group). Serial PK for plasma CAB concentrations were collected through 168 hours post dose and unbound CAB concentrations determined at 2 and 24 hours post dose. Non-compartmental PK analysis was performed; geometric least squares (GLS) mean ratios and 90% confidence intervals (CI) were generated.

Results. Sixteen subjects completed study; 12 (75%) male, mean age 54 years (range:35–69), mean BMI 28 kg/m^2 (range: 24–35), and mean CLcr 22 mL/minute (range: 17–29) and 121 mL/minute (range: 95–162) for renal impaired and healthy subjects, respectively. CAB PK parameters were similar between severe renal impairment and healthy subjects. Based on preliminary PK, GLS mean ratios (90% CI) for AUC(0-¥), Cmax, C24, CL/F, and t1/2 were 0.97 (0.835, 1.14), 1.01 (0.865, 1.17), 1.02 (0.868, 1.20), 1.03 (0.881, 1.20) and 0.93 (0.831, 1.04), respectively. Although highly protein bound, the unbound fraction was higher in subjects with severe renal impairment with GLS mean ratio (90%CI) of 1.31 (0.843, 2.03) at 2 hours and 1.51 (1.19, 1.92) at 24 hours post dose. One renal impairment subject developed grade 3 lipase elevation considered drug-related by investigator, otherwise all reported adverse events (AE) were Grade 1 in severity with no serious AEs reported.

Conclusion. Plasma CAB exposures in subjects with severe renal impairment were similar to healthy subjects; therefore, no dose adjustment of CAB is required in renal impairment. Although no data are available, CAB PK is not expected to be affected in subjects undergoing dialysis given CAB's non-renal clearance and high plasma protein binding (~99%).

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1390. Pharmacokinetics of Temsavir, the Active Moiety of the Prodrug Fostemsavir, in Subjects with Hepatic Impairment

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Background. Fostemsavir (FTR) is a prodrug of temsavir (TMR), a first-in-class attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into host CD4+ T cells. TMR is primarily metabolized via hydrolytic and oxidative pathways; impaired hepatic function may alter TMR pharmacokinetics (PK).

Methods. AI438053 (NCT02467335) was an open-label, nonrandomized study in healthy subjects (HS) and subjects with hepatic impairment (HI), defined by Child-Pugh (CP) score: mild (CPA), moderate (CPB), or severe (CPC). HS were matched for age, body weight, and sex. Subjects received a single oral dose of FTR 600 mg fasted and serial PK samples for TMR were collected up to 96 hours post-dose. Unbound TMR at 1 and 3 hours post-dose was determined. Total and unbound PK parameters were derived by noncompartmental methods. Geometric mean ratios (GMR) and 90% confidence intervals (CI) for HI vs.. HS were derived using linear mixed-effects models. Subjects were monitored for adverse events (AEs).

Results. 18 subjects with HI (N = 6/CP group) and 12 HS received FTR and completed the study. Total and unbound TMR exposures increased with increasing HI severity (see Table). Total and unbound TMR CLT/F decreased with increasing HI severity. Mean % protein binding of TMR was 81.0% in HS and 79.9%, 81.9%, and 76.5% in CPA, CPB, and CPC HI, respectively, and was independent of TMR concentration. There were no deaths, serious AEs, or discontinuations during the treatment period.

Table: TMR PK in HI and HS

TMR PK in HI vs HS [GMR(90% CI)]				
Total TMR	Cmax		AUC(0-T)	
CPA	1.34 (1.00–1.79)		1.18 (0.81–1.72)	
CPB	1.48 (1.11–1.97)		1.58 (1.08–2.29)	
CPC	1.72 (1.29–2.30)		1.74 (1.20–2.54)	
Unbound TMR	Cmaxu		AUC(0-T)u	
CPA	1.46 (1.05–2.04)		1.29 (0.83–2.00)	
CPB	1.42 (1.02–1.97)		1.51 (0.98–2.34)	
CPC	2.15 (1.55–3.00)		2.18 (1.41–3.39)	
TMR CLT/F in HS and HI [geometric mean (%CV)]				
HI Severity	HS	CPA	CPB	CPC
CLT/F (L/hours)	61.8 (30)	51.7 (60)	38.1 (43)	35.8 (33)
CLT/Fu (L/hours)	339 (42)	259 (58)	218 (54)	157 (31)

Conclusion. TMR exposures increase with increasing severity of HI. The increase in TMR exposures in patients with mild or moderate HI is not expected to alter the safety profile of FTR. The risk/benefit of higher TMR exposures in severe HI is under evaluation.

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1391. Efavirenz-metabolizing polymorphisms, viral suppression, and depression in HIV-infected individuals initiating antiretroviral therapy in southwestern Uganda

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Background. Single-nucleotide polymorphisms (SNPs) in *CYP2B6* have previously been associated with a 10-fold range in trough plasma efavirenz concentrations, but associations between these SNPs and efavirenz (EFV)-mediated viral suppression and tolerability remain unclear.

Methods. We evaluated three SNPs in *CYP2B6* (rs3745274, rs28399499, and rs4803419, Illumina OmniExpress) among HIV-infected Ugandans observed in a cohort study every 3–4 months from 2005–2015. Genotypes from these SNPs were used to group participants into previously described pharmacokinetic strata: extensive (EXT), intermediate (INT), and slow metabolizers (Figure 1). The primary outcomes were viral suppression, defined by an undetectable viral load in the first measurement a minimum of three months after ART initiation, and incident depression in the first two years, defined by a mean score >1.75 on the Hopkins Symptom Checklist. We fitted standard and generalized estimating equations (GEE) logistic regression models for viral suppression and depression, respectively. Models were adjusted for clinical and demographic covariates that reached a significance of $P <$ 0.25 in unadjusted models.

Results. Among 103 participants with genotyping, there were no differences in pre-ART viral load or depression by metabolism strata ($P > 0.5$). Minor allele frequencies for rs3745274, rs28399499, and rs4803419 were 33%, 7%, and 4%, respectively. Approximately 79%, 78%, and 94% of participants were suppressed at their first viral load measurement in the extensive, intermediate, and slow metabolizer strata, respectively (Figure 2; $P = 0.35$). In adjusted models, metabolism strata were not associated with viral suppression (AOR_{INT} 0.81, 95% CI 0.26–2.56; AOR_{SLOW} 3.92, 95% CI 0.39–39.40) or with depression (AOR_{INT} 1.95, 95% CI 0.75–5.09; AOR_{SLOW} 0.72, 95% CI 0.17–3.02; Table).

Conclusion. We did not identify an association between efavirenz-metabolizing polymorphisms and viral suppression or depression in a cohort of HIV-infected individuals initiating ART in southwestern Uganda. Future work should reassess these relationships with larger samples and longer-term outcomes and explore additional polymorphisms that may be associated with efavirenz metabolism in this population.

Figure 1.