

Consultation draft Addendum to BHIVA Treatment Guidelines

(British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Medicine* 2008; 9: 563–608)

Several pieces of information appeared at CROI 2009, in abstract form, of which the treating HIV physicians should be aware.

When to start

A North American study, NA ACCORD, and a collaboration of cohorts (ART Cohort Collaboration), both examined ways of adjusting for lead-time bias in cohort studies to address the question of when to start.

The NA ACCORD study came to the conclusion that mortality was reduced when starting treatment at about 500 cells/mm³. However, the European data suggested little evidence of a significant improvement in survival if a patient is started above a CD4 count >350 cells/mm³. The two studies differed in their methodology, but the NA ACCORD showed a high mortality in individuals with a CD4 count >500 cells/mm³. Whilst various confounding factors were corrected, the Writing Committee believes that the results of the NA ACCORD study may well be attributable to the socioeconomic group of patients, with potentially poor access to care and greater likelihood of mental health issues in those who were not started on treatment with a CD4 count >500 cells/mm³ and, in contrast, perhaps greater health-seeking behaviour in those who were treated at this level. Thus, we see no reason to change our present advice on individuals with a CD4 count of around 350 cells/mm³ who should seriously be considered for antiretroviral treatment, and for those with a CD4 count above this who need treatment if they have various concomitant diseases. We also note that a randomized trial of immediate versus deferred ART in people with a CD4 count >500 cells/mm³ (Strategic Timing of ART – START) has started, and we encourage recruitment into this trial where appropriate so that a more definitive answer to this important question can be obtained. Whilst awaiting further evidence it is important to contextualize the potential excess risks suggested by ACCORD compared to the European studies. Whereas any excess mortality is important to substantiate and avoid, the actual potential added risks for any individual are small. This possible, yet-to-be-substantiated advantage of therapy with a CD4 count of >500 cells/mm³ needs to be weighed against the potential adverse effects of commencing therapy at an early stage.

What to start with

Various data sets are now available which have been used to examine the association of Abacavir with increased cardiovascular risk. Three of the five cohort studies demonstrate such an association, viz the DAD study, SMART and the ANRS analysis. The two studies which do not are the ACTG and the GlaxoWellcome analysis of Abacavir used in randomized controlled trials (but often as part of the backbone rather than a randomized comparison). Both come from patient groups with relatively low cardiovascular risk. One randomized trial, the STEAL study, in which patients have a higher Framingham score, indicating a higher cardiovascular risk at study entry, had a marginally significant risk for cardiovascular disease

of all sorts in those treated with Abacavir compared with those given Tenofovir. This is in contrast to the largest study, DAD, in which myocardial infarction was the end point. A further randomized controlled trial comparing Tenofovir- and Abacavir-containing regimens, the Bi-combo study, has not shown an increase in cardiovascular risk but this is a small study in individuals with a relatively low Framingham score. The Writing Committee believes that these further analyses strengthen the chance that Abacavir is associated with a cardiovascular risk of unknown cause, although this is likely to be associated with a risk of plaque rupture and or thrombosis in the coronary arteries. The ANRS cohort demonstrated an increased risk only while on Abacavir for the first year of therapy, whilst the DAD study suggests that this risk continues throughout the period of observation and may even increase slightly for each year of follow-up. The Writing Committee believes that the strength of these data is important in deciding when Abacavir should be used as initial therapy. We also believe that patients currently on Abacavir-containing regimens should be carefully reviewed to see whether other options are available. The ANRS data suggest that the absolute risk of continuing therapy once the patients have been on Abacavir for a year may be absent. However both ANRS and DAD suggest that the risk is modifiable, and careful consideration should be given to switching from Abacavir to an alternative.

Again, it is important to put the excess risks of Abacavir into context. The risks attributed to modifiable risk factors such as smoking, hypertension and deranged lipids far outweigh the potential risks of Abacavir use. For any individual the excess risks of Abacavir are small, but of course it is important to address any avoidable risk. This should not be at the expense of addressing the other and more key modifiable risk factors.

It should be appreciated that those individuals with high cardiovascular risk are often the same individuals who may be at an enhanced risk of renal disease, but careful monitoring of the glomerular filtration rate can be undertaken and a switch back to Abacavir is possible for those in whom the GFR deteriorates.

Further data also appeared from the DAD study about the cardiovascular risk associated with a boosted PI. There was a risk with both Fosamprenavir and Lopinavir/Ritonavir which increased year by year. There were not sufficient individuals in the data set to look at the cardiovascular risk with Atazanavir/Ritonavir or with Darunavir/Ritonavir. Again, this reinforces the Writing Committee's overall view that an NNRTI-containing regimen, rather than a boosted PI regimen, should be first-line treatment. Where a boosted PI is required, Ritonavir/Saquinavir is not associated with an increased cardiovascular risk and is also a cheaper option.

Multiply experienced patients and switching for toxicity

The SWITCHMRK studies examined switching from a Lopinavir/Ritonavir-containing regimen in patients who were undetectable to one including Raltegravir. Whilst this improved the lipid profile of the individuals, when the two studies were combined the Raltegravir-containing arm failed to meet the pre-set criteria for virological noninferiority. These results are likely to have been driven by pre-existing resistance in the backbone relating to previous treatment. This reinforces the view that careful attention should be paid to pre-existing resistance when an attempt is made to switch from a boosted PI to Raltegravir for reasons of toxicity, and reinforces the view that, wherever possible, Raltegravir should be used with a backbone containing other active agents in multiply experienced patients.