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 (FTC) and tenofovir alafenamide (TAF) for treatment of HIV. MET is first-line therapy in dual use of MET 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 was increased 39% (GMR [90% CI]: 139 [113, 148]) with B/F/TAF vs placebo, with no change in median plasma t1/2 (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.  
Disclosures. J. Custodio, Gilead Sciences: Employee and Shareholder, Salary; S. West, Gilead Sciences: Employee and Shareholder, Salary; A. Yu, Gilead Science: Employee, Salary; H. Martin, Gilead Sciences: Employee, Salary; H. Graham, Gilead Sciences: Employee and Shareholder, Salary; E. Quirk, Gilead: Employee and Shareholder, Salary; B. Kearney, Gilead: Employee and Shareholder, Salary  
1387. Impact of Tablet Burden and Antiretroviral Therapy (ART) Choice on Virologic Outcomes in Treatment Naïve 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 in treating ART naïve patients in real world, inner city settings, has not been well established.  
Results. Among 390 eligible patients, 78% 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 EVF/FTC/TDF; 24% with EVG/cFTC/ TDF; and 8% with DTG/ABC/3TC. The most frequent MTR were B/F/TAF vs 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/lL (IQR) was 277 (115–407) in STR; 231 (37–371) in MTR.  
Conclusion. Resistance occurred in 18% (85% STR, 74% MTR, P < 0.01) of patients and in 19% of INSTI regimens (9% STR, 9% 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.  
Disclosures. 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.  
Disclosures. B. Tidwell, ViiV Healthcare: Research Contractor, Research support; S. Zelt, ViiV Healthcare: Employee and Shareholder, Salary and Stock; R. D’Amico, ViiV Healthcare: Employee and Shareholder, Salary and Stock; K. Schulman, ViiV Healthcare: Research Contractor, Research support  
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. Results. Non-compartmental PK analysis was performed; geometric least squares (Gls) mean ratios (hepatic impaired group/control group) and 90% confidence intervals (CI) were calculated.  
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.  
Disclosures. J. S. Shaik, GlaxosmithKline: Employee and Shareholder, Salary; S. Ford, PAREXEL International: Employee, Salary; Y. Lou, PAREXEL International: Employee, Salary; Z. Zhang, PAREXEL International: Employee, Salary; K. Bakshi, GlaxosmithKline: Employee and Shareholder, Salary; A. Tenorio, ViiV Healthcare: Employee and Shareholder, Salary; C. Trezza, ViiV Healthcare: Employee and Shareholder, Salary; W. Spreen, ViiV Healthcare: Employee and Shareholder, Salary; P. Patel, ViiV Healthcare: Employee and Shareholder, Salary  
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/min) matched for gender, age (±10 years), and body mass index (BMI) (±25%) (8 per
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 of subjects with hepatic impairment (HI) severity. Mean % protein binding of TMR was 81.0% in HS and 79.9%, 81.9%, and 81.5% in subjects with mild, moderate, and severe HI, respectively. Although highly protein bound, the unbound fraction was higher in subjects with severe HI. Total and unbound TMR exposures increased with increasing HI severity. Mean % protein binding of TMR was 81.0% in HS and 79.9%, 81.9%, and 81.5% in subjects with mild, moderate, and severe HI, respectively. Although highly protein bound, the unbound fraction was higher in subjects with severe HI.

Results. Sixteen subjects completed study; 12 (75%) male, mean age 54 years (range 28–67), mean BMI 24.4 (range 20.7–34.7), and mean CLcr 73 mL/min (range: 24–35), and mean CrCL 22 mL/min (range: 17–29) and 121 mL/min (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, GGL mean ratios (90% CI) for AUC(0–8) in Cmax, CAB, CL/F, and F/I 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 GGL 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.

Disclosures. R. Parasrampanra, GlaxoSmithKline: Employee and Shareholder, Salary; S. Ford, PAREXEL International: Employee; S. Y. Lou, PAREXEL International: Employee; L. Yang, PAREXEL International: Employee; S. C. Fu, PAREXEL International: Employee; S. K. Bakshi, GlaxoSmithKline: Employee and Shareholder, Salary; A. Tenorio, ViV HealthCare: Employee and Shareholder, Salary; C. Trezza, ViV HealthCare: Employee and Shareholder, Salary; W. Spreen, ViV HealthCare: Employee and Shareholder, Salary; P. Patel, ViV HealthCare: Employee and Shareholder, Salary.

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

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Session: 156. HIV: Antiretroviral Therapy
Friday, October 6, 2017: 12:30 PM

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 (rs745274, rs28399499, and rs4803419) 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 (SLOW). 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.

Results. 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.

Conclusion. Although 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 rs745274, 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 (AOREXT = 0.81, 95% CI 0.26–2.56; AORINT = 3.92, 95% CI 0.39–39.40) or with depression (AOREXT = 1.95, 95% CI 0.75–5.09; AORINT = 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.