ABCB1 Polymorphism Affects Tenofovir Exposure as Determined by Areas-Under-the-Time-Concentration-Curve with 24-hour Intensive Pharmacokinetic Monitoring

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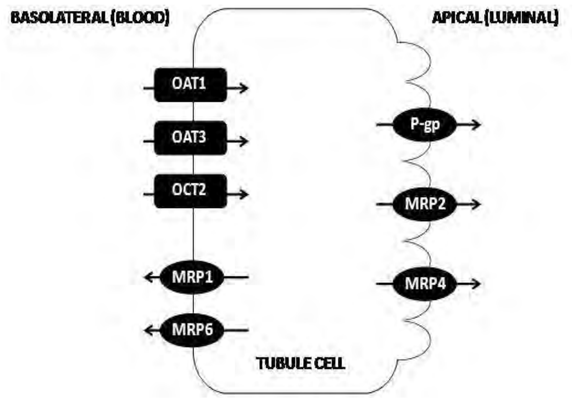
BACKGROUND

- Tenofovir disoproxil fumarate (TDF) is a commonly used antiretroviral in HIV treatment and prevention.
- Genetic factors play an essential role in the pharmacokinetic (PK) parameters of drug absorption, distribution, metabolism and excretion (ADME).
- The genetic factors that underlie TFV PK are poorly understood with evaluation of only a few single nucleotide polymorphisms (SNPs) or small numbers of patients.
- Studies evaluating pharmacogenomics under conditions of typical use and in minorities and women are rare, limiting generalizability.
- A comprehensive understanding of the genetic factors that contribute to tenofovir PK are warranted.
- We undertook intensive 24 hour PK sample collection and extensive SNP screening to evaluate the genetic factors associated with TDF exposure in a real-world prospective cohort of women living with HIV.

MATERIALS AND METHODS

- **Study population:** The Women's Interagency HIV Study (WIHS) is a multicenter, prospective cohort of HIV-infected women and at-risk HIV uninfected women in the US; this substudy included 105 women on TDF for at least six months who underwent 24 hour intensive PK sampling.
- **Intensive PK protocol methods:** Plasma drawn over 24 hours for TFV concentration under conditions of real use at 0, 4, 8, 15, 18 and 24 hours after witnessed dose of 300 mg of TDF orally.
- **Laboratory procedures:** Plasma levels of TFV were determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS) validated from 10 to 1000 ng/mL of TFV.
- **Covariates:** age, race, body mass index (kg/m^2), baseline kidney function (eGFRcr) and ritonavir use (yes/no).
- **Genetic factors:** SNPs with an allele frequency of >0.05 (n=88) were screened in 3 genes identified as important in TFV PK by literature review: ATP-binding cassette (**ABC**) **B1** (also known as P-glycoprotein 1 (P-gp)), **ABCC2** (also known as multidrug resistance-associated protein 2 (MRP2)), and organic anion transporter 1 (**OAT1**).

Figure 1. Transporter proteins possibly involved in tenofovir PK.



- **Outcome**: using the trapezoidal rule, Areas-under-the-time-concentration-curves (AUCs) used to estimate TFV exposure over the 24-hour dosing interval and calculated for each individual.
- **Statistical analysis:** **Multivariate linear regression** models assessed the relationship between genetic and non-genetic factors and TFV AUC (each SNP evaluated as a single addition to an existing model with non-genetic factors).

RESULTS

- Representative sample of women in the US living with HIV, with a high proportion of racial/ethnic minorities (61.3% African-American, 24.7% Hispanic) (**Table 1**).
- None of 88 SNPs met our a priori p<0.001 threshold for association with TFV AUC in multivariate modeling, but rs4728707 in ABCB1 (CC versus CA; 8.1% allele frequency, no AA) had the smallest p-value (1.29 fold effect, 95% CI 1.02-1.63; p=0.03) (**Table 2**).
- Increasing age, decreasing BMI, current use of ritonavir and lower eGFRcr were all associated with higher log TFV AUC (**Table 2**).

Table 1. Baseline characteristics of study participants (n=93).

Characteristic	Value
Natural log transformed TFV AUC, mean ± SD	2.39 ± 0.479
Natural log transformed TFV AUC, median (min, max)	2.41 (1.23, 3.44)
Age in years, median (min, max)	44.2 (22.9, 64.9)
BMI, median (min, max)	27 (15-62)
Race, n (%)	
African American	57 (61.3)
Hispanic	23 (24.7)
White	10 (10.8)
Other	3 (3.2)
Ritonavir use, n (%)	56 (60.2)
eGFRcr (ml/min/1·73m^2), median (min, max)	92.6 (6.9, 156.0)
eGFRcr < 70 ml/min/1·73m^2, n (%)	9 (9.7)
Viral load (copies/mL), median (min, max)	80 (80, 1400000)
CD4 cell count (cells/µL), median (min, max)	360 (4, 1460)
CD4 cell nadir (cells/µL), median (min, max)	199 (0, 551)
Diabetes mellitus, n (%)	23 (24.7)
Frequency of rs4728707 SNP, n (%)	15 (16.1)

Table 2. Multivariate model assessing factors associated with TFV AUC (n=93).

Factor	Effect on log TFV AUC (±95% CI)	p-value
Age (per 10 years)	1.16 (1.05, 1.29)	0.006
BMI (per 10 percent increase)	0.96 (0.93, 0.99)	0.01
Ritonavir use vs not	1.26 (1.06, 1.49)	0.01
African-American vs other	1.04 (0.87, 1.25)	0.67
eGFRcr < 70 vs ≥ 70	1.38 (1.00, 1.91)	0.05
rs4728707 in ABCB1 (CC versus CA)	1.29 (1.02, 1.63)	0.03

DISCUSSION

- Rs4728707 (SNP in ABCB1) demonstrated a large, 29% fold increase of TFV AUC, indicating an association with TFV metabolism.
- rs4728707 is intronic and may be in linkage disequilibrium with a functional SNP(s).
- Further study will be required to understand the relationship of these SNPs with proteins generally involved in ADME for TDF.
- Study currently underway evaluating the association of 27 literature driven SNPs from genes possibly involved in TDF ADME and TFV AUC, as well as genes from proteins known to be associated with them.

CONCLUSION

- This study was the largest assessment of SNPs on TFV exposure (as assessed by TFV AUCs) in a relatively representative cohort.
- Of 88 SNPs from three genes associated with TFV exposure, none were strongly associated with TFV AUC as assessed by an *a priori* p<0.001 threshold in multivariate models.
- rs4728707 in ABCB1 (CC vs CA) demonstrated an estimated 29% increase in tenofovir AUC in 24 hour PK monitoring.
- In multivariate models, increasing age, decreasing BMI, current use of ritonavir and lower eGFRcr were also associated with TFV AUC.
- Further study is indicated to better understand the genetic factors that contribute to higher tenofovir exposure, which is likely to be linked with outcome and toxicities.

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