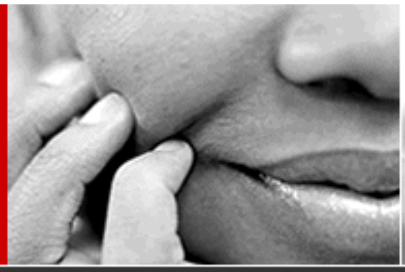

www.aidforaids.co.za

P.O. Box 38597, Pinelands, Cape Town, South Africa, 7430
Email: afa@afadm.co.za

Tel: 0800 227 700 or +27 (0)21 466 1700
Fax: 0800 600 773 or +27 (0)21 466 1744

Healthcare Professional Newsletter

December 2010 – Issue 27

Pre-exposure prophylaxis

The first randomised controlled trial of pre-exposure prophylaxis (PREP) with antiretrovirals (ARVs) to reduce HIV acquisition, the iPrEx study, has recently been published.[1] It is worth noting that a number of other PREP trials were prematurely halted or failed to start, primarily because of concerns about the lack of long term provision of ARVs after the study ended, provided the ARVs were proven to be effective.[2] Therefore this has been a very controversial method of preventing HIV infection.

The iPrEx study randomised high risk men who have sex with men who were HIV seronegative to receive the fixed dose combination of tenofovir and emtricitabine or matching placebo. Both the study participants and the researchers were blinded. The study was done in many centres, including South Africa. Rapid HIV tests were done monthly and renal function was monitored almost as often (to monitor for nephrotoxicity from tenofovir). The study drugs were well tolerated. HIV infections were reduced by 44% in men who were randomised to the tenofovir and emtricitabine arm, with approximately 60 men needing treatment for one year to prevent one HIV infection.

It may be possible to implement PREP for selected high risk groups. However, in Southern Africa there are no readily identifiable high risk groups. It would be logistically impossible to give long term PREP to all sexually active people in our region, monitor them frequently for HIV seroconversion and renal function. By lowering viral load, combination antiretroviral therapy (ART) for patients with HIV infection has been shown to reduce transmission. A mathematical model has shown that if HIV testing were to be scaled up and ART commenced immediately that HIV transmission could be eliminated.[3] Implementing this strategy would be extremely difficult, but probably easier than implementing PREP on a population scale in Southern Africa.

References

1. Anderson PL, et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. N Engl J Med 2010 Nov 23 [Epub ahead of print]

2. Weijer C, Leblanc GJ. The balm of Gilead: is the provision of treatment to those who seroconvert in HIV prevention trials a matter of moral obligation or moral negotiation? J Law Med Ethics. 2006 Winter;34(4):793-808.

3. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373:48-57.

Liberty Medical Scheme

Aid for AIDS is delighted to announce we have been appointed as the HIV disease manager for Liberty Medical Scheme as of 1 January 2011. The designated service provider for all HIV medication is Pharmacy Direct.

Contributors:
Prof. Gary Maartens
Prof. Mark Cotton
Prof. Graeme Meintjes

This newsletter has been edited by:
Dr. Leon Regensberg
Mrs. Colleen Whitelaw

CD4 counts and percentages in children

HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) is a meta-analysis of data from perinatally infected children from 17 European and US cohort studies and randomized trials, between 1983 and 2002 preceding the HAART era.[1] It has made many contributions to understanding the prognostic value of CD4 counts and percentages. The original study established the principal that the nadir threshold CD4 percentages predicting death or morbidity were higher in young infants and declined with age. The absolute CD4 count declines with age until 5 years of age when it approximates and has the same prognostic value as in adults. [2] Traditionally, the CD4 percentage has been used in children as it is more stable and declines only minimally as the child grows.

Many clinicians treating children have noted that lymphopaenic children may have low absolute CD4 counts but elevated CD4 percentages. Recent data from the HPPMCS showed that CD4 count / percentage discordance occurred quite commonly and that the CD4 count was actually a better prognostic marker for young children. [3]

The PENTA guidelines illustrate the declining threshold for initiating ART as the child grows. [4]

PENTA and AfA guidelines for initiating ART in children	
Age (Years)	**CD4 percentage and count (cells/mm^3)**
1 to <3	<25% or < 1000
3 to <5	<20% or < 500
Above 5	< 350

Clinical point
Clinicians and nurses treating children must look at both the CD4 count and percentage. A low CD4 count takes precedence over a high CD4 percentage.

References

1. HIV Paediatric Prognostic Markers Collaborative Study Group. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet* 2003;362(9396):1605-11.
2. Dunn D, Woodburn P, Duong T, Peto J, Phillips A, Gibb D, et al. Current CD4 cell count and the short-term risk of AIDS and death before the availability of effective antiretroviral therapy in HIV-infected children and adults. *J Infect Dis* 2008;197(3):398-404.
3. HIV Paediatric Prognostic Markers Collaborative Study Group. Discordance between CD4 cell count and CD4 cell percentage: implications for when to start antiretroviral therapy in HIV-1 infected children. *AIDS* 2010;24:1213-17.
4. PENTA Steering Committee. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Med* 2009;10:591-613.

Atripla® is now available in SA

- Atripla® is a fixed dose combination tablet containing efavirenz, emtricitabine and tenofovir.
- The dose of Atripla® is one tablet once a day, preferably at bedtime.
- The single exit price of Atripla® is R483.78 incl. VAT.

Please note that if an AfA patient is currently authorized on a combination of tenofovir, emtricitabine and efavirenz and you would like to switch them to Atripla® you should contact AfA (0800 22 77 00 or afa@afadm.co.za) so that the authorization can be updated. The Atripla® claim won't be able to be processed until our system has been updated. Please make sure that patients understand this change and know that they now only need to take one tablet once a day.

AZT intravenous infusion (ivi)

- AfA have previously recommended the use of AZT ivi for pregnant mothers during labour and delivery.
- Most of the AfA deliveries are by Caesarean section.
- If the woman is well controlled on ART and is treatment adherent, then there is no evidence that IV AZT confers any additional benefit
- AfA has stopped recommending the use of AZT ivi.

ART resistance, genotype resistance testing and archiving

When adherence to ART is not 100% there is a risk that there will be ongoing viral replication in the presence of suboptimal drug concentrations. This may result in the selection of drug resistant mutants in the viral population. Usually once resistance to one of the drugs in the ART regimen develops, virological failure ensues and then even if adherence subsequently improves the viral load will not suppress and there is accumulation of further drug resistance mutations in the viral population.

Certain drugs have a low barrier to resistance (e.g. 3TC, FTC, nevirapine and efavirenz) meaning that a single mutation in the viral genome at a key site will result in high level resistance. Other drugs have a high barrier to resistance (e.g. boosted protease inhibitors) meaning that it requires many resistance mutations in the viral genome to result in high level resistance. Resistance to drugs with a low barrier to resistance obviously develops relatively early if treatment is taken with poor adherence.

We advise monitoring the viral load 3-6 monthly. If the viral load is suppressed (lower than detectable limits or <50) it suggests good adherence and no resistance to that regimen. If the viral load does not suppress then efforts should be made to improve adherence by counseling and support (e.g. treatment buddy in household). If the viral load remains above 1000 on two or more occasions despite improved adherence this suggests viral resistance has developed and the regimen needs to be changed. Given that the resistance profile after first line failure is relatively predictable we advise the following second line regimens after first line failure:

First line	Second line advised
D4T + 3TC + NNRTI	TDF + FTC (or 3TC) + boosted PI
AZT + 3TC + NNRTI	TDF + FTC (or 3TC) + boosted PI
TDF + FTC + NNRTI	AZT + 3TC + boosted PI

Boosted PI = Aluvia® or atazanavir with ritonavir

In patients failing an ART regimen it is sometimes necessary to do a genotype resistance test to guide decisions regarding the next regimen. AfA specifically advises genotype resistance testing in the following situations, provided funds permit:

1. Failing second line ART
2. Patient failing a first line regimen that contained a PI (mainly in paediatric setting)

In addition, there are certain situations where AfA advises a genotype be done before ART is started:

1. In infants who have been HIV infected despite their mother receiving PMTCT
2. In adult patients where there is a strong suspicion that the patient has been infected with a resistant virus (e.g. sexual partner failing ART)

Important points regarding genotype resistance testing:

•The tests involves sequencing the viral gene coding for reverse transcriptase, protease and integrase enzymes (the target of the ART drugs) to detect resistance mutations at key points in these enzymes that are known to confer resistance to specific drugs.

•The test can only be performed in commercial laboratories if the viral load is > 1000 copies/ml.

•If the resistance mutation is present but in fewer than 20% of viruses in the viral population it will not be detected. This is termed “archiving”. This typically occurs when a patient has developed drug resistant mutations, but then stops ART. What happens over the next few weeks for most mutations is that the wild type virus (without the mutation) replicates faster than the resistant mutant (because most resistant mutants have a fitness cost to the virus) and thus the wild type comes to dominate the viral population in the absence of ART and the resistant mutant becomes archived. It is thus essential that the genotype resistance test is always performed while the patient is taking the failing regimen in order that the result fully detects all the mutations to that regimen that have developed.

•The genotype resistance test may not detect mutations that developed during the failure of a previous regimen because they are now archived. This is typically the case when a patient fails an NNRTI-containing first line and then has a genotype resistance test performed after second line failure. The NNRTI resistance mutations may be archived, but we assume that they are present based on the treatment history. Thus in deciding about the next ART regimen the genotype resistance test should always be interpreted together with a full treatment history.

•All genotype resistance test results should be referred to the AfA Clinical Committee for advice regarding the best subsequent regimen.

Amphotericin B

The optimal treatment of cryptococcal meningitis includes intravenous amphotericin B (AmB) 1mg/kg/day for 14 days. Amphotericin B has several potential toxicities, but monitoring and preventive strategies can reduce the effect of these.

Toxicity	Prevention	Monitoring	Treatment
Nephrotoxicity	Prehydrate with 1 litre normal saline given over 2 hours before AmB infusion	Creatinine twice weekly	Interrupt AmB and rehydrate. Restart AmB with additional prehydration if creatinine normalizes or switch to fluconazole 800mg PO daily if it does not normalize rapidly
Hypokalaemia	Supplement with oral potassium	Potassium twice weekly	IVI potassium supplementation
Hypomagnasaemia	Supplement with oral magnesium	Magnesium weekly	Increase oral supplementation or IVI supplementation
Chemical phlebitis (drip site)	Change IVI site regularly and flush drip after infusion	Drip site	Replace drip and monitor for secondary bacterial infection
Anaemia (expect 2-4 g/dl drop in Hb over 14 days on AmB)	-	FBC weekly	Consider transfusion if severe
Febrile reaction	-	Symptoms and temperature	Paracetamol prior to AmB infusion (if severe hydrocortisone 50mg IVI prior to AmB infusion)
Cardiotoxicity	Infusion over 4 hours prevents cardiotoxicity	-	-