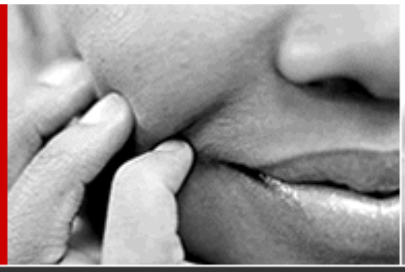

www.aidforaids.co.za

P.O. Box 38597, Pinelands, Cape Town, South Africa, 7430
Email: afa@afadm.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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Efavirenz Dose for Paediatric Patients

Please note that the WHO Dosing Guidelines for Children have amended the efavirenz (EFV) dose for children.

Previous EFV dose for paediatric patients (as per package insert)

Body weight	EFV dose
13 – <15 kg	200 mg od
15 – <20 kg	250 mg od
20 – <25 kg	300 mg od
25 - <32.5 kg	350 mg od
32.5 – <40 kg	400 mg od
≥ 40 kg	600 mg od

New EFV dose recommended for paediatric patients

Body weight	EFV dose
13 – <14 kg	200 mg od
14 – <25 kg	300 mg od
25 – <35 kg	400 mg od
≥ 35 kg	600 mg od

This revised dosing is supported by data reporting relatively low and often sub-therapeutic EFV levels in children receiving the usual label doses. AfA recommends that paediatric patients are dosed according to the new dosing recommendations.

There is an ongoing study looking at dosing for children <3 yrs of age and < 13kg body weight as there are currently no dosing recommendations for these patients.

However, clinicians should be aware that patients (including children) with the TT (homozygous) or GT (heterozygous) genotype of CYP 2B6 may have slower metabolism of EFV, possibly leading to CNS toxicity. (Lowenhaupt et al Clin Infect Dis 2007; 45: e128-30)

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

This newsletter has been edited by:
Dr. Leon Regensberg
Mrs. Colleen Whitelaw

medscheme

Raltegravir: What is the Place of the New Kid on the Block?

Raltegravir has just been launched in South Africa. This is an exciting addition to our antiretroviral armamentarium as it has a novel mechanism of action – inhibition of the HIV integrase enzyme, which is responsible for inserting proviral DNA into the genome of the CD4+ cell. This novel mechanism of action means that there will be no cross-resistance with the other antiretroviral drugs.

Raltegravir was first registered in high-income countries for use in salvage therapy following trials where raltegravir or placebo was added to optimised background therapy in patients with multidrug resistance.[1,2] These trials showed that raltegravir was highly effective, provided that it was used in conjunction with other agents to which the patient's HIV was susceptible. This is a key point in using raltegravir – it has a relatively low genetic barrier to resistance. Raltegravir was very well tolerated; adverse events thought to be drug-related occurred in similar proportions in the raltegravir and placebo arms.

Subsequently raltegravir was compared with efavirenz (both given with tenofovir and emtricitabine) in patients who were naïve to antiretroviral therapy (ART). There were no significant differences in patients achieving virologic suppression at 48 and 96 weeks.[3,4] The viral load became undetectable more rapidly in the raltegravir arm, but there were no discernible clinical benefits of this more rapid virologic response. Raltegravir was well tolerated. The proportion of patients with severe drug-related adverse events was low and similar in the efavirenz and raltegravir arms. However, there were more drug-related adverse events overall in the efavirenz arm. Rates of hepatitis were similar in the two arms. Rates of headache and insomnia were similar in the two arms, but dizziness occurred more commonly in the efavirenz arm. Rashes only occurred in the efavirenz arm. Total cholesterol was higher in patients on efavirenz, but the more clinically relevant ratio of total cholesterol to HDL cholesterol was similar in the two arms. In the 96 week follow up study there was no difference in fat gain between the two arms on DEXA scans.

Raltegravir is relatively free of drug-drug interactions. Rifampicin induces its metabolism and a pharmacokinetic study in healthy volunteers showed that doubling the dose of raltegravir is able to overcome this induction. A clinical trial is underway to assess the efficacy of this dose in HIV-infected patients with tuberculosis.

The current International AIDS Society-USA antiretroviral therapy guidelines recommend raltegravir as one of their preferred options for initial therapy, along with efavirenz, and boosted darunavir and atazanavir – all given together with two nucleoside reverse transcriptase inhibitors.[5] AfA continues to recommend either efavirenz or nevirapine in first line regimens for several reasons. Firstly, compatibility with state guidelines is important as patients often get treated sequentially in public and private sectors. Secondly, raltegravir is not superior to efavirenz. Thirdly, raltegravir is considerably more expensive. Finally, there is limited long term safety experience with raltegravir.

AfA recommends raltegravir in salvage therapy. Approval of raltegravir requires a genotype resistance test to ensure that there is enough antiretroviral activity of the companion drugs. AfA will consider the use of raltegravir in first- or second-line regimens when patients are intolerant to multiple antiretroviral drugs.

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When is the Optimal Time to Start ART in Patients with TB? Recent Findings.

In many patients with HIV infection in South Africa the HIV diagnosis is only made after they present to the health care services with active TB and a low CD4 count. The first priority in such patients is to diagnose and treat the TB. The question then is when to start ART. Because of the complexities of ART initiation in patients with TB (e.g. IRIS, shared drug toxicities, drug interactions and pill burden) many clinicians choose to defer ART. However, in patients with low CD4 counts this means that patients remain at high risk of HIV disease progression with associated mortality. To answer the question of when the optimal time to start ART in such patients is, a number of recent randomized strategy trials have compared different timing of ART initiation during TB treatment. These studies are discussed here followed by recommendations based on this evidence.

The CAMELIA study[1] conducted in Cambodia among patients with smear positive TB and CD4 $\leq$ 200 cells/microlitre compared starting ART 2 weeks versus 8 weeks after starting TB treatment. Patients in this trial had very advanced HIV with median CD4 = 25 cells/microlitre and BMI = 17. There was a 34% reduction in mortality in those who started at 2 weeks.

The ACTG 5221 STRIDE study[2] was a multi-country study that enrolled patients with confirmed or suspected TB and had a CD < 250 cells/microlitre . ART was started 2 weeks after TB treatment in the one arm and 8-12 weeks in the other. There was no difference in the combined endpoint of AIDS progression and death between the two arms. However, in a subanalysis of only those with CD4 $\leq$ 50 cells/microlitre AIDS progression and death was reduced by 42% among those who started at 2 weeks.

Similar findings were demonstrated in the SAPiT study[3] conducted in Durban. This study enrolled patients with smear-positive PTB and CD4 < 500 cells/microlitre. The most recent report from this study, presented at the 18th Conference on Retroviruses and Opportunistic Infections, compared outcomes in the two integrated arms of the study: one arm started ART within 4 weeks of starting TB treatment and the other within 4 weeks of the completion of intensive phase of TB treatment. There was no difference in the combined endpoint of AIDS progression or death comparing the two arms, but again in a subanalysis of those with CD4 < 50 cells/microlitre, earlier ART (at a median of 8 days) reduced AIDS progression or death by 68% (marginally significant, p=0.06).

In all three of these studies, the incidence of paradoxical TB-IRIS was approximately 2 to 3 fold higher among those starting ART in the earlier arm. Despite this, however, in patients with CD4 < 50 these studies demonstrated that the survival benefit of earlier ART outweighs the potential risk that earlier ART may cause excess TB-IRIS related deaths.

Finally, in a study of ART timing in patients with TB meningitis conducted in Vietnam[4] there was no difference in survival among patients starting ART immediately or deferring 2 months. Mortality at 9 months was around 60% in both arms. Patients in this study were treated with adjunctive high dose dexamethasone for the first 6-8 weeks of TB treatment. Grade 4 adverse events were encountered more frequently by patients who started immediately.

In conclusion, these studies demonstrate that TB patients with a CD4 < 50 cells/microlitre benefit from starting ART within 2 weeks of starting TB treatment with one study showing this reduced mortality and two demonstrating a reduction in AIDS progression/death among these patients. These patients (with CD4 < 50 cells/microlitre) should be prioritised for rapid medical work-up and counseling to allow them to start ART within 2 weeks of TB treatment. In patients with a CD4 close to 50 cells/microlitre or those with other stage 4 defining illnesses it may also be prudent to start after 2 weeks of TB treatment. Among those with higher CD4 counts deferring ART up to 2 months may reduce the risk of TB-IRIS without compromising outcome. In TB meningitis mortality is extremely high and unaffected by the exact timing of ART within the first 2 months of TB treatment and deferring ART a few weeks may reduce the risk of severe adverse events.

References

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African RCT of Influenza Vaccination in HIV Shows Benefit and Safety

It's that time of year again, when HIV-infected clients are counseled to have the influenza vaccination. Until the publication of a recent double blind, randomized controlled trial of trivalent influenza vaccine against placebo carried out by Madhi and colleagues in Johannesburg[1], the evidence for benefit from influenza vaccination came mainly from case reports documenting increased influenza complications and longer illness duration.

Madhi's study of 506 HIV-infected adults seen in Themba Lethu Clinic, Johannesburg, randomized patients to receive trivalent influenza vaccine containing H1N1, H3N2 and Influenza B strains, or a placebo control. Patients were either ART-naïve with CD4 count >100 cells/mm^3 or established on ART for >3 months. Overall efficacy of the trivalent vaccine against confirmed influenza illness was 75.5%, albeit with wide confidence limits, and seroconversion rates for H1N1, H3N2 and Influenza B was 52.6%, 60.8% and 53.6% respectively. There was no difference between frequency of adverse events in the study and placebo groups, with injection-site tenderness being the commonest finding. Interpretation of safety of the vaccine was limited to relatively healthy HIV-infected patients, as advanced HIV and patients with multiple co-morbidities were under-represented.

However, these results are important in demonstrating safety of influenza vaccination in HIV-infected patients with good efficacy. Seasonal and pandemic influenza is associated with increased hospital admission rates and secondary bacterial infections in HIV-infected patients and despite ART, the risk of severe influenza still outweighs that for the general population. Hence, all clients living with HIV should be offered influenza vaccination. The priority for clients with advanced HIV and/or CD4 counts of <100 cells/mm^3 should be to start ART in order to allow immune reconstitution. However, influenza vaccination is not contraindicated for clients with low CD4 counts and although the antibody response may not be optimal, high risk clients such as pregnant women with HIV or HIV-infected patients with chronic lung disease should be vaccinated.

Influenza vaccination should be performed annually as antibody titres wane over the 12 month period, reducing protection.

References

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Pathology Results

Please remember to mark you pathology request forms "copy to AfA". If this is done,

1. The lab will forward the result to AfA electonically (provided that the patient is registered on the AfA programme).
2. You do not have to fax the result to AfA.
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4. This will enable us to assist you in monitoring your patients.

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