Abstract Book
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Tenofovir exposure during pregnancy and postpartum in hepatitis B mono-infected women on TDF monotherapy compared to HIV-infected women on TDF-containing antiretroviral therapy

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Background: Tenofovir disoproxil fumarate (TDF) monotherapy is increasingly used for hepatitis B virus (HBV) mono-infected pregnant women with high HBV DNA to prevent mother-to-child transmission (MTCT). TDF is recommended as part of combination antiretroviral therapy (cART) to prevent MTCT of HIV. In HIV-infected women, tenofovir (TFV) exposure is reduced by about 20% during pregnancy. The impact of pregnancy on TFV in the absence of concomitant antiretrovirals is unknown. We assessed TFV exposure during pregnancy and postpartum in HBV-monoinfected women receiving TDF monotherapy and compared this to TFV exposure in HIV-infected women receiving TDF with and without ritonavir boosted protease inhibitors (bPI) as part of combination antiretroviral therapy (ART).

Methods: Data were combined from two clinical trials (1) the iTAP study, a randomized placebo-controlled trial in Thailand assessing the safety and efficacy of TDF to prevent HBV perinatal transmission (NCT01745822) and (2) the PANNA study, a European network studying antiretroviral pharmacokinetics in pregnancy and postpartum (NCT00825929). Within iTAP, women ≥18 years, with +HBSAg and +HBeAg tests, and ALT ≤60 IU/L were randomized to receive TDF (300 mg once daily) or placebo from 28 weeks’ gestational age (GA) to 2 months postpartum. Using a population pharmacokinetic approach individual TFV exposure (AUC0-24) and trough concentrations (C24) were estimated for women in iTAP during the 3rd trimester and postpartum. In the PANNA study, HIV-infected women ≥18 years on specific ART regimens had intensive PK sampling performed during late pregnancy and postpartum. HIV-infected pregnant/postpartum women on TDF-containing ART regimes enrolled in PANNA were included in this analysis.

Results: 166 women from the iTAP study were included: during pregnancy/delivery, samples were collected from women at a median of 35.9 weeks GA (range, 30.7-42.1), when median body weight was 64 kg (44-108) and creatinine clearance (CrCL) was 155 mL/min (86-303); samples were collected at 1 to 2 months postpartum when median body weight was 56 kg (39-99) and CrCL 105 mL/min (53-330). From the PANNA study, 26 HIV-infected women were on bPI-ART with a median GA of 34 weeks (33-35) and third trimester weight 76 kg (70-82) and 8 HIV-infected women were on non-bPI-ART with a median GA of 33 weeks (32.5-33.75) and third trimester weight 72 kg (65-80).

In HBV-monoinfected women receiving TDF-monotherapy, TFV AUC0-24 was 20% lower during pregnancy compared to postpartum, which was comparable to the decrease in HIV-infected pregnant women on cART (23% overall, 16% bPI-ART and 36% non-bPI-ART). In HBV-monoinfected women receiving TDF-monotherapy, median (IQR) TFV AUC0-24 were 1.83 µg.hr/mL (1.65-2.09) during pregnancy, and 2.28 µg.hr/mL (2.05-2.77) postpartum (p<0.0001), respectively.

TFV AUC0-24 was 30% lower during pregnancy in HBV-monoinfected women on TDF-monotherapy compared to HIV-infected women on bPI-ART but was only 13% lower during pregnancy compared to HIV-infected women on non-bPI-ART.

Conclusion: TFV exposure was 20% lower during pregnancy than postpartum in HBV monoinfected women, a similar magnitude historically observed in HIV-infected women. TFV levels were generally lower in HBV-infected women on TDF monotherapy vs. HIV-infected women on TDF-based ART, especially when ritonavir boosted protease inhibitors were part of ART.
Intracellular 007-TP Concentrations are Associated with Gradients of Adherence to Ledipasvir/Sofosbuvir

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Background: Sofosbuvir (SOF), a nucleotide analog used in the treatment of hepatitis C virus (HCV), is activated intracellularly to a uridine triphosphate analog (007-TP, also known as GS-461203). However, there are limited data on the pharmacology of 007-TP and no data on the association between SOF adherence and 007-TP exposures. The purpose of this analysis was to determine the association between adherence to ledipasvir/sofosbuvir (LDV/SOF) and 007-TP concentrations in peripheral blood mononuclear cells (PBMCs) and dried blood spots (DBS).

Methods: Individuals with HIV/HCV coinfection were randomized to receive directly observed (using a video-streaming smartphone app, DOT) or wirelessly observed (using a Wisepill device, WOT) once daily LDV/SOF therapy for 12 weeks. Concentrations of 007-TP were measured by LC-MS/MS in DBS (fmol/punch) and PBMC (fmol/10^6 cells) at weeks 2, 4, 6, 8, 10 and 12 of LDV/SOF treatment. The association between electronically measured (DOT and WOT) adherence (%ADH; #doses taken/#days between visits) and 007-TP concentrations in DBS and PBMCs was assessed using mixed models which account for repeated measures and inter/intra individual variability. %ADH was modeled both as a continuous variable and in gradients of ≤50%, >50-75%, and >75%. The effect of other demographic covariates (e.g., weight, eGFR) on the association between %ADH to LDV/SOF and 007-TP concentrations was also determined.

Results: Participants (n=39) were 85% male, 21% cirrhotic, 73% non-black, with a median (IQR) weight of 71 (63, 78) kg, age of 51 (46, 55) years and baseline eGFR of 84 (70, 102) mL/min/1.73m2. Median (IQR) 007-TP levels were 616 (447, 783) in DBS and 1820 (1212, 2596) in PBMCs. The approximate half-life (95% CI) of 007-TP was 104 (59, 182) hours in DBS and 26 (15, 110) hours in PBMCs. Median (IQR) %ADH was 94% (86%, 100%) and range was 7.1%, 100%. In DBS, for every 10% increase in %ADH there was a 7.0% (95% CI: 3.8%, 10%) increase in 007-TP concentrations (p<0.0001). In PBMCs, for every 10% increase in %ADH there was a 23% (95% CI: 15%, 31%) increase in 007-TP concentrations (p<0.0001). %ADH to LDV/SOF remained the most significant predictor of 007-TP concentrations after adjustment for other covariates in a multivariate model. In models with %ADH gradients of ≤50% (n=7, obs=14), >50-75% (n=14, obs=22), and >75% (n=38, obs=191), the geometric mean (95% CI) 007-TP in DBS were 424 (332, 540), 547 (349, 859) and 622 (397, 976), respectively. Geometric mean (95% CI) 007-TP in PBMCs in those with ≤50%, >50-75%, and >75% %ADH were 615 (387, 978), 867 (333, 2254), and 1853 (739, 4646), respectively. 007-TP concentrations in the three adherence categories were significantly different in both DBS (p=0.002) and PBMCs (p<0.0001).

Conclusion: Gradients of %ADH to LDV/SOF measured using electronic monitoring were strongly associated with 007-TP concentrations in DBS and PBMCs, highlighting the potential for 007-TP as a pharmacokinetic-based measure of adherence and cumulative drug dosing.
A Pharmacometabolomics Approach for Predicting Tenofovir diphosphate (TFV-DP) Concentrations in Dried Blood Spots (DBS)

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Background: Cumulative adherence and exposure to antiretroviral medications are significant predictors of clinical outcomes in the treatment and prevention of HIV. Intracellular TFV-DP concentrations in red blood cells (RBC), measured using DBS, can be used to objectively classify cumulative adherence and exposure. However, inter-individual variability in TFV-DP concentrations may lead to misclassification errors in adherence assessments. Our long-term goal is to understand mechanisms underlying TFV-DP variability. The primary aims of this study were to evaluate the association between an individual’s baseline metabolome profile (specific to RBC) with observed steady-state TFV-DP concentrations and to identify changes in metabolites associated with drug exposure.

Methods: DOT-DBS was a 36-week, randomized, cross-over pharmacokinetic study of TFV-DP in DBS in HIV-negative volunteers taking TDF/FTC as 33%, 67%, and 100% of daily dosing under directly observed therapy. Dosing regimens were 12 weeks in duration. DBS were collected at baseline (pre-drug) and bi-weekly throughout the study. Week 12 (steady-state) TFV-DP concentrations were dose-adjusted for analysis, assuming dose proportionality. LC-MS based metabolic profiling was performed on baseline and Week 12 DBS samples by measuring the abundance of 158 metabolites across a spectrum of RBC-specific metabolic pathways. Metabolite data were normalized through an autoscaled normalization algorithm. Because of multicollinearity and a large number of predictors, a least absolute shrinkage and selection operator (LASSO) regression analysis was conducted with baseline metabolite abundances to predict steady-state TFV-DP concentrations and to identify metabolites that strongly contributed to this prediction. Gender, race and age were also evaluated as predictors. The predictive performance of the model was tested with k-fold cross-validation, in which the original data was randomly partitioned into 7 equal subsamples for internal validation, and the model that minimized the predicted residual sum of squares was chosen. T-tests were performed to identify significant changes between baseline and Week 12 metabolite abundances and a Bonferroni adjustment was utilized to correct for multiple comparisons.

Results: Forty-five participants (24F/21M) had available metabolite and TFV-DP concentrations. When only metabolites were evaluated, the LASSO selected 17 metabolites, which explained 27% of the variability in TFV-DP concentrations. When gender was included as a predictor, the LASSO selected 27 metabolites as significant predictors, which explained 62% of the variability in steady-state TFV-DP concentrations. Major pathways associated with these metabolites included nucleotides, amino acids, glycerophospholipid synthesis and the TCA cycle. Between baseline and Week 12, 46 metabolites significantly changed. Although only four of these metabolites were also selected by the LASSO, there was significant congruence between the pathways of both metabolite groups. After correcting for multiple testing, seven metabolites remained significant.

Conclusion: Baseline RBC metabolites and gender predicted more than 60% of the variability observed in TFV-DP concentrations in this study. These findings provide insight into potential mechanisms and biological pathways that influence TFV-DP variability and exposure. Future studies will validate these results in other populations. If reproducible, RBC metabolomics and patient characteristics hold promise for predicting steady-state TFV-DP concentrations within an individual.
SLC22A2 Genetic Variants and Dolutegravir Trough Concentrations Correlate with Specific Psychiatric Symptoms In HIV-Positive Patients on Dolutegravir

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Background: The onset of neuropsychiatric symptoms (NPS) has been described during dolutegravir-containing antiretroviral therapy (ARV) and associated to higher dolutegravir trough concentrations (DtgC-t). Organic cation transporter 2 (OCT2), that is distributed in different organs and is inhibited by several drugs including dolutegravir, is implicated in monoamine clearance in the central nervous system. We hypothesize that polymorphisms in the SLC22A2 gene (encoding for OCT2), in addition or synergy with DtgC-t, might explain the individual neuropsychiatric susceptibility during dolutegravir therapy.

Methods: A cohort of HIV-positive, consecutively-enrolled patients from 2 clinical centers, treated with a dolutegravir-containing regimen, underwent determination of allelic discrimination for SLC22A2 rs316019 polymorphism and DtgC-t. The Symptom Checklist-90-R (that includes a general severity index, “GSI”, as well as 90 questions exploring 9 psychiatric domains) and an ad-hoc self-reported questionnaire were offered to investigate current NPS. The effects of DtgC-t and SLC22A2 polymorphisms on NPS were explored by multivariate logistic regression, after adjusting for clinical factors that resulted significantly associated at univariate analysis or that significantly differed among patients with higher DtgC-t and different SLC22A2 polymorphisms.

Results: A cohort of 203 patients was analyzed: 71.4% were male, 45.3% MSM, with 51 years of median age and 11 years of ARV exposure. Median time on dolutegravir was 18 months. Dolutegravir was associated to lamivudine in 79 cases (38.9%), abacavir/lamivudine in 72 (35.5%), tenofovir/emtricitabine in 40 (19.7%), other ARV in 12 (5.9%); most patients (98.0%) had HIV-RNA<50 copies/mL; median CD4 cell count was 650 cells/µL. SLC22A2 CA-genotype carriers were 31 (15.3%), had a shorter exposure to dolutegravir (p=0.023), and had more often an active psychiatric disease (APD) at dolutegravir start (p=0.048) compared to CC-genotype carriers.

Prevalence of SLC22A2 CA-genotype compared with CC was higher in patients reporting abnormal GSI (p=0.035), anxiety (p=0.022), hostility (p=0.047), and moderate-to-severe headache (p=0.041). An abnormal GSI was associated to CA-carriage (aOR: 3.08; p=0.040) and APD (aOR: 16.88; p=0.015). Pathological anxiety was positively associated to CA-genotype (aOR 2.95; p=0.042) and APD (aOR: 15.16; p=0.020) and inversely related to higher plasma total cholesterol (aOR 0.89; p=0.048). Pathological hostility was associated to CA-genotype (aOR 3.38; p=0.030), increasing DtgC-t (fourth versus first quartile aOR 5.56; p=0.012), younger age (per 10 year more aOR 0.60; p=0.012) and shorter time from dolutegravir initiation (per 1 month more aOR 0.95; p=0.025). Increasing DtgC-t were also independently associated to psychoticism (fourth versus first quartile aOR 18.76; p=0.008), especially when associated with 2 NRTIs (versus lamivudine-based dual ARV: aOR for abacavir/lamivudine 5.26; p=0.017; aOR for tenofovir/emtricitabine 4.96; p=0.039).

Other NPS were not associated to OCT2 polymorphism nor DtgC-t.

Conclusions: Genetic variants in SLC22A2 were associated to an increased risk of detecting both a more severe general psychiatric symptom index and specific NPS in patients on dolutegravir. A higher DtgC-t was associated to psychoticism and hostility and could explain the increased incidence of NPS in specific populations.
Age, Inflammation, Blood Brain Barrier Permeability and Single Nucleotide Polymorphisms in Transporters May Influence Cerebrospinal Fluid Antiretrovirals’ Concentrations

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Background: Antiretrovirals drugs’ (ARVs) central nervous system (CNS) exposure is relevant for compartmental residual replication and HIV-associated neurological disorders. Although recent data in animal models suggest that cerebrospinal fluid (CSF) may underestimate ARVs’ brain tissue concentrations, it may provide helpful insights into the determinants of this process. Aim of this analysis was to characterize ARVs’ CSF penetration according to several variables including compartmental inflammation, blood brain barrier (BBB) permeability and single nucleotide polymorphisms (SNPs) in transporters’ encoding genes.

Methods: HIV-positive patients receiving lumbar punctures for clinical reasons and participating to specific study protocols were included after signing a written informed consent. CSF and plasma were withdrawn less than 15 minutes apart and analyzed using validated HPLC/MS-MS methods. Genomic DNA was extracted using QiAamp whole blood mini kit (Qiagen, Valencia, CA, USA) according to the manufacturer’s instructions. Genotyping was conducted by real time-based allelic discrimination including the following SNPs in ABCB1 (rs1045642, rs1128503, rs2032582), ABCC2 (rs717620), SLC22A6 (rs4149170), SLCO1A2 (rs10841795, rs11568563), ABCG2 (rs2231142, rs13120400) and HNF4α (rs1884613). BBB permeability was estimated using Reibergrams (CSAR) and CSF neopterin trough ELISA methods. Multivariate linear regression analysis were performed including age, CSAR, CSF neopterin and plasma concentrations besides SNPs with univariate p values <0.20.

Results: We included 259 patients; they were mostly male (71.4%), of European ancestry (74.9%) with median age of 47.8 years (41-55). 405 paired plasma and CSF concentrations were measured showing highly variable exposures and ratios (ranging from 0.1 to 92.3%). CSF concentrations below the limit of detection were observed for tenofovir (31.8%), zidovudine (16.8%) and atazanavir (12.9%). A direct correlation was observed between CSF and plasma concentrations for all drugs except zidovudine, etravirine, nevirapine and lopinavir. After correction for multiple comparisons (p value threshold set at 0.005) no significant association was observed between SNPs and either CSF concentrations or ratios. At multivariate analysis age (p=0.003), CSAR (p=0.046), plasma concentrations (p<0.001) and ABCG2 A allele (rs2231142, p=0.014) were associated with CSF NRTI concentrations. CSF PI concentrations were predicted by plasma levels (p=0.001) and CSF neopterin (p<0.001). Plasma concentrations (p=0.020) and, borderline, ABCC2 A allele (p=0.056) were associated with CSF INSTI levels.

Conclusions: ARVs’ penetration into the CSF showed a large inter- and intra-class variability. Beside plasma concentrations, ARVs’ CSF levels may be predicted by age, BBB permeability and CSF inflammation (known to increase transporters’ expression); the association with SNPs in ABCG2 and ABCC2 warrant further evaluation and exploring its clinical relevance.
Bictegravir/Emtricitabine/Tenofovir Alafenamide Phase 3 Exposure-Response Analysis of Safety and Efficacy in the Treatment of HIV Infection

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Background: Bictegravir (BIC, B) is a novel, unboosted INSTI with a high barrier to resistance. When coformulated with the nucleoside analog reverse transcriptase inhibitors, emtricitabine (FTC, F) and tenofovir alafenamide (TAF), B/F/TAF was well-tolerated with high efficacy and no emergent resistance in four phase 3 studies of treatment naive and suppressed patients. A population-based pharmacokinetic/pharmacodynamic (PK/PD) analysis was conducted to evaluate the exposure-response relationships of BIC and TAF in ART naïve HIV-1 infected patients administered B/F/TAF (50/200/25 mg) once daily as a single tablet regimen (STR).

Methods: Using population PK modeling, BIC and TAF exposure estimates (AUCtau, Cmax and Ctau [BIC only]) were determined and the PK/PD relationships between BIC and TAF exposure parameters and efficacy/safety endpoints were evaluated for treatment naive HIV 1 infected patients who received B/F/TAF 50/200/25 mg STR in two randomized double-blinded Phase 3 studies (N = 634). The primary efficacy endpoint was the proportion of patients with HIV 1 RNA < 50 copies/mL at Week 48, as determined by the US FDA-defined Snapshot algorithm excluding patients with no virologic data in Week 48 window. The exposure-safety analysis was expanded to include Phase 2 data (N = 65 treated with BIC 75 mg + F/TAF 200/25 mg). Safety endpoints included incidence of the 5 most commonly reported adverse effects (diarrhea, headache, nausea, nasopharyngitis and fatigue) observed with B/F/TAF in the two Phase 3 studies.

Results: Across all exposure quartiles for BIC and TAF (N = 624 and 461, respectively), high virologic response rates were noted (≥ 95.7% with HIV-1 RNA < 50 copies/mL at Week 48). Median BIC Ctau was high at 15.7-fold above the protein-adjusted IC95 for wild-type HIV (IQ). The lowest exposure quartile for BIC Ctau had an IQ range of 4.7-12.2 and a 99.3% virologic response rate (n/N = 148/149). Exposures of BIC and TAF were similar regardless of the presence or absence of the evaluated adverse effects, indicating a lack of association between BIC and TAF exposure and the most common adverse events. The incidence of these AEs was low and comparable to the Phase 2 study. The highest observed individual BIC AUCtau in the Phase 2 and 3 studies was approximately 2.4-fold and 2.1-fold higher than the median Phase 3 BIC AUCtau, respectively.

Conclusions: Pharmacokinetic/pharmacodynamic analyses demonstrate that once daily administration of B/F/TAF 50/200/25 mg STR to treatment naive HIV-infected patients in Phase 3 studies resulted in high virologic response rates across the range of BIC and TAF exposure with no evidence for BIC or TAF exposure differences in patients with or without common adverse events.
Pharmacokinetic and virological efficacy of dolutegravir (50 mg BID) containing regimen in association with rifampin in HIV-infected patients using Dried Blood Spot: ANRS-12313 NAMSAL sub-study in Cameroon

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Background: Dolutegravir (DTG) is becoming 1st line alternative of efavirenz (EFV) in the WHO guidelines for antiretroviral treatment (ART). DTG is superior to EFV in term of virological efficacy with a high genetic barrier to resistance and tolerance. Tuberculosis (TB) is the first cause of death in HIV-infected patients and clinical trials have clearly shown that ART should be initiated early after TB diagnosis to reduce mortality. However, it is necessary to assess the potential drug interaction with TB drugs, particularly rifampin. DTG is substrate of UGT1A1 and CYP3A4 while rifampin is strong inducer of these enzymes. The objectives of this study were to assess the pharmacokinetics and efficacy of DTG 50mg BID containing regimen in association with rifampin-based TB treatment.

Methods: An ancillary study from the ANRS-12313 NAMSAL trial, was conducted in HIV-1/TB co-infected adults receiving DTG 50mg BID + lamivudine/tenofovir (300/300mg QD) after 2 weeks of rifampin/isoniazid/ethambutol/pyrazinamide treatment. The ANRS-12313 NAMSAL is a non-inferior multicenter study evaluating DTG 50mg QD versus EFV 400mg QD containing regimen as first-line treatment in HIV-1 infected patients from Cameroon. Dried blood spots (DBS) were collected at least 4 weeks after the start of ART (steady-state). Time between last drug intake and sampling was recorded. Antiretroviral DBS concentrations and TB DBS drugs were determined using UPLC-MS/MS (LOQ <10ng/mL and <50ng/mL, respectively). Median trough plasma concentrations (C12h and C24h) and HIV-1 RNA (VL) levels (IQR25%-75%) are presented. DTG C12h was interpreted using a 10-fold protein adjusted IC90 (~640 ng/mL) and the inhibitory quotient (C12h/IC90).

Results: Among 12 HIV-1/TB co-infected patients 10 (23 DBS) were enrolled: 8 women, age 40 years (34-44), bodyweight 60 kg (53.5-62), hematocrit 32% (31-36.5%) and baseline VL was 520,440 copies/mL (352,735-826,763). DTG C12h were 1,123 ng/mL (820-1,746; between subject variability BSV 63%; within subject variability WSV 6%), lamivudine C24h 23 ng/mL (20-36; BSV 48%; WSV 25%) and tenofovir C24h 86 ng/mL (68-177; BSV 55%; WSV 29%). TB drug concentrations suggested good adherence to TB therapy. After 24 weeks of ART, pVL decreased of -4.02 log10 copies/mL (3.91-4.52). At W48, all patients presented pVL <200 copies/mL and among them, two patients presented pVL >50 copies/mL with DTG C12h below 640 ng/mL corresponding to an inhibitory quotient of 0.1 and 5.

Conclusions: Among our HIV-TB co-infected patients, DTG 50mg BID containing regimen in association with rifampin 600mg QD as part of TB treatment presented good efficacy profile with adequate DTG C12h. Indeed, only 2 patients presented DTG trough concentrations <640 ng/mL: their low inhibitory quotients suggest that DTG 50mg BID containing regimen in association with rifampin should only be used in WT HIV integrase profile. Finally, as expected, rifampin did not significantly impact lamivudine and tenofovir plasma trough concentrations.
First report of dolutegravir unbound plasma concentrations during pregnancy in HIV-positive women

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Background: In pregnant women living with HIV, total dolutegravir plasma exposure is 25-51% lower during pregnancy compared to postpartum (Mulligan et al. 2018). For highly protein bound drugs such as dolutegravir (>99% bound), the known reduction in plasma proteins during pregnancy may translate into lower total drug concentrations, while unbound, and thus pharmacologically active, concentrations remain unaffected. Here, we evaluate unbound dolutegravir plasma concentrations in HIV-positive pregnant women.

Methods: An open-label, multi-centre, observational, phase IV study was conducted in HIV-positive pregnant women recruited in HIV treatment centers in Europe (PANNA Network). Patients treated with dolutegravir 50mg once daily during pregnancy had intensive steady-state 24-hour PK profiling under fed conditions in the third trimester and 3-7 weeks postpartum. From these PK-curves Cmin and Cmax samples were selected for further evaluation of total and unbound dolutegravir concentrations (through ultrafiltration) with a validated LC-MS/MS quantification method (LLOQ 0.5 µg/L). Geometric mean ratio (GMR) with 90% confidence interval (CI) was calculated with WinNonlin 6.3 to compare third trimester versus postpartum PK parameters. Non-parametric statistical tests were performed to compare the fraction unbound.

Results: Nine patients (7 black, 2 white) with a median age (range) of 30 (21-42) years were included in the analysis. Three patients dropped out of the study prior to the postpartum visit, hence only 6 patients provided both third trimester and postpartum data. Median (range) gestational age at delivery was 38 weeks (34-40). Approaching delivery all patients had a VL <50 cps/mL. Median (range) albumin plasma concentrations tended to be lower (36.5 (36-37) g/L, available for n=4) in the third trimester compared to postpartum (39.0 (37-43) g/L, available for n=3). In the third trimester geometric mean (variance, CV%) for total plasma Cmin and unbound Cmin were 710 (102) µg/L and 4.0 (80) µg/L (n=9), and postpartum 1070 (61) µg/L and 4.2 (70) µg/L (n=6), respectively. GMR (90% CI) for total dolutegravir Cmin in third trimester vs postpartum was 0.72 (0.40-1.29) (n=6); GMR (90% CI) for unbound Cmin was 0.98 (0.55-1.75) (n=6). Third trimester median (IQR) of the free fraction for Cmin was 0.63 (0.43-0.73)% and 0.33 (0.28-0.70)% postpartum, which was not statistically different (p=0.345). Results for total and unbound Cmax plasma concentrations were in line with results for Cmin due to the observed linear plasma protein binding.

Conclusions: Total dolutegravir exposure is lower in pregnancy, however unbound dolutegravir plasma Cmin remained unchanged in the third trimester as compared to postpartum. Although the sample size was small, these findings, coupled with the undetectable viral loads at delivery, suggests uncompromised efficacy of dolutegravir 50mg QD in pregnancy.
Medication safety issues associated with currently used first-line antiretroviral regimens in Uganda

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Background:
Clinically significant drug-drug interactions (CSDDIs) affect 26.7% of Ugandan outpatients taking antiretrovirals (ARVs). Drug-drug interactions (DDIs) may either increase the risk of drug toxicity, or reduce clinical effect of one or both of the drugs. In sub-Saharan Africa, recognition and management of DDIs is restricted by patients accessing medicines via separate silos of care, and un-regulated purchase of medicines. Adverse drug events (ADEs) may be under-reported in this setting, or tolerated due to lack of alternative regimens. These data originate from an ongoing longitudinal study (SAPU) in adult outpatients taking current ARVs at three diverse clinics in central Uganda. The study enrolled 868 patients, with this analysis describing an initial 416 patients taking first-line regimens, and the prominent medication safety issues of public health importance.

Methods:
Medication histories were taken by trained pharmacy technicians, including current side effects. Remote sites transferred information to a central medicines information centre using Android tablet devices. DDI screening and medication safety feedback was given to prescribers for each patient. Via structured questionnaires, prescribers gave feedback on the utility of DDI screening via the mobile feedback loop. Clinical significance of DDIs was assessed by the study team based on the therapeutic index of the drugs, and likelihood of impact on care.

Results:
Of 416 patients on 1st line regimens, 25% had ≥1 CSDDI. Of 37 women on 1st line ARV regimens who reported using hormonal contraceptives, 9 women were exposed to a DDI which put them at risk of contraceptive failure. Of 149 patients taking antimicrobials (antimalarials, antibiotics, antifungals, antivirals) 40.3% had a CSDDI. These affected 14.4% of the 416 patients on 1st line ARVs (accounting for ~40% of all CSDDIs). Prescribers were aware of only 3.5% of CSDDIs (n=144). Prescribers reported that DDI checks provided new information in 56.1% of cases (n=214), with prescribers reporting changing management of patients as a result of the feedback in 53.1% of cases (n=309). DDI checks saved time in 68% of cases (n=200), and added benefit in 72% (n=200). Of the patients on 1st line regimens, 43.3% had a current ADE at the time of interview, with 252 ADEs reported. 72.6% of ADEs were possibly or probably related to EFV. 56.7% of ADEs were nervous system/psychiatric disorders, 83.7% of which were not recorded in the clinical notes. Median duration was 22 months, (IQR 9-35.3 months) ongoing at the point of analysis. Some ADEs were not evaluable due to lack of baseline/routine laboratory monitoring.

Conclusions: Roll-out of newer ARVs with lower potential for DDIs and debilitating ADEs (such as dolutegravir) may: reduce risk of contraceptive failure, reduce risk of antimicrobial treatment failure and microbial resistance and reduce significant morbidity due to ADEs. Patients experiencing, or at high risk of ADEs or CSDDIs should be prioritized for switching to dolutegravir. Health systems may be unaware of the magnitude of sub-optimal prescribing and need to continually evaluate, and promote safer prescribing to minimize patient harm.
Intraindividual comparison of efavirenz, atazanavir, or ritonavir plasma pharmacokinetics before and during 21-days of vaginally administered hormone contraception

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Background: Contraceptive hormones (etonogestrel/ethinyl estradiol) delivered by a vaginal ring result in stable systemic hormone exposure over 21 days of use. Hormones may induce or inhibit drug-metabolizing enzymes, either through direct competition or by modulation of nuclear receptors that govern enzyme expression, with resultant potential to influence antiretroviral exposure. We hypothesized that plasma concentrations of efavirenz (EFV) or atazanavir/ritonavir (ATV/r), each combined with ≥ two NRTIs as antiretroviral therapy (ART), would be similar between baseline and after 21 days of vaginally-administered hormones.

Methods: A5316 was an international, multicenter, parallel group, pharmacokinetic (PK) evaluation of women ≥16 years old living with HIV. The results of the influence of ART on the PK of hormones have been presented (CROI Abstract 141); here we describe the influence of vaginally-administered hormones on the PK of two ART regimens. A vaginal ring releasing etonogestrel/ethinyl estradiol 120/15 mcg/day was inserted at entry (Day 0) in two groups of participants receiving ART containing EFV 600mg daily (EFV group) or ATV/r 300/100mg daily (ATV/r group). All participants were on stable ART and had HIV-RNA ≤400 copies/mL at screening. On Day 0, PK sampling for EFV or ATV/r occurred pre-ART dose (0h), then 1, 3, 4, 5, and 8 hours post-ART dose, but prior to vaginal ring placement. ART PK sampling was repeated on Day 21 prior to vaginal ring removal. EFV, ATV, and ritonavir (RTV) were assayed by validated LC/MS/MS methods. AUC0-24h was estimated by non-compartmental methods using Pharsight WinNonLin®, where the 0h value was imputed as the 24h result. Antiretroviral exposure was compared within each group by geometric mean ratio (GMR) with 90% CI (Day 21:Day 0).

Results: Overall, 74 women were enrolled in the parent study; participants were [mean (standard deviation)] 35 (7.6) years of age, 72.5 (24.2) kg, 37 (50%) identified as Black, and 26 (35%) as Hispanic. For assessment of antiretroviral PK, there were 24 participants evaluable in the EFV group and 23 participants evaluable in the ATV/r group. In the EFV group, the EFV Cmin [median (range)] was 2122 (904-13,620) ng/mL on Day 0 and 1766 (10-12,930) ng/mL on Day 21 [GMR 0.64 (0.42, 0.97)], and the AUC0-24h GMR was 0.87 (0.77, 0.99). In the ATV/r group, the ATV Cmin was 797 (10-2731) ng/mL on Day 0 and 599 (10-3599) ng/mL on Day 21 [GMR 0.70 (0.41, 1.21)], and the AUC0-24h GMR was 0.77 (0.57, 1.03). Also in the ATV/r group, the RTV Cmin was 70 (10-1042) ng/mL on Day 0 and 52 (10-917) ng/mL on Day 21 [GMR 0.67 (0.38, 1.19)], AUC0-24h GMR was 0.63 (0.45, 0.89).

Conclusions: In the same women before and during hormone therapy, EFV and ATV exposures were statistically lower based on the observed GMR (90% CI), while ATV exposure was not significantly different. We observed high variability in all antiretroviral PK parameters, and antiretroviral Cmin values remained within the expected range for each antiretroviral (Boffito et al. AAC 2011; Marzolini et al. AIDS 2001). Therefore, these changes are unlikely to be clinically significant.
Pharmacokinetics of Dolutegravir 100 MG Once-Daily with Rifampicin

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Background: Tuberculosis (TB) causes 25% of all deaths among HIV-infected individuals. Rifampicin (RIF) is a potent inducer of drug metabolising enzymes and coadministration with dolutegravir (DTG) can drastically reduce DTG exposure. Therefore the recommended dose is 50mg twice daily (BD) in patients ongoing TB-treatment. This study investigated the effect of RIF on the PK of DTG 100mg once-daily (OD) to establish whether doubling DTG dose over 24 hours (h) could provide an easier option versus 50mg BD to manage the drug interaction.

Methods: This is an open label, PK study, enrolling healthy volunteers receiving DTG 50mg or DTG 100mg OD in presence or absence of RIF 600mg. Participants were sequentially administrated: DTG 50mg for 7 days, DTG 100mg for 7 days, RIF only for 14 days, DTG 50mg+RIF for 7 days, and DTG 100mg+RIF for 7 days. Four steady-state full PK profiles were evaluated.

Results: 14/16 subjects completed the study, 1 withdrew consent and 1 stopped for allergy. 9 were males, median (range) age was 32 (22-55) years. DTG geometric mean ratios (GMR) (90% confidence intervals, CI) of PK3/PK1 (50mg) Cmax, AUC24h, and C24h were 0.65 (0.56-0.75), 0.43 (0.37-0.51), 0.14 (0.13-0.17). GMR (90%CI) (100mg) of PK4/PK2 of DTG 100mg Cmax, AUC24h, and C24h were 0.64 (0.56-0.73), 0.42 (0.36-0.49), 0.12 (0.10-0.15). When comparing PK parameters of DTG 100mg in co-administration with RIF to DTG 50mg alone (PK4/PK1), GMR (90%CI) Cmax, AUC24h, and C24h were 1.09 (0.98-1.20), 0.74 (0.65-0.85), 0.24 (0.20-0.28). Mean DTG 50 mg OD Cmax, C24h and AUC0-24 were 3969 ng/mL (coefficient of variation [CV], 34%), 1061 ng/mL (CV, 59%) and 52,101 hr*ng/mL (CV, 42%) versus DTG 100 mg OD + RIF that were 4312 ng/mL (CV, 38%), 251 ng/mL (CV, 56%) and 38731 hr*ng/mL (CV, 38%). No subjects developed clinically significant liver toxicity and study drugs were well tolerated.

Conclusions: Although there were substantial reductions in DTG key PK parameter C24h when co-administered with RIF, concentrations of DTG 100 mg OD with RIF were still above the protein binding-adjusted IC of 64 ng/mL, suggesting the need for further study of this dose.
Rifabutin (RBT) Decreases Cabotegravir (CAB) Exposure following Oral Co-administration

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Background: CAB is an integrase strand transfer inhibitor (INSTI) in development as a long-acting (LA) injectable formulation with an oral CAB lead-in for the treatment and prevention of HIV. Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide and TB/HIV co-infection is common, often requiring simultaneous treatment of both conditions. CAB is metabolized primarily by UGT1A1, with minor contribution by UGT1A9. RBT is an antimycobacterial agent for TB and a moderate inducer of UGT and CYP enzymes. This study was conducted to determine the impact of RBT on the pharmacokinetics of oral CAB.

Methods: This Phase I, single-center, open label, two period, fixed-sequence, drug interaction study evaluated the effect of RBT on the steady state pharmacokinetics (PK) of oral CAB in healthy adult subjects. Subjects received oral CAB 30mg once daily for 14 days in Period 1 and co-administered with RBT 300mg once daily for 14 days in Period 2. Serial PK sampling was performed on Days 14 and 28. Geometric least squares (GLS) mean ratios with associated 90% confidence intervals (CIs) were calculated to compare CAB non-compartmental PK parameters following CAB+RBT to CAB alone. Safety was assessed during the study via vital signs, ECG, laboratories including chemistries, CBC and liver function tests, ocular exams and adverse event reporting through completion of follow-up.

Results: Fifteen male subjects enrolled and 12 completed all treatments. Subjects were 93% Caucasian with median age of 44 years and median weight of 84kg. Comparing CAB+RBT to CAB alone, the GLS mean ratios (90% CIs) for CAB AUC(0-τ), Cmax, and Cτ were 0.79 (0.74, 0.83), 0.83 (0.76, 0.90) and 0.74 (0.70, 0.78), respectively. Eleven subjects reported a total of 24 AEs primarily during CAB+RBT treatment (3 drug-related) and 2 AEs (non-drug related) during CAB treatment. The majority of AEs were Grade 1, except one drug-related Grade 3 ALT elevation SAE which occurred 3 weeks after CAB+RBT treatment completed, one non-drug related Grade 4 lymphopenia attributed to a viral syndrome, and four Grade 2 non-drug related AEs. No ocular related events occurred. All AEs resolved by end of study.

Conclusion: RBT had a modest impact on plasma CAB exposure following oral co-administration resulting in overall plasma CAB trough concentrations above those of the 10mg oral dose shown to maintain suppression of HIV in Phase 2 studies. RBT may be administered with oral CAB without dose adjustment. A modest decrease in plasma CAB following CAB LA administration with RBT is expected, and simulations will be performed to inform potential dosing strategies with long-acting CAB.
Rifabutin PK and Safety among HIV/TB Coinfected Children Receiving Lopinavir

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Background: For HIV/tuberculosis (TB) coinfected children requiring protease inhibitor (PI)-based antiretroviral therapy (ART), TB treatment options are deficient. For adults on PIs, rifabutin is the preferred rifamycin, but the one study to date evaluating rifabutin among children on PIs was stopped early due to severe neutropenia.

Methods: The pharmacokinetics (PK) of rifabutin were evaluated in coinfected Nigerian children aged 3-15 years on lopinavir/ritonavir (LPV/r)-based ART and rifabutin (2.5 mg/kg daily)-containing TB treatment. Intensive 24-hour PK sampling occurred at 2, 4, and 8 weeks after rifabutin initiation. The area under the curve (AUC0-24) at each visit was determined via noncompartmental methods and compared to adults receiving rifabutin 300mg daily without ART (mean 3.8 μg·h/ml). The safety threshold was defined as AUC0-24 ≤3.2 μg·h/ml as this was associated with rifamycin resistance in the TBTC-22 study. Clinical and laboratory (white blood cell count, absolute neutrophil count, hemoglobin, platelet count, alanine aminotransferase, and creatinine) monitoring occurred at baseline, at 9 visits while on rifabutin, and through 48-weeks.

Results: At interim analysis, 8 children (2 female) with median (range) age 14 (12-15) years and weight 28.5 (19.0-45.5) kg had 20 PK visits. The median (IQR) rifabutin AUC0-24 was 4.77 (3.84-6.75) μg·h/ml. Three participants had an AUC0-24 ≤3.2 μg·h/ml at week 2; however, all were >3.8 μg·h/ml at the 4 and 8-week visits. Serious adverse events (SAEs) were uncommon: of 407 follow-up laboratory results, Grade 3 and 4 abnormalities occurred in 11 (3%) and 2 (0.5%) instances, respectively. Specifically, Grade 3 neutropenia occurred in 3 instances, all of which resolved without treatment interruption or clinical sequelae. Grade 3 or 4 anemia in 8 (12%) and 2 (3%) instances, respectively, improved or remained stable over time. No other Grade 3/4 abnormalities occurred. One child died at week 4 of HIV-related complications. The remaining 7 improved clinically with 6 achieving resolution of TB symptoms and virologic suppression by 6 months.

Conclusions: In children, rifabutin 2.5 mg/kg daily achieved AUC0-24 comparable to adults, and favorable HIV and TB outcomes were observed with rare SAEs. Neutropenia was rare, mild, and improved with ongoing rifabutin therapy. These data support the use of rifabutin for HIV/TB coinfected children who require LPV/r given the paucity of options for this vulnerable population.
Assessment of maternal and fetal dolutegravir exposure by integrating ex vivo placental perfusion data and physiologically-based pharmacokinetic modeling

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Background: Pregnancy is associated with a variety of physiological and anatomical changes that can alter antiretroviral pharmacokinetics. Subtherapeutic maternal dolutegravir exposure may result in virologic breakthrough and mother-to-child transmission of HIV. On the other hand, fetal dolutegravir exposure following maternal dosing could be a determinant of fetal toxicities but may also have potential as pre-exposure prophylaxis. Pregnancy physiologically-based pharmacokinetic (p-PBPK) models can be of great value to assess maternal and fetal drug exposure. However, to simulate fetal exposure using a p-PBPK model, data on placental drug transfer is necessary. Here, we studied placental dolutegravir transfer via ex vivo dual-side cotyledon perfusion experiments. We integrated these data into the p-PBPK model and simulated maternal and fetal dolutegravir exposure in third trimester pregnant women to explore the clinical implications of standard dolutegravir dosing for mother and child.

Methods: A PBPK model for dolutegravir exposure in healthy volunteers was established and model performance was verified against clinical pharmacokinetic datasets of several dolutegravir dosing regimens. In a next step, physiological parameters were modified to reflect maternal physiological changes during pregnancy. The p-PBPK model was extended with a feto-placental unit and parameterized using dolutegravir transplacental kinetics obtained by performing ex vivo dual side cotyledon perfusion experiments using healthy term human placentas. Subsequently, the model was used to simulate maternal and fetal exposure after maternal dosing and simulations were compared with available clinical pharmacokinetic data from the PANNA network1 and the IMPAACT group2.

Results: The initial PBPK model was able to adequately capture clinical dolutegravir pharmacokinetics in healthy volunteers. Based on six successful perfusions, dolutegravir cotyledon clearances (mean±SD) were 1.03±0.06 mL/min and 1.03±0.23mL/min for the maternal-to-fetal and the fetal-to-maternal direction, respectively. Scaled placental transfer data were incorporated into the established p-PBPK model. Simulations suggested that administration of 50mg dolutegravir QD would result in a maternal C24h of 0.98mg/L, which is in line with clinical pharmacokinetic data of third trimester HIV-1-infected women obtained by the PANNA network and the IMPAACT group (C24h: 0.7mg/L and 0.93mg/L, respectively). Based on the predicted fetal C24h level of 0.65mg/L, a fetal-to-maternal C24h concentration ratio of 0.66 could be calculated, which is in the range of the clinically observed umbilical cord blood-to-maternal blood concentration ratios (0.32-1.6, n=5)1. Furthermore, the predicted fetal C24h is above the EC90 for viral inhibition (0.064µg/L)3.

Conclusions: The integrated approach, in which in-vitro-to-in-vivo extrapolation of cotyledon perfusion data is incorporated into a p-PBPK model, enables simulation of maternal and fetal pharmacokinetics simultaneously. It provides a tool to guide maternal dosing and ensure safety of the mother and her unborn child. Following this approach, the model suggested that a dose of 50mg dolutegravir QD should result in maternal therapeutic exposure and may have potential for fetal pre-exposure prophylaxis.

3 FDA Clinical Pharmacology Review, Dolutegravir
Does hepatic impairment affect the exposure of monoclonal antibodies?

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Background: Currently limited information is available on the effect of hepatic impairment (HI) on PK of mAbs based on FDA guidance, EMA guidance, or literature. Although an earlier report was published that evaluated the effect of HI on therapeutic proteins (TPs), including mAbs approved through 2013, the effect was unclear due to the limited number of TPs with HI information at that time. Considering patients with HI are included in the targeted patient population for many mAbs, and patients may develop hepatic dysfunction as viral and other diseases progress, it is essential to understand the effect of HI on mAbs to provide an accurate dosing strategy for those patients.

Methods: Between Jan 2013 and Mar 2018, an additional 49 TPs have either been approved for the first time (n=45) or had new HI data submitted and reviewed by FDA (n=4). For the 45 novel TPs, including 33 mAbs, the labeling, clinical pharmacology review summaries, and population pharmacokinetic (PK) analysis reports were reviewed to identify whether HI information is available. For those TPs with HI information (the majority being mAbs), further investigation was conducted to evaluate subject numbers and the magnitude of effect (if any) in each HI category, and also the potential mechanism. The updated labeling for those ~90 TPs approved before 2013 were also reviewed for updated information.

Results: Most of the available HI data were from mAb development programs, with data available for 22 mAbs (2 are antibody-drug-conjugates [ADC]), 2 fusion proteins, 1 growth factor and 1 hormone. For the 22 mAbs, further investigation indicates there is almost no data for severe HI (subject number ≤1 for all). There are limited data for moderate HI; 6 mAbs with subject number ≥5, and 3 with a significant effect (AUC decreased by 35 to 70%). There are sufficient data for mild HI; ~20 mAbs with tens to hundreds of subjects and 2 show a significant effect on drug exposure. The largest effect was observed for ado-trastuzumab emtansine, with ADC AUC decreased by 40 and 70% in patients with mild and moderate HI, respectively. For brentuximab vedotin, ADC AUC was decreased by 35% in patients with moderate HI. The trend for AUC decrease was also observed for several other mAbs (e.g., bezlotoxumab, alirocumab).

Conclusion: A significant decrease in AUC has been observed for multiple mAbs in subjects with moderate HI (3 out of 6 mAbs with available data), and it is unknown if the decrease will be more dramatic for severe HI. Multiple potential mechanisms may contribute to the exposure decrease (e.g., competition for FcRn binding with higher endogenous IgG level due to HI, increased binding with FcγR). Our findings suggest that hepatic dysfunction may impact the disposition of mAbs. Additional data are needed to more fully evaluate the effect of HI, particularly moderate and severe HI, on the PK of mAbs.
Reduced nevirapine concentrations among HIV-positive women receiving mefloquine for intermittent preventive treatment for malaria control during pregnancy

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Background: Over one million pregnancies are complicated by co-infection with malaria and HIV, particularly in sub-Saharan Africa where the public health burden of each pathogen is high. Clinical trials have demonstrated intermittent preventive treatment in pregnancy (IPTp) with mefloquine (MQ) reduced malaria rates among pregnant women, yet an unexpected higher risk of MTCT of HIV among HIV-positive women receiving MQ has also been observed. We performed a retrospective cross-sectional analysis of antiretroviral drugs (ARVs) among HIV-positive women participating in a clinical trial of MQ efficacy to determine if interactions between ARVs and MQ could contribute to the increased MTCT observed in women receiving MQ.

Methods: Peripheral blood plasma (maternal plasma) and cord blood plasma (cord plasma) were collected at delivery from 186 mothers participating in a randomized clinical trial of MQ compared to placebo in Kisumu, Kenya. Women received directly observed MQ (250 mg/tablet) or placebo tablets at three monthly antenatal clinic visits and self-reported use of ARVs was documented on study forms. Zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP) were selected for analysis, as they were the ARVs reported to be used by greater than 60% of women participating in the clinical trial. AZT, 3TC and NVP concentrations were measured in a single assay by high-performance liquid chromatography-tandem mass spectrometry.

Results: AZT, 3TC and NVP were detected in maternal plasma and cord plasma specimens in similar proportions between the two study arms. There was also no difference in the distribution of combinations of ARVs detected in maternal plasma and cord plasma specimens. Median concentrations of AZT and 3TC were not significantly lower in the MQ arm compared to the placebo arm for maternal plasma and cord plasma (p > 0.05). However, median NVP concentrations were significantly lower in the MQ study arm compared to the placebo study arm in both maternal plasma (1597 ng/mL vs. 2353 ng/mL, Mann-Whitney Rank Sum, p = 0.023) and cord plasma (2038 ng/mL vs. 2434 ng/mL, p = 0.048).

Conclusions: Reduced NVP concentrations in maternal and cord plasma of women receiving MQ suggest MQ may affect NVP metabolism for both mother and infant. While NVP and MQ are unlikely to be used as future clinical interventions, a better understanding of pharmacologic interactions between newer ARV regimens and antimalarial drugs will be critical to maintain efficacy of both drug classes. Such data collected through pharmacokinetic studies can provide valuable information for large clinical efficacy trials and reduce the likelihood of undesired outcomes due to unrecognized drug-drug interactions.
Elvitegravir pharmacokinetics during Pregnancy and Postpartum

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Background: Adequate exposure to antiretroviral agents is important to achieve treatment efficacy and prevent development of viral resistance. Physiological changes may result in lower antiretroviral exposure. Elvitegravir combined with cobicistat(c)+NRTIs is a recommended first line antiretroviral treatment option in non-pregnant adults. Best et al. show substantially lowered elvitegravir exposure during pregnancy compared to postpartum. Based on these data, DHHS perinatal guidelines do not recommend elvitegravir/c for initial use in pregnancy. However, limited pharmacokinetic data of elvitegravir/c during pregnancy and placental passage are available. In 2008, a European network was established to study the pharmacokinetics of newly developed antiretroviral drugs during pregnancy (PANNA). We present preliminary data on elvitegravir third trimester exposure.

Methods: An open-label, multi-centre, observational, phase IV study was conducted in HIV-infected pregnant women recruited in HIV treatment centers in Europe (PANNA Network). Patients treated with elvitegravir/c 150/150mg+2NRTIs once daily during pregnancy had intensive steady-state 24-hour PK-profiling (10 samples) in the third trimester and 5-7 weeks postpartum. Optional cord blood (CB) and matching maternal blood (MB) samples were taken at delivery. Virological efficacy and safety were evaluated. Elvitegravir plasma concentrations were determined with a validated LC-MS/MS method. The minimum effective concentration of elvitegravir was defined as 0.13mg/L (EC90 derived from DeJesus et al.). Pharmacokinetic parameters were calculated with WinNonlin 6.3.

Results: Seven patients (5 black, 2 white) with a median (range) age of 32 (25-40) years were included in the analysis. One patient switched treatment late third trimester due to resistant virus and had no postpartum curve taken. Gestational age at delivery was 39 (36-40) weeks and birth weight 3140 (2240-4480) grams (both median and range). Six paired (third trimester and postpartum) PK curves were available. The results are presented as geometric mean (variance, CV%). AUC0-24h (mg*h/L) was 11 (37%) in the third trimester and 16 (36%) postpartum. Cmax (mg/L) was 1.1 (31%) in the third trimester and 1.4 (33%) postpartum. Ctrough (mg/L) was 0.06 (113%) in the third trimester and 0.17 (58%) postpartum. Geometric mean ratios (90% CI) of PK parameters third trimester/postpartum were: 0.67 (0.47-0.96) for AUC0-24; 0.79 (0.61-1.02) for Cmax; 0.35 (0.0.16-0.76) for Ctrough. Five out of 7 of the patients had a sub-therapeutic Ctrough in the third trimester, one out of 6 postpartum (McNemar Test p=0.125). The median (range) CB:MB elvitegravir plasma concentration ratio was 0.87 (0.3-1.2; n=4).

Approaching delivery 6/7 patients had a VL<50 cps/mL, one patient had a viral load of 6363 copies/mL 6 weeks prior to delivery. No serious adverse events were reported. All children were HIV uninfected and no birth defects were reported.

Conclusions: In this small population (n=7) exposure to elvitegravir seems lower during pregnancy (third trimester) than postpartum. During pregnancy 71% of the patients showed sub-therapeutic Ctrough versus 17% postpartum. One patient had a detectable viral load prior to delivery. The CB:MB elvitegravir plasma concentration ratio indicates substantial fetal exposure around delivery. These data need to be confirmed in a larger group of patients, but support the recommendations in perinatal guidelines.
Comparison of 5 online free access expert databases to check drug-drug interactions between antiretroviral drugs and co-prescribed medications from a French cohort of HIV-infected outpatients.

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Background: Objectives: to search DDI between 4 ARV triple therapies (ART) (based on third agent as DTG, RPV, EVG/c and DRV/r) and co-prescribed medications using 5 online free access expert databases (OFAED) and to determine their performances in 17,127 HIV-infected French outpatients.

Methods: retrospective study based on longitudinal delivery data from 7,052 French retail pharmacies. ART deliveries records were analyzed during one year corresponding to >6 pharmacy’s visits, with stable ARV, as 2 NRTIs (ABC/3TC or FTC/TDF) + third agent. According to the whole list of different co-medications (n=1,566), homeopathic and topical treatments were eliminated for their low potential DDI. Among the rest of co-medications (n=927), the more prescribed drugs reported in >2% of patients were selected to check DDI using the 5 OFAED and to determine their performances in 17,127 HIV-infected French outpatients.

Results: after selecting co-medications, 97 (10.5%) for ABC/3TC/DTG, 81 (8.7%) for RPV/FTC/TDF, 86 (9.3%) for EVG/c/FTC/TDF and 79 (8.5%) for DRV/r + ABC/3TC or FTC/TDF were analyzed. When co-medications were referenced in OFAED, no statistical difference in the capacity of DDI detection was demonstrated between (L), (M), (E) and (D), except in (T) poorly documented. The proportion of “Not referenced” DDI in OFAED (25-30%) was not statistically different between (L), (M), (E) and (D), except in (T) (80-95%). Regarding DTG/ABC/3TC and metformin DDI, similar concordant results were observed as “Modify dose” between (L), (M), (E) and (D) while “DDI with no impact” was mentioned in (T). Regarding RPV/FTC/TDF and PPIs, all 5 OFAED recommended “Contraindicated”. Then, some slight differences were observed between OFAED: EVG/c/FTC/TDF was “contraindicated” with domperidone in (L) (not referenced in other OFAED) and “not recommended” with rosvastatin in (T) and “no DDI” in other OFAED except (D) “modify dose”; with betamethasone or prednisone “use an alternative” in (D) and (T) and “no DDI” or “DDI with no impact” in other OFAED. Association DRV/r with mometasone was “not recommended” in (L) and (M), “contraindicated” with escitalopram in (M) and metronidazole in (L) and (E) (“not referenced” in other databases) and “contraindicated” with quetiapine (<2% of co-medications in our database) in (L), (D), (T) and “use alternative” in (E). Nevertheless, association between other booster and quetiapine was “not referenced” in EMA for EVG/c/FTC/TDF and classed on “monitor/use with precaution” in FDA and “use alternative” in (M).

Conclusions: Except in (T), slight differences in OFAED performances were detected. Physicians demonstrated good compliance regarding DDI prescriptions. Despite 25-30% “not referenced” co-medications in outpatient’s population, results of DDI’s check in OFAED were very concordant. Finally, such survey of OFAED performances had to be completed by data as convenience and accessibility of web applications.
Polypharmacy, Drug-Drug Interactions and Potentially Inappropriate Prescribing in Elderly Patients of the Swiss HIV Cohort Study

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Background: Comorbidities, age-related physiological changes and the care by multiple healthcare providers predispose elderly individuals living with HIV to polypharmacy, drug-drug interactions (DDIs) and inappropriate prescribing. The extent of prescribing issues traditionally observed in geriatric medicine has not been thoroughly evaluated in the aging HIV population. The main objective of this study was to determine the prevalence of polypharmacy, deleterious DDIs and potentially inappropriate prescribing in elderly participants of the Swiss HIV Cohort Study (SHCS), a nationwide prospective observational study.

Methods: Eligible individuals were ≥75 years old; this age cut-off was selected to better reflect age-related effects on pharmacokinetics/pharmacodynamics and physiology. Comorbidities and medications at the latest registered SHCS follow-up visit were obtained by reviewing retrospectively the patient medical chart. Socio-demographic, clinical, and laboratory parameters were extracted from the SHCS database. DDIs between HIV and non-HIV medications were screened using the Liverpool HIV interactions database and DDIs between non-HIV drugs from the package insert and published DDIs studies. DDIs were not considered if the dosage of the victim drug had been altered to overcome the DDI and/or if an adequate clinical response was documented (i.e. blood pressure, glucose and cholesterol within the target range for older patients) or if DDIs were of weak clinical relevance. Potentially inappropriate prescribing was screened using the Beers, STOPP/START criteria. Inappropriate prescribing was defined as: i) drugs administered at incorrect dosage, ii) drugs prescribed without clinical indication, iii) prescribing omission in elderly with specific medical conditions, iv) drugs not recommended in elderly, v) deleterious DDI between HIV and non-HIV drugs, vi) deleterious DDI between non HIV-drugs, vii) drugs administered beyond the recommended treatment duration.

Results: In the analysis, 111 participants (81% were male) with a median age of 78 years were included. The median (IQR) number of non-HIV comorbidities per participant was 7 (3;8) with the most prevalent included cardiovascular, metabolic, and musculoskeletal conditions. Accordingly, the most prescribed non-HIV medications were metabolic, blood and cardiovascular therapeutic classes. Polypharmacy (excluding HIV drugs) was prevalent (60%). 28%, 36% and 48% of the participants were receiving a HIV regimen including a PI and/or NNRTI and/or INI, respectively. Two thirds of the participants had at least one potentially inappropriate prescribing issue. Approximately 40% of the overall detected issues could possibly lead to deleterious clinical consequences. Prescribing issues were more frequent for drugs used to treat non-HIV comorbidities. Overall potential prescribing errors included: i) inappropriate dosage (25%), ii) inappropriate indication (21%), iii) prescription omission (19%), iv) inappropriate drugs (19%), v) DDIs HIV/non-HIV drugs (11%); vi) DDIs non-HIV/nonHIV drugs (2%); and vii) inappropriate treatment duration (2%). The proportion of participants with more than one inappropriate prescribing was significantly higher in the group of patients with polypharmacy compared to those prescribed ≤4 comedICATIONS.

Conclusion: Polypharmacy and potentially inappropriate prescribing were highly prevalent in ≥75 years old participants of the SHCS. Education on geriatric medicine principles and the periodic review of prescriptions by clinical pharmacologists or pharmacists could help to reduce polypharmacy and inappropriate prescribing in this vulnerable, growing population.
Population Pharmacokinetics and Pharmacokinetics/Pharmacodynamics of Etravirine in HIV-positive Children Ages 1-<6 Years

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Background: Etravirine (ETR) is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral with a high genetic barrier to the development of drug resistance mutations. The population pharmacokinetics of ETR have previously been described in adults, adolescents, and children >6 years old but not in younger populations. This study aimed to characterize the population pharmacokinetics (PK) and pharmacokinetic/pharmacodynamic relationships of ETR in HIV-positive children ages 1-<6 years.

Methods: IMPAACT P1090 is a Phase I/II, multicenter, open-label study designed to determine the PK, optimal dosage, safety, and tolerability of ETR in treatment-experienced HIV infected children ages 1 to <6 years. Participants received ETR with ≥2 other active ARV, one of which was a ritonavir-boosted protease inhibitor (PI/r). Weight-based and weight-band based ETR doses were evaluated. A 12-hour intensive PK was performed two weeks after initiating ETR and sparse samples were collected through Week 48. Nonlinear mixed effects modeling was used to develop a population PK model of ETR. Influential covariates tested included country (US, South Africa, Brazil), age, weight, BSA, PI/r, and ETR administration method (swallowed whole vs. dispersed in water) in a forward/backward stepwise selection. Model performance was verified by visual predictive checks and inspection of residual and predicted vs. observed plasma concentration plots. ETR AUC₁₂, C₁₂, and Css from intensive PK visits were compared in those with HIV-1 RNA <400 vs. ≥400 copies/mL and <50 vs. ≥50 copies/mL at Week 24 using unpaired t-tests.

Results: Twenty-five children (14M/11F; 16 African-American/9 Hispanic; 4 ± 1 years; 15 ± 4 kg; PI/r: 16 lopinavir/8 darunavir/1 atazanavir) with 299 ETR concentrations were analyzed. A one-compartment model with first-order absorption, lag time (1 hour) and a log-additive residual error best described the data. Random effects (Eta) could not be estimated for Vd/F. Administration mode was identified as a significant predictor of CL/F, decreasing inter-individual variability from 60% to 50%. Weight and age were not significant predictors in the model. Typical values (%CV, 95% CI) for children who took the dispersed form for CL/F, Vd/F and ka were estimated to be 32 L/hr (12%, 25-39 L/hr), 364 L (13%, 273-456 L) and 0.47 hr⁻¹ (24%, 0.25-0.70 hr⁻¹). CL/F was 50% lower in children who swallowed the tablet whole (n=6; exponent -0.72 (35%, -1.22-0.22)). Country and PI/r approached significance but over-parameterization of the model precluded their inclusion in the final model. ETR AUC₁₂, C₁₂, and Css at Week 24 did not differ in those with HIV-1 RNA <400 vs. ≥400 copies/mL or <50 vs. ≥50 copies/mL.

Conclusion: We described the population PK of etravirine in children 1-<6 years and found that the apparent oral clearance was 50% lower in those who swallowed the tablet whole versus dispersed in water, potentially driven by lower bioavailability and/or incomplete absorption/dosing in children taking ETR dispersed. This model can aid in comparisons of ETR PK parameters in this population versus those previously reported for adults, adolescents, and children >6 years and in ETR dose selection in this population.
Differential brain tissue penetration of antiretrovirals and fluconazole

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Background: The central nervous system (CNS) is believed to be a significant reservoir for pathogens such as HIV and Cryptococcus; however, current understanding of drug penetration into the CNS is limited and largely based on cerebrospinal fluid (CSF) concentrations. However, CSF is not brain tissue. Herein we used tissues collected post-mortem from HIV-infected Ugandan subjects co-infected with Cryptococcus to characterize the relative distribution of antiretrovirals and antifungal agents across plasma and CNS compartments.

Methods: Following obtainment of written, informed consent from next of kin, post-mortems were performed on five subjects co-infected with HIV and cryptococcal meningitis. Tissues from cerebellum, pons, and CSF were snap frozen in liquid nitrogen. Whole blood was collected from femoral vein into EDTA tubes and stored on ice for 1 hour before separating plasma from cell pellets. All samples were transferred to -80°C for storage. Following tissue homogenization, drug quantification was performed using high performance (efavirenz) or ultrahigh performance (tenofovir, lamivudine, fluconazole) liquid chromatography coupled with triple quadrupole mass spectrometer. Calibrator standards and quality control (QC) samples were prepared in the matrix to match the sample tested; bovine brain homogenate was used for brain tissue, a solution of salt and proteins for CSF, and lithium heparin for plasma. Data are reported as median (range) unless otherwise noted.

Results: Post-mortems were performed 5.2 (2.2-13.7) hours following death. Three individuals receiving daily tenofovir/lamivudine/efavirenz (300/300/600 mg) had detectable drug in all tissue compartments. Likewise, four individuals receiving fluconazole (400-1200 mg daily) had detectable drug in all compartments. CSF: plasma ratios were similar to values reported in the literature. Tissue to CSF ratios ranged from 0.09-1.48 for tenofovir, 0.09-0.32 for lamivudine, 8.25-16.77 for efavirenz, and 0.10-0.23 for fluconazole.

Conclusions: Tenofovir, lamivudine, and fluconazole exposure in CSF over-predicted brain tissue penetration. In contrast, CSF exposure of efavirenz under-predicted brain exposure. These findings highlight the limitations of CSF as a surrogate for overall CNS drug exposure. Validation in larger cohorts is warranted. These data support the use of post-mortem tissues to assess drug distribution to and within the CNS, relevant for HIV reservoir eradication.
Clinical Pharmacology of Raltegravir
Once Daily: Regulatory Experience
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Background: The US FDA approved raltegravir 1200 mg (2 x 600 mg tablets) once daily for the treatment of HIV-1 infection, in combination with other antiretroviral agents, in adults and pediatric patients weighing at least 40 kg who are treatment-naïve or whose virus has been suppressed on an initial regimen of raltegravir 400 mg twice daily. The objective of this work is to share the regulatory clinical pharmacology considerations for this regulatory action, specifically, how to construct the regimen, dosing in pediatrics and patients with hepatic impairment, and some drug interactions mitigation strategy.

Methods: The applicant’s study reports were used as a starting point for FDA review. We conducted exploratory analyses of the applicant’s data and requested additional analyses from the applicant as needed.

Results: Pediatric dosing: We recommended approving the adult 1200 mg QD dose for pediatric patients weighing ≥40 kg. The recommendation is supported by predicted comparable raltegravir exposure in pediatric patients weighing ≥40 kg relative to adults, safety data for six such pediatric subjects who received raltegravir BID and had exposures in the range of predicted exposures from raltegravir QD in pediatric patients, and 18 adults weighing 39-49 kg who received raltegravir QD.

Hepatic Impairment: We concluded that raltegravir 1200 mg QD in patients with mild to moderate hepatic impairment is not recommended. This is based on our conclusion that results of a raltegravir 400 mg single dose study in subjects with mild to moderate hepatic impairment cannot be extrapolated to the 1200 mg dose because the impact of hepatic impairment on pharmacokinetics could differ at a 1200 mg vs a 400 mg dose.

Drug Interactions: The following dosing recommendations were made based on submitted drug-drug interaction data:
1. Coadministration of raltegravir with etravirine is not recommended because raltegravir would be most likely used with etravirine in a treatment-experienced population where there is more concern over reduced raltegravir Ctrough (Ctrough Ratio = 0.68).
2. No dose adjustment is necessary when raltegravir is co-administered with atazanavir because a mean 67% increase in raltegravir AUC is not a safety concern given raltegravir’s safety profile and lack of exposure-safety relationships.
3. Coadministration of raltegravir with strong inducers of drug metabolizing enzymes other than rifampin is not recommended because the impact of these drugs on raltegravir exposure is unknown.

Conclusions: The clinical pharmacology review of the raltegravir submission resulted in significant changes to the proposed dosage and administration (construction of the regimen, pediatric dosing, and dosing in patients with hepatic impairment) and drug interactions (co-administration with etravirine, atazanavir, and strong inducers of drug metabolizing enzymes) sections of labeling.
Clinical Pharmacology of Letermovir: Regulatory Experience

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Background: The US FDA approved letermovir in 2017 for cytomegalovirus prophylaxis. The objective of this work is to share the regulatory clinical pharmacology considerations during the review of the NDA, mainly, suitability of the proposed dosing regimen, dosing in patients with renal and hepatic impairment, and some drug interactions mitigation strategy.

Methods: The applicant’s study reports were used as a starting point for FDA review. We conducted exploratory analyses of the applicant’s data and requested additional analyses from the applicant as needed.

Results: Letermovir dosing regimen: Despite significant differences in letermovir exposure observed in the phase 3 study depending on the route of administration and cyclosporine coadministration, we recommended approval of the proposed letermovir IV and oral dosing regimen of 480 mg, which is reduced to 240 mg when coadministered with cyclosporine, as evaluated in the pivotal trial. The highest exposures were observed at a letermovir dose of 480 mg IV without cyclosporine. Given the absence of a safety signal with the IV letermovir formulation and no clear associations between letermovir exposure and adverse events, we agreed with the proposed dose. Optimal (i.e. lower) IV letermovir doses will be further explored by the applicant in a future study.

Renal and hepatic impairment: We accepted data from renal and hepatic impairment PK studies using subclinical doses as being applicable to the clinical dose of letermovir. This is because the subclinical dose may represent the worst-case scenario in that a relatively low dose, saturable elimination processes responsible for greater than dose proportional letermovir exposure are less likely to be saturated. This hypothesis was supported by physiologically-based PK simulations in the hepatic impairment population where the effect of reduced OATP abundance (observed in cirrhosis) and the effect of hepatic impairment on PK were predicted to be greater at a letermovir dose of 30 mg vs 480 mg.

Drug interactions: The following recommendations were made based on drug-drug interaction data:
1. Based on a study of a subclinical letermovir dose (240 mg) conducted in healthy subjects and known letermovir PK differences between healthy volunteers and transplant recipients (lower concentrations than healthy subjects with the same oral dose), we concluded that letermovir is a moderate CYP3A inhibitor at 480 mg in patients.
2. Because letermovir and cyclosporine are both OATP and CYP3A inhibitors, coadministration of letermovir in combination with cyclosporine is not recommended with atorvastatin or repaglinide.
3. We requested an in vitro study (post marketing commitment # 3295-4) of whether letermovir induces CYP2C8, CYP2C9, or CYP2C19. This request was based on observed induction of CYP3A, which means CYP2C8 induction should also be evaluated. Second, letermovir reduces voriconazole exposure, which may be explained by induction of CYP2C9 or CYP2C19. Finally, contradictory results were obtained for induction of CYP2C19 by letermovir.

Conclusions: The FDA clinical pharmacology review of the letermovir NDA resulted in significant changes to the applicant’s proposed drug interactions labeling, mainly, effect (letermovir alone or letermovir + cyclosporine) on drugs that are CYP3A substrate, co-administration with atorvastatin or repaglinide.
Integrated Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients with Psychiatric Disorders

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Background: The once daily combination of glecaprevir (NS3/4A protease inhibitor; developed by AbbVie and Enanta) and pibrentasvir (NS5A inhibitor; coformulated as G/P) demonstrated sustained virologic response rate at post-treatment week 12 (SVR12) of ≥97% across HCV genotypes 1 through 6 and a favourable safety profile in clinical studies. The prevalence rates of psychiatric illness in patients with HCV infection are higher than those rates in the general US population. Herein we report the integrated efficacy and safety of G/P from ten Phase 2 and 3 studies in patients with psychiatric disorders.

Methods: Data were pooled from SURVEYOR-I and -II, MAGELLAN-I, ENDURANCE-1, -2, -3, and -4, and EXPEDITION-1, -2 and -4 studies. Treatment-naive and -experienced patients were classified as having a psychiatric disorder if they were taking a psychiatric medication at the time of G/P initiation or had a medical history of a psychiatric disorder. Efficacy was assessed as the percent of patients achieving SVR12 (HCV RNA < lower limit of quantification) using an intent-to-treat analysis. Safety was assessed in all patients.

Results: Of the 2,522 HCV-infected patients included, 789 (31%) were classified as having a psychiatric disorder most commonly due to history of (n, %) depression (506, 64%), anxiety (216, 47%), and/or bipolar disorder (57, 7%). Patients with psychiatric disorders were also more often male (403, 51%), white (685, 87%), >65 years old (703, 89%). The most common psychiatric drugs taken concomitantly by patients with psychiatric disorders were antidepressants (396, 50%), opioids (272, 34%), anxiolytics (244, 31%), antiepileptics (217, 28%), hypnotics/sedatives (159, 20%), and antipsychotics (117, 15%). Overall SVR12 rates (%; n/N) were 97% for both patients with (97.3%; 768/789; 95% CI = 96.2 – 98.5) and without psychiatric disorders (97.5%; 1689/1733; 95% CI = 96.7 – 98.2). Among patients with psychiatric disorders, SVR12 rates were >96% regardless of the number of diagnosed psychiatric disorders or concomitant psychiatric drugs used. Overall, G/P was well-tolerated in patients with psychiatric disorders with no DAA-related serious adverse events (0/789) and <1% (5/789) adverse events leading to discontinuation of G/P.

Conclusions: Use of G/P in chronic HCV genotype 1-6 infected patients who were either receiving concomitant CNS drugs or had a history of a psychiatric disorder was well-tolerated and achieved high SVR12 rates.
Development of Prodrug Approaches for Long-Acting Nanoformulations of Emtricitabine-Based Regimens

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Background: Most current antiretroviral (ARV) medications for HIV treatment and prevention necessitate lifelong daily dosing, and require high levels of patient adherence to be effective. Long-acting injectable (LAI) ARVs would allow less frequent administration, improving adherence. Technologies currently used to produce LAI-ARVs are incompatible with the nucleos(t)ide reverse transcriptase inhibitors (NRTIs) due to their high water solubility. Most current ARV combination therapies include NRTI backbone therapies, so overcoming these limitations is warranted.

Methods: We synthesized a series of low-melting carbamate-based emtricitabine (FTC) prodrugs to increase hydrophobicity and improve compatibility for solid drug nanoparticle (SDN) formation. Prodrug activation kinetics were assessed in vitro via HPLC in human muscle, plasma, and liver fractions. Prodrugs were then screened for SDN compatibility using an emulsion templated/freeze drying method, which unlike other approaches is compatible with low-melting point molecules. Hits from these screens were defined as having: Z-average diameter <1000 nm, polydispersity index of <0.5, and dispersible in water at a prodrug concentration of 1 mg/mL. Prodrug release from SDNs and subsequent enzymatic conversion to FTC was quantified by HPLC in human muscle fractions in vitro.

Results: Carbamates bearing longer alkyl chains (C6, C7, and C8) were most efficiently activated under all conditions. Hydrolysis rates were higher in liver than plasma or muscle. Carbonate moieties at the 5'-position were hydrolyzed more efficiently than the carbamate moiety under all conditions. Nanoparticle screening at 10 wt% prodrug in solid formulations demonstrated a correlation between calculated logP and the number of hits obtained for carbamate/carbonate prodrugs (39/42 hits, $R^2 = 0.89$), but not for carbamate-only prodrugs (4/42 hits, $R^2 = 0.13$). Formation of nanoparticles with higher drug loadings was also demonstrated with a hit for an octyl carbamate/carbonate FTC prodrug SDN achieved at 70 wt%. Structure-activity relationship studies at the 5'-OH of the octyl carbamate FTC prodrug demonstrated a tolerance for branching in close proximity to the core of the molecule by esterases responsible for prodrug cleavage. However, increasing the distance between the site of cleavage and the site of branching decreased the efficiency of cleavage.

Conclusions: Taken together, this work suggests that carbamate-based prodrug approaches offer a promising starting point for development of tunable LAI FTC toward a complete NRTI-based LAI regimen.
Effects of Low and High Mineral Content Water on the Relative Bioavailability of a Co-Formulated TRIUMEQ (Abacavir/Dolutegravir/Lamivudine) Dispersible Tablet in Healthy Adults

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Background: TRIUMEQ is a fixed dose combination (FDC) immediate release tablet of abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) approved in the US and the EU for adults and adolescents weighing ≥ 40 kg. A co-formulated dispersible tablet formulation of TRIUMEQ is in development to improve ease of administration in younger pediatric patients. Because DTG is a metal-binding molecule, the divalent metal concentration in dispersion media and time lag following dispersion may affect the solubility and potentially the bioavailability of DTG. Thus, the primary objectives of this study were to evaluate relative bioavailability of a co-formulated TRIUMEQ dispersible tablet as compared to the co-administration of non-dispersible tablets of DTG plus ABC/3TC. Neither mineral content of the water nor dispersion time affected the exposures of individual components. The dispersible FDC tablet was both safe and well tolerated, and the palatability was acceptable.

Methods: This was a Phase I, single-center, single-dose, randomized, open-label, 5-period crossover, relative bioavailability study in healthy adults (Study 200402; NCT02893488). Participants received a series of five single dose treatments that included four dispersible TRIUMEQ FDC tablets each containing ABC 150 mg/DTG 10 mg/3TC 75 mg under conditions with varying mineral content of water (zero or high-mineral content) and dispersion times (immediately or after 30-min delay), as well as four non-dispersible tablets containing DTG 10 mg plus one non-dispersible EPZICOM tablet (reference treatment) under fasted conditions. There was a 7-day washout period between treatments. The primary end points assessed for DTG, ABC, and 3TC were area under the plasma concentration-time curve from time 0 extrapolated to infinity (AUC0-inf) and maximum observed plasma concentration (Cmax). Non-compartmental PK analysis was performed; geometric least squares (GLS) mean ratios and associated 90% confidence intervals (CI) for primary end points were generated. Standard safety assessments were monitored throughout the study and a palatability questionnaire was administered to each participant within 10 minutes of dosing to address color, overall taste, sweetness, bitterness, and mouth feel.

Results: Following a single dose oral administration of dispersible FDC formulation, the relative bioavailability of DTG was 53% to 58% higher in AUC0-inf and 56% to 59% higher in Cmax whereas ABC and 3TC demonstrated bioequivalence when compared to co-administration of non-dispersible tablets of DTG plus ABC/3TC. Neither mineral content of the water nor dispersion time affected the exposures of individual components. The dispersible FDC tablet was both safe and well tolerated, and the palatability was acceptable.

Conclusions: These results demonstrate higher DTG bioavailability and equivalent ABC/3TC bioavailability from the dispersible FDC tablet compared with non-dispersible tablet regardless of mineral content and delay in dispersion administration. In addition to the safety data, PK and palatability results support further development of the dispersible FDC tablet for future use in pediatric patients.
Integrating duodenal sampling in a mass balance study to characterize the true A(D)ME processes of JNJ-53718678.

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Background: JNJ-53718678 is being developed as an oral treatment of RSV infection. Hepatocyte metabolic in vitro data and initial human PK data, collectively, suggested that biliary elimination of parent drug, glucuronidation and CYP3A4 metabolism contributed approximately 1/3rd each to the drug clearance. In a standard mass balance study stools and urinary output are collected to determine a drug’s elimination pathways holistically. However, in vivo and in vitro data available prior to this study suggested that a significant amount of JNJ-53718678 may be excreted in feces through different processes, e.g. 1) incomplete absorption, 2) biliary excretion of parent drug, or 3) drug glucuronidation/biliary glucuronide excretion/intestinal hydrolysis back to parent drug. To avoid non-interpretable feces data, duodenal sampling was incorporated. Collecting accurate information on metabolic pathways is particularly essential in this project to translate PK and DDI information from adults to the target pediatric population or between pediatric age groups.

Methods: A single oral dose (500-mg 14C-JNJ 53718678, 88.5 µCi) was administered fasted to 6 healthy male adult volunteers. Parent drug, three CYP3A4-associated (dealkylated) metabolites (M5, M12 and M19) and the primary glucuronide M8 were quantified in plasma, feces, urine and duodenal liquid samples: in view of the latter, a nasoduodenal tube was placed 1 hour before drug administration. Four hours after drug intake gall bladder contraction was stimulated through consumption of Ensure Plus®, before and after which duodenal samples were collected. For each of the analytes the biliary clearance CLbil ratios were estimated based on the respective partial AUC4h and duodenal concentration ratio’s. Based on the relative amounts of the analytes excreted into bile and the TR recovery in feces, the contribution of glucuronidation and biliary excretion pathways were estimated.

Results: JNJ-53718678 represented 47% of the total radioactivity plasma AUC. M12, M19, M5 and M8 represented 18%, 5%, 4% and 1%, respectively. 70.6% of TR was recovered in feces and 19.9% in urine (total recovery: 90.5%). 1.56% of the dose was excreted in urine as unchanged JNJ-53718678. The duodenal TR concentration-time curve revealed a sharp peak in all study participants within 15-60 min after Ensure Plus® intake confirming robustness of the implemented procedure.

M8 was efficiently cleared in bile. It was estimated that biliary excretion of JNJ-53718678, M5, M12 and M8 represents 11.6%, 5.7%, 1.1% and 10.4% of duodenal TR, respectively. However, 10-16% of TR in feces was JNJ-53718678, 5-8% M5, <1% M12, <1% M8, confirming that data from feces and urine only would have been insufficient to determine the relevance of glucuronidation. Glucuronidation and direct biliary excretion contributed 7% and 8%, resp., to the elimination of JNJ-53718678.

Glucuronidation and direct biliary excretion contributed both 8% to the elimination of JNJ-53718678 instead of 1/3rd each. CYP3A4 is the major metabolic enzyme involved.

Conclusions: Contrary to a standard holistic assessment, a mass balance study with integrated duodenal sampling can enable dissociating hepatic metabolism from intestinal processes occurring upon biliary excretion and bridging in vitro and in vivo information.
Comparative bioavailability of two grazoprevir (GZR) and elbasvir (EBR) pediatric formulations to that of the elbasvir/grazoprevir (EBR/GZR) adult fixed-dose combination tablet

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Background: GZR, a once-daily competitive inhibitor of the hepatitis C virus (HCV) NS3/4A protease and EBR, a HCV NS5A replication complex inhibitor have been developed for the treatment of chronic HCV infection. In order to support pediatric development, a comparative bioavailability study of proposed pediatric formulations and the adult formulation of the fixed dose combination (FDC) of EBR/GZR was done.

Methods: An open-label, single-dose, randomized, 5-treatment, 3-period study was done in 24 healthy male and female subjects, aged 18-55 years of age. All subjects received single doses of GZR and EBR and each subject was randomized to one of 12 treatment sequences. In treatment A, subjects received 100 GZR uncoated oral granules (1 mg/oral granule) and 100 EBR coated oral granules (0.5 mg/oral granule); in treatment B, subjects received 100 GZR coated oral granules and 100 EBR uncoated oral granules; in treatment C, subjects received 100 MK-GZR uncoated oral granules and 100 EBR uncoated oral granules; in treatment D, subjects received 100 GZR coated oral granules and 100 EBR coated oral granules; in treatment E, subjects received EBR/GZR FDC tablets. All treatments were administered following an overnight fast, and treatments A-D were mixed and co-administered in 1 tablespoon (15 mL) applesauce. All treatment periods were separated by at least a 10-day washout interval. Safety, tolerability, and PK (of GZR and EBR) were assessed using standard methods. Taste was assessed via a questionnaire. Palatability of the formulations was assessed as part of the overall assessment of the oral granules.

Results: All treatments were generally well tolerated. A total of 22 subjects completed the study; two subjects discontinued from the study. Comparative PK for GZR and EBR for the coated and uncoated formulation vs the FDC were generally similar. GZR Cmax, C24hr, and AUC were slightly lower than the adult tablet for coated granules, and slightly higher than the adult tablet for uncoated granules. EBR Cmax, C24hr, and AUC were slightly higher for both coated and uncoated granules, compared to the adult tablet.

Conclusions: The comparative bioavailability of GZR and EBR were generally similar in comparison with the FDC tablet for the uncoated formulation. The exposures of coated formulation of GZR were generally numerically lower than the uncoated formulation whereas those of the EBR were similar. There was no preference for coated oral granules versus uncoated oral granules with respect to taste, texture, swallowability, and aftertaste.
Comparison of Relative Bioavailability of TIVICAY Immediate Release and Dispersible Pediatric Tablets to Immediate Release TIVICAY adult tablets

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Background: The integrase inhibitor TIVICAY(dolutegravir[DTG]) is approved as a 50 mg-immediate release (IR) tablet for the treatment of HIV infection in adults and adolescents. Alternate formulations [(lower strength 25mg and 10mg IR] have been developed for pediatric patients and a 5-mg dispersible tablets (DT)) is currently in development. This study evaluated the pharmacokinetics and safety of the alternative IR and DT vs. either the 50 or 25 mg IR tablets, respectively after single-dose administration to healthy subjects.

Methods: This was a 2-part, open-label, randomized, crossover study in healthy adult subjects (18-65 years old; NCT03095638;GSK205893). In Part 1, subjects were randomized to receive 5 tablets of 10mg IR (TRT-A) or 1X 50mg IR tablet (TRT-B, reference) over two dosing periods. In part 2, subjects received 5 tablets of 5mg DT administered as a dispersion and immediately taken (TRT-C) or 5 tablets of 5mg DT administered direct to mouth (TRT-D), or a 25mg IR tablet (TRT-E, reference) over 3 dosing periods. There was a washout of at least 7 days between doses of study medication. Plasma DTG concentrations were determined following collection of serial PK samples for 72 hours after each dose of study drug. Non-compartmental PK analysis was performed; geometric least squares (GLS) mean ratios and 90% confidence intervals (CI) for comparator versus reference were generated. Safety assessments included monitoring of adverse events, clinical lab tests, vital signs, ECGs and physical exam.

Results: All 14 subjects completed Part 1 and all 24 subjects completed Part 2 of the study. Demographics, including age, body mass index (BMI), height and weight were similar between study parts. In Part 1, following administration of 1X 50mg DTG tablet. In Part 2, geometric mean systemic exposure to DTG were approximately 1.5-fold to 1.8-fold greater with TRT-C and TRT-D than that observed following TRT-E. GLS mean ratios (90% CI) of TRT-C versus TRT-E and TRT-D versus TRT- E for AUC(0-inf), Cmax, and AUC(0-t) were 1.62 (1.50, 1.76) and 1.55 (1.43, 1.67), 1.79 (1.62, 1.98) and 1.80 (1.63, 1.99), and 1.63 (1.50, 1.77) and 1.55 (1.43, 1.68), respectively. The terminal elimination half-lives for all treatments ranged from 15.5 to 16.2 hours. All formulations of DTG were safe and well tolerated. There were no clinically significant findings in clinical laboratory values, vital sign measurements, or ECG findings during the study.

Conclusions: Higher bioavailability was observed with the pediatric dispersible tablet formulation while the lower strength immediate release tablet showed similar bioavailability to the higher strength tablet reference. Both pediatric formulations were well tolerated. The 5mg DT is suitable for further use in pediatric clinical trials.
Highly active antiretroviral treatment increases the short-term risk of incident opportunistic infections among people living with HIV/AIDS

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Background: Highly active antiretroviral therapy (HAART) causes a rapid increase in CD4+ T cells during the first 6 months of treatment and may enhance the development of opportunistic infections (OIs). This nationwide, population-based cohort study aimed to determine the short-term and long-term effects of HAART on the development of incident OIs in people living with HIV/AIDS (PLWHA) in Taiwan.

Methods: From Jan. 1, 2000, we identified adult PLWHA from Taiwan CDC HIV Surveillance System. HIV-infected individuals were defined as positive HIV-1 Western blot. Methods: All PLWHA were followed until a diagnosis of OI, death, or December 31, 2014. A time-dependent Cox proportional hazards model was used to determine the short-term (≤180 days) and long-term (>180 days) effects of HAART on incident OIs among PLWHA, while considering death as a competing risk event.

Results: Of the 26,258 PLWHA, 6,413 (24.4%) developed OIs during a mean follow-up period of 5.09 years. After adjusting for age, sex, comorbidities, and AIDS status, PLWHA who received HAART were more likely to develop OIs than those who did not receive HAART. While considering the short-term and long-term effects of HAART on the development of OIs, HAART was a risk factor for the development of OIs in the short term, but was a protective factor against OIs in the long term.

Conclusions: HAART increased the risk of OIs development in the short-term. PLWHA receiving HAART should be monitored carefully for OIs development during the early phase of treatment.
HIV Viral Load Suppression status and associated factors among patient on ART in Ethiopia

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Background: With the rapid scale-up of antiretroviral treatment (ART) availability in sub-Saharan Africa, the need for appropriate treatment monitoring has also increased. The World Health Organization (WHO) recommends viral load test as the preferred monitoring approach to diagnose and confirm ART failure. In Ethiopia, immunologic and clinical parameters have been used to monitor HIV patients on ART. Recently the government has implemented a VL testing in multiple testing centers across the regions; however, the viral suppression rate is not well studies. The aim of this study was therefore, to determine the level of viral suppression and associated factors among HIV patients on active ART.

Methods: We used routine VL program data of 8,389 adults and children, measured for patient clinical monitoring at Ethiopian public health institute, HIV national reference laboratory. The laboratory received biological sample (Plasma, whole blood or dried blood spot) to determine the viral load from 70 health facilities referral linkage. The laboratory diagnostic result was entered in to a database built for this purpose on daily basis by trained data clerk. Duration of client on ART was at least six months at the time of viral load measurement. The main outcome variable of the study was VL measured by Abbott Real Time and Cobas Ampliprep/Cobas Taqman plat forms. Socio-demographics and baseline clinical characteristics were used as exposure variable. Multivariable regression analysis was employed to identify the associated factors with high viral load. P value less than 0.05 was used to declare the statistical significance.

Results: Of the participants 5,038(60%) were female, 1,136 (13.6%) were children (less than 15). The overall viral load suppression (HIV RNA copies<1000 copies/ml) was found to be 86%. The VL suppression was not significantly different between the two genders. Advanced WHO clinical stage and poor adherence were significantly associated with impaired virologic suppression.

Conclusion: This study showed generally sub optimal viral suppression among patient under ART which might pose a question on the success of ART program in Ethiopia. This finding would supplement to serve as the evidence for tracking the progress towards the third of the 90-90-90 UNAIDS ambitious plan.

Keywords: HIV, Antiretroviral drugs, viral load, viral suppression
Molecular Docking and Pharmacokinetics studies of Natural Compounds to Investigate Potential Antivirals Against Chikungunya Virus

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Molecular Docking and Pharmacokinetics studies of Natural Compounds to Investigate Potential Antivirals Against Chikungunya Virus

Background: Chikungunya virus (CHIKV) positive single-stranded RNA virus is transmitted by Aedes mosquitoes. CHIKV geographical distribution is worldwide, including America and European countries. After incubation of 3-5 days, CHIKV symptom like fever with joint pains, maculopapular rashes and others start appearing. No effective antiviral treatment available for CHIKV. The aim of this study, we performed the computational study for a screening of potential antivirals against CHIKV targeted proteins (nsP2). Further, the analyzed the highest scoring compound to toxicity profile.

Methods: 3D structures of CHIKV nsP2 (3TRK) were retrieved from Protein Data Bank (PDB). We performed molecular docking on natural product against CHIKV non-structural proteins (nsP2). All chemical structures of these compounds were sketched in ChemBioDraw Ultra 12.0 (CambridgeSoft). Molecular docking was performed using AutoDock Vina 1.5.6. All highly scoring compound, the Lipinski’s values were computed and compared with the available data from PubChem. This high-affinity compound is analyzed for the AMDET properties were calculated by DruLito (Drug LiknessTool) (www.niper.gov.in/pi_dev_tools/DruLiToWeb/DruLiTo_index.html) and Molinspiration Online tool (http://www.molinspiration.com/).

Results: We observed that compound1, compound 5, compound17 and compound 20 interacts with CHIKV proteins has the highest binding affinity with nsP2 at respectively -8.5Kcal/mol, -7.8 Kcal/mol, -6.7 Kcal/mol and -7.9 Kcal/mol. The compounds used in this study also follow the Lipinski’s rule of five in addition nearby similar properties to that of in PubChem. Further, the computational study confirmed any toxicity of the compound to different toxicity testing species.

Results: In this study, we aim to investigate the potential inhibitory effects of plant derivatives, natural plant on CHIKV non-structural proteins. In-silico study, finding high-scoring potential compounds to inhibit the CHIKV replication. These compounds are needed to validate in-vitro and in-vivo study.
Impact of High-Titer Immune Plasma on the Pharmacokinetics of Haemagglutination Inhibition Titers in Hospitalized Adults with Severe Influenza

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Background: Passive immunotherapy approaches have been investigated for the treatment of severe viral diseases, including Ebola, Spanish flu, and Middle East Respiratory Syndrome. Though frequently used, there is no pharmacokinetic (PK) analysis available to inform the anticipated antibody response expected during passive immunotherapy studies. A randomized phase 2 trial was performed to assess the efficacy and safety of anti-influenza plasma in patients with severe influenza. The pharmacokinetics of haemagglutination (HAI) antibody titers following these two treatments were assessed.

Methods: Hospitalized patients with influenza A (H1N1, H3N2) or B and severe disease were randomized to either plasma + standard of care (SOC) versus SOC alone and were followed for 28 days. Patients randomized to plasma received 2 units fresh frozen plasma with an HAI titer of 1:80 or greater to their infecting influenza strain. All patients received SOC antivirals. Serial PK samples were collected on study days 0 (predose), 2, 4, 7, 14 and 28. “Dose” was determined by multiplying administered plasma volume with HAI titer then adjusted by weight (Dw). Area under the curve (AUCb) was calculated from baseline-adjusted HAI titers (Tb) using non-compartmental methods (Phoenix WinNonlin 7.0). The percentage achieving a HAI titer > 1:40, which is associated with protection in vaccine studies, was compared between treatment groups. As HAI titers are anticipated to rise naturally due to infection, patients with measurable titers were analyzed by the strain with which they were infected (matched analysis) vs. with what they were not infected (non-matched analysis). P-values were calculated using unpaired t-test.

Results: Patients (plasma+SOC group) with influenza H3N2/Texas had positive correlation between Dw and Tb on days 2 (r2=0.48) and 7 (r2=0.47), and between Dw and AUCb,0-2 days (r2 = 0.4). No positive correlation was observed in patients with influenza H1N1. There were an insufficient number of patients with influenza B to assess a PK relationship. In the matched analysis, the average HAI AUCb,0-2 days of patients in the plasma+SOC group was numerically higher compared to the SOC group (p>0.05). In the non-matched analysis, the average HAI AUCb,0-2 days was also higher in the plasma+SOC group but reached statistical significance only with the H1N1 strain (p<0.01). The percentage of patients with HAI titer > 1:40 was similar between treatment groups, except on day 2 when the plasma+SOC group had a higher percentage than the SOC group (84.4% vs. 59%, p=0.02).

Conclusion: Plasma immune titers correlated with dose for the H3N2/Texas subtype, but only during the first 2 days post anti-influenza immune plasma treatment. More patients who received immune plasma achieved raw titers > 1:40 by day 2. Inability to distinguish innate immune response from those antibodies received from immune plasma administration was the challenge, as titers increase from baseline over time regardless of treatment received. Our results suggest that anti-influenza immune plasma administration may have some utility in boosting the initial haemagglutination titers against the influenza virus before natural immune response can mount. A phase 3 trial is underway to further assess the clinical benefit of this intervention.
Pharmacokinetic-Pharmacodynamic of Rilpivirine in treatment-naïve HIV-1-infected patients treated with the single-tablet regimen rilpivirine/emtricitabine /tenofovir disoproxil fumarate
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Background: Rilpivirine (RPV) presents an important inter-individual pharmacokinetic (PK) variability. Trough plasma concentration (Ctrough) of RPV was correlated with virologic response but no clear threshold value was established. Consequently, we first developed a population PK (PopPK) model to describe the RPV PK and its variability in HIV-infected patients. A shorter half-life than reported in the Summary of Product Characteristics was found, confirming the result of Aouri et al. The aim of the present study was to develop a pharmacokinetic-pharmacodynamic (PK-PD) model to establish concentration-response relationships for future treatment optimization.

Methods: We conducted a multicenter, retrospective and observational study in naïve and pre-treated patients treated with RPV/emtricitabine (FTC)/tenofovir disoproxil fumarate (25/200/300mg QD) regimen, for whom sparse RPV plasma concentrations were determined within the context of routine therapeutic drug monitoring (November 2012 to November 2015). Plasma HIV-RNA load (VL), CD4 cells (CD4) and drug-resistance associated mutations were collected at baseline and during the monitoring. PK-PD analysis was performed with Monolix2016R1 software. The individual Ctrough were predicted based on the previously developed PopPK model using Bayesian approach. A HIV dynamics model was developed to estimate the effect of RPV plasma concentrations both on the infection rate of CD4 cells by the virus and on the VL.

Results: Sixty-three treatment-naïve patients were included in the PK-PD analysis, with a follow-up ranging from 2 to 30 months. At baseline, median VL was 15,800 copies/ml (interquartile range (IQR): 4,445-31,300), with three patients having VL >100,000 copies/ml. Median baseline CD4 was 441 cells/mm3 (IQR: 345-589). Seventeen patients stopped treatment. VL was <40 copies/ml in 50/55 (91%) patients at M6, 48/53 (91%) at one year and 41/43 (95%) at two years. At baseline, among the 59 patients with available genotype, 2 had RPV specific resistance mutations (E138A n=1; V179L n=1). Virologic failure was observed in 4 patients: two of them developed RPV specific resistance mutations at M11 (E138K) and M20 (Y181C+M230L), respectively. The parameters of the PD model were the production rate constant of uninfected target cells (S₀), elimination rate constant of infected cells (δ), production rate constant of free virions (c), VL at baseline (VL₀), CD4 cell count at baseline (CD4₀) and the RPV concentration producing 50% of the maximum effect (C50RPV). The model was over-parameterized and δ needed to be fixed to the previously reported value of 15.2 per month. The interindividual variability (IIV) of δ, S₀ and c could not be accurately estimated, and were consequently fixed to zero. The first estimated value of C50RPV was in line with the empirical currently acknowledged target RPV Ctrough of 50 ng/ml. However, a bias associated with an underestimation of the highest VL values at baseline was observed, and the model lacked stability.

Conclusion: The estimated value of C50RPV was within the same range as efficacy target RPV Ctrough currently used in clinical practice. However, our PD model showed some limitations. Consequently, we plan to test alternative HIV dynamics models to improve stability and performance of the PK-PD model, in order to better define the target Ctrough.
Race/Ethnicity and Protease Inhibitor Use Influence Plasma Tenofovir Exposure in Adults Living with HIV-1 in AIDS Clinical Trials Group Study A5202

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Background: AIDS Clinical Trial Group A5202 was a phase 3b, randomized, partially blinded equivalence study of open-label atazanavir/ritonavir or efavirenz, plus either placebo-controlled tenofovir disoproxil fumarate/emtricitabine, or abacavir/lamivudine in treatment-naïve adults living with HIV-1, evaluating efficacy, safety and tolerability. We report an analysis on the contribution of participant characteristics to the disposition of tenofovir plasma concentrations.

Methods: Tenofovir drug concentration data were available in the majority of study participants (n = 817). Pharmacokinetic analysis of tenofovir was performed using nonlinear mixed-effects modeling. One- and two-compartment models with first-order absorption and first-order elimination were evaluated. An exponential error model was used for examination of inter-individual variability (IIV), and a proportional and mixed error model was assessed for residual variability.

Results: The final structural model contained two compartments with first-order absorption and elimination. IIV was estimated for apparent clearance (CL/F) and the first-order absorption rate constant (ka), and a proportional residual variability model was selected. Final mean parameter estimates were: ka = 2.87 hr⁻¹, CL/F = 37.2 L/hr, apparent volumes of the central and peripheral compartments = 127 and 646 L, and apparent inter-compartmental clearance = 107 L/h.

In addition to race/ethnicity, creatinine clearance, and assignment to atazanavir/r or efavirenz were significantly associated with CL/F (p < 0.001).

Conclusions: Race/ethnicity is associated with tenofovir oral CL in HIV-1 positive, treatment-naïve adults. This covariate relationship may provide further insights into potential differences in efficacy and the risk of adverse events in different patient populations, especially moving forward with the known benefits of pre-exposure prophylaxis, considering tenofovir disoproxil fumarate is the primary medication used.
Population pharmacokinetic analysis for darunavir and tenofovir alafenamide in HIV-1-infected patients on the darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) single-tablet regimen (AMBER and EMERALD studies)

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Background: Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10mg, the first once-daily, darunavir-based, HIV-1 single-tablet regimen (STR), is approved in the EU and under regulatory review in the US. Efficacy and safety of D/C/F/TAF is under investigation in two randomized Phase 3 studies in HIV-infected patients (AMBER [NCT02431247], EMERALD, [NCT02269917]). The current analysis evaluated darunavir and TAF pharmacokinetics (PK) in these studies.

Methods: Sparse samples (up to Week 48) were obtained from patients receiving D/C/F/TAF in AMBER and EMERALD, to quantify plasma concentrations of DRV (AMBER, EMERALD) and TAF (AMBER only) using validated LC-MS/MS methods. For TAF, also rich sampling from healthy volunteer studies and rich and sparse sampling from a Phase 2 study (HIV-infected patients) was used. The existing population PK model for cobicistat-boosted darunavir was updated using these data, and a new population PK model for TAF (administered with darunavir/cobicistat) was developed. For each analyte, the impact of selected demographic factors was evaluated and incorporated as a covariate in the final model, as appropriate. Final models were used to derive individual exposure metrics (C0h and AUC24h for DRV; AUCtau for TAF) for HIV-1-infected patients using D/C/F/TAF in EMERALD and/or AMBER.

Results: The PK profile of TAF, a tenofovir prodrug, is characterized by rapid absorption, with median tmax of approximately 0.50 hours, and rapid elimination, with median half-life of approximately 0.40 hours. TAF plasma concentrations are typically undetectable by 5 to 6 hours post-dose. The TAF PK were best described by a one-compartment disposition model with absorption described by a dual input (slow and fast pathway). Absorption via the slow pathway was described by a first-order absorption rate constant, while absorption via the fast pathway was described by a series of transit compartments following an absorption lag time. Covariate effects of lean body mass and α1-acid glycoprotein on TAF apparent clearance were included in the model. Based on estimated individual exposure metrics, the TAF mean (SD) AUCtau in HIV-1-infected patients using D/C/F/TAF in AMBER (n=355) was 132 (41) ng·h/mL.

For darunavir, the population PK model consists of a 2-compartment disposition model with sequential zero-order input into the depot compartment followed by first-order absorption. Effects of total daily dose, α1-acid glycoprotein and body weight on darunavir apparent clearance were included in the model. Based on estimated individual exposure metrics, the darunavir mean (SD) C0h and AUC24h in HIV-1-infected patients using D/C/F/TAF was 1,899 (759) ng/mL and 87,909 (20,232) ng·h/mL, respectively, in AMBER (n=355) and 1,813 (859) ng/mL and 85,972 (22,413) ng·h/mL, respectively, in EMERALD (n=750). Darunavir and TAF PK were not affected by age, race or gender, and there were no apparent relationships with efficacy or safety parameters in AMBER and EMERALD.

Conclusions: Population PK models for TAF and darunavir were successfully developed to describe the TAF and darunavir PK and associated variability, when administered as the D/C/F/TAF STR. Darunavir and TAF PK parameters in HIV-1-infected patients treated with the D/C/F/TAF STR in AMBER and EMERALD were comparable to those in historical studies with boosted darunavir or TAF in other antiretroviral combinations.
Predicted Pharmacokinetic Interactions of Rifampicin with Ritonavir-Boosted Darunavir

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Background: Tuberculosis (TB) is the most common severe comorbidity in HIV patients, significantly impacting prognosis and survival rates in co-infected patients. However, co-administration of rifampicin (RIF) and boosted darunavir (DRV) is contra-indicated due to significant pharmacokinetic interactions that may reduce efficacy of DRV. This study aimed to assess the effects of RIF on the pharmacokinetics of ritonavir (RTV)-boosted DRV (DRV/r) and evaluates strategies to overcome the pharmacokinetic interaction. In vitro results were implemented in physiologically-based pharmacokinetic (PBPK) models to identify treatment regimens with the highest probability of successful clinical outcomes.

Methods: To investigate the complex interplay between CYP3A induction, inhibition, metabolism and hepatic transport, studies were performed using the Hepatopac™ system which displays a singular capacity in capturing all relevant pathways. Cultures were incubated in the presence or absence of RIF (3 µM) for 3 days, followed by a pre-incubation (18 h) with RTV (0.033-1 µM) to simulate steady-state-like conditions. Finally, DRV (0.5 µM) was added and metabolism was assessed over 48 h. All metabolism experiments were performed in the presence of RTV and/or RIF. In vitro data were fed into purpose-built PBPK models to assess pharmacokinetic interactions for the dosing regimens of interest.

Results: In vitro inhibition studies confirmed the potent inhibition of RTV of the metabolism of DRV (IC50 RTV:14 nM), which was counteracted by the induction observed following RIF treatment (IC50 RTV:46 nM). Custom PBPK models were built for DRV, RTV and RIF to ensure all relevant interaction mechanisms were adequately captured. Simulated DRV/r pharmacokinetic parameters accurately predicted observed values (in clinical studies) for DRV Cmax, AUC24h, and Ctrough of DRV/r 800/100 mg qd. Addition of 600 mg RIF resulted in a pronounced decrease of DRV Cmax, AUC24h, and Ctrough in the various simulated regimens (800/100 mg qd DRV/r, 1600/200 mg qd DRV/r and 800/100 mg bid DRV/r).

Conclusions: The current study generated a framework of in vitro data aimed at supporting the development of accurate PBPK models for predicting the pharmacokinetics of DRV/r as well as to predict potential DDI following co-administration of RIF. Based on these findings, changing the DRV/r regimen from 800/100 mg qd to 800/100 mg bid was identified as the most promising regimen to counter the interaction of 600 mg qd RIF in HIV patients co-infected with TB.
Darunavir unbound concentrations in plasma is the relevant concentration to predict darunavir efficacy in subject of different body mass index.

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**Background:** Darunavir (DRV) is highly bound to plasmatic protein. Unbound DRV plasma concentration (Cu) is the driving concentration controlling pharmacological effects. Paradoxically, Cu is unexplored for the therapeutic drug monitoring (TDM), mainly for practical reasons. Conversely, Cu could be more relevant than the total concentration (Ct) to monitor DRV regimen, especially in the context of monotherapy. Indeed, virological failures are even more often reported during DRV/r monotherapy, compared to combined or dual therapy, despite efficient Ct. Our objectives were(i) to develop a POPPK model accounting simultaneously for total and unbound plasma DRV concentrations,(ii) to identify relevant covariates able to explain between-subject variability (BSV) (iii) to predict by simulation the ability of Cu to control the DRV concentration into HIV reservoirs.

**Methods:** A population pharmacokinetic model, using a non-parametric NPAG algorithm in Pmetrics, was developed from measured Cu and Ct of 57 HIV patients. A model, graphically evaluated, including body mass index (BMI) as the most relevant covariate to explain the BSV of Cu, was used to predict diffusion in a HIV sanctuary, the cerebro-spinal fluid (CSF).

**Results:** A one-compartment model, with first order elimination described adequately the kinetic profiles of Cu and Ct. BMI improved the model through an influence on intrinsic clearance (Clint) and affinity constant of DRV for plasma protein. Probability of target attainments of concentration above inhibitory concentrations 50 and 90 ranged between 24.4-99.7% and 18.7-99.7% for DRV in CSF, depending on BMI, dosing regimen and selected Cu CSF/plasma ratio.

**Conclusion:** Our study inaugurates the unbound form modeling, fitting simultaneously DRV Cu and Ct. From this, two key points emerged, imperceptibles from Ct: (i) patients with a large BMI were those with the highest Clint, being the clearance controlling Cu; (ii) high BMI was also associated with a higher affinity between DRV and plasmatic protein. Then, the total clearance (CL) that control Ct is minimally affected by BMI, a decrease of Clint being compensated by an increase of bound DRV, by higher affinity with its transport protein. This confounding effect of BMI on the two components of CL renders useless TDM based on Ct for patients with high BMI. In contrast a TDM based upon Cu could detect underexposed patient, especially those having a high BMI, allowing a dosing adjustment to compensate for a high intrinsic clearance despite normal Ct.
Evaluation of Tenofovir and Emtricitabine in the Penile Compartment of Men Receiving Oral Pre-exposure Prophylaxis for HIV Prevention

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Background: Pre-exposure prophylaxis (PrEP) using tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has been shown to be highly effective at preventing HIV infection among adherent persons. Penile HIV acquisition accounts for nearly half of total HIV infections yet pharmacokinetic studies assessing mucosal distribution of antiretroviral drugs to inform PrEP development have largely focused on rectal and vaginal tissues. This study sought to measure tenofovir (TFV) and FTC concentrations in the urethra and glans of men receiving TDF/FTC as PrEP to define drug penetration into penile tissues that are relevant to HIV acquisition in men.

Methods: Urethral, glans surface, rectal, and blood plasma specimens were collected from HIV-negative men who have sex with men, 18-49 years old, at 4 and 24 hours after a single oral dose of TDF/FTC (n=9), or after 4 and 10 days of daily oral TDF/FTC (n=9). Polyester swabs were inserted into the urethra (urethral swabs), prewet with saline and rolled along the glans surface (glans swabs), or collected from the rectal mucosa via rigid sigmoidoscopy (rectal swabs). Tenofovir (TFV) and FTC were extracted from swabs and plasma using 80% methanol and measured by high performance liquid chromatography-mass spectrometry.

Results: TFV and FTC were detected on 18 and 28 of 36 urethral swabs, respectively, but only 6 and 12 of 28 glans swabs, respectively. A wide range of TFV (median: 62 ng/swab, range: 13-2800 ng/swab) and FTC (median: 61 ng/swab, range: 11-9685 ng/swab) concentrations were observed on urethral swabs, yet TFV and FTC concentrations correlated with each other (r=0.816, p<0.001). TFV and FTC concentrations in urethral secretions were estimated to be 18 and 12-fold as high in paired plasma specimens for TFV and FTC, respectively. TFV (median: 162 ng/swab, range 58-1725 ng/swab) and FTC (median: 207 ng/swab, range: 16-9855 ng/swab) levels on glans swabs containing detectable drug levels were similar to drug levels on urethral swabs.

Conclusions: Penile specimens collected from men receiving TDF/FTC as PrEP document distribution of both FTC and TFV to the urethra but much less to the glans surface. Levels of TFV and FTC measured in the urethra were greater than those in blood plasma and generally paralleled rectal drug levels. Data point to the possible role of urethral TFV and FTC in PrEP protection of men against penile HIV acquisition.
Pharmacokinetics of tenofovir-monoester following single-dose administration of tenofovir disoproxil fumarate

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Background: Tenofovir (TFV) disoproxil fumarate (TDF) is a prodrug nucleotide reverse transcriptase inhibitor that undergoes multiple conversion and phosphorylation steps to form the intracellular active moiety, tenofovir-diphosphate (TFV-DP). Following oral administration, tenofovir disoproxil is hydrolyzed by esterases in the blood/gut/liver to TFV-monoester, which is then converted to TFV. TFV-monoester reportedly circulates at low levels following TDF administration, but its clinical pharmacokinetic profile, to our knowledge, has not been established. Physiochemical characteristics and in vitro studies suggest that TFV-monoester can penetrate cells more efficiently than TFV, potentially influencing the cell pharmacology of TFV-DP. Here, we describe the pharmacokinetics of TFV-monoester in humans following single-dose administration of TDF 300 mg/emtricitabine (FTC).

Methods: Samples were obtained from a previously conducted intensive bioequivalence study in healthy volunteers. Participants received a single oral dose of TDF/FTC following an overnight fast (>10 hours). Blood samples were collected at time 0 (pre-dose), 0.25, 0.5, 1, 2, 4, 6, 10, 24, 48, and 72 hours post-dose. TFV-monoester and TFV concentrations were quantified using LC-MS/MS methods, with lower limits of quantitation (LLOQ) of 0.1 and 10 ng/mL, respectively. PK parameters for TFV-monoester and TFV were calculated using noncompartmental methods with linear up-log down trapezoidal rule (Phoenix WinNonlin, v8.0). Geometric mean (GM) and geometric coefficient of variation (%CV) PK results were calculated from log-transformed data.

Results: Samples were available from 24 healthy volunteers (11 males; 19 white, 3 black, 2 Hispanic). Following oral administration of TDF/FTC, TFV-monoester levels were rapidly quantifiable and reached peak concentrations of 131.6 ng/mL (69.8%) at a median (range) of 0.5 (0.25 – 2) hours post-dose. TFV-monoester area-under-the-curve from time 0 to infinity (AUC∞) was 93.9 ng*h/mL (46.8%). TFV-monoester concentrations exhibited monophasic decline, with a half-life of 0.44 hr (31.0%). By 4 hours post-dose, 7/24 samples were below the LLOQ for TFV-monoester. In comparison to plasma TFV concentrations through 4 hours post-dose, TFV-monoester Cmax and AUC0-4h were 59.2% and 20.8% of circulating TFV levels, respectively. When extrapolated out to infinity, TFV-monoester accounted for 4.7% of TFV AUC∞. TFV AUC0-4h correlated with TFV-monoester AUC0-4h (R2 = 0.173, p=0.043), though this relationship weakened with TFV vs. TFV-monoester AUC∞ comparisons (R2 = 0.135, p=0.078).

Conclusions: TFV-monoester appeared rapidly in plasma with Cmax concentrations that were more than half that of TFV, and thereafter declined with a half-life of 0.44 hr, suggesting rapid blood/tissue/liver metabolism. Further research is needed to determine the relevance of circulating TFV-monoester on cell loading and the resulting cellular pharmacology of TFV-DP.
Successful use of the potent enzyme inducer enzalutamide in a treatment-experienced HIV positive male with prostate cancer

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Background: A 57-year-old treatment-experienced HIV-positive Caucasian male diagnosed in 1988 was virally suppressed with CD4 count above 500 cells/mm3 on darunavir 600 mg BID, ritonavir 100 mg BID, etravirine 200 mg BID, raltegravir 400 mg BID, and tenofovir/emtricitabine 300 mg/200mg once daily. In 2014 he was diagnosed with Gleason 4 + 5 prostate cancer with bone metastases and experienced progression of his cancer while on bicalutamide and leuprolide. He then required enzalutamide for metastatic, castration-resistant prostate cancer.

Enzalutamide, a pure androgen receptor signaling inhibitor used in prostate cancer, has an elimination half-life of 5.8 days and is a potent CYP3A4 inducer and moderate inducer of CYP2C19 and 2C9, as well as CYP2B6 and UGT1A1/4. It reduces midazolam, omeprazole and S-warfarin AUC by 86%, 70%, and 56%, respectively. Enzalutamide therefore has the potential to significantly reduce antiretroviral plasma concentrations with the risk of possible virologic failure.

We describe the successful use of enzalutamide in an HIV treatment-experienced patient with significant antiretroviral resistance, including high level resistance to all nucleoside reverse transcriptase inhibitors, all first generation non-nucleoside reverse transcriptase inhibitors, and all protease inhibitors except for darunavir (low-level resistance).

Methods: Prior to start of enzalutamide, raltegravir was changed to dolutegravir 50 mg BID to provide a higher genetic barrier to resistance and to compensate for the induction effect of enzalutamide. Baseline therapeutic drug monitoring (TDM) one week after switch to dolutegravir was obtained for dolutegravir, darunavir, and etravirine. One week after starting enzalutamide therapy, the ritonavir dose was increased to 200 mg BID to counter the impact of enzalutamide on enzyme induction. Follow-up TDM at weeks 1, 4, and 8 after start of enzalutamide initiation was obtained to ensure adequate plasma concentration of his antiretrovirals.

Results: Our findings showed no change in darunavir concentrations at Week 1 of concomitant therapy, a 25% reduction compared to baseline at Week 4, and a further 8% reduction at Week 8 reflecting the long half-life of enzalutamide. A non-significant decrease in etravirine concentration by Week 8 was observed. An impact of enzalutamide initiation on dolutegravir concentrations was not observed. After 7 months of concomitant therapy with enzalutamide, prostate-specific antigen (PSA) improved from 1.1 to 0.11 ug/L. At two years follow-up, the patient remains on the same medications. His PSA continues to be low at 0.13 ug/L, his CD4 is 398 cells/mm3 and his viral load remains suppressed.

Conclusions: Etravirine and dolutegravir concentrations did not significantly change with initiation of enzalutamide. Doubling the ritonavir dose appeared to counteract the induction effect of enzalutamide on darunavir concentrations. Long-term virologic suppression was maintained in a treatment-experienced HIV patient along with sustained efficacy of his treatment for prostate cancer. A preemptive strategy of adjusting antiretroviral treatment and implementing TDM may be necessary during concomitant therapy with other drugs that may have a significant effect on antiretroviral plasma concentration.
Pharmacokinetics, Metabolism and Excretion of Radiolabeled Fostemsavir Administered with or without Ritonavir in Healthy Male Subjects.

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Background: Fostemsavir (FTR), a prodrug of temsavir (TMR), is a first-in-class attachment inhibitor currently in Phase 3 for use in heavily treatment experienced HIV-1 infected patients. This study was conducted to investigate the pharmacokinetics (PK), biotransformation and routes of elimination of FTR and to investigate the impact of ritonavir (RTV) on TMR.

Methods: This was an open-label, single-dose study [BMS study AI438005, GSK study 206265] in 18 healthy male subjects assigned to one of four groups receiving one 300-mg dose of [¹⁴C]FTR (100 μCi) administered ± RTV. Subjects in groups A (n=6) and B (n=3) were dosed with [¹⁴C]FTR alone on Day 1. Subjects in groups C (n=6) and D (n=3) received RTV 100-mg twice daily with food on Days 1 to 9, a single dose of [¹⁴C]FTR, along with RTV, on Day 10 and a final dose of RTV with food 12-hours later. Bile samples were collected continuously through an oral-gastro-duodenal tube from 3 to 8 hours post [¹⁴C]FTR dose from subjects in groups B and D. Blood, fecal and urinary outputs were collected from all groups for PK, total radioactivity assay and biotransformation analyses.

Results: Seventeen subjects completed the study. The total recovery of administered dose of FTR averaged 78% or 89%, when dosed alone or with RTV, respectively. Approximately 44% to 58% of the dose was excreted in urine, and 20% to 36% in feces; biliary excretion was about 5%. These percentages were not significantly altered by RTV. TMR had a half-life of 5 to 10 hours; metabolites became major circulating species in the plasma at the 8 hour sample time with the levels of oxidative metabolites (formed by CYP3A4) being reduced with RTV treatment. The geometric means of TMR Cmax and AUC(INF) were 45% and 66% higher with RTV compared to FTR alone, respectively; total radioactivity AUC(INF) was decreased by approximately 68% in the presence of RTV, likely due to inhibition of production of circulating metabolites with long half-lives by RTV. Metabolic profiling showed that following administration of FTR, TMR was extensively metabolized by hydrolytic and oxidative pathways, accounting for 36.1% and 21.2% of recovered dose, respectively, suggesting that hydrolysis is the major clearance pathway. Only trace levels of glucuronide metabolites were detected (by mass spectrometry) in bile suggesting that UGT-mediated metabolism is a minor clearance pathway.

Conclusions: The major route of TMR elimination is biotransformation (primarily hydrolytic and oxidative pathways) with the majority excreted as metabolites (<2% as unchanged TMR) in the urine and feces. The impact of RTV was reduced oxidative biotransformation resulting in increased exposure of TMR.
Pomalidomide Pharmacokinetics in Patients with HIV on Antiretroviral Therapy

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Background: Pomalidomide is a treatment option for Kaposi Sarcoma (KS) in patients with HIV on antiretroviral therapy (ART). Data on the effects of ART on pomalidomide are lacking. We analyzed pomalidomide pharmacokinetics (PK) in patients receiving ART and compared the differential boosting effects of ritonavir (RTV) versus cobicistat (COBI) on pomalidomide, a CYP3A4/P-glycoprotein (P-gp) substrate.

Methods: Pomalidomide plasma samples were obtained from patients enrolled in 2 studies, NCT01495598 and NCT02659930, who either received oral pomalidomide 5mg or oral pomalidomide (2, 3 or 4mg doses) plus intravenous liposomal doxorubicin (20mg/m2) for KS treatment. Pomalidomide was administered daily for 21 days of a 28-day cycle and PK samples were collected on cycle 1 day 1 (C1D1; first dose) at pre-dose, 1, 2, 3, 4, 6, 8, and 24 hours post dose. Noncompartmental analysis (Pharsight Corp) was used to calculate pomalidomide plasma PK. Maximum concentration and area under the curve were dose normalized (CmaxD and AUC0-infD). Statistical analyses were performed using the nonparametric Mann-Whitney U-test.

Results: Samples from 29 patients with HIV on ART were analyzed; 13 of which were on RTV (6) or COBI (7) boosted ART. C1D1 pomalidomide CmaxD and AUC0-infD were higher in patients on COBI boosted regimens compared to RTV: geomean (5th and 95th %) = 13.4ng/ml/mg (10.5-16.3) vs. 6.6ng/ml/mg (3.2-9.9); p = 0.022 and 136.1 hr*ng/mL/mg (90.6-181.7) vs. 62.7 hr*ng/mL/mg (19.5-105.8); p=0.052, respectively. Patients on boosted RTV had a larger apparent volume (V/F): 120.5 L (95%CI: 94.9 -146 L); p=0.0043 and a faster clearance (CL/F): 15.9 L/hr (95%CI: 9.93 – 21.9 L/hr); p=0.052 than patients boosted with COBI, Vz/F: 62.2 L (52.6-71.8 L); CL/F: 7.35 L/hr (3.88 – 10.8 L/hr), respectively. Half-lives were similar in RTV and COBI groups: geomean (5th and 95th %) =5.2 hours (3.1-7.4) and 5.8 hours (3.8-7.9), respectively. When comparing boosted vs. unboosted (n=16) regimens, only patients on COBI-boosted ART (n=7) were included, as prior studies have shown a lack of PK interaction between RTV and pomalidomide. Pomalidomide CmaxD (p=0.46) and AUCinfD (p=0.97) were similar between groups. Concomitant medications were assessed and additional clinically relevant drug interactions were not identified.

Conclusion: CmaxD and AUCinfD of C1D1 pomalidomide were higher in patients receiving COBI boosted ART, but only reached statistical significance with CmaxD. Half-lives in both booster groups were about 5 hours and similar to single dose PK of pomalidomide only reported in healthy volunteers. P-gp is likely the predominant mechanism of this drug interaction and COBI is the more potent inhibitor. Although pomalidomide CmaxD and exposure were higher in patients on COBI boosted ART, exposure was similar to the unboosted ART group. This was an unexpected observation without a clear explanation. Additional analyses should be performed to attempt to explain this observation. Overall, pomalidomide PK in the COBI group was consistent with drug interaction data of other strong CYP3A4/P-gp inhibitors (i.e. ketoconazole) and therefore may be used concomitantly with COBI or RTV boosted ART without need for dosage adjustment.
Management Strategies for Clinically Significant Drug-Drug Interactions with Bictegravir: Overview of the Regulatory Thought Process

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Background: The US FDA approved a fixed dose combination (FDC) of bictegravir (BIC), emtricitabine (FTC) and tenofovir alafenamide (TAF) as a complete regimen for the treatment of HIV-1 infection in adults. The objective of this work is to share the regulatory thought process that informed the clinical pharmacology recommendations regarding the effect of bictegravir on serum creatinine and managing drug interactions with medications or oral supplements containing polyvalent cations or metformin.

Methods: The applicant’s study reports were primarily used for the review. During the review process, frequent literature searches were conducted, exploratory analyses of the applicant’s data was performed and additional analyses from the applicant were requested.

Results: Effect BIC on Serum Creatinine: Clinical pharmacology assessment concluded that the effect of BIC on serum creatinine is not due to renal injury and can be attributed to inhibition of renal transporters. The conclusion is based on 1) in vitro studies demonstrating that BIC inhibits renal transporters such as OCT2 and MATE1, 2) in vivo trial where there was no change from baseline in the actual glomerular filtration rate measured using iohexol following the administration of BIC 75 mg for 21 days; 3) similar behavior was seen with several other drugs including another integrase inhibitor, dolutegravir.

Drug Interactions: Clinical pharmacology assessment of drug interaction data led to the following recommendations in the prescribing information:

1) Medications or Oral Supplements Containing Polyvalent Cations: Specific actionable information was included regarding concomitant and staggered co-administration of the FDC and antacids or supplements, including some recommendations for scenarios that were not evaluated in a drug-drug interaction trial.
2) Metformin: Healthcare professionals are referred to the prescribing information of metformin for assessing the benefit and risk of concomitant use of the FDC and metformin. The recommendation is consistent with metformin labeling recommendation for the co-administration of drugs that increase in metformin exposure similar to that observed following the co-administration of the FDC and metformin.
3) DDI data pertaining to other antiretroviral drugs was not included in the prescribing information because the FDC is a complete regimen for the treatment of HIV-1 infection and the safety and efficacy of concomitant HIV-1 antiretroviral therapy is unknown.
4) List of drugs in Section 7.6 “Drugs without Clinically Significant Interactions with BIKTARVY” of the prescribing information was restricted to only those drugs for which a DDI trial was conducted with the FDC (or components of the FDC) and the results of the trial showed no significant DDIs. Considering the complexity of predicting DDIs due to simultaneous involvement of multiple enzymes and transporters, predictions involving specific drugs based solely on in vitro data alone were deemed to be unacceptable for inclusion in Section 7.6.

Conclusions: The clinical pharmacology review of the FDC NDA resulted in significant changes to the management strategies of DDIs with medications or oral supplements containing polyvalent cations and metformin.
DDI Liability Evaluation and Risk Management Strategy for Drugs with No Clinical DDI Studies—A story from co-administration of Vosevi with statins

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Background: Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX, Vosevi®) was approved in 2017 for treatment of chronic HCV infection in adults who have failed prior direct-acting antiviral (DAA)-based therapies. SOF/VEL/VOX has significant DDI liabilities when co-administered with statins, increasing AUC and Cmax of pravastatin and rosuvastatin up to 7- and 19-fold, respectively. However, clinical DDI studies were not performed for five other marketed statins for which there is also a high likelihood for a significant DDI. An in-depth DDI liability analysis was employed to inform a risk management strategy that reduces the potential for myopathy, including life-threatening and rare rhabdomyolysis, which may be associated with increased statin exposure.

Methods:
• SOF (metabolite: GS-331007)/VEL/VOX: DDI liability evaluation as perpetrators
  Source: in vitro DDI assays and clinical DDI studies included in SOF/VEL/VOX submission
• Five statins (pitavastatin, atorvastatin, fluvastatin, simvastatin, lovastatin): DDI liability evaluation as victims
  Source: Statin labeling and published literature reports for DDI potential or transporter polymorphism
• Supporting DDI evidence from other inhibitor(s), like cyclosporine (CsA), with similar inhibition mechanism
  Source: statin/CsA labeling or published literature reports for DDI potential
• Statin adverse event (AE) evaluation
  Source: statin labeling/FDA FAERS database

Results:
• SOF (GS-331007)/VEL/VOX as DDI perpetrators:
  No inhibition/induction of CYP/UGT1A1 enzymes;
  Inhibition of transporters: P-gp/BCRP/OATP1B1/3
• Five statins (pitavastatin, atorvastatin, fluvastatin, simvastatin, lovastatin) as DDI victims:
  Not only substrates of enzymes (e.g., CYP3A4), but also substrates of transporters (e.g., OATP1B1/3, P-gp and BCRP)
  • CsA inhibition on statins:
    CsA increases exposure of rosuvastatin and pravastatin by a comparable magnitude as SOF/VEL/VOX;
    CsA significantly increases exposure of all marketed statins 4 to 12-fold, except for fluvastatin.
  • Statin AE severity evaluation:
    Increased pitavastatin dose (>4 mg) is associated with severe myopathy. Increased rates of myopathy (>25-fold) have been associated with increased simvastatin dose (~4-fold).

The above analysis indicates a significant DDI potential for the co-administration of five other statins with SOF/VEL/VOX, using CsA as a model inhibitor as it increases exposures of rosuvastatin and pravastatin by a comparable magnitude as SOF/VEL/VOX, based on clinical DDI studies. The following recommendations were developed as the risk management strategy:
• Pravastatin: dose ≤40 mg (AUC/Cmax ↑ 2.2/1.9X)
• Rosuvastatin: not recommended (AUC/Cmax ↑ 7/19X)
• Statins with no clinical DDI studies (atorvastatin, fluvastatin, lovastatin, pitavastatin and simvastatin): use the lowest approved statin dose. If higher doses are needed, use the lowest necessary statin dose based on a risk/benefit assessment.

Conclusions: In vitro and/or in vivo DDI studies are usually performed to inform clinical management of drug interactions in labeling. However, as it is infeasible to conduct a DDI trial for every suspected drug interaction, use of a risk management strategy is prudent to enable prediction of a potential for a PK-based interaction using known in vitro parameters and in vivo studies borrowed from compounds with similar DDI mechanisms. While applicable in this case, further study would be needed to confirm this approach before it can be applied to other cases.
Increased tenofovir-monoester concentrations with ledipasvir/sofosbuvir

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Background: We previously found that intracellular concentrations of tenofovir-diphosphate (TFV-DP) were significantly increased in HIV/HCV co-infected patients taking tenofovir disoproxil fumarate (TDF) in combination with sofosbuvir (SOF)-containing Hepatitis C virus (HCV) treatment. The mechanism behind this drug-drug interaction is unclear. A recent in vitro study suggested that SOF may reduce TDF hydrolysis to TFV via inhibition of carboxylesterase 2 (CES2). However, clinical data to support this proposed interaction are not available. TFV-monoester is an intermediate formed during TDF hydrolysis into TFV. Inhibition of CES2 may lead to increased TFV-monoester concentrations in persons on TDF and SOF, which may augment cell loading by virtue of its lipophilicity relative to TFV. This mechanism could contribute to the several-fold increased levels of intracellular TFV-DP in patients on TDF with SOF. Thus, we sought to examine the concentrations of TFV-monoester in individuals receiving TDF with ledipasvir/sofosbuvir (LDV/SOF).

Methods: HIV/HCV co-infected participants receiving TDF with a ritonavir-boosted protease inhibitor were sampled prior to (baseline) and 4 weeks after initiating LDV/SOF. Samples were obtained at pre-dose, and 1 and 4 hours post-dose. All participants received a standardized meal and PK assessments were conducted after directly observed dosing of their prescribed medications. TFV and TFV-monoester in plasma and TFV-DP in peripheral blood mononuclear cells (PBMCs), red blood cells (RBCs) and dried blood spots (DBS) were quantified using LC-MS/MS methods. PK data were log-transformed and compared between study visits to generate geometric mean ratios (GMRs) with 95% confidence intervals (CI). P-values reflect paired t-tests.

Results: Ten participants (8 males; 3 white, 4 black, 3 Hispanic; 7 on atazanavir, 3 on darunavir) had complete data available from the baseline and week 4 study visits. Mean (SD) age was 48.2 (10.4) years and weight was 72.1 (14.3) kg. At baseline, geometric mean [95% CI] TFV-monoester plasma concentrations at 1 and 4 hours post-dose were 97.4 ng/mL [33.0, 287.5] and 0.74 ng/mL [0.27, 2.06], respectively. Following the initiation of LDV/SOF, these increased to 167.8 ng/mL [45.8, 615.3] and 3.73 ng/mL [2.34, 5.97], respectively. The 4 hour post-dose TFV-monoester plasma concentration was 5.02-fold higher ([95% CI 1.40, 18.05]; p=0.019) with LDV/SOF. TFV-monoester was not statistically different at 1 hour post-dose at week 4 vs. baseline, presumably due to variability from sampling during the absorption phase, and was not detectable pre-dose at baseline or week 4. TFV plasma concentrations at 4 hours post-dose were 1.43-fold higher ([95% CI 1.29, 1.58]; p<0.0001) at week 4 vs. baseline. TFV-DP in PBMCs, RBCs, and DBS samples were increased with LDV/SOF by 2.80-fold ([95% CI 1.71, 4.57]; p=0.001), 10.96-fold ([95% CI 5.96, 20.15]; p<0.0001), and 7.31-fold ([95% CI 4.47, 11.95]; p<0.0001).

Conclusions: TFV-monoester plasma concentrations were higher in individuals receiving TDF concomitantly with LDV/SOF, which supports inhibition of TDF hydrolysis. These findings are consistent with elevated TFV-monoester enhancing cell loading as a mechanism for higher intracellular TFV-DP concentrations. Additional research is needed to establish the magnitude and clinical relevance of interactions occurring at the level of nucleotide prodrug conversion.
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