SOUTH AFRICAN PUBLIC SECTOR ADULT ANTIRETROVIRAL TREATMENT GUIDELINES

Antiretroviral therapy (ART) has been shown to reduce HIV-related morbidity and mortality substantially.[1]

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South Africa has a huge burden of HIV disease, with an estimated 5 million HIV-infected individuals, and more than 500 000 currently requiring ART.[2] This poses a challenge to all health care workers, both in the public and private sector.

The World Health Organization (WHO) 3 by 5 Initiative aims to have 3 million HIV-infected people on ART worldwide by the end of 2005. In order to achieve this, a 'public health approach' to ART has been formulated. Key tenets of this approach are the following:[3]

- ART programmes should be scaled up with the goal of 'universal access', i.e. treatment for all people fulfilling medical criteria for therapy.
- ART regimens should be standardised and simplified to facilitate implementation.
- Guidelines should be based on sound scientific evidence and be realistic with regard to human resources, health system infrastructure, and socioeconomic resource constraints.

Initiating ART in those for whom it is clinically indicated is only a small part of the challenge of successful HIV treatment. The bigger challenge is development and maintenance of effective strategies in the public sector to support long-term patient adherence to ART, so that HIV-infected patients may derive durable benefit from available ART options.

This article outlines the first- and second-line ART regimens used in the public sector in South Africa. Clinical criteria for initiation of ART are described, as well as psychosocial issues, which should be considered before ART initiation. Recommendations for efficacy and safety monitoring are described. Evaluation of treatment failure is discussed. Treatment of pregnant women fulfilling treatment criteria is described, as well as ART in patients with tuberculosis (TB).

INITIATION OF ART

Medical criteria for ART in the public sector are as follows:[4,5]

- WHO stage 4 disease (with the exception of TB, which is not a criterion for initiating ART unless CD4 count < 200 cells/µl) *or*
- WHO stage 1, 2 and 3 patients with CD4 count < 200 cells/µl.

These clinical criteria are more stringent than both WHO[3] and current Southern African HIV Clinicians Society Guidelines[6] (both of which recommend ART in patients with symptomatic WHO stage 3 or 4 disease and CD4 count < 350 cells/µl). The aim of the public sector treatment guidelines is to target the large numbers of people who currently have advanced, WHO stage 4, HIV disease.

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In addition to fulfilling the above clinical criteria, the following psychosocial criteria[4,5] should be considered before treatment initiation, because they identify factors that have a negative impact on patient adherence if not resolved before treatment starts:

- active alcohol or other substance abuse
- untreated active depression
- disclosure – it is strongly recommended that clients have disclosed their HIV status to at least one friend or family member *or* have joined a support group
- reliability (as demonstrated by attendance of 3 or more scheduled visits to an HIV clinic)
- insight – clients need to have accepted their HIV-positive status, and have insight into the consequences of HIV infection and the role of ART before starting it.

It is irresponsible for a prescriber to start ART without first providing the patient with information about it, ideally in their own first language, and attempting to resolve issues which are known to have a negative impact on treatment adherence. Poor adherence may result in the development of resistance, decreasing treatment efficacy and limiting future treatment options. It is recommended that the final decision to initiate or delay initiation of ART be made by the ART site multidisciplinary team, and that the patient be involved in making this decision.[5]

HIV is a disease that affects families, and all patients started on ART should be encouraged to bring sexual partners and family members to the clinic so that they may be offered voluntary counselling and testing and appropriate treatment if found to be HIV infected.[4]

PROPHYLAXIS AGAINST OPPORTUNISTIC INFECTIONS

It is important that opportunistic infection prophylaxis is not interrupted prematurely when ART is commenced.[4,5] It is recommended that co-trimoxazole prophylaxis be continued in all patients on antiretrovirals until the CD4 count is above 200 cells/µl. Patients taking fluconazole 200 mg daily as secondary prophylaxis after a diagnosis of cryptococcal meningitis should continue fluconazole prophylaxis until the CD4 count is above 200 cells/µl.[4,5]

ANTIRETROVIRAL REGIMENS

Two regimens have been selected for the national antiretroviral public sector programme, designed such that the second-line regimen will still be effective despite failure of the first. The selected first-line antiretroviral public sector regimen requires pills to be taken twice daily, with a low pill burden and no food restrictions or requirement for refrigeration of medication. The first-line nucleoside reverse transcriptase inhibitors (NRTIs), stavudine (d4T) and lamivudine (3TC), have been chosen as they are easily tolerated initially and allow a viable, non-toxic second-line option (zidovudine (AZT) and didanosine (ddI)) should the initial regimen fail. These regimens are recommended by the WHO as initial ART for antiretroviral-naïve patients.[3]

First-line therapy: Regimen 1

All men, as well as women using injectable contraception, are started on the following treatment regimen (regimen 1a)[5]:

- d4T 40 mg every 12 hours (or 30 mg every 12 hours if < 60 kg), with
- 3TC 150 mg every 12 hours, and
- efavirenz EFV 600 mg at night.

Women of childbearing potential who have expressed the desire to fall pregnant or are not prepared to use injectable contraception should not be started on EFZ, as it is teratogenic. These patients are started on regimen 1b, as follows:

- d4T 40 mg every 12 hours (or 30 mg every 12 hours if < 60 kg), with
- 3TC 150 mg every 12 hours, plus
- nevirapine (NVP) 200 mg daily for 2 weeks, followed by 200 mg every 12 hours.

Patients entering the public sector with a history of previous ART should have an individualised regimen constructed from the antiretrovirals available in the public sector, taking prior treatment and any history of previous treatment failure into account.[4]

TREATMENT FAILURE

In the public sector, efficacy of ART is assessed by regular clinical assessment, immunologically by 6-monthly CD4 count measurement, and virologically by measurement of viral load at baseline and 6-monthly thereafter. The 6-month viral load should be fully suppressed (i.e. below the limit of detection of the viral load test) in all adherent patients started on first-line treatment. If the patient's viral load is not suppressed, or suppresses and then rebounds, it is important to assess adherence to therapy and give intensive adherence support before concluding that the/she has developed resistance to first-line therapy. Viral load measurement is then repeated, as outlined in Table I. If the viral load still

Table I. **Response to changes in viral load according to South African National Treatment Guidelines**

Viral load (VL)	Response
< 400 copies/ml	6-monthly monitoring continues Routine adherence support
400 - 5 000 copies/ml	Repeat viral load in *6 months* Begin step-up adherence package. Review at next 6-month viral load and respond as follows: • 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 in 6 months • If > 5 000, despite stepped up adherence support, switch to second-line therapy
> 5 000 copies/ml	Repeat viral load in *3 months* Begin step-up adherence package. Review at 3-month viral load and respond as follows: • if < 400 – return to routine 6-monthly monitoring and adherence support • if viral load has dropped to between 400 and 5 000 – continue with step-up adherence package, repeat viral load in 6 months • If > 5 000, despite stepped up adherence support, switch to second-line therapy

fails to suppress, despite good adherence, the patient should be switched to second-line therapy.[4,5]

Second-line therapy: Regimen 2

Patients who have failed first-line therapy are changed to regimen 2:[4,5]
- ddI 400 mg once a day (250 mg daily if < 60 kg), with
- AZT 300 mg every 12 hours, and
- lopinavir/ritonavir (Kaletra) 400/100 mg every 12 hours.

It is important that patients receive clear treatment education and that adherence knowledge is reinforced before starting second-line therapy, which has a higher pill burden than first-line therapy. ddI tablets are dissolved in water and must be taken alone (i.e. not with other medicines), and on an empty stomach, at least an hour before a meal.[4] Lopinavir/ritonavir needs to be kept cool at < 25°C.

There are currently no third-line therapy options available in the public sector for patients who fail second-line therapy.[4]

TREATMENT OF PREGNANT WOMEN

Pregnant women with early-stage HIV disease, who do not meet clinical criteria for ART initiation, are managed during pregnancy according to the provincial protocol for prevention of mother-to-child transmission (PMTCT). These women may be started on ART after pregnancy, when they fulfil the clinical criteria for therapy.[4,5]

Women who require ART according to clinical criteria and present before 34 weeks of gestation should be started on treatment wherever possible. It is logistically very difficult to complete the process of clinical work-up and treatment preparedness in women presenting later than 34 weeks of gestation. These women should be managed according to the standard PMTCT protocol and started on ART as soon as possible after delivery. The national treatment protocol recommends initiation of regimen 1b (d4T with 3TC and NVP).[5] In the Western Cape AZT 300 mg every 12 hours is used in place of d4T,[4] with monthly monitoring of haemoglobin level and neutrophil count.

ART should not be started in the first trimester of pregnancy unless the woman is severely ill or has a CD4 count less than 50 cells/µl. Treatment preparedness and clinical work-up should be completed in as short a time as possible in order to maximise time on ART before delivery. However, it is important that issues affecting patient adherence be dealt with timeously.[4]

If pregnancy does occur in a woman receiving EFV, she should be counselled about potential teratogenicity.[7] If a decision to continue the pregnancy is made, EFV should be replaced with NVP, particularly when pregnancy is diagnosed in the first trimester.[5] According to the national treatment protocol, women falling pregnant while on d4T, 3TC and NVP are continued on this regimen throughout pregnancy.[5] In the Western Cape, AZT is substituted for d4T for the duration of the pregnancy.[4]

ROUTINE MONITORING

Regimen-specific recommendations for routine laboratory safety and efficacy monitoring are outlined in Table II.

ART IN PATIENTS WITH TB

TB is the primary cause of morbidity and mortality in HIV-infected South Africans. ART is protective against TB and may reduce the incidence in HIV-infected patients by more than 80%.[8] However, background incidence of TB is high, and many patients present with active TB while on ART. In addition, many HIV-infected patients are found to have TB during clinical assessment for ART.

According to current public sector treatment guidelines, ART is not

clinically indicated in a patient with a CD4 count of more than 200 cells/µl and no history of WHO stage 4 illness. The need for ART in this group of patients should be reassessed on completion of TB treatment. In a patient with TB and a history of WHO stage 4 illness, or a CD4 count of less than 200 cells/µl, ART should be started after completion of 2 months of TB therapy in order to minimise additive side-effects and additive drug toxicity. If a patient has a CD4 count of less than 50 cells/µl or severe HIV-related illness, ART may be started after 2 - 3 weeks of TB treatment once it is certain that the patient is tolerating and responding to the latter.[4,5]

Rifampicin is a potent inducer of hepatic metabolism of many drugs, and has clinically significant interactions with a number of antiretrovirals. Patients should receive standard, rifampicin-based TB treatment, with modification of the antiretroviral treatment regimen where necessary. EFV and NVP levels both decrease in the presence of rifampicin, but this is not clinically significant.[9] NVP should be used with caution, because of concerns of additive hepatotoxicity. Lopinavir levels drop considerably in the presence of rifampicin,[9] and additional ritonavir must therefore be added to the treatment regimen.

Table II. **Routine monitoring of antiretroviral regimens[3 - 5]**

Regimen	Test	Frequency
d4T/3TC/NVP	• CD4 • VL • ALT	• Staging, 6-monthly • Baseline, 6-monthly • Baseline, week 2, 4 and 8, thereafter 6-monthly
d4T/3TC/EFV	• CD4 • VL	• Staging, 6-monthly • Baseline, 6-monthly
AZT/3TC/NVP (during pregnancy)	• CD4 • VL • FBC and white cell differential count • ALT	• Staging, 6-monthly • 6-monthly • Baseline and monthly until delivery Baseline, week 2, 4, thereafter monthly until delivery
AZT/ddI/ lopinavir/ritonavir	• CD4 • VL • FBC and white cell differential count	• Staging, 6-monthly • 6-monthly • Baseline, then monthly for 3 months, then 6-monthly (with CD4 and VL) thereafter (monthly during pregnancy)
	• Fasting cholesterol and triglyceride	• Baseline, 6 months and thereafter every 12 months
	• Fasting glucose	• Every 12 months

Staging = initial testing for all patients when being referred for antiretroviral therapy. Baseline = testing for antiretroviral-eligible patients at initiation of ART.

Guidelines for ART regimens in patients with TB are as follows:[4,5]

- Patients diagnosed with TB before ART, and fulfilling clinical criteria for treatment outlined above, should be started on d4T, 3TC and EFV.
- Patients diagnosed with TB while treated with d4T, 3TC and EFV do not require any change to their antiretroviral regimen.
- Patients developing TB while on d4T, 3TC and NVP, and who are stable on this treatment regimen, may be switched to EFV, or continued on NVP with monthly monitoring of transaminases.
- Patients developing TB while on AZT, ddI and Kaletra should have additional ritonavir added to their treatment regimen at a dose of 300 mg 12-hourly (to make a total dose of lopinavir 400 mg 12-hourly and ritonavir 400 mg 12-hourly). The additional ritonavir should be continued until 2 weeks after completion of TB treatment and then stopped.

CONCLUSION

The national antiretroviral programme uses available, cost-effective antiretrovirals to maximal effect by describing user-friendly, simple-structured regimens that are scientifically proven to be virologically superior, together with clear guidelines for complexities involving antiretroviral toxicity, pregnancy and TB. Attention to adherence is an integral part of this programme, which aims to allow antiretroviral access for all HIV-infected South Africans.

References available on request.