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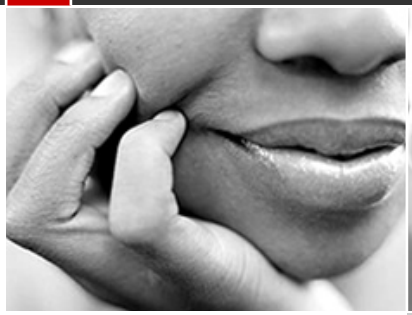

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Antiretroviral therapy and the risk of myocardial infarction

Cardiovascular disease is an important cause of morbidity and mortality in HIV-infected patients on antiretroviral therapy (ART). The D:A:D Study Group (Data Collection on Adverse Events of Anti-HIV Drugs) combines data from a number of antiretroviral cohorts in industrialised countries to evaluate adverse events associated with ART, with a particular focus on the risk of myocardial infarction (MI). They previously showed that the risk of MI was associated with cumulative exposure to protease inhibitors, after controlling for known cardiovascular risk factors[1]. The magnitude of this risk was "similar to the increment in risk attributable to diabetes mellitus or cigarette smoking and is greater than that associated with a family history of cardiovascular disease" [1]. It is unclear whether the increased MI risk would occur with protease inhibitors that are less associated with dyslipidaemia (e.g. atazanavir), but the MI risk was independent of lipid concentrations[1], suggesting that protease inhibitors may enhance atherosclerosis in other ways. There was no increased risk associated with ART based on non-nucleoside reverse transcriptase inhibitors.

Recently the D:A:D Study Group evaluated whether there was an increased MI risk associated with nucleoside reverse transcriptase inhibitors (NRTIs) [2]. They reasoned that the thymidine analogue NRTIs, stavudine (d4T) and zidovudine (AZT), cause mild dyslipidaemia and insulin resistance, which may result in atherosclerosis. They found no association between d4T or AZT use and MI, but unexpectedly there was an association with abacavir (ABC) and didanosine (ddI) use. The association was with recent rather than cumulative use[2].

How should clinicians react to these findings? Experts in evidence-based medicine teach us to be sceptical about associations found in cohort studies, as these are often subsequently found not to be causal. Cohort studies can never control for differences between groups. The evidence of the increased MI risk with protease inhibitors appears to be robust and is cumulative. The increased MI risk with ABC and ddI is not cumulative and the magnitude of the risk is modest at less than a two-fold increase (epidemiologists prefer an increase of threefold or more). Clinicians need to address modifiable risk factors in all patients on ART. If such risk factors exist, it may be prudent to avoid ddI and ABC. Protease inhibitors are a critically important class of antiretrovirals, especially for second-line regimens, so it is not possible to avoid their use.

References

1. The D:A:D Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007; 356: 1723–35.
2. D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet 2008;371:1417–26

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Aluvia tablets replace Kaletra

Kaletra capsules (each containing lopinavir 133mg and ritonavir 33mg) are being replaced by Aluvia tablets, the manufacturers Abbott announced this month. Each tablet of Aluvia contains lopinavir 200mg and ritonavir 50mg. Thus while the adult dose of Kaletra is 3 capsules 12 hourly, the dose of Aluvia is 2 tablets 12 hourly. Aluvia is heat stable and thus (unlike Kaletra) does not require refrigeration. A further advantage is that Aluvia does not have to be taken with food. The lower pill burden and absence of food restriction is likely to result in better adherence.

The drug interaction profile is exactly the same as with Kaletra. Two important and common interactions are with rifampicin and the NNRTI s (Nevirapine and Efavirenz). The serum levels of lopinavir are reduced by these drugs. The dose of Aluvia should thus be increased as follows when co-administering:

With rifampicin: increase dose to 4 tablets 12 hourly
With NNRTIs: increase dose to 3 tablets 12 hourly

Frequent monitoring of LFTs is essential if Aluvia is administered in double dose with rifampicin at week 2, week 4, and monthly until the end of TB treatment.

Diagnosis of Mycobacterium Avium Complex (MAC) infection

MAC infection is the most frequent non-tuberculous mycobacterial infection occurring in HIV-infected patients. The commonest manifestation is disseminated MAC which occurs predominantly in patients with advanced HIV infection (typically CD4 count < 100). Patients typically present with fevers, weight loss and other constitutional symptoms, abdominal symptoms and/or cytopaenias from bone marrow involvement. Disseminated MAC is diagnosed by culture of the organism from blood (using specialized mycobacterial blood culture bottle), bone marrow biopsy or gastro-intestinal biopsy.

Pulmonary MAC is uncommon in patients with HIV infection. The diagnosis of pulmonary MAC is complicated by the fact that the finding of MAC on sputum (or bronchial washing) culture does not necessarily mean that MAC is causing pulmonary disease. MAC may contaminate a sputum culture or colonise the airways (especially in patients with underlying bronchiectasis) giving rise to a positive culture while not causing pulmonary disease. Thus the American Thoracic Society guidelines [1] advise that pulmonary MAC should not be diagnosed on a single sputum (or bronchial washing) culture isolate. Their criteria require that the patient has pulmonary symptoms, chest radiography showing disease compatible with pulmonary MAC and alternative diagnoses are excluded. In addition, MAC should either be isolated from 3 sputum (or bronchial washing) cultures or there should be two positive cultures for MAC with an AFB positive smear. If only one sample growing MAC is available then the smear should be 2+ or greater (together with the clinical and radiological criteria above) for the diagnosis of pulmonary MAC to be made.

Although the finding of MAC on sputum is not by itself diagnostic of pulmonary MAC, patients who demonstrate MAC in the sputum without having pulmonary disease are at increased risk of disseminated MAC if their CD4 declines to less than 100.

1. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. This official statement of the American Thoracic Society was approved by the Board of Directors, March 1997. Medical Section of the American Lung Association. Am J Respir Crit Care Med. 1997 Aug;156(2 Pt 2):S1-25.

TDF (Tenofovir Disporoxil Fumarate) in special situations

Pregnancy:
TDF has been categorised as a class B teratogen (Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters).
TDF is thus not contraindicated in pregnancy, but there are concerns regarding its renal toxicity and reduction in bone mineral density. There is currently minimal pregnancy data in humans. Therefore it is prudent to avoid TDF in pregnancy until there is more data, unless there are compelling reasons for its use (e.g. resistance or intolerance to other NRTIs).

Children and Adolescents:
TDF causes a mild reduction in bone mineral density in adults, which is of doubtful clinical significance. Two small studies in adolescents report more dramatic decreased bone mineral density which reversed on discontinuation of TDF. No fractures were seen in either study.

No data on renal safety is available in children. In addition, there exists no dosing formulation for children, and the adult pill form should not be crushed or broken.
Until larger studies are available in adolescence or children, AfA recommends that TDF should not be used unless resistance testing suggests that TDF is the most effective or only option available. Advice should be sought from the Aid for AIDS clinical committee regarding how to administer TDF and how to monitor for safety.

Antiretroviral resistance testing (genotyping)

This test may be funded by for most medical schemes if treatment failure is suspected, provided certain criteria are met:

- The test must be pre-authorized (contact AfA toll-free on 0800 227 700). If pre-authorization is not obtained, the patient will be liable for the full costs. (Approximately R4,000).
- The patient must be adherent to therapy and on the failing regimen at the time of doing the test in order for resistance mutations to be demonstrated, unless the presence of primary resistance is strongly suspected.
- The viral load must be > 1000 copies.
- The medical scheme option the patient has selected must allow for genotyping. Certain limited pathology or PMB-only options do not provide for genotyping. Contact AfA for further details.

The interpretation of the results and the construction of new/salvage regimens is often complex. Please submit the results to AfA for analysis by our expert panel and advice on further management.

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