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
March 2007 – Issue 16

Contraception and antiretroviral therapy

HIV infection reduces fertility and ill patients often have reduced libido. However, both libido and fertility improve with effective antiretroviral (ARV) therapy. Patients often initially decide not to have children, but change their mind as they get well on ARVs. Contraception and family planning are important components of care. Drug interactions with ARVs are important considerations with hormonal contraception. It is especially important to use effective contraception in women on efavirenz, as this is a known teratogen. Sterilisation should be offered to those who have completed their families.

Barrier methods

There are compelling reasons to always recommend barrier methods in addition to other contraceptive measures as this will reduce the risk of transmission of HIV, the acquisition of super-infection with ARV-resistant HIV, and infection with other pathogens (notably herpes simplex). It should be noted that the contraceptive efficacy of barrier methods is sub-optimal, with annual failure rates of approximately 5%[1]. Thus additional contraception methods should always be taken.

Intrauterine devices

Early fears that these would be associated with increased risk of infection in HIV seropositive women have not been borne out in prospective studies[2]. The progestogen-eluting devices are effective when used with enzyme-inducing drugs as they have a local action. Thus these are likely to be effective when used with ARVs[1].

Hormonal contraception

There are important drug interactions with some ARVs (notably the protease inhibitors and the NNRTIs) and hormonal contraception, resulting in alteration in the hormone concentrations. There is limited data on the contraceptive efficacy of hormonal agents when co-administered with ARVs[1,3] (see table for recommendations). There is insufficient data on progestogen-only pills and on patches to make a recommendation.

ARV	Ethinyl-oestradiol concs	Progestogen concs	Recommen-dation
RTV - boosted PI	Significantly reduced	Reduced	COCP not recommended. Depot progestogens may be adequate
EFV	Slightly increased	DMPA unaffected	COCP or depot progestogens
NVP	Significantly reduced	Reduced norethisterone (DMPA unaffected)	COCP not recommended. Depot DMPA.

RTV = ritonavir COCP = combined oral contraceptive pill
EFV = efavirenz DMPA = Depo-medroxyprogesterone acetate
NVP = nevirapine

References

1. Waters L, Barton S. Contraception and HIV: what do we know and what needs to be done? J Fam Plann Reprod Health Care 2006;32:10-4.
2. Sinei SK, Morrison CS, Sekadde-Kigondu C, et al. Complications of use of intrauterine devices among HIV infected women. Lancet. 1998;351:1238-41.
3. Cohn SE, Park JG, Watts DH, Stek A, Hitti J, Clax PA, Yu S, Lertora JJ. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. Clin Pharmacol Ther. 2007 Feb;81(2):222-7.

Monitoring lipids and glucose

Protease inhibitors are associated with an increased risk of dyslipidaemia and insulin resistance. Elevated triglycerides are the commonest lipid abnormality, but LDL cholesterol can also be increased.

Impaired glucose tolerance is not uncommon, but overt diabetes is rare.

In keeping with international guidelines, AfA recommends monitoring fasting lipids and glucose after 3-6 months on PIs, and annually thereafter.

Reference

Schambelan M et al. Management of Metabolic Complications Associated With Antiretroviral Therapy for HIV-1 Infection: Recommendations of an International AIDS Society-USA Panel. JAIDS 2002;31:257-75

The SMART study

Antiretroviral therapy is lifelong and with time carries the risks of cumulative metabolic and cardiovascular toxicities, the accumulation of viral resistance mutations and treatment fatigue with adherence lapses. This had led to an interest in the concept of structured treatment interruptions (STIs) – providing breaks in therapy in a structured fashion to minimise the long term complications of HAART while not compromising the long term benefits of therapy or putting patients at risk of immunosuppression-related events during these breaks.

The Strategies for the Management of Antiretroviral Therapy (or SMART) study was conducted across 33 countries to investigate the safety of such a strategy. It was a prospective randomized trial comparing a Virological Suppression or VS arm (patients stayed on continuous HAART) to a Drug-Conservation or DC arm (in which patients interrupted or deferred HAART with a CD4 count > 350 cells/mm^3 and restarted when CD4 dropped below 250 cells/mm^3). A total of 5472 patients had been enrolled in the study by the time it was terminated by the DSMB in January 2006 because of an increased risk of disease progression and death in the DC arm. The characteristics of the whole cohort were:

- Median age: 43
- Median CD4 at entry: 597 cells/mm^3
- 72% had a viral load (VL) <400 copies/ml at study entry
- Median CD4 nadir was 250 cells/mm^3 (25% of patients had a nadir CD4 less than 155 cells/mm^3)
- 5% were ART naïve
- Median of 6 years on ART
- 24% had an AIDS defining illness previously

The primary endpoint was a combined outcome of death and opportunistic infection. The rate of this was 3.3/100 person-years in the DC arm and 1.3/100 person-years in the VS arm giving a hazard ratio = 2.6 (95% CI= 1.9 – 3.7). When stratified, even those with a nadir CD4 > 400 cells/mm^3 showed an increased risk of this primary endpoint in the DC arm. Death was also significantly more common in the DC arm (hazard ratio = 1.8). Thus the CD4-guided strategy to maintain CD4 > 250 cells/mm^3 and allow STIs was associated with a greater than 2-fold higher short-term risk of opportunistic infections and all-cause mortality. What was surprising given that STIs would be thought to reduce drug side effects by reducing drug exposure, was that major cardiovascular, hepatic and renal complications were actually significantly more common in the DC arm (hazard ratio = 1.7). This was attributed to organ-specific effects of HIV progression during interruptions by the authors.

This study demonstrated a clear increase in the risk of morbidity and mortality using an STI strategy. Other smaller studies have shown STI to be safe and this may result from differences in study design and patient population.

STIs, including patients requesting drug holidays, should be strongly discouraged.

It should also be remembered that STIs in a southern African context may carry additional risks such as increasing the risk of TB.

Reference

N Engl J Med 2006;355:2283-96.

Breast feeding in HIV-infected and exposed infants – paradigm shift

HIV is transmitted through breast milk and breastfeeding is responsible for 9 to 12 percent of transmission to infants.[1,2] Mixed feeding is associated with the highest risk.

Recent data, however, has emphasized the dangers of formula feeding and protective effects of breast milk in both HIV-infected and uninfected infants. The benefits of not having a HIV-infected infant are counterbalanced by increased morbidity and mortality, mainly through diarrhoeal disease as shown in the Mashi study, recently conducted in Botswana.[3]

Both breast and formula feeding are important options, but each demands a high standard of care. Over and under-dilution of formula milk occur. Formula feeding requires attention to cleanliness. Boiled water should be used and bottles, cups and teats need to be kept clean. Adherence to exclusive breastfeeding is poor as many mothers need to go to work after a few months. Mastitis may also increase transmission. Under circumstances where formula milk can be safely prepared, it remains the best option to reduce HIV transmission.

References

1. Iliff PJ, Piwoz EG, Tavengwa NV, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. Aids 2005;19(7):699-708.
2. Coutsoudis A, Dabis F, Fawzi W, et al. Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. J Infect Dis 2004;189(12):2154-66.
3. Thior I, Lockman S, Smeaton LM, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. Jama 2006;296(7):794-805.

Antiretroviral therapeutic drug monitoring

Antiretroviral therapeutic drug monitoring (TDM) is an additional monitoring tool to assist in the management of HIV-infected patients. The general characteristics that make drugs suitable for TDM include:

- A narrow therapeutic window
- Good correlation between drug concentration and effect or toxicity
- Variable pharmacokinetics in different individuals
- The availability of a reliable assay

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) have most of the characteristics that make them potentially suitable candidates for TDM, but NRTIs do not, and TDM is not recommended for NRTIs. Several laboratories in South Africa are now offering antiretroviral TDM.

Randomised controlled trials of TDM in routine care have shown contradictory results, and routine TDM is not recommended. Therefore TDM should only be considered in selected circumstances:

- Potentially significant drug-drug interactions where the interacting drug is reported to alter the concentration of NNRTIs/PIs – e.g. rifampicin. Note that it is preferable to use an alternative non-interacting drug if possible.
- Patients with significant hepatic or gastrointestinal disease
- Children – particularly neonates and young children.
- Pregnancy – many physiological changes in pregnancy affect pharmacokinetics. This has been shown to reduce the concentrations of PIs, although with ritonavir-boosted PIs the concentrations are generally adequate
- In treatment-experienced patients with PI mutations as higher concentrations of PIs have been shown to overcome resistance, provided it is not at too high a level. Note that it is not possible to increase NNRTI concentrations to overcome resistance as a single NNRTI resistance mutation confers high level resistance.
- To monitor adherence

In general a trough sample is most helpful for TDM, as efficacy correlates with trough concentrations. As efavirenz is dosed at night, TDM samples are usually taken 12 to 20 hours after the last dose. It is essential to indicate the time of sampling and the time of taking the last dose in order to adequately interpret the drug concentration.

References

1 La Porte CJ, Back DJ, Blaschke T et al. Updated guidelines to perform therapeutic drug monitoring for antiretroviral agents. Reviews in Antiviral Therapy 2006;3:4-14

2. Maartens G. Antiretroviral therapeutic drug monitoring. Southern African Journal of HIV Medicine, June 2006.

3. Marcelin AG, Cohen-Codar I, King MS, et al. Virological and pharmacological parameters predicting the response to lopinavir-ritonavir in heavily protease inhibitor-experienced patients. Antimicrob Agents Chemother 2005;49:1720-6.

Monitoring and promoting adherence to therapy with courier pharmacies

Few would disagree that adherence to therapy is critically important to ensure the effectiveness and durability of HAART. Aid for AIDS has validated the use of pharmacy claims data as an important tool for assessing adherence.[1]

Ensuring and monitoring treatment adherence becomes particularly challenging, however, when medication is "passively" delivered to patients on a regular monthly basis by courier or postal pharmacies.

Aid for AIDS has met with Pharmacy Direct to develop a system which would encourage patients to play a more active role in their treatment, and enable adherence to be more effectively monitored.

Pharmacy Direct will SMS all registered patients a week before their next medicine supply is due, and request them to re-order their medicines for the next month. This will be a simple "yes" or "no" response. By having to actively reply to trigger the next delivery, it will not only encourage adherence to therapy, but also provide Aid for AIDS with a measure of adherence that can be used to identify patients who require additional support and counseling, as well as assist with evaluating requests for genotyping.

Patients who do not respond to the SMS will be sent 3 further SMS reminders and thereafter will be contacted telephonically by Aid for AIDS. Medicines will still be delivered for a further month. Deliveries will only be held back after 2 months after all reasonable attempts to contact the patient have failed.

All patients registered with Pharmacy Direct will be contacted to explain the system and request an update of their contact information.

The system will be piloted with one medical scheme for several months from February, and if successful will be rolled out to other schemes afterwards. We believe this approach is a positive move that will allow better monitoring of adherence and ensure that patients gain the maximal benefit from antiretroviral therapy.

References

1. Nachega JB, Hislop M et al. Adherence to HAART assessed by pharmacy claims predicts survival in HIV-infected South African adults. JAIDS 2006;43:78-84.

Printed copies of the 6th edition of the AfA Clinical Guidelines are now available. 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.