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# National Antiretroviral Treatment Guidelines

FIRST EDITION

HIV AND AIDS POLICY GUIDELINE • DEPARTMENT OF HEALTH



# National Antiretroviral Treatment Guidelines



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National Department of Health  
South Africa 2004



# FOREWORD

South Africa's response to HIV and AIDS has evolved significantly over the last four to five years. Our response has been guided by our Strategic Plan for HIV and AIDS, 2000 – 2005, and the Comprehensive Plan for the Management, Care and Treatment of HIV and AIDS in South Africa.

**Government's response to HIV covers the full range of interventions including:**

- Information, education and communication;
- Prevention programmes, including access to barrier methods such as male and female condoms;
- Increased access to voluntary counselling and testing;
- Prevention of mother to child transmission of HIV;
- Robust nutritional interventions; and
- An emphasis on individual choice of treatment.

In order to ensure optimal therapy and good clinical outcomes, the Ministry and Department have developed these national guidelines for use of ART.

These guidelines complement all other existing guidelines. Patients who are on ART need to comply with their treatment schedules. To facilitate this, counselling and family support, as well as robust nutritional interventions, are critical.

Health care providers and clinicians in the public and private sector are encouraged to familiarise themselves with the content of these guidelines. This will ensure that we provide safe, sustainable and effective care to all our citizens.

These guidelines will be subject to ongoing review in line with emerging evidence, as well as the information gathered from surveillance and pharmacovigilance monitoring.

Partnerships with the private sector and civil society are critical for the successful implementation of these guidelines.



**DR MANTO TSHABALALA-MSIMANG  
MINISTER OF HEALTH**

## INTRODUCTION

These guidelines serve to assist the clinic team in the management of patients on antiretroviral drugs as outlined in the Comprehensive Plan for HIV and AIDS Care, Management and Treatment. The approach adopted is that of the continuum of care, with a holistic patient focus in an integrated health system.

This system will be integrated from primary to tertiary levels, as well as from the clinic to the community and from pre-diagnosis to palliation whichever is appropriate. The focus is at the primary level within the context of the district health system being implemented throughout the country. These guidelines will be revised as necessary to reflect the changing world of the treatment of HIV. This will ensure the highest possible standard of care for all South Africans.

## ACKNOWLEDGEMENTS

The development of such a challenging document for ART in the context of South Africa required the collaboration of experts in the HIV and AIDS field.

As such, the Department of Health wishes to recognise South African, international and regional expert paediatricians, obstetricians and physicians who contributed to development of this guideline.

The Clinical Care Team of the HIV and AIDS Cluster worked tirelessly, and we thank them. A special word of thanks to Dr Ashraf Grimwood for his clinical and editorial support.

The list of contributors are included on page 93.

**DR NP SIMELELA**

**CLUSTER MANAGER: HIV, AIDS and TB**

## PREFACE

South Africa's response to HIV and AIDS has evolved rapidly over the last few years. The Strategic Plan for South Africa 2000-2005 provides for a comprehensive framework for a multi-sectoral response involving all spheres of our society. Government has committed to providing a comprehensive package of care for HIV and AIDS, and has now taken steps to provide antiretroviral treatment (ART) to patients in the public sector.

Mounting an effective ART programme requires more than just the drugs. Establishing an adequate cadre of well-trained health care professionals, laboratory technicians, pharmacists and community workers is critical for the success of this programme.

Mobilisation of the community to participate and fully understand the benefit and limitations of ART is essential for maximum adherence.

The purpose of these guidelines is to set standards as the basis for the use of ART drugs in South Africa on which training- and support-programmes should be based.

All health care workers in the public and private sector are urged to familiarise themselves with the content of these guidelines so that we, together, provide the best possible and safest care for those with HIV and AIDS in South Africa.

The field of ART is dynamic and changes fairly rapidly, thus these guidelines will be reviewed periodically to ensure that South Africa continues to provide quality care.

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# SECTION 1: ANTIRETROVIRAL TREATMENT (ART) IN ADULTS

## Goals of antiretroviral treatment

**The primary goal of ART is to decrease HIV-related morbidity and mortality.**

- The patient should experience fewer HIV-related illnesses.
- The patient's CD4 count should rise and remain above the baseline count.
- The patient's viral load should become undetectable (<400 copies/mm<sup>3</sup>), and remain undetectable on ART.

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

- An increase in voluntary testing and counselling with more people knowing their status and practising safer sex;
- Reducing transmission in discordant couples (discordant couples means one partner is positive and one negative);
- Reducing the risks of HIV transmission from mother to child.

## Patient selection criteria

### Indication for ART

Medical criteria:

- CD4 count <200 cells/mm<sup>3</sup> irrespective of WHO stage
- OR**
- WHO Stage IV disease irrespective of CD4 count

### Psycho-social considerations (not exclusion criteria):

- Demonstrated reliability, i.e. patient has attended three or more scheduled visits to an HIV clinic.
- No active alcohol or other substance abuse.
- No untreated active depression.
- Disclosure: it is strongly recommended that patients have disclosed their HIV status to at least one friend or family member OR have joined a support group.
- Insight: patients need to have accepted their HIV-positive status. They need to have insight into the consequences of HIV infection and the role of ART before commencing therapy.
- Patients should be able to attend the antiretroviral centre on a regular basis or have access to services that are able to maintain the treatment chain. Transport may need to be arranged for patients in rural areas or for those far away from the treatment site.

**N.B.**

**Patient selection: the final decision to treat will be taken by the multi-disciplinary team at the ART centre, who will initiate treatment. The patient or caregiver must be involved in this decision.**

**Table 1: Criteria for ART initiation in adults and adolescents**

Adults and adolescents – including pregnant women
<ul style="list-style-type: none"> <li>■ CD4 &lt;200 cells/mm<sup>3</sup> irrespective of stage</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>■ WHO Stage IV AIDS-defining illness, irrespective of CD4 count</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>■ Patient expresses willingness and readiness to take ART adherently</li> </ul> <p><i>Note: see WHO staging tables in Appendix 1, page 78.</i></p>

## ANTIRETROVIRAL TREATMENT (ART) IN ADULTS

### Treatment readiness assessment

#### Process for initiation of ART – induction schedule

#### First screening visit: 2 – 4 weeks before starting ART

- Confirm the selection criteria: clinical and laboratory (make sure TB and pregnancy have been excluded).
- Treat any opportunistic infection.
- Patient's information records need to be completed.
- Patient must meet with the multi-disciplinary team for group and individual information sessions.
- Treatment counsellor/patient advocate will discuss treatment with the patient.
- 28-day supply of co-trimoxazole is given to patient.
- Patient is given a date of return.

#### In the meantime the treatment counsellor will visit the patient at home to assess:

- Home circumstances
- Correctness of the contact details
- Support structures including disclosure
- Drug storage facilities (e.g. refrigerator)

#### Before the second visit the multi-disciplinary team should meet and assess patient readiness. They should take all available information into account. Patient's readiness criteria include the following:

- Patient's acceptance of the status and ART
- Have the medical criteria been met
- Absence of severe medical contra-indication (active disease that is not stabilised, including depression)
- Understanding of the importance of adherence and attendance to all scheduled pre-treatment visits

### Second visit

- Clinical assessment
- Information and education session
- Pill count (co-trimoxazole)
- Adherence counselling for patient and treatment counsellor if available

### Multi-disciplinary team discussion

Patients who do not meet the treatment readiness criteria should be referred back to their local clinic with a detailed letter. This should include reason for deferment of ART, and possible solutions to enable treatment uptake at a later stage.

### ART commencement visit

ART is not an emergency treatment.

The pharmacist should be involved as part of the multi-disciplinary team.

- Re-assess patient's readiness.
- Do co-trimoxazole pill count.
- Provide detailed description of the drugs.
- Discuss further information and adherence issues with the patient and his/her counsellor or advocate.
- Re-inforce drug-dosing details before the patient leaves the clinic.
- Ensure that instructions are clearly written on the container with a permanent marker.

## ANTIRETROVIRAL TREATMENT (ART) IN ADULTS

### Recommended regimens in adults

Two ART regimens are recommended for use in the South African public sector. Patients who fail both regimens will be referred for individual evaluation by ART specialists. New developments in ART will determine options for salvage therapy.

**Table 2: Recommended ART regimens**

Regimen	Drugs
1a	d4T / 3TC / efavirenz
1b	d4T / 3TC / NVP
2	AZT / ddI / lopinavir / ritonavir

### First-line therapy – Regimen 1

#### Antiretroviral naïve adult patients

Unless contra-indicated, all patients will commence therapy on:

- Stavudine (d4T) 40 mg every 12 hours (or 30 mg every 12 hours if <60 kg)

#### WITH

- Lamivudine (3TC) 150 mg every 12 hours

#### 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 every 12 hours after this.

**N.B.**

**It is important to ensure reliable contraception in women of child-bearing age. This should preferably be an injectable contraceptive as well as using a barrier method. If unable to guarantee reliable contraception, nevirapine will be substituted for efavirenz.**

### Antiretroviral non-naïve patients

Patients who have been exposed to ART in the past, need to talk to an antiretroviral expert before a treatment regimen is commenced.

- Those patients controlled on their antiretroviral medication should continue on their treatment or swop to the appropriate treatment protocol.
- Those patients who stopped for several reasons, but who were controlled, could recommence therapy and be monitored as per schedule.
- Those patients who have failed a previous regimen should be started on appropriate drugs they have not been exposed to before.

### Clinical and laboratory monitoring of patients on Regimen 1

#### Scheduled visits

Patients must attend clinics monthly to collect medication. They are seen by the professional nurse to monitor drug tolerance, adverse events and adherence. Ideally drugs should be counted at each scheduled visit by the clinic nurse, doctor, pharmacist or therapeutic counsellor. Patients on NVP should be seen by the nurse at 2 weeks (in addition to the visits above) to check:

- for adverse events
- do more blood tests (ALT)
- ensure the correct dosaging

Patients should be seen by the doctor at 4, 8 and 12 weeks and 3-monthly thereafter if they are well. If they are not well, patients should be seen more frequently as determined by the treating doctor or nurse.

Safety bloods are taken as per schedule. CD4 count and viral load are done 6-monthly while patients are on Regimen 1.

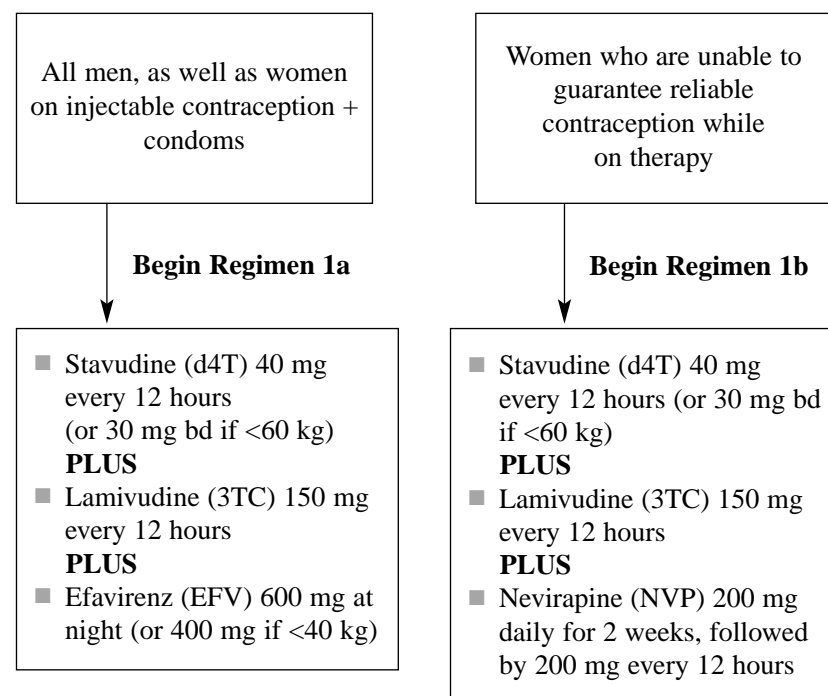
Different approaches will be adopted to ensure adherence.



**Figure 1: First-line therapy for adults (Regimen 1a and 1b)**

**N.B.**

The treatment of patients who have been exposed to ART in the past needs to be discussed with an ART expert BEFORE a treatment regimen is commenced.



**N.B.**

Any swapping of drugs must be made by a doctor trained in ART.

**Table 3: Time events schedule**

Assessment	Screening week 4	Commence ART week 0	Week 2	Week 4	Week 8	Week 12	Monthly	3 Monthly	6 Monthly
Education/therapeutic counsellor visit	C	C	C	C	C	C	C	C	
Treatment readiness assessment		Whole team							
History	D	D							
Physical exam	D	D					N	D	D
Complete registers	N	N						N	N
Safety bloods Regimen 1 with NVP		N <sup>a</sup>	N <sup>b</sup>	N <sup>b</sup>	N <sup>b</sup>				N <sup>a</sup>
Safety bloods Regimen 2 <sup>b</sup>		N <sup>b</sup>	N <sup>b</sup>	N <sup>b</sup>	N <sup>b</sup>	N <sup>b</sup>			N <sup>b</sup>
Viral load		N,D							N
CD4 count	N								N
Adverse events		N, P	N, P	D, P	D, P	D, P	N, P		
Adherence check		TC, N	PA, TC, N	P, N, TC, D	P, N, TC, D	P, N, TC, D	P, N, TC, D	P, N, TC, D	P, N, TC, D

C = counsellor; D = doctor; N = nurse; TC = therapeutic counsellor; PA = patient advocate; P = pharmacist  
\* for information on a, b, c, see the following page

## ANTIRETROVIRAL TREATMENT (ART) IN ADULTS

- For details of safety bloods see Table 4, page 10, and Table 6, page 15. Additional safety bloods will be required in pregnancy. For patients on nevirapine, ALT will be taken at baseline, Week 2, 4 and 8, then 6 monthly.
- For patients on Regimen 2, FBC will be done monthly for 3 months, then 6 monthly. Fasting cholesterol, triglycerides and fasting glucose will be done as in Table 6, page 15.
- Calculate monthly adherence = (tablets dispensed – tablets returned)/(tablets prescribed), e.g.  $(30 - 5)/28 = 25/28 = 0.9$  (90%).

**Table 4: Summary of adult ART Regimen 1 and routine monitoring**

Regimen	Drugs	Monitoring tests	Frequency
1a	d4T / 3TC / efavirenz	<ul style="list-style-type: none"> <li>■ CD4</li> <li>■ VL</li> <li>■ ALT</li> </ul>	<ul style="list-style-type: none"> <li>■ Staging, 6-monthly</li> <li>■ Baseline, 6-monthly</li> <li>■ Symptomatic</li> </ul>
1b	d4T / 3TC / NVP	<ul style="list-style-type: none"> <li>■ CD4</li> <li>■ VL</li> <li>■ ALT</li> </ul>	<ul style="list-style-type: none"> <li>■ Staging, 6-monthly</li> <li>■ Baseline, 6-monthly</li> <li>■ Baseline, week 2, 4 and 8, thereafter 6-monthly</li> </ul>

**Staging** = initial testing for all patients when being referred for ART

**Baseline** = testing for ART eligible patients, at initiation of ART

### Immune reconstitution syndrome

- Patients with advanced HIV disease, particularly those with a CD4 count of less than 50 cells/mm<sup>3</sup>, may become ill with an immune reconstitution illness during the first few weeks of ART. They may have signs and symptoms of sweats, loss of weight, cough, persistent fever, shortness of breath, decreasing visual acuity, to name a few.
- Immune reconstitution illnesses occur when improving immune function unmasks a previously occult opportunistic infection. This means an infection that was present in the patient's body, but was not clinically evident.
- Tuberculosis is a common immune reconstitution illness in South Africa.
- An immune reconstitution illness is not indicative of drug failure or drug side effects. It is not a reason to stop ART, or to change the antiretroviral regimen.
- Opportunistic infections may present in atypical ways during this phase of immune reconstitution. Patients need to be referred to an experienced HIV clinician for advice regarding investigation and management.

### Reasons for changing ART

**Treatment failure can be defined as virologic, immunologic and/or clinical.**

- Treatment failure results from failure to suppress viral replication with the development of viral resistance.
- Secondary virologic failure is a 1-log (10 fold) increase in the lowest recorded level.
- Immunologic failure is defined as a 30% drop in CD4 count from peak value, or a return to pre-ART baseline or lower.
- Clinical failure is progression of disease with the development of opportunistic infections or malignancy occurring 3 months or more after initiation of ART.

## ANTIRETROVIRAL TREATMENT (ART) IN ADULTS

**Clinical failure must be distinguished from immune reconstitution syndrome.**

- A favourable CD4 T-cell response can occur with incomplete viral load suppression, and might not indicate an unfavourable prognosis. This must be considered with regard to the urgency of changing therapy in the presence of low-level viraemia.
- Continuation of existing therapy does not lead to rapid accumulation of drug-resistant virus in every patient.
- A reasonable strategy is maintenance of the regimen, with redoubled efforts at optimising adherence and increased monitoring.
- If it is determined that a patient should switch regimens due to treatment failure, there should be a switch from their first-line combination to a completely new standardised second-line regimen.

**N.B.**

**Patients who have experienced virological failure with good adherence may be changed to second-line therapy:**

- The patient's response to therapy will be monitored by CD4 count and viral load.
- Assessment will be after 6 months.
- At each visit the patient's viral load will place them into one of three categories. Their category will determine further outcome and programme response (See table on next page).

**Table 5: Viral load monitoring**

Viral load (VL)	Response
<400 copies/mm <sup>3</sup>	<ul style="list-style-type: none"> <li>■ 6-monthly viral load monitoring continues.</li> <li>■ Routine adherence support.</li> </ul>
400-5 000 copies/mm <sup>3</sup>	<p><b>Repeat viral load in 6 months</b></p> <ul style="list-style-type: none"> <li>■ Begin step-up adherence package. Review at next 6-month viral load check.</li> <li>■ If &lt;400, return to routine 6-monthly monitoring and adherence support.</li> <li>■ If still between 400 and 5 000, continue with step-up adherence package. Repeat viral load at 6 months.</li> <li>■ If &gt;5 000, despite stepped-up adherence support, switch to second-line therapy only if adherence is &gt;80%.</li> </ul>
>5 000 copies/mm <sup>3</sup>	<p><b>Repeat viral load in 3 months</b></p> <ul style="list-style-type: none"> <li>■ Begin step-up adherence package. Review at next 6-month viral load check.</li> <li>■ If &lt;400, return to routine, 6-monthly monitoring and adherence support.</li> <li>■ If between 400 and 5 000, continue with step-up adherence package. Repeat viral load again after a further 6 months.</li> <li>■ If &gt;5 000, despite stepped up adherence support, switch to second-line therapy only if adherence is &gt;80%.</li> </ul>

## ANTIRETROVIRAL TREATMENT (ART) IN ADULTS

### Second-line therapy – Regimen 2

Patients who continue to fail virologically despite demonstrated adherence may be changed to Schedule 2. Before changing to Schedule 2, the patient should go through the treatment readiness and education process again. This would need to be carefully monitored as some patients might hide their non-adherence. Most patients will commence Schedule 2 as follows:

#### Figure 2: Second-line therapy for adults (Regimen 2)

- Zidovudine (AZT) 300 mg every 12 hours
- WITH**
- Didanosine (ddI) 400 mg once a day (250 mg daily if <60 kg), taken alone, dissolved in water on an empty stomach
- AND**
- Lopinavir/ritonavir (LPV/r) 400/100 mg every 12 hours

Patients need to keep their lopinavir/ritonavir safe, cool & dry (<25°C).

**N.B.**

**Didanosine must be taken alone, on an empty stomach, at least an hour before, or at least 2 hours after a meal. Less than 50% is absorbed if taken immediately after a meal. Tablets should be dissolved in at least 30 ml of water. No other liquids may be used to dissolve the tablets. You do not need to dissolve the enteric-coated version.**

### Clinical and laboratory monitoring in Regimen 2

#### Scheduled visits

Patients starting Regimen 2 need to come monthly for the first 3 months to see the doctor. Thereafter they should come 6-monthly or as required. Drugs need to be collected every month.

**Table 6: Summary of adult ART Regimen 2 and routine monitoring**

Regimen	Drugs	Monitoring tests	Frequency
2	AZT / ddI / lopinavir / ritonavir	<ul style="list-style-type: none"> <li>■ CD4</li> <li>■ FBC</li> <li>■ Fasting cholesterol and triglyceride</li> <li>■ Fasting glucose</li> </ul>	<ul style="list-style-type: none"> <li>■ Staging, 6-monthly</li> <li>■ Baseline, then monthly for 3 months, then 6 monthly (with CD4 and viral load)</li> <li>■ Baseline, 6 months and thereafter every 12 months</li> <li>■ Baseline and 12 months</li> </ul>

**Staging** = initial testing for all patients when being referred for ART

**Baseline** = testing for ART-eligible patients, at initiation of ART

**There is currently no requirement for viral load monitoring for patients in Regimen 2, in the public health sector.**

## ANTIRETROVIRAL TREATMENT (ART) IN ADULTS

### Unscheduled visits

- Clinical judgement will be used to assess whether additional safety bloods are required if a patient presents with an adverse event.
- NO extra CD4 counts or viral loads should be done. The only exception is repeating the viral load 6 months after a previous viral load  $>5\ 000$  copies/mm<sup>3</sup>.

### Treatment failure with Regimen 2

- Patients on second-line therapy who begin to fail virologically should receive increased adherence support, as described above.
- If they continue to fail virologically, in spite of showing increased adherence, their ART should be continued until there is not further clinical benefit from treatment. Where adherence is consistently  $<80\%$ , ongoing education and counselling is needed.
- If patients experience AIDS-defining (WHO Stage IV) illnesses on second-line therapy, they should be referred to an expert to discuss stopping ART, and starting palliative care.

### Prophylaxis of opportunistic infections:

- Co-trimoxazole prophylaxis must be continued in all patients on ART until the CD4 count is  $>200$  cells/mm<sup>3</sup>. It should be recommended if the CD4 count drops to  $<200$  cells/mm<sup>3</sup> when therapy fails.
- Patients who have had cryptococcal meningitis must continue taking fluconazole prophylaxis until the CD4 count is  $>200$  cells/mm<sup>3</sup>.
- Patients on IPT who start RT should complete their IPT regimen and be given pyridoxin supplement to prevent the risk of developing peripheral neuropathy.

### Concomitant tuberculosis in adults

**It is important to investigate these patients for tuberculosis before starting ART:**

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

- Observed weight loss of  $\geq 1,5$  kg over the past 4 weeks
- Cough  $>2$  weeks
- Night sweats  $>2$  weeks
- Fever  $>2$  weeks

Tuberculosis is a common co-morbid illness with HIV. If an HIV-infected patient has symptoms suggestive of TB, 2 sputum specimens should be collected for 2 smears and a TB culture.

**If TB is diagnosed, there are 2 scenarios to consider:**

### The patient develops tuberculosis while on ART

ART should be continued throughout TB treatment, with changes to regimens and monitoring as follows:

- **Regimen 1:** A change to efavirenz is recommended for patients on nevirapine wherever possible. If this is not possible (e.g. intolerant of efavirenz or significant risk of falling pregnant), nevirapine may be continued in selected cases, with monthly ALT monitoring. Discuss these cases with an ART expert.
- **Regimen 2:** Lopinavir/ritonavir should change to lopinavir/ritonavir (dose: 400/400 mg every 12 hours – 3 extra caps of ritonavir). This should be continued until 2 weeks after completion of TB treatment, when the extra ritonavir can be stopped.

## ANTIRETROVIRAL TREATMENT (ART) IN ADULTS

### The patient presents with TB before commencing ART

- If the patient has no history of WHO Stage IV illness, and has a CD4 count of more than 200 cells/mm<sup>3</sup>, ART is not yet needed. The need for ART should be reassessed on completion of TB treatment.
- If the patient has a history of WHO Stage IV illness, and/or a CD4 count of less than 200 cells/mm<sup>3</sup>, complete 2 months of TB therapy before commencing ART.
- If the patient has a CD4 count of less than 50 cells/mm<sup>3</sup>, or other serious HIV-related illnesses, make sure that the patient is tolerating TB treatment before initiating ART. The patient should complete at least 2 weeks of TB treatment before initiating ART. Patients in this group should be started on first-line therapy consisting of stavudine, lamivudine and efavirenz. Nevirapine should generally be avoided because drug levels might decrease. There is also a danger that shared hepato-toxicity might increase.

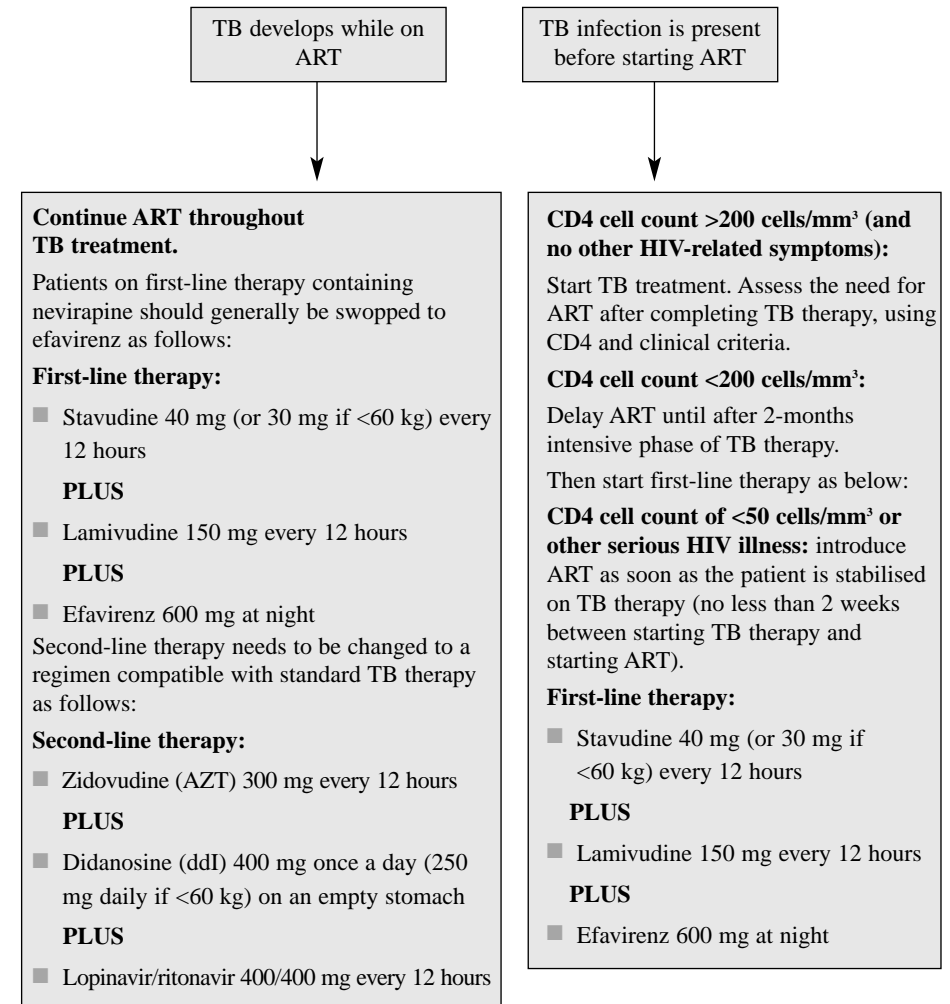
**Table 7: Shared side-effects of TB and ART**

Side effects	ART	Tuberculosis treatment
Nausea	didanosine, zidovudine, ritonavir, saquinavir	pyrazinamide
Hepatitis	nevirapine, efavirenz	rifampicin, isoniazid, pyrazinamide
Peripheral neuropathy	stavudine, didanosine	isoniazid
Rash	nevirapine, efavirenz	rifampicin, isoniazid, pyrazinamide

#### Patients should be counselled before therapy about the following:

- Treatment for TB together with ART involves taking a large number of tablets. Patients may struggle with adherence.
- When ART is commenced, the patient's TB symptoms may temporarily worsen as part of immune reconstitution.

**Figure 3: How to treat adult patients with concomitant tuberculosis**



**N.B.**

**Remember that patients on TB medication and ART are taking a large number of tablets. They should be counselled before therapy.**

## ANTIRETROVIRAL TREATMENT (ART) IN ADULTS

### Pregnancy and antiretroviral treatment

#### Timing of initiation of ART during pregnancy

- Patients must be at least <34 weeks gestation to begin evaluation for ART. You should use the best dating criteria available.
- ART must begin no later than 36 weeks gestation to ensure maximal viral suppression. You should use the best dating criteria available.
- Patients greater than 34 weeks when identified with AIDS or unprepared to start ART by 36 weeks will receive standard PMTCT treatment.

#### Women who fall pregnant on ART

- Women who fall pregnant on efavirenz must be counselled about potential teratogenicity (myelomeningocele has been described in humans). If they decide to continue the pregnancy, efavirenz must be stopped, and nevirapine started (in their 1st trimester). All cases to be discussed with an antiretroviral specialist.
- Women who fall pregnant on stavudine, lamivudine and nevirapine should continue their ART throughout pregnancy. ALTs should be performed monthly.
- Women who fall pregnant on second-line therapy (zidovudine, didanosine and lopinavir/ritonavir) should continue their ART throughout pregnancy. Full blood counts should be performed monthly.

#### Monitoring therapy during antenatal care

- If ART is provided in the antenatal clinic, patients should return weekly for visits for at least 4 weeks. They can go back to twice weekly visits until 38 weeks gestation. Then weekly visits can begin again.
- At each follow-up visit, providers should determine patient adherence to ART.
- At each follow-up visit, providers should determine if the patient is experiencing any adverse reactions to the ART.
- Routine lab testing should follow established national maternal guidelines.

### Therapy during delivery

- All ART initiated during antenatal care should be continued on the same schedule.
- For patients undergoing Caesarean section, efforts should be made to ensure that they receive scheduled ART.
- After delivery, and in the postpartum ward, efforts should be made to ensure that patients receive scheduled ART.

### Care from delivery until 6-weeks postpartum

- Patients discharged from the delivery facility will be asked to return to the delivery facility or the site where ART was administered during antenatal care. This is required for follow-up care until 6-weeks postpartum. This should improve postnatal care for these mothers.
- Follow-up care visits should be scheduled weekly.
- At the weekly visits, health care providers should ensure that patients are:
  - coping
  - adhering to their exclusive infant-feeding regimen
  - continuing to adhere to ART
- Providers should ensure that patients have adequate ART supplies.
- Providers should continue to monitor patients for complications related to delivery, HIV or ART. Patients with complications should be referred to the appropriate health care provider.
- Preparations should be made to transit the patient from the delivery or antenatal care ART site to the Service Point in the patient's community for long-term ART. Dedicated case managers should ensure that patients have:
  - An appointment for care at the ART Service Point. If appointments have not been kept, a suitable way to follow up patients must be implemented.
  - Directions to the ART Service Point
  - Transportation to the ART Service Point

## Transition to community care as part of the continuum of care

- Patients will be enrolled in the ART programme in the patient's community.
- Standard care guidelines will be applied to patients from 6 weeks after delivery.
- Patients who need palliative care should be referred to the appropriate agencies for:
  - home-based care
  - hospice care
  - families trained to provide such services with clinic back-up

**Figure 4: How to treat pregnant women**

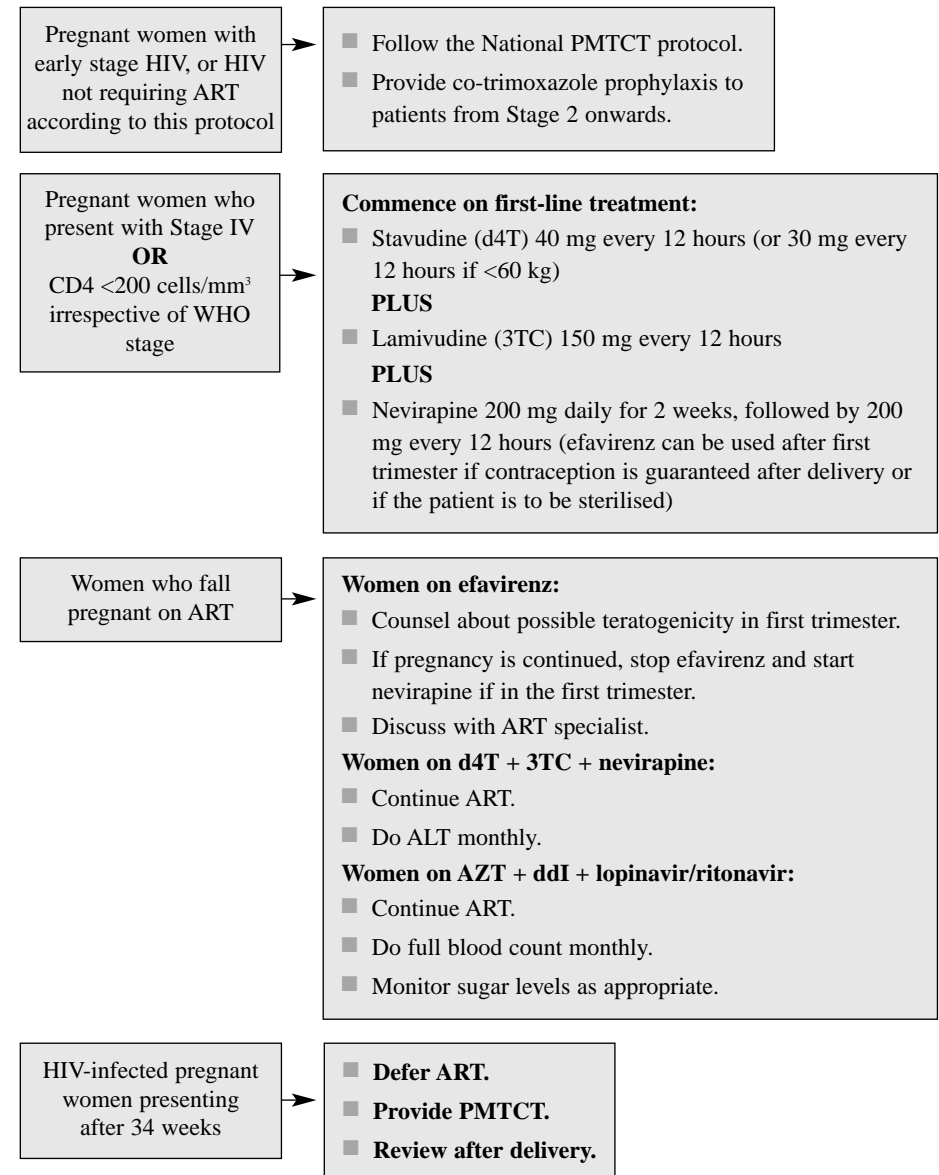
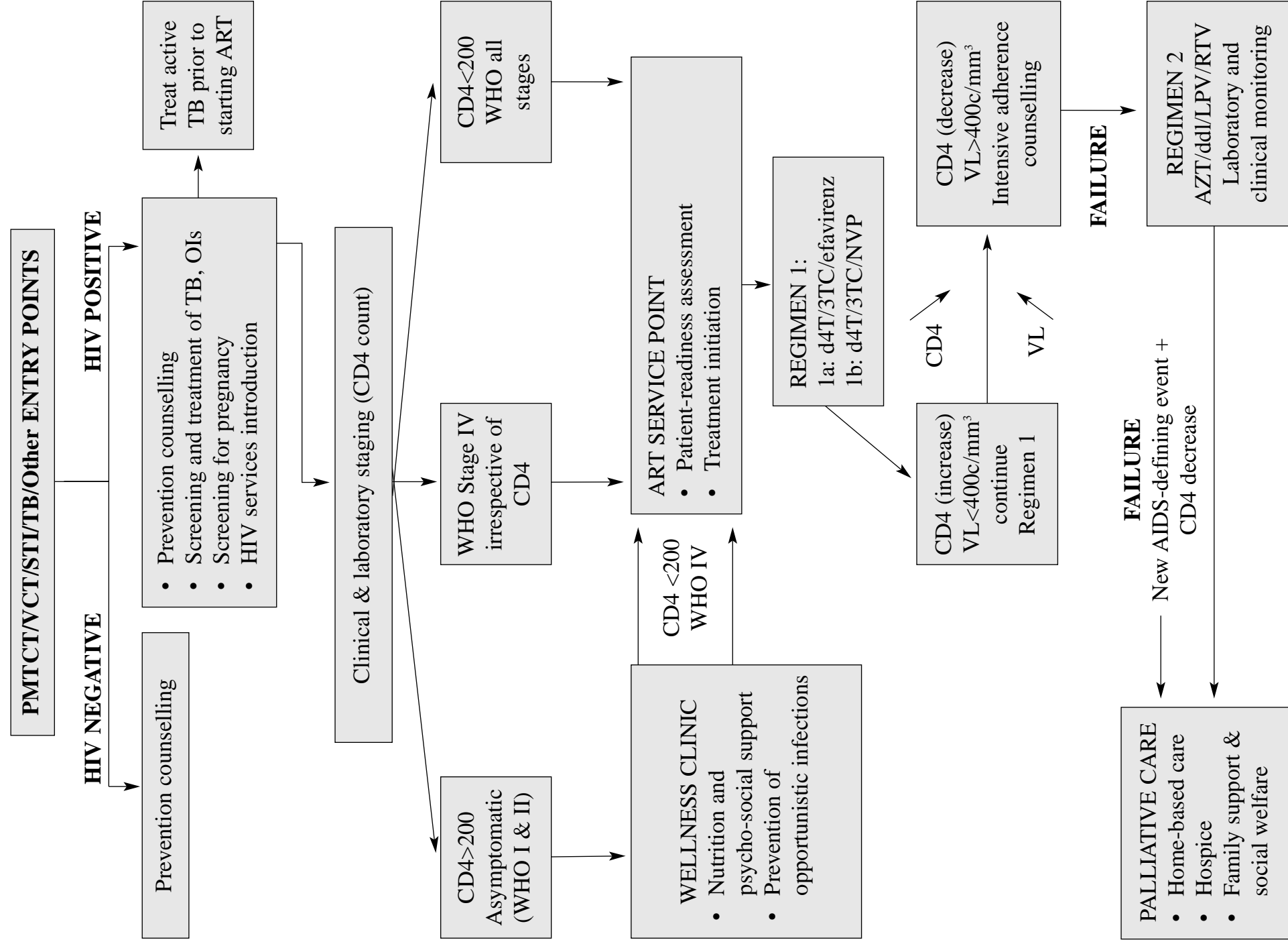




Figure 5: Adult HIV management flowchart



# SECTION 2: ANTIRETROVIRAL TREATMENT (ART) IN CHILDREN

## Diagnosing HIV infection in children

At present, the majority of children are diagnosed on the basis of symptomatic HIV disease and the positive HIV antibody test of the mother of the child. The child of an HIV-infected mother acquires HIV antibodies from his/her mother during pregnancy. These may persist in his or her blood until 15-18 months of age, even if the child is not infected with HIV. Thus a child may test HIV positive without actually being infected.

Therefore, when using the HIV antibody test, it is not possible to tell whether a newborn infant has already been infected with HIV.

Additional techniques exist for the detection of virus in children under 18 months. HIV infection can be diagnosed in most infected infants by the age 6 weeks by using DNA PCR technique.

### Testing for HIV should only be done after the following:

- Pre-test counselling has been provided to the parent(s) or legal guardian.
- Informed consent is obtained from the parent(s) or legal guardian.

Post-test counselling should be provided once results are available.

Figure 6, page 28, offers assistance in deciding when to test a child, based on the mother's HIV status.

**Rapid HIV testing** may be less reliable in children than in adults. **Rapid HIV tests should not routinely be performed in children.**

**N.B.**

**Remember: Be careful not to mislabel a child by assigning an HIV-positive status to the child if the mother is HIV positive. The correct term to use is HIV-EXPOSED. Also, no child should be labelled HIV-positive based on an HIV ELISA under 18 months of age.**

### HIV diagnostic protocol for abandoned infants 6 weeks of age

- Perform an HIV ELISA to assess HIV-exposure at birth (omit if the HIV ELISA of the mother is confirmed positive).
- If HIV antibody of mother or infant is positive, perform HIV DNA PCR.

### 3 months of age

- Repeat HIV DNA PCR to confirm 6-week result (omit if HIV ELISA was negative).

**N.B.**

- **A clinical examination to assess for signs and symptoms of HIV infection should be performed during all visits, and especially at 6 weeks and 3 months of age. The infant should thereafter be followed up as per recommendations for all children (see above).**
- **Postnatal transmission of HIV infection is likely to be evident by 6 weeks after termination of breast-feeding. However it is recommended that the final qualitative HIV PCR test on abandoned infants be performed 3 months after breast-feeding has ceased.**

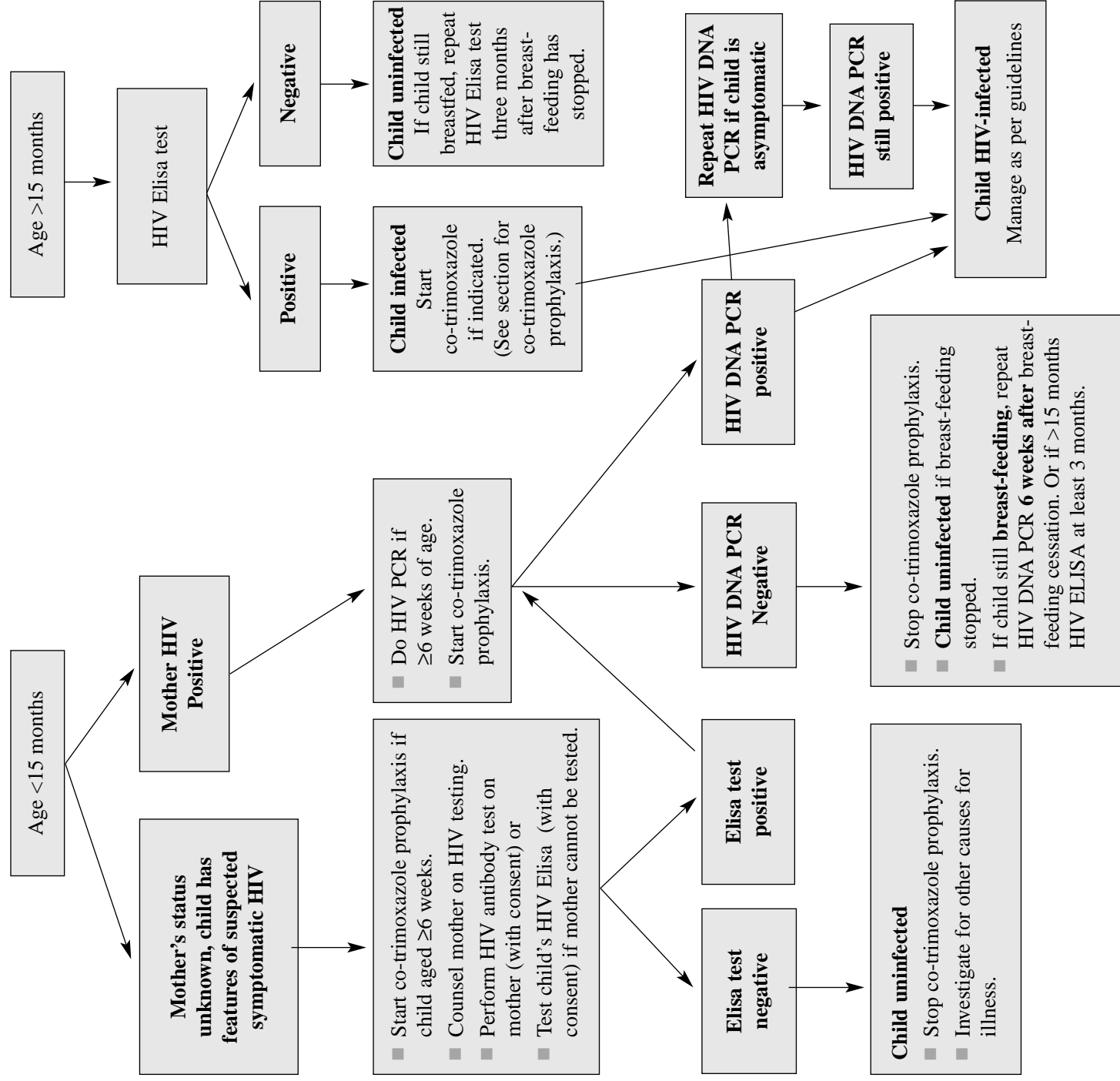
## Goals of antiretroviral treatment

The goal of ART for children is to increase survival, and to decrease HIV-related morbidity and mortality.

- The child's CD4 count should rise and remain above the baseline count.
- The child's viral load should become undetectable (<400 copies/mm<sup>3</sup>) and remain undetectable on ART.
- In some children, a suppressed though detectable viral load, with sustained elevation in CD4 count and absence of intercurrent and/or opportunistic infection, may be the best achievable goal.

Initially ART delivery will occur at higher levels of health care, and will be doctor-initiated as this is where expertise exists currently. However, as the programme expands, provision of this treatment will occur at all levels by doctors and nurses.

Figure 6: HIV testing guidelines in children



**N.B.**

- Contact laboratory if the results are inconsistent.
- PCR testing may not be available immediately at all centres.
- All children, regardless of exposure to HIV infection and of HIV status should be followed up monthly in the first year of life, and 3 months thereafter till the age of 5 years (according to IMCI and WHO guidelines for management of children).

## Selection of patients for antiretroviral treatment

### Criteria for commencing ART in children

Children being considered for ART will need to meet both medical and psycho-social criteria before starting therapy.

#### Medical criteria:

- Recurrent hospitalisations (>2 admissions per year) for HIV-related disease, or prolonged hospitalisation (>4 weeks)

**OR**

- Modified WHO Stage II or III disease

**OR**

- CD4 percentage <20% in a child under 18 months old, irrespective of disease stage

**OR**

- CD4 percentage <15% in a child over 18 months old, irrespective of disease stage.

(See Appendix 2 for Modified WHO Staging, page 80)

#### Psycho-social considerations (not exclusion criteria)

These factors are extremely important for the success of the programme, and need to be adhered to. The principle is that adherence must be at least probable.

- An identifiable adult who is able to administer medication (all efforts should be made to ensure that the social circumstances of vulnerable children, e.g. orphans, are addressed so that they too can receive treatment.
- Demonstrated reliability in the adult caregiver i.e. has attended three or more scheduled visits to the service point and the immunisation record of child is up-to-date.
- Supportive social environment as for adults (see adult section).
- Disclosure to another adult living in the same house is encouraged so that there is someone else who can assist with the child's ART.

Previous record of adherence to nutritional supplements or other chronic care regimens, such as TB drugs, may help to identify children who are at risk of poor adherence. The patient and caregiver have to be able to attend the antiretroviral centre on a regular basis. Transport may need to be arranged for patients in rural areas or for those remote from the treatment site.

### Treatment of mothers, caregivers and other family members

- Always ask about the caregiver's health, and the health of other members of the family.
- Ensure that mothers and other family members have access to medical care when necessary, including ART if needed.

## Process for initiation of antiretroviral treatment

### Induction schedule

### First screening visit 2 – 4 weeks before starting ART

#### When the child arrives with the referral letter:

- Complete the history and clinical evaluation, including weight and height.
- Update growth chart.
- Calculate surface area:  $BSA = \sqrt{\frac{Hgt(cm) \times Wgt(kg)}{3600}} \text{ m}^2$   
(see paediatric dosing schedule – Appendix 3, page 82).
- Ensure that TB is adequately excluded:
  - History of TB contact
  - Chest radiograph (CXR)
  - Gastric aspirates or induced sputum if abnormal CXR
  - Mantoux test if child is less than 5 years
  - Abdominal ultrasound (if clinically indicated and possible) for lymphadenopathy

- Name the caregiver responsible for medication, and make sure that this person is present during all discussions regarding ART.
- Explain the importance of adherence, as well as tools to help improve adherence. These include the use of pillboxes, syringes, diary cards. They should also bring back all empty containers and unused drugs at all follow-up visits.
- Explain the side-effects of ART with emphasis on problems associated with the chosen drug regimen.
- Exact drug schedule for the child must be explained to the guardian.
- Do baseline investigations according to Table 13, page 47.

### **In the meantime the treatment counsellor will visit the patient at home to assess:**

- Home circumstances
- Correctness of the contact details
- Support structures including disclosure
- Drug storage facilities

Before the second visit the multi-disciplinary team should meet and assess patient readiness (taking all available information into account).

### **Second Visit**

- Clinical and biological assessment
- Information and education session
- Adherence counselling to caregiver

### **Multi-disciplinary team discussion**

Children who do not meet the treatment readiness criteria should be referred back to their local clinic with a detailed letter. This should include reason for deferment of ART and possible solutions to enable treatment uptake at a later stage.

### **Treatment Initiation Visit 1**

- Complete history and clinical evaluation including weight and height.
- Update growth chart.
- Calculate surface area:  $BSA = \sqrt{\frac{Hgt(cm) \times Wgt(kg)}{3600}} \text{ m}^2$   
(see paediatric dosing schedule – Appendix 3, page 82).
- Check baseline blood results (taken at first screening visit).
- Explain the importance of adherence and illustrate tools to help improve adherence. This could include the use of pill boxes, syringes, diary cards, as well as the bringing back of all empty containers and unused drugs to all follow-up visits where feasible.
- Explain possible side-effects of ART with emphasis on the problems associated with the chosen drug regimen.
- Explain drug schedule for the child to the guardian, using the diary card.
- Commence ART.
- Prescribe medication for 2 weeks, calculating total volume of medicine and number of units required.
- Issue pillboxes, syringes and diary cards.
- Arrange adherence phone call in 1 week (if possible).
- Arrange follow-up visit after 2 weeks.

## Antiretroviral treatment visits

### Scheduled Visits

#### Treatment Visit 2 (2 weeks after therapy initiation)

- Complete history and clinical evaluation including weight and height.
- Update growth chart.
- Calculate surface area:  $BSA = \sqrt{\frac{Hgt(cm) \times Wgt(kg)}{3600}}$  m<sup>2</sup>  
(see paediatric dosing schedule – Appendix 3, page 82.)
- Adherence assessment (3 day recall).
- Reconcile returned empty containers with volume of medication prescribed for prior interval where feasible.
- Look for signs of toxicity (e.g. right upper quadrant tenderness, pallor, rash).
- Do safety investigations according to Table 13, page 47.
- Explain exact drug schedule for the child to the guardian, using the diary card.
- Issue medication for 2 weeks calculating total volume of medicine and number of units required.
- Issue pillboxes, syringes and diary cards where needed.
- Arrange follow-up visit after 2 weeks.

#### Treatment Visit 3 (4 weeks after initiation of treatment)

- Complete history and clinical evaluation including weight and height.
- Update growth chart.
- Calculate surface area:  $BSA = \sqrt{\frac{Hgt(cm) \times Wgt(kg)}{3600}}$  m<sup>2</sup>  
(see paediatric dosing schedule – Appendix 3, page 82).
- Adherence assessment (3 day recall).
- Reconcile returned empty containers with volume of medication prescribed for prior interval.
- Look for signs of toxicity (e.g. right upper quadrant tenderness, pallor, rash).
- Explain exact drug schedule for the child to the guardian, using diary card.
- Adjust drug schedule if needed (e.g. nevirapine).
- Do safety investigations according to Table 13, page 47.
- Issue medication for 4 weeks, calculating total volume of medicine and number of units required.
- Issue pill boxes, syringes and diary cards where needed.
- Arrange follow-up visit after 4 weeks.

## Treatment Visit 4 (8 weeks after initiating therapy)

- Complete history and clinical evaluation including weight and height.
- Update growth chart.
- Calculate surface area:  $BSA = \sqrt{\frac{Hgt(cm) \times Wgt(kg)}{3600}} \text{ m}^2$   
(see paediatric dosing schedule – Appendix 3, page 82).
- Adherence assessment.
- Reconcile returned empties with volume of drug issued at last visit.
- Look for signs of toxicity (e.g. right upper quadrant tenderness).
- Do safety investigations according to Table 13, page 47.
- Explain exact drug schedule for the child to the guardian.
- Issue medication for 4 weeks calculating total volume of medicine and number of units required.
- Enquire about full units of medication left over at home. Include these in assessment of adherence and calculation of number of units required for the next interval.
- Issue pillboxes, syringes and diary cards where needed.
- Arrange follow-up visit after 4 weeks.

## Schedule following visits at monthly intervals

This is to collect medication until Week 12 of therapy. Collect medication monthly with 3-monthly visits for clinical evaluation, toxicity bloods as per schedule. If unwell, they may need to be seen more frequently to exclude adverse events, immune reconstitution, infection or treatment failure.

### At each subsequent visit

- Repeat all the measures from Treatment Visit 4 above.
- When 3 monthly visits are initiated, make sure the guardian understands what it means to collect repeat medicines at monthly intervals until the next visit.
- At each visit, enquire about surplus units of medication at home. Include these in the calculation of volumes to be issued.

## Recommended regimens in children

See Table 8, below and Table 9, page 40.

## Paediatric first-line therapy – Regimen 1

Unless contra-indicated, all children will commence therapy on the regimen indicated in Table 8 below.

**Table 8: Paediatric first-line therapy – Regimen 1**

	6 months – 3 years	>3 years old and >10 kg
First-line	<ul style="list-style-type: none"> <li>■ Stavudine (d4T)</li> <li>■ Lamivudine (3TC)</li> <li>■ Lopinavir/ritonavir</li> </ul>	<ul style="list-style-type: none"> <li>■ Stavudine (d4T)</li> <li>■ Lamivudine (3TC)</li> <li>■ Efavirenz</li> </ul>

### General comments:

- All infants under 6 months of age who require treatment with ART should be started on treatment under specialist supervision.
- D4T solution require re Fridgeration. If no fridge is available, D4T capsules may be opened and dissolved, and the required amount administered to the child. The rest can be discarded.
- Nevirapine may be used in place of lopinavir/ritonavir if this has not been used to prevent mother-to-child transmission (PMTCT) of HIV.
- If nevirapine was used for PMTCT, one may consider using lopinavir/ritonavir in the first-line regimen for children under 3 years of age.
- Switch to tablets or capsules from syrups or solutions as soon as possible.
- Children may occasionally need to change a drug from the first-line regimen to one from the second-line regimen, because of intolerance or a serious adverse reaction. Swapping limits the patient's second-line treatment options. The decision to swop must be made by a doctor with antiretroviral experience.

- Lopinavir/ritonavir needs to be kept cool (<25 degrees Celsius).
- Didanosine must be taken alone, on an empty stomach, at least an hour before (or 2 hours after) a meal. Tablets should be dissolved in at least 30 ml of water. It is important to use 2 tablets of didanosine, e.g. if the child needs 100 mg prescribe 2 x 50 mg tablets.

**Swapping drugs must be made by a doctor trained in ART.**

**N.B.**

**Ritonavir and lopinavir/ritonavir can be substituted by nevirapine in children <3 years with no prior nevirapine exposure. For children >3 years, efavirenz can be used as 3rd drug.**

### Immune reconstitution disease (IRD)

#### Definition:

Paradoxical clinical deterioration after starting ART, due to the improving immune system interacting with organisms that have colonised the body during the early stages of HIV infection.

It is important to differentiate immune reconstitution disease with treatment failure.

#### Causes:

A wide range of pathogens may induce IRD including *Mycobacterium tuberculosis* (MTB), *Mycobacterium avium complex*, *Mycobacterium leprae*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Aspergillus terreus*, *Candida albicans*, *Pneumocystis carinii*, CMV, JC virus, Human Herpes viruses, Human Papilloma virus and hepatitis B and C viruses (HBV, HCV).

#### Presentation:

IRD usually presents during the first 6 weeks after starting ART. Clinical presentations vary and depend on the causative organism and the organ-system that is colonised. For example, IRD caused by MTB may present with:

- high fever
- lymphadenopathy
- worsening of the original tuberculous lesion, and / or deteriorating chest radiographic manifestations including the development of a military pattern or pleural effusion.

#### Management:

Includes specific antimicrobial therapy e.g. TB treatment for IRD caused by MTB. In severe reactions glucocorticosteroids and /or temporary discontinuation of ART may help.

## Paediatric second-line therapy – Regimen 2

#### Procedure for introduction of second-line therapy:

- Do not rush into second-line therapy.
- First check adherence. If it is not possible to improve adherence, attempt directly observed therapy (DOT) with a health care worker or trusted 'other' family member or friend.
- Ensure second-line therapy does not include any drugs used in first-line therapy.

Before considering a move to second-line therapy, consult a paediatrician expert in ART.



**Table 9: Reasons to move to second-line ART in children**

Virological	Clinical	Immunological
<ul style="list-style-type: none"> <li>Rebound of viral load to baseline.</li> <li>A detectable viral load may be tolerated in children, providing that growth and elevated CD4 count are sustained.</li> </ul>	<ul style="list-style-type: none"> <li>Persistent oral thrush, which is refractory to treatment.</li> <li>New evidence of Stage III disease (not immune reconstitution disease – see below).</li> </ul> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>Short intercurrent episodes of pneumonia, lower respiratory tract infection (LRTI) and gastro-enteritis should not be regarded as clinical failure.</li> <li>Presentation with TB while on first-line therapy is <b>NOT</b> an indication to switch to second-line therapy, even though it can present as progression to Stage III disease.</li> <li>Immune reconstitution disease may present as a new Stage III event. However, this will usually be associated with a CD4 count and / or percentage which have improved over time. This is <b>NOT</b> an indication to switch to second-line therapy.</li> </ul>	<ul style="list-style-type: none"> <li>A persistent decline in the CD4% over 2 months in the absence of TB.</li> </ul> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>The CD4% should <b>NOT</b> be measured during an intercurrent infection – but preferably a month post resolution.</li> <li>If there is a modest decline in CD4% (&lt;5%), and if no failure to thrive, do not change medication, but monitor closely.</li> </ul>

**Table 10: Paediatric second-line therapy – Regimen 2**

	6 months – 3 years	>3 years old and >10 kg
First-line	<ul style="list-style-type: none"> <li>Zidovudine (AZT)</li> <li>DDI</li> <li>Nevirapine</li> </ul>	<ul style="list-style-type: none"> <li>Zidovudine (AZT)</li> <li>DDI</li> <li>Lopinavir/ritonavir</li> </ul>

Didanosine must be taken alone, on an empty stomach, at least an hour before (or 2 hours after) a meal. Tablets should be dissolved in at least 30 ml of water.

**N.B.**

**For Regimen 2 where there has been prior exposure to nevirapine or efavirenz. Lopinavir/ritonavir can be substituted – as in Regimen 1.**

## Dosage of ART:

Provide antiretroviral dosages according to dosing table appendix 4. Paediatric doses apply to children who are prepubescent or in early puberty. Adult doses should be given to adolescents who are Tanner Stage 3-4. See Table 11 below.

**Table 11: Tanner Staging of Puberty**

Stage	Pubic Hair	Breasts
1	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, straight, medial border labia	reast and papilla elevated as small mound; areola diameter increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant but less than adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature; nipple projects, areola part of general breast contour

**Table 12: Paediatric dosages per body surface area**

Body surface (m <sup>2</sup> )	Volume (ml) of each dose MORNING / 12hrs later	Volume (ml) of each dose MORNING / 12hrs later	Amount per dose MORNING / 12hrs later
	Zidovudine 10mg/mg syrup	Ritonavir 80mg/ml syrup	Didanosine 25,50, 100mg tablets
0.30	5.5 ml	1.5 ml	25 mg
0.35	6.0 ml	1.75 ml	25 mg
0.40	7.0 ml	2.0 ml	25 mg
0.45	8.0 ml	2.25 ml	25 mg
0.50	9.0 ml	2.5 (or 2 x 100 mg caps)	50 mg
0.55	10.0 (or 1 x 100 mg caps)	2.75 ml	50 mg
0.60	11.0 ml	3.0 ml	50 mg
0.65	12.0 ml	3.25 ml	50 mg
0.70	13.0 ml	3.5 ml	50 mg
0.75	13.5 ml	3.75 ml	75 mg
0.80	14.5 ml	4.0 ml	75 mg
0.85	15.0 (or half 300 mg tab)	4.25 ml	75 mg
0.90	16.0 ml	4.5 ml	75 mg
0.95	17.0 ml	4.75 ml	75 mg
1.00	18.0 ml	5.0 (or 4 x 100 mg caps)	75 mg
1.05	19.0 ml	5.25 ml	100 mg
1.10	20.0 (or 2 x 100 mg caps )	5.5 ml	100 mg
			CONTINUE 100 mg EVERY 12 HRS UP TO 1.4 BSA

## Concomitant tuberculosis in children

Tuberculosis is a common co-morbid illness with HIV. There are two scenarios to consider:

### Child presents with TB before commencing ART

- Complete TB therapy if possible before commencing ART OR delay ART for at least 2 months.
- If the child has failed the nevirapine vertical transmission programme, or is less than 3 years old or weighs less than 10 kg, use lopinavir/ritonavir (with ritonavir at the same dosage as lopinavir) as a third drug.
- If the child was not on the nevirapine vertical transmission programme, and is more than 3 years old and weighs more than 10 kg, use efavirenz as the third drug.
- Monitor ALT monthly for the first 6 months of therapy, and then as clinically indicated.

### Child develops TB while on ART

- If the child is on lopinavir/ritonavir, then increase ritonavir to same dosage as lopinavir.
- If the child is on nevirapine, and is less than 3 years old or weighs less than 10 kg, switch to lopinavir/ritonavir (with ritonavir at the same dosage as lopinavir).
- If the child is on nevirapine, and is more than 3 years old and weighs more than 10 kg, switch to efavirenz.
- If the child is unable to tolerate the large number of drugs, ART may have to be interrupted until TB therapy has been completed. Discuss all cases with a paediatrician with antiretroviral experience, before interrupting therapy.
- Monitor ALT monthly.

**Discuss all cases with a paediatrician with antiretroviral experience, before interrupting therapy.**

**PCP prophylaxis** may be discontinued when the CD4 percentage is consistently >20% for >6 months.

# ANTIRETROVIRAL TREATMENT (ART) IN CHILDREN

**Table 13: Paediatric dosages per body weight**

Weight (kg)	Volume (ml) of EACH dose MORNING / 12 HRS LATER	Volume (ml) of EACH dose MORNING / 12 HRS LATER	Volume (ml) of EACH dose MORNING / 12 HRS LATER		Volume (ml) of EACH dose MORNING / 12 HRS LATER	Amount (mg) of ONE DOSE ONLY (bedtime)
	STAVUDINE (d4T) 1 mg / ml syrup	LAMIVUDINE (3TC) 10 mg / ml syrup	NEVIRAPINE 10 mg / ml		ABACAVIR 20 mg / ml	EFAVIRENZ 50 and 200 mg caps
	TWICE	TWICE	1 – 14 DAYS ONCE	AFTER 14 DAYS TWICE	TWICE	ONCE
4	4 ml	1.5 ml	1.5 ml	3.0 ml	1.6 ml	200 mg
5	5 ml	2.0 ml	2.0 ml	3.5 ml	2 ml	200 mg
6	6 ml	2.5 ml	2.5 ml	4.0 ml	2.4 ml	200 mg
7	7 ml	3.0 ml	3.0 ml	5.0 ml	2.8 ml	200 mg
8	8 ml	3.0 ml	3.0 ml	5.5 ml	3.2 ml	200 mg
9	9 ml	3.5 ml	3.5 ml	6.0 ml	3.6 ml	250 mg
10	10 ml	4.0 ml	4.0 ml	7.0 ml	4 ml	250 mg
11	11 ml	4.5 ml	4.5 ml	8.0 ml	4.4 ml	250 mg
12	12 ml	5.0 ml	5.0 ml	8.5 ml	4.8 ml	250 mg
13	13 ml	5.0 ml	5.0 ml	9.0 ml	5.2 ml	250 mg
14	14 ml	5.5 ml	5.5 ml	10.0 ml	5.6 ml	300 mg
15	15 ml	6.0 ml	6.0 ml	10.5 ml	6 ml	300 mg
16	16 ml	6.5 ml	6.5 ml	11.0 ml	6.4 ml	300 mg
17	17 ml	7.0 ml	7.0 ml	12.0 ml	6.8 ml	300 mg
18	18 ml	7.0 ml	7.0 ml	12.5 ml	7.2 ml	300 mg
19	19 ml	7.5 ml	7.5 ml	13.5 ml	7.6 ml	350 mg
20	20 ml	8.0 ml	8.0 ml	14.0 ml	8 ml	350 mg
21	21 ml	8.5 ml	8.5 ml	15.0 ml	8.4 ml	350 mg
22	22 ml	9.0 ml	9.0 ml	15.5 ml	8.8 ml	350 mg
23	23 ml	9.0 ml	9.0 ml	16.0 ml	9.2 ml	350 mg
24	24 ml	9.5 ml	9.5 ml	17.0 ml	9.6 ml	350 mg
25	25 ml	10.0 ml	10.0 ml	17.5 ml	10 ml	350 mg
26	26 ml	10.5 ml		18.0 ml	10.4 ml	350 mg
27	27 ml	11.0 ml		19.0 ml	10.8 ml	400 mg
28	28 ml	11.0 ml		19.5 ml	11.2 ml	400 mg
29	29 ml	11.5 ml		20.0 ml (1 x 200 mg tab)	11.6 ml	400 mg
30	30 ml	12.0 ml		20.0 ml (1 x 200 mg tab)	12 ml	400 mg
31	30 ml	12. ml		20.0 ml (1 x 200 mg tab)	12.4 ml	400 mg
32	30 ml	13.0 ml		20.0 ml (1 x 200 mg tab)	12.8 ml	400 mg
33	30 ml	13.5 ml		20.0 ml (1 x 200 mg tab)	13.2 ml	600 mg
34	30 ml	13.5 ml		20.0 ml (1 x 200 mg tab)	13.6 ml	600 mg
35	30 ml	14.0 ml		20.0 ml (1 x 200 mg tab)	14 ml	
36	30 ml	14.5 ml		20.0 ml (1 x 200 mg tab)	14.4 ml	
37	30 ml	15.0 ml (1 x 150 mg tab)		20.0 ml (1 x 200 mg tab)	14.8 ml	
>37 up to 39 kg	30 ml	15.0 ml (1 x 150 mg tab)		20.0 ml (1 x 200 mg tab)	300 mg tab	
> 40 up to 59 kg	30 ml	15.0 ml (1 x 150 mg tab)		20.0 ml (1 x 200 mg tab)	300 mg tab	
> 60 kg	40 ml	15.0 ml (1 x 150 mg tab)		20.0 ml (1 x 200 mg tab)	300 mg tab	



**Table 15: Dosage and frequency of ART in children**

Regimen	Test	Frequency
ddl / AZT / efavirenz	<ul style="list-style-type: none"> <li>■ CD4</li> <li>■ VL</li> <li>■ FBC</li> </ul>	<ul style="list-style-type: none"> <li>■ Staging, 6-monthly</li> <li>■ Baseline, 6-monthly</li> <li>■ Baseline, then monthly for 3 months, then 6 monthly (with CD4 and viral load) thereafter</li> </ul>
ddl / ABC / efavirenz	<ul style="list-style-type: none"> <li>■ CD4</li> <li>■ VL</li> </ul>	<ul style="list-style-type: none"> <li>■ Staging, 6-monthly</li> <li>■ Baseline, 6-monthly</li> </ul>
AZT / ddl / lopinavir / ritonavir	<ul style="list-style-type: none"> <li>■ CD4</li> <li>■ VL</li> <li>■ FBC</li>   <li>■ Fasting cholesterol</li> <li>■ Fasting glucose</li> <li>■ Fasting triglycerides</li> </ul>	<ul style="list-style-type: none"> <li>■ Staging, 6-monthly</li> <li>■ Baseline, 6-monthly</li> <li>■ Baseline, then monthly for 3 months, then 6 monthly (with CD4 and VL thereafter)</li> <li>■ Baseline, 6-monthly</li> <li>■ Baseline, 6-monthly</li> <li>■ Baseline, 6-monthly</li> </ul>

**Staging** = initial testing for all patients when being referred for ART.

**Baseline** = testing for ART eligible patients, at initiation of ART.

Drugs	Formulations	Dosage (per dose)	Frequency	Storage	Comments
<b>Nucleoside Reverse Transcriptase Inhibitors (NRTI)</b>					
Zidovudine (ZDV) Retrovir®	Susp: 10 mg/ml Caps: 100 mg, 250 mg	90-180 mg/m <sup>2</sup> 180 mg/m <sup>2</sup>	3 2	Room temperature	
Didanosine (ddl) Videx®	Susp: 10 mg/ml Tabs: 25 mg, 50 mg, 100 mg, 150 mg	90-120 mg/m <sup>2</sup>	2 Can give total daily dosage x 1 in older children	Refrigerate suspension	<ul style="list-style-type: none"> <li>■ Half hour pre-meals or 1 hour after meals.</li> <li>■ Use single daily dose if necessary for compliance.</li> </ul>
Stavudine (d4T) Zerit®	Susp: 1 mg/ml Caps: 20 mg, 30 mg, 40 mg	1 mg / kg	2	Refrigerate suspension	<ul style="list-style-type: none"> <li>■ Capsules stable in water suspension for 24 hours in refrigerator.</li> </ul>
Abacavir Ziagen®	Susp: 20 mg/ml Tabs: 300 mg	8 mg/kg	2 2	Room temperature	<ul style="list-style-type: none"> <li>■ BEWARE Hyper-Sensitivity Reaction</li> </ul>
Lamivudine (3TC®)	Susp: 10 mg/ml Tabs: 150 mg	4 mg/kg 2 mg/kg for neonates (up to 1 month old)	2	Room temperature	

(continues on following page.)

## ANTIRETROVIRAL TREATMENT (ART) IN CHILDREN

Drugs	Formulations	Dosage (per dose)	Frequency	Storage	Comments
<b>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)</b>					
Nevirapine Viramune®	Susp: 10 mg/ml Tabs: 200 mg	120-200 mg/m <sup>2</sup> start at 120 mg/m <sup>2</sup> daily for 14 days and increase to bd dosage if no rash or severe side-effects	2	Room temperature	Skin rash usually occurs in 1st 6 weeks; do not increase dosage until rash resolves. <b>BEWARE LIVER TOXICITY</b>
Efavirenz Stocrin®	Caps: 50,100 and 200 mg (Suspension available form manufacturer)	13-<15 kg: 200 mg 15-< 20 kg: 250 mg 20-<25 kg: 300 mg 25-<32.5 kg: 350 mg 32.5-<40 kg: 400 mg >40 kg: 600 mg	1	Room temperature	■ No data <3 yrs and <13 kg. Give at night to avoid CNS side-effects.
<b>Protease Inhibitors</b>					
Ritonavir Norvir®	Susp: 80 mg/ml	Start at 250 mg/m <sup>2</sup> /dose and increase by 50mg / m <sup>2</sup> every 2-3 days up to 400 mg/m <sup>2</sup> If <2 years of age 450 mg/m <sup>2</sup>	2		■ Take with food. Bitter; coat mouth with peanut butter or chocolate milk. ■ Take 2 hours apart from didanosine.

Drugs	Formulations	Dosage (per dose)	Frequency	Storage	Comments
Nelfinavir Vira-cept®	Susp: 50 mg/1gram Spoon and 200 mg per teaspoon  Tabs: 250 mg	Paediatric: 55 mg/kg (adolescent: 750 mg tds) Some experts use 35-45 mg/kg/dose tds <2 years of age	2		■ Give 2 hr pre-or 1 hr post-ddI. Best with light meal. Do not use with rifampicin. ■ Powder is 5% active drug and the rest is carrier powder. Most experts prefer to crush the tablets and suspend in milk or water or sprinkle on pudding.
<b>Protease Inhibitors</b>					
Lopinavir/ ritonavir Kaletra®	Oral solution 80 mg lopinavir (LPV) & 20 mg ritonavir (RTV) per ml caps 133 mg LPV/33 mg RTV	Patients not taking NVP or EFV – 230 mg LPV component/m <sup>2</sup> (max 400 mg LPV = adolescent dose) Patients taking NVP or EFV or ART experienced – 300 mg LPV component/m <sup>2</sup> max. 533 mg LPV = adolescent dose)	2		■ Oral solution and capsules should be refrigerated. ■ Can be kept at room temperature up to 250C if used within 2 months. ■ Administer with food. High-fat meal increases absorption, especially of the liquid preparation. ■ If co-administered with ddI, ddI should be given 1 hour before or 2 hours after lopinavir/ritonavir.

# SECTION 3: ANTIRETROVIRAL TREATMENT ADHERENCE

## General consideration

Adherence to ART is essential to maintain long-term health benefit and avoid development of drug resistance. It is not possible for health care providers to reliably predict which individuals will ultimately be adherent to their treatment plan. This is because adherence does not correlate with gender, cultural background, socio-economic or education level. Nor does it correlate with language barriers between provider and patient.

It is therefore essential to provide all patients with a comprehensive plan to support adherence. The plan must make use of multiple strategies and all members of the health care team, as well as family and community.

## Adherence assessment and monitoring

### Role of the health care team

There is evidence that there is less adherence as time progresses. Thus, monitoring and ongoing support of adherence is essential.

- New diagnoses or symptoms can influence adherence. For example, depression might require referral, management, and consideration of the short- and long-term impact on adherence.
- A trusting relationship between the patient and members of the health care team is essential.
- Optimal adherence requires full participation by the health care team: patient, family members and the community.
- Every patient interaction is an opportunity for reinforcement.
- Supportive and non-judgmental attitudes and behaviours will encourage patient honesty regarding adherence and problems.

### Clinicians should commit to the following:

- communication between clinic visits
- ongoing adherence, evaluation and monitoring
- timely response to any barriers such as adverse events or interim illness

Interim management during clinician holidays or other absences must be discussed with the patient. If there is sub-optimal adherence, there should be extra support e.g.:

- investigate new barriers
- recommend more visits
- enlist support of family/friends
- review teaching approach
- increase home visits

For all health care team members, specific training regarding ART and adherence should be offered and updated periodically. See Table 15 for adherence support methods, page 54.

## Adherence to ART

- Success of ART hinges on medication-taking behaviour.
- Ideal adherence means a patient must take more than 95% of their doses (i.e. missing less than 3 doses in a month).
- If a patient is taking less than 95% of their doses, they are at risk for developing viral resistance and ultimately virological failure.

**Patients taking <80% of their doses are unlikely to have any durable virological suppression. They should be targeted urgently for adherence improvement, and 6-month follow-up (see Table 16, page 54).**

**Table 16: Adherence strategies**

**Strategies to promote adherence**

- Spend time with the patient. Explain the goals of therapy and need for adherence as many times as is necessary.
- Consider monitoring of medications such as co-trimoxazole or by an alternative method prior to ART initiation.
- Negotiate a treatment plan that the patient can understand and to which he/she commits.
- Encourage disclosure to family or friends who can support the treatment plan.
- Inform patient of potential side-effects – severity, duration and coping mechanisms.
- Establish ‘readiness’ to take medications before ART initiation.
- Provide adherence tools where available: written calendar of medications, pill boxes.
- Encourage use of alarms, pagers or other available mechanical aids for adherence.
- Avoid adverse drug interactions. The patient must disclose any over-the-counter drugs and traditional medicines. Other medications as well as some traditional medicines cannot be taken concurrently with ART because they may cancel each other out or may lead to unacceptable adverse effects.
- Anticipate, monitor and treat side-effects.
- Include adherence discussions in support groups.
- Develop links with community-based organisations to support adherence.
- Encourage links with support groups.
- Create links with patient advocates.

**Table 17: Correlation between adherence and virologic response to ART**

Adherence to ART*	Viral load <400 copies/mm <sup>3</sup>
>95% adherence	78%
90% to 95% adherence	45%
80% to 90 % adherence	33%
70% to 80 % adherence	29%
<70% adherence	18%

\* (number of doses dispensed minus tablets returned) over (number prescribed)  
e.g. (30-5)/28=25/28=0.9 (90%)

**Basic adherence package at initiation**

**Pre-treatment**

- Pre-treatment information and education as per visit schedule.
- Patient is introduced to therapeutic counsellor and patient advocate, if available and agreed to or nominated by patient. The home visit is also arranged.
- Co-trimoxazole count is undertaken for one month prior to commencing therapy. This is not to be used to exclude people from ART. It is meant to reinforce daily medication-taking behaviour from the beginning. It is also meant to identify potential problems before starting ART.



### On treatment

#### At each visit the following needs to be done:

- ART pill-returns count (% doses missed) would be ideal, but this would depend on the clinic load and capacity to undertake this intensive activity. Adherence goal is >95% doses taken. Patients with adherence <80% require increased adherence support (see below).
- Tablet count may be done before the patient sees the doctor.
  - The count should be reviewed by the doctor during the early/initial visits to evaluate adherence.
  - This does take up time and might not be possible at all sites all the time.
- Missed/late clinic visits should trigger concerns about adherence.
- Routine adherence-discussion (education) with counsellor is of value. This should be an open-ended discussion, with time for questions and repetition.
- Feedback from therapeutic counsellors to the rest of team is important to get a better profile of the patient and their environment.
- Encourage participation in a support group.
- Continue monthly visit with therapeutic counsellors for first three months and quarterly thereafter.
- Arrange regular community visits by patient advocates.

### Step-up adherence package for people with reduced adherence or virological failure

This is necessary when the adherence assessment is <80% at any visit, with or without viral or clinical failure (see Table 11, page 41).

- The therapeutic counsellor/nurse or doctor needs to re-educate the patient (and their buddy) about the importance of adherence. The long-term benefits need to be re-emphasised.
- Evaluate the support structures in place.
  - Are they appropriate?
  - How can they be improved?
  - What alternatives are there?
- Consider the use of pillboxes and/or daily dosing diary.
- Insist on participation in a support group or link with a patient advocate.
- Consider doing a psychological profile.
- Check the family situation (through social worker and therapeutic counsellor).
- Redo the Case Assessment for alcohol abuse and other abused drugs.
- Increase home visits by therapeutic counsellors/patient advocates to daily or weekly, at a minimum (spot pill counts to be done at home).
- Consider directly-observed therapy for an agreed period.
- Promote self-efficacy training.

# SECTION 4: DIAGNOSIS AND MANAGEMENT OF ADVERSE EVENTS

## Principles of managing adverse events

- Establish whether the adverse event is due to antiretroviral agents, other medication or other illness.
- Never stop only one antiretroviral drug (the patient should always be on 3 drugs).
- Individual drugs may be switched due to intolerance as shown on Table 22, page 69.
- If there is a need to discontinue ART, all antiretroviral medications must be stopped together.
- Clinicians may continue ART if there is a Grade I or II adverse reaction.
- Clinicians should consider terminating treatment in Grade III reactions. Treatment should be stopped if there is a Grade IV adverse event (see Tables 18 – 20).
- Adverse events should be recorded and reported regularly to the HIV/AIDS programme at Head Office. Serious adverse events (SAEs) should be reported within 48-72 hours (Grade IV or death) to the MCC. Adverse event forms on yellow paper will be made available at all centres.

Report serious or unexpected suspected adverse reactions or suspected drug interactions to the National Adverse Drug Event Monitoring Centre, MCC, phone (012) 312-0000 Pretoria; or (021) 447-1618, fax: (021) 448-6181 Cape Town.

**N.B.**

**Contact your local Medicines Information Centre for advice regarding potential interactions and recommendations for dosage adjustment.**

Adverse reactions will be graded according to the AIDS Clinical Trial Groups (ACTG and PACTG) grading. Consider grading both laboratory and clinical abnormalities, and manage them as in the tables on page 59 – 62.

## Grading of adverse reactions in adults and adolescents

**Table 18: Laboratory adverse events in adults (ACTG)**

LABORATORY TEST ABNORMALITIES				
ITEM	GRADE I TOXICITY	GRADE II TOXICITY	GRADE III TOXICITY	GRADE IV TOXICITY
Haemoglobin	8.0-9.4 g/dL	7.0-7.9 g/dL	6.5-6.9 g/dL	<6.5 g/dL
Absolute neutrophil count	1-1.5 x 10 <sup>9</sup> /L	0.75-0.99 x 10 <sup>9</sup> /L	0.5-0.749 x 10 <sup>9</sup> /L	<0.5 x 10 <sup>9</sup> /L
ALT	1.25-2.5 x upper normal limit	>2.5-5 x upper normal limit	>5.0-10 x upper normal limit	>10 x upper normal limit
Triglycerides	3-4.51 mmol/L	4.52-8.48 mmol/L	8.49-13.56 mmol/L	>13.56 mmol/L
Cholesterol	>1.0-1.3 x upper normal limit	>1.3-1.6 x upper normal limit	>1.6-2.0 x upper normal limit	>2.0 x upper normal limit
<b>MANAGEMENT</b>	Continue ART. Repeat test 2 weeks after the initial test and re-assess.		Continue ART. Repeat test 1 week after initial test and reassess; if ALT still Grade III, consult expert about stopping ART.	Consult expert immediately before stopping ART.
	Lipid imbalances could be managed with diet, exercise and pharmacologically with the use of fibrates.			
IF IN DOUBT, ALWAYS SEEK EXPERT ADVICE				

ADVERSE EVENTS

**N.B.**

**The repeat tests may require additional patient's visits over and above the routine monitoring visits.**

## DIAGNOSIS AND MANAGEMENT OF ADVERSE EVENTS

**Table 19: Clinical adverse events in adults**

ITEM	GRADE I TOXICITY	GRADE II TOXICITY	GRADE III TOXICITY	GRADE IV TOXICITY
Paraesthesia (burning, tingling, etc.)	Mild discomfort; no treatment required	Moderate discomfort; non-narcotic analgesia required	Severe discomfort; OR narcotic analgesia required with symptomatic improvement	Incapacitating; OR not responsive to narcotic analgesia
Neuro-sensory	Mild impairment (decreased sensation, e.g. vibratory, pinprick, hot/cold in big toes) in focal area or symmetrical distribution.	Moderate impairment (moderate decrease in sensation, e.g. vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	Severe impairment (decrease or loss of sensation to knees or wrists) or loss of sensation of at least moderate degree in multiple different body areas (i.e. upper and lower extremities)	Sensory loss involves limbs and trunk.
Cutaneous/rash/dermatitis*	Erythema, pruritus	Diffuse, maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	Exfoliative dermatitis OR mucous membrane involvement OR erythema multiforme OR suspected Stevens-Johnson syndrome OR necrosis requiring surgery
<b>MANAGEMENT</b>	<ul style="list-style-type: none"> <li>■ Continue ART.</li> <li>■ Provide careful clinical monitoring.</li> <li>■ Consider change of a single drug if condition worsens.</li> </ul>		<ul style="list-style-type: none"> <li>■ CONSIDER STOPPING ALL DRUGS.</li> <li>■ CONSULT SPECIALIST IMMEDIATELY.</li> </ul>	

\* A rash in a patient on nevirapine with mucosal involvement **OR** associated with fever/systemic symptoms/derangement in liver functions should be treated as Grade IV toxicity. ALL antiretroviral drugs should be stopped immediately. Patients at primary care should be referred to a specialist for advice regarding restarting ART.

The patient should never be rechallenged with nevirapine or swapped with efavirenz if Grade IV or Stevens-Johnson syndrome occurs. If the reaction is non life-threatening or <Grade IV, efavirenz can be substituted with close monitoring.

**Table 20: Grading the severity of adverse reactions in children (PACTG)**

LABORATORY TEST ABNORMALITIES				
ITEM	GRADE I TOXICITY	GRADE II TOXICITY	GRADE III TOXICITY	GRADE IV TOXICITY
Haemoglobin >3 months – <2 years	9.0-9.9 g/dL	7.0-8.9 g/dL	<7.0 g/dL	Cardiac failure secondary to anaemia
Haemoglobin ≥2 years	10-10.9 g/dL	7.0-9.9 g/dL	<7.0 g/dL	Cardiac failure secondary to anaemia
Absolute neutrophil count	0.75-1.2 x 10 <sup>9</sup> /L	0.4-0.749 x 10 <sup>9</sup> /L	0.25-0.399 x 10 <sup>9</sup> /L	<0.25 x 10 <sup>9</sup> /L
ALT (SGPT)	1.1-4.9 x upper normal limit	5.0-9.9 x upper normal limit	10.0-15.0 x upper normal limit	>15 x upper normal limit
Triglycerides	–	1.54-8.46 mmol/L	8.47-13.55 mmol/L	>13.56 mmol/L
Cholesterol	–	4.43-12.92 mmol/L	12.93-19.4 mmol/L	>19.4 mmol/L

(continues on following page.)

## DIAGNOSIS AND MANAGEMENT OF ADVERSE EVENTS

CLINICAL ADVERSE EVENTS				
ITEM	GRADE I TOXICITY	GRADE II TOXICITY	GRADE III TOXICITY	GRADE IV TOXICITY
Peripheral neuropathy	Diagnosis of peripheral neuropathy is difficult in children. Screen motor function against milestones, and refer to specialist if peripheral neuropathy is suspected.			
Cutaneous/skin rash/dermatitis*	-	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR ulcers	Exfoliative dermatitis OR Stevens-Johnson syndrome OR erythema multiforme OR moist desquamation
<b>MANAGEMENT</b>	<ul style="list-style-type: none"> <li>■ Continue ART.</li> <li>■ Repeat laboratory test and clinical assessment within 2 weeks.</li> </ul>		<ul style="list-style-type: none"> <li>■ Continue ART.</li> <li>■ Repeat test and clinical assessment within 1 week. If Grade III toxicity persists, stop ALL ART and seek expert medical advice.</li> </ul>	

\* A rash in a child on nevirapine with mucosal involvement **OR** associated with fever/ systemic symptoms/derangement in liver functions should be treated as Grade IV toxicity. All ART should be stopped immediately. The patient should never be rechallenged with nevirapine or efavirenz after having presented Grade IV toxicity. Patients at primary care should be referred to a specialist for advice regarding restarting ART.

## Important adverse reactions

**Table 21: Important ART adverse reactions and safety monitoring**

Antiretroviral	Adverse Reactions	Recommended safety monitoring
Abacavir (ABC)	<p>A potentially fatal hypersensitivity reaction develops in approximately 3% -5% of patients. Symptoms usually appear within 6 weeks of treatment initiation. Suspect reaction if symptoms from 2 or more of the following groups are present:</p> <ul style="list-style-type: none"> <li>■ fever</li> <li>■ maculopapular pruritic generalised rash</li> <li>■ gastro-intestinal symptoms</li> <li>■ other symptoms (including pharyngitis, dyspnoea, cough, musculoskeletal disorders, malaise, fatigue, lymphadenopathy and paraesthesia)</li> </ul> <p>Never give abacavir to a child who has previously developed an abacavir-hypersensitivity reaction</p>	Fasting cholesterol and triglycerides at baseline, 6 months, and thereafter every 12 months.
Didanosine (ddI)	Pancreatitis, peripheral neuropathy, GIT effects (bloating, flatulence, nausea, diarrhoea), lactic acidosis.	Clinical
Efavirenz (EFV)	CNS disturbances (dysphoria, vivid dreams, distractedness, dizziness) GIT symptoms. Skin rash, <i>congenital anomalies – avoid during 1st trimester of pregnancy.</i>	Clinical
Lamivudine (3TC)	Diarrhoea, pancreatitis, lactic acidosis	Clinical

(continues on following page.)

Antiretroviral	Adverse reactions	Recommended safety monitoring
Lopinavir/ Ritonavir	GIT symptoms, lipid abnormalities (5%), lipodystrophic changes.	Fasting cholesterol and triglycerides at baseline, 6 months and thereafter every 12 months.
Nevirapine (NVP)	Skin rash (16%), nausea, vomiting, hepatitis (can be fatal).	ALT at baseline and at week 2, 4, and 8, and thereafter, every 6 months (taken with CD4 and viral load or when symptomatic).
Ritonavir	Bad taste, GIT symptoms, especially diarrhoea. Raised liver enzymes, raised cholesterol and triglycerides, lipodystrophic changes.	Fasting cholesterol and triglycerides at baseline, 6 months, and thereafter every 12 months.
Stavudine (d4T)	Peripheral neuropathy, hepatic steatosis, lactic acidosis, pancreatitis.	Clinical
Zidovudine (AZT)	Bone marrow suppression (anaemia, neutropenia), GIT symptoms, myopathy, lactic acidosis. Cardiomyopathy in children.	FBC with differential count at baseline, then monthly for 3 months, then 6 monthly (with CD4 and viral load).

**N.B.**

**Other adverse reactions not listed on this table may occur.**

## Management of specific adverse reactions

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

### Nausea

- Nausea due to antiretroviral medication must be actively managed, or adherence will suffer.
- Anti-emetics taken half an hour before the antiretroviral dose up to 3 times daily, may be helpful. If the nausea does not settle, refer for expert advice.

### Rashes on first-line therapy

- Do a clinical assessment to rule out any other causes of the rash. Enquire about systemic symptoms, and check the temperature in any patient presenting with a rash.
- Do a grading of the rash, and refer to tables for management.
- Both nevirapine and efavirenz may cause skin reactions. This usually occurs within the first 2 months of treatment. Concomitant (simultaneous) TB therapy may confuse the situation as these drugs can cause similar adverse events.

### Abdominal pain

- Abdominal pain in a patient on ART can be caused by a number of serious problems, and should never be ignored.
- Important causes include lactic acidosis, pancreatitis, hepatitis, hyperlactataemia (increased serum lactate) and disseminated tuberculosis.
- Recommended investigations: liver functions, lipase and serum lactate. Refer for further investigations as needed.
- Seek expert help if you are unsure of the cause of the pain.

### Hyperlactataemia and lactic acidosis

- Asymptomatic elevation of lactate is common in patients taking antiretroviral drugs (up to 20% per year). Routine monitoring of lactate is not recommended if the patient is asymptomatic.
- Patients on ART can occasionally develop symptomatic hyperlactataemia (1-2% per year), and, more rarely, lactic acidosis (0.1-0.2% per year).
- Risk factors for lactic acidosis include:
  - female gender
  - obesity
  - prolonged ART and excellent adherence
  - chronic renal failure
  - pregnancy
- Symptoms are non-specific:
  - unwellness, generalised fatigue, weakness
  - gastro-intestinal symptoms (nausea, vomiting, abdominal pain, abdominal distension and bloatedness)
  - shortness of breath, dyspnoea, tachypnoea
  - neurologic symptoms (disequilibrium, motor weakness)
- Confirmed laboratory test (hyperlactatemia).

### Management of hyperlactatemia in adults

- Lactate 2-5 mmol/L: monitor monthly, and be alert for clinical symptoms and signs described above.
- Lactate 5-10 mmol/L with symptoms: STOP all ART and seek urgent expert help. Other causes of raised lactate must be excluded:
  - sepsis
  - renal failure
  - diabetic ketoacidosis

- Lactate >10 mmol/L: STOP all antiretroviral drugs immediately and seek urgent expert help (30% mortality in case series).
- Metabolic acidosis with raised lactate: STOP all ART and seek urgent expert help.
- After recovery, seek expert advice regarding antiretroviral selection. Stavudine and didanosine should be avoided.

### Management of hyperlactatemia in children

- Discuss with a treatment expert.
- ART should be discontinued in patients with these symptoms.
- Symptoms associated with lactic acidosis may continue or worsen following discontinuation of ART.
- Therapy is primarily supportive: fluid, bicarbonate administration and respiratory support.

### Lipodystrophy

- HIV-associated lipodystrophy include fat loss and/or fat accumulation in distinct regions of the body. This includes increased fat around abdomen, buffalo hump, breast hypertrophy, and fat loss from limbs, buttocks and face.
- Association with antiretrovirals: lipodystrophy more common in individuals taking NRTIs or protease inhibitors.
- Management: There are no established methods for treating lipodystrophy, but the following is recommended:
  - encourage exercise to reduce fat accumulation.
  - some patients improve if switched from a protease inhibitor to an NNRTI.
  - fibrates are effective at lowering cholesterol and triglyceride levels.
  - insulin resistance can be improved with anti-diabetic agents.

## Hyperlipidaemia

- Patients on lopinavir/ritonavir who develop hyperlipidaemia should be counselled about lifestyle modification:
  - weight loss if obese
  - increasing exercise
  - stopping smoking
  - reducing cholesterol and saturated fat intake
 Refer to a dietician, if available, for dietary advice.
- Severe hyperlipidaemia may require drug management. If triglyceride >5.6 mmol/L after dietary changes or LDL >4.9 mmol/L or LDL >3.4 mmol/L with 2 or more other ischaemic heart disease risk factors, commence fibrates (or atorvastatin).

## Zidovudine related anaemia or neutropenia

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

## Substitutes for intolerance in adults

**For children, consult expert before switching drugs.**

All switches should be made by a doctor trained in ART.

**Table 22: Recommended substitutions for specific side-effects (Grade III or IV toxicity)**

Regimen	Toxicity	Drug substitution
D4T/3TC/EFZ	<ul style="list-style-type: none"> <li>■ d4T-related neuropathy or pancreatitis</li> <li>■ EFZ-related persistent CNS toxicity</li> </ul>	<ul style="list-style-type: none"> <li>■ Switch d4T to AZT</li> <li>■ Switch EFZ to NVP</li> </ul>
D4T/3TC/NVP	<ul style="list-style-type: none"> <li>■ d4T-related neuropathy or pancreatitis</li> <li>■ NVP-related severe hepatotoxicity</li> <li>■ NVP-related severe rash (but not life-threatening)</li> <li>■ NVP-related life-threatening rash</li> <li>■ Stevens-Johnson syndrome</li> <li>■ Lactic acidosis</li> </ul>	<ul style="list-style-type: none"> <li>■ Switch d4T to AZT</li> <li>■ Switch NVP to EFZ (except early pregnancy)</li> <li>■ Switch NVP to EFZ</li> <li>■ Switch NVP to EFV or lopinavir/ritonavir</li> <li>■ Switch to lopinavir/ritonavir</li> <li>■ Consult expert</li> </ul>
AZT/ ddI / lopinavir / ritonavir	<ul style="list-style-type: none"> <li>■ AZT related anaemia or neutropenia</li> <li>■ ddI related GIT side effects</li> <li>■ ddI related pancreatitis or hepatitis</li> <li>■ LPV/r related GIT symptoms</li> <li>■ LPV/r related hypercholesterolaemia</li> <li>■ Lipodystrophy</li> <li>■ Impaired glucose tolerance</li> </ul>	<ul style="list-style-type: none"> <li>■ Switch AZT to d4T (monitor closely for peripheral neuropathy and lactic acidosis)</li> <li>■ Switch ddI for enteric coated ddI</li> <li>■ Consult expert</li> <li>■ Consult expert</li> <li>■ Consult expert</li> <li>■ Consult expert</li> <li>■ Antidiabetic agents (warning: metformin increases risk of acidosis).</li> </ul>

**Drug interactions**

Protease inhibitors (e.g. lopinavir/ritonavir) and NNRTIs (efavirenz and nevirapine) can interact with a number of other drugs, through changes in drug metabolism in the liver.

Traditional remedies, phytotherapeutics, as well as other complimentary medicines, when used together with ART, could cause liver enzyme induction. They could also bind the drug in the gut, leading to decreased blood levels of ART drugs and ultimately resistance. Little information exists on these interactions and so they are not illustrated here.

Table 23, page 71, shows examples of drugs that should be avoided when administered with efavirenz, nevirapine, lopinavir/ritonavir or all 3 drugs.

**N.B.**

**Beware of other drug interactions that may require dosage adjustment (i.e. anticonvulsant, psychiatric, anti-infective, cholesterol lowering drugs etc.). Seek expert advice if your patient is taking one of these drug combinations.**

**Table 23: Prohibited drug combinations with specific ART**

Agent by class	Agents prohibited with lopinavir/ritonavir	Agents prohibited with ritonavir	Agents prohibited with NVP and EFV
Anti-arrhythmic agents	Flecainide Propafenone	Amiodarone Flecainide Propafenone Quinidine	
Anti-histaminics	Astemizole Terfenadine	Astemizone Terfenadine	Astemizone Terfenadine
Anti-infectives	Rifampicin	Rifabutin	Systemic Ketoconazole
Cholesterol lowering agents	Lovastatin Atorvastatin Simvastatin		
GI motility	Cisapride	Cisapride	Cisapride
Psychiatric medications	St. John's Wort ( <i>Hypericum perforatum</i> )		St. John's Wort ( <i>Hypericum perforatum</i> )
Sedative/hypnotics	Midazolam Triazolam	Midazolam Triazolam	Midazolam Triazolam
Other	Dihydroergotamine Ergonovine Ergotamine Methylergonovine	Bepridil (Calcium Channel blocker) Pimozide Ergot derivatives Disulfiram Metronidazole	Dihydroergotamine Ergotamine Methylergonovine

ADVERSE EVENTS



# SECTION 5: POST-EXPOSURE PROPHYLAXIS (PEP)

## Prophylaxis after occupational exposure to HIV

### Introduction

Health care workers have a low but measurable risk of HIV infection after accidental exposure to infected blood or body fluid.

Compliance with infection control recommendations in handling sharps is the mainstay in the prevention of occupational HIV infection. Additional prevention strategies now include post-exposure prophylaxis with ART.

### Risk of infection

#### Factors that increase the risk of sero-conversion include:

- Exposure to large inoculum of infected blood indicated by:
  - a deep injury
  - visible blood on device
  - procedures involving needles
- Source patient with terminal HIV infection

### When to commence treatment

Treatment has to commence as soon as possible within 1 to 2 hours of exposure – **the sooner the better.**

The HIV status of the injured person needs to be known as initiating HIV prophylaxis in an infected person could endanger their future treatment options. This is because dual therapy could lead to resistance.

In situations where there is a high suspicion that the patient may be in the window period, consider HIV PCR testing. Starter pack prophylaxis should also be provided.

For further information, consult the national guidelines on “Management of Occupational Exposure to HIV”.

**Table 24: Recommendations for post-exposure prophylaxis (PEP) after occupational exposure**

This includes blood, CSF, semen, vaginal secretions and synovial/pleural/pericardial/peritoneal/amniotic fluid from HIV sero-positive patients.

Exposure	HIV status of source patient		
	Unknown	Positive	High risk*
Intact skin	No PEP	No PEP	No PEP
Mucosal splash/ non-intact skin	Consider 2-drug regimen	Recommend 2-drug regimen	Recommend 2-drug regimen
Percutaneous (sharps)	Recommend 2-drug regimen	Recommend 2-drug regimen	Recommend 3-drug regimen
Percutaneous (needle in vessel or deep injury)	Recommend 2-drug regimen	Recommend 3-drug regimen	Recommend 3-drug regimen

\* See text for definition of high risk exposures

**Table 25: Recommended PEP drug regimen**

Drug	Dose	Frequency	Duration
Zidovudine (AZT) Lamivudine (3TC)	300 mg 150 mg	12 hourly	28 days
Lopinavir/ritonavir in cases of high exposure	400 mg/100 mg	12 hourly	28 days

## POST-EXPOSURE PROPHYLAXIS (PEP)

### Monitoring after occupational exposure

- Prophylaxis must be given for 28 days.
- Following HIV exposure, there is a need for psycho-social support.
- Laboratory monitoring is done to exclude acquisition of HIV infection and, for those given PEP, to monitor toxicity.
- Health care workers should be tested for HIV infection at the time of the exposure, and again at 6 weeks, 3 months and 6 months.

### Prophylaxis after sexual assault

#### Prevention of the transmission of the Human Immunodeficiency Virus (HIV) in men and women who have been raped/sexually assaulted

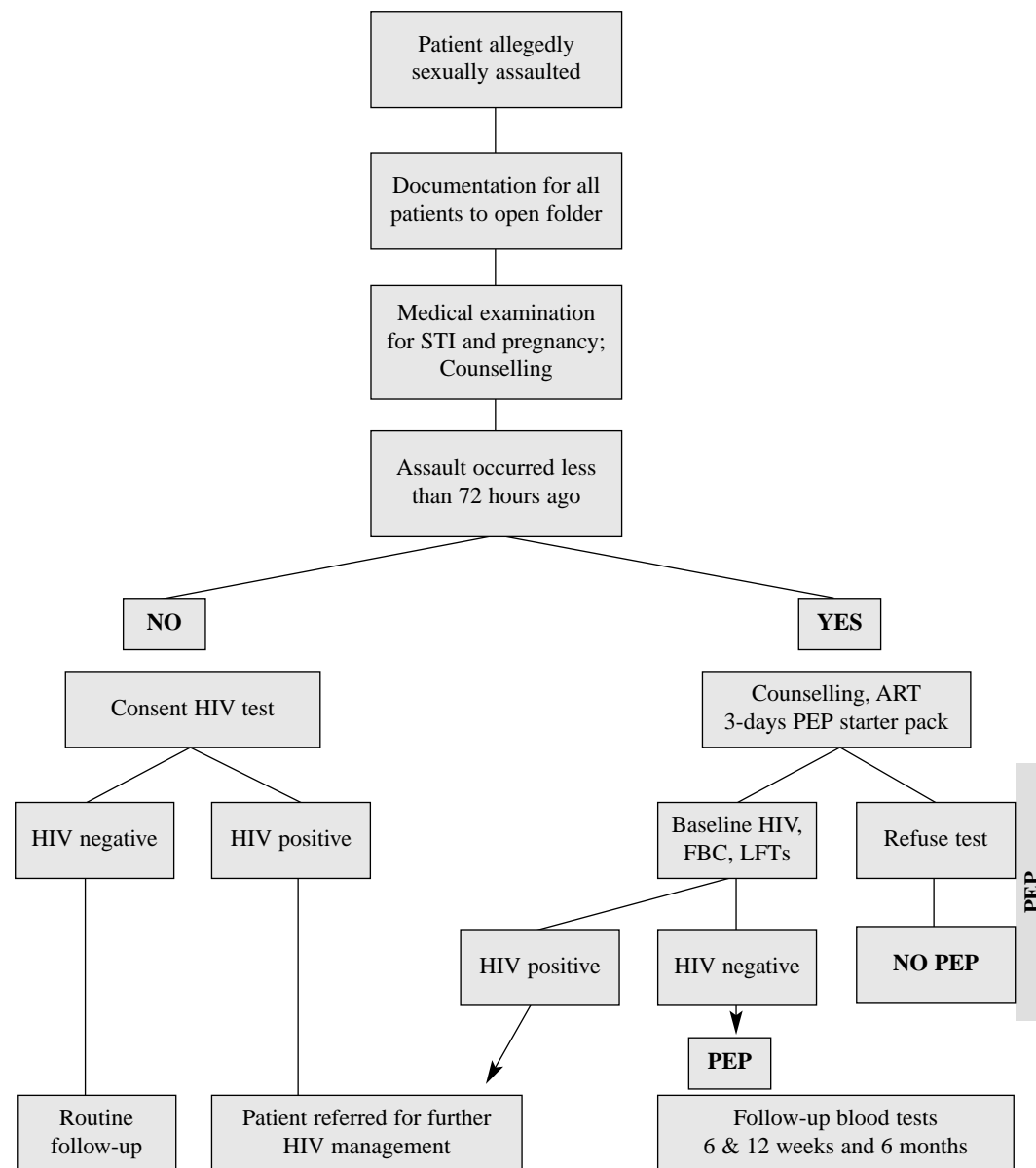
- All women and men, aged 14 years and older, presenting to a health facility after being raped, should be counselled by the examining health care worker about the potential risks of HIV transmission post-rape.
- Younger children need to be managed at specialised sites where there is the expertise in dealing with traumatised children and the prescription of ART.
- The following points should be covered in the counselling:
  - The risk of transmission is not known, but it exists.
  - It is important to know the victim's HIV status prior to using any ART. This is because using AZT and 3TC in an HIV-positive patient is not adequate therapy. It may also lead to viral resistance.
  - It is the patient's choice to have immediate HIV testing or, if she/he prefers, this could be delayed until 72 hours post-examination visit. Management guidelines on sexual assault provides for a 3-day starter pack for those who prefer not to test immediately, or those that are not ready to receive results immediately. Getting patients back after three days might present with logistical problems, especially if they have to return at Week 1 for other results or to revisit VCT.

- Patients presenting after 72 hours should be counselled about the possible risk of infection and the possibility of them transmitting infection during sero-conversion. They should be advised to return at 6 weeks and 3 months post-rape for voluntary confidential counselling and HIV testing. Patients who request prophylaxis at this stage, should be advised that there is not enough scientific evidence that the use of AZT (and 3TC) delayed this long after the rape, will have any impact on preventing HIV transmission.
- The patient should be made aware that the efficacy of AZT prophylaxis is still under study. The drug itself is not yet licensed for use in post-rape prophylaxis.
- All women and men, aged 14 years and older, presenting to a health facility within 72 hours of being raped, should be offered AZT and 3TC to prevent HIV transmission.
- A third drug, lopinavir/ritonavir 400/100 mg 12 hourly, added to the above, is recommended in severe cases as follows:
  - where there have been multiple perpetrators
  - anal penetration
  - obvious trauma to the genital areas
  - known HIV positivity of one of the perpetrators (not enough scientific evidence exists to support the three-drug regimen, but it is considered best practice in these circumstances).
- The treatment is AZT 300 mg bd for a period of 28 days, plus 150 mg 3TC bd for the same time period.
  - Patients should be given a week supply of AZT and 3TC. They should also be given a date to return within a week for reassessment, for ongoing counselling, and to review the test results (except the rapid HIV or to obtain the confirmatory ELISA, where positive).

## POST-EXPOSURE PROPHYLAXIS (PEP)

- For those patients who cannot return for their one-week assessment due to logistical or economic reasons, then a month's treatment supply, with an appointment date, should be given. This may be particularly relevant outside of the metropolitan areas.
- Ideally all patients should be seen one week post-rape to obtain results of all blood tests and to evaluate her/his condition. The remainder of the drugs should be given at this visit (i.e. a 3-week supply).
- The next visit should be at 6 weeks, and then 3 months and 6 months after the rape. HIV testing should be performed at each visit.
- Patients who are either known to be HIV positive, or found to be HIV positive, should not be offered prophylaxis. They should be referred to an appropriate health care clinic for long-term management of their HIV infection.
- The prophylaxis regimen against HIV transmission recommended by the National Department of Health will be reviewed periodically in light of any new information on HIV transmission and appropriate prophylaxis.
- Routine testing with a full blood count and liver enzymes for patients on AZT and 3TC is not recommended for such a short duration of therapy. Any blood tests should be performed according to patient's condition.
- Relative contra-indications to the use of AZT include significant renal or liver impairment and severe anaemia (Hb <6 g). Where in doubt about the use of AZT in individual patients, contact your local physician or hospital for advice.
- It is strongly suggested that AZT and 3TC be administered only in the context of using the comprehensive rape protocol.
- It is also strongly suggested that the implementation of AZT and 3TC for post-rape prophylaxis should be carefully monitored and evaluated.

**Figure 8: PEP after sexual assault**



# APPENDICES

## Appendix 1: World Health Organisation Adults HIV and AIDS Staging System

### Stage I

1. Asymptomatic
2. Persistent generalised lymphadenopathy (PGL)
3. Acute retroviral infection (sero-conversion illness) and/or performance Scale 1: asymptomatic, normal activity.

### Stage II

4. Unintentional weight loss <10% of body weight
5. Minor mucocutaneous (e.g. seborrhoea, prurigo, fungal nail infections, oral ulcers, angular cheilitis)
6. Herpes zoster within the last five years
7. Recurrent upper respiratory tract infection (e.g. bacterial sinusitis) (URTI) and/or performance Scale 2: symptomatic, normal activity.

### Stage III

8. Unintentional weight loss >10% of body weight
9. Chronic diarrhoea >one month
10. Prolonged fever >one month
11. Oral candidiasis
12. Oral hairy leukoplakia
13. Pulmonary TB within the last year (PTB)
14. Severe bacterial infections (pneumonia, pyomyositis)
15. Vulvovaginal candidiasis >one month / poor response to therapy and/or performance Scale 3: bedridden <50% of the day during the last month.

### Stage IV

16. HIV wasting (8+9 or 10)
17. *Pneumocystis carinii* pneumonia (PCP)
18. CNS toxoplasmosis (Toxo)
19. Cryptosporidiosis plus diarrhoea >one month
20. Isosporiasis plus diarrhoea
21. Cryptococcosis – non pulmonary
22. Cytomegalovirus infection other than liver, spleen or lymph node (CMV)
23. Herpes simplex infection; visceral or >one month mucocutaneous (HSV)
24. Progressive multifocal leucoencephalopathy (PML)
25. Disseminated mycosis (i.e. histoplasmosis, coccidiomycosis)
26. *Candida* oesophageal/tracheal/pulmonary
27. Atypical mycobacteriosis disseminated (MOTT)
28. Non-typhoidal *Salmonella* septicaemia
29. Extra-pulmonary tuberculosis (ETB)
30. Lymphoma
31. Kaposi's sarcoma (KS)
32. HIV encephalopathy (ADC)
33. Invasive cervical carcinoma and/or performance Scale 4: bedridden >50% of the day during the last month

## Appendix 2: Modified WHO clinical staging Paediatric HIV & AIDS classification

Please note: The South African National Paediatric HIV Consensus Team have modified the original WHO Clinical Staging Guidelines for practical reasons. WHO intends updating these in 2004, and the guidelines in this document will be updated to conform to the WHO modifications when they appear.

### Stage I

- Asymptomatic
- Generalised lymphadenopathy
- Hepatomegaly
- Splenomegaly
- Parotomegaly
- Chronic suppurative OM
- Eczema/ seborrhoeic dermatitis

### Stage II

- Unexplained chronic diarrhoea ( $\geq 2$  weeks)
- Failure to thrive
  - 60 - 80% expected body weight
  - Not responding to nutritional rehabilitation or anti-TB therapy (if clinically indicated). Other correctable causes excluded.
- Recurrent or severe bacterial infection ( $\geq 2$  episodes pneumonia or 1 episode meningitis)
- Oral candidiasis beyond neonatal period
  - Severe persistent or recurrent, not responding to topical therapy
- Haematological
  - Thrombocytopenia (platelet count  $< 40\,000 \times 10^9/l$ ) not responding to prednisone 2 mg/kg/day after 2 weeks
  - Neutropenia (neutrophil count  $< 500 \times 10^9/l$ ) not responding to switch from co-trimoxazole to dapsone

- Severe lymphoid interstitial pneumonitis:
  - Persistent hypoxia  $< 90\%$  in the absence of acute infection and/OR
  - Persistent tachypnoea in the absence of acute infection and/OR
  - Easy fatigability on exertion and/OR
  - Evidence of bronchiectasis and/OR
  - Cor pulmonale
- $\geq 2$  episodes zoster or severe herpetic disease

### Stage III

- Severe failure to thrive
  - $< 60\%$  expected body weight
  - Not responding to nutritional rehabilitation or TB therapy if clinically indicated
- Encephalopathy
- Recurrent septicaemia ( $\geq 2$  episodes)
- Bronchiectasis
- Cardiomyopathy
- Progressive nephropathy
- Candidiasis (oesophageal or pulmonary)
- Disseminated fungal infection (Coccidioidomycosis, Cryptococcosis, Histoplasmosis)
- Disseminated mycobacterial infection (M. tuberculosis, BCG, avium-intracellulare, Kansasii)
- CMV disease with onset at age  $> 1$  month (at site other than lymph nodes, spleen, liver)
- HSV causing mucocutaneous ulcer persisting  $> 1$  month, or oesophagitis, pneumonitis, oesophagitis in a child older  $> 1$  month
- Pneumocystis carinii pneumonia (PCP)
- Progressive multifocal leukoencephalopathy
- Cerebral toxoplasmosis with onset  $> 1$  month of age
- Recurrent/persistent salmonella ESBL
- Malignancies

### Appendix 3: Paediatric dosing schedule

Method 1:	Method 2:
<p>The body surface area of a child can be determined using the nomogram for infants and young children as stated in the Handbook of Paediatrics, 5th edition or on page 297 of the Paediatric Standard Treatment Guidelines 1998 (purple book)</p>	<p>Use the following formula:</p> $BSA = \sqrt{\frac{Hgt(cm) \times Wgt(kg)}{3600}} \text{ m}^2$ <p><b>For example:</b>                      Height: 80 cm                      Weight: 12 kg</p> $BSA = \sqrt{\frac{80(cm) \times 12(kg)}{3600}} \text{ m}^2$ <p>Use your calculator in the following way:                      Step 1: Press: 80 x 12 and =                      Step 2: Press: ÷ 3600 and =                      Step 3: Press: square root button  <b>Your answer = 0.52 m<sup>2</sup></b></p>

### Appendix 4: TB prophylaxis

#### Guidelines for tuberculosis (TB) preventive therapy among HIV-infected patients

##### Background

The dramatic spread of the HIV epidemic throughout sub-Saharan Africa in the past decades has been accompanied by up to a fourfold increase in the number of TB cases registered by the national TB programmes. Strategies to control TB must now include interventions to reduce HIV infection.

On the other hand, it is estimated that around 50% of new adult cases of TB in South Africa are co-infected with HIV. TB is the commonest

cause of morbidity and mortality among HIV-infected population in South Africa. Studies have shown that TB does accelerate HIV-disease progression. Therefore, preventive TB therapy should be offered in the package of care for people living with HIV. While it is not likely to reduce the incidence of TB in the community, it can provide real benefits to the individuals.

TB preventive therapy is the use of one or more anti-tuberculosis drugs given to individuals with latent infection with *M. tuberculosis* in order to prevent the progression to active TB disease.

Trials have shown that maximum benefits from TB preventive therapy are achieved in HIV-infected patients with evidence of TB infection as assessed by a positive tuberculin skin test. In these patients, the risk of developing TB is reduced by 60%, and their survival is also prolonged. However, some benefit is also shown in HIV-positive groups in general, regardless of the tuberculin test result.

#### TB preventive therapy and health services

TB preventive therapy is an intervention that should be part of the package of care for people living with HIV. It should only be offered in the following situations (pre-requisites):

- If quality voluntary counselling and rapid testing for HIV is available.
- If there is effective screening for active TB before initiating TB preventive therapy.
- If there is capacity for monthly follow-up and monitoring of patients to encourage adherence, address eventual side-effects and exclude active TB disease.
- If the local HIV/AIDS programme takes responsibility for implementation of preventive therapy.
- If there is strong collaboration between HIV/AIDS and TB programmes.

In order to provide comprehensive care to HIV/AIDS patients, all efforts should be put in place to ensure the implementation of TB preventive therapy in all public health services. Sites that have already implemented the service should be consulted to gain from local experience.

## Exclusion of active TB

It is essential to exclude active TB in every patient prior to starting preventive therapy. This is critical in order to avoid giving one drug to patients with TB disease who require the full regimen.

Patients interested in TB preventive therapy should be specifically asked about signs and symptoms of TB:

- Cough >2 weeks
- Fever >2 weeks
- Night sweats
- Other symptoms, like pleuritic chest pains, haemoptysis should also prompt investigations for TB
- Weight loss of >1.5 kg in the past 4 weeks: weight should be measured at each clinic visit to allow documented evidence of weight loss. A weight loss of >1.5 kg should be considered a positive screen indicator.

All patients with 1 or more signs and symptoms must be investigated further for TB. They are not immediately eligible for TB preventive therapy. Sputum specimens must be collected for the following investigations:

- 2 sputum samples for microscopy
- 1 sputum for culture

Trials have shown that a chest x-ray does not improve case detection, and is an additional barrier for people to access the intervention. Emphasis is on sputum samples and, where appropriate, on identification of extrapulmonary TB.

Chest x-ray is not recommended in the screening for TB preventive therapy, but still has a role in those who are TB suspects with negative sputum smears, as per the national TB guidelines.

## Eligibility for TB preventive therapy

Clinical trials have shown that the benefit of TB preventive therapy is greater in HIV-positive people with positive tuberculin skin test.

**All HIV-positive people, with no signs and symptoms suggestive of active TB, with positive tuberculin skin test, are eligible for TB preventive therapy.**

- Particular attention should be given to the following populations: miners, prisoners, TB contacts and health care workers.
- Patients with signs and symptoms suggestive of TB must be investigated for TB (see flowchart, page 88). If they are not confirmed with TB (smear and culture are both negative), and they recover from their illness, they can be re-assessed after 3 months for TB preventive therapy.
- HIV-positive people, with no symptoms, but with negative tuberculin skin test, should not be offered TB preventive therapy.
- Tuberculin skin test should be offered to all HIV-infected people. Staff should be trained to provide quality tuberculin skin test using the Mantoux technique.

## Tuberculin skin test

The tuberculin skin test measures the body's immune response to an injection of tuberculin purified protein derivative (PPD). The Mantoux test is the recommended technique that injects a known amount of PPD between the layers of the skin (intradermally). The injection must go into the skin and not under the skin. The reaction is measured at the site of injection 48-72 hours later.

The induration (not the eventual erythema) must be measured accurately: measure the diameter of the reaction at the widest points of the raised, thickened area. Record the result in millimetres. To help measure accurately, mark the edges of the induration at the widest point with a pen (two point pen method). Then measure the exact distance between the two points.

## Positive tuberculin skin test results:

Tuberculin test	Previous BCG	NO previous BCG	HIV positive
Mantoux	≥15 mm	≥10 mm	>4 mm

## What does a positive tuberculin skin test mean?

A positive test indicates infection with TB, but not necessarily TB disease. A positive reaction occurs after BCG immunisation and remains positive for several years thereafter. This reaction is usually weaker than the reaction to natural infection with *M. tuberculosis*.

### Conditions that may reduce or suppress the tuberculin skin test include:

- HIV infection
- malnutrition
- severe viral infections (e.g. measles, chicken pox)
- cancer
- immuno-suppressive drugs (e.g. steroids)
- severe disseminated TB

## Who is not eligible for TB preventive therapy?

- Patients with active liver disease or active alcohol abuse should not be offered TB preventive therapy. This is because of potential hepatotoxicity of the drug used for preventive therapy.
- Patients with history of TB treatment:
  - Any patient who had active TB in the past 2 years, should not be offered TB preventive therapy.
  - Any patient who was treated for TB more than 2 years ago, may be offered TB preventive therapy. The curative effect of TB treatment and prophylactic effect of INH lessens over time, and thus re-infection is common.
- Patients on ART should not be offered TB preventive therapy, as there is currently no evidence of added benefit. Patients who receive TB preventive therapy, and who require to start ART, can complete their TB preventive therapy even if the ART is started. This is because there is no interaction between isoniazid and the current ART regimen used.

## Recommended regimen

**The standard regimen for TB preventive therapy is:**

**Isoniazid (INH) daily.**

**The dose is: 5 mg/kg/day (maximum 300 mg per day).**

**The recommended duration is: 6 months.**

Additional Vitamin B6 (Pyridoxine) is part of the vitamin complex that HIV-infected patients receive in sufficient dosage to prevent the eventual occurrence of peripheral neuropathy.

At this stage the intervention should be given once only and the protective effect is expected to last for 18 months.

## When and how to start

Information about TB, including preventive therapy, should be made available to all people living with HIV/AIDS. Experiences from trials and operational research have stressed the importance of relevant information for the patients including the issue of adherence. TB preventive therapy must be discussed and adequately planned to ensure full understanding and adherence by the patients. During the post-test counselling, the patient is informed about the possibility of TB preventive therapy, and is told to come if she/he is interested. It is not recommended to offer TB preventive therapy immediately after breaking the HIV result to the patients.

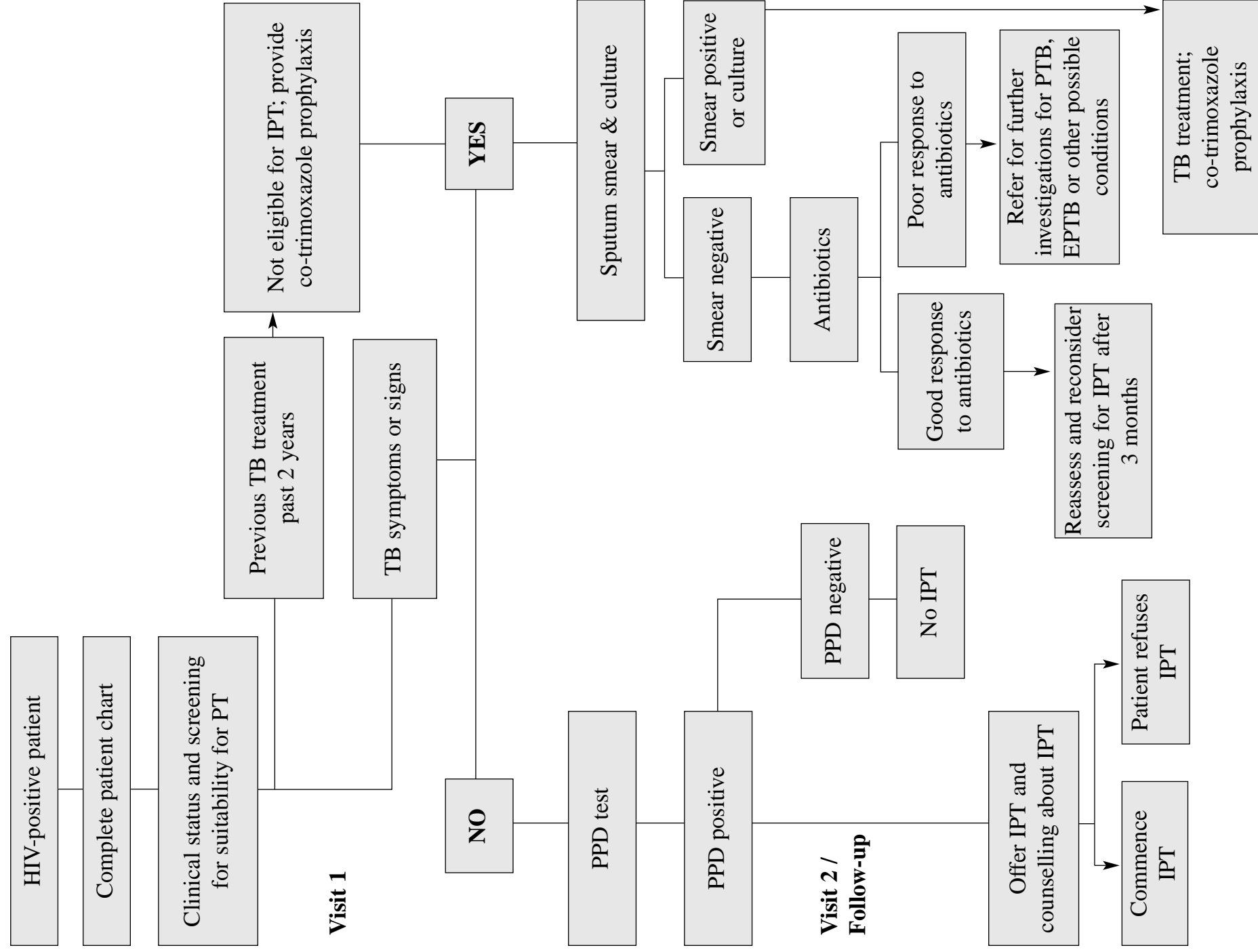
For people who know their HIV status for one month or longer, a two-visit schedule is recommended as follows:

### First visit

- The known HIV-infected patient is offered TB screening (symptomatic). This screening is essential to exclude any active TB that would require full treatment.
- The health worker must systematically enquire on the existence of the signs and symptoms discussed above and investigate as appropriate.
- It is only when the patient is free of the above symptoms that she/he is offered the tuberculin skin test.



**Figure 9: Screening for tuberculosis preventive therapy flowchart among HIV-infected patients**



### Second visit

- Three days (48-72 hrs) later, the patient is seen for reading the result.
- If the skin test is positive, the patient is offered TB preventive therapy, with adequate provision of information.
- If the test is negative, TB preventive therapy is not offered, and the patient may be given a subsequent appointment to review the condition, the clinical staging and CD4 status accordingly (see ART guidelines).
- During on-going counselling sessions, the patients will be informed about:
  - HIV
  - symptoms of side-effects of isoniazid (particularly hepatitis)
  - the importance of adherence
  - the symptoms of active TB
  - the importance of seeking care, if they develop an illness
- Patients starting TB preventive therapy should be given one-month supply at a time. They are expected to cover the 6 months therapy within a period of 9 months.

### Monitoring

Isoniazid 5 mg/kg daily is to be given for 6 months. Patients are requested to collect their supplies on a monthly basis. This visit is the opportunity for:

- on-going counselling
- identification of side-effects (minor: peripheral neuropathy; major: jaundice, vomiting and confusion, due to hepatitis)
- early detection of active TB

### Patients should come for review if any symptoms occur.

- If the patient develops active TB, stop the preventive therapy and start the full TB treatment regimen.
- In case of peripheral neuropathy, prescribe 100 mg pyridoxine (Vitamin B6) daily until symptoms disappear.
- If the patient develops signs and symptoms suggestive of hepatitis, stop INH preventive therapy immediately, and refer to a medical officer.
- If the patient interrupts therapy, enquire about the possible reasons for interrupting. Counsel on the importance of adherence appropriately. Restart the therapy after assessing the reasons for bad adherence. Ensure that the 6 months therapy is taken within a 9-month period. If the patient interrupts for the second time, consider stopping the therapy.

Preventive therapy has shown to benefit HIV-infected patients. It does not aim to control TB on a public health scale, and it is not an alternative to the DOTS strategy for controlling TB. It is a very effective intervention for HIV-infected patients prior to starting ART.

**These TB preventive guidelines may be reviewed upon evidence of new developments.**

## ACRONYMS AND ABBREVIATIONS

<b>3TC</b>	Lamivudine	<b>M&amp;E</b>	Monitoring and Evaluation
<b>ACTG</b>	AIDS Clinical Trials Group	<b>MCC</b>	Medicines Control Council
<b>AIDS</b>	Acquired Immune Deficiency Syndrome	<b>NGO</b>	Non-governmental Organisation
<b>ALT</b>	Alanine Amino Transferase	<b>NNRTI</b>	Non-nucleoside Reverse Transcriptase Inhibitors
<b>ANC</b>	Antenatal care	<b>NRTI</b>	Nucleoside Reverse Transcriptase Inhibitors
<b>ART</b>	Antiretroviral treatment	<b>NVP</b>	Nevirapine
<b>ARV</b>	Antiretroviral	<b>OI</b>	Opportunistic Infection
<b>AZT</b>	Zidovudine	<b>PACTG</b>	Paediatric AIDS Clinical Trials Group
<b>CBO</b>	Community Based Organisation	<b>PCR</b>	Polymerase Chain Reaction
<b>CHBC</b>	Community Home Based Care	<b>PEP</b>	Post-exposure Prophylaxis
<b>CHW</b>	Community Health Worker	<b>PI</b>	Protease Inhibitors
<b>CoC</b>	Continuum of Care	<b>PLWHA</b>	People Living with HIV/AIDS
<b>D4T</b>	Stavudine	<b>PMTCT</b>	Prevention of Mother-to-child Transmission
<b>ddI</b>	Didanosine	<b>RTV</b>	Ritonavir
<b>DOTS</b>	Directly Observed Therapy, short course	<b>STI</b>	Sexually Transmitted Infection
<b>EDL</b>	Essential Drugs List	<b>TB</b>	Tuberculosis
<b>EFV</b>	Efavirenz	<b>THP</b>	Traditional Health Practitioners
<b>EPI</b>	Expanded Programme on Immunisation	<b>TLC</b>	Total Lymphocyte Count
<b>HBC</b>	Home Based Care	<b>VCT</b>	Voluntary Counselling and Testing
<b>HIV</b>	Human Immunodeficiency Virus	<b>VL</b>	Viral Load
<b>INH</b>	Isoniazid		
<b>IPT</b>	Isoniazid Preventive Therapy		
<b>LPV</b>	Lopinavir		

## RESOURCES

AIDS Helpline:	0800 012 322
Circles of Support Information Hotline:	0860 222 777
Red Ribbon Resource Centre (for free booklets on ART):	(011) 880-0405
National Association of People with AIDS (National office):	(011) 873-0325
Department of Health (HIV/AIDS and STIs Directorate):	(012) 312-0121
Department of Social Development (National HIV/AIDS Co-ordinator):	(012) 312-7500

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