ANTIRETROVIRAL THERAPY: THE BASICS

Antiretroviral therapy (ART) is complex and requires the use of at least three drugs in combination.

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Patients on ART are required to take numerous tablets with the potential to cause adverse effects. Fortunately, new drugs are coming onto the market bringing with them increased dosing convenience and improved safety profiles. Good adherence is essential to decrease the risk of inducing viral resistance and treatment failure. Rigorous pre-treatment counselling is therefore vital.[1]

ART should not be started too early in the course of the disease. Early ART increases the risk of developing drug toxicity and viral resistance which, in turn, could increase the risk of transmission of resistant virus to the patient's sexual partner/s.[1] Present WHO guidelines for initiation of ART are based on clinical status and CD4 count of the patient. ART should be started when:

- WHO stage 4 HIV disease (Table I), irrespective of CD4 count
- WHO stage 3 HIV disease with consideration of using CD4 cell counts < 350 cells/mm^3 to assist decision-making
- WHO stage 1 or 2 HIV disease with CD4 cell counts < 200 cells/mm^3.[2]

Viral load is not used to determine whether treatment is necessary or not; rather the CD4 count should be reviewed regularly (every 6 months if < 350 cells/mm^3 or annually if > 350 cells/mm^3).

Before a decision to treat is made, rigorous pre-treatment evaluation and counselling is necessary. A complete medical and drug history must be taken, physical and laboratory examinations including evaluation for opportunistic infections need to be done, and both psychological and social factors must be assessed (Table II).

Ideally, ART should be started before the CD4 count falls to below 50 cells/mm^3 as significant immune recovery after this point may be more challenging to achieve. Adverse events and immune reconstitution illnesses are more frequent in this group. A CD4 count below 50 cells/mm^3 however should not exclude patients from receiving ART, as many such patients have done well even at this late stage.[1,4,5]

Patients can be divided into 'naïve' patients who have not received ART previously and 'non-naïve' patients who have previously received ART. It is vital to take full advantage of a patient's naïve status as the first regimen started is the one most likely to work for a sustainable period.[1] Most failures within the first 6 months of therapy are due to non-adherence.[1]

Table I. **World Health Organization staging system**

Stage 1
1. Asymptomatic
2. Persistent generalised lymphadenopathy
3. Acute retroviral infection (seroconversion illness)

Stage 2
4. Unintentional weight loss < 10% of body weight
5. Minor mucocutaneous manifestations, e.g. seborrhoea, prurigo, fungal nail infection, oral ulcers, angular cheilitis
6. Herpes zoster within the last 5 years
7. Recurrent upper respiratory tract infection, e.g. bacterial sinusitis

Stage 3
8. Unintentional weight loss > 10% of body weight
9. Chronic diarrhoea > 1 month
10. Prolonged fever > 1 month
11. Oral candidiasis
12. Oral hairy leukoplakia
13. Pulmonary TB within the last year
14. Severe bacterial infections, e.g. pneumonia
15. Vulvovaginal candidiasis > 1 month/poor response to therapy

Stage 4
16. HIV wasting (8+9 or 10)
17. *Pneumocystis carinii* pneumonia
18. CNS toxoplasmosis
19. Cryptosporidiosis + diarrhoea > 1 month
20. Isosporiasis + diarrhoea
21. Cryptococcosis – non-pulmonary
22. Cytomegalovirus infection other than liver, spleen or lymph node
23. Herpes simplex infection; visceral or > 1 month mucocutaneous
24. Progressive multifocal leucoencephalopathy
25. Disseminated mycosis
26. Oesophageal/tracheal/pulmonary candidiasis
27. Atypical mycobacteriosis disseminated
28. Non-typhoidal salmonella septicaemia
29. Extrapulmonary tuberculosis
30. Lymphoma
31. Kaposi's sarcoma
32. HIV encephalopathy
33. Invasive cervical carcinoma
34. Recurrent pneumonia

There are currently 3 classes of antiretrovirals available in South Africa. These are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). A fourth class, the fusion inhibitors (FIs), is available elsewhere in the world. The available drugs, their trade names and their common side-effects are listed in Table III.

Highly active antiretroviral therapy (HAART) implies a triple therapy combination. Although dual therapy is occasionally clinically necessary, it is NOT recommended and use thereof should be left to experienced HIV clinicians.[1] A number of different regimens can be used and the recommendations are constantly updated as new safety and efficacy data emerge.[4]

Patient or provider preferences and underlying co-morbidities may make an alternative regimen necessary.[4] For naïve patients suggested therapy is:

A backbone combination of two NRTIs: AZT or stavudine
plus either lamivudine or didanosine or abacavir
plus an NNRTI (nevirapine or efavirenz) or a ritonavir-boosted or unboosted protease inhibitor (e.g. lopinavir+ritonavir).[1,6]

Some combinations need to be avoided such as stavudine and didanosine (due to additive toxicities including peripheral neuropathy and lactic acidosis); and AZT and stavudine due to antagonism in their mechanisms of action.[4]

For non-naïve patients, or patients who have had treatment failure, all three drugs need to be changed. Ideally two new NRTIs should be used plus a third new drug, preferably from a new drug class. When a patient has remained on a failing regimen for an extended period, there is often cross-resistance among viral strains, which results in HIV resistance even to ARVs to which the patient was not exposed (class resistance). Resistance to an NNRTI - containing regimen usually results in class resistance to all NNRTIs. PIs and NRTIs are more 'forgiving' but some cross-resistance within the group is likely. Consequently, second-line therapy is less likely to achieve viral suppression than first line. On failure of second line the patient should be treated with salvage therapy.[1] Complete antiretroviral cessation, even in late failure, is not recommended as this may result in rapid progression of disease.[4]

Maintaining or achieving viral suppression after two treatment failures is difficult and treatment should be individualised and overseen, preferably by an experienced HIV clinician.

The goal of ART is to suppress HIV viraemia to a less than detectable level thereby preventing further immune deterioration and avoiding HIV-related morbidity and mortality and maintaining quality of life.

References available on request.

Table II. **Factors influencing adherence**[1]

	Promote adherence	Reduce adherence
Patient factors	Motivated patient Good understanding of HIV disease and therapy Education given in patient's home language prior to and during therapy Participation in a support group	Alcoholism Depression (or other affective disorder) Poor understanding of the disease or therapy Non-disclosure of HIV status (to close family/ friends)
Disease factors	Late or symptomatic HIV disease	Early, asymptomatic HIV disease
Therapy factors	Small number of tablets 12-hourly regimen Few adverse effects	Large numbers of tablets 8-hourly regimen Severe or ongoing minor adverse events

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ART should not be started too early in the course of the disease.

Pre-treatment evaluation and counselling is necessary.

Initiation of therapy is based on the clinical status and CD4 count.

Psychosocial factors should also be taken into account.

Three classes of antiretrovirals are available in SA.

Use of three antiretrovirals in combination is necessary.

The goal of ART is to suppress viraemia and improve quality of life.

Table III. **Available antiretrovirals and common side-effects**[4, 6-10]

Generic	Trade name	Adverse effect	Monitoring
Nucleoside reverse transcriptase inhibitors (NRTIs)			
Abacavir (ABC)	Ziagen	Systemic hypersensitivity reaction (90% occur within 6 weeks) Serious, can be fatal Stop ART, do **not** rechallenge with ABC	Clinical – fever, rash, fatigue, abdominal or respiratory symptoms
Didanosine (ddI)	Videx, Aspen-Didanosine	Pancreatitis Peripheral neuropathy Nausea; diarrhoea Rarely lactic acidosis with hepatic steatosis	Clinical
Lamivudine (3TC)	3TC, Cipla-Lamivudine, Aspen-Lamzid, Aspen-Lamivudine	Minimal toxicity reported Rarely, lactic acidosis with hepatic steatosis	Clinical
Stavudine (d4T)	Aspen-Stavudine, Stavir Zerit	Peripheral neuropathy – assess clinically prior to commencing therapy Lipodystrophy, hyperlipidaemia Pancreatitis Lactic acidosis with hepatic steatosis (higher incidence than with other NRTIs) **Note:** Avoid ddI/D4T combination due to shared adverse effect profile	Monitor ALT – baseline, 2, 4, 8 weeks on therapy, followed by 6-monthly Clinical – if peripheral neuropathy occurs, monitor closely May require switch to alternative NRTI to avoid permanent nerve damage

Table III. **Available antiretrovirals and common side-effects[4, 6-10] (continued)**

Generic	Trade name	Adverse effect	Monitoring
Zalcitabine (ddC)	Hivid	Peripheral neuropathy (10%) Stomatitis Rarely lactic acidosis and hepatic steatosis Pancreatitis	Clinical Rarely used
Zidovudine (AZT/ZDV)	Retrovir, Aspen-Zidovudine	Bone marrow suppression (macrocytic anaemia or neutropenia) GI intolerance Headache, insomnia Rarely lactic acidosis with hepatic steatosis	Monitor FBC baseline, then monthly for 3 months, then 6-monthly
Abacavir+ lamivudine+ zidovudine	Trizivar		
Lamivudine+ zidovudine	Combivir, Duovir		
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Efavirenz (EFV)	Stocrin	Rash Neuropsychiatric symptoms are common: dizziness, confusion, fatigue, headache, rarely psychosis Increased transaminases False positive cannabinoid test Teratogenic in monkeys	Clinical CNS symptoms usually subside within 2 - 4 weeks
Nevirapine	Viramune, Aspen-Nevirapine	Skin rash is common (life-threatening in 2%) Hepatotoxicity NB follow dose-escalation protocol	Monitor ALT – at baseline, and weeks 2, 4, 8 on therapy, followed by 6-monthly or if symptoms occur
Protease inhibitors (PIs)			
Indinavir	Crixivan	Nephrolithiasis **Note:** Increase fluid intake Nephrotoxicity GI intolerance Lipodystrophy, hyperlipidaemia hypergylcaemia Indirect hyperbilirubinaemia Headache, metallic taste, blurred vision, rash, alopecia, dizziness, thrombocytopenia, haemolytic anaemia	Monitor renal function Lipid profile 6-monthly
Lopinavir+ ritonavir	Kaletra	Shared adverse effect profile: GI intolerance Lipodystrophy (hyperlipidaemia/ fat maldistribution) Insulin resistance Osteonecrosis (usually femoral heads) Possible increased bleeding in haemophilia	Monitor lipid profile 6-monthly
Nelfinavir	Vira-Cept		
Ritonavir	Norvir		
Saquinavir	Forto-Vase Invi-Rase		

Adverse effects, both the serious (life-threatening) and the minor, commonly result in switching or discontinuation of treatment or non-adherence to therapy.[10] The table above shows the more common or severe adverse effects occurring with the antiretrovirals available in South Africa. The list is by no means exhaustive; more information should be sought from experienced specialists or by calling the Medicines Information Centre at 086 110 0531 or 021-406 6829.