Tel: 0800 227 700 or +27 (0)21 514 1700
Fax: 0800 600 773 or +27 (0)21 514 1744
Address: P. O. Box 38597, Howard Place,
Cape Town, South Africa, 7450
Email: afa@afadm.co.za
Website: www.aidforaids.co.za

SERVICE PROVIDER NEWSLETTER
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WHO clinical staging

In the revised AfA application form we have included the World Health Organisation's clinical staging classification for HIV disease. This system was developed in 1990 and is widely applied in developing countries. Numerous studies, including several from South Africa, have shown the prognostic value of the staging system. Its prognostic value is independent of the best laboratory prognostic marker, the CD4+ lymphocyte count, but it is best to use the clinical staging system in conjunction with CD4+ lymphocyte counts. The staging system is used for decisions on initiating antiretroviral therapy in the Southern African HIV Clinicians Society guidelines, as well as many others. There are 4 stages in the adult classification (the paediatric system currently has 3 stages, but this is undergoing revision with 4 stages being planned). Stage 4 disease consists of AIDS-defining diagnoses.

Approximate survival by WHO stage for South African public sector adult patients without access to antiretroviral therapy (adapted from SAMJ 1999;89:1255-8)

WHO Stage	Survival at 3 years
1	95%
2	85%
3	40%
4	15%

The role of tenofovir DF (Viread®)

- Tenofovir DF is a nucleotide reverse transcriptase inhibitor (NtRTI). The dose is 300 mg daily with food.
- Tenofovir is not yet registered in SA - MCC permission must be obtained.
- AfA will consider tenofovir for salvage therapy provided a genotyping has been done as certain thymidine analogue mutations also confer resistance to tenofovir.
- Tenofovir has activity against hepatitis B, but is not registered for this indication by the FDA. Severe acute exacerbations of hepatitis B have been reported in patients co-infected with hepatitis B and HIV who have discontinued tenofovir. In this setting careful monitoring of clinical features and liver function tests are recommended.
- Co-administration with didanosine (ddI) leads to a significant increase in ddI levels. See “Drug Interaction of the Month”.
- Renal function and urinalysis should be assessed at baseline then monthly for 3 months, followed by 3 monthly testing.
- Tenofovir can also cause elevated lactate, but it has a low potential for this (similar to lamivudine and abacavir).

Procedure to obtain tenofovir (Viread®)

As tenofovir is not yet registered in SA, MCC permission must be obtained for its use. AfA will only approve tenofovir if the AfA clinical committee has agreed to its use. Please let one of the AfA clinical staff have the details of the case and they will present the case to the clinical committee. Once AfA have approved the use of tenofovir the following procedure should be followed to obtain the tenofovir.

1. Doctor to apply to the MCC for authorization to prescribe tenofovir.

2. If the MCC approves the use of tenofovir the approval will be valid for 6 months.

3. Confirmation that the MCC has approved the use of tenofovir and a prescription should be forwarded to AfA and to the pharmacist which will dispense the medicines.

4. AfA will authorize the tenofovir for payment and send a letter to the doctor and patient confirming the medicines which have been authorized.

5. The dispensing pharmacist should request importation of stock from Gilead Sciences.

6. Gilead Sciences supplies a 6 month supply of Viread®. The price of the Viread® fluctuates as it is based on the rand dollar exchange rate.

Please note:

1. The MCC charge R200 for the 6 month approval of medicines which are not yet registered. The patient is responsible for the payment of this fee.

2. Chronic Medicine Dispensary (CMD) are happy to dispense and claim for tenofovir for AfA patients. CMD are also able to supply the MCC forms for the doctor’s application to the MCC. Marcelia van Reenen (pharmacist at CMD) can be contacted on 0860 633 420 or 011 237 9100. CMD currently charge R363.64 plus a delivery fee for a month’s supply of tenofovir. Any other pharmacy can dispense tenofovir, provided that they are prepared to follow the above process.

Drug interaction OF THE MONTH

Tenofovir (Viread®) and didanosine (Videx®)

Co-administration of tenofovir and didanosine will result in increased plasma concentrations of didanosine and a risk of toxic effects, especially pancreatitis.

It is recommended that if tenofovir and didanosine are given together the dose of didanosine be reduced to 250mg daily for adults weighing > 60kg. (There is no data to recommend a dose adjustment for adults weighing < 60kg.)

Protease inhibitor induced diarrhoea

Diarrhoea is a common presentation in patients with HIV. It impacts severely on quality of life, and can lead to malnutrition, loss of weight, associated immunosuppression, and susceptibility to opportunistic infections. It may diminish absorption of medications, and adversely affect adherence to antiretroviral agents. Diarrhoea is associated with a multitude of aetiologies and is a common adverse effect of the protease inhibitor (PI) class of antiretrovirals.

PI induced diarrhoea is more common in patients with lower CD4 counts, and in those treated with nelfinavir (Vira-cept®) > ritonavir (Norvir®, also a component of the combination PI Kaletra®) > saquinavir (Invi-rase®/ Forto-vase®) > indinavir (Crixivan®). The following treatments of PI induced diarrhoea have shown benefit in clinical trials: bulk forming agents (oat bran, psyllium husk), calcium carbonate, and antimotility agents such as loperamide. Often, combinations of the agents are used to control symptoms.

Reference: Sherman DS, Fish DN. Management of protease inhibitor-associated diarrhea. Clin Infect Dis 2000;30:908-14

Name of Product	Class of agent	Dose	Side effects
Oat Bran	Soluble fibre, bulk forming	1500mg / day in divided doses	Bloating,flatulence
Psyllium	Concentrated vegetable powder, bulk forming	1-2 tablespoonfuls 1-3 times daily	Bloating, flatulence
Loperamide	Opioid derivative with isolated peristaltic activity	4mg stat, then 2mg after each loose stool, max daily dose 16mg	Abdominal discomfort, potential aggravation of intestinal infections
Calcium Carbonate	Calcium supplement	500mg bd	Gastrointestinal irritation, nausea

Benefit Booking

A number of medical schemes administered by Medscheme have during the course of 2004 implemented **benefit booking** for medicine authorised by AfA. Benefit booking means that if a claim is valid, and where an authorisation number is requested, a message and the authorisation number will be sent back to the provider, indicating that the claim was accepted and will be paid. This service is available through the **Intepharm** real-time claiming facility and assists providers by assuring them of payment without their needing to make an additional call to AfA to validate the benefits.

The following schemes have implemented benefit booking for AfA authorised medicines: ABI, AECI, Barloworld, BMW medical scheme, Bonitas, DC Med, G5 Med, Massmart, Medshield, Parmed, SABC, Siemens, Stocksmed, University of Witwatersrand and Xstrata.

Pharmacy Direct

Pharmacy Direct are a new pharmaceutical courier company. They distribute antiretrovirals at a competitive rate. They can be contacted on 0860 103 810.

Stocrin® 600mg tablets

MSD have launched a new strength of Stocrin®. Stocrin® is now available as a 600mg tablet, in addition to the 200mg capsule and 50mg capsule. Patients on Stocrin® 600mg nocte only need to take one tablet at night - this reduces the pill burden and aids compliance.

30x Stocrin® 600mg tablet is also more cost effective (approximately 30% cheaper) than 90x Stocrin® 200mg capsules.

Please contact AfA on 0800 22 77 00 to change authorizations from Stocrin® 200mg to Stocrin® 600mg. Patients should be told that their usual dose of 3 capsules taken once daily will now only be **one tablet daily**.

Stocrin 200mg x 90: R309.02 cost price incl. VAT
Stocrin 600mg x 30: R214.31 cost price incl. VAT

Practice point
OF THE MONTH

Oropharyngeal candidiasis

Oropharyngeal candidiasis is a common presenting condition in both adult and paediatric HIV. In adults, HIV associated oral candidiasis is a WHO stage 3 defining condition and is an indication to start prophylactic co-trimoxazole (irrespective of the CD4 count). In paediatrics, oropharyngeal thrush is more common and is more difficult to use as a prognostic marker of HIV progression.

Early presentations of oral candidiasis are often asymptomatic. They may manifest in one or more of the following ways; pseudomembranous plaques (white plaques which may be scraped off the mucosal surface with or without bleeding); erythematous candidiasis (presenting as single or multiple red non-removable patches); angular cheilitis (presenting as linear fissures or ulcers at the corners of the mouth); hyperplastic candidiasis (presenting as white, adherent plaques on the buccal mucosa); median rhomboid glossitis.

Treatment of oral candidiasis:
Topical: (troches or lozenges are more effective because of the longer contact time)

- Amphotericin B lozenges 10 mg 6-hourly for 5-10 days
- 0.5% gentian violet solution painted in the mouth 3 x per day
- Nystatin suspension (100 000 IU/ml) 1 ml 4 x per day
- Daktarin® oral gel is helpful for angular cheilitis

Systemic (only for lesions that fail to respond to topical therapy):

- Fluconazole 50 - 100 mg for 3-7 days (This is not an accepted indication in the state sector.)

Oral candidiasis is a common manifestation in HIV positive patients and relapses following topical and systemic treatment are common. In the presence of dysphagia or odynophagia, a clinical diagnosis of oesophogeal candidiasis is made, requiring systemic treatment. This is an AIDS-defining condition.

Making major decisions on CD4+ counts

CD4+ lymphocyte counts are the most important laboratory prognostic marker of prognosis in HIV infection. In conjunction with clinical staging, CD4+ lymphocyte counts are used to initiate prophylactic cotrimoxazole or highly active antiretroviral therapy. However, CD4+ lymphocyte counts are variable with ±20% being the acceptable range for an individual. This means that if a patient's CD4+ lymphocyte count is 300 that in the short term the counts will range between 240 and 360 cells/mm^3. Furthermore, intercurrent illnesses can depress the CD4+ lymphocyte count. Laboratory error or delay in sample processing may also occur. **Because of the variability in CD4+ lymphocyte counts major therapeutic decisions should not be taken on the basis of a single count.** This is particularly true when the patient has no clinical evidence of advanced immune suppression.

In the table below the counts of 3 individuals treated in a single centre using the same laboratory is given over two and a half years. In each case a single count occurred which fulfilled guideline recommendations to initiate prophylactic cotrimoxazole and/or highly active antiretroviral therapy. However, because the low counts were out of keeping with the general trend, the counts were repeated without introduction of cotrimoxazole or highly active antiretroviral therapy. It is also worth noting the general variability of the counts in these patients.

Months	0	6	12	18	24	30
Patient #1	516	375	ND	**247**	489	452
Patient #2	545	ND	422	**235**	391	ND
Patient #3	410	328	356	575	**162**	351

Tuberculosis and Antiretroviral therapy (ART)

TB drugs and ART share many side effects. In addition, the enzyme induction caused by rifampicin dramatically affects the metabolism of many HIV drugs leading to sub-optimal serum levels with the development of resistance. The following guidelines should be followed when starting TB drugs in an HIV infected patient:

- If the patient is on ART already, changes to the ART may need to be made. Please contact AfA.

- If ART has not yet been started the CD4 count should be used to guide when to introduce ART:

  CD4 > 200: ART should be withheld until after TB therapy is complete (the CD4 will usually rise when TB has been treated).

  CD4 50 - 200: ART can be deferred until after the intensive phase (2 months) of anti-TB therapy. At this stage the number of anti-TB drugs is reduced with less chance of shared toxicity.

  CD4 < 50 or there is serious HIV related co-morbidity: ART should be started once the patient is tolerating anti-TB therapy, usually after about 2 weeks.

Immune reconstitution following commencement of HAART may cause a flare up of the TB, particularly if this occurs within the first 2 months of anti-TB therapy.

The usual guidelines for the treatment of TB should be followed. See issue 7 and 8 for ARV regimens which can be given with conventional TB therapy.

Generic Antiretrovirals

Generic Name	Product Name	Manufacturer	Cost Price (incl. VAT)	Availability
Didanosine	**Videx® 150mg**	**BMS**	**R196.50**	IHD*
Didanosine	Aspen Didanosine® 150mg	Aspen	R157.30	All major wholesalers
Didanosine	**Videx® 100mg**	**BMS**	**R130.95**	IHD*
Didanosine	Aspen Didanosine® 100mg	Aspen	R104.86	All major wholesalers
Didanosine	**Videx® 50mg**	**BMS**	**R130.95**	IHD*
Didanosine	Aspen Didanosine® 50mg	Aspen	R95.74	All major wholesalers
Didanosine	**Videx® 25mg**	**BMS**	**R130.95**	IHD*
Didanosine	Aspen Didanosine® 25mg	Aspen	R85.48	All major wholesalers
Lamivudine	**3TC® 150mg**	**GSK**	**R112.18**	Kinesis & other wholesalers
Lamivudine	Cipla-Lamivudine® 150mg	Cipla	R102.57	All major wholesalers
Lamivudine	Lamaid® 150mg	Thembalami	R86.38	See below
Nevirapine	**Viramune® 200mg**	**BI**	**R410.40**	IHD
Nevirapine	Nevran® 200mg	Thembalami	R214.43	See below
Stavudine	**Zerit® 40mg**	**BMS**	**R46.22**	IHD*
Stavudine	Aspen-Stavudine® 40mg	Aspen	R38.30	All major wholesalers
Stavudine	Stavir® 40mg	Cipla	R35.91	All major wholesalers
Stavudine	**Zerit® 30mg**	**BMS**	**R46.22**	IHD*
Stavudine	Aspen-Stavudine® 30mg	Aspen	R33.06	All major wholesalers
Stavudine	Stavir® 30mg	Cipla	R32.24	All major wholesalers
Stavudine	**Zerit® 20mg**	**BMS**	**R46.22**	IHD*
Stavudine	Aspen-Stavudine® 20mg	Aspen	R27.36	All major wholesalers
Zidovudine	**Retrovir® 300mg**	**GSK**	**R320.45**	Kinesis & other wholesalers
Zidovudine	Zidaid® 300mg	Thembalami	R176.26	See below
Zidovudine/ Lamivudine	**Combivir® 300 / 150mg**	**GSK**	**R365.94**	Kinesis & other wholesalers
Zidovudine/ Lamivudine	Avocomb® 300 / 150mg	Thembalami	R291.84	Currently **not** available
Zidovudine/ Lamivudine	Duovir® 300 / 150mg	Cipla	R303.67	Currently **not** available

*BMS products are also available from some of the other wholesalers.

Thembalami generics are available from Adcock Ingram Distribution, Alpha Pharm Distributors, City Medical Wholesalers, Transfarm and Freestate Buying. Provider also needs to open an account with Thembalami.

Original products are in bold. Prices as at 24 August 2004.
BMS: Bristol-Myers Squibb BI: Boehringer Inhelheim
GSK: GlaxoSmithKline Aspen: Aspen Pharmacare
Cipla: Cipla Medpro IHD: International Healthcare Distriburtors

Please note:

- Currently stavudine is the only product, which is listed on the Medscheme price list (MPL). All medical schemes that currently have MPL in place will only pay a base price for stavudine. If a patient received a more expensive stavudine the patient will have to pay the difference between the MPL price and the product dispensed. The other generic antiretrovirals will be added to MPL in due course.

- Cipla Medpro have a number of other generic antiretrovirals registered - zidovudine caps, zidovudine tabs, zidovudine syr, lamivudine syr and nevirapine tabs. These products are not currently available.

- Aspen Pharmacare have a number of other generic antiretrovirals registered. These products should be available shortly - nevirapine tabs, lamivudine tabs, lamivudine syr, zidovudine tabs, zidovudine syr and a zidovudine / lamivudine combination tablet.

- The following pharmaceutical courier services are able to supply the Thembalami generics:

Pharmacy Direct	0860 103 810
Chronic Medicine Dispensary	0860 633 420
Direct Medicines	0860 444 404
Freeway Pharmacy	011 893 2099