

Clinical tract

Module on

Advanced adult antiretroviral treatment guidelines

LEARNING OUTCOMES FOR SOCIAL WORKERS, LABORATORY TECHNICIANS, PHARMACISTS, NURSING STAFF AND DOCTORS

After completion of this module the learner should be able to:

- Understand the goals of ARV
- Know the criteria of initiating therapy
- Identify psychosocial considerations and offer adherence support to therapy
- Select a first line ARV regimen
- Evaluate non-naïve patients on ARV
- Select a second-line regimen
- Monitor safety, efficacy and compliance with ARV
- Differentiate between treatment success and failure
- Understand advantages and disadvantages of interruption of ARV
- Identify immune reconstitution illness
- Manage HIV-related Tuberculosis

This module is primarily meant to be studied by medically qualified health care workers. Counsellors and data typists are welcome to read it, but should not feel discouraged if they do not understand all the information.

1. INTRODUCTION

Use of triple drug antiretroviral (ARV) regimens has resulted in reduction in mortality, progression to AIDS, opportunistic infections and hospitalisations in patients who respond to therapy, particularly those with a substantial lowering in HIV-1 RNA levels

Countries are encouraged to adopt a public health approach in order to facilitate the scale-up of ARV use. Antiretroviral treatment programmes are developed and standardized in each country.

In South Africa, the Department of Health and HIV experts have compiled a standardized National ARV Rollout programme. The Southern African HIV Clinicians Society, as well as many of the medical aids also wrote treatment guidelines.

2. GOALS OF ANTIRETROVIRAL THERAPY (ARV)

Primary goals of antiretroviral therapy are:

- Decrease in the viral load to undetectable levels for as long as possible in order to halt disease progression and prevent/reduce resistant mutations
- Increase and maintain a high CD4+T cell count
- Improvement in duration and quality of life
- Reduction of HIV-related illnesses and death
- Reduction HIV transmission

Secondary goals of antiretroviral therapy are:

- Increase voluntary counseling and testing
- Decrease HIV transmission rates in discordant couples
- Reduce the risk of mother to child HIV transmission

3. PATIENT SELECTION CRITERIA IN ADULTS

The following factors should be considered before initiation of therapy.

1. The willingness, ability, and readiness of the persons to begin therapy
2. The degree of existing immunodeficiency as determined by the CD4+T cell count;
3. The likelihood, after counseling and education, of adherence to the prescribed treatment regimen.

WHO recommends that in ARV treatment programmes HIV infected adolescents and adults, should start ARV therapy when they have:
WHO stage IV HIV disease (clinical AIDS), regardless of CD4 cell count.

Studies have shown that the outcome is good and immune reconstitution occurs in most cases when ARV is started at a CD4 cell count above 200 cells/mm³; while toxicity and adherence problems discourages initiation of therapy at CD4 cell count above 350 cells/mm³.

The medical criteria according to the national antiretroviral treatment guideline of Department of Health South Africa 2004 are as follows:

- CD4 count < 200 cells/mm³ irrespective of WHO stage
OR
- WHO stage 4 disease irrespective of CD4 count
OR
- CD4 count between 200 cells/mm³ and 300 cells/mm³ and declining by more than 80 cells/mm³ per year according to the HIV clinicians society

(Refer module on Natural course of HIV for the definition of WHO stage 4 disease)

Psychosocial considerations

- 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, emotional distress or any diagnosable mental illness.
- *Social support:* patients must have disclosed their HIV status to a family member, a friend or joined a support group. Stable relationships and a network of social support also positively affect patient adherence. Bringing a buddy to every clinic/ doctor helps in adherence to treatment.
- *Insight:* Patient must accept their HIV status; understand the effects of HIV infection and the role of ARV before starting treatment. Long-term effectiveness of highly active antiretroviral therapy (HAART) depends on strict adherence to the prescribed regimen.
- *Access to the clinic:* Follow-up visits must be done regularly e.g. transport; patients without a regular place to stay and store their medications or without enough to eat will have more difficulty adhering.

ARV should be deferred if the patient is not ready to commit to ARV. The patient should however still be followed up, prophylaxis and treatment of opportunistic infections must continue and the patient must receive ongoing counselling.

4. ADHERENCE

The likelihood of adherence is discussed and determined by the health provider with the patient before therapy is initiated.

Adherence to the regimen is essential for successful treatment. It determines the degree and duration of viral suppression. Suboptimal adherence to treatment regimen is associated with virological failure. Ideal adherence means a patient must not miss more than 3 doses in a month (i.e. take more than 95% of their doses). Patients taking < 80% of their doses are unlikely to have any durable virological suppression and should be urgently targeted for adherence improvement.

Strategies to improve adherence (patient and medication related)

- Educate the patient about the expected or common side effects.
- Actively enquire about and treat side effects.
- Explain necessary food requirements in relation to treatment.
- Avoid unpleasant/dangerous drug interactions.

- If possible, reduce dose frequency and number of pills (bd is much easier than tds).
- Negotiate a treatment plan that is easy to understand and follow (the patient must commit it).
- Explain the regimen to the patient by showing the patient the instructions and medication visually.
- Spend time on a number of visits to teach, explain goals of therapy and need of adherence.
- Make sure that the patient is ready to take medication before writing/giving the first prescription.
- Encourage participation of family and friends to help or support in treatment plan.
- Plan regimen such that it does not interfere much with meals, daily routines and gives less side effects.
- Make available written schedule and pictures of medications; encourage the use of reminders like alarm clocks, pagers etc and other mechanical aids for adherence (e.g. daily or weekly pillboxes etc).
- Encourage adherence support groups.
- Encourage links with local community based organizations e.g. homecare-nurses, local clinic to support with further adherence, educational sessions and practical strategies.

5. TREATMENT READINESS ASSESSMENT

This is a process for initiation of ARV - induction schedule

First screening visit: 2-4 weeks before starting ARV

- Confirm the selection criteria: clinical and laboratory (make sure TB and pregnancy are excluded)
- Treat any opportunistic infections
- Patient's information records need to be completed.
- Patient must meet with the multi-disciplinary team for group and individual information sessions.
- Treatment counselor/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 a 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)

A home visit is ideal, but if this is not possible, it may not hinder access to the programme.

Before the second visit multidisciplinary team should meet and assess patient readiness. Patient readiness criteria include the following:

- Patient's acceptance of the status and ARV
- Have the medical criteria been met

- Absence of severe medical contra-indication (active disease that is not stabilized, including depression)
- Understanding of the importance of adherence and attendance to all scheduled pre-treatment visits

The importance of communication between the different clinic members cannot be overemphasized.

Second visit

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

Multi-disciplinary team discussion

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

ARV commencement visit

- ARV 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 further information and adherence issues with the patient and his /her counselor or advocate
- Re-enforce drug dosing details before the patient leaves the clinic
- Ensure that instructions are clearly written on the container with a permanent marker

6. FIRST LINE ARV REGIMEN

Selection of ARV treatment regimens is based on

- potency
- side effect profile
- the potential for maintenance of future treatment options
- the anticipated adherence of the patient population with a regimen
- coexistent conditions (e.g. co-infections, metabolic abnormalities)
- pregnancy or the risk thereof
- the use of concomitant medications (i.e. potential drug interactions) and
- the potential to acquire resistant viral strains.

Highly active antiretroviral therapy (HAART) is antiretroviral regimens that give maximally possible benefits in obtaining best clinical results and to prevent resistance. Combination of three synergistic antiretroviral agents is the standard care. Monotherapy and dual drug regimens give suboptimal clinical outcome, promote development of resistance and should therefore not be used.

Table 1. Antiretroviral drugs available

NRTI Thymidine analogue	NRTI Non-Thymidine analogue	NRTI Non- Thymidine analogue	NNRTI	PI
Stavudine (d4T) Zidovudine (AZT)	Didanosine (ddl) Zalcitabine (ddC) Lamivudine (3TC)	Abacavir (ABC)	Nevirapine (NVP) Efavirenz (EFV)	Nelfinavir (NFV) Indinavir (IDV) Ritonavir (RIV) Saquinavir (SQV) (soft gel formulation) Lopinavir/ritonavir combination

NRTI=Nucleoside reverse transcriptase inhibitors

NNRTI= Non-Nucleoside reverse transcriptase inhibitors

PI= Protease inhibitors

Taking all of these considerations except the cost of drugs into account, the preferred first-line antiretroviral regimens in adults and adolescents are listed in the Table 2.

The drug combination for initial therapy in ARV naïve patients is two NRTIs and an NNRTI.

Table 2. Recommended first line regimen

NNRTI based Regimens
1a) Stavudine + lamivudine (3TC) +efavirenz
1b) Stavudine + lamivudine (3TC) + Nevirapine

The adult dosage is as follows:

1. Stavudine

<60kg	one 30mg capsule every 12 hours
>60kg	one 40mg capsule every 12 hours
2. Lamivudine (3TC) one 150 mg tablet every 12 hours
3. Efavirenz (EFV) three 200mg capsules at night or one 600mg capsule at night
4. Nevirapine (NVP) 200 mg one tablet daily for the first 2 weeks, increasing to 200 mg one tablet every 12 hours after these 2 weeks.

Efavirenz is teratogenic, therefore not used during pregnancy (especially in the first trimester) or in women with a potential to get pregnant. Nevirapine should be used as a substitute for Efavirenz in those patients. Effective contraception i.e. injectable contraceptive and use of barrier method should be used if efavirenz is used.

7. ARV FOR NON-NAÏVE PATIENTS

An expert in HIV/AIDS should be consulted for management of non-naive patients

Try to obtain all previous results, before and after initiation of initial ARV. Do follow-up CD4 and viral load before making any decisions on change in regimen.

First decide whether the patient needs to be on antiretroviral therapy in view of previous and current results.

- Patients well controlled (having an undetectable viral load) on antiretroviral therapy can be changed to the First-line regimen of the National Roll out Plan if they are not on it yet.
- A two-drug regimen (usually stavudine and didanosine) may only be intensified with a third drug if the viral load is less than 5 000 copies/mL.
- Patients who stopped treatment for financial reasons, but were controlled on previous treatment, could recommence therapy and be monitored as required.
- Patient who failed a previous regimen should be started on a new regimen they were not exposed to before (changing all the drugs in the regimen).

8. CHANGING ARV

- Therapy should only be changed after careful consideration. ARV may need to be changed because of either treatment failure or toxicity. Toxicity is related to the ability to tolerate the side effects of the medication and to significant organ dysfunction that may result.
- If a change in regimen becomes necessary because of treatment failure, all the drugs in the regimen should be replaced with new ones.
- If a change in regimen is indicated because of toxicity, the drug causing the toxicity may be replaced by another drug from the same class of agents that does not have the same side effects.

Table 3. Guidelines to changing NRTIs because of toxicity

Initial agent	New agent
Zidovudine	Stavudine#
Stavudine	Zidovudine#
Didanosine	Lamivudine or Zalcitabine
Lamivudine	Didanosine* or Zalcitabine*
Zalcitabine	Abacavir, Stavudine or Zidovudine or other as determined by resistance testing
Abacavir	Determined by resistance testing
	*May exhibit reduced activity due to cross-resistance with Lamivudine
	#May exhibit cross-resistance

Changing non-nucleoside reverse transcriptase inhibitors (NNRTI)

- There is a high degree of cross-resistance among the currently available NNRTIs. Treatment failure on one drug in this class thus rules out further use of the class. For side effects one may change to another drug in the same class.
- Patients in whom an NNRTI-containing regimen fails may be candidates for abacavir-triple-nucleoside combination (if the viral load is <55 000 RNA copies/ml) or a protease-inhibitor containing regimen. The National Antiretroviral Treatment Guidelines recommends that the second regimen includes a PI.

Changing Protease inhibitors (PI)

- Consult an expert in HIV/AIDS.
- Resistance patterns to PIs overlap. Cross-resistance is less problematic with nelfinavir, making rescue treatment with other PIs more likely to succeed.
- Dual PIs due to its metabolic interaction allow an easier dosing regimen and a lower pill burden, hence increasing adherence and reducing the likelihood of side effects. The frequently used combinations are indinavir/ritonavir (indinavir as combination therapy with ritonavir has no meal restrictions), saquinavir/ritonavir, and lopinavir/ritonavir. These combinations can be used as second line regimens or as salvage therapy.

9. SECOND-LINE ARV REGIMEN

Treatment regimen failure (particularly virological failure with good adherence) is the main indication for starting a patient on second line ARV regimen. Second line regimen has to be drugs, which retain activity against the patient's virus strain and include at least three new drugs with at least one from a new class, to increase the likelihood of treatment success and minimize the risk of cross resistance.

Table 4.

PI Based Regimen	Pregnancy considerations
Zidovudine (AZT) + didanosine (ddI) + Lopinavir/ritonavir (co-formulated as Kaletra)	Lopinavir/ritonavir safety information insufficient.

The adult dosage is as follows:

1. Zidovudine (AZT) 300mg 1 tablets every 12 hours
2. Didanosine (ddI)
 - <60kg 250mg/day total daily dosage that can be taken as either one 100mg tablet 12 hourly plus one 25mg tablet 12 hourly **or** one 150mg tablet and one 100mg tablet once a day (2 tabs together)
 - >60kg 400mg/day total daily dosage that can be taken as either two 100mg tablets 12 hourly **or** two 150mg tablets and one 100mg tablet once a day (3 tabs together)
3. Lopinavir/ritonavir (LPV/r) three 400/100mg capsules every 12 hours

Lopinavir/ritonavir has to be kept in a safe, cool & dry place. (<25°C).

Didanosine must be taken alone, on an empty stomach, at least an hour before a meal. Tablets should be dissolved in at least 30 ml of water - no other liquids may be used to dissolve the tablets.

Table 4. Recommended substitutions for specific side effects (grade 3 or 4 toxicity)

Regimen	Toxicity	Drug substitution
Stavudine 3TC Efavirenz Or Nevirapine	Stavudine-related neuropathy or pancreatitis Efavirenz-related persistent CNS toxicity	Switch stavudine to zidovudine Switch Efavirenz to nevirapine
	Nevirapine-related severe hepatotoxicity, severe rash and/or life threatening rash (Stevens-Johnson syndrome) Lactic acidosis	Switch Nevirapine to Efavirenz (except in early pregnancy) Switch regimen to a PI (lopinavir/ritonavir) Consult HIV expert
Zidovudine Didanosine Lopinavir/ritonavir	Zidovudine-related anaemia or neutropenia Didanosine-related GIT side effects Didanosine-related pancreatitis or hepatitis LPV/r related GIT symptoms LPV/r related hypercholesterolaemia Lipodystrophy Impaired glucose tolerance	Switch zidovudine to stavudine Switch ddl for enteric coated ddl (not yet available in SA) Consult expert Consult expert Consult expert Consult expert Antidiabetic agents (warning - metformin increases risk of acidosis)

10. MONITORING ANTIRETROVIRAL THERAPY

Baseline evaluation and continuing monitoring of ARV therapy are important for effective intervention in the management of HIV/AIDS.

Clinical monitoring

A good medical history and physical examination is essential to document baseline medical conditions.

Table 5. Clinical Adverse Events in Adults

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
Symptoms of peripheral neuropathy Paresthesia (burning, tingling, etc.)	Paresthesia (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
Signs of peripheral neuropathy	Mild impairment (decreased sensation, e.g. vibratory, pinprick, hot/cold in great 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
MANAGEMENT	Continue ARV Provide careful clinical monitoring Consider change of a single drug if condition worsens		Consult specialist immediately before stopping ARV	

Laboratory monitoring for safety

To prevent occurrence of serious and potentially fatal side effects relevant laboratory investigations have to be monitored.

Bone marrow depression

Patients on zidovudine (AZT), hydroxurea (Hydrea) or co-trimoxazole may have abnormal full blood counts (FBC). Patients on zidovudine should have a routine FBC every 3 months. Haemoglobin, absolute white cell count, absolute neutrophils, and platelets levels are evaluated. Hydrea should not be used as part of any first or second line regimen. It is not necessary to do routine 3 monthly FBC on patients on co-trimoxazole.

Hepatotoxicity

Hepatotoxicity occurs in 8-18% of cases. It is more frequent in women and patients with higher CD4 cell counts. The event may be fatal.

Patients may present with non-specific gastrointestinal and flu-like symptoms. That can rapidly progress to hepatomegaly, jaundice, and hepatic failure within a few days. Because of this imminent danger, liver functions should be checked two weekly for the first eight weeks and thereafter every three months. Nevirapine must be discontinued if the ALT or AST increase to 5 times the upper limit normal. It may only be restarted once the values return to normal and the patient had no clinical signs or symptoms of hepatitis.

A lead-in dosage (50%) of nevirapine is always used, with increase to the full dosage at 14 days.

Other

Patients on protease inhibitors (e.g. lopinavir/ritonavir) may have hypertriglyceridemia, hypercholesterolemia and hyperglycemia. A fasting lipogram (cholesterol and triglyceride) and fasting glucose should be done at baseline, 6 months and then every 12 months.

Table 6. Important ARV safety monitoring

Antiretroviral	Recommended safety monitoring
Abacavir (ABC)	Fasting cholesterol and triglycerides at baseline, 6 months and thereafter every 12 months
Didanosine (ddI)	Clinical
Efavirenz (EFV)	Clinical
Lamivudine (3TC)	Clinical
Lopinavir/Ritonavir	Fasting cholesterol and triglycerides at baseline, 6 months and thereafter every 12 months
Nevirapine (NVP)	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	Fasting cholesterol and triglycerides at baseline, 6 months and thereafter every 12 months
Stavudine (d4T)	Clinical
Zidovudine (AZT)	FBC with differential count at baseline then monthly for 3 months then 6 monthly (with CD4 and viral load)

Note: Other adverse reactions not listed on this table may occur.

Table 7. Laboratory Adverse Events in Adults (ACTG)

LABORATORY TEST ABNORMALITIES				
ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 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 ⁹ /L	0.75-0.99 X 10 ⁹ /L	0.5-0.749 X 10 ⁹ /L	<0.5 X 10 ⁹ /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
MANAGEMENT	Continue ARV Repeat test 2 weeks after the initial test and re-assess		Continue ARV Repeat test 1 week after initial test and reassess; if ALT still grade 3 consult expert about stopping ARV	Consult expert immediately before stopping ARV
	Lipid imbalances could be managed with diet, exercise and pharmacologically with the use of fibrates. ALWAYS SEEK EXPERT ADVICE IN CASE OF DOUBT			

Note: the repeat tests may require additional patient's visits over and above the routine monitoring visits

MONITORING FOR EFFICACY

Monitoring viral load and CD4 cell count are methods used to assess effectiveness of ARV therapy.

The anticipated response to ARV therapy in a treatment naive patient adhering to treatment is

- a decline in viral load by at least 1 log₁₀ from pre-treatment levels after 6-8 weeks of antiretroviral therapy
- a viral load of less than 400 copies/ml at 24 weeks of treatment

CD4 cell count rises with time in individuals with maximal viral suppression (<50copies/ml). A much better rise in CD4 count is expected in patients initiating ARV with CD4 counts above 100 cells/mm³ than in patients initiating ARV with CD4 counts below 50 cells/mm³.

Monitoring for efficacy helps in recognizing virologic and immunologic failure early hence preventing development of drug resistance

HIV-1 RNA levels i.e. viral load measures whether the antiretrovirals are effective in controlling the HIV. Refer Table 8.

Table 8. Viral load monitoring

Viral load (VL)	Response
<400 copies/ml	6 monthly viral load monitoring continues Routine adherence support
400-5000 copies/ml	Repeat viral load in 6 months 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 5000, continue with step-up adherence package, repeat viral load at 6 months. If >5000, despite stepped up adherence support, switch to second-line therapy only if adherence is >80%.
>5000 copies/ml	Repeat viral load in 3 months 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 5000, continue with step-up adherence package, repeat viral load again after a further 6 months. If >5000, despite stepped up adherence support, switch to second-line therapy only (if adherence is >80 %.)

11. TREATMENT SUCCESS

Treatment success when using triple drug combinations is:

- a decline in viral load by at least 1 log₁₀ from pre-treatment levels after 6-8 weeks of antiretroviral therapy
- a viral load of less than 400 copies/mL at 24 weeks of treatment

12. ASSESSMENT OF TREATMENT FAILURE

Treatment failure is due to failure to suppress viral replication with the development of resistance. Possible reasons for failure are nonadherence, toxicity, pharmacokinetics, suboptimal virologic potency and resistance. Treatment failure can be divided into virologic, immunologic, and clinical failure.

To find the cause of treatment regimen failure; a good medical history should be taken and physical examination done on the patient.

For adherence: Causes for nonadherence must be identified and addressed e.g. substance abuse, lack of transport, high pill count etc.

For tolerability: Assess side effects and address them.

- Symptomatic treatment e.g paracetamol for headache
- Change with a drug within the same class. E.g. Stavudine for zidovudine; Nevirapine for neuropsychiatric symptoms of efavirenz

For pharmacokinetic issues: Review the following:

- food fasting requirements;
- likelihood of malabsorption;
- concomitant medication and dietary supplements for drug-drug interactions

When adherence, tolerability and pharmacokinetic issues are ruled out then virologic, immunologic, and clinical failure are considered.

Virologic failure is

- a sustained viral load above 5 000 copies/mL
- a decline in viral load less than 1 log₁₀ 6-8 weeks after initiating therapy
- a viral load 0.6 log₁₀ higher than its lowest point or a return to 50% of its pre-treatment value

Immunologic failure is failure to increase by 25-50 cells/mm³ above the baseline CD4 cell count over the first year of therapy or CD4 cell count decreases below the baseline level while patient on therapy.

Clinical failure is occurrence or recurrence of HIV related events after at least 3 months of therapy, this exclude immune reconstitution syndromes.

Viral load and CD4 count should be measured on two separate occasions before deciding that a regimen is failing.

These patients with treatment regimen failure must be discussed with an antiretroviral specialist or expert before therapy is commenced.

13. INTERRUPTION OF ARV

ARV might need to be discontinued temporarily or permanently for a number of reasons. All drugs should be stopped simultaneously. If the combination includes nevirapine or efavirenz, this should be stopped a few days earlier to prevent resistance developing, since these drugs have a longer half-life than other drugs. If therapy is interrupted; the patient should be monitored closely, including clinical and laboratory evaluations. Chemoprophylaxis against OIs should be initiated as needed on the basis of CD4 T cell count.

The concept of structured or supervised treatment interruptions (STI) vary, depending on patient populations, and encompass more than 3 major strategies:

- STI as part of salvage therapy
- STI for autoimmunization and improved immune control of HIV; and
- STI for the sole purpose of allowing less total time on antiretroviral therapy.

Salvage STI is intended for patients whose virus has developed substantial ARV drug resistance and who have plasma viremia and relatively low CD4 T cell counts despite receiving therapy.

Autoimmunization STI and *STI for the reduction of total time receiving ARV drugs* are intended for persons who have and relatively low CD4 T cell counts. The theoretical goal of autoimmunization STI is to allow multiple short bursts of viral replication to augment HIV-specific immune responses.

Due of insufficient data, STI is not recommended for use in clinical practice.

14. IMMUNE RECONSTITUTION

- 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 e.g. tuberculosis, PCP, etc.

- Tuberculosis is a common immune reconstitution illness in South Africa.
- Patients become ill during the first weeks of ARV, particularly those with CD4 count less than 50 cells/mm³ i.e. advanced HIV disease.
- An immune reconstitution illness is not indicative of drug failure or drug side effects. It is not a reason to stop ARV, 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.

15. MANAGEMENT OF HIV-RELATED TUBERCULOSIS

Many patients who are candidates of ARV have active tuberculosis (TB). Patients already receiving ARV therapy may develop TB. TB is a leading cause of death among HIV-infected patients

Two important clinical management issues

- Tuberculosis treatment with directly observed therapy (DOT), an adherence program, should be initiated promptly in diagnosed cases of TB. (Refer to Module on Opportunistic infections for TB diagnosis)
- Delaying ARV therapy (if possible) until TB treatment is completed simplifies the management of patients with both TB and HIV infections because standard regimens for both diseases can be utilized and there will be no drug interactions or less drug toxicity. However delaying ARV therapy can result in HIV-related illnesses and even death in patients with low CD4 cell count.

Initiation of ARV for patients with active TB or on TB treatment

- Patients with a CD4 cell count below 50 cells/mm³ and pulmonary TB or patients with extrapulmonary TB and must have tolerated two weeks of TB treatment before initiation of ARV. These patients are at very high risk of HIV disease progression and death.
- Patients with pulmonary TB and a CD4 cell count between 50-200 cells/mm³ should be started on ARV after they tolerated TB treatment for two months.
- Patients with pulmonary TB and a CD4 cell count above 200 cells/mm³ should have ARV delayed and CD4 cell count levels monitored.

Patients may experience a temporary exacerbation of symptoms, signs, or radiographic manifestations of tuberculosis while receiving TB treatment and ARV.

This clinical or radiographic worsening (paradoxical reaction) occurs in HIV-infected patients with active tuberculosis and is thought to be the result of immune reconstitution as a consequence of effective antiretroviral therapy. Symptoms and signs may include high fever, lymphadenopathy, expanding central nervous system lesions, and worsening of chest radiographic findings. Drug resistance and treatment failure are possible for both TB and ARV.

Table: Management of Tuberculosis

Situation	TB management	HIV/AIDS management
Pulmonary TB and CD4 cell count < 50 cells/mm ³ Or Extrapulmonary TB	Start TB therapy	Start ARV therapy only after two weeks of well tolerated TB treatment. d4T/3TC/EFV Or d4T/3TC/NVP
Pulmonary TB and CD4 cell count between 50-200 cells/mm ³	Start TB therapy	Delay ARV therapy for two months while the patient is on TB therapy.
Pulmonary TB and CD4 cell count between >200 cells/mm ³	Start TB therapy	Delay ARV therapy and Monitor CD4 cell count, then treat according to regimen in module on OIs

Patients on nevirapine should be changed to efavirenz wherever possible; except if the patient does not tolerate efavirenz or has significant risk of falling pregnant. Rifampicin reduces drug levels of nevirapine and causes hepatotoxicity too.

Lopinavir/ritonavir dose should be increased to lopinavir/ritonavir 400/400 mg every 12 hours – (i.e. 3 extra caps of ritonavir); it should be given in high doses for an extra two weeks after TB treatment is stopped.

REFERRAL TO SPECIALIST

Patient with the following should be referred to an HIV expert:

- AIDS defining (WHO stage 4) illness on second-line therapy;
- Treatment regimen 2 failure with good adherence
- Renal and hepatic impairment
- Atypical opportunistic infections

16. FURTHER READING

- World Health Organization, HIV/AIDS Department, Family and Community Health Cluster, April 2002. The full guidelines are available at <http://www.who.int>.
- Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents; 2004. Available and updated on the web at <http://aidsinfo.nih.gov/guidelines>.
- Yeni PG, Hammer SM, Carpenter CC, *et al.* Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *JAMA* 2002; 288:222
- Southern African HIV Clinicians Society Guidelines for Antiretroviral Therapy in Adults, June 2002 version. *Southern African Journal of HIV Medicine* 2002;2:22-29.
- Andrews S. Adherence to antiretroviral regimens. *Southern African Journal of HIV Medicine* 2002;8:18-21.
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