PA-069 CYP2B6 GENOTYPE BASED EFAVIRENZ DOSE RECOMMENDATIONS DURING RIFAMPICIN-BASED ANTITUBERCULOSIS CO-TREATMENT FOR A SUB-SAHARAN AFRICA POPULATION

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10.1136/bmjgh-2016-000260.102

Background Pharmacogenetics is a major determinant of the EFV–rifampicin interaction during HIV-TB co-treatment. We assessed genetic factors that influence EFV PK, treatment outcomes and provide genotype-based EFV dose recommendations for adult TB-HIV-1 co-infected Ugandans receiving rifampicin based anti-tuberculosis co-treatment.

Methods Steady state plasma EFV concentrations (n=1216) from 158 HIV-TB co-infected patients (76 females) treated with efavirenz/lamivudine/zidovidine and rifampicin-based TB treatment were analysed. Patient genotypes for *CYP2B6* (**6* & **11*), *CYP3A5* (**3*,**6* & **7*) and *ABCB1c.4046A>G*, baseline biochemistries and CD4 and viral load change from baseline were determined. A one-compartment population PK model with first-order absorption (NONMEMTM) was used to estimate genotype effects on EFV PK. Population genotype-frequency-based PK simulations predicted AUCs and trough concentrations were compared between the product label / known reference values and different dose simulations.

Results Compared to *CYP2B6*1/*1*, EFV post-induction CL/F was 2.5 and 1.7 times higher in *CYP2B6*6/*6* and *CYP2B6*1*/6*, respectively. A 23% increase in F1 was observed for the variant ABCB1 c.4046A>G. EFV mean AUC was significantly higher in *CYP2B6*6/*6* genotypes compared to *CYP2B6*1/*1* ($p < 0.0001$). Simulated AUCs for a 600 mg EFV dose were 1.2 and 2.4 times greater than the product label mean AUC for the Ugandan population in general and *CYP2B6*6/*6* genotypes, respectively. EFV daily doses of 450 mg and 250 mg for the general population and *CYP2B6*6/*6* genotypes respectively yielded simulated exposures that were comparable to the product label. Overall, only 8.9% patients had HIV RNA >40 copies/mL after 84 days of treatment.

Conclusions During rifampicin co-treatment, daily doses of 450 mg and 250 mg might meet the EFV dosing needs of HIV-TB infected Ugandans in general and CYP2B6*6 homozygous variants, respectively.