aid for aids

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, Pinelands,
Cape Town, South Africa, 7430
Email: afa@afadm.co.za
Website: www.aidforaids.co.za

HEALTHCARE PROFESSIONAL NEWSLETTER

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Dose of Stavudine

Stavudine (d4T) is widely used in Southern Africa, and is a component of first-line regimens in many state programmes. However, it frequently causes peripheral neuropathy, lipo-atrophy, and hyperlactataemia. For this reason it is no longer recommended as first-line therapy in the UK and USA. A meta-analysis presented at the recent International AIDS Conference examined the role of low dose d4T. They found that lower doses (30mg bid for body weight >60kg) were at least as effective and less toxic.

AfA supports the use of lower dose d4T. When tenofovir is registered, AfA will support the use of tenofovir in first-line regimens instead of d4T.

Reference

Hill A, Ruxrungtham K, Havanich M et al.Meta-analysis of efficacy and safety for clinical studies of d4T 40mg versus 30mg BID in 1008 patients. Abstract no. THPE0120. XVI International AIDS Conference, Vancouver 2006.

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.

Patients who Switch to Nevirapine with Higher CD4 Counts are not at Increased Risk of Hepatotoxicity

Antiretroviral-naïve patients who initiate nevirapine-containing HAART with higher CD4 counts (CD4>250 in women and CD4>400 in men) are far more likely to develop nevirapine-related hypersensitivity hepatitis and thus it is inadvisable to start nevirapine in these patients.

Until recently it has been unclear whether this risk also pertains to patients who need to switch to nevirapine after their CD4 counts have increased to above these thresholds on HAART. This situation frequently arises in women who are on efavirenz-containing regimens and then fall pregnant or express a desire for pregnancy.

A study was presented at ICAAC this year which showed that patients with undetectable viral loads who switch from current treatment to nevirapine when they have a CD4 count above the recommended threshold for starting the drug are no more likely to develop hepatotoxicity than women with CD4 cell counts below 250 or men with CD4 counts below 400. A meta-analysis of data from four studies (total 410 patients) was conducted. Of these patients, 277 were deemed 'high-CD4': females with CD4 cell counts of 250 or higher, and men with counts of 400 or higher. The remaining 133 participants were 'low-CD4'. Hepatoxicity was defined as increase in ALT from normal to above 200 or a greater than 3-fold increase if abnormal at baseline. The analysis showed a 2% risk of hepatotoxicity in the low-CD4 group, and a 4% risk in the high-CD4 group. However, the statistical difference between the two groups was not significant. The overall results showed essentially no difference in risk between the low- and high-CD4 groups.

Reference

De Lazzari E et al. *Risk of hepatotoxicity in virologically suppressed HIV patients switching to nevirapine according to gender and CD4 count.* 46th ICAAC, San Francisco, abstract H-1064, 2006.

Antiretroviral Resistance Testing

There are two methods of detecting resistance to antiretroviral drugs – genotyping and phenotyping. By using gene sequencing, genotyping detects mutations in the reverse transcriptase and protease genes of the patient's virus that are known to confer drug resistance. Phenotyping is currently not available in SA.

Resistance testing is used to make decisions regarding which drugs to switch to when virological failure occurs on a regimen. When compared with expert-guided decisions based on an assessment of prior drug exposure, genotype-guided therapy decisions show modest benefit in terms of improved virological outcomes.

Genotyping will only detect mutations if the patient's viral load is greater than 500-1000 copies/ml and the mutant virus constitutes more than 20% of the viral population. Genotyping should thus only be done when the patient is on the failing therapy and adherent to it otherwise the mutants are overgrown by wild type (virus that does not carry resistance mutations) and the mutations will not be detected. Similarly, even if the patient is on therapy, if they are not on a drug that selects for a given mutation it will not be detected even if it is archived*. For instance if a patient is on HAART and has previously failed a 3TC-containing regimen, but is not receiving 3TC at the time of the test then the 3TC-resistance M184V mutation may be archived and not detectable by genotyping. Thus if a patient has previous documented virological failure on a 3TC-containing regimen we assume 3TC resistance. The same applies for NNRTIs and NNRTI resistance.

AfA will consider requests for genotyping in the following circumstances:

1) Patient has documented virological failure on current ART regimen
2) Patient is still on failing regimen
3) Patient is assessed to be adherent to failing regimen
4) Viral load is > 1000 copies/ml
5) Clinical committee considers that the genotype result will be of use in decision regarding next regimen

*Archiving = a resistance mutation is selected out by drug pressure, but when the particular drug pressure that selected it is removed it is overtaken in the circulating viral pool by the fitter wild type. It however remains "archived" - persisting at low levels in circulating viral pool and as proviral DNA in the chromosomes of resting memory T-cells. If the drug is reintroduced later in a failing regimen the mutation will re-emerge rapidly.

We need your assistance……..

The hospital benefit management programme may email you indicating that one of the patients which you have registered on AfA has been admitted under the care of another doctor. We request that you provide the admitting doctor with any relevant clinical information.

Routine Testing for HIV Infection

In high HIV seroprevalence regions, including all of Southern Africa, routine HIV-1 testing should be performed with antibody assays, including laboratory ELISA and rapid tests. Confirmation of a positive test should be determined by further ELISA or rapid test assays, according to predetermined algorithms for confirmatory tests. The Western Blot assay is inappropriate in this setting, as it is an expensive investigation contributing no additional diagnostic information than is acquired by the use of ELISA or rapid test technology.

Western Blot assays for HIV are useful in distinguishing primary infection with HIV-2, in settings where positive ELISA assays are at odds with the CD4 and viral load (PCR/b DNA/NASBA) findings. These scenarios, which include the finding of an inordinately high CD4 count in the presence of an undetectable viral load in the HIV ELISA positive patient, are fortunately rare, but present diagnostic and therapeutic dilemmas, particularly in the pregnancy setting.

The Aid for AIDS clinical committee is available to assist with such cases, and it is recommended that Western Blot assays are not requested without prior consultation with the committee.

ICD10 Coding
Providers are reminded that the supplying of ICD10 codes to medical schemes is now a legal requirement. The AfA preferred ICD10 code is B24 – Human Immunodefiency Virus (HIV) disease (Unspecified).

Post Exposure Prophylaxis (PEP) – Remember to Assess the Risks & Benefits

A healthcare worker was taking zidovudine, lamivudine and lopinavir/ritonavir following a high risk injury with a hollow bore needle used to take blood from an HIV-infected source patient. On day 11 she developed rigors. A full blood count showed marked neutropenia (absolute neutrophil count 0.1 $\times 10^9$/L). Blood cultures were negative. She settled on intravenous cefepime.

PEP is often poorly tolerated, but serious adverse drug reactions are rare. However, the risk of HIV following occupational exposure is very low. Febrile neutropenia is a potentially life-threatening complication. In this case there was a good indication for PEP, but often this is not the case, or PEP is started after a long delay. An assessment of risks and benefit, as in all therapeutic decision-making, should be made in each case. In cases where PEP is of dubious benefit or not indicated, the risk of a severe adverse drug reaction far outweighs the benefit.

Pneumococcal Vaccine for Children

Pneumococcus is the most common bacterial cause of pneumonia and meningitis in immunocompetent and immunocompromised children.

The previously available polysaccharide-based vaccine is not immunogenic below 5 years of age. The conjugated pneumococcal vaccine (Prevenar®) is active against the 7 most common pneumococcal serotypes causing disease in children and is immunogenic from 6 weeks of age. Its design is similar to that of the conjugated vaccine against *Haemophilus influenzae*, which has all but eliminated invasive disease due to that organism in young children.

The cost of the vaccine is R427.73 (SEP incl. VAT) per dose. Children under 7 months require 4 doses, 7-11 months 3 doses, 12–23 months 2 doses and 24months – 9 yrs 1 dose.

AfA supports the use of Prevenar®. The cost of the vaccine will be covered by AfA provided that it has been preauthorized and that there are sufficient benefits.

Dilemmas in HIV Practice

A 34 year old HIV+ female was registered on AfA in March, 2006. Her doctor indicated she was pregnant with an EDD of the 8th August. She was an insulin-dependent diabetic with reasonable control of her blood glucose.

Her CD4 count was 260, with a viral load of 46 539 copies. It was considered appropriate to commence HAART.

Problems:

- Efavirenz is contra-indicated in pregnancy (risk of teratogenicity)
- Nevirapine is relatively contra-indicated in females with a CD4 count >250 (increased risk of drug-induced hepatitis)
- Protease inhibitors must be used with caution in diabetic patients because of the risk of adding to the glucose intolerance. This may be aggravated further by her pregnancy.

Discussion:
It was felt in discussion with her doctor that efavirenz was not an option at this stage in view of the pregnancy. There is a major risk of inducing hepatitis with nevirapine in women with a baseline CD4 count of 250 or more: the rate of severe hepatotoxicity is 11% compared to 0.9% in women with lower CD4 counts at baseline.

While insulin resistance is described in over 30% of patients treated with protease inhibitors, it should be possible to manage her diabetes by careful monitoring and adjustment of the insulin dose. She would require admission close to delivery to optimally manage her condition.

It was decided to start her on zidovudine, 3TC and Kaletra® for the duration of her pregnancy, monitor her diabetes closely as described above, and to change the Kaletra® to efavirenz after delivery.

Practice point
OF THE MONTH

Stavudine should be avoided in women with a body mass index >28 or weight >75kg due to the increased risk of hyperlactataemia.

The 6th edition of the AfA Clinical Guidelines will be available shortly. Please send us an email (afa@afadm.co.za) with your postal address or phone 0860 100 646 if you would like us to send you a free copy.