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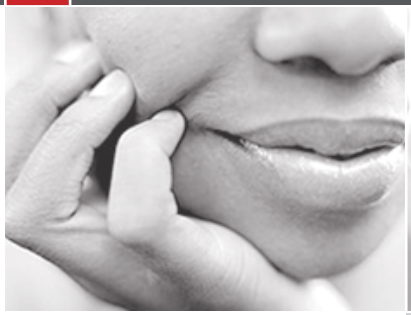

Healthcare Professional Newsletter

October 2009 - Issue 23

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WHEN IS THE BEST TIME TO START ANTIRETROVIRAL THERAPY?

The Aid for AIDS (AfA) clinical guidelines currently recommend that antiretroviral therapy (ART) should be initiated using the following criteria:

1) Patient must be ready for treatment
AND
2) have a WHO stage 4 condition (or other serious morbidity, for example thrombocytopenia or hepatitis B co-infection)
OR
3) Two CD4 counts less than 350 cells/μL done at least six weeks apart.

There is now convincing evidence from a randomized controlled trial (RCT) conducted in a developing country that patients who start ART when the CD4 is between 200 and 350 cells/μL have improved outcomes compared with those who wait until the CD4 is less than 200 cells/μL to start ART. The CIPRA HT001 study was an open-label RCT conducted in Haiti since 2005. It was terminated by its data and safety monitoring board prematurely earlier this year after 816 patients had been enrolled, because it was apparent that there was a survival advantage to starting with a CD4 count above 200 cells/μL. Among patients who were randomized to start ART only when the CD4 dropped below 200 cells/μL there were 23 deaths and 36 TB diagnoses. Whereas in those randomized to start with a CD4 between 200 and 350 cells/μL, there were 6 deaths and 18 TB episodes.

The question being asked in the HIV community internationally now is: should the CD4 threshold for starting ART be set even higher than 350 cells/μL? The reasons for considering earlier ART is that ART regimens are now more convenient to take, more potent, contain drugs with fewer side effects than previously and that there are more therapeutic options when patients develop resistance, particularly in the industrialized world, where several new classes of ART have been introduced. Earlier therapy may also protect against certain ART drug toxicities (eg. neuropathy), allow better immune recovery and prevent transmission of HIV. It is increasingly recognized that “non-AIDS conditions” such as cardiovascular disease, non-AIDS malignancies and renal disease contribute substantially to morbidity and mortality in HIV-infected people with relatively preserved CD4 counts. It is hypothesized that the chronic inflammatory state that characterizes untreated HIV infection may result in end-organ damage, and this may be ameliorated by earlier ART. Two recently published studies have addressed this issue. Both were retrospective cohort studies.

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WHEN IS THE BEST TIME TO START ANTIRETROVIRAL THERAPY? (*CONT.)*

The *NA ACCORD* study[1, 2] analysed data from 17 517 HIV-infected patients without prior AIDS-defining illness and no ART exposure in North America who entered care between 1996 and 2005. In those who delayed starting ART until their CD4 count dropped below 350 cells/µL, compared with those who started when the CD4 was between 350 and 500 cells/µL, there was a 69% increase in the relative risk of death that was statistically significant. In those who started when their CD4 was lower than 500 cells/µL there was a 94% increase in the relative risk of death, compared with those who started when their CD4 count was above 500 cells/µL. This was also statistically significant.

The When to Start Consortium[3] analysed data from 15 ART cohorts (including 21247 patients prior to ART and 24 444 after staring ART). Patients who started with a CD4 count 251-350 cells/µL had a 28% higher risk of AIDS and death and a 13% higher risk of death, compared with those who started with CD4 351-450 cells/µL. Both these findings were statistically significant.

The data from these two retrospective cohort studies are interesting, but need to be interpreted with a number of caveats:
1) AIDS and death events in patients with high CD4 counts are relatively rare so the absolute risk differences are small. This means that large numbers of patients need to be treated earlier to prevent a single event and that for the individual patient the benefit is relatively small.
2) Cohort studies are always potentially subject to confounding bias. The observed difference in mortality may not be caused by the fact that one group got ART earlier than the other, but rather be due to other factor(s) that were different between the two groups and were not adjusted for in the analysis ("unmeasured confounders"). Possible unmeasured confounders in these studies may have been differences in health-seeking behaviour patterns, adherence to therapy, socio-economic factors or lifestyle factors such as smoking. It is only through a randomized controlled trial that such confounders can be eliminated.
3) The duration of follow-up in these studies was relatively short. In the longer term it may be that the metabolic effects resulting from longer ART exposure in those treated earlier may counterbalance the benefits of earlier ART. For example, protease inhibitors increase the risk of myocardial infarction in a time-dependent manner.[4]
4) Earlier ART may result in more widespread ART resistance on a community level and this was not measured in these studies.

Therefore these two cohort studies do not definitively answer the question of whether the CD4 count threshold for starting ART in asymptomatic HIV patients should be raised. The START study is an RCT designed to answer this question. ART-naïve patients with a CD4 count above 500 cells/µL are being enrolled and randomized to: 1) start ART immediately or 2) defer until CD4 count is < 350 cells/µL or AIDS develops. The composite primary endpoint is AIDS, serious non-AIDS diagnoses and mortality. Projected enrollment is 4000 participants and the study is expected to be completed in 2015.

In the interim, AfA recommends that a CD4 count of 350 cells/µL continues to be used as the threshold for starting asymptomatic patients on ART. However, we will consider earlier ART initiation in patients with CD4 counts higher than 350 cells/µL who have symptoms related to HIV that are not necessarily Stage 4. This includes patients with severe dermatological manifestations of HIV infection and patients with a diagnosis of active TB. In addition we advise starting ART for the HIV-infected partner in a sero-discordant relationship, regardless of their CD4 count, as an HIV prevention strategy to go hand-in-hand with advice about condoms. All patients starting ART should be ready for lifelong therapy and adequately counseled before starting.

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ELECTIVE CAESAREAN SECTIONS AND HIV TRANSMISSION

Elective caearean section (c/s) prior to the onset of labour or rupture of membranes, has played an important role in reducing the risk of vertical transmission of HIV. When zidovudine was the major component of vertical transmission prophylaxis (VTP), elective c/s was associated with an 87% reduction in risk.[1]

Maternal viral load was identified as a key risk factor for HIV transmission.[2] However, transmission has been reported where viral load has been undetectable, but the data are from studies where viral loads were less sensitive. Even with viral loads under a thousand copies, data supports elective c/s. In data prospectively collected in the European collaborative study, among 560 women with undetectable viral loads (only 44% <50 copies), elective c/s was associated with a 93% reduction in risk compared to vaginal or emergency c/s.[3] Since then, as more pregnant women access HAART and more sensitive assays for measuring viral load are available, the role of elective c/s has been questioned.

Townsend has recently reported three transmissions from 2117 deliveries where women had viral loads below 50 copies per ml. Two were in utero and one intra-partum.[4] Based on these data, the current British HIV guidelines now support a trial of labour for women on HAART with viral load below 50 copies per ml.[5] An exception is co-infection with Hepatitis C, a condition seldom encountered in Southern Africa.

Aid for AIDS continues to recommend elective c/s for all HIV infected women, but if the viral load is known to be <50 copies/ml prior to delivery, an individual decision can be made after adequate counseling about the risks and benefits of the procedure.

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GENOTYPING TESTING FOR ANTIRETROVIRAL RESISTANCE

Determining antiretroviral resistance by genotyping has been shown to significantly improve outcomes in a meta-analysis of randomised controlled trials.1 In these trials resistance testing was done on all patients, but in half the patients the next regimen was selected on the basis of the resistance testing and in the other half the regimen was chosen based on expert “best guess”. This was thus a very robust study design. The benefits of resistance testing were that both the rates and the extent of virological suppression of the next regimen were significantly improved. Improved virological outcomes translate into better long term patient outcomes, with lower risk of hospitalisation and death.

Several different resistance assays are available, but the only assay that has been shown to significantly improve outcomes is genotyping and this is also the only assay available in South Africa. Genotype antiretroviral resistance testing is expensive, costing around R4,500. The test methodology is complex and it is unlikely that costs will come down considerably in the medium term. In developed countries it is now recommended to do resistance testing before starting antiretroviral therapy and at each regimen failure. In AfA resistance testing is only offered in selected individuals after failure of second-line therapy, or those failing first-line therapies with prior exposure to dual antiretroviral therapy.

The main argument in favour of doing resistance testing is an economic one. Several recent studies have shown that genotyping resistance tests are cost-effective.2,3 The cost effectiveness of resistance testing is based largely on the projected survival benefit to patients. However, no such study has been conducted in the South African health sector.

GENOTYPING TESTING FOR ANTIRETROVIRAL RESISTANCE *(CONT.)*

In the South African private sector a key argument in favour of resistance testing is that this will result in saving in direct costs of antiretroviral regimens without even considering the survival benefit to patients. The reason for this is that the newer antiretroviral agents that are becoming available for salvage therapy are more expensive than the older agents. For example the new protease inhibitor darunavir is becoming available in South Africa costing about R1,000 more a month the exitsing boosted protease inhibitors (PIs) that we recommend. The available data suggests that the majority of patients failing second line therapy do not have resistant mutations to the PI they are taking (provided this is their first PI exposure), and that the reasons for failure are poor adherence. Therefore the cost of the resistance test will be recovered in less than 6 months in most patients.

Other drugs for salvage that are coming soon (etravirine and raltegravir) are also likely to be considerably more expensive than standard therapy. Therefore the economic argument in favour of resistance testing is strengthening in South Africa.

To ensure that the test is used appropriately, HIV Genotyping is subject to confirmation of good adherence to therapy and pre-authorization by AfA. This has been communicated to all the major pathology laboratories and healthcare providers. Where the test has not been pre-authorized by AfA, the member will be liable for the cost of the investigation.

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USE OF STAVUDINE (D4T) AS PART OF COMBINATION THERAPY

D4T has been removed as a component of recommended first-line therapy in many clinical guidelines (including the Southern African HIV Clinicians Society) and the use of stavudine is also discouraged by the WHO in ART-naïve patients because of its adverse side-effect profile. The role of stavudine in the development of lipoatrophy is well described, together with a high incidence peripheral neuropathy and a risk of symptomatic hyperlactataemia/lactic acidosis.

Aid for AIDS recommends that stavudine should not be included in first-line therapy unless there are no other options available. Tenofovir, which is now widely available in the Southern African private sector, is preferred as it is better tolerated and offers the convenience of once daily dosing.

ANTIBIOTICS TO PREVENT STIs POST SEXUAL ASSAULT

Aid for AIDS (AfA) recommends treating all sexual assault victims with a combination of the following antibiotics to prevent sexually transmitted infections:

Cefpodoxime 200mg stat, Azithromycin 1g stat, Metronidazole 2g stat

Please note that cefixime 400mg stat can be used as an alternative to cefpodoxime. Cefixime is however not currently available in the private sector. If cefixime does become available again we would recommend rather using this agent as there is much better evidence for it.

This treatment will be approved, on request, by AfA together with antiretroviral prophylaxis. All medicines approved by AfA are paid from the HIV benefit and will not deplete the patient's routine medicine or day-to-day benefit.

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