Reviewer's report

Title: PXR and CAR single nucleotide polymorphisms influence plasma efavirenz levels in South African HIV/AIDS patients

Version: 1 Date: 20 August 2012

Reviewer: Eleni E Aklillu

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The study is comprehensive that involved NR1I2 and NR1I3 genotype and haplotype analysis in two different study populations (HIV infected patients and healthy subjects), determination of genotype effect on efavirenz plasma level and treatment change as well as search of novel SNPs. The authors investigated influence of genetic variation in NR1I2 and NR1I3, coding for PXR and CAR, on efavirenz plasma level in HIV/AIDS patients from South Africa. Genotyping for 6 SNPs in 301 HIV/AIDS patients and 163 healthy controls were done. Efavirenz plasma concentration was determined in 156 patients. The authors found significantly decreased efavirenz plasma concentrations in patients carrying the NR1I3 rs3003596C/C genotype. The authors also evaluated association of the genotypes with likelihood of changing of treatment regimens at 3, 6 and 12 months. DNA binding domains in NR1I2 and NR1I3 were also sequenced in 32 subjects and 3 novel SNPs were identified.

The manuscript is well written. The results were clearly presented in table, illustrated in figures and discussed very well.

Most previous efavirenz pharmacogenetic studies focused on genes coding for drug metabolism/transporter, mainly CYP2B6, UGT2B7 and ABCB1. Implication of genetic variation in NR1I2 and NR1I3 in influencing efavirenz disposition among HIV patients is not well investigated particularly in African population, where HIV/AIDS is a major problem and ART being widely used. This manuscript is very interesting and adds relevant new insight in this area and pharmacogenetic diversity of African population.

Discretionary Revisions: Use the term “healthy subjects” instead of “healthy controls”. The study is not a case-control study.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.