1386. Lack of Clinically Relevant Effect of Bictegravir (BIC, B) on Metformin (MET) Pharmacokinetics (PK) and Pharmacodynamics (PD)

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Background. BIC is a novel integrase inhibitor coformulated with emtricitabine (F) and tenofovir alafenamide (TAF) for treatment of HIV. MET is first-line therapy in diabetic HIV patients. *In vitro*, BIC inhibits renal transporters OCT2 and MATE1, which affect MET disposition. This study evaluated the effect of BIC on the PK and PD of MET following coadministration with the B/F/TAF.

Methods. This was a Phase 1, blinded, placebo-controlled, crossover study in 32 healthy subjects randomized 1:1 to either B/F/TAF or placebo QD for 9 days followed by a 3-day washout. Following 4 days of B/F/TAF or placebo, subjects received 850 mg MET at 12 hours postdose of B/F/TAF or placebo, and 500 mg BID for 4 additional days. Plasma and urine PK of MET were assessed on the last treatment day (Days 9 and 21 for B/F/TAF or placebo). Oral glucose tolerance test was performed before (Days 5 and 17) and after MET (Days 9 and 21). MET PD endpoints including plasma glucose, active Glucagon-Like Peptide 1 (GLP-1) and lactate were assessed after glucose intake. Geometric mean ratios (GMR) and 90% confidence intervals (CIs) for MET PK were calculated for B/F/TAF vs. placebo. Comparisons of PD responses within treatments (before vs. after MET) and comparisons between treatments (B/F/TAF vs. placebo) were done via nonparametric Wilcoxon signed-rank test ($P > 0.05$ denotes non-significance).

Results. MET plasma AUC_{tau} was increased 39% (%GMR [90% CI]: 139 [131, 148]) with B/F/TAF vs. placebo, with no change in median plasma $t_{1/2}$ (B/F/TAF: 6.4 hours; placebo: 7.1 hours). MET renal clearance decreased 31% with B/F/TAF vs. placebo. Following MET administration, statistically significant reduction of plasma glucose, and increase of plasma active GLP-1 and lactate levels relative to baseline were observed ($P < 0.001$) confirming their utility as PD endpoints. Importantly, PD responses were not statistically different when MET was administered with B/F/TAF vs. placebo ($p > 0.05$).

Conclusion. Inhibition of renal transporters OCT2/MATE1 by BIC led to a modest increase of MET plasma exposure upon coadministration with B/F/TAF; however, the PD characteristics of MET were not significantly affected by B/F/TAF relative to placebo. Based on these findings, prospective dose adjustment/restriction of MET is not required upon coadministration with B/F/TAF.

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1387. Impact of Tablet Burden and Antiretroviral Therapy (ART) Choice on Virologic Outcomes in Treatment Naive HIV+ Individuals Attending an Inner City Clinic

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Background. The durability and effectiveness of single tablet regimens (STR) in treating ART naïve patients in real world, inner city settings, has not been well established.

Methods. Data was abstracted from administrative/medical records at Henry Ford Health System, serving metropolitan Detroit, for HIV+ patients initiating ART (1/1/2007–9/30/2015), who were enrolled in the Health Alliance Plan (HAP) or had ≥1 clinician contact per year and ≥1 viral load (VL)/CD4 test result ≤90 days prior to ART initiation. Patients were followed from initiation to first of: change in ART, death, HAP disenrollment, study end (03/31/2016), or lost to follow-up. Cox regression estimated impact of tablet burden on ART regimen duration, achievement of viral suppression (VS) and viral failure—(VF) failure to suppress plasma HIV RNA to <50 copies/mL or rebound after VS.

Results. Among 390 eligible patients, 79% were male, 74% African-American. Median (IQR) age was 37 years (27–47), 49% MSM and 22% presented with AIDS. The majority (65%) initiated on an STR; 35% on multiple tablet regimens (MTR). The majority of STR initiators (63%) began with EFV/FTC/TDF; 24% with EVG/c/FTC/TDF; and 8% with DTG/ABC/3TC. The most frequent MTR were DRV+RTV+TDF/FTC (26%) and ATV+RTV+TDF/FTC (20%). Median (IQR) log10 VL at baseline was 4.8 (4.3–5.2) in STR; 4.8 (4.4–5.4) in MTR cohorts. Median CD4 cells/μL (IQR) was 277 (115–407) in STR; 231 (37–371) in MTR.

VL suppression occurred in 81% (85% STR, 74% MTR, $P < 0.01$) of patients and in 91% of INSTI regimens (91% STR, 90% MTR, $P = 0.757$).VF occurred in 19% (15% STR, 25% MTR, $P = 0.015$) and in 10% of INSTI regimens (9% STR, 13% MTR, $P = 0.459$). Resistance occurred in 15% of VF patients, predominantly with NNRTI mutations. A total of 22% of STR and 60% of MTR initiators experienced a change in their initial ART regimen ($P < 0.0001$). Cox model results suggest STR initiators were 59% less likely to experience regimen change ($P < 0.0001$), 46% less likely to experience VF ($P < 0.05$) and 30% more likely to achieve viral suppression ($P < 0.05$) compared with MTR initiators.

Conclusion. Inner city, HIV treatment naïve patients, initiating ART with a STR are significantly more likely to achieve viral suppression and less likely to experience a change in ART regimen.

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1388. Pharmacokinetics of Cabotegravir in Subjects with Moderate Hepatic Impairment

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Background. Cabotegravir (CAB) is an integrase inhibitor in phase 3 clinical trials for the treatment and prevention of HIV. CAB undergoes hepatic metabolism primarily via UGT1A1; thus hepatic impairment has the potential to affect CAB exposure.

Methods. This was a multi-center, single-dose, open-label, parallel group study to evaluate the effect of moderate hepatic impairment on the pharmacokinetics (PK) and safety of CAB. Adults with moderate hepatic impairment as determined by Child-Pugh classification score of 7–9 ($n = 8$) and matched healthy control subjects ($n = 8$) were enrolled. Control subjects were matched for gender, age (±10 years), and body mass index (BMI) (±25%). Subjects received oral CAB 30 mg as a single dose in the fasted state followed by serial PK sampling for 168 hours. CAB unbound concentrations at 2 and 24 hours after dosing were determined by equilibrium dialysis. Non-compartmental PK analysis was performed; geometric least squares (GLS) mean ratios (hepatic impaired group/control group) and 90% confidence intervals (CI) were generated.

Results. Sixteen subjects completed study; 12 (75%) male, mean age 59 years (range: 51–67), mean BMI 29 kg/m2 (range: 21–37), and total Child Pugh score in range of 7–9. CAB PK parameters were similar between subjects with moderate hepatic impairment and matched healthy subjects. The GLS mean ratios (90% CI) for AUC(0-∞), Cmax, C24, CL/F, and t1/2 were 0.73 (0.50, 1.06), 0.69 (0.51, 0.93), 0.73 (0.53, 1.02), 1.38 (0.95, 2.01), and 0.82 (0.65, 1.04), respectively. Although highly protein bound, the unbound fraction of CAB was increased in subjects with moderate hepatic impairment relative to healthy subjects with GLS mean ratio (90%CI) of 2.14 (1.57, 2.90) at 2 hours post dose and 1.90 (1.14, 3.18) at 24 hours post dose; this was associated with lower serum albumin concentrations and was not considered clinically significant. All adverse events (AE) were reported as mild (Grade 1) to moderate (Grade 2) in severity and no serious AEs were reported.

Conclusion. Plasma exposures of CAB in subjects with moderate hepatic impairment were similar to those in healthy subjects. No dose adjustment of CAB is required for subjects with mild to moderate hepatic impairment.

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1389. Pharmacokinetics of Cabotegravir in Subjects with Severe Renal Impairment

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Background. Cabotegravir (CAB) is an integrase inhibitor in phase 3 clinical trials for the treatment and prevention of HIV. CAB undergoes glucuronidation via UGT1A1 with <1% renal elimination of unchanged CAB. Renal impairment may affect PK of drugs that are primarily metabolized or secreted in bile; thus impact of renal impairment on CAB pharmacokinetics was evaluated.

Methods. This was a multi-center, single-dose study of oral CAB 30mg administered to subjects with severe renal impairment (creatinine clearance [CLcr] <30 mL/minute; not on renal replacement therapy) and to healthy controls (CLcr ≥90 mL/minute) matched for gender, age (±10 years), and body mass index (BMI) (±25%) (8 per

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.