PHARMACOGENETICS OF EFV & NVP BASED COMBINATION THERAPY AND POSSIBLE ASSOCIATED RISK OF SELECTING FOR HIV DRUG RESISTANCE MUTATION IN BOTSWANA

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Background

The burden of HIV in resource-limited countries has been lessened by the increased access to HAART. Affordable NNRTI's (i.e. Efavirenz & Nevirapine) combination based anti-retroviral therapy is the most used as a standard treatment in Botswana and the region. However, response to these drugs is often perturbed by the occurrence of suboptimal virology responses, drug toxicity, poor adherence and or emergence of drug resistance. Cytochrome P450 enzymes in the liver, in particular CYP2B6, metabolize NNRTI's. The inter-individual genetic variation of CYP2B6 gene influencing metabolism of NNRTIs has been found to be the cofactor in the selection of HIV drug resistance. Associations between *CYP2B6* polymorphisms and variable drug metabolism have been described, with a clear establishment of genotype-phenotype correlation. The metabolic phenotypes are categorized as ultra-rapid (UR), extensive, intermediate and poor metabolizers (PM). Intermediate and PM phenotypes can be associated with increased frequency of side effects linked to high plasma drug concentration, determining poor adherence and possible increased frequency of viral resistance. Conversely, UR metabolizers cannot achieve an effective inhibitory drug concentration exposing HIV to sub-therapeutic drug dosage with a potential increase of the window of selection for viral resistance. Here, we aim to test the hypothesis that human genetic variation is a co-factor in the selection of HIV drug resistance. Thus, we will evaluate genetic variation at *CYP2B6* gene (516G>T, 983T>C, PM alleles, and 785A>G, -82T>C, UR alleles, and their haplotype composition) on the risk to carry NNRTI HIV resistant mutations (K103N, V106M, Y181C and V108I) in samples from Botswana analyzed retrospectively.

Methods

This is a case controlled study with a population of 246 samples drawn from a larger study that had 649 participants. 41 cases and 205 matched controls. Sample size calculation (80% power)=41vs205: hypothesizing 7% of rapid metabolizers in controls and 20% in cases.

DNA extraction will be performed using QIAamp kit automatic platform according to manufacturer's instructions. The SNP genotyping will be performed using TaqMan Drug Metabolism genotyping Assays and PCR-RFLP method. An adopted new in-house PCR-RFLP protocol for analysis of SNPs 785A>G and -82T>C will be used. TaqMan Drug Metabolism genotyping assay will be used for SNPs 983T>C and 516G>T.

Results

The frequency of the 4 different SNPs will be determined and comparison between the *CYP2B6* status of the subjects without HIV resistant mutations and the *CYP2B6* status of subjects with HIV resistant mutations will be done. Arlequin v3.5 (Excoffier and Lischer.,2010) and Hardy Weinberg Equilibrium calculations will be used to test for the Linkage Disequilibrium between the four loci and haplotype reconstruction.

Conditional Logistic Regression Analysis will be applied to test the possible association between CYP2B6 genetic background and the dichotomous variable NNRT-sensitive/NNRTI-resistant HIV infections.

References:

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