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

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Abacavir-based regimens in patients with high viral loads

In a previous newsletter (December 2012, issue 33) we recommended against the use of abacavir in patients with high viral loads, in keeping with other international guidelines. The reason for this recommendation was largely based on a large randomised controlled trial (RCT), which had shown higher risk of virologic failure in patients with baseline viral loads >100,000 copies/mL randomised to abacavir rather than tenofovir.[1] However, a meta-analysis has just been published of 6 RCTs involving 4118 patients, which showed that abacavir has similar virologic efficacy to tenofovir in all patients (relative risk 0.98; 95% CI 0.94–1.03), as well as in those with baseline viral loads >100,000 copies/mL (relative risk 0.96; 95% CI 0.90–1.03).[2] Therefore AfA no longer recommends against using abacavir in patients with high viral loads.

References

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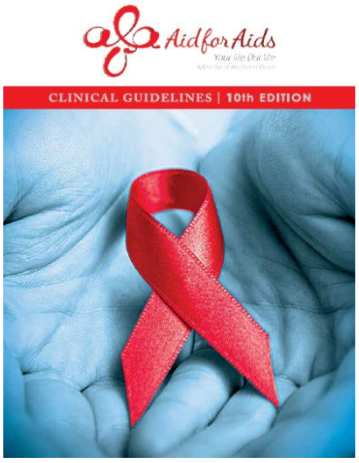
AfA is pleased to announce that the popular Clinical Guideline booklet will soon be available as a free App which can be used on any Apple or Android device.

The App will be a convenient and practical way of accessing and searching through the most up to date version of the guidelines. Several useful calculators, a comprehensive drug interactions table and a "Contact AfA page" will be included.

The launch date is expected to be early next year.



Contributors:
Prof. Gary Maartens
Prof. Graeme Meintjes
Prof. Mark Cotton
Dr. Helena Rabie
Prof. Marc Mendelson

This newsletter has been edited by:
Liezl Dunn
Dr. Leon Regensberg

Proton pump inhibitor, H2 receptor blocker and antacid drug interactions with atazanavir/ritonavir

Atazanavir boosted with low dose ritonavir (300mg atazanavir and 100mg ritonavir) is one of the options recommended by AfA as the protease inhibitor backbone in the 2nd line ART regimen. It has fewer gastro-intestinal side effects and a more favourable lipid profile than lopinavir/ritonavir and is taken once daily. However, one of its drawbacks is that it has important pharmacokinetic drug interactions with drugs that reduce gastric acidity. Atazanavir requires an acidic gastric environment for optimal absorption.

Proton pump inhibitors (PPIs): Concomitantly administered omeprazole reduces atazanavir AUC by 75%. PPIs should thus preferably be avoided in patients on atazanavir/ritonavir and are contra-indicated for patients who were PI-experienced when they commenced atazanavir/ritonavir. If PPI use is unavoidable in patients on atazanavir/ritonavir for whom atazanavir/ritonavir is their first PI, then a dose of omeprazole of 20mg (or equivalent) should not be exceeded and the PPI should be taken at least 12 hours before the atazanavir/ritonavir. European guidelines recommend increasing the atazanavir/ritonavir dose to 400mg/100mg daily in this setting. Monitoring of the viral load to detect breakthrough viraemia is important.

Antacids and medication buffered with antacids: These reduce atazanavir concentrations, but less so than PPIs. Atazanavir/ritonavir should be given at standard doses at least 2 hours before or 1 hour after antacids.

H2 receptor antagonists (H2RA): These drugs also reduce atazanavir concentrations but to a lesser degree than PPIs. The maximum dose of famotidine should be 20mg bd (or equivalent, such as cimetidine 200mg daily) when used with atazanavir/ritonavir-based 2nd line ART. The atazanavir/ritonavir dose should be standard and taken either simultaneously with the H2RA and/or > 10 hours after the H2RA. If the patient is on tenofovir, atazanavir/ritonavir and an H2RA then the atazanavir/ritonavir dose should be increased to 400/100mg in ART-experienced patients.

Unboosted atazanavir should not be used with PPIs and H2RA.

References

1. University of Liverpool Drug Interactions Website: www.hiv-druginteractions.org
2. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. US Department of Health and Human Services. 13 November 2014 update.

Update on the Mississippi child – a reality check

In April 2013 (issue 34), we reported on the Mississippi baby, a premature infant born at 35 weeks gestation to a mother whose HIV was diagnosed when she presented in active labour. Postnatal zidovudine was initiated and converted to combination ART at 31 hours of age. HIV infection was confirmed by demonstrating HIV DNA by PCR and plasma HIV RNA level at 19000 copies/mL. After loss to follow-up at 18 months, the infant reappeared 6 months later, clinically well and without evidence of HIV by standard tests. Traces of HIV were detected by very sensitive specialized assays.[1] Unfortunately, in July 2014 after approximately 3 years off ART, and confirmed by extensive testing, HIV RNA at 16,750 copies/mL was noted. Seventy-two hours later a repeat viral load was 10,564 copies/mL and ART was restarted.[2]

Despite the disappointing outcome for both this child and the 2 adult "Boston patients" who relapsed after allogeneic bone marrow transplant there are important lessons in these cases for the cure agenda.[3]

Very early diagnosis and therapy is absolutely essential for limiting reservoir size and resetting of viral control. Modelling suggests that reducing or limiting reservoir size can delay viral rebound by many years. The authors estimate that a 2000 fold reduction in reservoir size should allow interruption for a year.[4] Information from the "California baby" presented at CROI 2014[5] and 4 Canadian infants[6] accessing very early therapy and in whom HIV specific antibodies did not develop, supports this idea. These 5 children are still on treatment. The data on therapy interruption from the CHER study suggested very modest gains in infants initiating ART between 8 and 12 weeks. At the time the authors postulated that a longer duration on treatment may be required,[5] however it may well be that both earlier access to suppressive ART and a longer duration of primary therapy are required. It is likely that apart from very early ART additional intervention/s to eliminate latent HIV will be needed.

It is also clear that we still require better information on the sanctuary sites. No lumbar puncture was performed in the Mississippi baby; this may be an important "oversight".

There may be specific ART combinations required to achieve prolonged remission. Of note, both the Mississippi baby and the Canadian infants received nevirapine in the early phase of therapy. It is not clear whether integrase inhibitors or CCR-5 antagonists will give additional benefit.

Conclusion

Although, the relapse of the Mississippi child has given researchers in the cure agenda reason for pause, it has always been clear that we are a long way from curing HIV infection. Well-documented case studies are essential to the growing body of knowledge needed to ultimately cure HIV.

References

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Maraviroc

Maraviroc is an antagonist of the human chemokine receptor 5 (CCR5), which is a co-receptor (along with CD4) required for HIV to enter a cell. HIV binds to CCR5 in initial infection, but later on it can mutate to bind to an alternative co-receptor, chemokine receptor type 4 (CXCR4), either as the only co-receptor, or, more commonly, to use CCR5 or CXCR4, so-called dual tropism. The prevalence of CXCR4-tropic/dual tropic HIV is about 10-20% in ART-naïve patients and 40-50% in ART-experienced patients. HIV that is CXCR4-tropic or has dual tropism is resistant to maraviroc. It is therefore essential to determine the HIV chemokine tropism, which is done by either a phenotypic or a genotypic assay, in all patients before using maraviroc. Chemokine tropism assays are expensive and have limited availability in southern Africa.

Maraviroc was first tested in ART-experienced patients in the MOTIVATE 1 and 2 studies.[1] Patients with triple class resistance or failure were placed on optimised background therapy and randomised into one of three arms: maraviroc dosed once or twice daily, or matching placebo. Virologic suppression was achieved two to three times more often in both of the maraviroc arms than the placebo arm, which was a highly significant result. There were no differences in virologic outcomes with the once or twice daily maraviroc arms.

In the MERIT study[2] maraviroc 300 mg daily or 300 mg twice daily was compared with efavirenz (together with zidovudine and lamivudine for all three arms) in ART-naïve participants using a non-inferiority design. The maraviroc once daily arm was stopped early as it was not non-inferior (in the tortured language of non-inferiority studies – in other words the once daily arm was worse). At the end of the study maraviroc 300 mg twice daily was also shown to be not non-inferior to efavirenz (i.e. maraviroc was worse). However, the tropism assay used in the MERIT study was not very sensitive. A post hoc retrospective analysis of MERIT was done excluding patients who were shown to have CXCR4-tropic/dual tropic HIV using a more sensitive tropism assay, and suggested that maraviroc 300 mg twice daily was as effective as efavirenz.[2]

Maraviroc is generally well tolerated. Treatment discontinuation due to toxicity was 4.2% in the maraviroc arm versus 13.6% in the efavirenz arm in the MERIT study. Cough, upper respiratory tract infections, rash, and dizziness have all been reported more commonly with maraviroc than placebo in clinical trials. Systemic hypersensitivity reaction with rash has rarely been reported. Maraviroc is metabolised by the cytochrome P450 isoenzyme CYP3A. Dose adjustments are required when maraviroc is co-administered with CYP3A inhibitors (e.g. ritonavir-boosted protease inhibitors) or inducers (e.g. efavirenz, rifampicin). Maraviroc has immune modulating properties. It was hypothesised that it would increase CD4 counts in people who failed to develop a good immunological response despite effective ART, but two studies did not show a significant CD4 response.[3,4] Both studies showed other phenotypic changes in CD4 and CD8 lymphocytes, but these are of uncertain clinical benefit.

Because of its expense and the expense of the chemokine tropism assay, AfA currently only recommends maraviroc in selected patients needing salvage ART.

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A festive reflection - Prof. Marc Mendelson

The festive season is a time for re-telling of stories, some plausible, some less so. For example, it is completely plausible for Jesus to have been born in a stable, as everyone knows how hard it is to find a hotel room over Christmas. Less plausible is the fact that a rotund Santa Claus could fit down most of the worlds' chimneys. However, thanks to Tim Noakes, Santa is now on the Banting diet and will have a far easier job of it this year.

So for this festive reflection, I thought I would review HIV lore and remark on my favourite implausible story, that of epitrochlear lymph nodes being pathognomonic of HIV infection. Yes that old chestnut, which used to be ascribed to syphilis, has now been born again with HIV. Medical students pause dramatically during their presentations to give extra credence to the explosive information that they are imparting about this earth-shattering revelation.

Stop for a moment and reflect and on why the epitrochlear node would be particularly vulnerable to becoming enlarged in HIV as opposed to any other infection or disease? We are always taught that lymph nodes either enlarge because of 'draining' infection, 'over activity' or because of infiltration by cancer or infection. So why would the epitrochlear lymph node be so favoured in HIV? The only explanation I could come up with is that HIV is in fact transmitted during masturbation, gaining access via breaches in skin and inducing enlargement of the draining lymph node of the hand, i.e. the epitrochlear. Have I thus stumbled upon the missing link in the chain of explaining the dynamics of HIV? If so, one would expect unilateral enlargement, unless the proponent is ambidextrous. Or is there perhaps a more simple explanation, that it's all a load of tosh?

To prove the latter, your correspondent got hold of 110 consecutively presenting patients with HIV and had a good rummage around (unpublished observations). Overall, epitrochlear, axillary and cervical lymphadenopathy occurred in 11, 24 and 47 patients respectively. Only 18/110 patients (16%) exhibited lymphadenopathy at more that one of the 3 sites. Submandibular lymph nodes were the most commonly palpated. Patients receiving HAART had a reduction in the frequency of palpable lymph nodes compared to those that were ART-naïve. An intercurrent diagnosis of an OI, 60% of which were TB, was not surprisingly more commonly associated with lymphadenopathy at any site. The relative frequency of lymphadenopathy at the 3 sites remained consistent. No difference in CD4 T cell counts was observed in patients with lymph nodes at particular sites.

The festive moral to the story; better to trust in the good Lord than the bad Lore.