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SERVICE PROVIDER NEWSLETTER

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AfA awarded the HIV Disease Management contract for GEMS

In September 2005, Aid for AIDS submitted a tender to the Government Employees Medical Scheme (GEMS) to provide HIV management services. We are pleased to announce that the contract has been awarded to Aid for AIDS with effect from 1 January 2006.

GEMS has five options, three of which (Onyx, Ruby and Emerald) are contracted to Aid for AIDS. The remaining two (Beryl and Sapphire) are capitated options and will be managed by Primecure, with some additional services being provided by AfA.

Should you have any HIV+ patients who are registered members of GEMS (and on one of the three contracted options) please complete the AfA application form and submit it to us on our toll-free fax number (0800 600 773). If you have any queries, please phone us (toll-free) on 0800 227 700.

We are very proud to be associated with GEMS and look forward to providing services to all its members, beneficiaries and providers.

Discontinuing fluconazole prophylaxis following cryptococcal meningitis

Prior to the advent of effective antiretroviral therapy, secondary prophylaxis with fluconazole 200 mg daily was recommended lifelong as there was a high risk of recurrence. As with other opportunistic infections, the risk of recurrence of cryptococcal meningitis is dramatically reduced when immunity improves with effective antiretroviral therapy. Two studies have addressed the safety of discontinuing fluconazole prophylaxis after the CD4+ lymphocyte count has increased to >100 cells/mm3 on HAART1,2. The first study randomized patients to continue or stop if the CD4 was >100 for 3 months. There were no recurrences in either group after 48 weeks. In the second observational study very low recurrence rates of 1.53 per 100 person years were reported.

We recommend that fluconazole prophylaxis should be discontinued once the CD4 count has increased to >100 cells/mm3 on HAART for 3 months. It is important to note that the patients must have completed intensive therapy (preferably with Amphotericin B 0.7-1 mg/kg/day for 2 weeks, followed by fluconazole 400 mg daily for 8 weeks) and have at least 3 months of secondary prophylaxis. If the initial CD4 count at the time of diagnosing cryptococcal meningitis was >100 (which is uncommon), then individualized decisions should be taken in consultation with AfA – generally a higher CD4 count, such as >200, will be recommended.

1 Vibhagool A, Sungkanuparph S, Mootsikapun P, et al. Discontinuation of Secondary Prophylaxis for Cryptococcal Meningitis in Human Immunodeficiency Virus–Infected Patients Treated with Highly Active Antiretroviral Therapy: A Prospective, Multicenter, Randomized Study. Clinical Infectious Diseases 2003; 36:1329–31

2 Mussini C, Pezzotti P, Miro JM, et al. Discontinuation of Maintenance Therapy for Cryptococcal Meningitis in Patients with AIDS Treated with Highly Active Antiretroviral Therapy: An International Observational Study. Clinical Infectious Diseases 2004; 38:565–71

Tenofovir plus didanosine (DDI)

The nucleotide reverse transcriptase inhibitor Tenofovir (TDF) is available overseas and in several neighbouring countries, but is not yet registered in South Africa (it is available with MCC approval; please contact AfA for assistance). TDF is often used together with 3TC (or the closely related drug FTC, also not yet registered in SA) – this combination is very well studied and is as effective and at least as safe as 3TC with either stavudine or zidovudine.

However, the use of TDF plus didanosine (DDI) is problematic for several reasons:

- Pharmacokinetic studies have shown increased DDI levels when the drug is combined with TDF, necessitating a dose reduction of DDI (see below)
- There is a corresponding increase in DDI-related side-effects (peripheral neuropathy, pancreatitis, hyperlactataemia and lactic acidosis), especially when the dose of DDI is not reduced.
- Trials using TDF + DDI + NNRTI have shown significantly lower rates of virological suppression when compared with other dual nucleoside combinations.
- CD4 count has been reported to decline with TDF + DDI despite virological suppression, but this appears to be related to the dose of DDI (AIDS 2005;19:1987-94).

A dose reduction in DDI to 250mg daily (if weight > 60kg) is recommended if used with TDF. However, in view of the potential problems listed above and lack of clarity with regard to dosing in people weighing < 60kg, the combination will only be approved after review by the AfA Clinical Advisory Committee.

Providers are reminded that baseline renal function should always be obtained before prescribing TDF because of possible worsening in renal function, and that the drug should not be used in children because of uncertainty regarding long-term loss in bone mineral density.

Drug interaction
OF THE MONTH

Carbamazepine

A patient with a background of post-herpetic neuralgia, controlled on carbamazepine, fulfilled AfA's criteria for starting HAART. Before HAART was commenced, our clinical staff were asked about possible drug interactions with carbamazepine.

Carbamazepine is metabolized by the key cytochrome P450 isoenzyme, CYP3A4. This isoenzyme is inhibited by protease inhibitors, induced by nevirapine and either induced or inhibited by efavirenz. Thus the levels of carbamazepine will be elevated by inhibitors or reduced by inducers. Marked elevation of levels with toxicity has been well documented with protease inhibitors.

Equally worrying is the fact that carbamazepine is itself an inducer of CYP3A4. Protease inhibitors and non-nucleoside reverse transcriptase inhibitors are substrates of CYP3A4. Therefore co-administration with carbamazepine would result in lower levels of these antiretrovirals, resulting in virological failure and the selection of drug-resistant HIV. This has been documented with protease inhibitors.

Because of these adverse bi-directional drug interactions, we advised that carbamazepine be discontinued prior to commencing HAART. Amitriptyline, (which does not have significant interactions with HAART), was recommended instead of carbamazepine for the post-herpetic neuralgia. The other first-line anticonvulsants (phenytoin and phenobarbitone) also have similar adverse bi-directional drug interactions. Anticonvulsants that do not interact significantly with HAART include valproate, levetiracetam, gabapentin, topiramate and lamotrigine.

Switching stavudine (D4T) to an alternative agent

Of the NRTIs, stavudine (D4T) and didanosine (DDI) are most commonly associated with mitochondrial toxicity. The manifestations are varied and include: hyperlactataemia/lactic acidosis, hepatic steatosis, pancreatitis, peripheral neuropathy and lipoatrophy.

The diagnosis and management of hyperlactataemia/lactic acidosis was dealt with in a previous newsletter (Issue 12; October 2005). Here we address other reasons for switching from D4T to an alternative agent. The choice of alternative agent will depend on prior ARV exposure and the severity and nature of the side effect, but in general terms the choice is AZT, abacavir or tenofovir (or an NRTI sparing regimen in cases of lactic acidosis).

- **Neuropathy.** D4T may cause a painful sensory neuropathy. If this is progressive despite symptomatic treatment with amitriptyline, or severe at onset then patients should be switched to an agent that does not cause neuropathy such as AZT, abacavir or tenofovir. D4T has also been strongly associated with the HIV-associated neuromuscular weakness syndrome (HANWS). This syndrome is characterized by rapidly progressive ascending limb weakness with or without sensory or cranial nerve involvement. It mimics the Guillain-Barre syndrome and some patients may require mechanical ventilation because of neuromuscular respiratory failure. The syndrome results from mitochondrial toxicity causing a demyelinating neuropathy, axonopathy, myopathy or a combination. Ninety percent of cases are associated with D4T and the lacatate has been shown to be raised in 81% of patients.

  All patients with severe or rapidly progressive neuropathy should have lactate measured to exclude associated hyperlactaemia.

- **Pancreatitis.** Although DDI is more frequently associated with pancreatitis, D4T has also been implicated. If a patient develops pancreatitis on either of these drugs, all HAART should be stopped immediately, other causes excluded and the patient treated as for any cause of pancreatitis (IVI fluids and other supportive therapy). When HAART is restarted both D4T and DDI should be avoided. 3TC has also been implicated in cases of pancreatitis in children, but it is not thought to carry the same risk.

- **Lipoatrophy** is a pathological loss of subcutaneous fat particularly in the face, buttock and limbs. It is most frequently associated with D4T although AZT also carries a significant risk. If patients develop lipoatrophy on D4T it is best to switch to abacavir or tenofovir. Progression of lipoatrophy is usually stopped by this switch, but significant reversal takes years in severe cases. Thus it is important to switch early when lipoatrophy is first noted.

- **Prophylactic switch in women with BMI > 28.** Women who are overweight have been shown to be at a disproportionately high risk of developing hyperlactataemia/lactic acidosis on D4T. We would thus recommend that AZT rather than D4T be used when commencing these women on HAART. If women gain weight to a BMI >28 on HAART, then a prophylactic switch from D4T to AZT should be considered.

- **Hepatic steatosis (fatty liver)** often progressing to steatohepatitis results from the mitochondrial toxicity of drugs like D4T in hepatocytes. It is characterized by the insidious onset of hepatitis symptoms and hepatomegaly. LFT derangement may be cholestatic, a transaminitis or both. Ultrasound may be suggestive, but the definitive diagnosis is with liver biopsy. Often there is associated hyperlactataemia or lactic acidosis. In cases of hepatic steatosis, D4T should be switched to AZT, abacavir or tenofovir. However, if associated with lactic acidosis the NRTI class should be avoided.

In cases of mild non-life threatening manifestations of mitochondrial toxicity (eg. mild neuropathy, early lipoatrophy), if alternatives to D4T are unavailable the clinician could consider reducing the D4T dose (eg. from 40mg 12hrly to 30mg 12hrly for patients > 60kg).

Before switching a patient from D4T to AZT it is important to check the FBC and differential. If anaemia or neutropaenia are present, then an alternative agent such as abacavir or tenofovir should be used. It is also important to monitor the FBC and differential after the switch to AZT as per the AfA guidelines.

NOTE ➢

These recommendations regarding switching a single agent in a regimen because of toxicity only apply if the patient is virologically suppressed. If the patient is experiencing virological failure it is usually not recommended that they switch a single agent, but rather that their whole regimen is changed.

Medical Scheme Information

Protector Health

Protector Health is merging with Bonitas Medical Scheme from 1 January 2006. All existing AfA authorisations for Protector patients have been transferred across to Bonitas and therefore no patients need reapply to AfA. Medicines will continue to be dispensed by Pharmacy Direct.

Randwater

From 1 January 2006 Option B of Randwater Medical Scheme is also contracted to Aid for AIDS.

Selfmed

Selfmed is contracting with AfA from 1 January 2006. The following options are contracted to the programme:

- ☐ 80
- ☐ MedXXI
- ☐ MedXXI Chronic
- ☐ MedXXI Comprehensive
- ☐ Selfsure

Patients who were registered on the Old Mutual HIV management programme have been transferred over to AfA and will not have to reapply for their benefit.

Afrox

From 1 January 2006 Afrox Medical Aid Scheme will also be contracting with Aid for AIDS for the provision of the HIV disease management programme. All valid beneficiaries who require access to HIV related treatment should register with AfA in order to access the appropriate benefits. Registered patients will be required to obtain their medication from Direct Medicines.

ICD10 Coding:

Providers are reminded that the supplying of ICD10 codes to medical schemes is now a legal requirement. AfA is aware of the need to protect patient confidentiality and has requested Medscheme not to print ICD codes on Member statements.

The AfA preferred ICD 10 code is B24 – Human Immunodefiency Virus (HIV) disease (Unspecified).

Online HIV/AIDS Management Training

A comprehensive ten module online training course, as well as an annual one module update course is now available from *hivaidsclinic.com* at a significantly reduced rate for doctors who have registered patients on Aid for AIDS.

The update module is particularly useful for experienced busy practitioners who need to be brought up to date with recent developments in HIV medicine.

Both courses are accredited for CPD purposes.

For further information about course fees and how to register, email info@hivaidsclinic.com and refer to the AfA Newsletter.