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Abstract Book
Efavirenz pharmacokinetics in HIV/TB coinfected persons initiating ART while receiving high dose rifapentine

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Background: Tuberculosis Trials Consortium Study 31 (S31)/ AIDS Clinical Trials Group Study A5349 is a phase III trial comparing two short-course TB treatment regimens containing high dose daily rifapentine (RPT) to standard TB treatment. RPT is a known CYP inducer and efavirenz (EFV) is a CYP substrate; thus, there is a potential risk of decreased EFV exposure in patients receiving TB treatment including RPT. An objective of S31/A5349 was to evaluate the effect of RPT on EFV pharmacokinetics (PK) in antiretroviral therapy (ART)-naïve participants initiating EFV-containing antiretroviral therapy (ART) while receiving RPT-containing TB treatment.

Materials & Methods: This pharmacology substudy included participants initiating EFV-based (600mg) ART within the first 9 weeks of TB treatment, randomized to one of two regimens containing daily RPT (1200mg), isoniazid (H), pyrazinamide and either ethambutol or moxifloxacin. A CD4 cell count above 100 cells/mm3 was required for study enrollment. Plasma samples were collected 10-24 hours post EFV dose at two time points during concomitant RPT treatment (approximately four and eight weeks after EFV initiation), and one time point after TB treatment completion (study week 22). EFV concentrations were measured by a validated LC/MS/MS assay. Plasma HIV RNA was measured at baseline, approximately 8 weeks after EFV initiation, and study week 22. EFV apparent oral clearance (CL/F) was modeled using Bayesian estimation; population PK priors were taken from previous EFV PK studies. The two EFV concentrations measured during TB treatment were combined to estimate EFV CL/F during RPT/H therapy. The geometric mean ratio (GMR) and 90% confidence interval (CI) of the during to post RPT/H EFV CL/F values were calculated. The protocol specified that >80% of participants must have EFV concentrations ≥1 mg/L at both time points during TB treatment for enrollment of participants starting EFV to continue.

Results: Of 28 evaluable participants, 25% were female, 96% Black/African, and median (IQR) age was 36 years (30-42). The mean (IQR) baseline CD4+ count was 252 cells/mm3 (157-403). Median (IQR) EFV concentrations ~ 4 and 8 weeks post-EVF initiation were: 2.76 (2.12-4.67) mg/L and 2.86 (2.19-4.88) mg/L respectively. EFV concentrations measured at week 22 (post-TB treatment were: 2.86 (1.93-4.21) mg/L. The number (%) of participants with EFV concentrations >1mg/L at at ~4 and 8 weeks post-EVF initiation were: 25/28 (89%) and 26/28 (93%); 19/21 (90%) of participants had EFV concentrations >1mg/L at week 22. Median (IQR) EFV CL/F were: 7.28 (5.47-10.08) and 8.3 (6.17-10.66) L/hr during and post RPT/H respectively. The GMR (90% CI) of during to post RPT/H EFV CL/F was 0.89 (0.64-1.23). Median (IQR) baseline HIV-1 RNA (n=25) was 81,003 (27,171-343,245) copies/mL; 20 of 23 participants had undetectable HIV-1 RNA at week 22.

Conclusion: The CL/F of EFV decreased slightly during 17 weeks of daily RPT/H TB therapy as compared to post-TB treatment. The proportion of participants with EFV concentrations < 1 mg/L did not cross above the pre-specified threshold of 20%. These data provide preliminary support for initiating EFV-containing ART during co-administration of daily high-dose RPT for TB treatment.
In silico design of a microarray patch as a multipurpose prevention technology

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Background: The co-administration of antiretrovirals (ARVs) and contraceptives as a multipurpose prevention strategy may have utility for simplified dosing. Intradermal microarray patches (MAPs) may present an alternative delivery system for formulations developed as long-acting (LA) injectables. MAPs are minimally invasive and could address poor adherence to daily oral PrEP regimens. The aim of this study was to model the potential use of weekly and monthly intradermal MAPs for the simultaneous administration of LA cabotegravir (CAB) and norelgestromin (NGMN) using physiologically-based pharmacokinetic (PBPK) modelling.

Materials & Methods: A whole-body PBPK model was designed using Simbiology v. 5.8 (MATLAB 2018a). The model was qualified for CAB LA against available PK data of oral LA formulations from the LATTE-2 studies (first-order release rate: 0.00076 /h). The model was qualified for NGMN against available PK data of transdermal patches of varying sizes (10 cm², 15 cm², and 20 cm²) at a zero-order release rate of 0.006 /h. The PBPK models were qualified if the mean simulated values were within ± 50% of the mean observed values. Intradermal MAP administration for CAB and NGMN were simulated considering a combination of dose and release rates to obtain comparable exposure to existing formulations and therapeutic concentrations.

Results: For CAB, simulations indicate that minimum loading doses of 360 mg or 720 mg and maintenance dose of 90 mg or 540 mg were required for weekly and monthly MAPs, respectively, with a release rate of 0.00076 /h (equal to existing injectable formulation of CAB LA). A loading dose of 90 mg or 360 mg and maintenance dose of 90 mg or 360 mg may be sufficient for weekly and monthly CAB MAPs if release rates of 0.001 /h and 0.01 /h can be achieved, respectively. For NGMN, simulations indicated that a minimum weekly dose of 2 mg with release rates between 0.007 /h and 0.012 /h and a minimum monthly dose of 6 mg with release rates between 0.001 /h and 0.0025 /h were required.

Conclusion: PBPK models were successfully qualified against observed data for CAB LA and NGMN. The models were applied to rationalise the design of MAPs, identifying optimal characteristics (minimum dose and optimal release rates) to maintain therapeutic concentrations. Intradermal MAPs could be an effective method of delivery for CAB LA and NGMN, which may enable a future multipurpose prevention technology.
Population pharmacokinetics of VRC01 in infants and adults


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Background: VRC01 is a broadly neutralizing monoclonal antibody directed against the HIV-1 CD4 binding site and is capable of neutralizing the majority of HIV-1 strains. VRC01 has desirable characteristics for infant prophylaxis and intensive early treatment regimens. This study aimed to develop a VRC01 population pharmacokinetic (popPK) model from infants and adults to predict infants’ VRC01 exposure with repeat dosing.

Materials & Methods: VRC01 pharmacokinetic (PK) data from 3 separate studies were utilized for the analysis: healthy adults (VRC602, N=23), HIV-infected adults (VRC601, N=23), and HIV-exposed infants ≤ 72 hours of age (IMPAACT P1112, N=27). Adults were administered either one or two doses (28 days apart) of 5, 20 or 40 mg/kg intravenous (IV) or 5 mg/kg subcutaneous (SC) VRC01. Infants were administered a single SC dose of either 20 or 40 mg/kg VRC01 with the first 72 hours of life. A total of 1227 VRC01 concentrations, determined by ELISA, were collected up to 24 weeks post-dose and analyzed using NONMEM version 7.3, FOCEI method. Allometric scaling was incorporated into the popPK model before assessment of other covariates with clearance (CL) and intercompartmental clearance (Q) scaled as (WT/70)**0.85, and volumes of distribution (V1 / V2) as (WT/70)**1 [Deng et al. 2010]. Covariates were evaluated using a univariate followed by multivariate assessment. The final model was used for Monte Carlo simulations of 20-40 mg/kg SC every 4 weeks (Q4W) in infants.

Results: VRC01 concentration data were best described with a two-compartment model with zero order absorption following SC administration. The final popPK model is described as:

\[ CL (L/h) = 0.0237 \times (WT/70)^{0.85} \times 0.283 \times \text{INFT} \times \text{HIV} \]

\[ V1 (L) = 2.14 \times (WT/70) \]

\[ V2 (L) = 4.72 \times (WT/70) \]

\[ Q (L/h) = 0.0483 \times (WT/70)^{0.85} \times 0.674 \]

\[ R = 0.00702 \times 2.9 \times \text{INFT} \times \text{DOSE (mg/kg)} \]

Between subject variability for CL was 30%. CL/F was lower and absorption rate faster in infants than adults. HIV status was also independently predicted higher CL in adults, but dose level did not impact CL. This model predicts typical CL/F of 3.61, 5.46 and 8.55 mL/kg/d in infants, healthy adults and HIV-infected adults, respectively. Median [IQR] POSTHOC half-life (\( \beta \)) was longer in infants 26.5 [23.7-34.2] days than healthy adults 14.0 [12.5-16.6] days and HIV-infected adults 10.5 [9.1-12.3] days. The simulations predicted infant median [IQR] VRC01 concentrations on day 28 (CD28) after single 20 and 40 mg/kg SC doses were 49.3 [42.0-56.7] and 98.6 [84.0-113.4] \( \mu g/mL \) respectively, with 47.3% and 99.1% CD28≥50 \( \mu g/mL \). The predicted monthly median [IQR] steady-state VRC01 trough concentrations in infants with 20 mg/kg SC Q4W was 137.0 [105.8-166.3] \( \mu g/mL \) with 99.1% ≥50 \( \mu g/mL \).

Conclusion: Age and HIV infection are key factors in VRC01 pharmacokinetics. In HIV-exposed infants, a loading dose of 40 mg/kg SC rapidly achieves and exceeds target suppressive VRC01 plasma concentrations of > 50 \( \mu g/mL \) in virtually all for at least 28 days. Subsequent dosing of 20 mg/kg SC Q4W is predicted to maintain VRC01 concentrations above this target.
The initial Phase 1 evaluation of the safety, tolerability, and pharmacokinetics of GSK3640254, a next generation HIV maturation inhibitor, as assessed in healthy subjects

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Background: New antiretrovirals (ARVs) are needed to address gaps in drug resistance and longer-term safety/toxicity with existing agents. GSK3640254 is a next generation HIV-1 Maturation Inhibitor (MI) with a preclinical profile supporting additional clinical evaluation for potential treatment of HIV-1. The results from two initial Phase 1 studies investigating GSK3640254 in healthy subjects are described.

Materials & Methods: First, a randomized placebo controlled single/multiple ascending dose escalation (SAD/MAD) study investigated the safety/tolerability and PK of GSK3640254. Single doses of GSK3640254 1 to 700 mg or placebo were administered in the SAD and up to fourteen days of GSK3640254 50 to 320 mg QD or placebo were administered in the MAD. The SAD portion of the study was conducted in two cohorts in an interlocking fashion. Each cohort in the SAD and MAD randomized 8 subjects (6 who received GSK3640254 and 2 who received placebo). The MAD also contained a larger expansion cohort to further evaluate the safety/tolerability of GSK3640254 (18 who received GSK3640254 and 6 who received placebo). The SAD/MAD utilized a bis-hydrochloride salt capsule of GSK3640254 only. Second, a relative bioavailability (RBA) study primarily evaluated the single dose PK profile of GSK3640254 between two salt forms of GSK3640254 200 mg. In both studies, vital signs, physical exam, laboratory testing, ECGs, and PK sampling were performed at regular intervals. In both studies, GSK3640254 or matching placebo were administered with moderate fat meals.

Results: The SAD/MAD study randomized 78 healthy men: 20 in the SAD and 58 in the MAD. No deaths or serious adverse events occurred. Four subjects reported adverse events (AEs) leading to discontinuation from the trial, one of which was related to study medication (Grade 1 Rash Maculopapular). The most frequent AEs in the SAD were headache (one instance, Grade 2), contact dermatitis primarily due to ECG electrodes, and diarrhea. There was no dose/AE relationship. The most frequent AEs in the MAD were headache (two instances, Grade 2), contact dermatitis, dizziness, confusion, fatigue, and back pain. The PK of GSK3640254 was characterized by a slow absorption with a median Tmax ~ 4 hours after dosing and slow elimination with a half-life of ~ 24 hours. The accumulation ratios for Cmax and AUC were approximately 2 and 3-fold, respectively, and exposure was generally proportional to dose.

The RBA study randomized 14 healthy men, 7 of which experienced 11 AEs (all Grade 1). Two AEs were related to GSK3640254. In either study, there were no clinically significant changes in vital signs, ECG parameters, or laboratory parameters. The relative bioavailability of GSK3640254 between the two salt forms of GSK3640254 were comparable.

Conclusion: GSK3640254 was generally well tolerated and did not show any clinically significant safety findings when given to healthy subjects in two initial Phase 1 studies. Combined with a PK profile suggesting once-daily dosing, these results enabled the ongoing Phase 2a study in HIV-1 infected adults using the mesylate salt capsule formulation.
Changes in drug interaction profiles for first-line HIV therapy over the 20 years of the Liverpool Drug Interaction website.


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Background: The Liverpool Drug Interactions website was launched in 1999 when the issue of drug-drug interactions was first appearing in clinical practice due to the introduction of "Highly Active Antiretroviral Therapy". In the 20 years since its launch, the website has grown from ~900 interactions arising from 128 comedications and 7 antiretroviral drugs (4 PIs and 3 NNRTIs) to over 26,000 interactions from 726 comedications and 36 antiretrovirals drugs or regimens and is used by ~23500 users each month from ~220 countries. With the move towards simplification of treatment regimens, a retrospective analysis was performed using the drug interaction database to determine the interaction profiles of the currently recommended first-line regimens and those recommended around the time of the website launch.

Materials & Methods: Current regimens were identified from the USA (2018), European (2018) and UK (2016) treatment guidelines; historic regimens were available for the USA (2000) and UK (2000). Interaction profiles for antiretroviral regimens were determined by calculating the frequency of each type of interaction (red, amber, yellow, green). Where a complete regimen had not been assessed as a single entity, the most significant interaction for each of the individual antiretroviral drugs was used. Interactions were grouped according to those requiring an intervention (contraindicated/do not coadminister, dose modification, monitoring; red and amber) and those that could be used without such a priori actions (green and yellow). The interaction potential of comedications used to treat three comorbidity clusters (mental health, cardiovascular and metabolic, as identified by De Francesco et al, 2018) were also determined.

Result: A total of 28 regimens were identified in the historic guidelines and 16 regimens in at least one of the current sets of guidelines. When assessed against the current comedication list, the occurrence of interventional interactions in historic regimens ranged from 37% to 57%, with regimens containing a NNRTI having fewer interventional interactions than those containing a PI (44% vs 52%). For the current regimens, the percentage of interventional interactions ranged from 8% to 54%, with regimens containing a pharmacokinetic booster (cobicistat or ritonavir) having a greater percentage of interventional interactions than unboosted regimens (45% vs 12%). When matched for all other antiretrovirals, a difference in percentage of interventional interactions was also noted for tenofovir alafenamide versus tenofovir-DF containing regimens (28% vs 34%). The difference between boosted and unboosted regimens was more pronounced when classes of comedications for comorbidity clusters were assessed. For mental health, cardiovascular and metabolic comorbidity clusters the percentage of interventional interactions for boosted versus unboosted regimens were 52% vs 1%, 44% vs 5%, and 41% vs 6%, respectively.

Conclusion: The interaction profile of first-line regimens has declined over the last 20 years with the minimum percentage of interventional interactions decreasing from 37% to 8% for some current regimens. An awareness of the potential for drug-drug interactions with current first-line regimens, particularly when treating certain comorbidity clusters, is critical for appropriate patient management.
Drugs abuse and chemsex: A new challenge for antiretroviral drug-drug interaction


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Background: These last decades, a wide range of new psychoactive substances (NPS) has emerged in the party scene. NPS such as cathinones associated with other illicit drugs (cocaine, MDMA, gamma-hydroxybutyrate-gamma-butyrolactone (GHB/GBL)) have become more frequently used in a “Chemsex” context among the HIV-infected MSM population. Drug-drug interactions (DDI) between antiretrovirals and illicit drugs are a major concern as potential life-threatening toxicities may occur through pharmacokinetic (use of booster) or pharmacodynamic interactions. As part of our Therapeutic Patient Education Program (TPEP), we conducted a survey to collect data and describe illicit drugs consumption in our HIV population and to evaluate the risk of DDI.

Materials & Methods: This prospective survey was initiated in April 2018. HIV-infected patients who attended the unit for a follow-up visit as part of their TPEP were proposed to fill in self-administered questionnaires evaluating number, type and frequency of drugs consumption. Demographical characteristics and therapeutic data were collected at the time of the questionnaire from our electronic database. DDI were checked using both the online expert database of Liverpool (www.hiv-druginteractions.org) and knowledge on the drugs pharmacokinetics.

Data of 286 HIV-infected patients on ART (75% male; median age: 52 years [range: 19-83]) were analyzed. Overall, 33% of patients reported consuming illicit drugs (59%=1 drug; 41%>1), of whom 52% were MSM and 28% IVDU. Used drugs were cannabis (42%), poppers (17%), cocaine (16%), ecstasy/MDMA (7%), GHB/GBL (5%), cathinones (3%), methamphetamine derivatives (2%), ketamine (2%), synthetic cannabinoids (1%) and LSD (1%). Frequency of consumption was variable among drugs with > once a day in 55% for cannabis users, > once a week in 40% for cathinones users, > once a month in 69% and 33% for ecstasy/MDMA and cocaine users, respectively.

Results: Among consumers, 18% reported use in a “Chemsex” context and the most frequent drugs were: poppers (37%), ecstasy/MDMA (12%), GHB/GBL (10%) and cannabis (10%). ART regimens of consumers were mostly a triple therapy (62%), 60% were on a Single-Tablet Regimen (STR), 34% received ritapivirine and 33% a booster (ritonavir or cobicistat). We identified 38 DDI with ART, 25 of which potentially leading to severe toxicities through CYP2D6 and/or CYP3A4 inhibition by the presence of a booster with MDMA, methamphetamine, cathinone, GHB/GBL or ketamine use (n=10), or CYP2C9 inhibition by efavirenz, nevirapine or etravirine with cannabis use (n=6) or by concomitant use of cocaine and ripapivirine (n=9), both drugs known to prolong the QT interval. Thirteen other DDI with a lower risk of toxicity have been identified in patients treated with a boosted regimen while consuming either poppers (n=7) or cocaine (n=6).

Conclusion: More than one third of patients reported illicit drugs consumption of whom 18% in a “Chemsex” context. Overall, DDI risk was present in 13.3% of cases and a potential severe DDI was identified in 25 cases (8.7%) with the antiretroviral treatment only. Therefore, it appears critical to identify illicit drugs consumption in HIV-infected patients by implementing a systematic screening to avoid high risk of potential life-threatening toxicities by adjusting the antiretroviral regimen.
Effect of CYP2b6 metabolizer status on levonorgestrel pharmacokinetics when combined with efavirenz-based antiretroviral therapy

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Background: We previously described 57% lower levonorgestrel (LNG) concentrations in women receiving the LNG implant (150mg) plus efavirenz (EFV; 600mg)-based antiretroviral therapy (ART) compared to ART-naïve women. To overcome this interaction, we evaluated the impact of doubling the LNG implant dose (300mg) in combination with EFV-based ART (DoubLNG). Despite this dose adjustment, the LNG exposure remained 34% lower in the DoubLNG group compared to the same group of ART-naive Ugandan women in our prior study. In addition, we previously identified that CYP2B6 single nucleotide polymorphisms (SNPs) associated with slow EFV metabolism were also associated with lower LNG exposure when the standard dose LNG implant was combined with EFV. To extend those findings, we explored potential associations between CYP2B6 metabolizer status and LNG pharmacokinetics in DoubLNG.

Materials & Methods: We evaluated 28 Ugandan women receiving EFV-based ART with undetectable HIV-RNA. An LNG implant was placed in each arm (300 mg total) at study entry and a whole blood sample was collected for pharmacogenetic analysis. For the primary endpoint at week 24, plasma samples were collected at weeks 1, 4, 12, and 24 for determination of LNG concentrations. We genotyped three SNPs (CYP2B6 rs3745274 516G→T, CYP2B6 rs28399499 983T→C, CYP2B6 rs4803419 15582C→T) for classification of normal, intermediate, and slow CYP2B6 metabolizer status. The association between metabolizer status and LNG pharmacokinetics was explored through univariate and multivariate linear regression (P ≤ 0.05 classed as significant). The area under the curve of LNG from week 0-24 (AUC0-24wks) was calculated using the trapezoidal rule. All analysis and calculations were performed in R (v.3.5.2) using the stats and NonCompart packages.

Results: In DoubLNG, all women were Black African with median (IQR) age of 33.0 (28.0 - 40.5) years and weight of 58.0 (48.5 – 66.0) kg. CYP2B6 rs28399499 was not in Hardy-Weinberg equilibrium (χ² = 27.25), which compromises its interpretation. LNG concentrations (median (IQR)) at week 24, were 537.0 (529.5 – 597.0) pg/mL, 310.0 (253.0 – 344.8) pg/mL, and 167.0 (103.0 – 301.0) pg/mL for normal (n = 7), intermediate (n = 16), and slow (n = 5) metabolizers, respectively. CYP2B6 metabolizer status was correlated with LNG exposure (P = 2.50 x 10⁻⁶, β = -0.24, for log₁₀ week 24 concentration; P = 4.65 x10⁻⁵, β = -0.17, for log₁₀ AUC0-24wks). This association remained significant after adjusting for age, weight, and sex hormone binding globulin at baseline. Within DoubLNG, LNG AUC0-24wks (median) was 35% lower in intermediate metabolizers and 47% lower in slow metabolizers when compared with normal metabolizers. At week 24, higher log₁₀ EFV concentrations were associated with lower log₁₀ LNG concentrations (P = 3.37 x 10⁻⁷, β = -0.56).

Conclusion: This study provides further evidence that CYP2B6 genetic variants influence LNG pharmacokinetics when combined with EFV-based ART. In our Ugandan study participants, 75% were intermediate or slow EFV metabolizers, and participants with this metabolizer status exhibited lower LNG exposure. Impaired EFV metabolism may make it more difficult to use an increased LNG dose to overcome the interaction with EFV-based ART.
Infectious disease action plan for the global accelerator for paediatric formulations (GAP-f)

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The development of paediatric products lags unacceptably behind that of adults by nearly a decade – due to a number of challenges. Paediatric products are costly to develop and manufacture, young children cannot swallow tablets or capsules, acceptable palatability is difficult to achieve, drug doses need to be tailored to a child’s drug metabolism and weight, and drug approvals do not acknowledge dosing approaches based on weight bands. Together, these facts fragment the market for drugs to prevent or treat infectious diseases such as HIV, TB and Hepatitis and little has been done to provide market incentives.

The Global Accelerator for Paediatric Formulations (GAP-f) was created to provide a sustainable mechanism dedicated to ensuring that the most needed optimal paediatric formulations are developed and made available to children in a timely manner. GAP-f will work across the entire life cycle of drug development and delivery and bring efficiency through enhanced coordination across many partners, sponsors, and community stakeholders. GAP-f represents a new and exciting model to:

- increase collaboration and develop a clear prioritized drug portfolio that defines pediatric target product profiles, which includes dose as a function of weight band and finished drug formulation,
- ensure that efficient, clinical trials are completed to establish safety, dosing and efficacy (when needed) across all relevant weight bands for each product and ensure that relevant SRAs approve products for use,
- establish strategic alliances with industry and coordinate them across all parties,
- streamline and accelerate product development, regulatory approval and commercialization,
- collaborate with various research institutes to advance non-oral, long-acting dosing platforms, advanced formulations that reduce pill size, and develop approaches that increase API solubility and mask taste,
- accelerate in-country treatment delivery and improve monitoring in a coordinated manner, and
- ensure that healthcare providers are proficient and switching patients to these new treatment regimens.

GAP-f will share the status on finalizing and implementing a unified action plan that addresses each of the interrelated objectives noted above.
Infant exposure to dolutegravir through placental and breastmilk transfer: A population PK analysis of DolPHIN-1

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Background: Rapid reduction of HIV viral load is paramount to prevent peripartum transmission in women diagnosed late in pregnancy. DolPHIN-1 (NCT02245022) investigated the PK of dolutegravir (DTG) in pregnant women and their infants presenting with untreated HIV late in pregnancy (28-36 weeks gestation). We present a population PK model describing infant DTG exposure from residual intrapartum transfer and ongoing breastfeeding.

Materials & Methods: Pregnant women recruited from Uganda and South Africa were randomised (1:1) to receive daily DTG (50 mg) or efavirenz (EFV)-based therapy. DTG PK sampling (0-24 h) was undertaken 14 days after therapy initiation (third trimester; T3) and within 1-3 weeks of delivery (postpartum; PP), with matched maternal and cord samples at delivery. Infant and breastmilk (BM) sampling were performed PP, 2-6 and 24 h post-maternal dose. Mothers switched to EFV and a matched maternal and infant plasma sample and a BM sample taken 1, 2- or 3-days post-switch. Nonlinear mixed effects (NONMEM v. 7.3) was used to describe DTG disposition in all matrices. Growth [weight, body surface area (BSA)] and maturation descriptors [gestational age (GA), postmenstrual age (PMA; PNA+GA)], sex and study site were assessed as covariates.

Results: Twenty-eight women [14 Uganda, 14 South Africa; median (range) age 27 years (19-42), weight 67 kg (44-160)] contributed 533 plasma, 16 cord and 80 BM samples to the maternal model; n=27 paired T3/PP visits. A 2-compartment model described DTG in plasma, linked to a fetal (cord) and a BM compartment by first-order processes. Cord and BM exposures were 123.4% (123.3-123.6) and 3.3% (2.5-5.2) that of maternal plasma, respectively.

Individual predicted parameters were fixed to drive the infant model. Infants with recorded date and time of delivery (n=22; 65 samples) could be included [5 girls, 17 boys; median (range) weight, PNA, GA, PMA and BSA: 3.3 kg (2.50-4.3), 7 days (3-18), 39 weeks (35-43), 40.1 weeks (36.0-43.6), 0.22 m² (0.18-0.25)]. DTG dose at birth was simulated based on cord concentrations [39.9 mg (15.5-59.0) or 12.5 mg/kg (5.0-19.6)]. Infant DTG PK were described by a BM-to-infant transfer rate constant [estimate (RSE%): 2.5 h⁻¹ (8%)], elimination rate constant [0.016 h⁻¹ (6%); interindividual variability: 44.4% (67%)] and volume of distribution [24.9 L (11%)]; residual error was 33.9% (40%). No covariate effects were observed. Simulated infant DTG AUC₂₄, AUC₄₈, AUC₇₂, AUC₉₆ after the final maternal dose were 1.9 (0.6-10.7), 3.5 (1.1-17.5), 4.8 (1.3-21.7), 5.5 (1.5-24.2) mg.h/L, respectively corresponding to infant:maternal plasma ratios of 0.06 (0.02-0.28), 0.08 (0.02-0.36), 0.11 (0.03-0.43), 0.12 (0.03-0.47), respectively. Predicted DTG half-life and time to PA-IC₉₀ (0.064 mg/L) were 38.2 h (23.0-64.1) and 100.2 h (15.6-130.8; n=13).

Conclusion: As expected, infants exhibited slower DTG elimination than their mothers, likely due to immaturity of metabolic pathways. Breastfeeding contributed relatively little to infant plasma DTG exposures, and based on these elimination profiles, DTG is expected to provide 1-4 days additional prophylaxis to breastfed infants following maternal drug cessation (3-18 days after delivery). The impact of prolonged infant exposure to DTG is being evaluated as part of DolPHIN-2.
Pharmacokinetics of atazanavir boosted with cobicistat during pregnancy and postpartum

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Background: Atazanavir (ATV), a human immunodeficiency virus (HIV-1) protease inhibitor, is metabolized primarily by CYP3A and usually administered with a pharmacokinetic (PK) booster. The PK of ATV when co-administered with ritonavir (RTV) have been described in pregnancy; however, ATV boosted with cobicistat (COBI) has not been studied in pregnant women. This study described ATV exposure when administered in fixed-dose combination with COBI during pregnancy and postpartum.

Materials and Methods: IMPAACT protocol P1026s is an ongoing, nonrandomized, open-label, multicenter, prospective study of antiretroviral PK in HIV-infected pregnant women. Intensive steady-state 24 hour PK profiles of ATV following once-daily dosing of 300/150 mg ATV/COBI were performed during the 2nd trimester (2T), 3rd trimester (3T) and 6-12 weeks postpartum (PP). ATV plasma concentrations were measured by a validated high-performance liquid chromatography (HPLC) assay with UV detection. The lower limit of quantification of the assay was 0.047 μg/mL. The minimum exposure target for ATV was the 10th percentile area under the concentration-time profile over the dosing interval at steady state (AUCtau) in non-pregnant HIV infected patients receiving once daily ATV/RTV (28.4 μg*hr/mL).

Results: Six subjects from the United States were enrolled – 4 black non-Hispanic, 1 Hispanic, and 1 white non-Hispanic with a median age and body weight at delivery of 37.7 years (range 28.1 – 43.0) and 99.3 kg (range: 85.1 – 109.8), respectively. ATV PK data were available for 3 women in 2T, 5 women in 3T, and 5 women in PP. The median (IQR) AUCtau of ATV was 21.2 μg*hr/mL (20.6 – 22.5) in 2T, 17.0 μg*hr/mL (8.9 – 27.5) in 3T, and 27.4 μg*hr/mL (24.0 – 36.4) in PP. The frequency of participants meeting the target AUCtau was 0/3 in 2T, 1/5 in 3T, and 2/5 in PP. The median (IQR) 24-hour trough concentration at steady state was 0.16 μg/mL (0.14 – 0.22) in 2T, 0.12 μg/mL (0.09 – 0.19) in 3T, and 0.45 μg/mL (0.42 – 0.61) in PP. ATV trough concentrations in 2T, 3T, and PP were 20%, 15%, and 56%, respectively, of previously reported values in non-pregnant, HIV-1 infected adult patients receiving once-daily dosing of 300/150 mg ATV/COBI. One patient had a trough concentration below the lower limit of quantitation (0.047 μg/mL) which occurred in 3T. All other trough concentrations were above the threshold of the historical population average protein binding-adjusted 90% effective concentration (EC90) for ATV against wild-type HIV (0.014 μg/mL). Viral load at delivery was < 50 copies/mL for all 6 women. Median infant gestational age at birth was 36.4 weeks. Two of 6 infants were HIV-negative based on best available data, and 4 are indeterminate or pending thus far.

Conclusion: In women taking ATV in fixed-dose combination with COBI, ATV exposure appeared to be lower in pregnancy compared to postpartum, and compared to non-pregnant adults. Additional PK, safety, and outcome data in a larger cohort of pregnant women are needed before ATV/COBI can be considered for use during pregnancy.
Low isoniazid concentrations in pregnant and postpartum women treated for tuberculosis irrespective of efavirenz-based ART co-treatment

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Background: Physiological changes during pregnancy may alter drug pharmacokinetics. Trimester differences in isoniazid (INH) and rifampin (RMP) exposure in pregnant women treated for tuberculosis have not been described. We explored the effects of pregnancy on INH and RMP pharmacokinetics in women treated for tuberculosis with and without efavirenz (EFV)-based antiretroviral treatment (ART) co-treatment.

Materials & Methods: International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1026s is an ongoing, non-blinded, phase IV, prospective study of antiretroviral and antituberculosis pharmacokinetics in HIV-infected and uninfected pregnant women. Intensive steady-state 12-hour pharmacokinetic profiles of INH and RMP were performed during the 2nd trimester (2T), 3rd trimester (3T) and 2-8 weeks postpartum (PP). Daily antituberculosis fixed-dose combination tablets were given according to WHO-recommended weight-banded dosing guidelines. Additionally, HIV-infected women also received EFV-based ART. INH and RMP plasma concentrations were measured using High Performance Liquid Chromatography (HPLC); detection limits being 0.117 µg/ml and 0.098 µg/ml, respectively. The pharmacokinetic parameters were characterized using noncompartmental analysis and compared to published non-pregnant South African adult data. Exposure at each timepoint was compared between ART and non-ART groups using a Wilcoxon rank-sum test. Two-sided P-values <0.10 were considered statistically significant.

Results: Preliminary pharmacokinetic data are available for 25 participants; 14 African, 6 Thai and 5 of other descent. The median age at 3T was 29 (range 23-33) years and the median weight 58 (range 54-62) kg. Twelve women were HIV-infected on EFV-based ART, with 3T median CD4 count 534 (range 93-708) cells/mm3 and median viral load <40 copies/mL. The INH and RMP pharmacokinetic data in 2T, 3T and PP were available for 7, 10 and 7 women in the ART-group and 5, 11 and 8 women in the non-ART-group. All but 5 were sampled more than once. INH median AUC0-∞ was 7.9, 8.4 and 8.7 µg·h/ml and 6.2, 10.9 and 14.8 µg·h/ml in the 2T, 3T and PP groups with and without ART respectively. INH median Cmax was 2.8, 3.3, and 3.0 µg/ml and 3.0, 3.5 and 3.6 µg/ml respectively. INH exposure was low across all stages of pregnancy compared to historical South African non-pregnant INH exposure: AUC0-∞ 32.5 µg·h/ml and Cmax 6.5 µg/ml (45% male, 10% HIV-infected not receiving antiretrovirals, McIlleron et al. 2006). RMP median AUC0-∞ was 36.8, 35.8 and 31.2 µg·h/ml and 30.6, 41.4 and 32.7 µg·h/ml respectively. RMP median Cmax was 8.4, 6.1, and 6.6 µg/ml and 4.5, 6.9 and 7.9 µg/ml respectively. RMP exposure was similar or higher in 2T, 3T and PP compared to historical data. The respective INH and RMP exposures in each trimester were not statistically different between the ART- and non-ART-groups, though small sample sizes limited the statistical power to detect differences. Pregnancy outcomes, tuberculosis treatment outcomes and safety outcomes are being analyzed.

Conclusion: In pregnant women treated for tuberculosis, INH concentrations were lower compared to non-pregnant concentrations, irrespective of EFV-based ART co-treatment. RMP concentrations in pregnancy were similar or higher. The clinical relevance of low INH exposure when treating pregnant woman with tuberculosis needs to be determined.
Pharmacokinetics of tenofovir alafenamide 25 mg with PK boosters during pregnancy and postpartum

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Background: Tenofovir alafenamide (TAF) is a prodrug of tenofovir and a common component of antiretroviral (ARV) regimens for HIV treatment. We previously reported that plasma exposures of TAF 25 mg alone were significantly different between pregnancy and postpartum (PP), but were overall comparable to phase 3 data in non-pregnant adults living with HIV. Here, we described the PK of TAF 25 mg when co-administered with ritonavir or cobicistat during pregnancy and PP among women living with HIV.

Materials & Methods: IMPAACT 1026s is an international open-label, multicenter study examining the PK of ARV medications prescribed as clinical care to pregnant women living with HIV. Women receiving TAF 25 mg with ritonavir or cobicistat were eligible for this arm. Steady-state PK assessments were performed during the 2nd and 3rd trimesters (2T/3T) and 6-12 weeks PP. TAF plasma concentrations were quantified using a validated LC-MS/MS method; the lower limit of quantitation was 3.9 ng/mL. PK parameters were calculated using Bayesian estimation in NONMEM. Geometric mean ratios (GMR) with 90% confidence intervals (CI) were calculated within-participant between 2T vs. PP and 3T vs. PP, and PK parameters were compared using a two-sided Wilcoxon signed-rank test. P-values ≤0.10 were considered statistically significant.

Results: Seventeen women were enrolled from the US. PK data were available from 6, 14, and 8 women during 2T, 3T, and PP, respectively. Cobicistat was used in 83% during 2T, 64% during 3T, and 50% during PP; all others received ritonavir. Other concomitant antiretroviral medications included darunavir, atazanavir, emtricitabine, dolutegravir, and zidovudine. At delivery, mean (SD) maternal age was 30.2 (7.0) years, gestational age was 37.5 (2.8) weeks, and infant weight was 3200 (600) g. Median (IQR) area under the concentration-time curve (AUC) during 2T was 133 (128-720), 3T was 335 (192-549), and PP was 507 (221-693) ng*h/mL. These exposures were comparable or higher than historical data in adults receiving TAF 10 mg with cobicistat (mean 206.4 ng*h/mL). Paired data in both 2T and PP were available in only two women, thus GMR comparisons were limited to 3T vs. PP pending additional data. No statistically significant differences between 3T and PP were observed for TAF plasma AUC between 3T and PP (n=8; GMR -6% [90% CI -62%, 133%]; p=0.74), apparent oral clearance (GMR 6% [90% CI -57%, 161%]; p=0.64), or peak concentrations (GMR -38% [90% CI -65%, 10%]; p=0.15). HIV-1 RNA ≤50 copies/mL at delivery was achieved in all but one mother (94.1%). Six infants were HIV-negative, 7 indeterminate, 3 pending and 1 unknown. Adverse events (AEs) considered possibly treatment-related included five maternal AEs consisting of 3 preterm labor, 1 gestational diabetes mellitus, 1 abdominal pain; and 1 infant AE of premature birth.

Conclusion: Plasma exposures to TAF 25 mg with PK boosters did not significantly differ between 3T and PP, though confidence intervals were wide. Additional data on long-term safety, efficacy and intracellular PK of TAF during pregnancy are needed to optimize its use in this population.
Tenofovir-diphosphate in PBMC following increasing TAF vs. TDF dosing under directly observed therapy


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Background: Tenofovir is phosphorylated intracellularly to its active anabolite, tenofovir-diphosphate (TFV-DP) in PBMC, which contain HIV target cells. There are two fumarate salt prodrugs of tenofovir, tenofovir alafenamide (TAF) and tenofovir disoproxil (TDF). This study assessed TFV-DP concentrations in target cells (PBMC) following increasing dosing of TDF/emtricitabine (FTC) vs. TAF/FTC, to simulate different adherence levels, using directly observed dosing.

Materials & Methods: Two randomized studies were conducted among adults without HIV at low risk of infection to assess intracellular TFV-DP concentrations in dried blood spots (DBS) and PBMC following TDF/FTC and TAF/FTC, DOT-DBS (NCT02022657) and TAF-DBS (NCT02962739), respectively. Participants were randomized to two different dosing regimens (33%, 67%, or 100% daily dosing) of TDF/FTC or TAF/FTC for 12 weeks, separated by a 12-week washout period. For example, 33% dosing would be one day of dosing followed by two days without dosing, repeated for 12 weeks. Doses in both studies were observed in person or via video streaming. For the TDF/FTC study, the holiday dosing arms (doses missed by weeks, rather than days) were excluded from this analysis to ensure comparability between studies. TFV-DP concentrations in PBMC were determined using a validated LC-MS/MS assay. Available samples from the last dosing visit for each regimen (weeks 12 and 36) were pooled and analyzed.

Results: Forty-four TDF/FTC participants contributed 63 data points; 15 from 33%, 16 from 67%, and 32 from 100% daily dosing. Twenty-eight TAF/FTC participants contributed 39 data points; 13 from 33%, 13 from 67%, and 13 from 100% daily dosing. Median (IQR) TFV-DP for TDF versus TAF in the 33% arm was: 21 (15, 28) versus 194 (179, 269) fmol/106 cells; in the 67% arm was: 46 (33, 71) versus 354 (329, 445) fmol/106 cells; and in the 100% arm was: 71 (53, 97) versus 685 (566, 751) fmol/106 cells, respectively (p<0.001 for all comparisons).

Conclusion: Across the three dosing arms, TFV-DP concentrations in PBMC were 9.2, 7.7, and 9.6-fold higher following TAF/FTC compared with TDF/FTC for 33%, 67%, and 100% dosing arms, respectively. Additionally, TFV-DP was twice as high in the 33% dosing arm for TAF as compared with the 100% dosing arm for TDF. Together, this study shows that the enhanced delivery of tenofovir to target cells with TAF compared to TDF occurs across dosing/adherence levels. These results are relevant for studying alternative dosing strategies and pharmacologic forgiveness for HIV treatment and prevention.
An exploration of adherence measures to detect recent changes in Truvada® dosing patterns

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Background: Medication adherence, and valid measures of adherence, are crucial in optimizing the use of HIV prevention. TFVdp concentrations in red blood cells (RBCs) are an important adherence measure, reflecting averaged adherence over the past 3 months. However, adherence to Truvada® may frequently be episodic. This directly observed therapy (DOT) study assessed the ability of plasma, peripheral blood mononuclear cells (PBMC), upper layer packed cells (ULPC), dried blood spots (DBS), and whole blood microsamplers (Mitra®) to discriminate recent changes in Truvada® dosing patterns over the previous month.

Materials & Methods: A single center, open label, 3-arm, 3-phase, DOT study (NCT03218592) collected blood samples from 12 HIV negative healthy volunteers during visits across 3 1-month dosing strategies: single dose, daily dosing, and either no further doses, or 1 or 3 doses/week. Blood was collected on Days 3, 7, 14, 21, and 28 each month. At each visit plasma, PBMCs, DBS (Whatman 903 Protein Saver cards), ULPC, and Mitra® samples were obtained. Tenofovir (TVF)/emtricitabine (FTC) were measured in the plasma, and TFVdp/FTCtp concentrations, were measured in cells by LC-MS/MS using validated methods (LLOQ plasma = 1ng/mL; LLOQ cells <10,000 fmol/sample). One-half the LLOQ was imputed for values below the detection limit. Pearson correlations (r) were used to describe the dose-concentration response relationship within matrices (SigmaPlot®, v13.0). Statistical significance of the dose-concentration effect was evaluated using a linear mixed effects model predicting matrix-specific log10 concentrations based on the log10 number of doses per week (SAS/STAT®v15.1). Data are presented as median (25th-75th percentiles).

Results: Following daily dosing, TFV/TFVdp concentrations were 60.8 (51–81) ng/mL in plasma, 132 (106–199) fmol/106 cells in PBMCs, 850,500 (665,000–1,165,000) fmol/mL in ULPCs, 1,165 (946–1,320) fmol/punch in DBS, and 7,740 (6,558–9,970) fmol/sample in Mitra®. Following daily dosing, FTC/FTCtp concentrations, were 63 (49–90) ng/mL in plasma, 4,249 (3,789–5,797) fmol/106 cells in PBMCs, 353,500 (197,500–488,250) fmol/ mL in ULPCs, 310 (269–372) fmol/punch in DBS, and 2,175 (1,863–2,965) fmol/sample in Mitra®. The coefficient of variance (CV%) ranged from 21% (plasma TFV) to 105% (PBMC TFVdp). In all matrices, FTC/FTCtp concentrations strongly predicted doses per week (p< 0.001), with r=0.76. For TFV, plasma concentrations strongly predicted doses per week (p< 0.001), with r= 0.86. For TFVdp, PBMC concentrations strongly predicted doses per week (p< 0.001), with r= 0.92. TFVdp concentrations weakly predicted doses per week in ULPC, DBS and Mitra® (r=0.53 to 0.62).

Conclusion: The long half-life of TFVdp in RBCs could not discriminate changes in dosing patterns over one month. The short half-lives of TFV/FTC in plasma could only discriminate dosing changes over the past 7 days. The intermediate TFVdp and FTCtp half-lives in PBMCs were best able to detect recent changes in dosing patterns. These characteristics should be considered when interpreting adherence data from different sources.
Physiologically based pharmacokinetic modelling to determine pharmacokinetic alterations driving ritonavir exposure changes in aging people living with HIV

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Background: Life expectancy for people living with HIV (PLWH) has substantially increased, but clinical data regarding age-related pharmacokinetic alterations of antiretroviral drugs (ARV) are lacking resulting in uncertainty whether dose adjustment is necessary in aging PLWH. To overcome the sparse clinical data, physiologically based pharmacokinetic (PBPK) modelling was utilized to perform virtual clinical trials across adulthood to investigate the impact of adult age on ritonavir pharmacokinetics.

Materials & Methods: A whole-body PBPK model constructed in Matlab® 2017a was used with 18 compartments representing organs and tissues of the human body. Virtual individuals aged 20 to 99 years were generated considering age-dependent changes of organ weights and blood flows. Ritonavir was selected for this pilot study, because clinical data in aging PLWH are available for model validation.

The ritonavir PBPK model was verified in young adults (20-50 years) before carrying out simulations in PLWH older than 55 years without any changes to the ritonavir parameters. Predicted concentration-time profiles were visually compared against clinically observed data and PK parameters had to be predicted within 2-fold of clinical data for a successful simulation outcome.

The final ritonavir model was utilized to predict pharmacokinetics from 20 to 99 years in 500 virtual subjects (proportion of women: 0.5) per five years. The analysed PK parameters (maximal concentration: Cmax, time to maximal concentration: tmax, area under the curve: AUC, clearance: CL, volume of distribution: Vd, elimination half-life: t1/2) were normalized to the youngest investigated age group (20-24 years).

Results: The simulation of ritonavir (100 mg QD) correctly predicted the clinically observed data in young (20-50 years) and elderly (55-60 years) adults. The predicted AUC was in close agreement to clinical data in young (5,246 vs 5,296 ng*h/mL) and elderly (6,568 vs 6,609 ng*h/mL) individuals with a resulting AUC ratio elderly:young of 1.25 vs 1.25. Cmax and tmax were predicted within 1.25-fold and t1/2 was estimated within 1.5-fold, respectively, in young and elderly PLWH.

After successful model validation, the impact of adult age on ritonavir pharmacokinetics was examined. Cmax, tmax and Vd were independent of adult age. In contrast, AUC and t1/2 showed a progressive increase of 1.5% and 1.0% per year, respectively. Accordingly, ritonavir CL decreased with a maximum 2.0-fold difference compared to the youngest studied age group. Age-related changes being more than expected from interindividual variability (defined as the 1.25-fold interval) were apparent from the age of 55 years. Importantly, sex did not impact age-related changes.

Conclusion: This pilot study elucidated that drug elimination rather than absorption or distribution determines ritonavir exposure changes with advanced age. Importantly, the age-related pharmacokinetic changes of ritonavir are in the same range of those observed with non-HIV drugs suggesting that principally physiological changes such as the decrease in liver weight and hepatic blood flow are the key determinants for drug exposure changes in the elderly and are drug-independent. Thus, the results obtained for ritonavir might be extrapolated to other ARVs and are in line with the sparse clinical data demonstrating a limited effect of age on the pharmacokinetics of ARVs.
Physiologically-based pharmacokinetic modeling of rilpivirine during pregnancy

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Background: Pregnant women are typically excluded from HIV clinical trials due to practical and ethical concerns. However, a physiologically-based pharmacokinetic (PBPK) modeling approach may be used to assess the effect of pregnancy on drug pharmacokinetics (PK). To evaluate PBPK predictive performance in pregnant women with HIV, a PBPK model using rilpivirine (RPV), a nonnucleoside reverse transcriptase inhibitor (NNRTI) used during pregnancy, was developed. Women who have used rilpivirine as part of a successful, established regimen before pregnancy are recommended to continue throughout the course of their pregnancy.

Materials & Methods: We developed a PBPK model for RPV (Simcyp version 16.1) using physicochemical, in vitro, and clinical parameters obtained from literature. The model was verified with data from clinical trials in both healthy and HIV positive populations. The RPV PBPK model was then applied to a pregnancy PBPK model, modified to account for the progressive physiological changes of pregnancy. Simulated PK profiles using the pregnancy PBPK model were compared with observed data from three clinical trials of HIV positive, pregnant women. The pharmacokinetic parameters we considered in the validation process were maximum plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), area under the concentration-time curve (AUC), and minimum plasma concentration (Cmin).

Results: The PBPK model for the nonpregnant population predicted RPV pharmacokinetics within a two-fold error range of the mean observed clinical values in HIV-positive adults. In the pregnant population, the predicted values were within ± 50% of the mean (n = 30 in second trimester, n = 57 in third trimester) observed clinical values for Cmax, Tmax, AUC, and Cmin. Clinically, RPV exposure is reduced in the 2nd and 3rd trimester of pregnancy with a 30-40% decrease in both AUC and Cmin. The PBPK model captured these changes, with a predicted decrease in exposure of around 30% for both AUC and Cmin compared to the postpartum state.

Conclusion: Our PBPK model for rilpivirine could capture the effects of pregnancy on maternal exposure from 20 – 38 weeks gestation. The pregnancy model accounted for changes in plasma binding proteins, CYP3A4 enzyme activity, and glomerular filtration rate (GFR), resulting in differences in volume of distribution, fraction unbound, and clearance between the nonpregnant and pregnant population. Future work will investigate the effects of using laboratory values collected from the P1026s study to modify the healthy pregnant population to represent the HIV state. Models for additional antiretroviral compounds will be built to continue assessment of the predictive performance of pregnancy PBPK.
A semi-mechanistic population pharmacokinetic model is beneficial in quantifying hair concentrations of ritonavir-boosted atazanavir: A study of HIV-infected Zimbabwean adolescents

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Background: Adolescents experience higher levels of non-adherence to treatment of HIV. Measuring drug concentration in hair promises to be a reliable method for assessing exposure to antiretroviral drugs due to accumulation from plasma. Population pharmacokinetic modelling approaches are necessary to explore the usefulness of quantifying drug concentrations in hair for the benefit of measuring long term adherence. Drug plasma measurements cannot reliably be used for adherence monitoring especially in settings where patients took the drugs only towards clinic visits. We aimed at developing a pharmacokinetic model based on atazanavir and ritonavir concentrations determined in the hair and identify factors associated with variabilities in hair accumulation.

Materials & Methods: This study was secondary data analysis where data from previously published study was utilised in model development. The study was conducted in Zimbabwean adolescents on 2nd line HIV treatment for at least six months. Participants were randomised to the intervention or control study arms. Hair samples and other data variables were collected at enrolment and at three months follow-up. Model development was done using NONMEM 7.3. Previously published models describing population pharmacokinetics of atazanavir or ritonavir in plasma were utilised, and parameter estimates were fixed to literature values. Then the fraction of the drug that accumulated in hair was estimated while the hair volume of distribution was fixed to unit for both drugs. Stepwise covariate modelling strategy was used for covariate selection. Model validation included assessment of goodness-of-fit plots.

Results: Our findings show that there is 16% and 18% of the respective atazanavir and ritonavir concentrations in hair relative to steady-state trough plasma concentrations. At follow-up event, we estimated an increase of 30% and 42% in concentrations of the respective atazanavir and ritonavir concentrations that accumulated in hair compared to accumulation at enrolment. A unit increase in self-reported adherence measured was associated with 2% increase for both atazanavir and ritonavir concentrations in hair. Thinner participants had 54% higher hair concentrations, while overweight participants had 21% lower hair concentrations compared to normal weight participants. Adolescents receiving care from fellow siblings had atazanavir concentrations of at least 54% less compared to those receiving care from mature guardians. Participants in the control arm had 53% higher apparent volume of distribution of atazanavir in hair while those in earlier stages of disease progression at ART initiation had 37% lower volume of distribution of ritonavir in hair.

Conclusion: In this analysis, we demonstrated potential benefit for using modelling and simulation to quantify antiviral concentrations in hair. Most important determinants of increased concentrations in hair were monitoring at follow up event, body mass index-for-age and caregiver status. Measuring ART levels in hair promises to be more accurate and feasibly accomplished.
Utilization of physiologically based pharmacokinetic modelling (PBPK) to predict the effect of UGT enzyme inhibition and induction on the systemic exposure of Cabotegravir

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Background: Cabotegravir (CAB) is an HIV integrase inhibitor in development for HIV treatment for monthly or every other month administration as part of a combination therapy, and as monotherapy for HIV prevention. CAB is formulated as an oral tablet and long-acting (LA) injectable for intramuscular administration. CAB undergoes glucuronidation via UGT1A1 with a minor UGT1A9 contribution. In HIV/TB coinfection, co-administration with anti-TB agents, rifampin or rifabutin, may be required. Rifampin is a potent UGT inducer and reduced oral plasma CAB exposure by 59%. A reduction of 21% was observed with rifabutin, a weak UGT inducer. UGT inhibition effects on CAB exposure have not been clinically investigated. A physiologically based pharmacokinetic (PBPK) model of CAB was developed to prospectively assess the impact of potent UGT inhibition by atazanavir (1A1) and mefenamic acid (1A9), and a weak UGT1A1 inducer, phenobarbital.

Materials & Methods: A mechanistic PBPK model for CAB was built using Simcyp® (v17). Physicochemical properties were obtained from experimental data or estimated using in silico predictions. The UGT-mediated metabolism of CAB was modelled using in vitro enzyme kinetic parameters, along with the Simcyp® built-in tissue expression levels. Clinical PK data following oral 30 mg dosing was used for model validation. The Simcyp® DDI module, default Simcyp® files, and/or files created using available literature data (mefenamic acid) were used to predict UGT-mediated DDIs.

Results: Simulated CAB PK profiles were within 25% of observed clinical PK parameters following single and repeat oral CAB 30mg administration qualifying the model as sensitive for predicting clinical DDIs. The fraction of CAB metabolized by UGT1A1 was verified with the forecast impact of rifampin on plasma CAB AUC being within 30% of observed data. Prespecified upper and lower exposure limits were determined from Phase III and earlier trials where safety and efficacy were demonstrated. DDI simulations predicted a mean 11% increase in plasma oral CAB exposure when co-administered with UGT1A1 or UGT1A9 inhibitors, atazanavir or mefenamic acid, respectively, and were within the upper exposure limit for oral and LA CAB. DDI simulations with phenobarbital predicted a mean 28% decrease in oral CAB exposure, comparable to observed rifabutin data and within the prespecified exposure limits. Oral and LA CAB can be co-dosed with weak to moderate UGT inducers as concentrations maintained within exposure limits consistent with CAB safety and efficacy. Potent UGT inducers are expected to significantly decrease plasma CAB LA exposures increasing the percent of patients whose CAB levels fall outside the exposure limits.

Conclusion: A PBPK model of oral CAB was developed and validated to accurately predict human pharmacokinetics and the impact of potential DDIs on oral and LA exposure. DDI simulations predicted minimal effects on CAB exposure from potent inhibitors of UGT1A1 or UGT1A9 suggesting no restrictions being required with this class of inhibitor. Clinical DDI data and PBPK simulations indicated that the impact of UGT induction on CAB exposure was proportional to their induction potency. These data suggested that co-medication exclusions may need to be considered for inducers which are not weak to moderate.

Abstract 19 withdrawn
Management of antiretrovirals in seniors: the importance of assisted treatment for adherence to treatment

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Background: Associated with the aging of people living with HIV / AIDS are many other types of morbidity that need to be safeguarded. Medication prescribed for this population is not always fulfilled, either by forgetting, unwanted side effects or uncontrolled viral load. Medication management and adherence behavior to antiretroviral treatments are determinant for the efficacy of treatment and for the quality of life of these people, and assisted treatment is an important component in the care of the elderly who still live with shame and stigma associated with this disease.

The aim of this study was to diagnose adherence to antiretroviral therapy in a convenience sample comprised of seniors enrolled in the Project In.Porto.Me I - Project for Screening and Promotion of Quality of Life of HIV + Seniors from Porto (N = 63). We carried out the analysis of the records made, in a data collection instrument developed for this project, during the home visits made by the person in charge of the medication / assay management and by the psychologist. This instrument included socio demographic, socio-communitarian data, drug-therapeutic regimen and therapeutic relationship and psychopathological dimensions.

Materials & Methods: Of the 63 participants in the study, 27 were male and 36 were female between the ages of 67 and 88, with the majority living with their partner (married and / or union). We found that in Seniors Living With HIV there are some good practices conducive to therapeutic adherence: correct storage of medication (83%), compliance with medication prescription (72%), there were, however, aspects that may be improved: record of use of the drug (s) (87%); lack of support in medication compliance (78%); relationship between failure and therapeutic adherence (88%).

Regarding the psychopathological dimensions, it was observed that the majority experienced episodes of anxiety (67%), depression (59%) and stigma associated with the disease (89%). Most (78%) isolate themselves from friends and even from the extended family.

Results: The focus of this study was to understand the interdependence between the relationship and therapeutic adherence. In the course of the project, the participants revealed that the fact that they are regularly followed, able to talk, get their doubts and realize what was being explained facilitated their adherence to antiretroviral treatment. Many have reported seeing the relationship between the effectiveness of treatment and the regularity and compliance of the medication (even when taking many other medications) only possible with this direct relationship and systematic monitoring and proximity assistance. In addition, switching from three tablets to a single shot facilitated Another factor that seems important for the improvement of self-control and self-efficacy, autonomy and socialization of the participants was the psychological counseling and counseling where the psychopathological dimensions were worked out and improved.

Conclusion: Seniors living with HIV/AIDS, especially the most vulnerable due to their economic situation/social isolation, referred to when accompanied and monitored in various biopsychosocial dimensions, consolidate the skills of self-control over HIV infection that favors the maintenance and/or increase of adherence to therapy, the adoption of healthy living habits and the improvement of their quality of life.
Pharmacokinetics of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in a client on PrEP after a total gastrectomy with Roux and Y anastomosis (TGY).

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Background: Our case is a man of 32 years old, after a TGY in 2011, due to hereditary diffuse gastric cancer, who wanted to start PrEP. A TGY may influence pharmacokinetics (PK) of HIV medication, as part of the gastrointestinal tract is bypassed and pH increases. Furthermore, in obese HIV patients a transient decrease in tenofovir concentrations has been shown after bariatric surgery [1,2]. As seroconversion is the only clinical parameter to monitor the effect of PrEP, we decided to monitor emtricitabine and tenofovir concentrations during a standard regimen, and after obtaining the PK results, a double dose regimen.

Materials & Methods: Two full PK curves of emtricitabine and tenofovir were drawn at approximately 0, 1, 2, 3, 4 and 8h after administration of TDF/FTC. The pre-dose concentrations were also used as T=24h samples. The first curve was drawn after more than a month use of TDF/FTC once daily (200mg/245mg) as PrEP, the second after 5 days use of a double dose TDF/FTC once daily. No PrEP was used in between. Before each start of PrEP the client tested negative for HIV. At the start of PrEP at the standard dose he was 1.84m, 60.4kg, with an eGFR (CKD-EPI) of 144ml/min/1.73m². At the start of the double dose he was 62.4kg with an eGFR of 128ml/min/1.73m². AST and ALT were normal. NRTI plasma levels were measured by a validated LC-MS method. The client signed an informed consent for the publication of the results.

Results: The PK parameters after the standard dose showed an AUCL-24h of 73.2% and 44.3% compared to reference values for emtricitabine and tenofovir (7.83 versus 10.70h*mg/L; 1.24 versus 2.80h*mg/L) [3]. Cmin was 0.02mg/L for both emtricitabine and tenofovir (reference 0.08 and 0.05 mg/L). After the dose was doubled, the AUCL-24h increased to 148.9% and 132.5% for emtricitabine and tenofovir (15.93 and 3.71h*mg/L). Tmax of both emtricitabine and tenofovir was shorter in both dose regimens, 1.00-1.52h, versus 3h for emtricitabine, 1.00h versus 2.40h for tenofovir. Cmax of emtricitabine increased proportionally from 1.93 to 3.80 mg/L (reference 1.69 mg/L), whilst tenofovir Cmax increased disproportionally from 0.17 to 0.51 mg/L (reference 0.29 mg/L).

Conclusion: The use of a standard dose of TDF/FTC in our client with a TGY, resulted in lower AUC and Cmin when compared to population references for both substances, with potential consequences for suboptimal PrEP efficacy. Doubling the TDF/FTC dose reversed this, in particular for tenofovir. Because of the consequences of failure of PrEP, therapeutic drug monitoring might be useful in clients with a gastrectomy or gastric bypass on PrEP. Safety should be closely monitored if TDF/FTC dose is doubled.

References:
1. Muzard L et al. Tenofovir pharmacokinetics after sleeve-gastrectomy in four severely obese patients living with HIV. Obesity Research & Clinical practice 2017;11:108-113
Proficiency testing supports combined analysis of dolutegravir pharmacokinetic data

**Background:** Bio-analytical laboratories perform internal quality control to guarantee the accuracy of pharmacokinetic data. It is less well known that proficiency testing (PT) is required to become certified by regulatory bodies such as CLIA and ISO. Because laboratories often have different analytical methods and certifications, combining data sets of pharmacokinetic studies is not without risks, influencing the validity of data sharing. Recently, pharmacokinetic data for dolutegravir in children was collected in two separate studies, i.e. IMPAACT protocol P1093 and the Odyssey (PENTA20) trial. Combined analysis of the data is planned for upcoming submission of pediatric pharmacokinetic data of dolutegravir to the FDA and EMA. Both laboratories responsible for pharmacokinetic (PK) analysis of these two separate dolutegravir PK studies participate in the same PT program. PT results were compared to assure congruent quantification.

**Materials & Methods:** The DAIDS-supported Clinical Pharmacology Program for Quality Assurance (CPQA) organizes antiretroviral PT for international laboratories. Dolutegravir has been included as a testing analyte since 2016. Antiretroviral drugs are spiked into a plasma PT panel at five unknown concentrations encompassing the expected therapeutic range. Panels are shipped twice annually and results are reported back to the CPQA program. The program provided all dolutegravir data reported by both laboratories for comparison.

**Results:** Both laboratories participated in 4 rounds including a total of 20 samples. Dolutegravir concentrations ranged from 100-900 ng/mL. All reported dolutegravir concentrations from both laboratories were satisfactory (within ±20% final target value). The mean (n=20) deviation of the final target value was -6.1% (SD 5.8%) for one lab vs. +3.9% (SD 3.5%) for the other lab. Linear correlation analysis showed that both laboratories provided similar results: $Y = 1.0704X + 13.7$ (R-Squared: 0.9899) where $Y$ and $X$ are the dolutegravir concentrations (in ng/mL) reported by each laboratory.

**Conclusion:** The agreement of PT values reported for dolutegravir supports the combination of PK data from the IMPAACT protocol P1093 and Odyssey. It also demonstrates that sponsors should stipulate that laboratories involved in international PK studies participate in the same external PT program. In that way quantitative PK data can be objectively assessed for suitability of aggregation in future analyses and results become more reliable.
Plasma and intracellular pharmacokinetics of cobicistat in the clinical setting

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Background: Cobicistat (COBI) has replaced ritonavir as a booster for PIs and INIs. No data are available on COBI pharmacokinetics (PK) according to different companion drugs and to intracellular (IC) accumulation. Aim of our study was to evaluate COBI plasma and intracellular (IC) exposure when taken with Atazanavir (ATV) or Darunavir (DRV), in the clinical setting.

Materials & Methods: 51 patients (pts) were enrolled in our observational study (22 treated with ATV, 29 with DRV). Plasma samples were collected as Ctrough (median 2 for patient). Moreover 9 pts administered with ATV/c and 9 pts with DRV/c once daily, were included in our study and underwent to intensive PK analysis. COBI and PIs plasma concentration were measured at the end of dosing interval and 2, 4, 8, 12 hours after drug intake by means of HPLC-UV validate method and IC concentration by means of HPLC-MS validate method. Non-compartmental pharmacokinetic parameters were calculated and expressed as geometric mean (CI95%). Concentrations were expressed as ng/ml. Descriptive analysis were expressed as geometric mean (CI95%) and results analyzes by Mann Whitney and by Spearman test, as appropriate.

Results: 51 pts were 72% male, median age 53 (IQR 49,5; 56,5) and BMI 24,9 (IQR 22,0; 26,5). COBI area under the curve (AUC), Cmax and Cmin when dosed with DRV resulted to be 3710,0 (2259,4-5160,6) ng/h*mL, 541,0 (366,7-715,2) ng/mL and 11,3 (7,6-15,0) ng/mL, respectively. When dosed with ATV, COBI parameters resulted to be 11446,4 (8562,5-14330,4) ng/h*mL, 1273,6 (1108,7-1438,6) ng/mL and 60,3 (-16,8-137,4) ng/mL, respectively. All COBI PK parameters were significantly higher when dosed with ATV as compared with DRV (AUC p<0,001, Cmax p<0,001 and Cmin p=0,003). Dosed with ATV, COBI plasma and IC Ctrough resulted to be 47,7 (-78,9; 0; 174,5) ng/mL and 103,7 (-2,6; 210,0) ng/mL, respectively, and COBI ratio IC/plasma was 2,170 (0,899; 3,441); Dosed with DRV, COBI plasma and IC Ctrough were 14,4 (5,4; 23,4) ng/mL, and 54,6 (21,8; 87,5) ng/mL, respectively, and COBI ratio IC/plasma observed was 3,786 (2,407; 5,166). Difference of COBI IC ratio between ATV and RV was not significant (p=0,106). No correlation was found between gender, age and BMI and COBI, plasma and IC concentration, and ratio IC/plasma. Plasma and IC COBI concentrations showed to be significantly correlated (p=0,011).

Conclusion: This is the first evaluation of COBI plasma and IC PK in the clinical setting. As it was previously showed for RTV, COBI plasma exposure showed to be higher, by two-fold, when dosed with ATV/c as compared to DRV/c. Moreover, cellular accumulation ratio (IC to plasma ratio) of COBI, ranging from 2.17 to 3.7, was shown to be lower than reported for RTV (up to 9). These data could contribute to explain the differences of tolerability previously observed between RTV and COBI (e.g. lower lipids increase).

Abstract 24 withdrawn
Temsavir concentration (Cp)-QTc relationship following administration of fostemsavir

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Background: Fostemsavir (FTR) is a prodrug of temsavir (TMR), a first-in-class attachment inhibitor with demonstrated efficacy in heavily-treatment experienced HIV-1 infected patients in Phase 3 development. A thorough QT (TQT) study showed positive QT effect at a supratherapeutic dose of FTR (Hruska MW et al. 15th IWCPHT). Previously, an indirect response model was used to describe the Cp-QTc relationship (Landry I et al. 16th IWCPHT). The current analysis was performed to better characterize the Cp-QTc relationship to determine threshold TMR concentration for QTc safety.

Materials & Methods: TQT study data was examined for the Cp-QTc relationship graphically and via analysis of various linear and direct-response models using NONMEM®. The final model was selected based on diagnostic plots and visual predictive check; simulations were performed with 100 subjects/trial for 1000 trials. Simulated upper bound of 90% confidence interval (CI) of mean double-delta-QTcF at 10 msec was used to determine threshold concentration for QTc safety.

Results: No hysteresis was evident from the individual or mean exploratory plots of Cp-QTcF relationship indicating that an indirect response model was not appropriate. The relationship was best described by a linear slope-intercept model. Simulations using this model predicted a TMR threshold concentration of 7500 ng/mL consistent with the TQT study results and provided more realistic estimates than the indirect-response model.

Conclusion: The linear intercept-slope model is appropriate to estimate QTc change at a given TMR concentration. Exposures with FTR 600 mg BID with/without pharmacoenhancers are very unlikely to reach the levels associated with QTc prolongation.
Hepatotoxicity and associated risk factors in HIV-infected patients receiving antiretroviral therapy at a referral hospital in Ethiopia

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Background: In Human Immunodeficiency Virus (HIV) infected patients on antiretroviral treatment (ART), hepatotoxicity is life threatening. Its outcome may lead to liver failure and death. This study was conducted to determine the rate and determinants of elevated alanine amino transferase (ALT) (referred as > 40IU/L for both males and females).

Materials & Methods: A cross sectional study was conducted on HIV infected individuals who are on ART and presumptive of drug resistance at Felegehiwot Referral Hospital, Bahir Dar from July to December 2012. Venous bloods were collected from each patient and processed parallely to determine alanine aminotransferase, number of HIV RNAs, CD4 and CD8 T cells, anti-hepatitis C virus (HCV) and hepatitis B surface antigen. The level of alanine amino transferase (ALT) was measured on a Beckman Coulter Synchron Clinical Systems auto lab Analyzer (Beckman Coulter Inc. Fullerton, CA, USA). HIV RNA copies were determined using Abbott Real Time HIV-1 assay (Abbott Molecular Inc., Des Plaines, IL, USA). Absolute CD4 and CD8 T cells count was performed using a specific monoclonal antibody and fluorescence-activated cell sorting (FACS count) (BECTON DJICKINSON, USA). The presence of Hepatitis B surface antigens (HBsAg) was detected on sera using EILSA, (Linear chemicals, Joaquin Costa, Barcelona, Spain). Similarly, IgG and IgM antibodies to HCV were detected using ELISA, (Linear chemicals, Joaquin Costa, Barcelona, Spain). Independent sample T test was employed for group mean comparison of CD4 T cell counts. Pearson χ2 test and bivariate were used for categorical data to generate P-values and P-value < 0.05 was considered statistically significant. Multivariate logistic regression analysis was computed to identify the independent determinant factors of ALT elevations.

Results: Out of 269 HIV infected patients receiving ART, 32% were confirmed of grades 1-4 levels of elevated alanine aminotransferase. The rate of severe hepatotoxicity (grade 3 and 4) was 1.84%. Of the 269 ART patients who participated with known HBV/HCV serology, 30 (11.2%) were HBsAg positive, 51 (18.96 %) were anti-HCV positive and 8 (3%) were both HBsAg and anti-HCV positive. Patients with increased CD8 T cell counts (AOR=1.82; CI: 1.12 - 2.54), alcohol over use (AOR = 1.23; CI: 1.36-3.29) and detectable HIV-1 RNA copies (AOR =2.07; CI: 1.15-3.74) independently predicts the elevation of ALT.

Conclusion: In HIV infected patients on ART, extreme elevations of ALT were infrequent but minor elevations were common so that patient-linked variables such as use of alcohol intake must be taken in to account for better clinical management of ART patients. The role of active HCV co-infection on the treatment outcome of ART should be further studied.
Antiretroviral penetration and drug transporter concentrations in the spleens of three preclinical animal models and humans

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Background: The spleen, an HIV reservoir, contains 25% of the body’s lymphocytes. However, no data exist on ARV concentrations in this tissue. This study aims to quantify splenic ARV concentrations and determine whether drug transporter expression, sex, or infection status correlates with ARV concentrations in humanized mice, non-human primates (NHPs), and humans.

Materials & Methods: Hu-HSC-Rag (RagHu) mice (n=36; 18 HIV+ and 18 HIV-) and BLT mice (n=13; 7 HIV+ and 6 HIV-) were dosed with one of the following ARV regimens for 6-10 days: efavirenz (EFV) 10mg/kg PO alone, atazanavir (ATZ) 140mg/kg PO alone, or tenofovir (TFV) 208mg/kg PO, emtricitabine (FTC) 240mg/kg PO, raltegravir (RAL) 56mg/kg PO, and maraviroc (MVC) 62mg/kg PO. Ten SHIV+ and 8 SHIV- NHPs (12 male, 6 female) were dosed for 10 days with the following ARVs: FTC 16 mg/kg SQ, TFV 30 mg/kg SQ, EFV 200 mg/day PO, RAL 200 mg/day PO, MVC 300 mg/day PO, and ATZ 540 mg/day PO. 24h post-dose. Thirteen HIV+ human spleens from National NeuroAIDS Tissue Consortium were analyzed post-mortem (24h post-dose). ARV, emtricitabine triphosphate (FTCtp), tenofovir diphosphate (TFVdp), and endogenous nucleotide (dCTP, dATP) concentrations were measured in homogenized tissue by LC-MS/MS (LLOQ: 0.002-0.01 ng/mL) and reported in ng/g of tissue. Quantitative Targeted Absolute Proteomics (QTAP, LOD: 0.1 pmol/mg protein) for P-gp, Mrp1, Mrp2, Mrp4, Bcrp, Oatp2a1, Ent1, Oct2, and Oct3, was performed. Penetration ratios (PR: paired splenic ÷ plasma ARV concentrations) and metabolite to endogenous nucleotide ratios (MER: paired splenic metabolite ÷ splenic nucleotide concentrations) were presented as mean (SE). Statistical analyses included Kruskal-Wallis One Way ANOVA followed by Dunn test with Holm-Sidak p-value corrections for species differences, Mann-Whitney Rank Sum tests to evaluate roles of infection status and sex, and Spearman rank order correlation for transporter and ARV concentrations, (p<0.05) using R 3.5.2.

Results: Mouse spleen and plasma drug concentrations were 73% and 68% lower than NHPs (p<0.01) and 80% (p=0.2) and 94% (p<0.01) lower than humans, respectively. Sex, infection status, and measureable transporter concentrations did not significantly influence splenic concentrations. All ARVs had PRs ≥1 in all species except for RAL (PR = 0.3 in mice, 0.1 in NHPs, 1.7 in humans). NHP TFVdp:dATP ratios were 8-fold higher than mice (p<0.01), but similar to humans. FTCtp:dCTP were similar across species. Due to small size, QTAP analysis of the mouse spleens was limited. Three transporters were detected in NHPs (Mrp4, Bcrp, and Ent1), and 1 in humans (Ent1). Ent1 concentrations were 4-fold higher in SHIV- NHPs than SHIV+ NHPs (p=0.02). There were no significant correlations between transporters and ARV concentrations.

Conclusion: Sex, infection status, and measurable transporter concentrations did not influence splenic ARV concentrations or PRs. Splenic concentrations increased with higher plasma concentrations for all ARVs except RAL, suggesting not all splenic concentrations increase with increasing ARV dose. NHP PRs and MERs were similar to humans, suggesting analogous tissue penetration and intracellular processes. This is the first study to compare interspecies ARV penetration and transporter concentrations in spleens. These data can inform tissue pharmacokinetic scaling to humans to target HIV reservoirs.
Characterization of binding of dolutegravir to plasma proteins

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Background: The unbound concentration of a drug is considered the active moiety, which is available to cross cell membranes. In humans, dolutegravir (DTG) is highly bound to plasma proteins (>99%) with consequently, a low unbound concentration. This study aimed to characterize DTG protein binding to human serum albumin (HSA), to human alpha-1-acid glycoprotein (HAAG) and to human plasma proteins.

Materials & Methods: DTG protein binding was measured in vitro in blank human plasma samples from the Blood Bank which were spiked with DTG to final concentrations of 800 and 1,600ng/mL. DTG HSA binding and DTG HAAG binding were measured using a 40-g/L HSA solution and a 0.7-g/L HAAG solution, respectively, prepared in pH 7.4 phosphate-buffered saline and spiked with DTG to yield 8 final concentrations from 25 to 25,000ng/mL and 7 final concentrations from 200 to 7,500 ng/mL, respectively. The influence of pH on DTG HSA binding was studied in a 40-g/L HSA solution spiked with DTG at 800 and 1,600ng/mL at pHs ranging from 7.0 to 7.8. Each experiment was run in triplicate. Bound and unbound fractions were separated by ultrafiltration (Centrifree devices). Total and unbound DTG concentrations were measured by quality controls validated assays (LC-MS/MS). A graphical Scatchard plot method was used to estimate binding characteristic: association constant (Ka) and number of sites (n).

Results: In vitro, at the 800 and 1,600 ng/mL DTG total concentrations, mean DTG human plasma protein bindings were 99.4% (CV, 4.4%) and 99.1% (CV, 6.6%), respectively. The mean binding of DTG to HSA and to HAAG were 89.6% (range, 83.2%-94.7%) and 48.8% (range, 36.4%-53.0%), respectively, and independent of DTG total concentration. DTG was found to bind to two classes of albumin sites: one with high affinity (Ka=3.5×10⁶ M⁻¹; n=3.2×10⁻³) and one nonsaturable with low affinity (Ka=4.3×10⁵ M⁻¹; n=3.1×10⁻¹). Interestingly in the pH range from 7.0 to 7.8, a 0.2-U decrease in pH led to a 2% decrease in DTG albumin binding (P<0.0001). DTG bound to nonsaturable, low-affinity alpha-1-acyl glycoprotein sites with an nKa product of 6.2×10⁴ M⁻³.

Conclusion: DTG binds extensively to human plasma proteins, with preferential binding to HSA. The significant DTG HAAG binding to nonsaturable sites could partly explain the remainder of DTG binding rate. The observed pH sensitivity of DTG binding could be explained by pH-induced conformational changes in albumin. Therefore, it may favor diffusion within the cell as quiescent human peripheral blood mononuclear cells are pH homeostatic, maintaining an intracellular pH of 7.1 over an extracellular physiological pH of 7.4. These results remain to be confirmed for virological efficacy in HIV reservoirs and for the exact clinical significance in HIV-infected patients.
Pharmacokinetic (PK) and pharmacocokinetic/pharmacodynamic characterization of the two-drug anti-retroviral regimen (2DR) dolutegravir/rilpivirine following switch from current anti-retroviral therapy in the SWORD-1 and SWORD-2 Phase 3 studies


Background: SWORD-1 (NCT02429791) and SWORD-2 (NCT02422797) demonstrated that switching to the 2-drug regimen (2DR) dolutegravir and rilpivirine (DTG+RPV) was non-inferior for maintaining HIV-1 viral suppression compared with remaining on the current antiretroviral regimen (CAR) at Week 48 and that high level viral suppression was sustained through Week 100. Secondary objectives of the SWORD studies were to characterize DTG and RPV steady-state trough concentrations (C0) and to explore exposure-response relationships for efficacy and safety using pooled study data.

Materials & Methods: SWORD-1&-2 are identical Phase III, randomized, non-inferiority studies evaluating the efficacy, safety, and PK of switching to DTG+RPV from an INI-, NNRTI-, or PI-based CAR in virologically-suppressed HIV-1 infected adults. 1028 participants were randomized 1:1 to DTG 50mg + RPV 25mg once-daily with a meal (Early Switch group) or continue CAR. Participants randomized to CAR with confirmed viral suppression switched to DTG+RPV at Week 52 (Late Switch group). Blood samples were collected pre-dose (C0) at Weeks 4, 24, 48, 56, 76, and 100 in the Early- and at Weeks 56, 76, and 100 in the Late Switch groups for quantitation of DTG and RPV by LC/MS/MS. Plasma C0 were summarized by visit and over time for the overall population and NNRTI subset (switched from enzyme-inducing NNRTIs to 2DR) and by age (<50 and >=50years). The relationship between DTG or RPV C0avg (average C0 across visits) and efficacy (Snapshot virologic outcomes) at Week 100 was graphically explored. The relationship between C0avg and safety (5 most common adverse events and laboratory safety parameters) were analyzed by logistic regression and Pearson correlation, respectively.

Results: DTG and RPV C0 were relatively constant throughout Week 100 in early or late switch groups in both the overall population and the NNRTI subset. The geometric mean DTG (µg/mL) and RPV (ng/mL) C0avg (CV%) were 1.47 (54%) and 82.8 (43%), respectively, in the Early Switch group and 1.54 (60%) and 80.6 (54%), respectively, in the Late Switch group in the overall population (NNRTI subset: 1.50 (54%) and 83.8 (45%) in the Early Switch group and 1.52 (57%) and 85.1 (48%) in the Late Switch group). For age <50 and >=50, respectively, DTG C0avg was 1.47 (56%) vs 1.47 (48%) and RPV was 79.1 (41%) vs 92.9 (48%) in the Early Switch group while in the late switch group DTG was 1.58 (62%) vs 1.44 (52%) and RPV was 78.0 (54%) vs 88.0 (51%) No associations between C0avg and virologic failures (~2%) or safety endpoints at Week 100 was observed in either group.

Conclusion: DTG and RPV C0avg were comparable to those observed in prior studies and above their respective protein adjusted-IC90 in both the overall populations and the NNRTI subset. There was no relationship between DTG or RPV exposure and virologic response which was consistent with prior registration trials of single entities that also evaluated the approved once-daily doses of DTG 50mg or RPV 25mg. No clinically meaningful relationships between DTG or RPV exposure and safety endpoints and no relevant impact of age were observed through Week 100.
Alteration of hepatic OATP activity does not alter the pharmacodynamic effect of GS-0976, a liver targeted ACC inhibitor, on de novo lipogenesis

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Background: The Extended Clearance Model indicates that for an OATP substrate that exerts its effect in the liver, reduced OATP function will increase systemic exposure via transient exclusion from the liver, but will not ultimately alter its PD effect in the liver. This Phase 1 study was designed to demonstrate this concept utilizing the liver-targeted inhibitor of acetyl-CoA carboxylase (ACC), GS-0976 which is in development for the treatment of nonalcoholic steatohepatitis (NASH). GS-0976 is heptatically eliminated with OATPs significantly contributing to the hepatic uptake where GS-0976 exerts its PD effect of decreasing de-novo lipogenesis (DNL).

Materials & Methods: In this randomized, four-way cross-over, placebo-controlled study, fructose-stimulated DNL was measured in 28 healthy subjects after single dose administration of placebo (PBO), GS-0976 10 mg oral, GS-0976 10 mg oral + the OATP inhibitor rifampin (RIF) 300 mg IV, or RIF 300 mg IV (control for effect of RIF). Each treatment was separated by a 7-day washout. To evaluate fructose-stimulated DNL, subjects were administered an IV infusion of 1-13C labeled acetate prior to, during, and after administration of an oral fructose solution (0.18 g/kg every 30 minutes for 14 hours) on study treatment days. Plasma samples were collected for pharmacokinetic and PD assessments through 24 hours after each treatment. 13C-acetate incorporation into palmitate in total triglyceride particles was measured by GC/MS-MIDA to calculate hepatic DNL (area under the effect curve: AUEC) and its inhibition by GS-0976.

Results: 27 subjects completed all study treatments which were safe and well tolerated. When administered alone, RIF modestly increased hepatic DNL AUEC (36% vs PBO). Despite a 5.2-fold increase in systemic plasma exposure (AUCinf) of GS-0976 when administered with RIF, GS-0976 alone, and GS-0976+RIF had the same hepatic PD effect, 34.9% and 37.1% reduction in DNL AUEC, respectively.

Conclusion: With reduced OATP function GS-0976 systemic exposure was significantly increased without altering its pharmacodynamic effect exerted in the liver, providing clinical evidence in support of the Extended Clearance Model. These findings indicate that in settings of reduced hepatic OATP function (hepatic impairment or coadministration with OATP inhibitors) dose reduction of liver acting OATP substrates to maintain comparable systemic exposure would result in reduced efficacy. As such, characterization of safety over a range of systemic exposures may be necessary for use in patients with reduced OATP function.
**PBPK modelling and simulation of ritonavir-boosted atazanavir (ATV/r) dosing when co-administered with rifampicin (RIF)**


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**Background:** Rifampicin (RIF), a major component of first-line treatment of tuberculosis (TB), is an established inducer of drug transporters, CYP3A4 and other key drug disposition proteins. A significant proportion of patients undergoing treatment for TB is also receiving antiretroviral therapy. Enzyme induction by RIF causes a substantial reduction in plasma concentrations of boosted protease inhibitors (e.g. ritonavir boosted atazanavir – ATV/r) resulting in a higher risk of treatment failure. In silico modelling approaches can support a rational identification of strategies to optimise antiretroviral and anti-TB regimens. Physiologically-based pharmacokinetic (PBPK) models are an innovative instrument that allows the simulation of scenarios where there is a lack of clinical data. The aim of this research was to create a PBPK model for a co-administered regimen of ATV/r and RIF to predict optimal dosing to overcome the enzyme inducing effect of RIF.

**Methods:** A PBPK model was developed to investigate the interaction between RIF and ATV/r. A virtual cohort of 100 healthy individuals aged 18 to 60 (50% female) was generated. In vitro data describing ADME properties were obtained from the literature, including induction/inhibition parameters. Differential equations were used in concert to describe the anatomical and biochemical processes defining ADME. The PBPK model was qualified against clinical data for ATV/r, RIF and validated probes for ADME processes underpinning the DDIs. The impact of RIF (600mg) upon ATV/r pharmacokinetics was then simulated along with potential dosing strategies that may alleviate the interaction.

**Results:** Simulated ATV/r pharmacokinetic parameters were (mean ± SD) C_{trough} (1.12 ± 0.74 μg/ml), C_{max} (6.18 ± 1.15 μg/ml) and AUC (80.25 ± 24.06 μg/mLh), which was within acceptable range of observed PK data for ATV/r 300/100 mg in HIV-infected patients set out in PBPK guidelines: C_{trough} (0.97 ± 0.82 μg/ml), C_{max} (4.54 ± 6.03 μg/ml) and AUC (59.54 ± 48.41 μg/mLh). Simulations indicated that RIF resulted in a decrease in ATV/r exposure of 84% for AUC and 60% for C_{max}. Moreover, this interactions was predicted to be mitigated by increasing the ATV/r dose to 300/100 bid, 300/200 bid or 300/100 tid.

**Discussion:** The presented PBPK model was successfully qualified against the pharmacokinetics of ATV/r in patients and used to simulate the interaction with RIF. Based on these simulations, a change in regimen to 300/100 bid, 300/200 bid or 300-100 tid ATV/r may overcome RIF-mediated induction, resulting in >95% of patients achieving exposures above the protein adjusted IC90 for ATV. Although hepatotoxicity could represent a limiting factor for the co-administration of ATV/r and RIF, these dose adjustments would represent suitable strategies for further clinical investigations. The safety of such combinations would require careful and detailed assessment of liver function, particularly given recent safety data for other boosted protease inhibitors.
Model-based simulated 3TC exposure in HIV population by varying renal function

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**Background:** Lamivudine (3TC) is a nucleoside reverse transcriptase inhibitor active against human immunodeficiency virus (HIV) and hepatitis B virus. For HIV-infected adults, 3TC dose is 300mg QD or 150mg BID in combination with antiretrovirals (ARVs); 300mg BID had similar safety and efficacy in Ph3 studies. 3TC has linear/dose dependent pharmacokinetics (PK); 3TC clearance (CL/F) is dependent on renal function as the majority of 3TC is eliminated unchanged in the urine. 3TC dose recommendations by varying degrees of renal function were determined based on the relationship between 3TC CL/F and creatinine clearance (CLcr) from the two separate Ph1 renal impairment (RI) studies. This analysis used a population pharmacokinetic model (PPK) to predict 3TC exposure (AUC) and variability based on CLcr ranges.

**Materials & Methods:** A previously developed 3TC PPK model was parametrized using the Cockcroft-Gault equation to characterize CL/F, volume (V/F) and absorption rate (Ka) in a mixed population (n=417) of HIV patients from two Ph3 studies and two Ph1 RI studies. The PPK model was used to simulate steady-state 3TC AUC based on observed CLcr range 31.0-49.3mL/min (n=8) and 82.3 to 159 mL/min (n=15) and for CLcr ≥50mL/min (n=15). Results were compared to previous non-compartmental analysis (NCA) and linear regression model (LRM).

**Results:** Simulated median (range) steady-state 3TC AUC values in HIV patients with varying renal function in methods were 29.7 (25.8-42.4), 12.9 (10.4 – 16.4) and 16.7 (11.1-25.2), respectively. PPK simulated 3TC AUC values from two CLcr categories were comparable to previous LRM and NCA results.

**Conclusion:** PPK and LRM are appropriate methods to estimate 3TC AUC and dose based on renal function; the PPK model from HIV patients enhanced estimates of variability. With CLcr 30-49 mL/min, a ~2-fold increase in 3TC AUC is observed compared to CLcr ≥50mL/min which was consistent with HIV-patients receiving 300mg BID (600mg/day) and guided the 50% reduction in dose for this range. These results will further facilitate evaluation of dose for 3TC containing fixed dose combinations.
HBV infections among HIV-infected mothers on ART and their exposed infants in a tertiary hospital, Nairobi Kenya

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Background: Mother-to-child transmission (MTCT) of Hepatitis B virus (HBV) is responsible for more than one third of chronic HBV infections worldwide. We determined the prevalence and predisposing factors of HBV infections among HIV infected mothers and their exposed infants.

Materials & Methods: A structured questionnaire was used to capture socio-demographic data and factors associated with HBV infections. 4ml of paired whole blood obtained from HIV positive mothers and their exposed infants was analyzed for Hepatitis B surface antigen (HBsAg) using both rapid and Enzyme linked immune-absorbent assay (ELISA) tests. HBsAg positive samples were further screened for HBV envelope antigen (HBeAg) using ELISA. HBsAg positive samples with both ELISA and rapid tests were subjected to a nested Polymerized chain reaction (PCR) targeting the preS1 region.

Results: A total of 534 HIV infected mothers were recruited. Mean age of mothers was 31.2 years (SD 5.4 years) and infants’ median age of 6 months (IQR 3-10 months). A total of 502 (94%) of the mothers were taking TDF/3TC/NVP and 32(6%) were on AZT/3TC/NVP or EFV. 19 of 534 (3.6%) mothers were HBV positive by both HBsAg rapid and ELISA tests. All 19 HBsAg positive samples tested HBeAg negative. Of the 19 HBsAg positive samples, 12 also tested positive on PCR targeting the preS1 gene. All infants’ samples tested HBV negative with all tests. History of dental surgery was associated with increased rate of HBV infection (OR 3.3 (95% CI 1.1-9.6).

Conclusion: HIV HAART among infected pregnant mothers prevents vertical transmission of HBV infections from mothers to exposed infants.

Abstract 34 withdrawn
Tenofovir plasma concentrations in pregnant women: comparison of hepatitis B and HIV-infected patients

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Background: Tenofovir disoproxil fumarate (TDF) is one of the preferred drugs to prevent mother to child transmission in both hepatitis B (HBV) and HIV-infected pregnant women. Previously we found decreased exposure of approximately 20% in HBV mono-infected pregnant women and a similar decrease was observed in HIV-infected pregnant women. These results in HBV and HIV mono-infected women cannot be directly compared since HIV-patients may use co-medications such as ritonavir which increase tenofovir plasma concentrations. However, this comparison is interesting as infection itself could also have an effect on the drug exposure. For this reason, the aim of this study was to compare the effect of pregnancy on tenofovir exposure in women receiving TDF monotherapy for HBV mono-infection with tenofovir exposure in HIV-infected women on TDF with and without concomitant boosted protease inhibitors (b/PIs).

Methods: This is a retrospective data analysis using data from two clinical trials: iTAP and PANNA. iTAP studied HBV mono-infected women from Thailand which were randomized in pregnancy to receive TDF or placebo. Single random blood samples taken twice during pregnancy, at delivery and postpartum were used to estimate the area under the curve (AUCO-24) and trough concentration (Ctrough) with non-linear mixed effect modeling. The data of the first assessment in pregnancy (closest to PANNA) and postpartum (1 month) were used in this study. PANNA is a multicenter study in Europe which collects full pharmacokinetic curves of pregnant women on specific antiretroviral regimens in the third trimester (33 weeks) and postpartum (4-6 weeks after delivery). AUC0-24 and Ctrough are obtained using non-compartmental analysis. Next to the previously published pharmacokinetic tenofovir data of PANNA, 30 additional curves (without boosters) were analyzed for this study. To compare the pregnancy effect on the pharmacokinetic parameters of HBV- and HIV-infected patients descriptive statistics are used.

Results: 218 women were included of which 154 from the iTAP-study and 64 from PANNA (of which 34 using ritonavir boosted PIs). Although the age, weight and race differed between the two groups, the creatinine concentration was similar. Median (IQ range) was 53 μmol/L (44-58) and 55 μmol/L (50-60) for PANNA and iTAP respectively. In pregnancy the geometric mean (GM) with 95% confidence interval (95%CI) of the AUC0-24 was 2.44 µg.hr/mL (2.22-2.68) in HIV-infected patients on b/PIs, 1.92 µg.hr/mL (1.70-2.18) in HIV-infected patients without b/PIs and 1.84 µg.hr/mL (1.77-1.92) in HBV patients. The geometric mean ratio (GMR) of 3rd trimester vs postpartum (with 90% confidence interval; (90%CI) of AUC0-24 was 0.75 (0.67-0.84), 0.74 (0.69-0.81) and 0.79 (0.78-0.80) for HIV patients with b/PIs, HIV patients without b/PIs and HBV patients respectively. The GMR (90%CI) of the Ctrough was 0.79 (0.72-0.86), 0.67 (0.61-0.73) and 0.69 (0.68-0.71), respectively.

Conclusions: The retrospective data analysis of these two different trials showed that pregnancy had a similar effect on tenofovir AUC in HIV-infected patients as in HBV-infected patients. The Ctrough of tenofovir in HIV patients without b/PIs is similar to HBV patients.
Sofosbuvir and 007 pharmacokinetics among persons with HCV and active drug use

**Background:** Data on the pharmacokinetics of direct acting antivirals (DAAs) in persons who use drugs are limited. INCLUD (NCT02573376) is an open-label study to characterize adherence to and the pharmacology of ledipasvir/sofosbuvir in persons with HCV and active drug use. We examined the plasma pharmacokinetics of sofosbuvir and its metabolite, GS-331007 (007), in plasma on day 1 of therapy in this population, and explored the influence of demographic and clinical factors on plasma drug concentrations.

**Materials & Methods:** Persons with HIV/HCV or HCV mono-infection and self-reported drug use within 30 days of screening were eligible. On day 1, participants were administered a witnessed dose of ledipasvir 90 mg/sofosbuvir 400 mg following a standardized moderate-fat breakfast. Intensive PK samples were collected serially over 24 hours. A self-reported drug use questionnaire and urine toxicology screen were also obtained. Sofosbuvir and 007 concentrations in plasma were quantified via LC/MS-MS methods. Variables examined included age, sex, race, weight, estimated glomerular filtration rate (eGFR), liver stiffness (kPa), and cirrhosis (>12.5 kPa). Concomitant antiretroviral medications and recreational drug use were also examined. Sofosbuvir and 007 pharmacokinetics were calculated via noncompartmental methods and summarized as geometric mean (CV%). Covariates were screened for influence on loge-transformed sofosbuvir and 007 exposures (AUClast) using simple linear regression. Covariates with p<0.2 were further considered in a multivariable backward selection regression model retaining covariates with p<0.05.

**Results:** Data from 47 participants (43 HIV/HCV; 4 HCV) were available. Geometric mean (CV%) sofosbuvir and 007 AUClast were 2779 (39.6%) and 10290 (29.2%) ng*h/mL. Sofosbuvir peak concentrations (Cmax) were 1433 (57.2%) ng/mL at a median (IQR) of 2 (1-3) hours post-dose. 007 peaked at 770 (28.8%) ng/mL at a median (IQR) of 4 (4-6) hours post-dose. For sofosbuvir, factors associated with lower AUClast included eGFR (-4% per 10 mL/min/1.73 m2 increase, p=0.07), black race (-22.5%, p=0.04), and darunavir use (-36%, p=0.0005), while opioid use was associated with 30% higher AUClast (p=0.08). For 007, factors associated with lower AUClast included weight (-10% per 10 kg increase; p=0.0008), eGFR (-6% per 10 mL/min/1.73 m2 increase; p=0.0001), black race (-14%; p=0.13), and TAF use (-13%; p=0.11). Factors associated with higher 007 AUClast included age (9% per 10 year increase; p=0.06) and opioid use (29%; p=0.02). The final model for sofosbuvir AUClast retained darunavir (-40% [95% CI: -46%, -33%]; p<0.0001) and opioid use (43% [95% CI: 27%, 62%]; p=0.0054). The final model for 007 AUClast retained weight (-7% per 10 kg increase [95% CI: -10%, -4%]; p=0.0084), opioid use (21% [95% CI: 11%, 32%]; p=0.031), and eGFR (-5% per 10 mL/min/1.73 m2 increase [95% CI: -7%, -4%]; p=0.0003).

**Conclusion:** In this study of ledipasvir/sofosbuvir PK in persons who use drugs, sofosbuvir and 007 first dose plasma PK were similar to historic data. The reduction in sofosbuvir with darunavir is consistent with a prior study, whereas the association of increased sofosbuvir and 007 with opioid use has not been previously described and requires confirmation. Additional data are needed to determine the mechanism(s) and clinical relevance of these findings.
Influence of SLCO1B1 polymorphisms on lopinavir plasma concentration in Serbian HIV/AIDS patients

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Background: Lopinavir (LPV) is not a first line regimen but according to recent World Health Organization data, LPV usage in low- and middle-income countries accounted for approximately 52% of the adult and 23% of the paediatric protease inhibitor (PI) market in 2017. Since LPV is a substrate for the SLCO1B1 (OATP1B1) transporter, the aim of this study was to assess the impact of SLCO1B1 polymorphisms (rs11045819, rs4149032 and rs4149056) on LPV trough plasma concentrations (Ct) in Serbian patients.

Materials & Methods: Plasma samples from 104 HIV-infected Caucasians adults were collected and LPV Ct was quantified using liquid-chromatography mass spectrometry (LC-MS/MS). Genotyping was carried out using real-time PCR-based allelic discrimination. One-way analysis of variance, t-test and linear regression were used for data analysis.

Results: The overall mean (SD) plasma LPV concentration was 5885 (2755) ng/mL. Significant differences were seem between patients with different rs11045819 genotypes: CC (n = 70; LPV median Ct = 6072 ng/mL; 95% CI = 4318-7617 ng/mL); CA (n = 30; LPV median Ct = 4987 ng/mL; 95% CI = 4300 - 6295 ng/mL) and AA (n = 4; LPV median Ct = 3648 ng/mL; 95% CI = 1949 - 4072 ng/mL) (p = 0.005). Significant differences were also observed according to rs4149032 genotype: CC (n = 52; LPV median Ct = 6027 ng/mL; 95% CI = 4548 - 8250 ng/mL); CT (n = 37; LPV median Ct = 5553 ng/mL; 95% CI = 4300 - 6888 ng/mL) and TT genotype (n = 15; LPV median Ct = 4408 ng/mL; 95% CI = 3361 - 5233 ng/mL) (p = 0.007). For rs4149056 a statistically significant difference between T homozygotes (n = 82; LPV median Ct = 5434 ng/mL; 95% CI = 3855 - 6830 ng/mL), heterozygotes (n = 20; LPV median Ct = 6707 ng/mL; 95% CI = 5088 - 8063 ng/mL) and C homozygotes (n = 2; LPV median Ct = 13906 ng/mL; 95% CI = 12946 - 14866 ng/mL) was observed (p = 0.002). In multivariate regression analysis using backward elimination, only the SLCO1B1 rs4149056 polymorphism was independently associated with LPV concentration (β = 2834.5 ng/mL (1442 to 4226.9); p = 0.001).

Conclusion: Our results demonstrate a statistically significant influence of the SLCO1B1 rs4149056 polymorphism on LPV Ct in Caucasian HIV/AIDS patients.
Comparison of relative bioavailability of pediatric triumeq and pediatric dolutegravir/lamivudine dispersible tablets to conventional film coated tablets in healthy adults

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Background: TRIUMEQ is a fixed dose combination (FDC) of abacavir/dolutegravir/lamivudine (ABC/DTG/3TC; 600/50/300mg) approved for the treatment of HIV-1 infection in adults and adolescents weighing ≥ 40 kg. A DTG/3TC FDC tablet (50/300mg) is under clinical development as a once-daily 2-drug regimen for HIV-1 infection in adult and adolescent. Alternate lower strength dispersible tablets (DT) formulations, (Triumeq DT: ABC/DTG/3TC 60/5/30mg; DTG/3TC DT: DTG/3TC 5/30mg) were developed for pediatric patients. This study evaluated the relative bioavailability (BA) and safety of both Triumeq DT and DTG/3TC DT vs. the conventional Triumeq and DTG/3TC film-coated adult-strength tablets after single-dose administration to healthy subjects.

Materials & Methods: Study 205894 (NCT03441984) was a 2-part, open-label, single-dose, 3-period, 6-treatment (TRT) sequence, randomized, crossover study in healthy volunteers under fasted conditions. In part 1, the relative BA of 10-pediatric TRIUMEQ DT administered dispersed in water and taken immediately (Test, TRT-B) and administered direct-to-mouth (Test, TRT-C) was compared with an adult TRIUMEQ FDC tablet formulation (Reference, TRT-A) administered direct-to-mouth. In part 2, 10-pediatric DTG/3TC DT administered dispersed in water and taken immediately (Test, TRT-E) and administered direct-to-mouth (Test, TRT-F) was compared with an adult DTG/3TC conventional tablets formulation (reference, TRT-D) administered direct-to-mouth. There was a washout of at least 7 days between doses of study medication. Plasma DTG, ABC and 3TC concentrations were determined following collection of PK samples for 72 hours post-dose. Non-compartmental PK analysis was performed; geometric least squares (GLS) mean ratios and 90% confidence intervals for test versus reference were generated. Standard safety assessments were monitored.

Results: A total of 36 participants were enrolled: Seventeen participants (94.4%) in Part 1 and 18 participants (100%) in Part 2 completed the study. In Part 1, following single oral administration of TRT-B or TRT-C (test treatments) in healthy adult participants, peak plasma concentration, 24 hours post-dose concentration, and overall systemic exposure to DTG (Cmax, C24, AUC[0-t], and AUC[0-∞]) were 1.4-fold to 1.7-fold greater than that observed following single oral administration of Treatment A (reference). ABC and 3TC Cmax and AUC following TRT-B were equivalent to reference. In Part 2, following single oral administration of TRT-E or TRT-F (test treatments) in healthy adult participants, Cmax, C24, AUC[0-t], and AUC[0-∞] of DTG were 1.2-fold to 2.0-fold greater than that observed following single oral administration of Treatment D (reference). 3TC Cmax and AUC following TRT-B were equivalent to reference. Additionally, a comparison of the 2 administration approaches for pediatric TRIUMEQ DT and DTG/3TC DT showed that Cmax, C24, AUC[0-t], and AUC[0-∞] of DTG were 1.2-fold to 1.5-fold greater following administration as a dispersion (TRT-B or E) compared with direct to mouth administration (TRT-C or F). There were no deaths, SAEs, AEs leading to withdrawal, or clinically significant laboratory or ECG findings.

Conclusion: Higher DTG bioavailability was observed with the pediatric DT formulation, while ABC and 3TC bioavailability was equivalent to the conventional tablet. For both pediatric DT formulations, comparable exposures between dispersed and direct-to-mouth administration were obtained for all drugs. Single doses of both pediatric formulations and methods of administration were well-tolerated.
Review on drug interactions of ART and tuberculosis medications

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Background: Increased attention has been established towards pharmacological aspects of HIV-Tuberculosis co-infection. This is supported by reports on Tuberculosis being the leading infectious mortality factor among people living with HIV. The aim of this review was to investigate expected drug interactions between antiretroviral therapy and antituberculous agents recommended for treatment of latent or active Tuberculosis regardless of TB resistance rate. Particular attention has been given to analysis of MDR-/RR-TB treatment interactions with ART.

Materials & Methods: Searches were performed based on a number of local and international recommendations for HIV-TB co-infection treatment including the WHO “Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis”. Expected interactions were analyzed using HIV Drug Interaction Checker of Liverpool Drug Interactions Group.

Results: Over 60 drug interactions were identified among recommended for HIV treatment ARVs and Tuberculosis medications. Less than half of the expected interactions have been studied thoroughly enough for a therapeutic strategy to be developed. Generous analysis of Rifamycins use in patients with HIV-Tuberculosis co-infection has provided an impact on a guided decision making for healthcare professionals.

Conclusion: Although the amount of studies on drug interactions between ARVs and Tuberculosis medications is rising, a blind spot was detected in pharmacologic research for MDR- and RR-resistant Tuberculosis treatment in HIV-TB co-infection. The review presents useful clinical guidance alongside with perspective drug interactions to be studied.
Effect of tenofovir and bacavir on dolutegravir transport in vitro and in vivo

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Background: Dolutegravir (DTG) is a first line antiretroviral drug most commonly prescribed with an NRTI backbone including abacavir (ABC) or tenofovir (TFV). Recent data suggest that central nervous system side effects occur more frequently with DTG than was first apparent in clinical trials. DTG has been reported as a substrate for the ABCG2 transporter, which is known to be inhibited by ABC but not TFV. This study assessed potential transporter mediated interactions of ABC and TFV with DTG within in vitro and in vivo preclinical models.

Materials & Methods: Apparent oral absorption of 3H-DTG (1.5 or 3.5 µg/mL) was determined in the presence of ABC, TFV (both 10 µg/mL) or the BCRP transporter inhibitor fumitremorgin C (FUM-C) (20 µg/mL) across Caco-2 cell monolayers after 30 minute pre-incubation. ABC (84.2 µg/mL) and TFV (6.7 µg/mL) were intravenously administered to male Wistar rats 20 minutes prior to 3H-DTG (33 µg/mL). These doses were selected to provide plasma concentrations similar to those achieved after oral administration to humans. Plasma samples were obtained 0.5-3 hours post 3H-DTG dose. At 4 hours, plasma, cerebral spinal fluid (CSF) and brain was sampled and DTG concentrations were quantified by scintillation counting. An unpaired t-test was used to determine statistical significance.

Results: ABC, TFV and FUM-C increased 3H-DTG (1.5 µg/mL) apparent oral absorption in Caco-2 cells compared to DTG alone after 3 hours (P = 0.001, 0.006, <0.001, respectively). At higher 3H-DTG concentration (3.5 µg/mL) apparent oral absorption was significantly lower in ABC and TFV samples compared to DTG alone after 4 hours (P <0.001 and <0.001, respectively) and higher for FUM-C (P <0.001). For both ABC and TFV treated rats, DTG plasma and CSF concentrations were comparable to those for DTG alone. However, brain concentrations were significantly lower in ABC (P = 0.025) and TFV (P = 0.006) treated animals.

Conclusions: Co-administration of ABC or TFV with DTG in vivo mirrored the effect observed at higher concentrations of DTG in vitro suggesting decreased permeability into the brain when co-administered with TFV or ABC at clinically relevant concentrations. These observations are not supported by the initial hypothesis of BCRP inhibition, but indicate that unidentified transporters do contribute to an interaction of TFV and ABC with DTG that impacts distribution. Further studies are required to understand the mechanistic basis for these observations and understand the clinical significance.
High incidence of drug-drug interactions with hepatitis C direct-acting antivirals in patients hospitalized during their treatment

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Background: Direct-acting antivirals (DAAs) remain a challenge regarding drug-drug interactions (DDIs). Incidence of DDIs with DAAs in ambulatory cohorts is well established, but has not been assessed in inpatient populations. The study aims to assess the cumulative incidence of DDIs between DAAs and co-medications of patients hospitalized in the course of their hepatitis C virus (HCV) treatment. Secondary objectives are to assess the severity of DDIs and their predictive factors, and to measure virological success and describe hospital pharmacists’ interventions.

Materials & Methods: MONTREAL-C is a retrospective single-centre study at the Centre hospitalier de l’Université de Montréal, Québec, Canada. Patients hospitalized from December 2013 to December 2017 and treated with interferon-free DAA regimens were included and assessed for cumulative incidence of DDIs. Occurrence and severity of DDIs were evaluated using online drug interaction checker tools and, in the absence of available data, by a committee of three pharmacists with clinical expertise in HCV treatment. Predictive factors for DDIs were identified with univariate and multivariate logistic regression analyses using Stata (IC version 14.2). Treatment success was evaluated with the achievement of a sustained virologic response at week 12 (SVR). All other statistical analyses were performed with SPSS (IBM SPSS Statistics, Version 25).

Results: A total of 116 inpatients, accounting for 168 hospitalizations, were included. The median number of co-medications per hospitalization was 15 (interquartile range, IQR 10-20). Overall, 68.1% (95% CI 59.4%-76.9%) of patients and 64.6% (95% CI 54.7%-73.4%) of hospitalizations presented at least one potential DDI with a DAA regimen. Among the 235 DDIs identified, 3.8% were classified as contraindicated. Most frequently involved co-medications in DDIs in this study were gastric acid modifiers. Female gender (odds ratio (OR) 2.91 95% CI 1.21-7.00; p = 0.017) and polypharmacy of more than 10 co-medications (OR 5.64 95% CI 2.48-12.85; p < 0.001) were identified as predictive factors for DDI in the multivariate logistic regression analysis. Despite numerous DDIs and many patients treated with sofosbuvir/ribavirin (38%), 86.7% of patients achieved SVR. Out of the 56 interventions performed by hospital pharmacists, 53.6% were related to the management of DDIs.

Conclusion: This is the first study to report data on patients that have been hospitalized during their HCV treatment. Inpatients are at high risk for DDIs where polypharmacy is frequent. SVR rates remained high in patients being hospitalized during their HCV treatment. Caution is warranted to identify and manage DDIs in inpatients on DAAs and hospital pharmacists can play a key role.
Short-term intravenous proton pump inhibitors and histamine H2 antagonists do not negatively affect sustained virologic response in hepatitis C cirrhotic patients treated with ledipasvir or velpatasvir containing antiviral regimens: a case series


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Background: Oral acid suppressant agents (including histamine H2 antagonists and proton pump inhibitors (PPIs)) are known to cause drug-drug interactions (DDIs) with ledipasvir (LDV) and velpatasvir (VEL) and management of these DDIs has been established in the product monographs. However, there is no data regarding the clinical outcome and management of intravenous (IV) acid suppressant agents in patients receiving these direct-acting antivirals (DAAs). This case series aims to evaluate the impact of IV acid suppressant agents on sustained virologic response (SVR) in patients receiving LDV or VEL.

Materials & Methods: MONTREAL-C is a retrospective single-centre cohort of patients treated with interferon-free DAA regimens and hospitalized in the course of their hepatitis C treatment at the Centre hospitalier de l’Université de Montréal, Canada. Patients receiving IV acid suppressant agents (PPIs or histamine H2 antagonists) during their hospitalization while completing LDV or VEL based antiviral treatment were identified. Demographics and HCV related characteristics were collected. SVR was determined 12 weeks post-treatment.

Results: A total of 11 patients accounting for 12 hospitalizations were identified in the MONTREAL-C cohort. Eight (72.7%) patients were men. The median age was 58 years old (Q1-Q3: 53-59). All patients had cirrhosis and six (54.5%) patients were known for decompensated cirrhosis. Seven patients were infected with HCV genotype 1a, two with genotype 1b, one with genotype 3 and one with genotype 4. Overall, nine patients were treated with LDV/sofosbuvir +/- ribavirin while two patients received VEL/sofosbuvir treatment. All cases received either pantoprazole (n=6) or famotidine (n=5) as IV acid-suppressing drugs during their hospitalization. All patients on parenteral PPI received a high-dose pantoprazole continuous infusion (40-80 mg bolus followed by 8 mg/hour continuous therapy). The median treatment duration of IV high-dose pantoprazole continuous infusion was 13.1 hours (Q1-Q3: 7.3-16.7). All patients on IV famotidine received 20 mg IV every 12 hours. The median number of doses of IV famotidine was 3 doses (Q1-Q3: 2-3). Importantly, all patients received long-term oral PPIs (n=9), histamine H2 antagonists (n=1) or both (n=1) when IV acid suppressant agents were stopped. The proportion of SVR in this case series was 90.9%. The only antiviral treatment failure observed was described in the GT3 patient treated with VEL/sofosbuvir who stopped therapy at week 3 due to suspected non-adherence and the need to complete long-term treatment for esophagitis with high dose oral acid suppressant drugs. No pharmacokinetic data were available in this case series due to the retrospective study design.

Conclusion: These real-life data suggest that a short course of intravenous proton pump inhibitors or histamine H2 antagonists in cirrhotic patients receiving a LDV or VEL based DAA regimen does not negatively affect treatment success. Therefore, patients hospitalized during their HCV treatment should continue their antiviral regimen. Nevertheless, due to the small number of patients, more studies including pharmacokinetic analyses are needed to clarify the clinical management and impact of this potential drug-drug interaction.
Valproic acid co-administration is not associated with lower non-dolutegravir antiretrovirals’ exposures

Background: The life-long administration of combined antiretroviral therapy and the significant prevalence of co-morbidities expose people living with HIV (PLWH) to a high risk of drug to drug interactions. Our group recently reported that valproic acid (VPA) was associated with lower dolutegravir exposure in patients receiving both drugs. Since two mechanisms were proposed (either a decrease in drug absorption due to divalent cations or a CYP3A4/5 induction) it may be relevant to explore whether this effect could be observed with other antiretrovirals (ARVs) and in particularly in individuals receiving raltegravir (RAL).

Materials & Methods: Adult PLWH followed at the outpatient clinic of the University of Torino, Italy with available plasma concentrations while receiving cART were included in this therapeutic drug monitoring (TDM) registry analysis. At the time of withdrawal patients sign a written informed consent. Concomitant VPA was searched in the fields of “co-administered drugs” either using the generic or the trade names. ARVs’ concentrations were measured through validated HPLC-UV or MS/MS methods. Plasma exposures were compared to the reported maximal or trough concentrations or with 90% confidence intervals derived from patients not receiving VPA and stratified by 2-hour periods (from drug intake).

Results: One hundred and thirty-four patients were identified as concomitantly receiving VPA and ARVs. Median age and body mass index were 49.7 years (45-56) and 23.4 Kg/m2 (20.8-26.3); 78 were male (58.2%). 18 (13.4%) and 1 (0.7%) were chronically infected with HCV or HBV. The majority of samples were analysed in patients receiving NRTIs (FTC 45, TDF 35, 3TC 16, ABC 10) plus INSTIs (DTG 29, 27 RAL), PIs (ATV 24, DRV 13, LPV 4), NNRTIs (ETV 10, RPV 7, NVP 3, EFV 2) or MVC (17). With the exception of DTG no significant decrease in plasma exposure was observed for the other ARVs (beyond 90% confidence intervals). Specifically RAL-VPA recipients were compared to 1092 patients on RAL: no significant difference was observed at any time point including 2-4 hours (349 vs. 746 ng/mL, p=0.202) or 10-14 hours post-dose (384 vs. 216 ng/mL, p=0.513).

Conclusion: With the limitations of a TDM registry analysis no significant interaction was observed between several ARVs and VPA; specifically, RAL seems a pharmacologically safe option in patients concomitantly receiving VPA.
The valproic acid – dolutegravir drug-drug interaction is based on displacement of protein binding and unlikely to be clinically relevant


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Background: A recent retrospective analysis suggested that there is a drug-drug interaction (DDI) between dolutegravir (DTG) and valproic acid (VPA) that leads to decreased DTG plasma concentrations (>80% reduction)(Palazzo et al. JAC 2016). The mechanism for this putative DDI has remained unknown so far. A possible explanation could be the induction of DTG’s metabolizing enzymes by VPA, or impaired DTG absorption due to complexation of DTG by excipients in VPA formulations. Another explanation could be that these drugs compete for binding sites on plasma proteins, since both drugs are highly protein bound (>90%). We evaluated total and free DTG concentrations in HIV-infected subjects participating in “LRAs United as a Novel Anti-HIV strategy” (LUNA) study.

Materials & Methods: In this PK substudy HIV-infected subjects on a DTG-containing regimen were included. Intrasubject comparisons were made for DTG PK (50mg QD) with and without co-administration of valproic acid (Dipakine enteric®; 30mg/kg, divided over 2 doses per day, orally, for 14 days). Subjects took DTG (and VPA) in the morning with food. Samples for total and free DTG Ctrough plasma concentration were taken on Day 0 (prior to co-administration of VPA) and on Day 1, 7, 14 (all with VPA), and finally on Day 42 (without VPA). A 6h sample was also taken on Day 1. Subjects in study arms on DTG without VPA served as comparators.

Results: Four subjects were included; three used DTG + VPA; one subject was in the control arm of DTG only. One subject on DTG + VPA stopped VPA due to presumably related side effects. Total DTG trough levels in the three subjects prior or after VPA were on average (± SD) values of 0.89 (±0.57), 0.40 (±0.30) and 0.28 (±0.21) mg/L on Day 1, 7 and 14, respectively. In contrast, we observed a parallel increase in the free fraction of DTG: this was 0.54-0.70% during VPA administration vs. 0.29-0.30% without VPA administration. The increase in the free fraction of DTG was already visible in the 6h sample after the first dose of VPA: 0.30 (± 0.05) → 0.40 (± 0.05) %. Total DTG concentrations and free fraction in the control patient on DTG without VPA were in the same range as in the other three subjects before/after VPA. All free DTG concentrations were above the proposed in vitro EC90 value for unbound DTG of 0.9 microg/L (Kobayashi et al. AAC 2011).

Conclusion: Our data confirm the reported decrease in total DTG plasma concentrations after addition of VPA to DTG. This rapid and consistent decrease can be explained by displacement of protein binding of DTG by VPA. This drug-drug interaction is probably not of clinical relevance.

Abstract 45 withdrawn
Glecaprevir/pibrentasvir pharmacokinetics in HCV/HIV patients co-administered with antiretroviral drugs

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Background: Glecaprevir/pibrentasvir (Gl/Pib), a pangenotypic HCV treatment with excellent efficacy, is affected by potential drug-drug interaction when co-administered with CYP3A4 P-gp, BRCP, OATP-1B1, -1B3 inducers or inhibitors. Available data contraindicate use of atazanavir/ritonavir (ATV/R) due to increased risk of ALT elevations secondary to glecaprevir exposure and do not recommend darunavir/r or lopinavir/r. Same recommendation is provided for cobicistat when administered with darunavir (DRV/C), although no data are available with this combination. No concerns have been raised with Gl/Pib administered with elvitegravir/cobicistat/TAF/FTC (E/C/F/TAF) since glecaprevir exposures remained within safety limits. Aim of our study was to describe Gl/Pib pharmacokinetics when co-administered with different antiretroviral drugs (ARVs) in our real-life cohort of HIV/HCV patients.

Materials & Methods: HIV/HCV co-infected patients treated with Gl/Pib and receiving antiretroviral therapy (ARV) were enrolled. Gl/Pib plasmatic levels (Gl-pl and Pib-pl) (22±2 hours after last intake) were measured using UHPLC-MS/MS FDA and EMA validated method and reported as ng/mL. Stiffness and steatosis were measured through transient elastography with ultrasound based controlled attenuation parameter (CAP). Non-parametric tests were applied as required. Data are reported as medians (interquartile ranges, IQR) and numbers (percentages).

Results: Sixty-two determinations (2, 1:3 each) were collected from 30 patients: 70% males, age 51 (45;55), BMI 22 kg/m2 (20;24). Metavir score was 0-2, 3, 4 in 25, 4 and 1 patient respectively. Stiffness was 6,3 kPa (5,6;8), CAP 207 dB/m (179;229) respectively. Patients received following ARV (associated with TAF/FTC, TDF/FTC, ABC/3TC): 1 DRV/r, 2 DRV/C, 21 dolutegravir (DTG) and/or rilpivirine (RPV), 6 EVG/C. Three patients were treated with DRV/R or DRV/C for resistance issues. Median Gl-pl and Pib-pl in study population were 16 ng/ml (7,2;43,5) and 11 ng/mL (7,75;22,2) respectively. A significant difference was observed between those receiving DRV/R or DRV/C, EVG/C, DTG and/or RPV: Gpl 42 (15;42), 42 (17,2;77), 10 (5;12), p=0,049, respectively. No difference was observed between Pib-pl with different ARV (p=0,178). One female with DRV/C and metavir score 2 showed high GL-pl (896 ng/mL) and bilirubin increase with itchy rash during treatment. DRV/C was switched to raltegravir with symptoms regression and bilirubin normalisation. Glecaprevir AUC, Cmax, Ctrough were 14773, 1913, 62 ng/mL and 13242, 1971, 7 in two patients treated with E/C/F/TAF. One with DRV/C had Glecaprevir AUC, Cmax, Ctrough 13772, 1502, 42 ng/mL respectively. All had metavir score 1. A positive correlation was observed between Pib-pl and CAP (p=0,048, rho=0,370). No significant difference in Gl-pl or Pib/pl with different metavir score (p=0,392, p= 0,897) or between gender (p=0,482, p= 0,529) was reported.

Conclusions: Glecaprevir and pibrentasvir plasmatic concentrations in our cohort of patients administered with different ARV regimens resulted comparable to values reported from literature with significant higher glecaprevir exposures when administered with boosting agents. Intensive dose/time analysis in 2 patients with E/C/F/TAF and 1 with DRV/C, however, showed glecaprevir exposures remaining within safety limits (3-fold increase compared to Gl-pl alone in non cirrhotic patients). Our results support safe Gl/Pib co-administration with E/C/F/TAF and selectively in low metavir score patients when DRV/C have to be administered for shortage of therapeutic options.
Cobicistat (COBI)-boosted Protease Inhibitors (PIs) plasma and intracellular (IC) pharmacokinetics (PK) in nicotine users

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Background: Substance Users among HIV positive patients (pts) are numerous and in the real life setting Nicotine Users (NU) are the most frequent. The impact of nicotine and its metabolites on antiretroviral (ARV) therapy has been scarcely described in vitro and in vivo, underlying a role of nicotine as inductor of membrane transporters (Pgp and BRCP) and cytochromes (Cyp1A1, Cyp1B1, UGT etc) involved in ARV metabolism. Aim of our study was to evaluate the role of nicotine on the COBI-boosted PIs PK both at plasma and intracellular level comparing Smoking (S) and Non-smoking (NS) pts.

Materials & Methods: Sixty-eight patients (pts) administered with COBI-boosted PIs, 32 S and 36 NS were enrolled in our study. Plasma and IC samples were collected at midpoint (12 hours) or at the end (24 hours) of dosing interval. COBI, ATV, DRV plasma and IC concentration were measured by means of HPLC-UV and HPLC-MS validated methods, respectively and results compared between S and NS. Non-compartmental pharmacokinetic parameters were calculated and expressed as geometric mean (CI95%). Concentrations were expressed as ng/ml. Descriptive analysis were expressed as median (IQR) and geometric mean (CI95%) and patients characteristics were compared by Mann Whitney and Correlation analyzed with Spearman test.

Results: 68 pts were 72% male, median age 51 (IQR 48; 56), BMI 25.4 (IQR 23; 27.5).

COBI plasma, IC concentration and ratio IC/plasma in S and NS pts were respectively 26.9 (-70.2; 124.1) and 65.2 (-21.2; 151.6) ng/ml; 85.7 (-7.0; 178.4) ng/ml and 156.2 (-25.9; 338.5) ng/ml; 3.177 (0.268; 6.087) and 2.396 (1.383; 3.409). ATV plasma, IC concentration and ratio IC/plasma in S and NS pts were respectively 519.6 (215.6; 823.6) and 920.6 (281.8; 1559.3) ng/ml; 798.8 (488.4; 1109.2) and 1229.1 (582.9; 1875.4) ng/ml; 1,537 (0.985; 2,089) and 0.866 (0.476; 1,255). We found a significative reduction of plasma and IC concentration of COBI (p= 0.021 and p=0.059) and ATV plasma concentration (p=0.037) in S pts. All plasma and IC COBI, ATV and DRV concentrations showed to be significantly correlated (p<0.001) both in S and NS pts.

Conclusion: The impact of Nicotine on ARV PK in HIV positive population is scarcely described. In our study a significative decrease of ATV plasma concentration was confirmed, as previously described, and, for the first time, a significative reduction of COBI plasma exposure and a trend toward significance for IC Cobi penetration in S population were showed. The role of nicotine in induction of efflux pump, as P-gp or BCRP, and the impact on cytochrome metabolism has to be taken into account in smoking population and further analysis should investigate the potential drug-drug interactions with ARV PK.
An assessment of the effects of dolutegravir on gene expression and levonorgestrel clearance in human hepatocytes in vitro

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Background: Dolutegravir (DTG) is reported to have a favourable safety profile and a low potential for drug-drug interactions (DDIs). However, the possible risk of teratogenicity following administering DTG in early pregnancy underlines the importance of effective contraception in women receiving DTG therapy. The prospect of DDIs occurring between DTG and the hormonal contraceptive levonorgestrel (LNG) has thus far not been examined experimentally. We aimed to address this by quantifying the effects of DTG on both LNG apparent intrinsic clearance (LNG CLint.app.), and the expression of key cytochrome P450 enzymes (CYPs), using a primary human hepatocyte model of drug metabolism.

Materials & Methods: Cryopreserved primary human hepatocytes were plated on collagen-coated 96-well cell culture plates, and overlaid with Geltrex™. Twenty-four hours post-plating, hepatocytes were incubated with DTG (0.033—10 μM); rifampicin (RIF; positive control); or methanol (0.3% v/v; vehicle control), in Williams' Medium E (WME) incubation medium, once-a-day for three days, after which hepatocytes were incubated with LNG (1 nM) for 60 minutes by rapid equilibrium dialysis. To assess the effects of DTG on gene expression, total RNA was extracted from hepatocytes from one donor at 72 hours post initial incubation with DTG (0.00033—10 μM), and real-time qPCR analysis of CYP1A2, CYP2B6 and CYP3A4 expression was conducted in triplicate, with results expressed as mean fold-change in expression above vehicle control ± SD.

Results: Under control conditions, LNG CLint.app. was 22.4 (5.0) μl/min/106 cells, while incubation with 10 μM RIF increased LNG CLint.app. to 46.7 (6.9) μl/min/106 cells (p=0.008). DTG fu in WME incubation medium was 0.43 (0.09) (mean (SD); n=9). Incubation with 0.033 μM DTG (unbound DTG concentration = 14.2 nM), resulted in a LNG CLint.app. of 34.5 (9.2) μl/min/106 cells (p=0.114). At total concentrations ≥1 μM (unbound DTG concentrations ≥431 nM), DTG induced expression (by ≥2-fold above vehicle control) of CYP3A4, with 10 μM DTG (unbound DTG concentration = 4.31 μM) eliciting a maximal 6.0 ± 0.9-fold induction in CYP3A4 expression. Incubation with 10 μM DTG (unbound DTG concentration = 4.31 μM) induced expression of CYP2B6 by 2.7 ± 0.1-fold, whereas DTG did not induce expression of CYP1A2 at any of the concentrations tested.

Conclusion: Incubation with DTG at unbound concentrations spanning the range of median unbound concentrations of DTG in plasma (24.6—57.2 nM), resulted in a trend towards elevated LNG CLint.app. in a primary hepatocyte-based in vitro model of drug metabolism. In this model, at unbound concentrations higher than would be normally observed in plasma, DTG also induced expression of CYP2B6 and CYP3A4, but did not induce expression of CYP1A2. Whilst this study is the first to experimentally investigate the effects of DTG on LNG, establishing the clinical significance of these findings would require further investigation in clinical studies.
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<td>Physiologically based pharmacokinetic modelling to determine pharmacokinetic alterations driving ritonavir exposure changes in aging people living with HIV</td>
<td>15</td>
<td>17</td>
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<tr>
<td>Van Schalkwyk, M</td>
<td>Low isoniazid concentrations in pregnant and postpartum women treated for tuberculosis irrespective of efavirenz-based art co-treatment.</td>
<td>11</td>
<td>13</td>
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<tr>
<td>Vlasakakis, G</td>
<td>Model-based simulated 3tc exposure in HIV population by varying renal function</td>
<td>32</td>
<td>32</td>
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<tr>
<td>Yager, J</td>
<td>Tenofovir-diphosphate in PBMC following increasing TAF vs. TDF dosing under directly observed therapy</td>
<td>13</td>
<td>15</td>
</tr>
</tbody>
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