

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/mm³), 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/mm³ 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"> ■ CD4 <200 cells/mm³ irrespective of stage <p>OR</p> <ul style="list-style-type: none"> ■ WHO Stage IV AIDS-defining illness, irrespective of CD4 count <p>AND</p> <ul style="list-style-type: none"> ■ Patient expresses willingness and readiness to take ART adherently <p><i>Note: see WHO staging tables in Appendix 1, page 78.</i></p>

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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.

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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

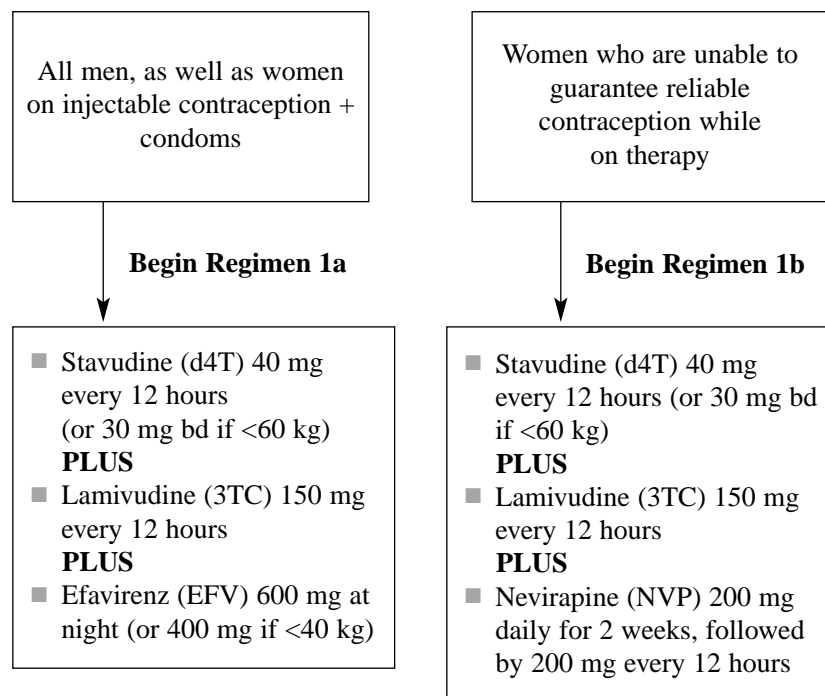
Patients should be seen by the doctor at 4, 8 and 12 weeks and 3-monthly thereafter if they are well. If they are not well, patients should be seen more frequently as determined by the treating doctor or nurse.

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	
Treatment readiness assessment		Whole team							
History	D	D							
Physical exam	D	D		D	D	D	N	D	D
Complete registers	N	N						N	N
Safety bloods Regimen 1 with NVP		N ^a		N ^a	N ^a				N ^a
Safety bloods Regimen 2 ^b		N ^b		N ^b	N ^b	N ^b			N ^b
Viral load		N,D							N
CD4 count	N								N
Adverse events			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

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

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/mm³, 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.

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

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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"> ■ CD4 ■ FBC ■ Fasting cholesterol and triglyceride ■ Fasting glucose 	<ul style="list-style-type: none"> ■ Staging, 6-monthly ■ Baseline, then monthly for 3 months, then 6 monthly (with CD4 and viral load) ■ Baseline, 6 months and thereafter every 12 months ■ Baseline and 12 months

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.

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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/mm³.

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/mm³. It should be recommenced if the CD4 count drops to <200 cells/mm³ when therapy fails.
- Patients who have had cryptococcal meningitis must continue taking fluconazole prophylaxis until the CD4 count is >200 cells/mm³.
- 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.

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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/mm³, 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/mm³, complete 2 months of TB therapy before commencing ART.
- If the patient has a CD4 count of less than 50 cells/mm³, 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.

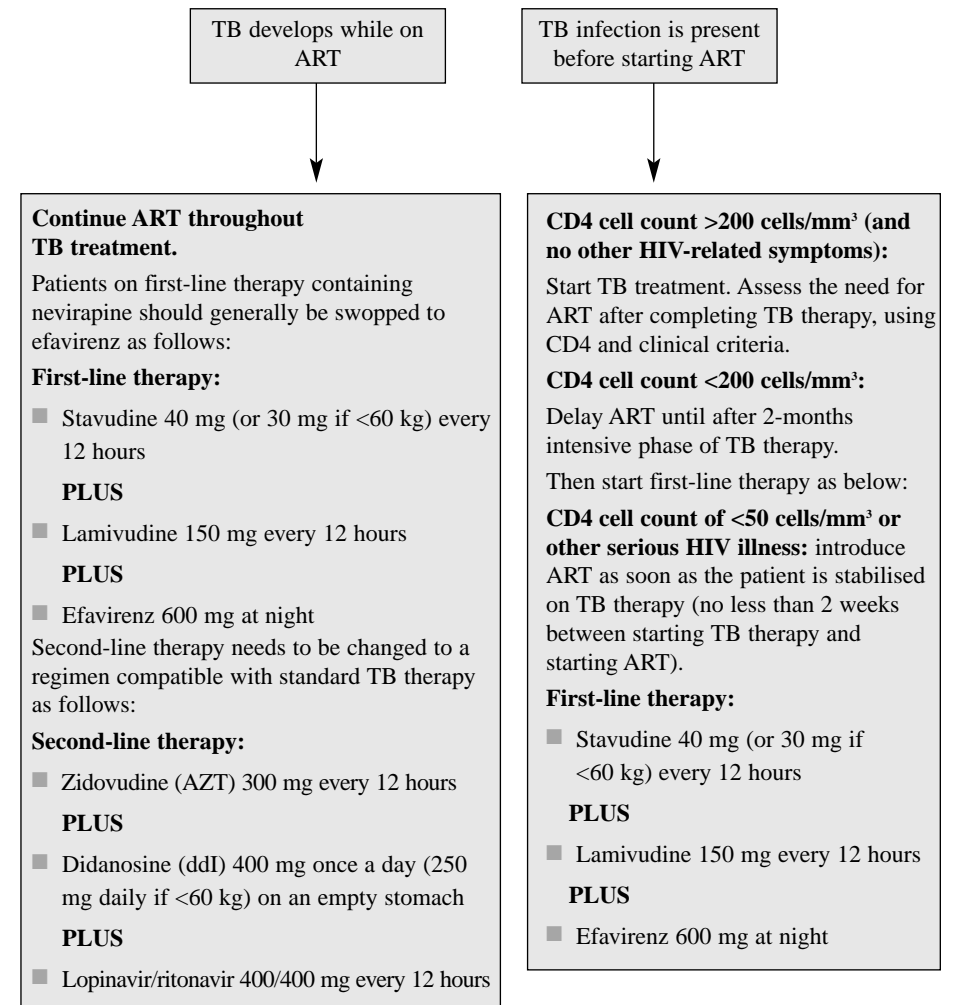
Table 7: Shared side-effects of TB and ART

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.

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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. ARTs 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

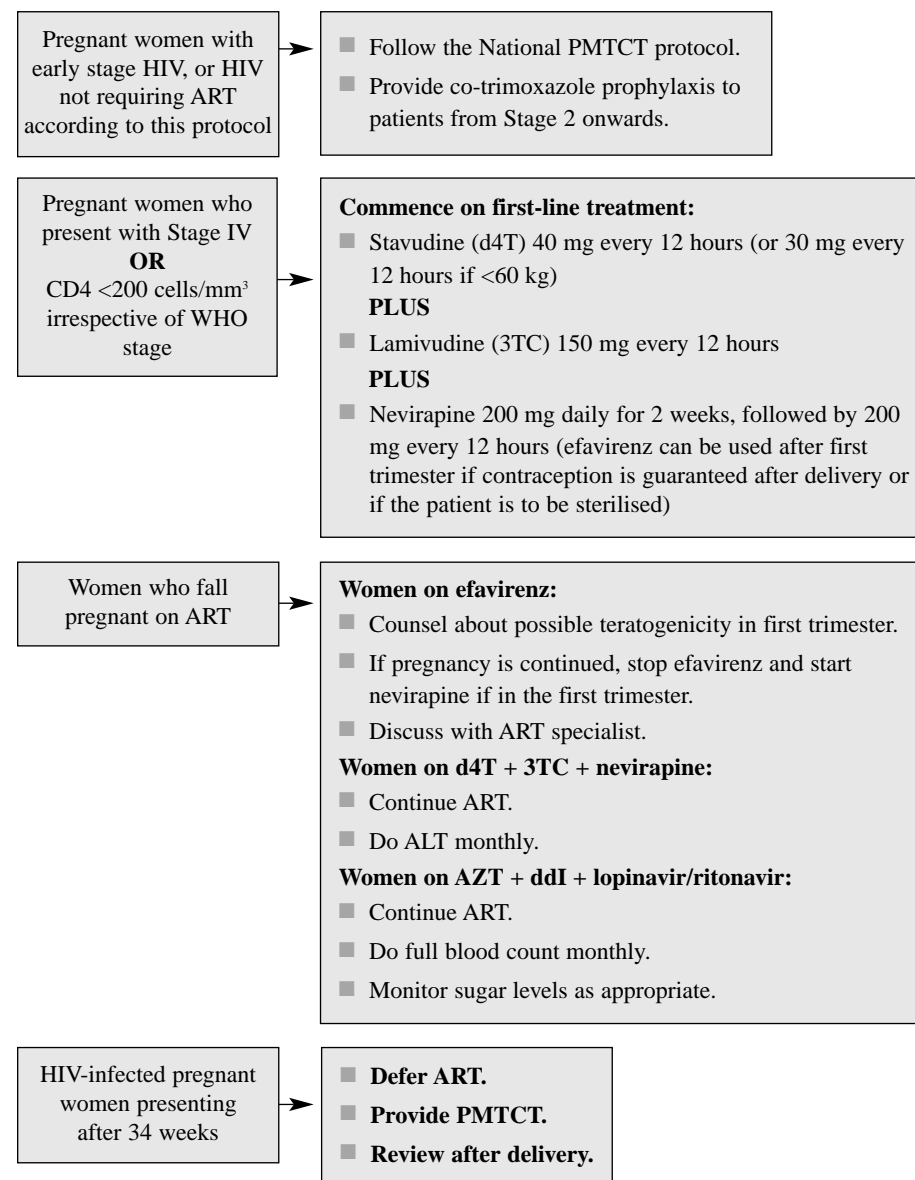


Figure 5: Adult HIV management flowchart

