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Statement on the use of Efavirenz in children less than 3 years of age

On 02 May 2013, the US Food and Drug Administration (FDA) expanded the indication for efavirenz (EFV) to include paediatric patients at least three months old and weighing at least 3.5 kg. Historically efavirenz has not been used in children < 3 years of age or < 10kg because the correct dosing was uncertain. Now that there is a dosage for efavirenz in young children, there are two major concerns about using EFV routinely in children < 3 years and < 10 kg namely, efficacy and toxicity.

1) Efficacy

The study IMPAACT p1060, done in young children under 3 years with no single dose nevirapine (SD-NVP) exposure, showed double the failure rate in those treated with a NNRTI (NVP) regimen compared to a PI regimen (lopinavir/ritonavir (LPV/r))¹. This study supports South Africa's use of a LPV/r regimen in children under 3 years of age. The use of daily NVP for PMTCT will exacerbate this effect even further. We do not know if this is a class effect (NNRTI) or a drug effect (NVP), and until we have a head to head study comparing EFV with LPV/r in the under 3 years group, we cannot take a chance that the efficacy of EFV in young children will be similar to that of NVP. Therefore we should continue to use LPV/r regimens in children younger than 3 years or < 10kg.

2) Toxicity

EFV is usually dosed according to weight bands using capsules or tablets (50mg and 200mg). In general, young children often have increased metabolism of drugs compared to older children and adults and therefore require higher doses in order to maintain therapeutic plasma drug concentrations similar to adults. In the case of EFV, it has been found that some children (and adults) are genetically slow metabolisers of EFV and higher doses may result in toxicity while others are genetically fast metabolisers of EFV and require higher doses than usual to maintain therapeutic plasma levels of EFV. Carriage of the gene associated with slow EFV metabolism has been found to be relatively common amongst African adults (36-60%). Children who inherit this gene from both parents will be slow metabolisers of EFV and are at risk of EFV toxicity with the higher doses that have been recommended for younger children (<3 years and <10kg)^{2,3}. Genetic analysis to predict whether children are slow or fast EFV metabolisers is not available outside of

research studies. Routine therapeutic drug monitoring to assess plasma levels of EFV and adjust EFV doses accordingly is also not widely available.

For these reasons, the Child and Adolescent committee of the Southern African HIV Clinicians Society recommend that EFV not be routinely given to children less than 3 years of age or whose mass is less than 10kg.

References

- ¹ Violari A, Lindsey JC, Hughes MD et al Nevirapine versus Ritonavir-Boosted Lopinavir for HIV-Infected Children. N Engl J Med 2012;366:2380-9.
- ² Bolton C, Samson P, Capparelli E et al. Strong influence of CYP2B6 genotypic polymorphisms on EFV pharmacokinetics in HIV+ children <3 years of age and implications for dosing. 19th Conference of Retroviruses and Opportunistic Infections, 5–8 March 2012, Seattle. Poster abstract 981.
- ³ Siccardi et al. Pharmacokinetics of efavirenz dose optimisation in paediatric patients using an *in vitro*–*in vivo* extrapolation Model. 19th Conference of Retroviruses and Opportunistic Infections, 5–8 March 2012, Seattle. Poster abstract 619.

