany the patient to visits and assist with daily adherence to ART. The MoHSS advises 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 identify a treatment supporter 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

1.5 Antiretroviral medications

There are currently six classes of antiretroviral agents*:

- **Nucleoside/or Nucleotide 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).
- **Non-Nucleoside Reverse 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), etravirine (ETV), rilpivirine (RPV) and delavirdine (DLV).
- **Protease inhibitors (PIs)**: These medications 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).
- **Integrase strand transfer inhibitors (ISTIs):** These medications prevent the newly synthesized viral DNA from bcleing integrated into the host cell DNA. This class includes two medicines: raltegravir (RAL) and dolutegravir (DTG).
- **Entry inhibitors**: This class consists of one CCR5 co-receptor antagonist which prevents the virus from attaching to the host cell CD4 co-receptor CCR5. This class includes maraviroc (MVR).
- **Fusion inhibitors:** These medications 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).

**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 ART regimens

Recommended ART regimens consist of a combination of 2-3 NRTIs plus an NNRTI or PI. For individuals who cannot tolerate the recommended regimens or who experience failure on the second line regimens, an HIV specialist should be consulted.

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 ART regimens in Namibia

The first line and second line ART regimens for Adults, Adolescents ≥ 10 years who weigh at least 35 kg, and Pregnant and Breastfeeding women are listed in Tables 1.2 and 1.4 below respectively.

Table 1.2. Recommended First Line ART regimens in Namibia

1st line ART	Preferred 1st line Regimens	Alternative 1st line Regimens[2]
Adults (including adolescents ≥ 10 years old and weigh at least 35 kg), pregnant and breastfeeding women, adults with TB disease and adults with HBV coinfection	TDF + FTC (or 3TC[1]) + EFV (once daily FDC)	AZT + 3TC + EFV AZT + 3TC + NVP[3] TDF + FTC (or 3TC) + NVP ABC + 3TC + EFV (or NVP[2])

[1]it is anticipated that the current stock of TDF/3TC/EFV will be replaced with TDF/FTC/EFV
[2]Alternative regimens should only be used if the preferred first line regimen is not an option.
[3]NVP should not be initiated in women with a CD4 count of >250 or men with a CD4 count of >400. Due to metabolism issues, nevirapine treatment is always initiated as once daily therapy for the first 14 days, and then it is increased to twice daily.

TDF is included in the preferred first line regimen. The most important side effect of TDF is nephrotoxicity and declining renal function, although the incidence of these complications is relatively rare.TDF nephrotoxicity is characterized by proximal tubular cell dysfunction (indicated by proteinuria or glycosuria) that may be associated with acute kidney injury or chronic kidney disease. **Creatinine clearance must be calculated for each patient before starting TDF and regularly during therapy.** The formula for this calculation is given in Figure 1.2 below. It is considered safe to use TDF in a patient with a creatinine clearance ≥60 ml/minute. If the creatinine clearance at baseline is <60ml/minute an alternative to TDF should be included in the ART regimen unless the patient is co-infected with HBV.

Figure 1.2 Formula for the calculation of creatinine clearance in adults and adolescents ≥18 years old

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

Pregnant women require immediate initiation of ART in order to provide optimal HIV prevention for their infants. For this reason, a decision to initiate TDF should be based on anormal result of a urine dipstick while waiting for the creatinine clearance result. In case proteinuria and or glycosuria are detected, an alternative to TDF should be initiated while awaiting the creatinine clearance.

TDF can still be used in specific patients with renal insuffiency when its use is unavoidable (e.g. hepatitis B co-infection) but should be carefully monitored and the dosage should be adjusted according to the recommendations concerning use of TDF in renal failure in Table 1.3 below.

Table 1.3 Recommendations for Tenofovir Dose Adjustment in Patients with Altered Creatinine Clearance[1].

Creatinine Clearance (ml/min)	Recommended Dosing of TDF 300 mg
≥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)

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

Table 1.4 Recommended second line ART regimens in Namibia

Preferred Second-Line ART Regimens		
Target population	**Regimen**	**Remarks**
HIV+ adults	AZT[1]/TDF/3TC/LPV/r	Where standard first line regimens were used
HIV+pregnant and breastfeeding women		
HIV/HBV co-infection		
HIV/TB co-infection	AZT[1]/TDF/3TC/LPV/RTV	Increase dose of RTV: i.e., LPV/r 400mg/400mg[2]

[1]Patients who were anaemic at start of ART may have initiated treatment with d4T, however these patients do not have "AZT-induced anaemia" and it is safe to use AZT unless the current Hb<7.5. **For patients with true previous AZT toxicity, consult HIV specialist.**

[2]This regimen is poorly tolerated in some patients due to gastro-intestinal tract (GIT) side effects. Discuss management options with an HIV specialist.

Third Line Regimen
Consult HIV specialist

Third line regimens are complicated, very costly and should only be implemented following the recommendation and close supervision of an HIV specialist. All patients failing second line regimens should undergo HIV resistance testing following consultation with an HIV specialist in order to select the most effective regimen.

1.8 Sexual and Reproductive Health considerations

1.8.1 Contraception

The use of barrier contraception methods is recommended for all male and female patients receiving ART 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 methodis recommended for all women of childbearing age.Reversible contraceptive methods include an intrauterine contraceptive device (IUCD), injectable progesterone-based contraceptives (depo-medroxyprogesterone acetate, DMPA). **Permanent contraceptive methods include bilateral tubal ligation for women and vasectomy for male partners – client education must be provided and written informed consent must be obtained from clients prior to undergoing these procedures.**

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. It is recommended that if both partners are HIV-positive, and wishing to have a child, ART should be initiated prior to conception.

Refer to the PMTCT section for more detailed guidance regarding reproductive considerations for HIV-positive individuals who intend to have children (See Part 2).

1.8.2 Cervical Cancer and HIV

Globally and in Namibia, cervical cancer is the second most common cancer (after breast cancer) among women. HIV-positivewomen 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
- 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 recommended for all women with HIV infection. All women with abnormal PAP smear results should be referred for further evaluation and treatment as appropriate.

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. ART may need to be changed due to therapy failure or medication toxicity, but there must be a very strong clinical justification for doing so.

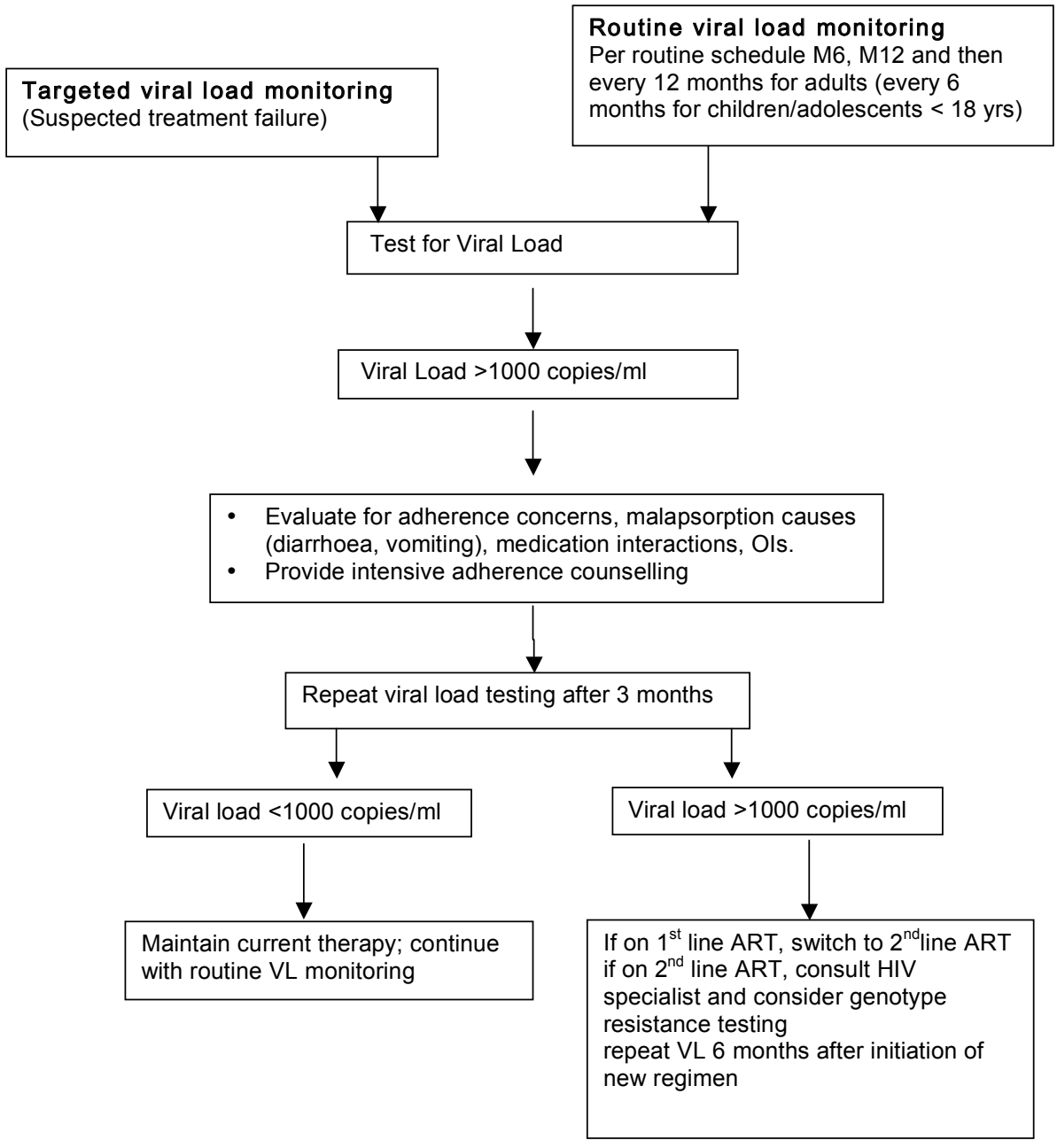
1.9.1 Changing due to toxicity

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. This is further discussed in Section 1.13. When it is not possible to identify the offending medication, discussion with an HIV specialist is recommended. In some cases, it may be possible to re-introduce medications after short intervals.

1.9.2 Changing due to treatment failure

Treatment failure can be suspected 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. Virological failure is defined as a viral load >1,000 copies/ml 6 months after starting ART or viral rebound to >1,000 copies/ml on two consecutive measurements after a period of viral suppression. Routine viral load testing as described in Table 1.6, Section 1.12 is recommended for treatment monitoring in order to facilitate earlier detection of virological failure. An algorithm for evaluating suspected treatment failure is shown in Figure 1.3 below.

Figure 1.3 Algorithm for evaluating suspected treatment failure



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 and/or an HIV specialist.

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 ART regimen should include at least two new ARVs, with at least one from a new class of antiretrovirals.

After a switch from first line to second line or from second line to third line, a VL should be done after 6 months to assess response to treatment, followed by routine yearly VLs.

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 is essential for patients who have 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 the test may only provide information about resistance to the current regimen the patient is on.

1.9.3 Elimination of use of D4T based regimens

D4T is no longer a preferred ARV due to its well-documented long term intolerable side effects. **No new patients should be started on D4T and all patients currently on D4T MUST be assessed for transition to another NRTI as per guidance below.**

1.9.4 Transitioning adults to the new first line Fixed-dose Combination formulation

In order to take advantage of the new and now preferable daily dose Fixed Dose Combination (FDC) formulation preferred first line regimen it is important to consider whether the patient has virologic suppression on the current regimen before making a change. It is recommended that HCWs identify adults currently on AZT- and d4T -based first line regimens, and those on NVP as first line. HCWs should then carefully assess whether or not the patient is eligible for a direct substitution or if a regimen switch is required.

Thymidine analogues (e.g. d4T and AZT) can be considered interchangeable because their mutation patterns are similar. Non-thymidine analogues (e.g.ABC and TDF) are also interchangeable for the same reason. However changing from a thymidine analogue to a non-thymidine analoque or *vice versa* in the presence of virologic failure could compromise future 2nd line options – it would be essentially introducing one new ARV into a failing regimen. For this reason, results of the most recent viral load should be reviewed to inform the appropriate regimen change. If the most recent VL is more than 6 months previously, it should be repeated.

If a patient's VL is <20 copies/ml and in the absence of specific toxicities experienced by the patient, the following regimen changes are appropriate:

From (d4T or AZT) + 3TC + (NVP or EFV) ***to*** TDF + FTC(or 3TC) + EFV
If the patient's VL is >20copies/ml and in the absence of specific toxicities experienced by the patient, ARV regimens should be as follows:

From d4T/3TC/NVP ***to*** AZT/3TC/NVP (this is a fixed dose combination given bd – do not change the NNRTI to EFV)

If on AZT/3TC/NVP do not change the regimen.

Table 1.5 provides further details on the management of patients whose VL is >20 copies/ml.

Table 1.5 Transitioning safely to the new preferred first line regimen

Current ARVs	VL within last 6 months	
	VL<20	VL≥20
D4T/3TC/NVP	Change to TDF/ FTC/EFV	Change to AZT/3TC/NVP FDC while intensifying adherence counseling and follow-up, and evaluating for treatment failure and possible 2nd line if VL remains>1000 copies/ml
D4T/3TC/NVP but previous AZT toxicity[1]	Change to TDF/ FTC/EFV	Confirm if truly previous AZT toxicity[1]. If yes, keep on d4T/3TC/ NVP while intensifying adherence counseling and follow-up, and evaluating for treatment failure and possible 2nd line if VL remains>1000 copies/ml. If not true AZT toxicity, manage as above
AZT/3TC/NVP	Change to TDF/ FTC/EFV	Continue AZT/3TC/NVP FDC while intensifying adherence counseling and follow-up, and evaluating for treatment failure and possible 2nd line if VL remains >1000 copies/ml
TDF/3TC + NVP	Change to TDF/ FTC (or 3TC)/EFV	Change to TDF/FTC(or 3TC)/EFV

[1]patients who were anaemic at start of ART may have initiated treatment with d4T, however these patients do not have "AZT-induced anaemia" and it is safe to use AZT unless the current Hb<7.5. For patient with true previous AZT toxicity, and who have significant side effects caused by d4T, consult HIV specialist.

1.11 Clinical monitoring of PLHIV

1.11.1 Baseline clinical assessment

The baseline medical history should be recorded in the standardised patient care booklet 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, date of last menstrual period, 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.

1.11.2 Clinical monitoring during follow-up visits

Prior to initiation of ART, patients should be seen every 3-6 months for clinical evaluation with WHO clinical staging and for CD4 counts as applicable. As the patient's CD4 count gets closer to 500 cells/mm^3, the frequency of visits should increase.

Once ART 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). Regularvisits 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 ART:

1. **Is ART adherence ≥95%? If not, find out why not and discuss 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 ART may indicate clinical failure, but early in treatment may also be attributable to Immune Reconstitution Inflammatory Syndrome (IRIS) (see section 1.19.1)**

Patients should be informed about the symptoms of ARV toxicities and when to seek care. Clinical evaluation of the effectiveness of ART is important, and patients should have relevant physical examinations. 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 (fevers, diarrhoea).
- Physical findings, such as signs of Immune Reconstitution Inflammatory Syndrome (e.g., lymph node swelling), signs of immune improvement (e.g., regression of Kaposi's sarcoma lesions or molluscum contagiosum), signs of HIV-related disease progression (e.g., oropharyngeal and/or vulvovaginal candidiasis, etc.), or signs of medication toxicities (rash, lipodystrophy).

1.12 Laboratory Monitoring of PLHIV

1.12.1 Routine laboratory monitoring

Specific laboratory investigations are recommended as the basic level of care that is necessary to safely start ART. Laboratory tests are also 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 in Table 1.6 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 taking appropriate management decisions for the patient. Sites should therefore implement Point of Care testing where feasible and/or schedule patient visits in a way that allows for the patient to receive results in a timely fashion. Efforts should continue to improve laboratory specimen handling as well as access to results and improved turn-around time (TAT) by increasing access to testing and availability of terminals or SMS printers at health facilities.

Table 1.6 Laboratory assessment for adults for ART initiation and monitoring

Phase of HIV management	Tests	Frequency
At HIV diagnosis	CD4	Once
	HBsAg	Once; if positive, repeat after 6 months
	CrAg[1]	Once if CD4<100
Pre ART	CD4	Every 3 to 6 months
ART initiation	Hb	Once
	Cr Cl	Once
	Urine dipstick[2]	Once
Treatment monitoring	VL	M6,12 (then every 12 months)
	CrCl[3]	M1,3,6,12 (then every 12 months) if on TDF
	Urine dipstick[3]	M1,3 (then every 3 months) if on TDF
	Hb	2w, 6w, M3 **if on AZT**
HBsAg positive	ALT	2w, 6w, M3 (then every 6 months)
Suspected treatment failure	VL	Anytime after the first 6 months of ART provided non-adherence and OIs excluded
Virological failure	1) CD4[4]	1)Every episode of virologic failure
	2) HIV Drug Resistance	2) Before Switching to a 3rd line regimen all ages
Secondary fluconazole prophylaxis following cryptococcal meningitis	CD4[5]	6-monthly while on fluconazole prophylaxis until 2 consecutive values >200 cells/mm^3

Notes:

[1]CrAg: plasma Cryptococcal Antigen: lab will do this automatically for patients with CD4<100

[2]note particularly urine protein and glucose

[3]CrCl and Urine dipstick for patients on TDF containing regimens ONLY. Even if the laboratory gives a CrCl result on the laboratory slip, clinicians should calculate using the patient's parameters (see Figure 1.2 for the CrCl calculation formula)

[4]Check CD4 count to assess immunological status and inform clinical management (eg. assess for possible OIs)

[5]Check CD4 count to determine when fluconazoleprophylaxis can safely be stopped

Other laboratory tests may be indicated based on the suspicion of a medication toxicity (such as signs of liver toxicity or rash with NVP, signs of glucose intolerance if on PIs, etc) or clinical disease progression.

Additional baseline and routine laboratory monitoring may be needed if the patient has existing co-morbidities such as diabetes.

Appendix 3 provides a summary of the routine monitoring laboratory tests to be done based on the ARV regimens used.

1.12.2 CD4 Lymphocyte counts

CD4 levels are important markers of immune function. CD4 testing is recommended at baseline to determine eligibility for ART.

Because viral load is a more sensitive and an earlier indicator of treatment failure, Namibia is transitioning to routine viral load monitoring rather than CD4 count for treatment monitoring. However if a patient has virologic failure or shows signs of clinical deterioration, a CD4 count should be done.

1.12.3 Plasma HIV-RNA levels (viral load)

Routine viral load (VL) monitoring is recommended to facilitate earlier detection of treatment failure. VL levels should reach undetectable levels by 6 months of therapy in fully adherent patients. All patients initiating therapy will routinely have a viral load assay done at 6 and 12 months after beginning therapy and every 12 months thereafter (every 6 months for children/adolescents <18 years).

The aim is to earlier identify patients who are having suboptimal responses to ARV therapy and whose immunologic and clinical responses may not have deteriorated at this stage. These patients have VLs > 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. In addition routine viral load measurements will allow analysis of the ART program at the population level. VL assays are also recommended for patients already on treatment who are showing evidence of immunologic and or clinical failure. The test should be repeated in this category of patients 6 month safter changing therapy, to evaluate response to the new regimen and to evaluate the level of adherence in this group of patients.

Regions and districts must be made aware that to ensure validity of VL results, blood specimens must reach NIP laboratories **within 6 hours**. Due to reduced validity of results from old specimens, specimens reaching the laboratory for processing after 6 hours will be rejected. At a minimum, samples need to be spun down and separated within that critical period. For districts and facilities which do not have easy access to an NIP lab, alternative arrangements should be made with an NIP lab or NIP visiting sites on specified days. HCWs should use the 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.

1.13 Adverse Reactions Associated with Antiretroviral Medicines

No medicine is 100% safe. Antiretrovirals, like other medicines, may cause adverse reactions (AR). This section provides information on the ARs associated with ARV medicines, and the recommended clinical response. Like all medication toxicities, antiretroviral toxicities are categorized according to severity. The categories are: mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) and death related to the adverse reaction (grade 5).

Some toxicities are class-related; others are related to one particular ARV. The frequency and severity of class-related toxicities also vary among medicines within the same class. **Clinicians working with patients on ART should be aware of the common and serious adverse reactions associated with these medications and to immediately report any medicine adverse reactions to the Therapeutics Information and Pharmacovigilance Center (TIPC) using the appropriate form**. See Appendix 9 for the Adverse Medicine Reaction Reporting Form. Some serious ART-related toxicity are summarised in Table 1.7 below along with ART management recommendations. Management of specific toxicities is in the following section.

1.14 Management of toxicities associated with ART

1.14.1 Rash

Rash is a common reaction following initiation of ART. The frequency of rash is estimated at 20% in patients starting NVP-based ART, and 4.6% in those starting EFV-based ART. EFV-induced rashes are generally mild to moderate. Like NVP, however, EFV may also provoke severe and life-threatening rashes such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme major, but the frequency of the later is lower than that observed for NVP.

Abacavir (ABC) also causes hypersensitivity reactions. Any rash in a patient on 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. Symptoms become worse with continued use and include fever, skin rash, malaise, nausea, vomiting, diarrhea, abdominal pain, dyspnea, arthralgia, headache, myalgia, chills and respiratory symptoms. The average onset of reaction is within 9 days of initiation and within hours after rechallenge.

Rash is also commonly seen in patients taking cotrimoxazole and other non-ARV medicines used in conditions related to HIV disease.

Rashes should be categorized according to the criteria in section 1.13 above, because the management of the rash depends on its severity. Figure 1.4 below summarises recommendations for the management of rash due to specific ARVs.

Figure 1.4 Recommendations for themanagement of ARV-induced rash

For patients initiated on EFV-based ART

- **When a mild or moderate rash associated with EFV occurs and it does not resolve on observation or following antihistamine therapy, replace EFV with LP/r**.
- **When a severe or life-threatening rash associated with EFV occurs, stop all treatment at the same time. After resolution of the rash, replace EFV with LPV/r or another PI. Do not replace with NVP.**

For patients initiated on NVP-based ART

- **When a mild or moderate rash associated with NVP**
  - Measure ALT and check for signs of hepatitis
  - **Do not escalate dose of NVP,** continue "lead-in" dose once daily for a further week.
  - Provide supportive treatment (antihistamine) and advise patient to return before one week if rash worsens.
- When rash has resolved after 1-2 weeks, there is no sign of hepatitis and ALT<5xULN
  - Escalate dose to 200mg bd (or appropriate paediatric dose)
- **When rash does not resolve on observation for 2 weeks or does not respond to antihistamine therapy, replace NVP with EFV. The replacement may be immediate.**
- **When a severe or life-threatening rash associated with NVP occurs, stop all treatment. After resolution of the rash, replace NVP with LPV/r or another PI. Do not replace with EFV**

For patients on ABC

- **Any rash in a patient on abacavir requires immediate clinical evaluation.**
- **If rash is suspected to be due to ABC, replace ABC with another NRTI**
- **Patients should not be rechallenged with ABC if there is suspicion of hypersensitivity reaction.**

1.14.2 Hepatotoxicity

Both EFV and NVP may cause severe or life-threatening hepatotoxicity, although hepatotoxicity occurs at a higher frequency with NVP than with EFV, and with an earlier onset, usually within 2 weeks of starting treatment. PIs can also cause hepatotoxicity. Some PIs (e.g. atazanavir/ritonavir and indinavir/ritonavir) may result in the development of unconjugated hyperbilirubinaemia with normal ALT levels. This generally does not require treatment.

The risk of developing hepatotoxicity is higher when NVP-based ART is initiated in an ART naïve patient with a high baseline CD4 count: ≥250 and ≥400 cells/mm^3 in females and males, respectively. Other risk factors include pre-existing liver dysfunction, hepatitis-B or C co-infection, and concomitant administration of ARVs with other potentially hepatotoxic medicines e.g. antituberculosis medicines.

Figure 1.5 Recommendations for the management of ARV-induced hepatotoxicity

For patients on any ARVs causing hepatotoxicity
• Stop or substitute relevant hepatotoxic medications in symptomatic patients if ALT is more than 5 times the upper limit of normal, and consult a specialist physician for further management. • If the ALT is more than 10 times the upper limit of normal in asymptomatic patients, stop all medications immediately.

1.14.3 Haematologic toxicity

Anaemia, leucopaenia, lymphopaenia and thrombocytopaenia are found in 30% to 40% of patients with HIV. As the most common condition is anaemia, all patients have Hb done before intitating ART. Zidovudine (AZT) can be bone marrow toxic, resulting in anaemia, neutropaenia, or both. The use of AZT as an alternative first-line treatment should be avoided in patients with baseline Hb < 7.5gm/dl. Patients initiating AZT require Hb monitored regularly for the first 3 months, the time when AZT-induced anaemia is most likely to occur. (See table 1.6). If Hb drops at all, refer to doctor for evaluation. Doctors should investigate for any other causes of anaemia. If the drop is >10% but <25%, repeat Hb in one week. If the drop is ≥25%, substitute with another NRTI.

Patients on AZT:
AZT should be substituted immediately if Hb falls below 7.5 gm/dl or drops by more than 25%.

1.14.4 Lactic acidosis

This life-threatening complication of ART (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 recognize 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 and ddI use; although it has been reported with most NRTIs (abacavir and tenofovir are exceptions). Co-administration of TDF with some non-ARVs such as tetracycline (antibiotic) and metformin (anti-diabetic) is a risk factor. Additional risk factors include female gender and obesity, chronic HCV, CD4 count <350 cells/mm^3, and nutritional factors such as riboflavin or thiamine deficiencies (HSS Panel 2012a). Patients with lactic acidosis often have had excellent virological and immunological response to their ARVs. The clinical symptoms of lactic acidosis are summarized in Figure 1.6 below.

Figure 1.6: Clinical symptoms of lactic acidosis

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

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 among patients on ART and requires no treatment. Early intervention can lead to resolution of lactic acidosis. Treatment must include immediate discontinuation of ART.

Patients with lactic acidosis may present with acute multi-organ failure, such as fulminant hepatic, pancreatic, and respiratory failure. 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).

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 ART following lactic acidosis can only occur after complete resolution and recovery from the acidosis. Modified ART regimens will be required hence consultation with a specialist is essential. See section 1.15 for further details on changing or stopping regimens. Monitor patients monthly for at least 3 months.

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). Patients experiencing abdominal or epigastric pain should be informed to report these side effects to the HCWs. 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 section 1.15 for further details on changing or stopping regimens. High amylase is common in asymptomatic HIV patients and is usually not due to pancreatitis but to sialoadenitis (inflammation of the salivary glands).

1.14.6 Lipodystrophy and lipid abnormalities

Antiretroviral medicines are known to cause fat- related ARs. The NRTIs are associated with lipoatrophy and fat accumulation in the abdomen and back, while the PIs and NNRTIs (EFV) are associated with abnormalities of lipid levels in plasma. This section provides recommendations on how these ARs are managed. Some patients receiving ART 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 ART regimens with major effect seen in LPV/r combination. However, it has also 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., stop 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 ART is discontinued or delayed.

EFV, too, has been associated with elevation in plasma cholesterol (both total cholesterol and high density lipoprotein cholesterol) and triglycerides. The use of statins is recommended by WHO for individuals with 10 years or more cardiovascular risk exceeding 30% or people with history of cardiovascular disease. (Refer to the Appendix 10 for information on interactions between statins and ARVs).

1.15 Considerations when changing or stopping ART

Substitution of ARVs should not be delayed in cases ofsevere adverse drug effects in order to avoid harm and poor adherence to treatment which will ultimately lead to drug resistance and poor treatment outcome. 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 often be done without stopping treatment. For example, a patient taking a TDF-containing regimen who develops renal insufficiency can have the TDF replaced by ABC.

In situations where the adverse reaction is mild or moderate (grade 1 or 2), but the substituting medicine can cause similar reactions, it is advisable to withdraw the causative agent and allow the adverse reaction to resolve before substituting. If immediate substitution is done the reaction may worsen and both medicines will be lost from the regimen, hence narrowing future treatment options for the patient.

When NNRTIs (NVP or EFV) must be stopped, and the patient is on either AZT or d4T, patients should discontinue the NNRTI first and continue with the NRTIs at their usual dosage for 14 days. This will decrease the risk of developing NNRTI (cross-) resistance. If the patient is taking either TDF or ABC with an NNRTI, the whole regimen can be stopped at the same time.

If cross-reaction is not expected, then immediate substitution may be made following grade 1 and 2, and higher grade reactions. For example when a patient develops serious CNS symptoms associated with EFV, an immediate replacement with NVP can be made.

Patients with life-threatening toxicity on EFV (or NVP), 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, ART can be restarted without using an NNRTI, to avoid recurrence of the toxic event.

A regimen that combines 2 NRTIs with a PI can safely be stopped at once.

Table 1.7 summarises ARV-associated and the substitutions that are required.

Table 1.7: ARV-Associated Toxicities and ARV Substitution

Adverse Reaction	Associated agent(s)	Common signs	Clinical response /ARV Substitution
Potentially fatal adverse effects			
Acute pancreatitis	d4T ddI	Upper abdominal pain which radiates to the back and is exacerbated by the ingestion of food. Abdominal swelling & tenderness, indigestion, steatorrhea, nausea, vomiting & pyrexia	Stop immediately After resolution, check latest VL; if done < 6 mo *prior to* the adverse event and VL was <20copies/ml, resume ART with TDF; if VL was not suppressed, use AZT and work on adherence.
Skin rash with or without hypersensitivity reaction	ABC	Pyrexia and rash, malaise, nausea, headache,myalgia,arthralgia, diarhea,shortness of breath , systemic anaphylaxis, arthralgia, ,	Stop Immediately. Never re-challenge. After resolution, resume ART with TDF. If cannot use TDF, and if <3 months since start of ART, use AZT or consult an HIV specialist
	NVP EFV-less commonly		For mild to moderate rash, substitute NVP with EFV
Toxic epidermal necrolysis (TEN) or Steven's Johnsons Syndrome	NVP EFV-less commonly	Diffuse, moist desquamation, maculopapular rash involving mucous membranes. Skin peeling leading to formation of painful sores, flu-like symptoms	Stop immediately. Never re-challenge. After resolution, resume ART with a boosted PI instead of an NNRTI
Lactic acidosis	All NRTIs (particularly d4T, ddI and AZT)	Gradual onset of nausea/emesis, unexplained weight loss, fatigue, dyspnoea (late) motor weakness, and may include mental status changes and organ failure.	Stop immediately After resolution, check latest VL; if done < 6 mo *prior to* the adverse event and if VL was <20copies/ml, resume ART with TDF; if cannot use TDF, give ABC. If VL was not suppressed, discuss with an HIV specialist
Hepatitis	All ARVs (particularly NVP)	Jaundice , hepatomegaly, elevation of liver enzymes, darkened urine and stool, abdominal pain, diarrhoea, nausea, vomiting & pyrexia	If ALT is >5 times the upper limit of normal,discontinue ART and monitor. After resolution, restart ART, replacing the causative drug.
Haematological toxicity (bone marrow suppression: macrocytic anaemia or neutropaenia)	AZT	Dizziness, syncope, palpitations, chest pain, shortness of breath, pale skin, menorrhagia in females, inability to concentrate, cold hands and feet ,	Substitute AZT with TDF if a) within the first 3 months of treatment or b) more than 3 months after start of treatment if recent VL in last 6 months is <20 copies/ml Substitute AZT with d4T if VL unknown or >20 copies/ml, until VL is suppressed

Adverse Reaction	Associated agent(s)	Common signs	Clinical response /ARV Substitution
Renal toxicity (renal tubular dysfunction)	TDF	Often asymptomatic , occasionally decreased urine outputFluid retention, causing swelling in your legs, ankles or feet	If HBV-coinfected, decrease dose of TDF according to the dose adjustment table for renal insufficiency (Appendix 5). If not HBV coinfected, change TDF to ABC
Disabling adverse effects			
Peripheral neuropathy	All NRTIs worse w/ d4T ddI	Distal extremity painful dysesthesias, allodynia, severe burning pain, pins and needles sensations,	Replacement of d4T with AZT or, if VL<20 in the last 6 months then with TDF Symptomatic treatment
Osteonecrosis/ osteoporosis	Origin uncertain (TDF, PIs?)	Bone pain or tenderness, limited range of motion, joint stiffness, or limping, muscle spasms, progressive bone damage leading to bone collapse, neck or low back pain, loss of height , stooped posture	Manage osteoporosis
Male gynaecomastia	EFV, PIs	Significant enlargement of breasts; painful breast tissue	Substitute EFV with NVP
Neuropsychiatric changes	EFV	Abnormal dreams, Depression, suicidal ideation, or mentalconfusion	Dreams are usually self-limited, without the need to discontinue ART. New onset depression, psychiatric illness or suicidal ideation replace EFV with NVP
Long-term adverse effects			
Lipoatrophy and lipodystrophy	NRTIs d4T> AZT All PIs and EFV	Significant loss of subcutaneous fat; abnormal fat distribution	Replace suspected ARV with less toxic agent
Dyslipidaemia	All NRTIs, (d4T worst NRTI) All PIs and EFV	Asymptomatic	Consider replacing the suspected ARV. *NB: currently lipids and cholesterol not monitored routinely in the state sector*
Insulin resistance	All PIs d4T, AZT, ddI	Polyuria, polydipsia, polyphagia, Unexplained weight loss, and fatigue or weakness	Discuss with specialist
Myopathy	AZT, RAL	Muscle pain, weakness, rhabdomyolysis	Do CPK. If elevated stop the ARV and discuss with HIV specialist
Rapidly progressive neurologic weakness	D4T	Ascending muscle weakness similar to Guillaine Barre syndroms	Stop d4T, consult HIV specialist

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. Antiretroviral therapy 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. Some interactions between medications and food are as follows:

- The effect of certain foods on how medicine works in the body-how medicines are absorbed, metabolised, distributed, and excreted).
- The effect of certain medicine on how food is used in the body - how nutrients from foods are absorbed, metabolised, distributed, and excreted).
- The side-effects of a medication, which, in turn, can affect food intake and nutrient absorption.
- Side-effects caused by combinations of certain medications and foods.

Most ARVs can be taken with or without food. One exception is ddI which has special requirements (see Table 1.7). Proper nutrition management interventions can help alleviate some of these negative effects and can help people living with HIV 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), and high fatty food and increases the bioavailability of TDF (Pronsky et al., 2001) and absorption of PIs. The clinical significance with regard to ARV effectiveness of this is not clear.

1.16.2 Nutrition-related 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.

While ARVs contribute to improved nutritional status, they occasionally create nutritional problems, which require nutritional and other life-style 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 not uncommon condition is felt as numbness, tingling, burning sensation in the toes, feet, fingers or hands. It might be attributed to HIV, medical treatment or nutritional deficiencies. Thus the cause must be determined in order to provide specific treatment. The condition is usually treatable and reversible. Supplementation with B vitamins is only useful where nutritional deficiency is considered likely.
- **Diabetes:** Some PIs and NRTIs can affect carbohydrate metabolism which may cause insulin resistance and thus, increases patient's risk of developing diabetes. Relevant lifestyle advice should be given.

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. Therefore, nutrition counseling 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 Nutrient requirements of people living with HIV

Nutritional assessment, counseling, support, and monitoring are essential components when providing care to HIV patients. Clinical and dietary assessment at enrollment and during management helps in determining additional contributory factors to poor response to therapy. This can promote timely and appropriate interventions. Meal planning should correspond to nutritional requirements of the ARV regimen and should be feasible for clients.

There should be counseling sessions provided by healthcare workers (HCW) to patients and household members if possible, that is directed at helping them to understand the impact of therapy on nutritional status and vice versa. HCWs should also work with patients to identify feasible options.

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 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 PLHIVis 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 counseling should be provided to all clients on ART from the start of therapy.

Increased energy needs

Asymptomatic adult PLHIV require an additional 10% energy foods while symptomatic adult PLHIV require an additional 20-50% depending on disease stage. To achieve the additional energy needs, PLHIV should be counseled 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).

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 and 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 counseled/educated on nutrition using appropriate guidelines. For the management of moderate/severe malnutrition in HIV positive adults refer to Appendix 7.

1.15 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-vitamins as prescribed by a health worker
- Other supplements including traditional herbs and remedies that claim to boost the immune system or cure disease should be discouraged as they have potential adverse medicine interactions with ARVs.
- In particular, when on EFV, NVP or LPV/r, patients should avoid any supplements
- Patients on all ARV regimens should avoid alcohol use.

1.16 Prophylaxis of opportunistic infections

1.16.1 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, diarrhoea and bacteraemia, and it may reduce diarrhoea from Isospora sp. Cotrimoxazole also reduces morbidity and mortality in TB patients who are co-infected with HIV.

Cotrimoxazole prophylaxis (two x 400/80mg tablets equivalent to 800/160mg total -daily) is recommended for all adults with HIV who either have WHO Clinical Stage 3 or 4 disease (see Appendix 1) or any WHO clinical stage with a CD4 cell count ≤ 350. The eligibility criteria for initiating CPT has not changed from the previous guideline. Patients with known allergy or those who develop allergy to cotrimoxizole and whose CD4 count is <350 cells/mm3 should be given Dapsone 100mg once daily as an alternative. In such cases it is necessary to re-check CD4 every 6-months and discontinue once the CD4 is >350 for 2 consecutive readings.

As previously, HIV-positive pregnant women who are receiveing sulfadoxine/pyrimethamine (SP) for malaria prophylaxis should not be given CPT.

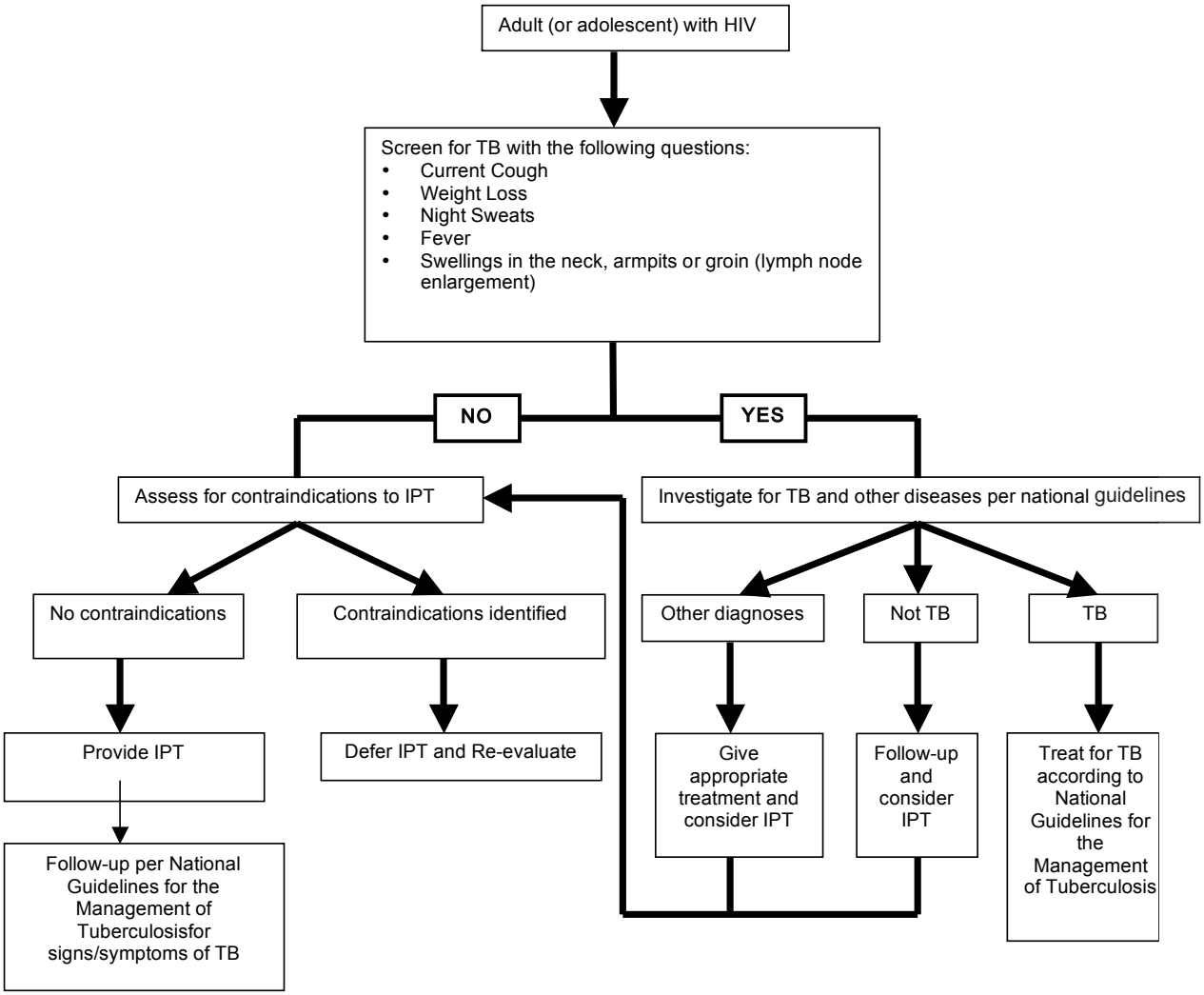
> ***In contrast to previous guidelines*, lifelong CPT is now recommended for any patient who initiates CPT unless there is a contraindication or clinical indication for discontinuation. In the event of severe renal, liver or BM suppression, discontinue CPT until the clinicial situation has improved**

1.16.2 TB screening and Isoniazid (H) preventive therapy for prevention of tuberculosis (TB-IPT)

TB-IPT is very effective in preventing TB disease in individuals who have latent TB infection. Individuals with both HIV infection and latent TB have a 5-10% risk of developing active TB 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. IPT reduces the risk of TB in HIV-infected patients by at least 60% and, in combination with ART, the risk reduction exceeds 80%.

All people living with HIV should be screened for TB including asking about TB exposure/contact history at each encounter with a health worker or visit to a health facility. See figure 1.7 below for algorithm for TB screening and IPT among adults and adolescents living with HIV.

Figure 1.7: Algorithm for TB screening and TB-IPT among Adults and Adolescents with HIV



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 TB, however, should never be started on TB-IPT.

To be eligible for TB-IPT the HIV-positive individual must:

- Have no symptoms or signs of TB – such as cough, fever, weight loss, night sweats, fatigue, blood in sputum, chest pain, diarrhoea, shortness of breath, enlarged lymph nodes, loss of appetite (*NB: TB-IPT should not be given to patients who are unwell and where there is no explanation of the illness*)
- No current history of alcohol misuse
- Have no history of active liver disease, liver insufficiency, or jaundice
- Have no history of hypersensitivitytoisoniazid
- Have no history of exfoliative dermatitis
- Be motivated for TB-IPT after being educated about the benefits, possible side-effects and risks

In addition HIV-positive persons who are close contacts of patients with infectious TB should receive IPT even if they have completed a previous course of IPT

Precautions:

- Persons starting TB-IPT must be warned about the possible side-effects of isoniazid. Isoniazid-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 isoniazidand 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 they come to collect isoniazid.

TB –IPT regimen:

- Isoniazid is given daily for a period of 9months at a dosage of 300mg/per day.
- Pyridoxine 25 mg daily is administered with the isoniazid 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 9months of treatment within a 12month 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 registerand in the patient care booklet. In addition either the TB-IPT identity card should be attached to the patient's passport or details of IPT provision should be in the patient's passport. Clinicians should list isoniazid in the list of medications prescribed in the health passport for patients on IPT.

Anine (9)-month course of TB-IPT is given to an individual patient. This is a change from the previous guidelines in which 6 months of IPT were recommended. Its efficacy lasts for approximately 1-2years, after which PLHIVhas 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.

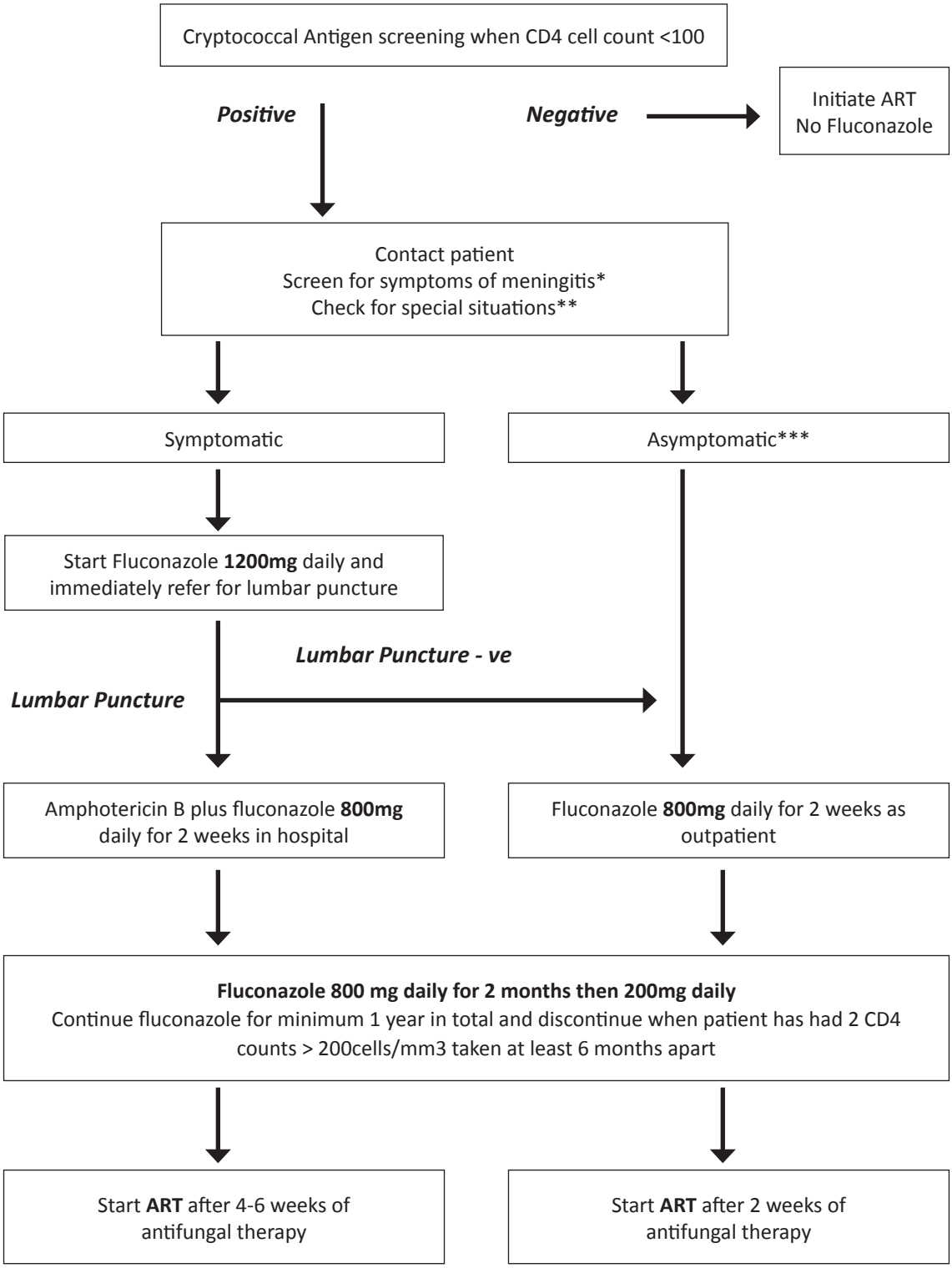
1.16.3 Cryptococcal Screening; Pre-emptive treatment and Secondary prophylaxis

Cryptococcal meningitis (CM) is a leading cause of mortality among HIV-infected adults with severe immunosuppression. Early identification of asymptomatic patients and provision of presumptive therapy for patients with a positive cryptococcal antigen test remarkably improves outcomes for these patients. HIV-positive adults with CD4 count <100 cells/mm^3 should be screened for cryptococcal antigenaemia. There are insufficient data to recommend routine cryptococcal screening of HIV-positive children and adolescents, among whom the incidence of CM is much lower.

Patients diagnosed with and treated for cryptococcal meningitis should receive secondary prophylaxis with fluconazole 200mg daily for at least one year. This should only be stopped after 2 successive CD4 count results at least 6 months apart are >200cells/mm^3

Figure 1.8 shows the current recommended management protocol for HIV-positive patients with positive cryptococcal antigen test.

Figure 1.8. Screening and pre-emptive treatment



**Symptomatic for meningitis if either of the following present: headache; confusion*
***Special situations include: prior cryptococcal meningitis; pregnancy or breastfeeding mother*
****A lumbar puncture may be considered if available*

1.17 Immune reconstitution

Improvement in a patient's condition in 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.

1.17.1 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 ART. 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 ART is failing (clinical deterioration), these patients are actually undergoing robust improvements in their immune systems. Examples of infections or conditions which have been associated with IRIS include tuberculosis, MAC, cryptococcal meningitis, herpes zoster; PML, CMV vitritis, and Kaposi Sarcoma. Recommendations for management vary by pathogen and clinical expression, but most involve medications directed against the pathogen with or without corticosteroids.

1.18 Special populations

1.18.1 People with Tuberculosis and HIV co-infection

The close association between TB and HIV is well-established. In Namibia, TB is the most common opportunistic infection in individuals who are HIV-positive.In 2012 the TB case notification rate in Namibia was 529 per 100,000 persons. Among TB cases with known HIV status, 47% were HIV-positive. 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). HIV-positive TB patients with profound immunosuppression (such as CD4 counts less than 50 cells/ mm^3) should receive ART immediately within the first two weeks of initiating TB treatment.

Starting ART within the first 8 weeks of TB treatment does carry a risk of Immune Reconstitution Inflammatory Syndrome (IRIS). However, there is significant evidence that mortality risk from delaying the start of ART in TB co-infected children, adolescents and adultsgreatly outweighs the risk from IRIS (see 3.7 section for the management of IRIS and Chapter 8 of the National Guidelines on the Management of TB).

Intensified TB Case-finding (ICF)

All people living with HIV should be screened for TB including asking about TB exposure/contact history at each encounter with a health worker or visit to a health facility; eligible PLHIVshould be offered IPT.

TB Infection Control (TB IC)

PLHIV are at high risk of acquiring TB in health care facilities and congregatesettings. Each health care facility should have a TB infection control plan for the facility that includes administrative, environmental and personal protection measures to reduce the transmission of TB in these facilities and surveillance of TB disease among workers. Health care workers with HIV should be provided with ART and TB-IPT if they are eligible.

TB diagnosis for PLHIV

All PLHIV found to have symptoms of TB should promptly be investigated for TB, with sputum examination (smear microscopy and Xpert MTB/Rif) as the preferred diagnostic tests,as per the National Guidelines for the Management of Tuberculosis. Due to the rapidly changing recommendations in the approaches to diagnosis of TB, it is envisaged that the diagnostic algorithms will be regularly updated accordingly.

HIV Treatment

Rifampicin, an important component of TB treatment, interacts with many medications, including many ARVs. Therefore, only certain ART 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.

Preferred 1st line ART regimen:
TDF + FTC (or 3TC) + EFV

For patients on rifampicin, alternatives to efavirenz are:

1. A lopinavir based regimen super boosted with ritonavir:

TDF or AZT + 3TC with LPV/r 400mg+ritonavir 400 mg BD (LPV/RTV)*

* This regimen is more potent than a triple NRTI regimen, and therefore is preferred if the patient can tolerate it.

NB: These combinations are short term and the patient should be switched to a standard regimen two weeks after completing rifampicin-based TB treatment

2. Triple nucleoside regimens:

tenofovir (TDF) + emtricitibine (FTC) (or lamivudine (3TC)) + zidovudine (AZT)

NB: These combinations are short term and the patient should be switched to a standard regimen two weeks after completing Rifampicin-based TB treatment

If a patient is already on 2nd line ART, discuss management with HIV specialist.

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

Patients with chronic HBV are candidates for ART regardless of CD4 and clinical staging. Namibia has a high prevalence of HBV infection. According to a 1997 study of 1,074 first-time blood donors to the Namibian National Blood Transfusion Service, 14.8% tested positive for markers of current HBV infection and 53 % showed markers for past exposure to HBV (Seidel et al.). Although the prevalence of HIV/HBV co-infection is not known in Namibia, studies in other sub-Saharan African countries have shown that HBV sero-prevalence in HIV positive individuals is at least as high as it is in the general population, suggesting that nearly 15% of all HIV infected persons in Namibia can be expected to be co-infected with HBV (Burnett et al).

In addition to the liver damage caused by chronic HBV co-infection, patients on ART are also at risk for hepatotoxicity associated with many ART regimens. Patients may also experience accelerated liver damage following immune reconstitution (HBV-associated IRIS). Patients eligible for ART should be assessed at enrolment for hepatitis B surface antigen, and if HBsAg positive should haveALT monitoring. 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 ART without tenofovir. Patients with HIV/HBV co-infection on ART 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, and 12 weeks, and 6-monthly thereafter. Elevated ALT arising during therapy may have many causes, and needs to be carefully evaluated for each patient.

Table1.9. 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 NNRTIs and PIs	
	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 withdrawel 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 ART temporarily
	Alcoholic liver disease	Alcoholic steatosis, acute alcoholic hepatitis	Reduce or eliminate alcohol use
Jaundice Bilirubin	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, nl 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	Hepatoma, lymphoma, liver metastasis	See table 1.8
	Malignancies		Sonogram helpful, liver biopsy diagnostic

1.18.3 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 3). Discuss with colleagues or where possible consult with an HIV specialist before starting ART in a patient with renal failure or when renal failure develops in a patient on ART. Figure 1.2 contains the formula for the calculation of CrCl.

1.19 Non-Communicable HIV-associated diseases in Namibia

1.19.1 Common cardiovascular conditions

Non-communicable diseases also affect HIV-infected patients. These diseases include hypertension, diabetes mellitus, and ischaemic and rheumatic valvular heart disease. Generally, cardiovascular conditions particularly pericarditis and dilated cardiomyopathies may be HIV, OI, or medication-related. Pericarditis may be constrictive or effusive, and is predominately caused by TB.

In few cases, it is due to Kaposi's sarcoma and lymphoma. In the cases of dilated cardiomyopathies, it can be following previous myocarditis. Important differential diagnoses consist of:

- Large pericardial effusion.
- Rheumatic valvular heart disease.

The differential is based on 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 constant screening of such complications of treatment as indicated.

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

1.19.2 Haematological conditions

Common problems may present as anaemia, leukopaenia, thrombocytopaenia, and pancytopaenia. Possible causes are:

- HIV-related bone marrow suppression.
- Medication (ARV, 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 including reticulocyte count.
- Bone marrow biopsy.

Treatment for Immune Thrombocytopaenic Purpura (ITP) includes steroids and ART. There is an increased risk of thrombotic events such as deep vein thrombosis (DVT) in HIV patients, especially those with CD4 <200.

1.19.3 Central nervous system conditions

Increased incidence of multipathogenic meningitis:

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

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

Seizures

Look for space-occupying lesions (SOL) such as those caused by toxoplasmosis. **Any HIV patients with seizures must be investigated**.The following mayalso 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 toxo serology is positive, then treat for toxoplasmosis. If toxoplasmosis is negative and the patient does not respond to empiric toxoplasmosis treatment, then one should treat for tuberculosis meningitis (TBM).

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

- Myelopathy, due to TB, Varicella zoster virus (VZV), syphilis, or HIV, amongst others.
- Spinal cord compression.
- Spinal root pathologies/radiculopathy/poliomyelitis.
- Neuropathy: Guillain Barre, acute inflammatory demyelinating polyneuropathy (AIDP), or chronic inflammatory demyelinating polyneuropathy (CIDP) – which is steroid responsive, unlike AIDP which does not respond to steroids. Other causes of neuropathies are: -HIV-related. -Medication-related (INH, 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.

1.19.4 Confusion/delirium in HIV 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).

1.19.5 Rheumatologic conditions

Rheumatological 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

1.20 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.
- Expensive/costly special investigations

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.)

Factors that increase the risk of mother-to-child transmission can be divided into obstetrical, maternal, foetal and viral factors as shown in Table 2.1.

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 condition • STIs • New HIV infection • Maternal TB	• Prematurity • Multiple births • 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 subsequent visits if not already tested and have no record of HIV positive results. Pregnant women who initially test HIV-negative should be re-tested for HIV at 36 weeks or later.

All HIV positive women should receive further counselling and clinical care during follow-up for the pregnancy (ANC), labour and delivery, and breastfeeding period in order to optimize PMTCT as well as the health status of the woman and her infant. Lifelong ARV treatment using an appropriate triple antiretroviral regimen should be provided for all HIV-infected pregnant and breastfeeding women regardless of WHO clinical stage or CD4 cell count and promote safe feeding practices.

Infants of mothers receiving ART and who are breastfeeding or replacement feeding should receive *at least* 6 weeks of infant prophylaxis, as described under the different scenarios below.

2.2 Management of ARVs in pregnancy according to clinical scenarios

ART regimens in pregnant women reduce HIV transmission by significant reductions in maternal viral load. All recommended ART 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 ART should be familiar with the various regimens.

A daily fixed-dose combination of TDF + FTC (or 3TC) + EFV is recommended as first-line ART for pregnant and breastfeeding women, including women in their first trimester of pregnancy.

Infants of mothers who are receiving ART and are breastfeeding should receive *at least* six weeks of infant prophylaxis with daily NVP. In many cases the duration of infant NVP prophylaxis will be longer.

If infants are receiving replacement feeding, they should be given six weeks of infant prophylaxis with daily NVP. Infant prophylaxis should begin at birth or as soon as HIV exposure is recognized postpartum, as long as the infant presents for care within 72 hours of birth. Simplified infant NVP dosing recommendations are given on Table 2.2. If NVP causes toxicity in the infant (or if NVP is not available), 3TC can be substituted only after discussions with an HIV specialist.

Table 2.2. Simplified infant NVP dosing recommendations

First 6 weeks

Infant Age	NVP Dosing	Dose (ml)	Required Volume	Amount to be dispensed
Birth weight <2 kg	2mg/kg once daily	-	-	50ml
Birth weight 2-2.499 kg to 6 weeks	10mg once daily	1ml	42ml	50ml
Birth weight ≥ 2.5kg to 6 weeks	15 mg once daily	1.5ml	63ml	70ml

Monthly thereafter

Infant Age	NVP Dosing	Dose (ml)	Required Volume	Amount to be dispensed
≥ 6 weeks to < 6 months	20mg once daily	2ml	56ml	70ml
≥ 6 months to <9 months	30mg once daily	3ml	84ml	100ml
≥ 9 months to four weeks beyond end of breast feeding	40mg once daily	4ml	112ml	240ml

HIV DNA PCR test should be done for HIV-exposed infants according to recommendations on early infant diagnosis in section 3.2.1, figure 3.1.

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

If a woman becomes pregnant while receiving ART the woman should remain on her current ART regimen unless there is a reason to change it such as side effects or virologic failure. This includes maintaining TDF and EFV in women who were already taking TDF and EFV as previous concerns about use of TDF and EFV in pregnancy have been largely relieved by a volume of accumulated pregnancy data.

It is important to check the most recent routine VL to ascertain if the VL is suppressed. If a VL was not done within the last 12 months, it should be repeated at the first visit and adherence counseling should be done. If the VL was/is >1000 copies/ml, intensive adherence counseling should immediately be done and the VL should be repeated in 3 months. If the VL is still >1000 copies/ml, and adherence is assured, the woman should urgently switch to 2nd line for her health and to decrease the chance of HIV transmission to her infant.

ARVs should be continued as usual during labour and the postpartum period.

Discontinuing treatment during pregnancy or breastfeeding increases the risk of MTCT and compromises the health of the mother. Nurses should consult a medical officer if ART in a pregnant or breastfeeding woman needs to be switched or interrupted.

Infant:

Breastfeeding infants
Breastfeeding infants should receive daily nevirapine from birth until at least 6 weeks. They should remain on daily nevirapine for longer than 6 weeks if the mother's VL is not suppressed. Nevirapine can be stopped 4 weeks after the mother's VL is <20 copies/ml or 4 weeks after cessation of breastfeeding, whichever is sooner.

Non-breastfeeding infants
Give daily nevirapine from birth until 6 weeks of age.

2.2.2 Scenario 2: HIV positive pregnant women diagnosed before or during pregnancy and not yet on lifelong ART

All pregnant women testing positive for HIV must be initiated on lifelong ART irrespective of their CD4 count levels or clinical stage. 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.

What to Start in HIV Positive Pregnant Women?

The preferred first line regimen:
Tenofovir +Lamivudine +Efavirenz (TDF+FTC [or 3TC]+EFV)

The dosages for the preferred first line ART regimen in pregnant women are the same as in other adults and are given in Appendix 4.

Women who have received previous PMTCT with single dose NVP should initiate ART with LPV/r and not with an NNRTI to maximize the chance of having a durable first line regimen (see alternative regimen IV below).

ARVs should be continued as usual during labour and the postpartum period and beyond. HCWs should remember to check the VL after 6 months of ART as with all patients initiating ART.

Alternative regimens include:

1. **Tenofovir +Lamivudine + Efavirenz (TDF+FTC [or 3TC] +EFV):** For women with significant psychiatric co-morbidity (do not use NVP if CD4≥250 cells/mm^3 due to risk of hypersensitivity including severe rash or hepatotoxicity or if on treatment for active TB)
2. **II. Zidovudine+ Lamivudine +Efavirenz (AZT + 3TC + EFV):** For women with renal insufficiency (CrCl<60ml/min - unless HBsAg positive) - (do not use AZT if Hb<8g/dl)
3. **Zidovudine+ Lamivudine + Nevirapine (AZT+3TC+NVP):** For women with both significant psychiatric co-morbidity and renal insufficiency (note CD4 and Hb restrictions above in I and II)
4. **Tenofovir + Emcitricitabine (or Lamivudine) + Ritonavir-boosted Lopinavir (TDF+ FTC [or 3TC]+LPV/r):** For women with CD 4 ≥ 250cells/mm^3 and Hb <8g/dl or **those who have previously had PMTCT that included sdNVP.**

When to Start ART in HIV Positive Pregnant Women?

- A pregnant woman should be offered to initiate ART on the same day she tests positive for HIV at ANC/maternity or during breastfeeding period.
- All HIV infected pregnant women should be assessed for TB signs and symptoms – if TB suspected investigate before initiation of ART. Also assess for other contraindications before initiating ART.
- Ensure patient is counselled and given appropriate information on the importance of ART for her own health and prevention of vertical transmission, adherence, side effects and follow up care.

- Do physical examination and WHO clinical staging. Collect blood samples for CD4 count and other baseline assessments.
- Initiate the preferred first line regimen (or an alternative if there is a known contraindication to the preferred first line) giving the patient a 4 week prescription – do not wait for baseline lab results.
    - A decision to initiate TDF should be based on a normal result of a urine dipstick while waiting for the creatinine clearance result. In case proteinuria and or glycosuria are detected, an alternative to TDF should be initiated while awaiting the creatinine clearance result.
- Make appointment in 2-weeks' time for review of laboratory results and for substantive intensive counselling on adherence and side effects.
    - *Note that this differs from ART initiation in other adults whereby ART is only initiated after laboratory results are received and the patient has received several counselling sessions.*
- Follow up and patient laboratory monitoring should be in line with ANC and PNC care services and the general ART patient's recommendations as indicated in Table 1.6 in section 1.12. It is of paramount importance that the routine VL is done at 6 months and that action is taken if the VL is not suppressed.

How and when to switch from option A to option B+ (lifelong ART)?

HIV positive pregnant or breastfeeding women who are receiving AZT prophylaxis (option A) should be switched to lifelong ART

- AZT and Sd NVP should no longer be dispensed when medicines for lifelong ART become available at respective PMTCT sites.
- All pregnant and breastfeeding women on AZT (option A) attending ANC, Maternity and postnatal services:
    - Counsel on the need to switch to ART, importance of adherence, side effects and follow up care
    - Do physical examination and WHO clinical staging. Collect blood samples for CD4 count and other baseline assessments
    - Switched to lifelong ART on the same day and give the woman a 2-week follow up visit.
    - Advise them to stop taking the AZT prophylaxis and not to take a SD NVP at onset of labour.
    - Instruct them to bring all unused AZT and NVP tablets back to the health facility for proper disposal.

Social considerations and treatment supporter are important for people on ART including HIV positive pregnant and lactating women BUT should not be a reason to deny or delay treatment to an HIV positive pregnant or lactating woman. Social considerations should be assessed and challenges addressed during subsequent counselling sessions. It is important to encourage pregnant women initiated on ART to bring a treatment supporter during the next follow up visit. 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.

Breastfeeding infants

Breastfeeding infants should receive daily nevirapine from birth until at least 6 weeks. They should remain on daily nevirapine for longer than 6 weeks if the mother's VL is not suppressed. Nevirapine can be stopped 4 weeks after the mother's VL is <20 copies/ml or 4 weeks after cessation of breastfeeding, whichever is sooner.

Non-breastfeeding infants

Give daily nevirapine from birth until 6 weeks of age.

Please see Table 2.2 for doses.

2.2.3 Scenario 3: HIV positive women diagnosed during labour, immediate postpartum and breastfeeding period.

A. HIV positive pregnant women who are not on ART and those diagnosed in labour or immediately postpartum should be initiated on lifelong ART without delay. The women should be counselled on the need to initiate ART, importance of adherence, side effects and follow up care. However, where full counselling cannot be given, women should be informed of the treatment and initiated on ART and counselled soon after delivery. Ensure that baseline laboratory tests are done and the woman should be reviewed at the 6 day follow up visit.

B. HIV positive breastfeeding mothers who are not on ART and those diagnosed during breastfeeding period should be initiated on lifelong treatment. The women should be counselled on the need to initiate ART, importance of adherence, side effects and follow up care. Do baseline assessment and schedule a follow up visit at 2 weeks.

Follow up and patient laboratory monitoring should be in line with ANC and PNC care services and the general ART patient's recommendations as indicated in section xx on page xx. It is of paramount importance that the routine VL is done at 6 months and that action is taken if the VL is not suppressed.

2.2.3.1 What to Start?

Mother:

Same regimens and considerations as in Scenario 2 above.

Infant:

Breastfeeding infants

Breastfeeding infants should start daily nevirapine from birth or from as soon as mother is diagnosed HIV-positive and remain on daily nevirapine until the mother's VL is not suppressed. Nevirapine can be stopped 4 weeks after the mother's VL is <20 copies/ml or 4 weeks after cessation of breastfeeding, whichever is sooner.

Non-breastfeeding infant

Non-breastfeeding infants who are less than 72 hours of age should receive daily nevirapine until they are 6 weeks of age.

Non-breastfeeding infants who present more than 72 hours after delivery should **not** receive nevirapine prophylaxis.

Please see Table 2.2 for doses.

2.2.4 Scenario 4: HIV positive pregnant or breastfeeding women who refuse or interrupt lifelong ART.

A. An HIV positive pregnant or breastfeeding woman may refuse initiation of lifelong ART after being given all the necessary information and reasonable counselling on the importance of taking ART for life. In this case, the woman should be counselled to take triple ARV prophylaxis starting at the time of diagnosis, continued intrapartum and through childbirth if not breastfeeding or until 4 weeks after cessation of all breastfeeding in order to protect her child.

B. When a mother receiving ART interrupts treatment while breastfeeding (due to toxicity, stock outs, or refusal to continue), it is important to determine an alternative ART regimen or solution, and counsel her on the need to continue treatment without interruption.

It is important to conduct WHO clinical staging, CD4 count test and other "baseline" investigations so that ART eligibility for her own health can be determined. If the baseline CD4 is <500 cells/mm^3 the mother should be counseled on her additional need to take lifelong ART for her own health.

All efforts should be made to continuously counsel women who refuse or interrupt lifelong ART on the importance of continuing ART for life. If a woman maintains her desire to stop ART after cessation of breastfeeding and her CD4 count is >500 cells/mm^3 or she is in WHO clinical stage 1 or 2, ART can be stopped. Most women will be on an EFV-based ART regimen. If the NRTIs include TDF or ABC, the whole regimen can be stopped immediately.

If the NNRTIs include AZT or d4T it is important to stop the EFV first and continue the AZT or d4T for an additional 2 weeks due to the long half life of EFV. This will prevent development of resistance to EFV and therefore enable EFV to be safely used in the future for that patient. Properly counsel the woman on the importance of continuing with HIV chronic care and support to ensure timely re-initiation of ART when she becomes eligible later in life.

Nurses should consult a medical officer if ART in a pregnant or breastfeeding woman needs to be interrupted or stopped.

2.2.4.1 What to Start?

Mother:

Same regimens and considerations as in Scenario 2. Please see above.

Infant:

Breastfeeding Infant

If mother is not on ART, daily nevirapine from birth until 4 weeks after cessation of breast feeding.

If mother agrees to start or to re-start ART, breastfeeding infants should remain on daily nevirapine from birth until the mother's VL is suppressed. Nevirapine can be stopped 4 weeks after mother's VL is <20 copies/ml or 4 weeks after cessation of breastfeeding, whichever is sooner.

Non-breastfeeding Infant

Non-breastfeeding infants who are <72 hours of age should receive daily nevirapine until they are 6 weeks of age.

Non-breastfeeding infants who present more than 72 hours after delivery should **not** receive nevirapine prophylaxis.

Please see Table 2.2 for NVP doses.

Table 2.3: Summary of maternal and infant ARV prophylaxis for different clinical scenarios

Scenarios	Maternal ARV	Duration of Infant Daily NVP Prophylaxis	
		Breastfeeding infants	Non-breastfeeding infants
1. HIV infected pregnant women already on lifelong ART	Continue ART	From birth until 4 weeks after mother's VL<20 copies per ml or 4 weeks after cessation of breastfeeding, whichever is sooner	From birth until 6 weeks of age
2. Pregnant women diagnosed HIV positive before or during pregnancy and are not on lifelong ART	Initiate lifelong ART	From birth until 4 weeks after mother's VL<20 copies per ml or 4 weeks after cessation of breastfeeding, whichever is sooner	From birth until 6 weeks of age
3 Mothers diagnosed HIV positive during labour and immediately postpartum, after delivery and during breastfeeding period			
A. Mothers diagnosed HIV positive during labour and immediately postpartum*	Initiate lifelong ART*	From birth until 4 weeks after mother's VL<20 copies per ml or 4 weeks after cessation of breastfeeding, whichever is sooner	From birth until 6 weeks of age
B. Mothers diagnosed HIV positive after delivery or during breastfeeding period	Initiate lifelong ART	From birth until 4 weeks after mother's VL<20 copies per ml or 4 weeks after cessation of breastfeeding, whichever is sooner	If presents <72 hours of age should receive daily nevirapine until 6 weeks of age.
4. HIV positive pregnant or breastfeeding women who refuse or interrupt lifelong ART			
A. HIV positive pregnant or breastfeeding women who refuse lifelong ART	Initiate triple ARVs (same combination as for lifelong ART) and counsel on the importance of lifelong ART	From birth until 4 weeks after cessation of breastfeeding	If presents <72 hours of age should receive daily nevirapine until 6 weeks of age.
B. Mothers who interrupt lifelong ART while breastfeeding	Counsel on the importance of uninterrupted lifelong ART	From birth until 4 weeks after cessation of breastfeeding	(Not applicable, infant in this scenario is breastfeeding)

* If it is CONFIRMED that the HIV positive mother will NOT breastfeed the baby after delivery, give infant NVP from birth until 6 weeks of age but assess mother for treatment eligibility and should be enrolled into HIV care.

2.3 Infant feeding recommendations

1 **Mothers who are known to be HIV uninfected or whose HIV status is unknown** should exclusively 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.

Mothers with unknown HIV status should be offered HIV testing and counseling. Breastfeeding mothers with a negative HIV status should be encouraged to test regularly preferably at a 6 month interval and to practice safer sex. Partner involvement at this stage is encouraged and is an opportunity to provide partner testing if not previously done.

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 or longer. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided

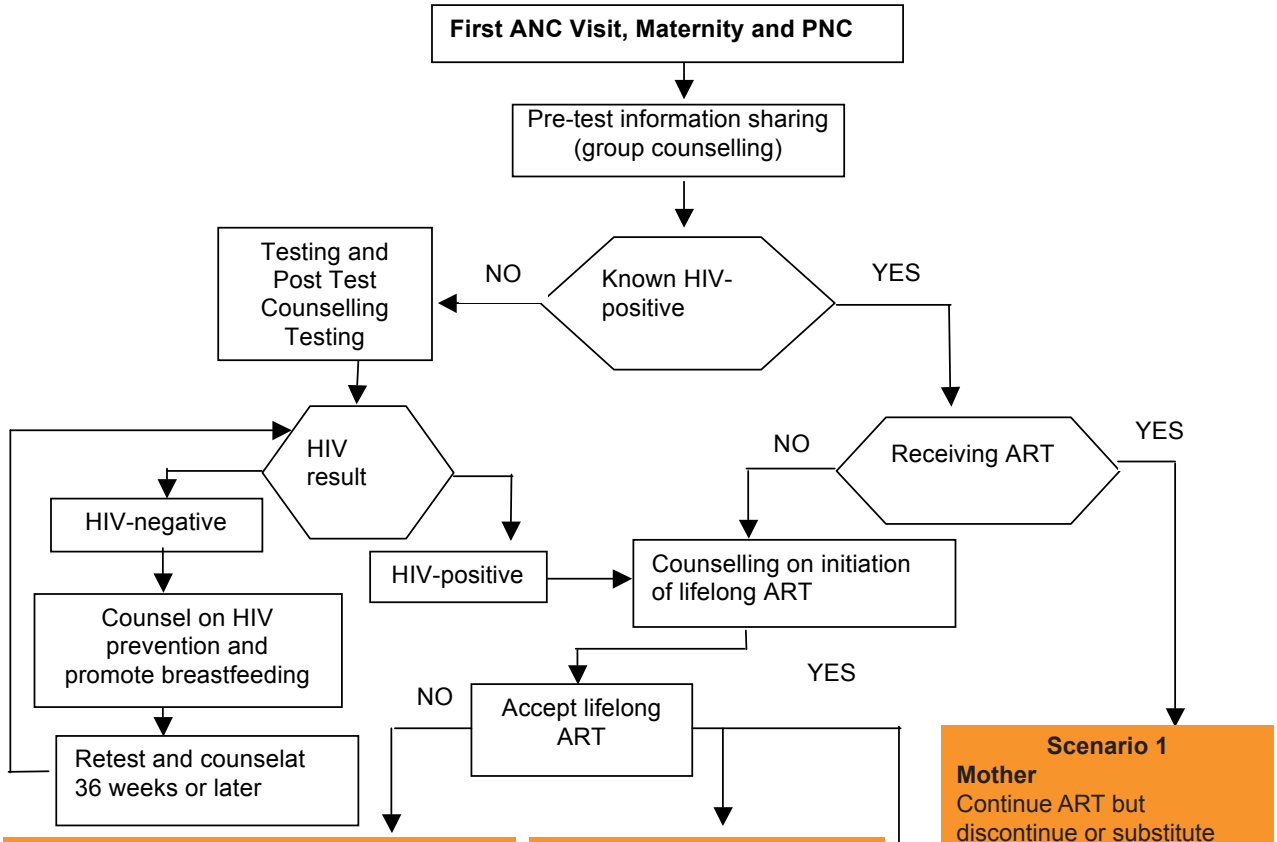
All HIV infected mothers should be on ART during the breastfeeding period. Those not yet on ART should be counselled and initiated on lifelong treatment regardless of their CD4 count and clinical stage. All infants should receive NVP prophylaxis until 4 weeks after the mother's VL is <20 copies/ml or 4 weeks after cessation of breastfeeding, whichever is sooner.

3 **When infants and young children are known to be HIV infected**, mothers should be counselled to 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 stop NVP prophylaxis and initiate ART as per the guidelines.

Table 2.5: Summary of infant feeding recommendations

	Mothers who are known to be HIV uninfected or whose HIV status is unknown	Mothers known to be HIV-infected and whose infants are HIVuninfected 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 thereafter and continue breastfeeding for the first twelve months of life or longer.	Introduce appropriate complementary foods atsix months and continue to breastfeed up to 24 months or beyond.

Figure 2.2: Algorithm for use of lifelong ART in PMTCT at ANC, Maternity and PNC



Scenario 1
Mother
Continue ART but discontinue or substitute if severe toxicity or side effects; check most recent VL

Infant: breastfeeding: NVP for at least 6 weeks. They should remain on NVP until 4 weeks after mother's VL<20 copies per ml or 4 weeks after cessation of breastfeeding, whichever is sooner
Non-breastfeeding: NVP until 6 weeks of age

Scenario 2:
Mother: Start ART: TDF+3TC+EFV

Breastfeeding infant:
NVP for atleast 6 weeks. They should remain on NVP until 4 weeks after mother's VL<20 copies per ml or 4 weeks after cessation of breastfeeding, whichever is sooner

Non- breastfeeding infant:
NVP until 6 weeks of age

Scenario 3:
Mother: Start ART: TDF-3TC + EFV

Breastfeeding Infant:
NVP until 4 weeks after mother's VL<20 copies per ml or 4 weeks after cessation of breastfeeding, whichever is sooner

Non Breastfeeding infant:
If presents <72 hours of age should receive daily nevirapine until 6 weeks of age.

If presents >72 hours of age, should not receive NVP

Scenario 4:
Mother:

- **Start Triple ARVs : T**DF-3TC + EFV if woman **refuses lifelong ART**

Assess mothers' eligible for ART for own health counsel on the importance of lifelong ART

- **Interrupts ART while breastfeeding:** counsel and determine solutions

Breastfeeding Infant:
If mother not on ART, daily NVP from birth until 4 weeks after cessation of breast feeding.

If mother agrees to start or to re-start ART, daily NVP from birth until 4 weeks after mother's VL is <20 copies/ml or 4 weeks after cessation of breastfeeding, whichever is sooner.

Non-Breastfeeding infant
If presents <72 hours of age should receive daily nevirapine until 6 weeks of age.
If presents >72 hours of age, should not receive NVP

2.4 Clinical monitoring for pregnant and breastfeeding women placed on ART

2.4.1 Baseline Clinical Assessment

The Baseline medical history should include:

- Essential demographic characteristics
- Gestational age
- Obstetric and gynaecological history (including PMTCT)
- Past medical history including major illnesses, hospitalisations and surgery
- Length of time since the diagnosis of HIV infection and if already on ART most recent viral load or CD4 count result
- Current medications and known allergies including those related to ARVs
- Review of symptoms (including screening for TB)
- Psychosocial history
- Family testing history for HIV (e.g. have partner and other children received HIV counselling and testing?)

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 ART has commenced, clinical monitoring must include follow-up visits at twoand six weeks after initiation and monthly thereafter. As much as possible the follow up visits should coincide with antenatal care visits and postnatal care visits during the first 6 weeks after delivery.Patients should be assessed by a trained member of staff every month - this visit should include clinical monitoring, medicine dispensing, lab monitoring as per schedule, 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

2.4.2 Baseline laboratory assessment for pregnant women

For all HIV-positive pregnant women the following laboratory assessments will be done as part of routine ANC work up:

Hb	Urinalysis
HBsAg	RH factor
RPR	

Additional baseline lab tests for HIV-positive women include a creatinine clearance and CD4. Patients with a normal urinalysis can be initiated on TDF based regimen while waiting for creatinine clearance results. If the creatinine clearance result is <60 ml/min, an alternative to TDF should be initiated while awaiting the creatinine clearance result.

Refer to Appendix 3 for the detailed schedule of laboratory tests to be performed for each different ART regimens.

2.5 Management of pregnant HIV-positive women with concurrent diseases

2.5.1 Tuberculosis

All HIV infected individuals including pregnant and lactating women with active TB should start ART regardless of CD4 count. TB in pregnant women is associated with prematurity, low birth weight, and perinatal tuberculosis; it has also been associated with an increased risk for mother-to-child transmission of HIV among HIV-positive pregnant women. A pregnant woman should be advised that successful treatment of TB with the standard regimen is important for successful outcome of pregnancy.

All HIV infected pregnant women should be assessed for TB signs and symptoms at each visit and those presenting with any of the following: cough, fever, night sweats, weight loss, enlarged lymph nodes should be evaluated for active TB. If none of these exist, assess for contraindications for IPT

If active TB is confirmed, TB treatment is started first before initiation of ART. The first line anti-TB medicines are safe for use in pregnancy except streptomycin which is ototoxic to the foetus and should generally not be used during pregnancy. ART should be started as soon as TB medications are tolerated.

The preferred ART regimen for HIV pregnant women with TB coinfection is TDF+3TC+EFV. **NVP should NOT be used**.

If EFV is contraindicated, a triple NRTI regimen (e.g. AZT+3TC+TDF or AZT+3TC+ABC) can be used for the duration of the TB treatment. The option of giving 2 NRTIs with "super-boosted" Lopinavir (400 mg lopinavir + 400 mg ritonavir) while on TB therapy is unlikely to be tolerated by pregnant women and therefore is not recommended.

See Figure 1.x, section 1.xx for TB screening algorithm in patients with HIV.

2.5.2 Hepatitis B

Viral hepatitis is an increasing cause of morbidity and mortality among people living with HIV, including those on ART. All HIV positive people including pregnant women should have an HBsAg test as part of routine care. 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.

Pregnant women with Hepatitis B should be initiate or continued on**: TDF + 3TC + EFV**
ALT should be checked according to the schedule in Table 1.6.

Infants of mothers who are Hepatitis B surface Antigen positive (HBsAg) must receive Hepatitis B immunoglobulin and Hepatitis B vaccine within 24 hours of birth.

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 5)

Consult with a specialist physician before starting ART in a patient with a creatinine clearance <60ml/min or when renal failure develops in a patient on ART. Refer to section 1. 20, for more detailed coverage regarding the use of ARVs in "Special Populations".

2.6. Anaemia in pregnancy

Anaemia is the most common medical disorder in pregnancy. It is important that appropriate measures are taken to prevent and treat anaemia in pregnant women. The World Health Organization (WHO) recommends a level of at least 11.0g/dl for pregnant at term but the Steering Committee of the Ministry of Health and Social Services (MoHSS) on the 7th March 2012, recommended that all pregnant women should aim for a haemoglobin level of 12.0 g/dl or more when a pregnant women reaches term.

Recommended Action
Women with Hb below 10.0 g/dl while receiving adequate doses of Pregamol should be recommended for further investigation and referral to the medical doctor. All pregnant women should have Hb estimation at 36 weeks irrespective of the Hb level during the course of pregnancy.

1. **If Hb is more than 12.0 g//dl.**
- Give standard pregamol prophylaxis 1 tab daily until 6-8 weeks after delivery.

2. **If Hb level is between 10.0-12.0 g/dl**
- Determine the possible cause clinically
- Advise on diet
- Give oral Pregamol 1 tab twice per day
- Repeat Hb after two months or at 36 weeks

3. **If Hb level is less than 10.0 g/dl**
- Take history; take blood specimen for Full Blood Count (FBC) with differential and reticulocyte count
- Collect stool specimen for microscopy
- Inform the medical doctor in charge about results to determine the type of anaemia
- Treat the cause of aneamia, give advice on diet and give oral pregamol 1 tab three times per day if thought to be iron deficiency anaemia.
- Repeat Hb two weeks after initiation of treatment (in iron deficiency anaemia Hb rises by at least 1 g/dl per week when adequatedose of iron is administered).
- If there is no improvement consider further investigations.

Blood transfusion may be considered:
- In patients who show signs of cardiac decompensation
- Any patient with Hb ≤ 6.0 g/dl

If an HIV-positive woman is on AZT-based ART, Hb should be monitored at the clinic 2 weeks after initiation of AZT based ART and then monthly. If the Hb falls below 8g/dl or drops by more than 25% from the baseline level, AZT should be substituted.

2.7. When to consult a specialist

In the following circumstances, consult a specialist:

- Combined pathologies (renal failure, diabetes, neoplasia, etc.).
- Severe medicine toxicities.
- Pregnant women receiving any other regimen than the recommended ones.

2.8. Reproductive considerations when one or both sexual partners are HIV positive

The success of ART has resulted in HIV- infected people living longer healthier lives and therefore having to make informed reproductive choices. However, it is important that those planning to have children do so carefully in consultation with health care providers to minimize the risk of infection to the sexual partner and their child. The first step towards addressing the issues of fertility and childbearing is to regularly and repeatedly raise these with HIV-positive patients, to understand their desires and related health care needs. Use of family planning services is imporatnt to avoid unplanned and unwanted pregnancies. Adherence to ART is critical to insure suppressed viral load before getting pregnant.

If a Couple Wishes to Have a Child

- Determine HIV status of both sexual partners – HIV counselling and testing is a prerequisite if the HIV status of both partners is not known.
- Counsel on the risks of MTCT
- Discuss alternatives e.g. adoption
- Advise on use of family planning services including condoms
- Check CD4 count/viral load, screen for syphilis, other STIs, check haemoglobin and screen for cervical cancer (female)
- Identify and manage co-morbidities. For conditions with short-term management (e.g. TB or acute infections), recommend delay in attempts at conception until treatment is completed.

1. **HIV Sero-Concordant Couple (Female and Male HIV-infected)**
   - **If both partners are on ART–**
     - Assess adherence and check viral load. If viral load is suppressed (<20 copies/ml) in both – advise couple on peri-ovulatory unprotected sexual intercourse (between days 10 and 18 of her menstrual cycle) for 3 months. Emphasise consistent use of condom outside this period.
     - If viral load is not suppressed (>20 copies/ml) in either partner, evaluate the patient(s) for inadequate adherence and other causes of failure and possible 2nd line treatment if VL>1000 copies/ml. Advise a delay in conception until the VL is <20 copies/ml.

   - **If one or both partners are not on ART**
     - Initiate ART according to guidelines if either one or both partners are not on treatment
     - Check viral load in both after 3-6 months. If viral load is suppressed (<20copies/ml) in both – advise couple on peri-ovulatory unprotected sexual intercourse (between days 10 and 18 of her menstrual cycle) for 3 months. Emphasise consistent use of condom outside this period.
       - If viral load is not suppressed (>20copies/ml) evaluate the patient(s) for inadequate adherence and other causes of failure and possible2nd line treatment if VL>1000 copies/ml. Advise a delay in conception until the VL is <20 copies/ml.

2. **HIV Sero-discordant Couples (Male HIV-positive)**
   - **If not on ART-** start treatment as soon as possible and check viral load after 3 -6 month
   - **If on ART** – assess adherence and check viral load.
     - If man's viral load is suppressed (<20 copies/ml):
       - Check the woman's
         - HIV antibody test (repeat if not done within last 3 months)
         - Creatinine clearance
       - If confirmatory antibody test is negative and CrCl is normal, provide PrEP (TDF +FTC (or 3TC)) to the woman daily one week prior to and until one month following the period of exposure. Monitor woman's CrCl every 3 months.
       - Advise the couple on peri-ovulatory unprotected sexual intercourse (between days 10 and 18 of her menstrual cycle) for 3 months. Emphasise consistent use of condom outside this period.
     - If male's viral load is not suppressed (>20 copies/ml) evaluate the patient for inadequate adherence and other causes of failure and possible 2nd line treatment if VL>1000 copies/ml. Advise a delay in conception until the VL is <20 copies/ml.
   - **If woman conceives:** Repeat HIV testing during pregnancy and breastfeeding period is important with appropriate management if she becomes infected.

3. **HIV Sero-discordant Couples (Female HIV-positive)**
   - **If woman not on ART-** start treatment as soon as possible and check viral load after 3 -6 month
   - **If woman on ART** – assess adherence and check viral load.
     - Check male partner's HIV antibody test. If negative, advise ejaculate collection using a cup and draw ejaculate up into a syringe. Woman should then do self-intra-vaginal insemination. This method avoids exposure of the male partner to acquiring HIV infection and is therefore the safest method.
     - If woman's viral load is suppressed (<20 copies/ml) and the couple is unable or unwilling to use the artificial insemination method described above,
       - Check the man's
   - HIV antibody test (if not done already)
   - Creatinine clearance
       - If confirmatory antibody test is negative and CrCl is normal, provide PrEP (TDF + FTC (or 3TC)) to the man daily one week prior to and until 3 months following the period of exposure. Monitor CrCl every 3 months.
       - Advise the couple on peri-ovulatory unprotected sexual intercourse (between days 10 and 18 of her menstrual cycle) for 3 months. Emphasise consistent use of condoms outside this period.
     - If woman's viral load is not suppressed (>20 copies/ml) evaluate the patient for inadequate adherence and other causes of failure and possible 2nd line treatment if VL>1000 copies/ml. Advise a delay in conception until the VL is <20 copies/ml.

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 unique 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. (seeTable 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/ mm³)
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 classification, however they include some conditions specifically targeting children such as stunting, unexplained parotid enlargement, symptomatic lymphoid interstitial pneumonitis, and others. Although the WHO clinical stage is not an eligibility criterion for children <15 years old to initiate ART, it is important to be aware of and to record the child's stage of disease and to recognize co-existing conditions which need treatment. As with adults, clinical staging is still one of the criteria used to determine whether or not an adolescent from 15 – 19 years old is eligible for ART initiation. This is another reason why 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.

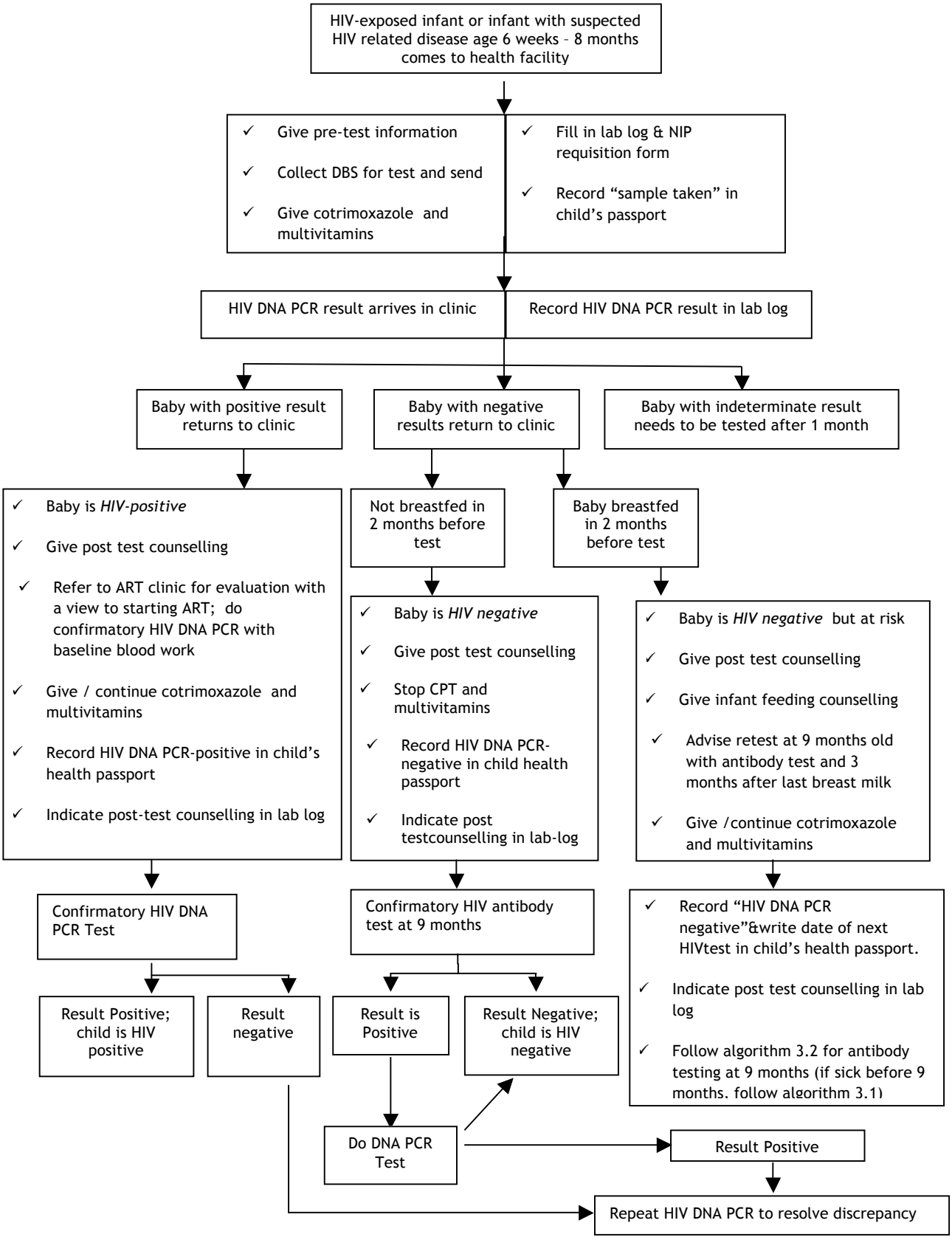
The polymerase chain reaction (PCR) test can reliably and accurately detect HIV DNA from whole blood or from a dried blood spot (DBS) specimen at an early age. This test detects the genetic material of HIV rather than of anti-HIV antibodies, and therefore is not affected by the trans-placental transfer 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 also 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. Algorithm for early infant diagnosis of HIV using diagnostic DNA PCR



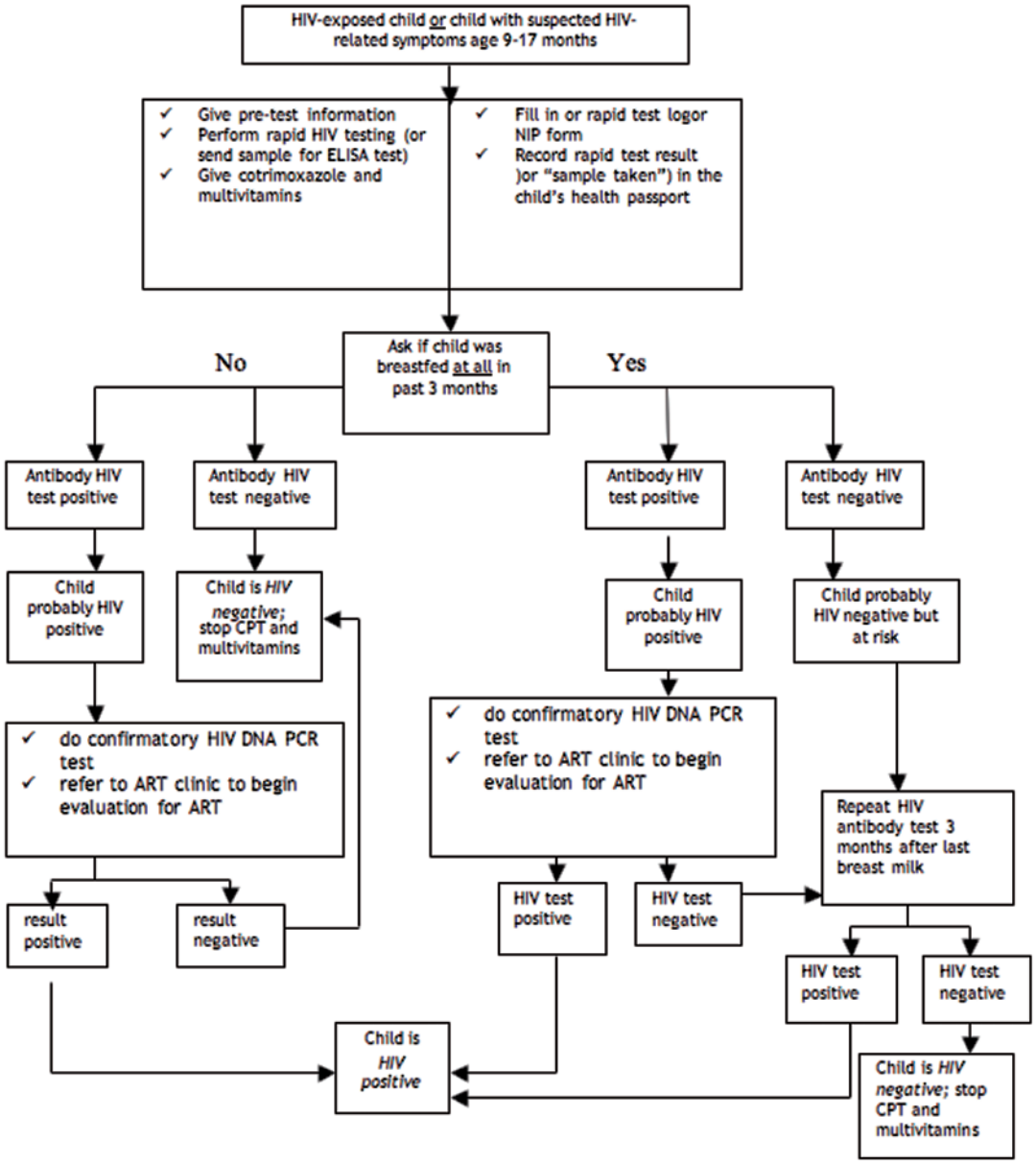
3.2.2 HIV antibody testing

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 up to 18 months of age.

The algorithm for HIV diagnosis using rapid testing (or ELISA) is outlined in Figure 3.2 for infants 9-17 months of age who are HIV-exposed and/or who show signs or symptoms consistent with HIV-related disease. In summary: following HIV antibody testing at 9 -17 months of age, 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, in that case there is no need to do further HIV testing. If the child tests positive before 18 months of age, an HIV DNA PCR test should be performed to determine if child has HIV infection.

Figure 3.2. Algorithm for diagnosis of HIV in children using HIV antibody testing



3.2.3 Criteria for diagnosis or exclusion of HIV

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 <15 years old are medically eligible to start ART once HIV infection is confirmed by HIV DNA PCR (if <18 months old) or rapid test if ≥18 months old 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 ART 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.

Children who test HIV positive in early infancy with HIV DNA PCR should have a confirmatory HIV test done, because otherwise life-long treatment will be given on the basis of a single blood test. A repeat HIV DNA PCR (confirmatory test) must therefore be done for HIV-positive infants <18 months old at the same time as the baseline blood tests are taken, however ART should be commenced based on the first result - **do not wait for the results of the confirmatory HIV DNA PCR to initiate ART.** If the confirmatory test is positive, there is no need to ever repeat a diagnostic HIV test.

Serologic and/or DNA PCR reversion can occur in HIV positive children who start ART early and whose viral load is persistently maximally suppressed (VL<20 copies/ml) through excellent adherence. This means that standard antibody tests (RT) and/or the DNA PCR test give negative results while the child is actually HIV positive. If ART is discontinued in that child, the HIV viral load will rebound and the child can become ill. *It is important for all health care workers and counselors to be aware of this phenomenon to ensure that no child is inadvertently taken off treatment in the mistaken belief that the child is no longer infected with HIV.*

In the rare event that a child was diagnosed HIV positive on the basis of a single HIV DNA PCR test (no confirmatory DNA PCR result is found), a detectable viral load test result can serve as the confirmatory test. If all viral load results are undetectable (<20 copies/ml) in such children, and the HIV diagnosis is in doubt, **do not stop ART.** Consult an HIV specialist before taking further action.

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 coinciding with the measles immunisation. (see section 3.2.1)

3.3 Prevention of opportunistic infections in children

3.3.1 Cotrimoxazole preventive treatment

Cotrimoxazole (sulfamethoxazole (SMZ) plus trimethoprim (TMP)) has been shown to have protective effects against pneumocystis pneumonia, and other bacterial and parasitic infections, including malaria. It is recommended to initiate cotrimoxazole preventive therapy (CPT) for all HIV-exposed children from the age of 6 weeks and only discontinue if the child is proven to be HIV negative according to the criteria mentioned in section 3.2.3.2 above.

All HIV positive children and adolescents at whatever age they are diagnosed should receive CPT and should continue on it through adulthood.

Table 3.2. Recommended oral doses of cotrimoxazole for Cotrimoxazole Preventive Therapy

	Once daily cotrimoxazole dosage (SMZ/TMP)		
Weight (kg)	Suspension 200/40mg	Tablets 400/80 mg	Tablets 800/160mg
3-5.9 kg	2.5 ml	-	-
6-13.9 kg	5 ml	½ tablet	-
14-24.9 kg	10 ml	1 tablet	½ tablet
≥25 kg	-	2 tablets	1 tablet

3.3.2 TB screening and isoniazid preventive therapy (TB-IPT) for children

Children and adolescents with HIV should be screened for TB including asking about TB exposure/contact history at each encounter with a health worker or visit to a health facility; eligible children and adolescents with HIV should be offered IPT (see Figure 3.3 below for algorithms for TB screening and IPT among children and adolescents with HIV).

TB Screening Questions for Children:

- Poor weight gain
  - defined as reported weight loss, very low weight (weight-for-age < -3 z-score), underweight (weight-for-age < -2 z-score), confirmed weight loss >5% since last visit, or growth curve flattening
- Fever
- Current Cough
- Lymph node enlargement
- Contact with person with confirmed or presumptive infectious TB

If the answer to any of the screening questions is “Yes”, investigations for TB and other diseases is required; patients who have signs and symptoms of active TB, should never be started on TB-IPT.

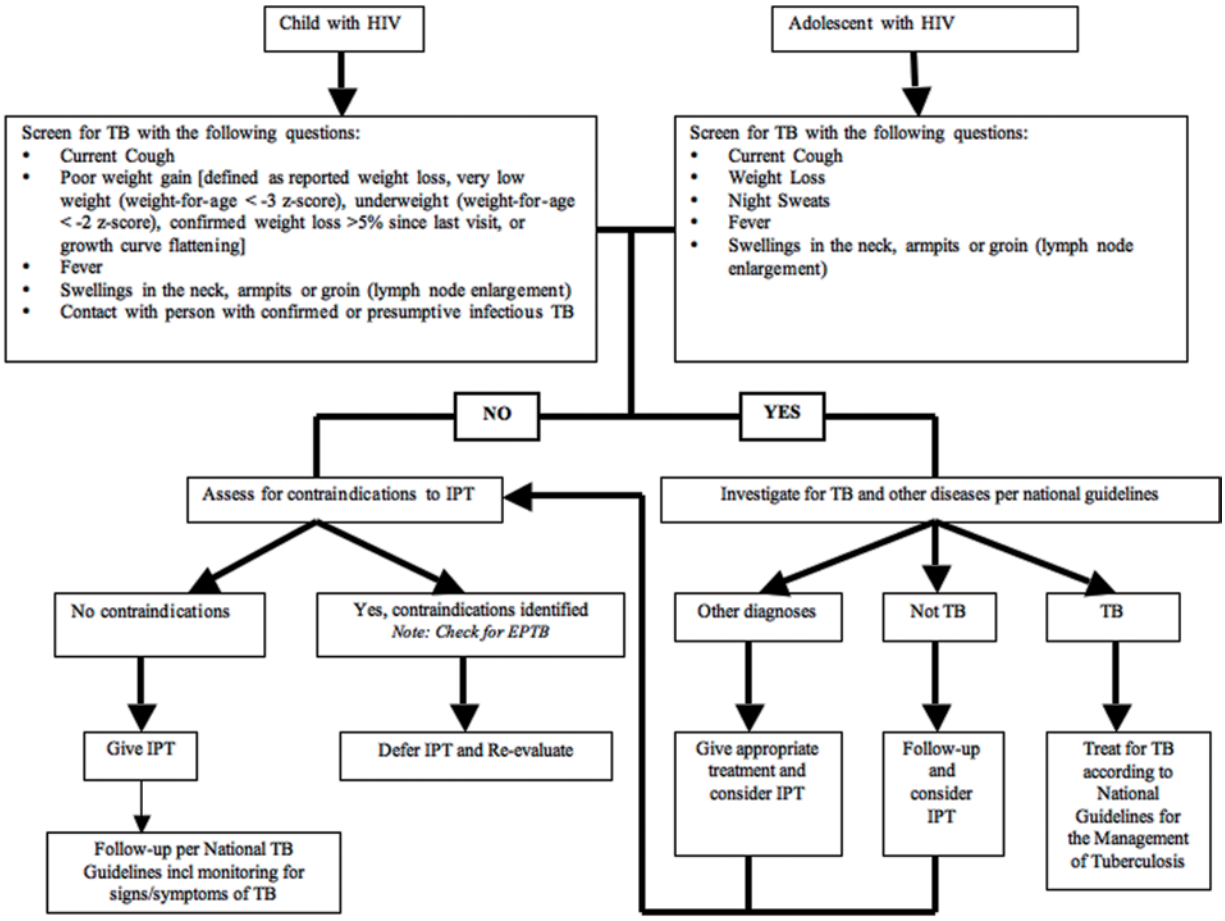
For all children <5 years old (whether HIV positive or negative) and all HIV-positive children and adolescents (regardless of age) who have had contact with someone with infectious TB, and infants born to mothers with untreated pulmonary TB disease, supervised isoniazid preventive therapy (TB-IPT) should be given once active TB disease has been excluded.

HIV-positive children and adolescents in whom active TB has been excluded are eligible for TB-IPT, whether there has been a documented exposure to active TB or not.

In addition, even if a child has already taken a course of TB-IPT and is subsequently re-exposed to a patient with infectious TB, another course of IPT should be given.

Answers to the TB screening questions and follow-on evaluations/decisions should be recorded in the appropriate page of the pediatric patient care booklet.

Figure 3.3. Algorithm for TB screening and TB-IPT among Children and Adolescents with HIV



The isoniazid dosage for children is 10 mg/ kg (range: 7-15 mg per kg; maximum 300mg) daily. See table 3.3 below for simplified weight-based dosing for children. The recommended duration of IPT treatment has been increased from 6 to 9 months in these guidelines.

Table 3.3. Simplified paediatric weight-based dosing for isoniazid

Weight (kg)	Once daily dose (mg)	Number of 100mg isoniazid tablets per dose
4 - 6.4 kg	50	½ tablet
6.5 - 9.9	100	1 tablet
10 - 13.9	150	1½ tablets or ½ of a 300 mg tablet
14 - 19.9	200	2 tablets
20 - 24.9	250	2½ tablets
≥ 25	300	3 tablets or one adult 300mg tablet

Pyridoxine should be given along with isoniazid to prevent isoniazid associated neuropathy in children from 5 years of age. The dose of pyridoxine is 12.5mg/day (1/2 tablet) for children 5-11 years old and 25mg/day for children ≥12 years old. This is also an increase in dose compared to the previous guidelines.

3.4 ART in children and when to start

3.4.1 Response to ART in children

The immunological response to ART in children with HIV is better than in adults. Children restore their CD4 cell counts and percentages better and more rapidly than adults, even in late stages of HIV-1 infection. Moreover, normalisation of CD4 cell count in HIV-1-infected children taking ART 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. During counseling sessions it is very important to fully assess, discuss and address issues to do with adherence with caregivers and, if of appropriate age, with the children themselves. This is always essential, and can be particularly challenging if an HIV-infected child is eligible for ART initiation based on age only and does not have any signs of HIV disease.

3.4.3 When to start ART in children and adolescents <15 years old

In order to reduce short and long term, often permanent, morbidity in children with HIV, and to minimize loss to follow-up:

ALL children and adolescents <15 years old are eligible for ART and should be initiated on ART irrespective of CD4 count and clinical stage

3.4.4 When to start ART in adolescents ≥ 15 years of age:

Children ≥15 years of age should initiate ART according to adult initiation criteria. These include:

- CD4 ≤500 cells/mm^3 regardless of WHO Stage
- WHO Stage 3 or 4 regardless of CD4 count
- Active TB disease regardless of CD4 count
- Hepatitis B virus co-infected regardless of CD4 count or clinical stage

3.5 The choice of ARVs for children

The choice of ARVs in children depends upon age, weight, previous PMTCT nevirapine exposure and co-morbidities. Children who have had NVP as part of PMTCT may have HIV resistance mutations that were selected at that time and therefore initiating an ART regimen containing NNRTIs to those children would not be expected to be durable.

The general principles followed in selecting ARVs for children include:

- It is preferable to use an age-appropriate fixed dose combination for any regimen if such a formulation is available
- Oral liquid or syrup formulations should be avoided where possible, especially if dosage volumes are large
- Where children use adult formulations, care must be taken to avoid underdosing. Adult tablets that are scored are more easily split
- Tablets that are not easily split should be cut at the dispensing pharmacy using tablet cutters
- Children must be weighed at each clinic visit and appropriate dose changes made as children grow and gain weight

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 millilitre (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) liquid needs refrigeration and is unstable in solution making it unsuitable for the pharmacy to mix in advance.

Several manufacturers have developed paediatric versions of single ARV and 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. Most 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.

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 3.4 and 3.5 for paediatric dosages of ARVs.

Table 3.4 Paediatric Dosage chart for NRTIs

Weight	Abacavir* (ABC)		Lamivudine (3TC)		ABC/3TC*		Zidovudine (AZT)		AZT/3TC		Tenofovir (TDF) Once daily (od) Max 300mg daily	Stavudine (d4T)/3TC	
	Once daily (od) Max 600mg daily		Twice daily Max 150 mg bd		Once daily (od) Max 600mg/300mg daily		Twice daily Max 300mg bd		Twice daily Max 300/150mg bd			Twice daily Max 30mg/150mg bd	
Kg	Dispers. tablet 60mg	Tablet 300mg	Oral solution 10mg/ml	Tablet 150 mg	Dispersible tablet 60mg/30mg	Tablet 300mg/ 150mg	Dispersible tablet 60mg	Tablet 300mg Capsule 100mg	Dispersible tablet 60mg/30mg	Tablet 300mg/150mg	Tablet 300 mg daily	Dispersible tablet 6mg/30mg	Tablet 30mg d4T/ 150mg 3TC
3-5.9	2 tabs od		3ml bd		2 tabs od		1 tab bd		1 tab bd			1 tab bd	
6-9.9	3 tabs od		4ml bd		3 tabs od		1.5 tabs bd		1.5 tabs bd			1.5 tabs bd	
10-13.9	4 tabs od		5ml bd		4 tabs od		2 tabs bd		2 tabs bd			2 tabs bd	
14-19.9		1 tab od		0.5 tab bd		1 tab od	2.5 bd	0.5 tab bd		0.5 tab bd		2.5 tabs bd	
20-24.9		1.5 tabs od		1 tab am 0.5 tab pm		1.5 tabs od	3 tabs bd	1 tab am 0.5 tab pm		1 tab am 0.5 tab pm		3 tabs bd	1 tab am 0.5 tab pm
25-39.9		2 tabs od		1 tab bd		2 tabs od		1 tab bd		1 tab bd	≥35 kg = 1 tab od	4 tabs bd	1 tab bd

**please note: Abacavir is now given once daily. This is a change from the previous guidelines in which the total daily dose was divided into two and given bd.*
NB: at the time of the printing of these guidelines, some of the formulations were not yet available

Table 3.5 Paediatric Dosage chart for NNRTIs, NNRTI-containing FDCs and PIs

Weight	Efavirenz (EFV)	Nevirapine (NVP)						D4T/3TC/NVP		AZT/3TC/NVP		Lopinavir/ritonavir (LPVr)		
	Once daily (od) Max 600mg od	**Twice daily* Max 200 mg bd**						**Twice daily* Max 30/150/200mg bd**		**Twice daily* Max 300/150/200mg bd**		**Twice daily Max 400mg/100mg bd**		
		Induction dose* once daily (od) for first 14 days			Maintenance dose* twice daily			Dispersible tablet 6mg d4T/ 30mg 3TC/ 50mg NVP	Tablet 30mg/ 150mg/ 200mg	Dispersible tablet		Liquid	Heat stable tablet ***Must swallow whole***	
Kg	Capsules 50mg, 200mg	Oral susp. 10mg/ml	Dispers. tablet 50 mg	Tablet 200mg	Oral susp. 10mg/ ml	Dispers. tablet 50mg	Tablet 200mg	Maintenance dose*	Maintenance dose*	60mg AZT/ 30mg 3TC/ 50mg NVP	Tablet 300/150/ 200mg	80mg LPV /20mgRTV per ml	100mg LPV/ 25mg RTV	Tablet 200mg LPV/ 50mg RTV 1 tab bd
3-5.9	3-4.9 kg: 100 mg od 5-7.4 kg: 150 mg od	5ml od	1 tab od		5ml bd	1 tab bd		1 tab bd		1 tab bd		1 ml bd		
6-9.9	7.5 – 14.9 kg: 200mg od	8ml od	1.5 tabs od		8ml bd	1.5 tabs bd		1.5 tabs bd		1.5 tabs bd		1.5 ml bd		
10-13.9		10ml od	2 tabs od	0.5 tab od	10ml bd	2 tabs bd	0.5 tab bd	2 tabs bd		2 tabs bd		2ml bd	2 tabs am 1 tab pm	
14-16.9	15–19.9 kg: 250 mg od			0.5 tab od			1 tab am 0.5 tab pm	2.5 tabs bd		2.5 tabs bd		2.5 ml bd	2 tabs bd	1 tab bd
17-19.9				1 tab od						2.5 tabs bd		2.5 ml bd		
20-24.9	300mg od							3 tabs bd	1 tab am 0.5 tab pm	3 tabs bd	1 tab am 0.5 tabs pm	3 ml bd		
25-34.9	25- 32.4 kg: 350mg od						1 tab bd	4 tabs bd	1 tab bd		1 tab bd		3 tabs bd	2 tabs am 1 tab pm
35-39.9	32.5–39.9 kg: 400mg od													2 tabs bd
≥40 kg	600mg od			1 tab od			1 tab bd		1 tab bd		1 tab bd			2 tabs bd

**any child or adolescent initiating nevirapine should start with an "induction" dose which is generally half of the daily maintenance dose for 2 weeks.*
If there is no rash or other sign of hypersensitivity, the patient can be given the bd maintenance dose.This means that if a child is initiating ART with an FDC that contains nevirapine, the child should take the triple FDC in the morning and the dual FDC (e.g. ABC/3TC or AZT/3TC) in the evening for the first 2 weeks.

Initiating treatment

The preferred first line ART regimen in children depends upon age, weight, prior PMTCT nevirapine exposure and the presence of co-morbidities.

In this guideline, PMTCT NVP exposure is defined as any duration of NVP prophylaxis given to HIV-exposed infants as part of PMTCT.

Preferred first line ART regimen for:

- <3 years old or <10 kg: **ABC/3TC/LPV/r** [ABC/3TC as a once daily dose, LPV/r given twice daily]
- 3 to 9 years old ***and*** 10 kg to <35 kg:
  - NO previous PMTCT NVP exposure:
    give **ABC/3TC/EFV** [all once daily doses]
  - Previous PMTCT NVP exposure:
    give **ABC/3TC/LPV/r** [ABC/3TC as a once daily dose, LPV/r given twice daily]
- ≥35 kg***and*** at least 10 years old : **TDF/3TC/EFV** [all once daily doses]

NB: Children generally reach 35 kg by 10-12 years of age**.** ***Tenofovir should NOT routinely be given to any child <10 years old even if that child weighs ≥35 kg.***

The box below summarises the preferred first line ART regimens for children and adolescents in Namibia:

Preferred 1st line ART regimens

Children <3 years old or <10 kg
ABC/3TC/LPV/r

Children 3 to 9 years old and 10 kg to <35 kg
NO previous PMTCT NVP exposure: give ABC/3TC/EFV
Previous PMTCT NVP exposure: give ABC/3TC/LPV/r

Children and adolescents ≥35 kg and at least 10 years old
TDF/3TC/EFV

Alternative regimens

If any of the preferred first line ARVs cannot be used, **alternative ARVs are suggested in Table 3.6 below.**

In the rare instance when there is a hypersensitivity reaction to ABC and the child's regimen needs to be changed to AZT, it is important to remember to check that the Hb is ≥7.5 g/dl before initiating AZT, and that follow-up Hbs are done at 2 weeks, 6 weeks and 3 months after initiating AZT.

Namibia is phasing out the use of both d4T and ddI for children due to their unfavourable side effects and resistance profiles as well as their decreasing availability on the market. **See section 3.5.2.2 for guidance on how to safely change from d4T to another NRTI.**

If a child cannot use EFV for any reason, and needs to change to NVP, care should be taken to ensure its appropriate and safe initiation. 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, increasing the dose to twice daily if the child has no signs or symptoms of hypersensitivity. Induction dosing is associated with a lower incidence of NVP rash and hepatotoxicity. 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.

Table 3.6 Severe toxicities associated with ARVs and suggested substitutions for children

ARV	Most Frequent or Significant Toxicity	Suggested ARV Substitution
ABC	Hypersensitivity reaction	If <3 months after start of ART, use AZT
TDF	Renal insufficiency (CrCl<60ml/min)	ABC if not HBV co-infected. If HBV co-infected, decrease TDF dose according to dose adjustment table in Appendix 5
AZT	Severe anaemia (<7.5 g/dl,)[1] or severe neutropenia (<500 cells/mm^3)	if <3 months after start of ART, use ABC If >3 months, consult HIV specialist
	Lactic acidosis	ABC if a) < 3 months after start of ART or b) >3 months after start of ART and VL in last 6 months <20 copies/ml. If VL not suppressed, consult HIV specialist
	Severe gastrointestinal intolerance that prevents ingestion of ARVs (persistant nausea and vomiting)	if <3 months after start of ART, use ABC If >3 months, consult HIV specialist
D4T	Peripheral neuropathy	ABC if VL in last 6 months <20 copies/ml AZT if VL not suppressed with later change to ABC if VL suppressed
	Lactic acidosis	
	Lipoatrophy/metabolic syndrome	
	Pancreatitis	
EFV	Persistent and severe central nervous system toxicity (hallucinations, psychosis)	NVP
NVP	Acute symptomatic hepatitis or asymptomatic hepatitis with ALT>5x ULN	EFV[2] if ≥3 years old and ≥10 kg, unless severe hepatitis[d] If <3 years old or < 10 kg, consult HIV specialist
	Severe or life threatening rash (Stevens Johnsons Syndrome (SJS)[3]	Substitute with LPV/r
	Hyper sensitivity reaction	

[1] Exclude malaria in areas of endemic malaria

[2] EFV may cause hepatitis but much more rarely than NVP. If severe may need to change to LPV/

[3] Hospitalization is required for all patients with SJS

3.5.2.2 Transitioning children from AZT or D4T to ABC or TDF and from NVP to EFV

In order to take advantage of preferable dosing schedules, side effect profiles and mutation sequencing and to allow harmonization with preferred ART regimens for adults, HCWs should identify children and adolescents currently on AZT and d4T and should carefully plan a change to ABC or TDF as appropriate.

Particular attention should be paid to children currently on stavudine (d4T). d4T is a potent cause of lipoatrophy in children and adolescents. In addition d4T may cause lipohypertrophy and dyslipidaemia. Therefore children and adolescents who are currently taking d4T/3TC as the NRTI backbone should change to other NRTIs under the conditions noted below.

Thymidine analogues (e.g. d4T and AZT) can be considered interchangeable because their mutation patterns are similar. Non-thymidine analogues (e.g.ABC and TDF) are also interchangeable for the same reason. However changing from a thymidine analogue to a non-thymidine analoque or *vice versa* in the presence of virologic failure could compromise future 2nd line options – it would be essentially introducing one new ARV into a failing regimen. For this reason, results of the most recent viral load should be reviewed to inform the appropriate regimen change. If the most recent VL is more than 6 months previously, it should be repeated.

Other principles to note when considering transitioning children from the previous regimens to new regimens:

- ABC/3TC should be given as a daily dose. There is an advantage therefore to changing from NVP to EFV in children using these NRTIs, as EFV is also a daily dose
- if any child cannot change to ABC/3TC because the VL is not suppressed while on a regimen with AZT(or d4T)/3TC/NVP, then it is best to keep the child on an FDC containing NVP given bd rather than change the NVP to EFV which would introduce a higher pill burden
- children are only eligible for a change from NVP to EFV if they are ≥3 years old and ≥10kg. If they are <3 years old or <10 kg and are on NVP, they should remain on NVP

Table 3.7 summarises the guidance on changing regimens described below.

For children <10 years old or adolescents <35 kg:

Table 3.7.Transitioning safely from previous ART regimens to new preferred regimens

		VL within last 6 months	
No.	**Current NRTIs**	**VL<20**	**VL≥20**
1	D4T/3TC/NVP	Change to ABC/3TC + (if ≥3 yrs and ≥10kg) EFV	Change to AZT/3TC/NVP[1] as an FDC while intensifying adherence counseling and follow-up, evaluating for treatment failure and possible 2nd line if VL>1000
2	D4T/3TC + LPVr	Change to ABC/3TC + LPVr	Change to AZT/3TC + LPVr while intensifying adherence counseling and follow-up, evaluating for treatment failure and possible 2nd line if VL>1000
3	D4T/3TC/NVP but previous AZT toxicity[2]	Change to ABC/3TC + (if ≥3 yrs and ≥10kg) EFV	Confirm if truly previous AZT toxicity[2]. If yes, continue d4T/3TC/NVP as an FDC while intensifying adherence counseling and follow-up, evaluating for treatment failure and possible 2nd line if VL>1000. If not true AZT toxicity, manage as in 1 above
4	D4T/3TC + LPVr but previous AZT toxicity[2]	Change to ABC/3TC + LPVr	Confirm if truly previous AZT toxicity[2]. If yes, keep on d4T/3TC + LPVr while intensifying adherence counseling and follow-up, evaluating for treatment failure and possible 2nd line if VL>1000. If not true AZT toxicity, manage as in 2 above
5	AZT/3TC/NVP	Change to ABC/3TC + (if ≥3 yrs and ≥10kg) EFV	Continue AZT/3TC/NVP as an FDC while intensifying adherence counseling and follow-up, evaluating for treatment failure and possible 2nd line if VL>1000
6	AZT/3TC + LPVr	Change to ABC/3TC + LPVr	Continue AZT/3TC + LPVr while intensifying adherence counseling and follow-up, evaluating for treatment failure and possible 2nd line if VL>1000

[1] *Adherence is likely to be better by maintaining the AZT/3TC/NVP as an FDC given bd rather than changing to AZT/3TC given bd plus EFV given daily*

[2] Patients who were anaemic at start of ART may have initiated treatment with d4T, however these patients do not have "AZT-induced anaemia" and it is safe to use AZT unless the current Hb<7.5

For children ≥10 years old and ≥35 kg: replace ABC/3TC with TDF/FTC in the above table

3.5.3 Second Line ART

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 is an indication to investigate for possible virologic 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 viral loads >1000 copies/ml need urgent attention paid to adherence to help determine any factors that negatively impact on adherence. ARV 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 OIs (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 ART 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 challenges are solved and it is anticipated that adherence to second line will be good.

3.5.3.2 Second line regimens

As a general rule, when considering switching to second line therapy in children, health care workers at the clinic should meet as a group to thoroughly review all aspects of the patient's case. In addition it is recommended that a second opinion from an HIV expert may be sought.

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

**If a child <10 years old who was on LPV/r in first line, and was given NVP for PMTCT as an infant, an NNRTI should not be used because of possible resistance mutations acquired during the period on NVP. Seek advice of an HIV specialist and do an HIV resistance test (see section 3.5.3.3)*

Preferred 2nd line ART regimens

Children < 3 years old and < 10 kg who had PI-based first line
NO previous PMTCT NVP exposure: give ABC + AZT + 3TC + NVP
*Previous PMTCT NVP exposure**: consult an HIV specialist and get a resistance test

Children 3 to 9 years old and 10 kg to <35 kgwho had PI-based first line
NO previous PMTCT NVP exposure: give ABC + AZT + 3TC + EFV
*Previous PMTCT NVP exposure**: consult an HIV specialist and get a resistance test

Children <10 years old or <35 kgwho had NNRTI-based first line
ABC + AZT + 3TC + LPV/r

Children and adolescents ≥35 kg and at least 10 years oldand who had LPV/r-based first line
TDF + AZT + 3TC + EFV

3.5.3.3 Resistance testing

Resistance testing provides identification of HIV mutations that may have been selected and which might be causing virological failure in a patient who is adhering well to ART. 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 is essential for a child or adolescent who has failed a second line regimen and a third line regimen is needed. In addition, children who have been exposed to NVP for PMTCT and have failed LPV/r as a first line regimen, qualify for resistance testing to allow for selection of an effective 2nd line regimen. 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.

Eligibility for resistance testing in children who are adhering well to ARVs:

- Virologic failure in the presence of confirmed good adherence on 2nd line ART
- Virologic failure in the presence of confirmed good adherence in children <10 years old who have been on LPV/r as part of first line and who have a history of having had NVP as PMTCT in infancy

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 full information about resistance to the current regime the child is on. Mutations selected by a previous regimen that the child was taking may be "archived" (still present but not in high enough quantity to be detected by the resistance test) and if that ARV is given again, the mutation will become more prominent and the ARV will not be effective. Interpretation of results should be done in consultation with a specialist. An HIV Drug Resistance panel meets monthly to review cases and reaches a consensus decision on the way forward in management of specific patient. Particularly if the mutation pattern assessment results in a recommendation for buying out of ARVs not routinely available, it is important that the case is discussed at the HIV DR panel meeting.

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. Children with HV are more likely to be exposed and infected with TB than children without HIV because they are more likely to live in households with TB and HIV and are, therefore, more likely to be a close contact of a case of active TB disease. If infected with TB, children with HIV are more likely to develop TB disease. TB screening and preventive therapy to reduce the risk of TB disease following TB exposure and infection are key interventions to reduce the impact of TB among children with HIV.

Children and adolescents with HIV should be screened for TB including asking about TB exposure/contact history at each encounter with a health worker or visit to a health facility; eligible children and adolescents with HIV should be offered IPT. **See section 3.3.2 for algorithms for TB screening and IPT among PLWH and Section1.18.2 for more detail regarding TB-IPT.**

TB Screening Questions:

- Poor weight gain
    - defined as reported weight loss, very low weight (weight-for-age < -3 z-score), underweight (weight-for-age < -2 z-score), confirmed weight loss >5% since last visit, or growth curve flattening
- Fever
- Cough
- Lymph node enlargement
- Contact with person with confirmed or presumptive infectious TB

All children and adolescents with HIV who have signs and/or symptoms suggestive of TB should be evaluated for TB disease including careful history, thorough physical examination, chest radiography and possibly a TST along with any other relevant tests. Bacteriological confirmation should be sought whenever possible and specimens should be sent for mycobacterial culture and Xpert MTB/Rif due to the low sensitivity of smear microscopy (see Chapter 6 in the National Guidelines for the Management of TB for details regarding specimen collection in children). A negative test does not rule out TB.

Answers to the TB screening questions and follow-on evaluations/decisions should be recorded in the appropriate page of the pediatric patient care booklet.

Please refer to the National Guidelines for the Management of Tuberculosis for help with diagnosing and treating TB in children and adolescents.

3.6.1 When to start ART in HIV/TB co-infected children and adolescents

HIV-infected children and adolescents with pulmonary tuberculosis have WHO Clinical Stage 3 disease and those with extra-pulmonary TB have WHO Clinical Stage 4 disease. ART should be started in all children and adolescents with TB disease, including those with drug-resistant TB, irrespective of the CD4, and, therefore both groups are eligible for ART.

ART should be started in any child oradolescent with active TB disease as soon as possible and within eight weeks of starting antituberculosis treatment irrespective of the CD4 count and clinical stage. Such children with profound immunosuppression (e.g. CD4<50 cells/mm^3) should receive ART immediately, within two weeks of initiating TB treatment as this carries a survival advantage in this group.

HCWs should be aware that starting ART within the first 8 weeks of TB treatment does carry a risk of Immune Reconstitution Inflammatory Syndrome (IRIS). However, there is ample evidence that mortality from delaying the start of ART in TB co-infected children and adolescents greatly outweighs the risk from IRIS (see 3.7 section for the management of IRIS).

3.6.2 ART regimens for children with TB being treated with rifampicin-based regimen

Not all antiretrovirals should be used in combination with rifampicin. Rifampicin increases metabolism of and hence 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 nevirapine resistance can be selected, which may compromise future ARV choices. At standard doses, efavirenz remains effective in the presence of rifampicin. For this reason, efavirenz is preferred for use in children needing rifampicin-based TB treatment if they are at least 3 years old, 10 kg and have not had previous nevirapine as PMTCT.

Lopinavir “super-boosted” with ritonavir results in a therapeutic blood level of lopinavir in children on rifampicin. “Super-boosting” means adding additional ritonavir to bring the dose of ritonavir equal to that of lopinavir. .

If a child or adolescent presents with TB and is not yet on ART, start ART with the following regimens:
<3 years old or weight <10 kg:

- AZT + 3TC + ABC (until 2 weeks after TB treatment competed and then change to the standard ART regimen)
- preferred regimen once paediatric ritonavir solution is available:
    - ABC + 3TC + super-boosted lopinavir/ritonavir (LPV/r + R)

3 – 9 years old and weight 10 kg to <35 kg

- *If the child has had NO previous PMTCT NVP exposure* ABC+ 3TC + EFV
- *if the child has had previous PMTCT NVP exposure*
    - ABC + 3TC + super-boosted lopinavir/ritonavir (LPV/r + R) or
    - ABC+3TC+AZT
    - *NB: two weeks after TB treatment is completed, change to the standard ART regimens*

≥35 kg and at least 10 years old:

- TDF + 3TC + EFV

If a child is on first line ART and is diagnosed with TB, make the following temporary changes to the ART regimen:

- **If <3 years or <10 kg and already on NVP or LPV/r,** change to ABC + AZT + 3TC
  - If on LPV/r, once paediatric ritonavir solution is available, give: ABC + 3TC + LPV/RTV (super-boosted lopinavir).
  - *NB: two weeks after TB treatment is completed, change to the standard ART regimens*
- **If ≥ 3 years old and ≥10 kg and already on NVP**, change NVP to EFV
- **3 - 9 years old *and* 10 kg to <35 kg and already on LPV/r**, add ritonavir to achieve super-boosted lopinavir/ritonavir (LPV/RTV) or if not possible, give ABC + AZT + 3TC.
  - *NB: two weeks after TB treatment is completed, change to the standard ART regimens*
- **If ≥35kg and at least 10 years old and already on LPV/r,** add ritonavir to achieve super-boosted lopinavir/ritonavir (LPV/RTV) or change to TDF + AZT + 3TC
  - *NB: two weeks after TB treatment is completed, change to the standard ART regimens*
- **If a child is on second line ART and is diagnosed with TB**, make the following temporary changes to the ART regimen:
  - If already on 3 NRTIs + EFV: leave unchanged
  - If already on 3 NRTIs + NVP and ≥ 3 years old and ≥10 kg: change NVP to EFV
  - If already on any other regimen or <3 years old or <10 kg, consult an HIV specialist and consider discussing TB regimen change with CCRC (Clinical Case Review Committee)

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

NB: 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 ensure that they receive pyridoxine. The dose of pyridoxine is 12.5mg/day (1/2 tablet) for children 5-11 years old and 25mg/day for children ≥12 years old. This is an increase in dose compared to the previous guidelines.

3.7 Children with chronic Hepatitis B virus (HBV) and HIV co-infection

3.7.1. Background

The prevalence of chronic HBV among children with HIV throughout Namibia is not known however it is thought to be as high 8-9%. Children who are infected with HBV can clear the infection or can become chronically infected. The likelihood of chronic HBV infection, defined as persistence of HBsAg for at least 6 months, varies by the age at which the child is acutely infected. Chronic HBV develops in 90% of infants infected, 25-50% of 1-5 year olds and 6-10% of older children and adolescents.

Two antiretroviral medicines used in Namibia also treat HBV: lamivudine (3TC) and tenofovir (TDF). Studies in children show that giving 3TC as part of an ART regimen without TDF results in a 20% per year HBV mutation rate. Thus, giving "3TC monotherapy" for HBV can compromise future HBV treatment options However, there are challenges with giving tenofovir to young children.

There is little known about the long-term significance of potential side effects of tenofovir such as decreased bone mineralization and renal insufficiency, and hence routine use of tenofovir in children<10 years old and <35 kg is not recommended. However in children with HBV/HIV co-infection who need treatment for their HBV disease, the potential benefits of averting selection of HBV mutations may outweigh the potential risks of giving tenofovir together with lamivudine to these children. However, currently no paediatric formulations of tenofovir are available in Namibia because they have not yet been WHO pre-qualified. Once they become available tenofovir should be used in younger children (2-9 years old and <35 kg) with chronic HBV. Older children who weigh at least 35 kg already qualify for routine initiation on a tenofovir-containing regimen.

3.7.2 Diagnosis of chronic HBV in children

It is important to determine if a child who has one positive HBsAg result is actually chronically infected with HBV or if the infection is acute and will clear with time. A repeat HBsAg done 6 months after the first positive one will allow this distinction to be made. Therefore:

- **All children and adolescents with one HBsAg positive result should have a repeat HBsAg test done 6 months after the initial positive test.**

If the result of the 2nd HBsAg is non-reactive, it can be concluded that the child does not have chronic HBV infection.

However if the repeat test is positive, the child has chronic HBV infection. Such children who are <35 kg in weight will initiate ART with ABC/3TC, and it is important to monitor ALT 6-monthly to identify active liver disease should it occur. In addition, they should have the NRTI backbone of their ART regimen changed to TDF/3TC as soon as they weigh at least 35 kg. Children who already weigh at least 35 kg should initiate ART with TDF/3TC/EFV.

3.8 Immune Reconstitution Inflammatory Syndrome (IRIS) in children

IRIS has been observed in children who have initiated ART, especially in 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 ART 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.

3.9 Monitoring in HIV-infected children, before and after ART initiation

3.9.1 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. In addition, HIV has been associated with nutritional disorders and impaired immune function. HIV-infected children require more energy and nutrients than non-infected children. 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).

3.9.1.1 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 in the patient care booklet 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.

3.9.1.2 Neurological and cognitive development

HIV can interfere with the normal neurological and cognitive development in a child. Therefore it is very important that for children < 5 years old, achievement of developmental milestones be monitored and recorded in the 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., Referral to a physiotherapist / occupational therapist (physical delay) or a social worker (cognitive delay) should be done as appropriate. All children <15 years old are eligible for ART and developmental challenges are a further reason to expedite initiation of ART. Screening for normal neurological development need not take much time. A tool such as the one shown in Table 3.8 below offers a quick screen for assessing achievement of developmental milestones.

Table 3.8: 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

3.9.1.3 Nutrient requirements of HIV-infected children

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

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.

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. Fruits and vegetables are important sources of vitamins and minerals and should be part of a children's diet. The deep colored varieties of vegetables contain abundant amounts of minerals and vitamins that are useful to the immune system. 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. Vitamins and minerals such vitamin A, C, E, selenium are important antioxidants in the body.

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. However the delay should be minimized.

- When complications are found during the assessment of acute malnutrition in an HIV-infected child, 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 child has stabilized on this treatment and has 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.

Nutrition Assessment, Counseling and Support

Nutrition assessment is an analysis of an individual's medical and diet history, laboratory values, and anthropometric measurements to identify nutritional risk or malnutrition and identify underlying causes so that appropriate nutrition intervention can be planned and initiated

Weight-for-height is an indicator for wasting. Children under 5 years of age with a z-score (SD) of <-2 are classified as malnourished (<-3 SD is severe malnutrition). For the same age group, a mid upper arm circumference of < 11.5cm is also categorized as severe malnutrition. Older children have different cut-offs for malnutrition. The Ministry of Health and Social services is implementing a nutrition programme at health facilities throughout the country. The nutrition assessment, counselling and support (NACS) is an approach designed to:

- Provide food and nutrition services as part of care and treatment on an outpatient basis, with strong links to community service
- Prescribe food to malnourished target individuals for a limited time, based on clearadmission and discharge criteria to improve nutrition and health outcomes

Health workers should encourage mothers and caregivers to routinely bring their children to the facility for assessment and counseled/educated using appropriate guidelines. Any child who is identified as malnourished should receive the therapeutic food products as per the national guidelines.

All children with severe malnutrition are at risk for a number of life-threatening problems and urgently require therapeutic feeding (WHO 2009). For the management of moderate and severe malnutrition in HIV positive children and adolescent, refer to Appendix 8

3.9.2 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.** Then determine how long it is until the next dose is due.

- 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 normalschedule
- 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 thenormal 6AM/6PM schedule.

3.9.3 Disclosure of HIV status

Disclosure of HIV status to children is challenging for parents/ caregivers and health care 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. When children reach 6 years old, they should be enrolled into specific activities that start the partial disclosure process and HCWs should begin discussions with the caregivers. The ultimate aim is that by the child's 10th birthday, he/she knows his/her HIV status, and that the child should be told in a safe and supportive way.

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 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. To guide this process, there is a list of 17 questions in the pediatric patient care booklet that should be answered to ensure that the most important issues are covered and resolved with caregivers.

Some caregivers are comfortable disclosing HIV status to their children, and HCWs 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 HCW 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 HCWsbuild 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 correctunderstanding and to detect any problems that may arise. Notes about these discussions should be recorded by the HCW in the HIV disclosure form included in the paediatric patient care booklet.

A booklet called “Why I take my medicines” is available in clinics in several local languages and should be used to help children understand, with increasing levels of complexity depicted in 5 chapters, why they need to take medicines every day and on time in order to stay healthy. Messages are positive, and the child’s understanding should be assessed and re-enforced at every visit. The main themes of the chapters are as follows:

- **Chapter 1**: Young children 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 HCW’s expectation is that if they continue taking their medicines correctly, they can achieve the life goals they set for themselves. This is re-inforced in this chapter by asking the child what he/she would like to do when he/she grows up.
- **Chapter 2**: Slightly older children usually understand the allegory introduced in this chapter of a “bad guy” who attacks “body soldiers” making them weak and fewer in number, such that they can no longer fight off infections and the child gets sick. 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.
- **Chapter 3**: This chapter re-enforces the importance of adherence to taking tablets, to taking them at the right time of day, to taking all of the prescribed tablets, and to remembering them even if traveling.
- **Chapter 4**: This chapterintroduces concepts of what can happen if one forgets to take medicines (the “bad guy” wakes up”) and of resistance to ARVs if the child forgets too often.
- **Chapter 5**: For the child who fully understands the allegory above, the next step is full disclosure and the introduction of adult terminology, referring tothe interactions between **HIV**, **antiretroviral medicines** and **CD4 cells**. This chapter serves as aguide to HCWs and caregivers for this full disclosure. Before using the word “HIV”, however, it is important to check with the caregiver(s) once again to ensure that they are ready for full HIV disclosure.

Following full HIV disclosure it is important to offer the child an appointment in 2 weeks to ensure that any unanswered questions or worries are resolved early.

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 care 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. (see section 3.8.4)

3.9.4 Adolescents - special concerns

WHO defines adolescents as children between 10-19 years of age.These includeadolescents who acquired HIV perinatally, from sexual activities, from injecting drug use or from use of unsafe injections (WHO 2013). Namibia developed National Guidelines on Adolescents Living with HIV in 2012, which outline the strategic guidelines for the provision of multi-sectoral services to ALHIV. To meet the objective of delivering comprehensive adolescent-focused clinical HIV services to ALHIV the following key components should be highlighted:

- **Disclosure of HIV status to children living with HIV:** It is important to disclose HIV status to adolescents living with HIV (ALHIV) so that they fully understand and engage in their care. Parents and guardians of adolescents should seek support from the clinical team to inform the adolescents of their HIV infection and why they are taking treatment for HIV and or prophylaxis for opportunistic infections. (see section 3.8.3) When an adolescent indicates their intention to disclose their HIV status to family members, friends or significant others, they should be empowered to do so safely (MoHSS 2012a:30). Therefore, health care providers should purposefully support facility-based and home disclosure. Early disclosure will facilitate access to a wide range of care and support services, including sexual reproductive health and rights (MoHSS 2012a:29)
- **Transition to Adulthood:** Adolescents are in transition from childhood to adulthood and it is a difficult period even for those without HIV. They experience physical as well cognitive changes and maturations. Changes in their bodies may affect their emotions and behavior. HIV is an added burden and adolescents who have previously adhered to therapy from childhood often start to rebel against taking their medicines in their adolescence. Health Care workers should anticipate this and discuss it with caregivers as part of the treatment plan. It is also a critical time for the clinical team to prepare the adolescent to transition from pediatric to adult care and services. They should support the adolescents as they seek independence and decision making in their care. See Table 3.9.

Table3.9: Adolescent Transition implementation goals per age group

Age Group	Transition Goals
10 -14 years	**Phase 1 Goals** • Full HIV disclosure • Understand disease process • Understand disease markers • Understand prevention measures
15-19 Years	**Phase 2 Goals** • Medication independence • Maintain >95% adherence • CD4 >350 • Positive living • Undetectable viral load • Identify and enroll in adult ART clinic

Source: (MoHSS 2012a: National Guideline for ALHIV, Annexure C: Adolescent Transition Implementation Algorithm, pg. 51)

Sexual Reproductive Health: Adolescents in HIV and ART care should be provided with age and developmentally appropriate sexual reproductive health services. Discuss with adolescent the advantages of delayed sexual debut.

For sexually active adolescents dual protection with a condom should also be discussed and safe sex with consistent condom use encouraged. It is important to provide individual family planning counseling and methods to prevent unintended pregnancy; where possible family planning commodities should be made available in the clinic where the adolescent is receiving ART. If applicable, partner testing and disclosure should be encouraged (MoHSS 2012a: 30). Providers should ask all sexually active adolescents about whether they have specific signs and symptoms of sexually transmitted infections (STIs), and should discuss the importance of prevention and treatment of STIs (MoHSS 2012a: 31).

Cervical Cancer prevention and screening. It is now known that cervical cancer is caused by infection with human papilloma virus (HPV) infection. WHO (2013) recommends HPV vaccination for girls between the ages of 9-13 years who are not yet sexually active as a primary cervical cancer prevention strategy. The HPV vaccination schedule is a 3 doses schedule with second dose administered 1-2 months after the first dose and third dose given 6 month after the second dose . The MoHSS is currently considering providing HPV vaccination in Namibia.

The risk of developing cervical cancer is higher in HIV-infected women compared with HIV-uninfected women. For this reason, although in general cervical cancer screening is not recommended before the age of 30, in sexually active women with HIV-infection, earlier screening is recommended. HIV-infected women should be screened at yearly intervals irrespective of their age. For adolescent girls, cervical cancer screening should be done 3 years after their sexual debut. (MoHSS 2012b:98). For additional information, see the Cervical Cancer page 97-101 of the National guideline for Family planning.

Retention and adherence: To promote better adherence and retention in care for this vulnerable age group, it helps to schedule more frequent visits if possible to allow more interactive discussion and counseling.

- Provide positive feedback to the adolescent for any success in adherence to the visit and/or to medications
- Ensure that disclosure is done and positive re-enforcement is 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:
    - Providing some group activities for the adolescent as they wait to see the HCWs
    - Grouping the adolescents to be seen in clinic on the same day of the week where it is feasible

Psychological support:

In the ART Clinic, space and time should be created for adolescents. Consider having adolescent-designated clinic days and a room where only adolescents are seen. HCWs should be trained to be adolescent friendly in their approach to adolescents. Provide some group activities for adolescents as they wait to see the HCWs. Start adolescent peer support groups and “teen clubs”. Teen-clubs are ideal for promoting knowledge transfer, skill building and sharing of experiences among peers. For more information on psychological support and “Teen Clubs” see MoHSS 2012a:p. 32 -34. During “Teen Club” sessions, facilitators should lead the group to talk about issues and needs of adolescents including topics such HIV treatment literacy, life skills, communication and negotiatios, adherence support, substance abuse etc.

The parents and caregivers of adolescents living with HIV require psychosocial support to be able to work together with the HCWs in providing expected guidance and support on key concerns facing adolescents. Provide health education and skills building to parents and emphasise their role during adolescent transitioning to adulthood. Promote bonding and better understanding of adolescent transition among parents. Similarly, knowledge and skills on sexual reproductive health can remove barriers surrounding cultural taboos and increase open dialogue among parents and caregivers. For more information on Guardian clubs see the national guidelines on ALHIV service provision (MoHSS 2012a, 34)

Re-inforce the need for Career planning: Treatment for HIV infection is lifelong and with good quality care, HIV becomes a chronic diseases that, when managed well, will allow the adolescent living with HIV to lead a productive life into adulthood. Discussions about future career goals should be part of clinical care and the transition plan. These could include referral to an appropriate department or office for counseling on career choices so that the ALHIV faces the future with hope and optimism, with the ability to reach their goals, realize their dreams, provide for their families and live productive lives.

3.9.5 Clinical assessment and monitoring

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

Baseline clinical assessment following confirmation of HIV infection includes:

1. Weight, length or height, and head circumference (for <3 year olds). Plot on growth appropriate growth charts in the Paediatric Patient Care Booklet
2. Assessment of developmental milestones achieved (for <5 year olds) or school performance for school-aged children – record in the Paediatric Patient Care Booklet
3. WHO Clinical Staging
4. Identification of concomitant conditions (e.g., TB screening, other OIs, pregnancy in adolescent girls)
5. Screening for isoniazid preventive therapy (IPT) eligibility
6. Immunisation status
7. Nutritional status including assessment of quality and quantity of intake
8. Detailing of concomitant medications (e.g., cotrimoxazole, traditional medications)
9. For those eligible for ART (all < 15 years of age and older adolescents meeting the "adult" criteria), assessment of child's and caregiver's preparedness for therapy

Routine monitoring of children who are not yet on ART consists of:

1. Clinical evaluation and CD4 count and % every 6 months. ***NB: all children <15 years old are eligible for ART once confirmed HIV positive irrespective of clinical stage or CD4 count***
2. Weight, length or height, and head circumference (for <3 year olds). Plot on appropriate growth charts in the Paediatric Patient Care Booklet
3. Assessment of developmental milestones achieved (for <5 year olds) or school performance for school-aged children - record in the Paediatric Patient Care Booklet
4. WHO Clinical Staging
5. Identification of concomitant conditions (e.g., TB screening, other OIs, pregnancy in adolescent girls)
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 caregiver's preparedness for therapy
11. Other laboratory tests as required or symptom-directed

Routine monitoring of children on ART includes:

1. Clinical evaluation every 3 months
2. Weight, length or height, and head circumference (for <3 year olds). Plot on appropriate growth charts in the Paediatric Patient Care Booklet
3. Assessment of developmental milestones achieved (for <5 year olds) or school performance for school-aged children - record in the Paediatric Patient Care Booklet
4. WHO clinical staging should be done at each visit using the standard WHO Clinical Staging of HIV in infants and children chart. Since the child is on ART, this staging is termed "T-stage" and it should recorded in the Patient Care Booklet as "T1, T2, T3 or T4" in the column "WHO Clinical Stage"
5. Identification of concomitant conditions, especially TB screening
6. Screening for isoniazid preventive therapy (IPT) eligibility
7. Nutritional status including assessment of quality and quantity of intake
8. Evaluation of adherence to ARV therapy and to cotrimoxazole and vitamins. Discuss adherence issues with the child and caregiver(s)

9. For children ≥6 years old, enroll in HIV disclosure activities and record at each visit on the appropriate form in the Paediatric Patient Care Booklet . Engage caregiver into discussions about disclosure until full HIV disclosure is achieved. (see section 3.8.3)
10. Discussion of symptoms and observation for signs of medicine toxicity or intolerance
11. Discussion of symptoms and observation for signs of treatment failure (e.g., poor growth progression, development ofneurological symptoms or poor development, development of new infections)
12. Laboratory monitoring as per Table 3.10
13. Appendix ? gives details of the laboratory monitoring required depending on the ART regimen the child is on

3.9.6 Laboratory monitoring

Table 3.10 below lists routine bioclinical monitoring tests that should be done at different phases of HIV management.

Table 3.10. Baseline and monitoring laboratory tests for children and adolescents prior to and after starting ART

Phase of HIV management	Tests	Frequency
At HIV diagnosis	CD4 HBsAg	Once Once. If positive, repeat after 6 months
Pre ART	CD4	<15 years old: not applicable, eligible for ART ≥15 years old : every 3 - 6 months until eligible for ART
ART initiation "baselines"	Hb CrCl Urine dipstick HIV DNA PCR ***repeat***	Once Once if initiating TDF Once if initiating TDF Once if <18 months old. ***Do not wait for result to start ART***
Treatment monitoring	VL CrCl Urine dipstick Hb	M 6 (then every 6 months) M1,3,6,12 (then every 12 months) if on TDF M1,3 (then every 3 months) if on TDF 2w, 6w, M3 if on AZT
HBsAg positive	ALT	2w, 6w, M3 (then every 6 months)
Suspected treatment failure	VL	Anytime after the first 6 months of ART provided non adherence and OIs excluded
Virological failure	1) CD4[2] 2) HIV Drug Resistance	1) Every episode of virologic failure 2) Children <10 years old who have been on LPV/r as part of 1st line with PMTCT NVP exposure in infancy At any age, before switching to 3rd line ART

[1] *the creatinine clearance calculation for adults is not applicable to children <18 years old. The equation (SCHWARTZ equation) which should be used to estimate creatinine clearance (CrCl) in children from 1 week – 18 years of age is shown in figure 3.4*

[2] *Check CD4 count to assess immunological status and inform clinical management (eg. assess for possible OIs)*

The Swartz equation shown in Figure 3.4 should be used to estimate creatinine clearance (CrCl) in children from 1 week – 18 years of age

Figure 3.4 Creatinine Clearance calculation for use in children <19 years old

SCHWARTZ equation

CrCl (ml/min/1.73m²) ≈[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 3.11 below gives normal GFR values for children and young adults:

Table 3.11. Normal GFR in children and young adults

Age (gender)	Mean GFR ± SD (ml/min/1.73m3
> 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

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

3.10 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.

3.11 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 children and adolescents. 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 Ab, 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 yet proven whether 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 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

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 ART:

If the source patient has been on ART 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 ART 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	TDF/FTC/EFV
Low risk exposure	offer	TDF plus 3TC
Intact skin Low risk fluids HIV- negative source	Do not offer	

4.1.5 Accompanying measures

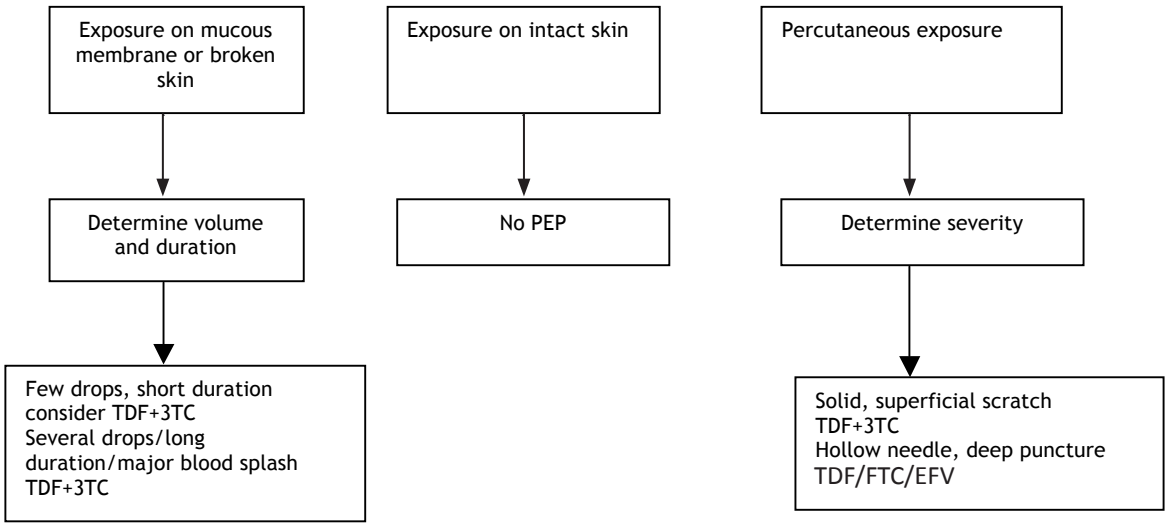
To ensure that the risk for occupational exposure is minimised and PEP is administered according to the guidelines, it is recommended that the following measures be taken:

- 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.

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

Step 2: Type of exposure – determine the type of exposure

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 FDC TDF+FTC+EFV 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 antibody 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/FTC/EFV 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.

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

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.

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.

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

4.2.4 PEP regimen after rape

The recommended antiretroviral regimen following rape is: TDF+FTC+EFV daily for 28 days.

If the survivor cannot tolerate efavirenz, lopinavir may be substituted for efavirenz.

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:

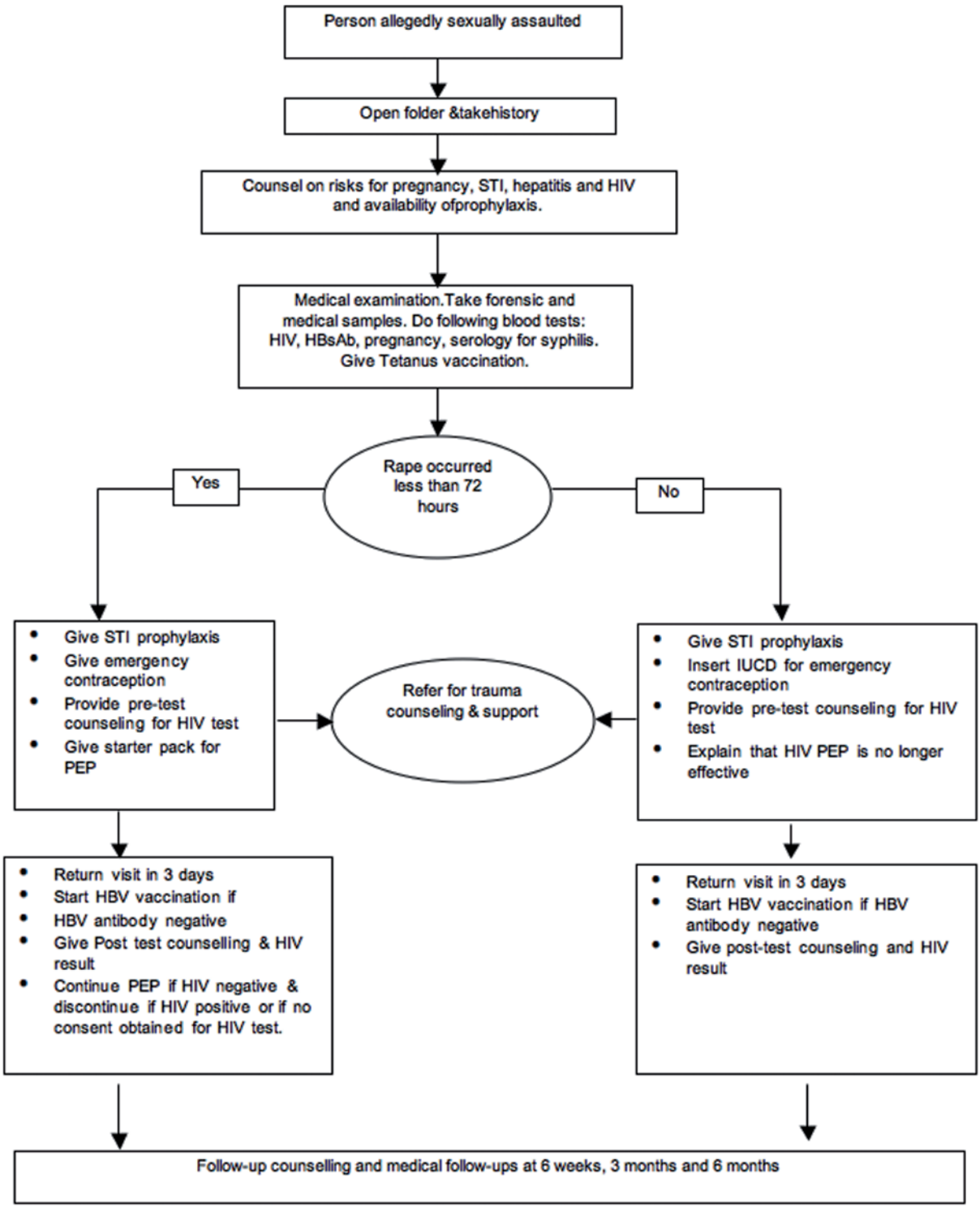
1. STI prophylaxis: presumptive prophylaxis should be given in the form of cefixime 400 mg or ceftriaxone 250 mg IM STAT plus metronidazole 2 gram STAT plus azithromycin 1g STAT .
2. Emergency contraception within 72 hours: norgestrel 0.5mg (500 mcg) and ethynyl oestradiol 0.05mg (50 mcg) (Ovral) given 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 should offer PEP , but counseling concerning correct condom use and risky behavior is essential. PEP regimen is the same as detailed above. For repeated accidental sexual exposure, counsel the client for PrEP (client to be on TDF/FTC for as long as he/she in on repeated exposure)
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 survivor



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
- Pneumocystispneumonia
- Recurrent severe bacterial pneumonia
- Chronicherpessimplexinfection(orolabial,genital,oranorectalofmorethanonemonth'sdurationorvisceralatanysite)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary tuberculosis
- Kaposi's sarcomasystem
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous 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 Asi*

APPENDIX 2. WHO CLINICAL STAGING OF HIV IN INFANTS AND CHILDREN (2007)

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	W 2	M1	W 6	M3	M6	M9	M12	M15 & every 3 months thereafter	M18 & Every 6 months thereafter	M24 & Every 12 months thereafter
TDF/[FTC or 3TC]/NVP		*CrCl* *Urine dipstick*		*CrCl* *Urine dipstick*	*CrCl* *Urine dipstick* *VL*	*Urine dipstick*	*CrCl* *Urine dipstick* *VL*	*Urine dipstick*	*VL if<18y*[1] *Urine dipstick* *3-monthly*	*CrCl* *VL* *Urine dipstick* *3-monthly*
TDF/[FTC or 3TC]/EFV		*CrCl* *Urine dipstick*		*CrCl* *Urine dipstick*	*CrCl* *Urine dipstick* *VL*	*Urine dipstick*	*CrCl* *Urine dipstick* *VL*	*Urine dipstick*	*VL if<18y*[1] *Urine dipstick* *3-monthly*	*CrCl* *VL* *Urine dipstick* *3-monthly*
AZT/3TC/NVP	*Hb*		*Hb*	*Hb*	*VL*		*VL*		*VL if<18y*[1]	*VL*
AZT/3TC/EFV	*Hb*		*Hb*	*Hb*	*VL*		*VL*		*VL if<18y*[1]	*VL*
TDF/[FTC or 3TC]/AZT/ LPV/r	*Hb*[2]	*CrCl* *Urine dipstick*	*Hb*[2]	*Hb*[2] *CrCl* *Urine dipstick*	*CrCl* *Urine dipstick* *VL*		*CrCl* *Urine dipstick* *VL*		*Urine dipstick* *3-monthly* *VL if<18y*[1]	*VL* *Urine dipstick* *3-monthly*
ABC/3TC/EFV					*VL*		*VL*		*VL if<18y*[1]	*VL*
ABC/3TC/LPV/r					*VL*		*VL*		*VL if<18y*[1]	*VL*
ABC/AZT/3TC/LPV/r	*Hb*[2]		*Hb*[2]	*Hb*[2]	*VL*		*VL*		*VL if<18y*[1]	*VL*
ABC/AZT/3TC/EFV	*Hb*[2]		*Hb*[2]	*Hb*[2]	*VL*		*VL*		*VL if<18y*[1]	*VL*

Notes: [1]Viral Load testing at M18 and 6 monthly thereafter only for children <18 years old
[2]Only do Hb if patient has NOT had AZT in first line

Any other Lab test can be requested as clinically deemed necessary

APPENDIX 4. SUMMARY INFORMATION ON ANTIRETROVIRAL FORMULATIONS FOR ADULTS

ARV	Formulation /Strength	Dose for adults*	Special Considerations	Adverse effects
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
Zidovudine (AZT)	Tablet : 300mg, 250mg, 100mg	300 mg bd	With or without food	Anaemia, neutropenia, Gastrointestinal intolerance, Headache, insomnia, myopathy Lactic acidosis with hepatic steatosis (rare)
Abacavir (ABC)	Tablet: 300mg	600 mg od (or 300 mg bd if part of an FDC)	With or without food	Hypersensitivity reaction (can be fatal) Fever, rash, fatigue Nausea, vomiting, anorexia Respiratory symptoms(sore throat, cough) Lactic acidosis with hepatic steatosis (rare)
Lamivudine (3TC)	Tablet : 150mg	150 mg bd (or 300 mg od if given with TDF or ABC)	With or without food	Minimal toxicity Lactic acidosis with hepatic steatosis (rare)
Emtricitabine (FTC)	Tablet: 200mg (as part of FDC)	200 mg od	With or without food	Headache, nausea, skin rash and discoloration Lactic acidosis with hepatic steatosis(rare)
Stavudine (d4T)	Capsule: 30mg, 20mg, 15mg	30 mg bd	With or without food	Pancreatitis Peripheral neuropathy Lactic acidosis with hepatic steatosis (rare) Lipoatrophy
Didanosine (ddI)	Capsule (delayed release): 250mg, 400mg	<60 kg:125 mg bd or 250 mg od >60 kg: 200 mg bd or 400 mg od	Empty stomach (1/2h prior or 2 h after meals) doses reduced by half with TDF	Pancreatitis Peripheral neuropathy Nausea, diarrhoea Lactic acidosis with hepatic steatosis (rare)
Nucleotide Reverse Transcriptase Inhibitor (NtRTIs)				
Tenofovir (TDF)	Tablet: 300 mg (tenofovir disoproxil fumarate equivalent to 245 mg tenofovir disoproxil)	300 mg od	Take with food	Abdominal pain, anorexia, asthenia, diarrhoea, dizziness, dyspnoea, flatulence, headache, hypophosphatemia, lactic acidosis, nausea, pancreatitis, renal impairment, rash, vomiting, lactic acidosis with hepatic steatosis (rare)

ARV	Formulation /Strength	Dose for adults*	Special Considerations	Adverse effects
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Efavirenz (EFV)	Tablet: 600mg	600 mg od	With or without food; Bed time administration to avoid CNS symptoms	CNS Symptoms: dizziness, somnolence, insomnia, confusion, hallucinations, agitation Elevated transaminase levels Skin rash
Nevirapine (NVP)	Tablet 200 mg	200 mg od x 14 days, then 200 mg bd	With or without food	Skin rash, Stevens-Johnson Syndrome Elevated serum aminotransferase levels Hepatitis, life-threatening Hepatic toxicity
Etravirine (ETV)	Tablet: 200mg, 100mg	200 mg bd	Take with food	Skin rash, nausea, and diarrhoea, elevation in serum cholesterol, triglyceride, glucose, and hepatic transaminase levels.
Protease Inhibitors (PIs)				
Lopinavir + ritonavir (LPV/r)	Tablet (heat-stable): 200mg/50 mg	400 mg/100 mg bd	With food	GI intolerance, nausea, vomiting, elevated transaminase enzymes, hyperglycaemia, fat redistribution and lipid abnormalities
Ritonavir (RTV)	Capsule: 100 mg	Use only as booster PI	Take with food. High-fat snacks may reduce side effect	Gastrointestinal intolerance, nausea, vomiting, paraesthesia, hepatitis and pancreatitis, hyperglycaemia, fat redistribution and lipid abnormalities
Atazanavir (ATV)	Tablet: 300mg, 150mg	300mg od (must be used in combination with ritonavir 100mg)	Take with a light meal	Benign increase in bilirubin, prolonged QT (caution with conduction defects or drugs that do this), increased glucose, lipodystrophy, and increased haemorrhage in patients with haemophilia.
Darunavir (DRV)	Tablet: 600mg, 300mg,	600mg bd (must be used in combination with ritonavir 100mg)	Take with food	Nausea, diarrhoea, GI discomfort, headache, hypercholesterolemia, hypertriglyceridemia, lipodystrophy, increased glucose, transaminitis, inflammation of the nose and throat, and increased haemorrhage in patients with haemophilia.

ARV	Formulation /Strength	Dose for adults*	Special Considerations	Adverse effects
Integrase Inhibitor				
Raltegravir (RAL)	Tablet: 400mg	400 mg bd	Take with or without food	Diarrhoea, nausea, and headache. Use with caution in patients who are at increased risk for myopathy and rhabdomyolysis, which includes patients using other medications known to cause these conditions.
Fixed-Dose Combinations (FDC)				
Tenofovir + Lamivudine	FDC Tablet: TDF 300mg + 3TC 300mg	One tablet once daily	Refer to the corresponding single formulations above	
Tenofovir + Lamivudine + Efavirenz	FDC Tablet: TDF 300mg + 3TC 300mg + EFV 600mg	One tablet once daily		
Tenofovir + Emtricitabine	FDC Tablet: TDF 300mg + FTC 200mg	One tablet once daily		
Tenofovir + Emtricitabine + Efavirenz	FDC Tablet: TDF 300mg + FTC 200mg + EFV 600mg	One tablet once daily		
Zidovudine + Lamivudine	FDC Tablet: AZT 300mg + 3TC 150mg	One tablet twice daily		
Zidovudine + Lamivudine + Nevirapine	FDC Tablet: AZT 300mg + 3TC 150mg + NVP 200mg	One tablet twice daily		
Abacavir + Lamivudine + Zidovudine	FDC Tablet: ABC 300mg + 3TC 150mg + AZT 300mg	One tablet twice daily		
Stavudine + Lamivudine	FDC Tablet: d4T 30mg + 3TC 150mg	One tablet twice daily		
Stavudine + Lamivudine + Nevirapine	FDC Tablet: d4T 30mg + 3TC 150mg + NVP 200mg	One tablet twice daily		

**For appropriate paediatric formulations and dosage, please see table 3.5 in section 3.5.1*

APPENDIX 5: ANTIRETROVIRAL MEDICATION DOSAGE ADJUSTMENTS FOR RENAL AND HEPATIC FAILURE

Medicine Name	Form	Usual adult dose	Renal failure dosing				Liver failure dosing
			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
Didonasine (ddl)	25, 50, 100, 200mg tablets	<60kg: 250mg od	125mg od	125mg od	125mg od	125mg od	Usual dose Monitor for toxicity
	250mg, 400mg EC tablets	>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
Stavudine (D4T)	15, 20, 30, 40mg tablet	30mg BD*	15mg BD	15mg od	15mg od	15mg od	Usual dose
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)
Tenofovir (TDF)	300mg tablet	300mg od	300mg q48h	300 mg twice per week	300mg weekly	300mg weekly	Usual dose

APPENDIX 6. 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.
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.

Illness	Diet	Care and nutrition practices
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

APPENDIX 7. ALGORITHM FOR CLASSIFICATION OF MALNUTRITION IN ADULTS

ASSESS				
HISTORY	**LOOK FEEL AND MEASURE**	**CRITERIA**	**CLASSIFICATION**	**TREATMENT/CARE**
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?	**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).	**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	**Severe acute malnutrition (SAM) with complication** (fever, hypothermia, severe anaemia or dehydration, vomiting, bilateral oedema +++) **or no appetite**	**Inpatient treatment** **Refer to therapeutic feeding programmes**
			SAM with appetite and no complication	**Outpatient treatment** **Refer to therapeutic feeding programmes**
		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	**Moderate/mild malnutrition** **Significant weight loss**	**Refer to supplementary feeding programmes**
		Severe lung disease Active TB (first 3 months of treatment) Chronic diarrhoea Difficulty swallowing	**Signs of symptomatic disease**	
		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	**Normal**	**Nutrition counselling**

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**	**Inpatient treatment** **Refer to therapeutic feeding programmes**
			Without medical complication and with appetite Clinical wellness Alertness Caregiver able/willing to manage SAM at home and return to clinic every 14 days	**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

Adverse Medicine Reaction Reporting Form

Safety Yellow Form
Confidential

A) PATIENT INFORMATION

Patient initials or Hospital Reg. No.		DOB DD/MM/YYYY Age	Gender: ☐ Male ☐ Female	Weight (Kg):

B) ADVERSE EVENT INFORMATION

Type of report: **Initial:** ☐ **Follow up:** ☐ Write AMR ID number

DESCRIPTION OF ADVERSE EVENTS: Indicate provisional/final diagnosis of the adverse event	**Date event started**	**Date event stopped**	**Action taken:** (E.g. Medicine withdrawn/ substituted/Dose reduced /medical treatment etc...)

Seriousness
☐ Hospitalization ☐ Disability or permanent damage ☐ Congenital anomaly/ birth defect
☐ Life-threatening ☐ Other serious medical event ☐ Non serious adverse event

Relevant Laboratory tests	**Test date**	**Result**
	DD /MM / YYYY	

Patient Outcome
☐Recovered ☐ Recovered with sequela
☐Recovering ☐ Not recovered
☐Unknown

Died ☐Due to reaction ☐ Reaction maybe contributory
☐ unrelated to reaction Date of death DD /MM / YYYY

RELEVANT MEDICAL HISTORY: including pre-existing medical conditions (allergies, pregnancy, alcohol use, liver problems,..)

C) INFORMATION ON MEDICINES: ***For vaccines please indicate the batch number***

List Medicines Used in the Last 3 Months Tick Suspected Medicines Enter FDC as One Medicine		**Strength**	**Frequency**	**Route of Admin**	**Start date**	**Stop date or ongoing**	**Indication**
	☐						
	☐						
	☐						
	☐						
	☐						

D) REPORTER INFORMATION

Name (last, first)		Region		Email	
Profession		Telephone		Date	DD /MM / YYYY
Health Facility Name		Fax			

Please tick if you need ☐ *AMR forms* ☐ *Additional information*

Please note that submission of a report does not constitute an admission that medical personnel or the medicine caused or contributed to the event

Send/ Fax/Email to TIPC: Therapeutics Information and Pharmacovigilance Centre
Room 21, Basement Area, Windhoek Central Hospital. Windhoek.
Tel: 061 203 2312 Fax: 061 22 66 31/ 088 618 776. Email: info@tipc.com.na

APPENDIX 10. INTERACTIONS BETWEEN ARVS AND SOME COMMONLY USED MEDICINES

Note: All the drug interaction tables are derived from the University of Liverpool's drug interaction website: http://www.hiv-druginteractionslite.org

Antiepileptics	Antiretrovirals			Comments and/ recommendations
	EFV	NVP	LPV/r	
Carbamazepine				Carbamazepine effect not achieved (with NNRTIs) or side effects occur (with PIs). Use alternative that is sodium valproate or newer antiepileptics if available, which include lamotrigine, topiramate and gabapentin.
Phenytoin				Reduction in phenytoin plasma concentration. Coadministration not recommended. Use alternative that is sodium valproate or newer antiepileptics if available, The new one include lamotrigine, topiramate and gabapentin.
Phenobarbital				Reduction in phenobarbital concentration (with NNRTIs); reduction in LPV/r concentration. Use alternative. Use alternative that is sodium valproate or newer antiepileptics if available, The new one include lamotrigine, topiramate and gabapentin.
Valproate			or	Concentration of valproate not changed with NNRTI, but with PI valproate plasma concentration may reduce.
Lamotrigine			or	
Topiramate				
Gabapentin				

Symbols explained:

- ↓= plasma concentration of other medicine decreases: this means that the therapeutic effect may be lost;
- ↑ = plasma concentration of other medicine increases: this means that toxicity (side effect) may occur;
- ↔ = plasma concentration of other medicine not affected: this means that the clinical effect is not affected

Antidepressants	Antiretrovirals			Comments and/or recommendations
	EFV	NVP	LPV/r	
Amitryptyline				Monitor for amitriptyline side effects if given with LPV/r
Imipramine and Trimipramine				Monitor clinical effect of Imipramine with EFV and N VP, and side effects with LPV/r
Fluoxetine			or	Monitor for fluoxetine clinical and side effects if given with LPV/r
Citalopram			or	Monitor for clinical effect of citalopram if given with NNRTIs and both clinical and side effects if given with PIs
Paroxetine			or	Monitor for paroxetine clinical and side effects if given with LPV/r
Sertaline				Increase dose of sertaline based on clinical effect
Fluvoxamine				No clinically important interactions occur

Symbols explained:

- ↓= plasma concentration of other medicine decreases: this means that the therapeutic effect may be lost;
- ↑ = plasma concentration of other medicine increases: this means that toxicity (side effect) may occur;
- ↔ = plasma concentration of other medicine not affected: this means that the clinical effect is not affected

Anticoagulants	Antiretrovirals			Comments and/or recommendations
	EFV	NVP	LPV/r	
Warfarin	or	or		With NNRTIs warfarin effect may increase or decrease. Close monitoring of INR is advised and warfarin dose adjusted appropriately. If given with PIs, effect of warfarin may decrease. Monitor INR closely and increase the dose of warfarin appropriately

Symbols explained:

- ↓= plasma concentration of other medicine decreases: this means that the therapeutic effect may be lost;
- ↑ = plasma concentration of other medicine increases: this means that toxicity (side effect) may occur;
- ↔ = plasma concentration of other medicine not affected: this means that the clinical effect is not affected

Calcium channel blockers	Antiretrovirals			Comment and/or recommendation
	EFV	NVP	LPV/r	
Nifedipine	↓	↓	↑	When CCB are co-administered with NNRTIs, their concentration of CCBs in plasma may be reduced. Monitor clinical effect of CCBs and adjust the dose. When CCB are co-administered with LPV/r their concentration in plasma may be increased. Since CCBs and LPV/r both increase the PR interval, co-administration of these medicines must be done with caution
Verapamil	↓	↓	↑	
Diltiazem	↓	↓	↑	
Amlodipine	↓	↓	↑	
Felodipine	↓	↓	↑	

Symbols explained:

- ↓= plasma concentration of other medicine decreases: this means that the therapeutic effect may be lost;
- ↑ = plasma concentration of other medicine increases: this means that toxicity (side effect) may occur;

Rifamycins	Antiretrovirals			Comments and/or recommendations
	EFV	NVP	LPV/r	
Rifampicin	↔	↓	↓	Rifampicin should not be coadministered with NVP. When given with LPV/r the dose of the PI should be adjusted by one of the following options: • Double the dose of LPV/r: 800/200mg twice daily or • Increase the dose of ritonavir: 400/400mg of LPV/r twice daily.
Rifabutin	↓	↑	↑	When rifabutin is given with EFV its plasma concentration is reduced. Increase rifabutin dose by 50%. When given with NVP, rifabutin's concentration in plasma increases. Monitor the patient for rifabutin's adverse effects. When given with LPV/r rifabutin's plasma concentration is increased 3fold. The dose should be reduced by 75%

Symbols explained:

- ↓= plasma concentration of other medicine decreases: this means that the therapeutic effect may be lost;
- ↑ = plasma concentration of other medicine increases: this means that toxicity (side effect) may occur;
- ↔ = plasma concentration of other medicine not affected: this means that the clinical effect is not affected

Statins	**Antiretrovirals**			**Comments and/or recommendations**
	EFV	NVP	LPV/r	
Artovastatin	↓	↓	↑	When given with NNRTIs plasma concentration of artovastatin in plasma is reduced. Monitor clinical effect and adjust dose accordingly When co-administered with LPV/r plasma concentration is increased fivefold. Use alternative statin e.g. pravastatin or fluvastatin
Lovastatin and Simvastatin	↓	↓	↑	When given with NNRTIs the plasma concentration of these statins in plasma is reduced. Monitor clinical effect and adjust dose if necessary Coadministration of these statins with LPV/r is contraindicated. If coadministered, the concentration of lovastatin and simvastatin in plasma may increase significantlyleading to myopathy including rhabdomyolysis. ur.
Pravastatin	↓	↔	↔	Coadministration with EFV would reduce plasma concentration of pravastatin. Adjust dose based on clinical effect.
Fluvastatin	↑	↔	↔	Coadministration with EFV could result in an increase in plasma concentration of fluvastatin. Monitor toxicity of fluvastatin.

Symbols explained:

- ↓= plasma concentration of other medicine decreases: this means that the therapeutic effect may be lost;
- ↑ = plasma concentration of other medicine increases: this means that toxicity (side effect) may occur;
- ↔ = plasma concentration of other medicine not affected: this means that the clinical effect is not affected

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