



health

Department:
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CLINICAL GUIDELINES FOR THE MANAGEMENT OF HIV & AIDS IN ADULTS AND ADOLESCENTS

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South Africa 2010**



Table of Contents

Foreword.....	4
Abbreviations	5
Introduction	7
1. Standardised National Eligibility Criteria for Starting ART Regimens for Adults and Adolescents.....	8
2. Standardised National ART Regimens for Adults and Adolescents	9
3. Standardized National Monitoring for Adults and Adolescents with HIV.....	10
4. Standardised National ART and ARV Regimens for HIV Positive Pregnant Women and their Infants	11
5. Visit Scheduling for Adults with HIV	12
6. Recommended ART Regimens for Treatment-Naive Adults and Adolescents.....	14
6.1 First Line Therapy for Treatment-Naive Patients.....	14
a) Primary Treatment for ART-Naive Patients	14
6.2 Clinical and Laboratory Monitoring of Patients on First Line Treatment.....	16
Routine Monitoring	16
7. Adherence Support, Assessment and Monitoring	17
7.1 General Principles	17
8. What to Expect in the First Four Months of Therapy.....	19
9. When to Switch ART Regimens	20
9.1 Substituting Drugs in First Line Regimen	20
9.2 Treatment Failure	20
9.3 When to Switch from First Line to Second Line Therapy.....	21
9.4 Clinical and Laboratory Monitoring of Patients on Second Line Treatment.....	21
9.5 Management of Treatment Failure After Second Line Treatment	21
9.6 Management of Patients Previously Treated with Antiretroviral Therapy.....	22
9.7 Treatment Interruptions	22
10. Special Considerations	23
10.1 TB Patients	23
10.2 Hepatitis B Patients	24
10.3 Patients with anaemia	24
11. Expectations Regarding Care	25
12. Diagnosis and Management of Adverse Events	26
12.1 Principles of Managing Adverse Events	26
12.2 Important Adverse Events	26
13. Patient Management	28
13.1 Routine Patient Management.....	28
a) Patient weight.....	28

b) TB Screening, INH Prevention and TB Diagnosis	28
c) INH Prophylaxis	29
d) Clinical HIV Stage	29
e) Opportunistic Infection Diagnosis and Management.....	30
f) CD4 and Viral Load monitoring	30
g) Cotrimoxazole Prophylaxis.....	30
h) STI Screen.....	31
i) Pap Smear	31
j) Immunizations.....	31
k) Family Planning	31
l) Mental Health Screen.....	32
m) Adherence Check	32
n) Prevent HIV Transmission and Reinfection	32
o) Provide Support.....	32
Annexure A: Creatinine Clearance Tables	33
Annexure B: Patient Adherence Record.....	38
Annexure C: Adverse Drug Reaction Reporting Form	39
Annexure D: WHO Clinical Staging.....	41

Tables

Table 1: Eligibility Criteria	8
Table 2: National ART Regimens	9
Table 3: Standardized Monitoring (Pre-ART and on ART).....	10
Table 4: Maternal Regimens	11
Table 5: Infant Regimens	11
Table 6: Visits Checklist	13
Table 7: Primary Regimen for ART-Naïve Patients.....	14
Table 8: Containdications and Special Considerations	14
Table 9: Contraindications and Special Recommendations for Those Patients on Treatment.....	16
Table 10: Monitoring Tests	16
Table 11: Viral Load Monitoring and Recommended Responses.....	20
Table 12: Recommended Second Line Treatment for Patients Failing First Line Regimen	21
Table 13: Contraindications and Special Recommendations	21
Table 14: Rotoutine Monitoring Tests for All HIV Positive Initiating/On Second Line Treatment.....	21
Table 15: Common Shared Side-Effects of TB and ART	24
Table 16: Important ART Adverse Reactions and Safety Monitoring	26

Foreword

It is with pleasure that I present the new guidelines for the management of HIV-infected adolescents and adults.

Government has adopted a new outcome-based approach to accelerate attainment of the objectives outlined in the MTSF (Medium-Term Strategic Framework) 2009-2014; one of the objectives being to improve the health profile of all South Africans. The 10 point plan of the Health Sector is aimed at creating a well functioning health system capable of producing improved health outcomes. Priority 7 of the 10 point plan alludes to accelerated implementation of the HIV/AIDS plan and the reduction of mortality due to TB and associated diseases.

On the 1st December 2009, on World AIDS Day, the Honourable President Jacob Zuma announced the new key interventions to improve antiretroviral treatment (ART) access to special groups (all HIV-infected infants, and pregnant women and people with TB and HIV at CD4 less or equal to 350/mm³), in order to decrease the disease burden, to address maternal and child mortality and to improve life expectancy.

This document serves as a new guidance to health practitioners with regard to the comprehensive management of HIV infected adults and adolescents. The new ART regimens are described as well as laboratory and clinical monitoring at diagnosis, at initiation of antiretroviral treatment and whilst on treatment. It prioritizes integration of HIV with TB, maternal and child health (MCH), sexual and reproductive health (SRH), scaling up of TB preventive therapy (IPT), sexually transmitted infections (STI) and access to contraceptives. Furthermore all HIV positive multi/extensive drug resistant TB (MDR/XDR-TB) patients will commence ART regardless of CD4 count.

The many comments, additions and overall involvement from internal and external stakeholders is commended and has contributed to the excellence of the guidelines. I would like to thank them all for the development of these guidelines despite their busy schedules.

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MINISTER OF HEALTH
DATE:

Abbreviations

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired immune deficiency syndrome
ALT	Alanine Transaminases
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Zidovudine
BCG	Bacille Calmette Guerin (TB vaccine)
Bd	Twice-daily
BMI	Body mass index
CD4	CD4 cell or T4 'helper' lymphocyte
Cr	Creatinine
CSF	Cerebrospinal fluid
CPT	Cotrimoxazole preventive therapy
ddI	Didanosine
d4T	Stavudine
DOT	Directly observed treatment
E	Ethambutol
EFV	Efavirenz
ELISA (HIV)	Enzyme-linked immunosorbent assay (A type of HIV antibody laboratory test)
EPTB	Extrapulmonary tuberculosis
FBC	Full blood count
FTC	Emtricitabine
GFR	Glomerular filtration rate
GIT	Gastrointestinal tract
Hb	Haemoglobin
HBc	Hepatitis B core
HCT	HIV counselling and testing
HDL	High density lipoproteins
HepBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
INH	Isoniazid
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
LDH	Lactose dehydrogenase
LFT	Liver function tests
LOW	Loss of weight
LPV/r	Lopinavir/Ritonavir
MCC	Medicines Control Council
MCH	Maternal and child health
MC&S	Microscopy, culture and sensitivity
MDR-TB	Multi-drug resistant tuberculosis
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine

Od	Once daily
OHL	Oral hairy leukoplakia
OI	Opportunistic infection
P24	HIV antigen test
PAP smear	Papanicolaou test
PCR	Polymerase chain reaction (a laboratory HIV detection test)
PEP	Post-exposure prophylaxis
PHC	Primary health care
PI	Protease inhibitor
PMTCT	Prevention of mother to child transmission
PPD	Purified protein derivative
PTB	Pulmonary tuberculosis
PLWHA	Person living with HIV/AIDS
QID	6 hourly
R	Rifampicin
RBC	Red blood count
S	Streptomycin
SANAC	South African National AIDS Council
SRH	Sexual and reproductive health
STI	Sexually transmitted infections
TMP-SMX	Trimethoprim/sulphamethoxazole – also known as cotrimoxazole
TB	Tuberculosis
TBM	Tuberculous meningitis
TDF	Tenofovir
TID	8 hourly – 3 times a day
VAS	Visual analog scale
VL	Viral load (HIV)
WBC	White blood count
WHO	World Health Organization
XDR-TB	Extensively drug resistant Tuberculosis
Z	Pyrazinamide
ZAP	Zoster-associated pain

Introduction

These guidelines complement existing HIV/AIDS and TB management guidelines, and are the result of extensive consultation through the SANAC Treatment Technical Task Team. The guidelines aim to achieve the following:

Goals of the Programme

- Achieve the best health outcomes in the most cost-efficient manner;
- Implement nurse-initiated treatment;
- Decentralise service delivery to primary health care (PHC) facilities;
- Integrate services for HIV, TB, maternal and child health (including prevention of mother to child transmission), sexual and reproductive health, and wellness;
- Diagnose HIV earlier;
- Prevent HIV disease progression;
- Avert AIDS-related deaths;
- Retain patients on lifelong therapy;
- Prevent new infections among children, adolescents, and adults; and
- Mitigate the impact of HIV/AIDS.

Objectives

- To contribute to strengthening of the public and private health sectors' capacity to deliver high quality integrated health and wellness services;
- To ensure timely initiation of antiretroviral drugs (ARVs) for treatment and prevention according to the Presidential mandates;
- To minimize unnecessary drug toxicities.

Specific Objectives

- To prioritise ARVs for:
 - Patients with CD4 counts < 200 cells/mm³ or with severe HIV disease irrespective of CD4
 - Patients co-infected with TB/HIV
 - Pregnant women
- To ensure access to ART within 2 weeks in pregnant women, those with low CD4 counts, very ill patients, and those with MDR-TB or extensively drug resistant TB (XDR-TB);
- To standardise first and second line therapy for children, adolescents, and adults in the public and private sector;
- To reduce the use of Stavudine;
- To expand the use of fixed-dose and co-packaged formulations;
- To enable nurses to initiate ARVs for treatment and prevention;
- To enable PHC facilities to initiate, manage, monitor and refer patients.

1. Standardised National Eligibility Criteria for Starting ART Regimens for Adults and Adolescents

Table 1: Eligibility Criteria

Eligible to Start ART
CD4 count ≤ 200 cells/mm ³ irrespective of clinical stage <p style="text-align: center;">OR</p> CD4 count ≤ 350 cells/mm ³ <ul style="list-style-type: none"> ○ In patients with TB/HIV ○ Pregnant women <p style="text-align: center;">OR</p> WHO stage IV irrespective of CD4 count <p style="text-align: center;">OR</p> MDR/XDR-TB irrespective of CD4
Require Fast-Track* (i.e. ART initiation within 2 weeks of being eligible)
Pregnant women eligible for lifelong ART <p style="text-align: center;">OR</p> Patients with very low CD4 (<100 200 cells/mm ³) <p style="text-align: center;">OR</p> Stage 4, CD4 count not yet available <p style="text-align: center;">OR</p> MDR/XDR-TB
Not Yet Eligible for ART
<ul style="list-style-type: none"> • Transfer to a wellness programme for regular follow up and repeat clinical assessment/CD4 testing 6-monthly. • Advice on how to avoid HIV transmission to sexual partners and children • Initiate INH prophylaxis if asymptomatic for TB • Contraceptive advice and Pap smear

* All other patients should receive ART within 2 months of clinical staging event or qualifying CD4 count

2. Standardised National ART Regimens for Adults and Adolescents

Table 2: National ART Regimens

1st Line		
All new patients needing treatment	TDF + 3TC/FTC + EFV/NVP	For TB co-infection EFV is preferred. For pregnant women or women of child bearing age, not on reliable contraception, NVP is preferred.
Currently on d4T-based regimen with no side-effects	d4T + 3TC + EFV/NVP	Remain on d4T if well tolerated. Early switch with any toxicity. Substitute TDF if at high risk of toxicity (high BMI, older, female, TB treatment)
Contraindication to TDF: renal disease	AZT+ 3TC +EFV/NVP	
2nd Line		
Failing on a d4T or AZT-based 1 st line regimen	TDF + 3TC/FTC + LPV/r	Virological failure must be followed by intensive adherence management, as resuppression is often possible. If repeat VL remains >1000 in 3 months despite adherence intervention, switch.
Failing on a TDF-based 1 st line regimen	AZT + 3TC + LPV/r	Virological failure must be followed by intensive adherence management, as resuppression is often possible. If repeat VL remains >1000 in 3 months despite adherence intervention, switch.
Salvage Therapy		
Failing any 2 nd line regimen	Specialist referral	Virological failure on protease inhibitors is almost always due to non-adherence. Intensively exploring and addressing issues relating to causes of non-adherence will most often lead to resuppression. If VL remains high, refer where possible, but <u>maintain</u> on failing regimen.

3. Standardized National Monitoring for Adults and Adolescents with HIV

Table 3: Standardized Monitoring (Pre-ART and on ART)

At Initial Diagnosis of HIV	Purpose
Check HIV result	Ensure that the national testing algorithm has been followed
Clinical staging if HIV positive	To assess eligibility for ART; To assess eligibility for fast-tracking
Ask if pregnant or planning to conceive	To identify women who need ART or ARV for PMTCT (see section 6)
Screen for TB symptoms	To identify TB/HIV co-infected
CD4 count	To identify eligibility for ART or ARVs if pregnant
Hb or FBC if available	To detect anaemia

At Routine Follow-Up Visits	Purpose
Check that CD4 has been done in the last 6 months	To see if they have become eligible for ART
WHO clinical staging	To see if they have become eligible for ART
Screen for TB symptoms	To identify TB/HIV co-infection

If Eligible for ART	Purpose
Serum creatinine and clearance if starting on a TDF-based regimen	Refer urgently if estimated creatinine clearance is less than 50; if referral not available, start AZT/3TC/EFV (or NVP), but dose adjust AZT and 3TC
ALT if starting on a NVP-based regimen	If ALT raised >100, avoid NVP if possible; if no alternative, closely monitor the patient

Only patients who have a calculated creatinine clearance greater than 50 should receive Tenofovir. While the serum creatinine gives an indication of renal function patients can have significantly reduced renal function with a serum creatinine in the high normal range. This is particularly the case in older people and those with low body weight where the serum creatinine is a poor indication of renal function.

It is essential to calculate the creatinine clearance in all patients with:

Age > 50 years

Weight < 50kg

Serum creatinine > 100

In all other patients where serum creatinine is < 100 the calculated creatinine is likely to be > 50 and they can safely start Tenofovir.

Creatinine may be elevated in acute illness, and repeat measurement when the patient is recovered may give a better reflection of clearance.

See Annexure A for the creatinine clearance tables.

4. Standardised National ART and ARV Regimens for HIV Positive Pregnant Women and their Infants

Table 4: Maternal Regimens

Woman	Regimen	Comment
Eligible for lifelong ART (i.e. CD4 \leq 350 or WHO clinical stage 3 or 4)	TDF + 3TC/FTC + NVP	Start lifelong ART within 2 weeks
Currently on lifelong ART	Continue ART	Substitute EFV with NVP if in first 12 weeks of pregnancy
Contraindication to TDF (renal disease)	AZT+ 3TC + NVP	
Not eligible for ART i.e. CD4 > 350 and WHO stage 1 or 2	AZT from 14 weeks sdNVP + AZT 3hrly in labour TDF + FTC single dose (stat) after delivery	
Unbooked and presents in labour	sdNVP + AZT 3hrly in labour TDF + FTC single dose after delivery	Assess maternal ART eligibility before discharge

* See the PMTCT Guidelines for full diagnosis and treatment of mother and infant, including breastfeeding options

Table 5: Infant Regimens

Infant	Regimen	Comment
Mother on lifelong ART	NVP at birth and then daily for 6 weeks irrespective of infant feeding choice	
Mother on PMTCT regimen	NVP at birth and then daily for 6 weeks continued as long as any breastfeeding	If formula fed baby can stop NVP at 6 weeks
Mother did not get any ARV before or during delivery	NVP as soon as possible and daily for at least 6 weeks continued as long as any breastfeeding	Assess ART eligibility for the mother within 2 weeks
Unknown maternal status because orphaned or abandoned	Give NVP immediately* Test infant with rapid HIV test. If positive continue NVP for 6 weeks. If negative discontinue NVP	Follow-up 6 week HIV DNA PCR

* If rapid HIV test can be done within 2 hours, then wait for HIV result before commencing NVP

5. Visit Scheduling for Adults with HIV

First Visit

- Screen:
 - Complete medical history, with specific TB symptom screening;
 - Physical exam including documenting height, weight, body mass index (BMI, weight in kg/height in cm squared), blood pressure, temperature, respiratory rate and heart rate;
 - Establish clinical stage
- Conduct laboratory tests and screenings (*see Table 3*);
- Perform a Pap smear for all women if not done in the last twelve months;
- Identify and treat any opportunistic infection;
- Start Cotrimoxazole if indicated;
- Promote adherence;
 - Do a basic psychosocial assessment to document social issues and current psychological state, focusing on factors that impact on adherence
 - Discuss issues around the need for treatment, the rationale for adherence and strategies to overcome barriers to adherence
- Schedule dates for patient to return for further clinical assessment and ongoing adherence counseling, training and education, and possible ART initiation.

Subsequent Visits

- Physical exam
- Clinical stage
- Evaluate psychosocial support
- Evaluate laboratory results (*see Table 10*)
- Information and education session
- Adherence check if on Cotrimoxazole and/or INH
- Initiate ART if patient fulfills the criteria and is assessed as ready
- Initiate INH if no symptoms of TB and not on ART

ART Commencement Visit

- Multidisciplinary team should reassess ART readiness criteria i.e.:
 - Patient's understanding of:
 - Their HIV status
 - The need for ART
 - Importance of adherence and the link to treatment outcomes, specifically VL suppression
 - Commitment to scheduled visits

- Absence of severe medical contraindication (active disease that is not stabilised, including active substance abuse or severe depression)
- Do a physical examination
- Document clinical stage
- Review outstanding laboratory investigations
- Initiate recommended ART regimen
- Dispense ART, including:
 - Detailed description and dosing of the antiretroviral drugs
 - Ensure that dosing instructions are clearly written on the container

Avoid starting Cotrimoxazole and ART concurrently; rash may complicate either, and it can be difficult to work out which is the offending drug. Cotrimoxazole ideally should be started during the ART preparation phase, but should never delay ART; can usually be safely deferred until ART is established.

Table 6: Visits Checklist

Visits Checklist		
First Visit	Subsequent Visit	ART Commencement Visit
<ul style="list-style-type: none"> ● Confirm eligibility criteria ● Complete medical history ● Physical exam ● Laboratory tests ● Screen for TB ● Check on need for Pap smear ● Identify & treat OIs ● Promote adherence ● Schedule return visit ● Start Cotrimoxazole or INH as clinically indicated 	<ul style="list-style-type: none"> ● Physical exam ● Evaluate psychosocial support ● Identify need for lab tests ● Evaluate laboratory results ● Promote PMTCT or contraception ● Information and education session ● Initiate ART as per next column, if eligible 	<ul style="list-style-type: none"> ● Reassess ART readiness ● Conduct a physical examination ● Review laboratory investigations ● Prescribe ART regimen based on laboratory results ● Dispense ART

6. Recommended ART Regimens for Treatment-Naive Adults and Adolescents

6.1 First Line Therapy for Treatment-Naive Patients

Standard antiretroviral therapy (ART) consists of the use of at least three antiretroviral (ARV) drugs to maximally suppress HIV and stop the progression of HIV disease. Treatment-naive patients should be initiated on triple therapy, which consists of one non-nucleoside reverse transcriptase inhibitor (NNRTI) (e.g. Nevirapine or Efavirenz) and two nucleoside reverse transcriptase inhibitors (NRTI) in combination (e.g. Tenofovir and Lamivudine/Emtricitabine).

Use fixed-dose combinations (FDCs) wherever possible to make adherence easier for the patient and reduce complexity of prescribing and dispensing.

a) Primary Treatment for ART-Naive Patients

The primary treatment regimen should be prescribed to all patients unless there is a contraindication. Substitutions for well known contraindications are described below.

Table 7: Primary Regimen for ART-Naive Patients

Primary Regimen for ART-Naive Patients
Tenofovir (TDF) 300mg daily AND Lamivudine (3TC) 300mg daily or 150mg 12 hourly (Emtricitabine, FTC, may in future replace 3TC) AND Efavirenz (EFV) 600 mg at night (or 400 mg if <40 kg) OR Nevirapine (NVP) 200 mg daily for the first 2 weeks, increasing to 200 mg BD if no hypersensitivity reaction

Table 8: Contraindications and Special Considerations

Contraindication	Contraindicated ARV Drug	Replacement Drug
If creatinine clearance is <50ml/min	Tenofovir	AZT
Patients on psychoactive drugs (except for Tryptanol for peripheral neuropathy)	Efavirenz	NVP
Pregnant women or women desiring pregnancy	Efavirenz	NVP
ALT elevation >100	Nevirapine	Consider using EFV. Identify cause, check hep B status (may require referral); ensuring patient is aware of hepatotoxicity symptoms, and monitoring LFTs is essential

Only patients who have a calculated creatinine clearance greater than 50 should receive Tenofovir. While the serum creatinine gives an indication of renal function patients can have significantly reduced renal function with a serum creatinine in the high normal range. This is particularly the case in older people and those with low body weight where the serum creatinine is a poor indication of renal function.

It is essential to calculate the creatinine clearance in all patients with:

- Age >50 years
- Weight <50kg
- Serum creatinine >100

In all other patients where serum creatinine is <100 the calculated creatinine is likely to be >50 and they can safely start Tenofovir.

Creatinine may be elevated in acute illness, and repeat measurement when the patient is recovered may give a better reflection of clearance.

See Annexure A for the creatinine clearance tables.

Note: Patients on NVP must be seen two weeks after initiation of ART, in addition to their regular schedule, to monitor:

- NVP dosing: NVP 200mg daily, 200mg BD after the first 2 weeks (if patient already started on Efavirenz, can switch immediately to 200 mg NVP BD)
- NVP reactions may be more common at higher baseline CD4 counts, especially in women with CD4>200 cells/ul, or men with CD4 counts>400cells/ul. Careful weighing of the risk or benefit is required when initiating NVP at this level.
- Adverse events: severe NVP related side-effects occur in the first 3 months of therapy, especially in the first few weeks, and can be fatal; all patients should be warned to return to clinic immediately if they develop a rash, any significant muco-cutaneous reactions, fever, jaundice or abdominal pain; patients with severe symptoms or more than two of the above, require immediate hospitalisation, investigation and monitoring. Interrupt ART in these cases.
- Monitor ALT levels according to symptoms; check ALT in all cases of rash, as concomitant hepatotoxicity is common.
- Ensure correct dosing change at 2 weeks. Do not increase the dose to 200 mg BD in the presence of a rash. Delay increase until the rash stabilises. If it does not resolve within a week or worsens, change to alternative drug e.g. EFV.
- While side-effects in the first three months can be severe, long-term Nevirapine is very safe. Any patient started on Nevirapine with no side-effects should not be changed to another drug unless virological failure occurs.

Table 9: Contraindications and Special Recommendations for Those Patients on Treatment

Contraindication	Contraindicated Drug	Replacement Drug
BMI >28 (weight in kg/height in metres squared)	Stavudine	TDF
Patients with symptoms of pre-existing neuropathy	Stavudine	TDF
Previous history of severe d4T toxicity (lactic acidosis, significant lipoatrophy)	Stavudine	TDF
Patients with a positive hepBsAg screen	All regimens NOT containing TDF/3TC (or FTC)	TDF with 3TC (or FTC)

Example of BMI calculation: Patient is 1.86 m tall and weighs 88kg: $88/1.86^2 = 25.4$

6.2 Clinical and Laboratory Monitoring of Patients on First Line Treatment

Routine Monitoring

See Annexure A for the creatinine clearance tables.

Table 10: Monitoring Tests

On ART	Purpose
Clinical stage	To monitor response to ART
CD4 at month 6, 1 year on ART and then every 12 months	To monitor response to ART
VL at month 6, 1 year on ART and then every 12 months	To monitor response to ART To identify problems with adherence
ALT if on NVP and develops rash or symptoms of hepatitis	To identify NVP toxicity
FBC at month 1, 2, 3 and 6 if on AZT	To identify AZT toxicity
Creatinine clearance at month 3 and 6 then every 12 months if on TDF	To identify TDF toxicity
Fasting cholesterol and triglycerides at month 3 if on LPV/r	To identify LPV/r toxicity

7. Adherence Support, Assessment and Monitoring

Patients who are supported in their adherence efforts are much more likely to maintain VLs that are undetectable. Explaining the link between VL suppression and clinical outcome, and adherence, allows patients to identify obstacles to successful adherence.

See Annexure B for the patient adherence record.

7.1 General Principles

- Monitor and offer ongoing support of adherence. Be supportive and non-judgmental to encourage patient honesty
- Provide ongoing education to patients on their disease, including any new diagnoses, unexplained symptoms or opportunistic infections
- Reassure on the transient nature of nausea and vomiting, if a patient experiences these at treatment initiation
- Address adverse events, interim illness, issues around stigma and disclosure
- Treat depression and substance abuse
- Identify food insecurity and actively address this through government support programmes
- Ensure communication between clinic visits and between referral points
- Ensure that interim management is available during holidays or other absences; discuss absences with patient
- If there is sub-optimal adherence, provide extra support:
 - Recommend more visits with more frequent adherence checks
 - Enlist support of family/friends/ partners/ support group members/community adherence support workers
 - Increase home visits if possible
 - Use reminders and reinforce with adherence tools
 - Actively address food security

7.2 Issues Which Impact Adherence

Issues which impact adherence can be personal, and/or environmental.

Personal:

- Internalized stigma; external discrimination
- Denial of diagnosis
- Unresolved grief reaction
- Lack of disclosure, guilt
- Alcohol and other substance abuse/addiction
- Mental illness
- Dementia

Environmental:

- Pill burden and side-effects
- Income and food insecurity – underlying starvation
- Negative staff attitudes
- Lack of training of staff; perceived lack of caring by health facility and staff
- Shift work; time off work to attend appointments

7.3 Strategies to Promote Adherence

- The whole clinic team needs to support adherence at all points of intervention.
- Adherence counsellors (where possible, patient advocates; community health care workers, treatment supporters) need to:
 - Spend time with the patient and explain the disease, the goals of therapy and why the need for adherence that ensures virological suppression as often as it is needed
 - Consider monitoring of medications such as co-trimoxazole prior to ART initiation; this should, however, never delay ART
 - Negotiate a treatment plan that the patient can understand and to which he/she commits
 - Explain to patients how to avoid adverse drug-drug interactions. Herbs and other over the counter preparation can lead to renal and liver toxicity, complicating the clinical picture of adverse events, and may have unknown drug interactions affecting antiretroviral drug levels. The patient should understand the the possible consequences of unknown content and the danger of over-the-counter drugs and traditional medicines.
- Arrange home visit if available to be undertaken by the nominated community care giver, or trained home-based carer or other health care worker to facilitate:
 - Access to drug and alcohol counseling
 - Social welfare for grant access
 - Emergency relief for nutritional support
 - Support with disclosure
- Encourage attendance and participating in a support group. These should be ideally run by community members but might need to be supported by the clinic staff or adherence/therapeutic counselors or social workers.
- Missed appointments for medicine pick-ups are a powerful predictor of poor adherence, and should trigger immediate questions about issues that may affect attendance and adherence.
- Pill counts can be used to calculate pill usage.
- Reinforce the use of adherence tools e.g. pillboxes and/or daily dosing diary.
- Consider using a ‘treatment buddy’ or even directly observed therapy for an agreed period.
- Use recall of missed pills to assess non-adherence

8. What to Expect in the First Four Months of Therapy

Viral Load

- Undetectable at 6 months

Early ARV Side-Effects

- Common symptoms include gastrointestinal and flu-like symptoms, headache, dizziness, vivid dreams, rash, and hepatitis.

Immune Reconstitution Inflammatory Syndrome (IRIS)

General considerations

- IRIS occurs when improving immune function unmasks a previously occult opportunistic infection which subsequently presents with an unusually aggressive inflammatory presentation, or causes paradoxical deterioration of an existing opportunistic disease.
- Patients with advanced HIV disease, particularly those with a CD4 count <100 cells mm^3 , may become ill with an immune reconstitution inflammatory syndrome (IRIS) usually during the first 3 months of ART.
- Most cases can be managed as an outpatient, with disease-specific therapies and anti-inflammatories. Very ill or complex patients may need to be referred for advice regarding investigation and management.
- Tuberculosis is the commonest presenting IRIS reaction in South Africa. About a third of patients starting ART when on treatment for tuberculosis will experience recurrence of their TB symptoms/signs or worsening or new manifestations.
- The commonest of these presentation is with enlarging lymph nodes, often with extensive caseous necrosis. In addition, lung infiltrates or effusions may worsen. It is important to exclude multi-drug resistance in all these cases.
- MDR/XDR appears to be common in these patients, and TB culture of sputum, blood, lymph nodes and other affected tissue is essential.
- Opportunistic infections may also present in atypical ways during this phase of immune reconstitution.
- Rashes (including zoster, herpes, molluscum and others), cryptococcal meningitis, and hepatitis due to hepatitis B/C that occur in the first weeks and months after ART initiation are other manifestations of IRIS.

Note: IRIS is not indicative of drug failure or drug side-effects. It is not a reason to stop ART, or to change the antiretroviral regimen. However, careful counselling is needed to ensure that the patient understands this.

9. When to Switch ART Regimens

9.1 Substituting Drugs in First Line Regimen

Symptoms of drug toxicity and of immune recovery are common immediately after initiation of ART, but usually resolve spontaneously. However, if severe or not resolving symptoms are due to drug side-effects, drug substitutions can be made easily and safely. Substitution of an offending drug may be all that needs to be done to solve drug toxicity. The offending drug can be replaced with another drug from the same class that does not have the same adverse effect e.g. NVP for EFV (e.g. if patient experiences severe and non-resolving dizziness on Efavirenz).

9.2 Treatment Failure

In these guidelines, treatment switches are only made for virological failure (VL>1000 copies/ml on two occasions, despite intensive adherence counselling). Virological failure is almost always due to poor adherence, often due to poor attention by the clinician to drug toxicity, or where social factors have not been addressed.

Rapid attention to drug toxicity or social factors, with better adherence, may allow resuppression of the virus in many cases.

Patients who fail clinically (new OIs while on treatment) or immunologically (CD4 count dropping) without virological failure are unlikely to benefit from treatment switches, and require clinical assessment and appropriate investigation.

Adherence may be improved, but sufficient resistance has occurred for first line therapies to be ineffective. Patients who have experienced virological failure with good adherence may be changed to second line therapy.

Table 11: Viral Load Monitoring and Recommended Responses

Viral Load (VL)	Response
<400 copies/ml	<ul style="list-style-type: none">• 6-monthly viral load monitoring and routine adherence support
400-1000 ies/ml	<ul style="list-style-type: none">• Assess adherence carefully• Repeat viral load at 6 months
>1 000 copies/ml	<ul style="list-style-type: none">• Intense adherence assessment• Repeat viral load in 3 months; check hepatitis B status, if not done already*• If <1000, return to routine 6-monthly monitoring• If > 1000 and adherence issues addressed, switch to second line therapy after hepatitis B status checked

* Hepatitis B status is checked if there is consideration of stopping TDF; stopping TDF in patients with chronic hepatitis B may lead to a fatal hepatitis flare

9.3 When to Switch from First Line to Second Line Therapy

Consider switching patients on the drug regimen if the patient has experienced virological failure (viral load > 1000 copies/ml on two occasions) in spite of a good adherence record.

- Recommended second-line treatment for patients failing primary regimen (see table below)
- All patients being assessed for switching should have their hepatitis B status checked, especially if on TDF and 3TC/FTC. Withdrawal of these can be associated with fatal hepatitis in chronic hepatitis B (hepatitis B surface antigen positive) patients.

Table 12: Recommended Second Line Treatment for Patients Failing First Line Regimen

Second Line Treatment
Zidovudine (AZT) if previously on TDF; or TDF if previously on d4T or AZT AND Lamivudine (3TC) (or FTC) AND Lopinavir + Ritonavir (LPV/r)

If surface hepatitis B antigen positive, do not stop TDF; add the above to TDF.

Table 13: Contraindications and Special Recommendations

Contraindication	Contraindicated Drug	Replacement Drug
Raised fasting blood glucose > 6 mmol/l	Lopinavir + Ritonavir	Atazanavir + Ritonavir
Inability to take Lopinavir/Ritonavir due to gastrointestinal side-effects	Lopinavir + Ritonavir	Atazanavir + Ritonavir
Raised serum/total cholesterol > 6 mmol/l	Lopinavir + Ritonavir	Atazanavir + Ritonavir

9.4 Clinical and Laboratory Monitoring of Patients on Second Line Treatment

Table 14: Routine Monitoring Tests for All HIV Positive Initiating/On Second Line Treatment

Test	Frequency
CD4	At start of second line 6 months into second line ART, then every 12 months if virologically suppressed
VL	At 6 months, then 12 months annually

9.5 Management of Treatment Failure After Second Line Treatment

- Patients failing second line therapy have few treatment options. Failure is almost always due to poor adherence, and every effort should be made to address this, as resuppression is often possible on the failing drugs.
- Studies have shown clinical benefit in continuing on second line therapy despite virologic failure; if no options exist, the patient should be left on the failing regimen.

- Alternative regimens may be available at selected referral sites, research groups, or through the private sector, and this should be explored.

9.6 Management of Patients Previously Treated with Antiretroviral Therapy

- If a patient is referred in on ART (e.g. from the private sector), and the regimen is successful (VL undetectable and no side-effects), in general the patient should be continued on this regimen wherever possible.
- If the patient has interrupted treatment, and was on a previous regimen as above, or where the prior regimen is unknown, take a full history to establish why the treatment was stopped. If the interruption was NOT due to toxicity or clear virological failure, restart first line treatment as above and check the VL after 3 months.
- If patients have failed a previous regimen, initiate appropriate second line treatment.

9.7 Treatment Interruptions

- Establish the cause of the interruption.
- If due to social or psychological factors, address these aggressively.
- If due to side-effects, subsequent drug choices should be carefully evaluated.
- If interruption was due to drug supply issues, and there were no adherence, resistance or toxicity issues, ART should be reinitiated as soon as possible.
- Nevirapine deserves special consideration; if Nevirapine is restarted after an interruption of >1 week, recommence with the 2 week lead-in dose, and monitor ALT closely for the first 3 months of treatment.

10. Special Considerations

10.1 TB Patients

Tuberculosis is a common co-morbid illness with HIV. HIV positive patients are at higher risk of developing TB compared to the general population, especially during the period immediately after initiating ART. All patients with HIV should have screening for TB. If an HIV positive patient has symptoms suggestive of TB, investigate appropriately using sputum and TB culture as per guidelines. It is very important to investigate patients for tuberculosis before starting ART and to routinely screen patients on ART.

There are no changes to the guidelines below, in women who are pregnant.

Suspect TB if 2 or more of the following are present:

- Cough >2 weeks
- Sputum production which may occasionally be blood stained
- Fever
- Drenching night sweats
- Unexplained weight loss
- Loss of appetite, malaise, tiredness
- Shortness of breath, chest pains
- New palpable lymphadenopathy

The patient that presents with TB before commencing ART:

- TB/HIV carries a very high mortality if ART is deferred unnecessarily
- Complete 2 to a maximum of 8 weeks of TB therapy before commencing ART if the patient has CD4 count ≤ 350 cells/mm³
- In general, ART should be initiated as soon as the patient is tolerating their TB therapy; this is usually within 2-4 weeks
- EFV-based regimens are generally preferred in patients with active TB; however, other regimens are also effective

Patient developed tuberculosis while on ART:

- ART should be continued throughout TB treatment.
- Patients on Lopinavir/Ritonavir should have their dose doubled slowly over two weeks (to 800/200 mg twice a day); all other regimens can be continued unmodified. Monitor and investigate appropriately for hepatotoxicity symptoms.
- Continue these changes to Lopinavir/Ritonavir until two weeks after completion of TB treatment.

Table 15: Common Shared Side-Effects of TB and ART

Side-Effects	ART	Tuberculosis Treatment
Nausea	Didanosine, Zidovudine, protease inhibitors	Pyrazinamide
Hepatitis	Nevirapine, Efavirenz	Rifampicin, Isoniazid, Pyrazinamide
Peripheral neuropathy	Stavudine, Didanosine	Isoniazid
Rash	Nevirapine, Efavirenz	Rifampicin, Isoniazid, Pyrazinamide

* TB therapy carries significant side-effects, and attention by the health care worker to this is as important as with ART

10.2 Hepatitis B Patients

- TDF/3TC (or FTC) should always be used in the regimen.
- Interruption of TDF has been associated with life-threatening hepatitis flares.

10.3 Patients with anaemia

- Patient should have a full clinical history, an examination, and have a full FBC, smear and reticulocyte count to characterise the anaemia. Decisions regarding further investigation can be made once this has been done. AZT may complicate this further, and should be used with care and close monitoring in these patients.
- Anaemia pre-ART: Anaemia is very common in patients with low CD4 counts, and those who are relatively asymptomatic or who are have a serious OI (e.g. TB) that explains the anaemia should have their ART started right away and monitored carefully. In other patients, an Hb<8 g/dl with no clear cause should generally trigger additional investigations; usually, there is an underlying serious OI, often TB, and this requires urgent diagnosis and treatment. A low Hb is an independent poor prognostic factor in HIV, so these patients should not delay ART if at all possible.
- Anaemia immediately after ART initiation: Confirm that the Hb has dropped, by comparing previous results. Again, a full history, examination and interpretation of a FBC/smear/reticulocyte count is helpful. Common causes of anaemia in the first few weeks and months of treatment include IRIS, disseminated TB, and AZT containing regimens, although many other conditions can cause this.
- Anaemia once on established ART (>6 months): This is unusual, and often suggest a serious OI or a condition unrelated to HIV.

11. Expectations Regarding Care

- All patients should be clinically staged, have ART initiated and monitored by nurses, midwives or other appropriate health care worker
- Adequate adherence counselling is essential and must be done as rapidly as possible
- Appropriate and rapid referral services should exist for complex cases
- All antiretrovirals should be available at a primary care level; drug substitutions should be immediately available and at clinic discretion
- INH and cotrimoxazole prophylaxis should be initiated but should not delay ART

Timelines

- Fast-track patients should receive ART within 2 weeks of clinical staging
- All other patients should receive ART within 2 months of clinical staging event, or CD4 measurement that qualifies them for ART
- If this is not achievable, it is the Clinic Manager's responsibility to notify the District Manager, and prepare a plan urgently to achieve these timelines
- VL and CD4 count to be taken at 6 months, 12 months, and then annually

12. Diagnosis and Management of Adverse Events

12.1 Principles of Managing Adverse Events

- Identify the adverse event and assess its possible cause: antiretroviral agents, other medication or other illness.
- If the reaction is mild or moderate, do not discontinue ART. Implement symptomatic therapy and counsel and monitor patients.
- If there is intolerance due to an individual drug, a single drug substitution can be made. A single drug substitution should not be made if the patient is known to be virologically failing.
- If there is a need to discontinue ART, all antiretroviral medications must be stopped together. Stopping only one drug can lead to resistance.
- If the patient experiences life threatening side-effects, such as lactic acidosis, severe drug-induced hepatitis, kidney toxicity, pancreatitis, severe drug rash or abacavir hypersensitivity reactions, all therapy should be immediately interrupted.
- Record and report adverse events regularly to the HIV/AIDS programme at Head Office. Serious adverse events (SAEs) and deaths should be reported within 48-72 hours to the MCC National Adverse Drug Event Monitoring Centre, phone (012) 312-0000 or (021) 447-1618, fax: (021) 448-6181.
- *See Annexure C for an adverse event form.* Event forms should be available at all clinical sites.

12.2 Important Adverse Events

Table 16: Important ART Adverse Reactions and Safety Monitoring

Antiretroviral	Adverse Reactions	Recommended Safety Monitoring
Didanosine (ddI)	Peripheral neuropathy, GIT effects (bloating, flatulence, nausea, diarrhoea), hyperlactataemia, lactic acidosis, pancreatitis,	Clinical
Efavirenz (EFV)	CNS disturbances (dysphoria, vivid dreams, distractedness, dizziness, depression) Skin rash, hepatitis Possible link to congenital anomalies – avoid during 1st trimester of pregnancy	Clinical
Lamivudine (3TC) and Emtricitabine (FTC)	Generally well tolerated	Clinical
Lopinavir/Ritonavir	GIT symptoms (mainly diarrhoea), lipid and glucose abnormalities, lipodystrophic changes	Fasting cholesterol and triglycerides and glucose at 3 months

Antiretroviral	Adverse Reactions	Recommended Safety Monitoring
Nevirapine (NVP)	Skin rash (from mild to life threatening) Hepatitis (can be fatal)	ALT at baseline and at week 2, 4, and 8, and 12 and any time hepatitis symptoms occur
Stavudine (d4T)	Peripheral neuropathy, lipodystrophy/atrophy, hepatic steatosis, hyperlactataemia, lactic acidosis, pancreatitis	Clinical
Tenofovir (TDF)	Nephrotoxicity	Check creatinine at baseline, monthly x3, 6 months and then annually
Zidovudine (AZT)	Bone marrow suppression (anaemia, neutropenia), GIT symptoms, lipoatrophy, myopathy, headaches, hyperlactataemia, and lactic acidosis	FBC at baseline, then at months 1, 2, 3 and 6

13. Patient Management

HIV is a chronic condition. Regular routine HIV care and immunological monitoring can prevent AIDS and other HIV complications by:

- Preventing, identifying early and managing opportunistic conditions
- Commencing ART as quickly as possible
- Providing nutritional advice and support
- Providing ongoing HIV education and support

A primary care approach to initiation of ART in eligible patients is to be taken: all patients should be evaluated for ART through clinical and laboratory assessment at the point of entry into the health service.

The patient should be seen six monthly if well, more often if unwell or newly started on ART. This chapter provides a routine approach to the consultation with the adult with HIV.

“Adult” has many age definitions. Care for adolescents should be provided by the most appropriate and experienced available clinician. Ideally, adolescents are managed in specialised clinics attached to paediatric clinics, but this may not be available.

13.1 Routine Patient Management

At each visit, the history, physical examination and appropriate investigations should focus on the following aspects of care:

a) Patient weight

- Record weight at every visit, and calculate BMI.
- Investigate unintentional weight loss > 1.5 kg in a month. Loss of appetite and weight loss in the patient on ART should prompt investigation for opportunistic infections, particularly TB, malignancies, and hyperlactataemia.
- If the patient has lost significant weight, see the South African National Guidelines on Nutrition for People Living with HIV, AIDS, TB and other chronic debilitating conditions 2007 or nutritional advice, assessment and management.
- Consider multivitamin supplements (which provide no more than 100% of the Recommended Dietary Allowances) if the patient has a poor appetite and/or financial constraints that compromise meeting requirements for vitamins and minerals through diet alone.

b) TB Screening, INH Prevention and TB Diagnosis

- Ask about TB symptoms at each visit.
- Suspect TB if any of the following are present:

- Cough \geq 2 weeks
- Shortness of breath
- Sputum production
- Drenching night sweats
- Fever
- Unexplained weight loss
- Loss of appetite, malaise
- Cough should be current to exclude patients with long-standing cough due to chronic obstructive airways disease or bronchiectasis
- Sputum culture is an essential part of working up TB suspects, and will often identify patients with sputum negative on staining
- Have a high suspicion for TB in the period surrounding ART initiation; TB is often missed prior to starting ART, and there is high TB risk in the immediate period after ART initiation. While ART decreases long term risk of TB, this risk remains higher than in uninfected people.

For patients who develop TB, see the TB Guidelines, and also refer to section 10.

c) INH Prophylaxis

- TB preventive therapy is an effective intervention for HIV infected individuals prior to starting ARV.
- Screening for symptoms as described above is essential before starting INH. A chest X-ray does not significantly improve case detection in the absence of symptoms. Emphasis is on sputum samples and, where appropriate, on identification of extra-pulmonary TB.
- In patients not on ART with no TB signs or symptoms, TB prophylaxis with isoniazid preventive therapy should be started, unless adherence or side-effects are a concern, 5mg/kg to a maximum dose of 300mg daily, with pyridoxine 25mg/day, for 6 months,. A PPD is not required. Pregnancy is not a contraindication to INH prophylaxis.
- Interrupt INH if adherence is a concern, peripheral neuropathy is progressive, or hepatitis develops.
- Do not delay ART in favour of INH prophylaxis. ART effectively decreases long-term TB risk.
- INH has not been shown as yet to be effective in those on ART; hence INH prophylaxis is not recommended. However, TB risk in those on ART remains higher than the general population, and clinicians should have a high index of suspicion for investigation.

d) Clinical HIV Stage

- Assess the HIV stage according to findings from medical history, symptom screening and complete physical examination signs. Ill patients should be evaluated for underlying opportunistic infection. *See Annexure D for South African Adapted WHO staging.*
- All patients with stage 4 HIV disease need ART.

- A new stage 4 condition or any new HIV-linked complication in the patient more than 3 months on ART may suggest treatment failure, and viral load should be assessed immediately.

e) Opportunistic Infection Diagnosis and Management

- Diagnose and manage HIV-related opportunistic conditions according to National Standard Treatment Guidelines (Primary Health Care 2008; Hospital Level 2006).
- Immune reconstitution inflammatory syndrome (IRIS) is common, and covered above in section 8.
- Fluconazole and Cotrimoxazole secondary prophylaxis may be stopped if asymptomatic, CD4 over 200 cells/mm³ and total Fluconazole use is more than 6 months, once on ART.
- Pregnant women should discontinue Fluconazole as it is teratogenic; if required for secondary prophylaxis, women who desire pregnancy should delay pregnancy until fluconazole can be safely discontinued.

f) CD4 and Viral Load monitoring

- Check CD4 counts 6 monthly if the patient has a CD4 over 350 cells/mm³ and is not on ART.
- Initiate ART if CD4 or clinical state indicates this, as per guidelines above, and monitor accordingly.
- Pregnant woman with CD4 above 350 cells/mm³ needs PMTCT. (*See the National PMTCT Guidelines, and section 4 for a summary of the recommendations.*)

g) Cotrimoxazole Prophylaxis

- Cotrimoxazole markedly reduces hospitalization and mortality and provides protection against:
 - Pneumocystis jiroveci (formerly P. Carinii pneumonia [PCP]), toxoplasmosis many bacterial infections, diarrhoea caused by Isospora belli or Cyclospora species, and malaria.
- Patients with CD4 \leq 200 cells/mm³ or stage 2, 3 or 4 HIV disease (including TB) need Cotrimoxazole prophylaxis.
- Prescribe 160/800 (2 single strength tablets) orally once daily.
- Do not delay ART in favour of Cotrimoxazole initiation. Ideally, initiate Cotrimoxazole immediately at first adherence visit, if not done already, prior to ART.
- Cotrimoxazole's commonest side effect is a maculopapular rash. Prophylaxis may be continued in the presence of mild rash or interrupted and then reintroduced. Treatment should not be continued in the presence of fever, hepatitis or mucous membrane lesions e.g. Stevens-Johnson syndrome.
- Neutropenia is a rare side effect of prophylactic Cotrimoxazole – routine blood count monitoring is not necessary.

- Use Dapsone 100 mg a day for patients who have had a mild reaction to Cotrimoxazole. Dapsone should not be used after severe reactions, as there may be cross-reactivity. Dapsone does not provide protection against bacterial infections and provides only limited protection against toxoplasmosis.
- Stop Cotrimoxazole prophylaxis only once well on ART and CD4 > 200cells/mm³
- Recommence Cotrimoxazole when CD4 drops below 200 if ART fails or a new opportunistic infection develops.
- Cotrimoxazole is safe to use in pregnancy. Pregnant women should continue on Cotrimoxazole prophylaxis

h) STI Screen

- Ask about symptoms of sexually transmitted infections, including ulcers and discharge, and treat accordingly.
- Treat syndromically according to South African National STI guidelines.

i) Pap Smear

- All HIV positive women need cervical cancer screening on diagnosis and if normal every 3 years yearly, irrespective of ART status.
- Repeat abnormal PAP smears according to the result:
 - ASCUS repeat in one year and if still ASCUS, refer baseline colposcopy.
 - LSIL, repeat in one year and if still LSIL, refer baseline colposcopy.¹
 - HSIL, refer colposcopy
 - Carcinoma in situ: refer immediately

j) Immunizations

- Influenza vaccine is recommended annually prior to the influenza season for all HIV patients.

k) Family Planning

- Screen for pregnancy in all women.
- Discuss plans for future pregnancies with all patients – men and women.
- Dual contraception (condoms plus injectable or oral hormonal contraceptive) reliably prevents pregnancy. Avoid Efavirenz in women of childbearing age not using reliable contraception.
- While side-effects in the first three months can be severe, long-term Nevirapine is very safe. Any patient started on Nevirapine with no side-effects should not be changed to another drug unless virological failure occurs.

¹ More than 40% of HIV positive women have LSIL

l) Mental Health Screen

- Mental health problems like depression, anxiety, substance abuse and sleep problems are more common among HIV positive people than those who are HIV negative. They may occur prior to HIV infection or as a complication of HIV infection, and may increase risk for infection.
- Depression is a common cause of loss of weight, adherence failure, and loss to follow-up. Rule out an underlying physical cause when an exacerbation occurs even when major mental illness is recurrent.
- Manage a psychiatric diagnosis according to National Standard Treatment Guidelines.
- Many cases of supposed HIV-associated dementia respond well to ART.
- Avoid Efavirenz in the patient with untreated depression or who is using psychoactive drugs.

m) Adherence Check

- Adherence accounts for almost all failures to ART, and is commonly due to inadequate attention by the provider to side-effects or integrating medication in to the patient's routine.
- If quickly identified, re-emphasising adherence may result in a large number of patients achieving undetectable viral loads.
- Adherence processes should not slow initiation of ART, unless absolutely necessary; adherence obstacles should be addressed urgently.

Note: See section 7 for additional adherence guidance.

n) Prevent HIV Transmission and Reinfection

- Demonstrate proper use of male/female condoms and ensure adequate supplies are available for patients attending clinic.
- While ART appears to significantly decrease sexual transmission, unsafe sex on failing ART can still transmit HIV, especially drug resistant HIV, which can lead to subsequent treatment failure in the partner.
- Routinely discuss fertility intentions with women of child bearing age; unwanted pregnancy suggests unsafe sex, with HIV risk to both HIV-negative sexual partners and the child.

o) Provide Support

- Encourage disclosure to friend or family member.
- Connect to counsellor and support group.
- HIV is a family disease – offer to screen partners and children for HIV.

Annexure A: Creatinine Clearance Tables

These tables are provided to assist with manual calculation. Please note though that the new NHLS forms incorporate creatinine clearance calculation (see form following these tables) using 3 data points: gender, age and weight.

Creatinine Clearance in ml/min

$$\frac{(140 - \text{age}) \times \text{weight in kg} \times 1.04}{\text{pCr in umol/liter}}$$

Table 1: Female, age 15-40 years

Weight in kg	30-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70
	30 35	36 40	41 45	46 50	51 55	56 60	61 65	66 70
PCr in umol/liter								
60	52 to 76	62 to 87	71 to 98	80 to 108	88 to 119	97 to 130	106 to 141	114 to 152
70	45 to 65	53 to 74	61 to 84	68 to 93	76 to 102	83 to 111	91 to 121	98 to 130
80	39 to 57	47 to 65	53 to 73	60 to 81	66 to 89	73 to 98	79 to 106	86 to 114
90	35 to 51	42 to 58	48 to 65	53 to 72	59 to 79	65 to 87	70 to 94	76 to 101
100	31 to 46	37 to 52	43 to 59	48 to 65	53 to 72	58 to 78	63 to 85	69 to 91
110	28 to 41	34 to 47	39 to 53	43 to 59	48 to 65	53 to 71	58 to 77	62 to 83
120	26 to 38	31 to 43	36 to 49	40 to 54	44 to 60	49 to 65	53 to 70	57 to 76
130	24 to 35	29 to 40	33 to 45	37 to 50	41 to 55	45 to 60	49 to 65	53 to 70
140	22 to 33	27 to 37	31 to 42	34 to 46	38 to 51	42 to 56	45 to 60	49 to 65
...								
290	11 to 16	11 to 18	15 to 20	16 to 22	18 to 25	20 to 27	22 to 29	24 to 31
300	10 to 15	16 to 17	14 to 20	16 to 22	18 to 24	19 to 26	21 to 28	23 to 30
350	9 to 13	13 to 15	12 to 17	14 to 19	15 to 20	17 to 22	18 to 24	20 to 26
400	8 to 11	12 to 13	11 to 15	12 to 16	13 to 18	15 to 20	16 to 21	17 to 23
450	7 to 10	10 to 12	10 to 13	11 to 14	12 to 16	13 to 17	14 to 19	15 to 20
500	6 to 9	9 to 10	9 to 12	10 to 13	11 to 14	12 to 16	13 to 17	14 to 18
550	6 to 8	9 to 9	8 to 11	9 to 12	10 to 13	11 to 14	12 to 15	12 to 17
600	5 to 8	8 to 9	7 to 10	8 to 11	9 to 12	10 to 13	11 to 14	11 to 15
650	5 to 7	7 to 8	7 to 9	7 to 10	8 to 11	9 to 12	10 to 13	11 to 14
700	7 to 12	10 to 14	9 to 8	7 to 9	8 to 10	8 to 11	9 to 12	10 to 13

Creatinine Clearance in ml/min

$$\frac{(140 - \text{age}) \times \text{weight in kg} \times 1.04}{\text{pCr in umol/liter}}$$

Table 2: Female, age 41-65 years

weight in kg	30-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70
PCr in umol/liter	30 35	36 40	41 45	46 50	51 55	56 60	61 65	66 70
40	59 to 90	70 to 103	80 to 116	90 to 129	99 to 142	109 to 154	119 to 167	129 to 180
50	47 to 72	56 to 82	64 to 93	72 to 103	80 to 113	87 to 124	95 to 134	103 to 144
60	39 to 60	47 to 69	53 to 77	60 to 86	66 to 94	73 to 103	79 to 112	86 to 120
70	33 to 51	40 to 59	46 to 66	51 to 74	57 to 81	62 to 88	68 to 96	83 to 103
80	29 to 45	35 to 51	40 to 58	45 to 64	50 to 71	55 to 77	59 to 84	73 to 90
90	26 to 40	31 to 46	36 to 51	40 to 57	44 to 63	49 to 69	53 to 74	65 to 80
100	23 to 36	28 to 41	32 to 46	36 to 51	40 to 57	44 to 62	48 to 67	58 to 72
110	21 to 33	26 to 37	29 to 42	33 to 47	36 to 51	40 to 56	43 to 61	53 to 66
120	20 to 30	23 to 34	27 to 39	30 to 43	33 to 47	36 to 51	40 to 56	49 to 60
...								
220	11 to 16	13 to 19	15 to 21	16 to 23	18 to 26	20 to 28	22 to 30	27 to 33
230	10 to 16	12 to 18	14 to 20	16 to 22	17 to 25	19 to 27	21 to 29	25 to 31
300	8 to 12	9 to 14	11 to 15	12 to 17	13 to 19	15 to 21	16 to 22	19 to 24
350	7 to 10	8 to 12	9 to 13	10 to 15	11 to 16	12 to 18	14 to 19	17 to 21
400	6 to 9	7 to 10	8 to 12	9 to 13	10 to 14	11 to 15	12 to 17	15 to 18
450	5 to 8	6 to 9	7 to 10	8 to 11	9 to 13	10 to 14	11 to 15	13 to 16
500	5 to 7	6 to 8	6 to 9	7 to 10	8 to 11	9 to 12	10 to 13	12 to 14
550	4 to 7	5 to 7	6 to 8	7 to 9	7 to 10	8 to 11	9 to 12	11 to 13
600	4 to 6	5 to 7	5 to 8	6 to 9	7 to 9	7 to 10	8 to 11	10 to 12

Creatinine Clearance in ml/min

$$\frac{(140 - \text{age}) \times \text{weight in kg} \times 1.23}{\text{pCr in umol/liter}}$$

Table 3: Male, age 15-40 years

weight in kg	30-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70
	30 35	36 40	41 45	46 50	51 55	56 60	61 65	66 70
PCr in umol/liter								
70	53 to 77	63 to 88	72 to 99	81 to 110	90 to 121	98 to 132	107 to 143	116 to 154
80	46 to 67	55 to 77	63 to 86	71 to 96	78 to 106	86 to 115	94 to 125	101 to 135
90	41 to 60	49 to 68	56 to 77	63 to 85	70 to 94	77 to 103	83 to 111	90 to 120
100	37 to 54	44 to 62	50 to 69	57 to 77	63 to 85	69 to 92	75 to 100	81 to 108
110	34 to 49	40 to 56	46 to 63	51 to 70	57 to 77	63 to 84	68 to 91	74 to 98
120	31 to 45	37 to 51	42 to 58	47 to 64	52 to 70	57 to 77	63 to 83	68 to 90
130	28 to 41	34 to 47	39 to 53	44 to 59	48 to 65	53 to 71	58 to 77	62 to 83
140	26 to 38	32 to 44	36 to 49	40 to 55	45 to 60	49 to 66	54 to 71	58 to 77
150	25 to 36	30 to 41	34 to 46	38 to 51	42 to 56	46 to 62	50 to 67	54 to 72
160	23 to 34	28 to 38	32 to 43	35 to 48	39 to 53	43 to 58	47 to 62	51 to 67
170	22 to 32	26 to 36	30 to 41	33 to 45	37 to 50	41 to 54	44 to 59	48 to 63
...								
350	11 to 15	13 to 18	14 to 20	16 to 22	18 to 24	20 to 26	21 to 29	23 to 31
400	9 to 13	11 to 15	13 to 17	14 to 19	16 to 21	17 to 23	19 to 25	20 to 27
450	8 to 12	10 to 14	11 to 15	13 to 17	14 to 19	15 to 21	17 to 22	18 to 24
500	7 to 11	9 to 12	10 to 14	11 to 15	13 to 17	14 to 18	15 to 20	16 to 22
550	7 to 10	8 to 11	9 to 13	10 to 14	11 to 15	13 to 17	14 to 18	15 to 20
600	6 to 9	7 to 10	8 to 12	9 to 13	10 to 14	11 to 15	13 to 17	14 to 18
650	6 to 8	7 to 9	8 to 11	9 to 12	10 to 13	11 to 14	12 to 15	12 to 17
700	5 to 8	6 to 9	7 to 10	8 to 11	9 to 12	10 to 13	11 to 14	12 to 15
750	5 to 7	6 to 8	7 to 9	8 to 10	8 to 11	9 to 12	10 to 13	11 to 14
800	5 to 7	6 to 8	6 to 9	7 to 10	8 to 11	9 to 12	9 to 12	10 to 13

Creatinine Clearance in ml/min

$$\frac{(140 - \text{age}) \times \text{weight in kg} \times 1.23}{\text{pCr in } \mu\text{mol/liter}}$$

Table 2: Male, age 41-65 years

weight in kg	30-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70
PCr in $\mu\text{mol/liter}$	30 35	36 40	41 45	46 50	51 55	56 60	61 65	66 70
50	55 to 85	66 to 97	76 to 110	85 to 122	94 to 134	103 to 146	113 to 158	122 to 170
60	46 to 71	55 to 81	63 to 91	71 to 101	78 to 112	86 to 122	94 to 132	101 to 142
70	40 to 61	47 to 70	54 to 78	61 to 87	67 to 96	74 to 104	80 to 113	87 to 122
80	35 to 53	42 to 61	47 to 68	53 to 76	59 to 84	65 to 91	70 to 99	76 to 107
90	31 to 47	37 to 54	42 to 61	47 to 68	52 to 74	57 to 81	63 to 88	68 to 95
100	28 to 43	33 to 49	38 to 55	42 to 61	47 to 67	52 to 73	56 to 79	61 to 85
110	25 to 39	30 to 44	34 to 50	39 to 55	43 to 61	47 to 66	51 to 72	55 to 77
120	23 to 36	28 to 41	32 to 46	35 to 51	39 to 56	43 to 61	47 to 66	51 to 71
130	21 to 33	26 37	29 42	33 47	36 52	40 56	43 61	47 66
...								
260	11 to 16	13 to 19	15 to 21	16 to 23	18 to 26	20 to 28	22 to 30	23 to 33
300	9 to 14	11 to 16	13 to 18	14 to 20	16 to 22	17 to 24	19 to 26	20 to 28
350	8 to 12	9 to 14	11 to 16	12 to 17	13 to 19	15 to 21	16 to 23	17 to 24
400	7 to 11	8 to 12	9 to 14	11 to 15	12 to 17	13 to 18	14 to 20	15 to 21
450	6 to 9	7 to 11	8 to 12	9 to 14	10 to 15	11 to 16	13 to 18	14 to 19
500	6 to 9	7 to 10	8 to 11	8 to 12	9 to 13	10 to 15	11 to 16	12 to 17
550	5 to 8	6 to 9	7 to 10	8 to 11	9 to 12	9 to 13	10 to 14	11 to 15
600	5 to 7	6 to 8	6 to 9	7 to 10	8 to 11	9 to 12	9 to 13	10 to 14

Annexure B: Patient Adherence Record

Folder No.	Date: (dd/mm/yy)
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Self Reporting

Question	Yes	No
When you feel better, do you sometimes stop taking your medication?		
Thinking back over the past four days, have you missed any of your doses?		
Sometimes if you feel worse when you take the medicine, do you stop taking it?		

Visual Analogue Scale (VAS)

0	1	2	3	4	5	6	7	8	9	10	Score %

Pill Identification Test (PIT)

Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken			Knows any additional instruction
			Morning (hour)	Evening (hour)	Considered Acceptable (Y/N)	

Pill Count

Did the client return the medication containers?	Yes *	No
*If yes, check that the client only used medication from this container since the date of their last visit. If leftover medication had been used or an emergency prescription obtained, then the calculations will be invalid – skip to adherence assessment		

$$\% \text{ Adherence} = \frac{\text{Dispensed} - \text{Returned}}{\text{Expected to be taken}} \times 100$$


Adherence Assessment

Self reporting	Answered 'No' to all questions	Answered 'Yes' to 1 question	Answered 'Yes' to 2 or more questions
VAS	> 95%	75-94%	< 75%
PIT – Client knows the...	Dose, Time, and Instructions	Dose and Time	Dose only or confused
Pill count	>95%	75-94%	<75%
Overall Adherence	High	Moderate	Low

Annexure C: Adverse Drug Reaction Reporting Form

ADVERSE DRUG REACTION AND PRODUCT QUALITY PROBLEM REPORT FORM

(Identities of reporter and patient will remain strictly confidential)

 <p>health Department: Health REPUBLIC OF SOUTH AFRICA</p>	<p>NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE NADEMC</p> <p>The Registrar of Medicines Private Bag X 828 Pretoria 0001</p> <p style="font-size: small;">Fax: (021) 448-6181 Tel : (021) 447-1618</p> <p style="font-size: x-small;">In collaboration with the WHO International Drug Monitoring Programme</p>
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PATIENT INFORMATION

Name (or initials): Patient Reference Number:
 Sex: M F Age: DOB: / / Weight (kg): Height (cm):

ADVERSE REACTION / PRODUCT QUALITY PROBLEM (tick appropriate box)

Adverse reaction and/or Product Quality problem Date of onset of reaction:/...../.....
 Time of onset of reaction:hour.....min

Description of reaction or problem (Include relevant tests/lab data, including dates):

1. MEDICINES / VACCINES / DEVICES (include all concomitant medicines)

Trade Name & Batch No. <small>(Asterisk Suspected Product)</small>	Daily Dosage	Route	Date Started	Date Stopped	Reasons for use

ADVERSE REACTION OUTCOME (Check all that apply)

<input type="checkbox"/> death <input type="checkbox"/> disability <input type="checkbox"/> congenital anomaly <input type="checkbox"/> required intervention to prevent permanent impairment/damage	<input type="checkbox"/> life-threatening <input type="checkbox"/> hospitalisation <input type="checkbox"/> Other.....	<p>Event reappeared on rechallenge: <input type="checkbox"/> Y <input type="checkbox"/> N <input style="width: 100px;" type="text" value="Rechallenge not done"/></p> <p>Reaction abated after stopping medicine: <input type="checkbox"/> Y <input type="checkbox"/> N</p>	<p>Recovered: <input type="checkbox"/> Y <input type="checkbox"/> N</p> <p>Sequela: <input type="checkbox"/> Y <input type="checkbox"/> N</p> <p>Describe Sequelae:</p> <p>.....</p> <p>.....</p> <p>.....</p>
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COMMENTS: (e.g. Relevant history, Allergies, Previous exposure, Baseline test results/lab data)

2. PRODUCT QUALITY PROBLEM:

Trade Name	Batch No	Registration No	Dosage form & strength	Expiry Date	Size/Type of container

Product available for evaluation? Y N

REPORTING HEALTHCARE PROFESSIONAL:

NAME: QUALIFICATIONS: :.....
 ADDRESS:

This report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:

- medications (drugs, vaccines and biologicals)
- medical devices (including in-vitro diagnostics)
- complementary / alternative medicines (including traditional, herbal remedies, etc)

Please report especially:

- adverse drug reactions to newly marketed products
- serious reactions and interactions with all products
- adverse drug reactions which are not clearly reflected in the package insert.

Report Product Quality Problems such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labelling
- therapeutic failures

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Important numbers:

Registered Medicines and Traditional and Herbal remedies:

- fax: (021) 448-6181
- phone: (021) 447-1618

Investigational Products and Product Quality Problems:

- fax: (012) 312-3114
- phone: (012) 312-0243

Adverse Events Following Immunisation:

- fax: (012) 312 3110
- phone: (012) 312 0032

Confidentiality: Identities of the reporter and patient will remain strictly confidential.

Your support of the Medicine Control Council's adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of medicine safety and therapy in South Africa.

Annexure D: WHO Clinical Staging

CLINICAL STAGE 1

- Asymptomatic
- Persistent generalized lymphadenopathy

CLINICAL STAGE 2

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Fungal nail infections
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)

CLINICAL STAGE 3

- Unexplained moderate malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5°C intermittent or constant for longer than one month)
- Persistent oral candidiasis (after first 6–8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lymph node tuberculosis
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including bronchiectasis
- Unexplained anaemia (< 8 g/dL), neutropaenia ($< 0.5 \times 10^9$ per litre)
- And/or chronic thrombocytopaenia ($< 50 \times 10^9$ per litre)

CLINICAL STAGE 4

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after one month of life)
- HIV encephalopathy
- Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
- Extrapulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
- Chronic cryptosporidiosis
- Chronic isosporiasis

- Disseminated non-tuberculous mycobacterial infection
- Cerebral or B-cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy
- HIV-associated rectovaginal fistula