

Clinical Tract

Module on

Basic adult antiretroviral therapy

LEARNING OUTCOMES FOR ALL PARTICIPANTS

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
- Understand the purpose of laboratory monitoring
- Know how to calculate monthly adherence
- Understand the role of adherence in treatment success and failure

1. INTRODUCTION

Use of triple drug antiretroviral (ART) 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 (ART)

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 treatment programmes HIV infected adolescents and adults, should start 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:

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 to the 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. Sub optimal 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 of care. Monotherapy and dual drug regimens give sub optimal 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 (RV) 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 part of the regimen.

7. MONITORING THE PATIENT ON THE ARV

We are interested in whether the drugs are

- taken correctly
- safe
- effective

Monitoring for Adherence

Do a pill count on each visit and calculate monthly adherence
 $= (\text{tablets dispensed} - \text{tablets returned}) / (\text{tablets prescribed})$,
e.g. $(30-5)/28 = 25/28 = 0.9$ (90%)

The patient can also be questioned about his use of pills, what he/she does to remember his/her medication and where the medicine is kept. If human resources exist, home visits are an excellent way of checking up on that. The buddy or friend that comes along to the visit, can also confirm whether the medication is used correctly.

We are striving for more than 95% adherence.

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.

If anaemia develops during zidovudine use, change of dosage or interruption of treatment leads to full recovery of the bone marrow.

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 patients using nevirapine. It is more frequent in women and patients with higher CD4 cell counts. The event may be fatal.

The patient must be educated beforehand to seek medical advice if severe vomiting and upper abdominal pain develops. The patient must also always take all medication along for any consultation with any health care provider.

Patients may present with non-specific gastrointestinal and flu-like symptoms. This 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 for patients on protease inhibitors.

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

Treatment failure is due to failure to suppress viral replication with the development of resistance. Possible reasons for failure are. nonadherence, toxicity, pharmacokinetics, sub optimal virologic potency and resistance.

