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Abstracts Oral Presentations
Abstract: O_01

The effect of Cobicistat on Cytochrome P450 2D6, 2B6 and P-glycoprotein using phenotypic probes

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Introduction: Cobicistat (COBI) is being developed as a pharmacoenhancer ("booster") to increase the systemic exposure of co-administered agents metabolized by cytochrome (CYP) 3A enzymes, including elvitegravir and/or HIV protease inhibitors that require boosting. In vitro studies have demonstrated that COBI does not inhibit CYP1A2, CYP2C8, CYP2C9 or CYP2C19, and is a weak inhibitor of CYP2D6 and P-glycoprotein (P-gp). To identify the ability of COBI to mediate non-CYP3A interactions, a metabolic probe study was conducted using phenotypic probes (CYP2D6: desipramine, CYP2B6: efavirenz and P-gp: digoxin) for a selected panel of metabolizing enzymes/transporter.

Methods: This was an open-label, three-cohort crossover study. Within each cohort, subjects were randomized to the order of receiving a single dose of the probe drug alone (reference treatment), and following 10-days of COBI dosing, with the single dose of probe drug on Day 10 (test treatment). Treatments were separated by a 14-day washout (cohort 1: desipramine and cohort 2: digoxin) or 20-day washout (cohort 3: efavirenz).

PK samples were collected over 72 hours for desipramine and digoxin or over 336 hours for efavirenz analysis. Plasma concentrations were measured using LC/MS/MS. PK parameters were calculated by non-compartmental analysis. Geometric least squares mean ratios and 90% CIs for AUC<inf>inf</inf>, AUC<sup>last</sup> and C<sub>max</sub> of the probe drugs (test versus reference) were estimated using ANOVA with PK equivalence boundaries of 80-125%. COBI exposure over 24 hours was descriptively compared to historical data.

Results: The study enrolled 10, 25 and 18 subjects in Cohorts 1, 2 and 3, respectively. Nine subjects (Cohort 1), 22 subjects (Cohort 2) and 17 subjects (Cohort 3) completed study. Single doses of probe drugs and COBI were safe and well-tolerated. Treatment-emergent AEs were generally of mild severity (Grade 1). One treatment-emergent severe (Grade 3) AE of GERD occurred in Cohort 2 after 9 days of the test treatment and led to study discontinuation.

Coadministration of COBI with desipramine resulted in AUC<sup>last</sup>/AUC<inf>inf</inf> and C<sub>max</sub> increases of ~58-65% and 24%, respectively. A small reduction in efavirenz Cmax (~ 13%) and an increase in digoxin C<sub>max</sub> (~ 41%) were observed with COBI. Efavirenz AUC<sup>last</sup>/AUC<inf>inf</inf> and digoxin AUC<inf>inf</inf> remained unchanged with coadministration. COBI PK were similar to historical controls.

Conclusion: All study drugs were safe and well-tolerated. COBI may be classified as a weak CYP2D6 inhibitor based on < 2-fold increase in desipramine exposure parameters with coadministration. A small reduction in the Cmax of efavirenz and an increase in digoxin C<sub>max</sub> were observed upon coadministration with COBI. The aforementioned changes do not require dose modifications. Additional drug-drug interaction studies with COBI and substrates of CYP2D6, CYP2B6, or P-gp are not required.

Financial relationship(s): All authors are employees of Gilead Sciences, Inc
Abstract: O_02

Effects of enzyme inducers, tipranavir and efavirenz, on the pharmacokinetics of the integrase inhibitor, Dolutegravir (S/GSK1349572)

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Introduction. Dolutegravir (DTG, S/GSK1349572) is an unboosted, once daily integrase inhibitor currently in late stage development for the treatment of HIV infection. Two studies evaluated the effects of the enzyme inducers, efavirenz (EFV) and tipranavir/ritonavir (TPV/RTV) on DTG pharmacokinetics (PK) in healthy adult subjects.

Methods. The first study was an open label, single sequence crossover to evaluate the effect of EFV on the pharmacokinetics, safety and tolerability of DTG 50 mg once daily. Twelve healthy subjects received DTG 50 mg once daily for 5 days, followed by the combination of DTG 50 mg once daily and EFV 600 mg once daily for 14 days. The second was an open-label, three-period study to evaluate the effect of TPV/RTV on the pharmacokinetics, safety and tolerability of DTG 50 mg once daily. Eighteen subjects received DTG 50 mg once daily for 5 days. Subjects were then administered TPV/RTV 500/200 mg twice daily for 7 days followed by the combination of DTG 50 mg once daily and TPV/RTV 500/200 mg twice daily for 5 days. Safety assessments were performed throughout the studies and serial PK samples for DTG were collected during each period of DTG alone and in combination. Non-compartmental PK analysis was performed and geometric least squares mean ratios (GLS-MR) and 90% confidence intervals (CI) were generated by the mixed effect model for within-subject treatment comparison.

Results. The combination of DTG and EFV was generally well-tolerated, while TPV/RTV co-administration required close monitoring for liver enzyme elevations known to be associated with TPV/RTV. No SAEs occurred in either study and no subject withdrew from the EFV study. Four subjects discontinued the TPV/RTV study due to increases in ALT, which were initially noted during TPV/RTV dosing alone and which were considered related to TPV/RTV. Co-administration with EFV resulted in 57%, 39%, and 75% decrease in plasma DTG AUC(0-t), Cmax, and Ct, respectively. Co-administration with TPV/RTV resulted in 59%, 46%, and 76% decrease in plasma DTG AUC(0-t), Cmax, and Ct, respectively.

Conclusion. EFV and TPV/RTV decreased exposure of DTG, likely through enzyme induction of UGT1A1 and CYP3A4. Despite these reductions, DTG concentrations remain well above the protein adjusted-IC90 for wild type HIV. DTG can be administered with EFV or TPV/RTV in integrase-naive subjects without dosage adjustments.

Financial relationship(s): Employee of GlaxoSmithKline
Abstract: O_03

Using Adaptive/Bayesian methodology to evaluate four different formulations of GSK2248761 in a relative bioavailability and food effect study

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Background: GSK2248761 is a novel, third-generation NNRTI candidate being developed for the treatment of HIV-1 infection. The original Gelucire capsule formulation used in earlier clinical trials has limitations with storage, manufacture, and use for fixed dose combination. Five additional formulations were developed and evaluated for use in Phase 2b clinical trials. To reduce the study duration, dropout rate, study cost and to account for the large PK variability, an adaptive Bayesian method was used in this study design instead of a traditional crossover study design.

Materials & Methods: This adaptive study utilized Bayesian methodology to evaluate up to three new formulations of GSK2248761 and to compare the relative bioavailability and food effect of these formulations to the original formulation. This was a single-center, randomized, two part, open-label, single dose, crossover study in 24 healthy adult subjects. Part A evaluated two new formulations given with and without food compared to the current Gelucire formulation with food in a two 3*3 balanced crossover designs. Part B evaluated one additional formulation if the bioavailability of any of the two formulations in Part A met pre-specified criteria. Safety evaluations and serial PK samples were collected during each treatment period. A follow-up visit occurred 7-10 days after the last dose of study drug. Preliminary pharmacokinetic data from Part A were evaluated after completion of Period 3 of Part A. The ratio of comparisons of Test/reference treatments (RBA) and corresponding 90% confidence intervals were constructed. If predictive probability Prob(RBA ratio>0.8 | observed data) from a Bayesian model was less than 50%, then Part B was initiated to evaluate a third formulation. Trial simulations were done to compare Bayesian decision vs traditional point estimates.

Results: Pre-specified criteria were determined by the team prior to dosing based on Bayesian predicted probability for the estimated ratio, the cost of goods, easy of manufacture and ability to make a fixed dose combination product. This design gave the team an opportunity to make a decision with a new information obtained in Part A to determine whether to continue for Part B dosing or stop the trial after three periods of dosing versus running a traditional 7 period crossover. Based on 200 trial simulation runs, assuming a within-subject variability of 30% and test: reference ratio (RBA) of 0.8, with a sample size of 10, it was estimated that using Bayesian predictive probability Prob(RBA ratio>0.8)>50%, i.e. target criteria, the mean (range) of simulated ratios is 0.88(0.79 – 1.06). The Bayesian method would have a few percent more chance (based on the simulation) to meet the criteria than the traditional point estimate.

Conclusions: Adaptive Bayesian design trial and trial simulation can facilitate a better decision on the formulation selection in a small sample size trial with an opportunities to cut cost and lower dropout rate.

Financial relationship(s): Employee of GlaxoSmithKline
Abstract: O_04

Single and multiple dose pharmacokinetics and safety in non-HIV-infected healthy subjects dosed with BMS-663068, an oral HIV attachment inhibitor

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Background: BMS-663068, a prodrug of BMS-626529, is an oral HIV Attachment Inhibitor that binds to the viral envelope glycoprotein gp120 and interferes with attachment of virus to the cellular CD4 receptor. BMS-626529 exhibits a spectrum of activity against clinical isolates with a median protein binding adjusted EC90 of 9.6 ng/mL (n=46) as measured by the Monogram Biosciences PhenoSense Entry Assay in a recent trial in HIV infected individuals. Single (SAD) and multiple ascending dose (MAD) studies were conducted to assess the pharmacokinetics (PK) and safety of BMS-663068 in non-HIV infected healthy subjects.

Materials & Methods: The objectives of these double-blind, randomized, placebo-controlled SAD and MAD studies were to evaluate the PK, safety and tolerability of BMS-663068 in non-HIV-infected healthy subjects. Healthy men or women, 18 to 45 years of age with a BMI of 18 to 30 kg/m² received a total daily dose of 20 to 2400 mg of BMS-663068 as an immediate-release (IR) or extended-release (ER) formulation for up to 10 days. In selected cohorts, the drug was given with or without ritonavir (RTV).

Results: A total of 66 and 30 subjects received BMS-663068 in the SAD and MAD, respectively. Following oral administration, BMS-663068 was rapidly converted to its active form BMS-626529, reaching steady-state by Days 2 to 3. Relative to the IR formulation, the ER formulation resulted in lower Cmax and higher C12 values. Geometric mean BMS-626529 C12 values at steady state from BMS-663068 600 mg BID + RTV 100 mg BID and 1200 mg BID alone or with RTV 100 mg BID were 333, 338 and 1399 ng/mL, respectively. Co-administration with RTV moderately increased the overall exposure to BMS-626529. All doses were generally well tolerated. One serious adverse event (SAE) of viral meningitis deemed unlikely related to BMS-663068 occurred in the SAD, and one BMS-663068 600 mg ER + RTV-recipient discontinued due to rash in the MAD. Otherwise, there were no BMS-663068-related deaths, serious adverse events (SAEs), or discontinuations due to adverse events (AEs). The most frequent AEs in BMS-663068 recipients were nausea (11%) and headache (9%) in the SAD and pruritus (18%), nausea (15%), headache (15%), flatulence (13%), and rash (10%) in the MAD. Exposure to BMS-663068 had no clinically relevant effects on ECGs, laboratory values, vital signs or physical examinations in either study.

Conclusions: BMS-663068 is an oral HIV Attachment Inhibitor with a desirable PK profile when administered as an ER formulation. BMS-663068 was generally well tolerated in non-HIV-infected healthy subjects administered up to a total daily dose of 2400 mg. Longer term clinical trials of BMS-663068 as part of a HAART regimen in HIV-1 infected individuals are warranted.

Financial relationship(s): employee and stock holder of Bristol-Myers Squibb.
Abstract: O_05

Pharmacokinetics of plasma lamivudine (3TC), and its active intracellular anabolite 3TC-triphosphate (3TC-TP) over a 24 hour dosing interval, following administration of 3TC 300 mg and 150 mg once daily (od) to HIV-negative healthy volunteers. The ENCORE2 Study.

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Background: There is interest in evaluating the efficacy of lower unit doses of some key antiretroviral drugs for clinical care. Data from clinical trials to guide the design of this research are limited. As a preliminary to considering trial designs to assess the safety and efficacy of reduced dose 3TC we wished to determine the bioequivalence of plasma and intracellular concentrations of parent drug and active metabolite following the administration of two different doses.

Material and Methods: ENCORE2 was a randomized crossover study to compare the steady-state pharmacokinetics of plasma 3TC and intracellular 3TC-TP in human peripheral blood mononuclear cells (PBMCs) following administration of od 3TC 300 mg and 150 mg in HIV-negative volunteers. 24 subjects (13 female) were randomised to receive 3TC 300 mg and 3TC 150 mg separately for 10 days (Arm 1; n=13), or vice versa (Arm 2; n=11), each treatment phase separated by a 10 day washout. Clinical, biochemical and haematological data were recorded. Pharmacokinetic profiles were assessed for each phase on day 10 and 30 over 24 hours. Plasma 3TC concentrations were quantified by HPLC-MS/MS after solid-phase extraction (range 5-5000 ng/mL). Intracellular 3TC-TP concentrations were quantified from PBMCs via an ion-pair reverse-phase HPLC-MS/MS method [range 1-100 ng/sample (2-200 pmol)]. Pharmacokinetic parameters (AUC_{24h}, C_{max}) were calculated by non-compartmental modelling techniques (WinNonlin) and within-subject changes in drug exposure evaluated by geometric mean ratios (GMR; 150mg/300mg; adjusted for study arm, period and intra-individual variation) and 90% confidence intervals (CI). All pharmacokinetic variables were log transformed for statistical analysis and the results back transformed for reporting. Regimens were considered bioequivalent if 90% CI for the GMR fell within the acceptance range of 0.8-1.25.

Results: All 24 participants completed per protocol. Geometric mean (90% CI) plasma 3TC AUC_{24h} (ng.h/mL), C_{max} (ng/mL) for the 300 mg and 150 mg od doses were as follows: 8354 (7609-9172), 60.8 (53.4-69.2) and 1344 (1247-1448); 4773 (4408-5169), 38.1 (34.0-42.7) and 757 (688-833). Bioequivalence in plasma 3TC pharmacokinetic parameters (AUC_{24h}, C_{max}, C_{max}) following 300 and 150 mg od regimens, was not demonstrated: GMR (90% CI), 0.57 (0.55-0.60), 0.63 (0.59-0.67) and 0.56 (0.53-0.60).

Geometric mean (90% CI) intracellular 3TC-TP AUC_{24h} (pmol.h/10^6 cells), C_{max} (pmol/10^6 cells) for the 300 mg and 150 mg doses were: 59.5 (51.8-68.3), 1.49 (1.19-1.86) and 4.1 (3.59-4.69); 44.0 (38.0-51.0), 1.23 (1.0-1.52) and 2.95 (2.47-3.51). Bioequivalence in intracellular 3TC-TP pharmacokinetics (AUC_{24h}, C_{max}, C_{max}) following 300 and 150 mg od regimens, was not demonstrated: GMR (90% CI), 0.73 (0.64-0.83), 0.82 (0.68-0.99) and 0.70 (0.61-0.82). No serious adverse events related to study medication were recorded.

Conclusions: For key pharmacokinetic parameters, 3TC at 150 mg is not bioequivalent to the standard regimen of 300 mg. This indicates that saturation of cytosine
phosphorylation pathways is not achieved at a dose of 150 mg od.

No conflict of interest

Abstract: O_06

The cellular pharmacology of zidovudine and lamivudine according to HIV-status and gender

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Background: Zidovudine (ZDV) and lamivudine (3TC) are long-standing nucleoside analogs commonly used for treatment or prophylaxis of HIV in resource limited settings and/or in special populations. ZDV/3TC require sequential phosphorylation intracellularly to the active triphosphate moiety. Previous studies suggested possible differences in the intracellular profiles of ZDV/3TC by HIV infection status and gender. The objective of this study was to prospectively evaluate the cellular pharmacology of ZDV/3TC in HIV-negative and HIV-positive men and women.

Methods: HIV negative volunteers received 12 days of ZDV 300mg/3TC 150mg twice daily. HIV positive volunteers received the same doses of ZDV/3TC as part of their antiretroviral regimen for care. Blood was collected at 2, 5, and 8 hours post dose at first dose, day 3, day 7 and day 12. Peripheral blood mononuclear cells (PBMC) were assayed for ZDV and 3TC mono-(MP), di-(DP), and tri-phosphates (TP) with validated LC-MS/MS. Non-compartmental methods were used for concentration data, which were then averaged for each person. Concentration data were log transformed and analyzed with parametric tests. Units for ZDV-phosphates are fmol/10⁶ PBMC versus pmol/10⁶ PBMC for 3TC-phosphates.

Results: Sixteen HIV-negative (8 women) and 21 HIV-positive (5 women) participants completed all four PK profiles. Four HIV-negative and 2 HIV-positive (1 woman) subjects completed <4 visits. Median (IQR) Css average values for ZDV-MP, ZDV-DP, and ZDV-TP in HIV negative volunteers were 243 (142 – 418), 30.9 (25.2 – 51.7), and 37.2 (27.2 – 46.4), respectively. Values of ZDV-MP were 1.8-fold higher in HIV-positive versus HIV-negative volunteers (P=0.004). Median ZDV-DP and ZDV-TP were <20% different between groups (P>0.17). In HIV-negative volunteers, plasma ZDV concentrations were associated with ZDV-MP (P=0.01), but not ZDV-DP or ZDV-TP. ZDV-TP levels were similar in men versus women, 37.6 (25.1 – 42.1) and 35.2 (24.8 – 43.3), respectively (P=0.9). These results did not change when analyzing HIV-negative or HIV-positive groups only, or when evaluating ZDV-MP (P>0.44) or ZDV-DP (P>0.2). ZDV-TP accumulated 1.3-fold over 12 days of dosing. Median (IQR)Css average values for 3TC-MP, 3TC-DP, and 3TC-TP in HIV-negative subjects were 3.0 (2.3 – 4.7), 2.9 (2.3 – 4.2), and 5.3 (4.7 – 6.1), respectively. Values were significantly lower in HIV-positive volunteers, for example, the 3TC-TP values were 3.9 (2.2 – 5.4); P=0.01. Plasma 3TC concentrations were significantly associated with intracellular 3TC in HIV-positive, but not HIV-negative subjects. 3TC-TP were similar in men versus women, 4.5 (3.4 – 5.6) and 4.9 (3.9 – 6.2), respectively (P=0.24 overall, P=0.28 HIV negative, and P=0.8 HIV-positive). 3TC-TP accumulated approximately 3-fold over 12 days.

Conclusions: HIV-infection influences the cellular pharmacology profile of ZDV and 3TC in humans, but gender did not in this study. Intracellular ZDV-MP was higher in HIV-infected than HIV-negative volunteers, consistent with cell activation-dependent ZDV phosphorylation. Intracellular 3TC-phosphates were lower in HIV-positive volunteers, consistent with resting cell dependent phosphorylation. These findings suggest enhanced risk of adverse events linked to ZDV-MP in HIV-positive versus HIV-negative patients. Intracellular 3TC differences may have relevance for understanding PK-response for treatment.
Abstract: O_07

Use of accelerator mass spectrometry (AMS) to determine the pharmacokinetic profile of intracellular tenofovir diphosphate (TFV-dp)

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Background: Tenofovir (TFV) is one of the most commonly used ARVs world wide. AMS is an ultrasensitive technique that can be used to detect trace amounts of radiolabeled drugs and drug metabolites. We used AMS to measure intracellular TFV-dp in subjects receiving a radiolabeled microdose with or without the standard therapeutic dose of tenofovir disoproxil fumarate (TDF).

Materials & Methods: Six HIV seronegative volunteers were given a single oral dose of 100 µg (20 µCi) of \(^{14}\)C-labeled TDF (microdose, MD), and after 30 days a second dose of 100 µg (20 µCi) of \(^{14}\)C-labeled TDF combined with 300 mg nonradioactive oral TDF (standard dose, SD). TFV-DP was isolated from total PBMCs or isolated CD4+ cells by column extraction and measured as total \(^{14}\)C using AMS at pre-dose, 4, 12, 24, 72, and 168 h post-dose. Total plasma \(^{14}\)C was measured simultaneously.

Results: With both regimens, intracellular TFV-DP concentrations plateaued between 12 and 72 hours post-dosing in all 6 subjects. After the plateau, the SD elimination phase had median (range) \(t_{1/2}\) of 63 (14-127) and 59 (22-284)h in PBMC and CD4+ cells, respectively. For MD, the \(t_{1/2}\) was 83 (32-186) h for PBMC and 66 (38-153) h for CD4+ cells. Normalized median PBMC TFV-DP \(C_{\text{max}}\) was 13.1 (4.9-16.9) and 10.4 (8.6–13.3) fmol/10^6 cells, for MD and SD, respectively. Normalized median CD4+ TFV-DP \(C_{\text{max}}\) was 13.2 (6.1-14.1) and 5.1 (3.8–11.8) fmol/10^6 cells, for MD and SD, respectively (p>0.05 for all comparisons). The normalized TFV-DP AUC for PBMC and CD4+ cells was not different between MD and SD (nonparametric paired analysis p>0.05).

Conclusions: AMS can be used to assess TFV-DP in PBMCs, allowing low blood volumes and frequent sampling. The microdose and standard dose results in this study were similar. A prolonged 72 hour plateau phase in all subjects suggests balanced formation and elimination of TFV-DP. The \(t_{1/2}\) estimates, based on only 2 values, the first of which may be earlier than the terminal elimination phase, may be underestimates. These findings may have important implications for assessing TFV-DP in HIV treatment and prevention studies.

No conflict of interest

Abstract: O_08

Exposure-response analyses of an oral HIV attachment inhibitor BMS-663068 following 8 days of monotherapy in HIV-infected patients

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(Brazil-positive) versus prevention (HIV-negative).

No conflict of interest
Background: BMS-663068 is an oral HIV attachment inhibitor that achieved proof-of-concept during 8-day monotherapy in HIV-infected patients. Exposure-response (E-R) analyses were conducted to explore baseline and pharmacokinetic parameters that are associated with antiviral activities and safety and to select optimal dose for further development.

Methods: HIV-infected treatment naive and experienced patients (n=50) were randomized to receive either A: BMS-663068 600 mg Q12H + RTV 100 mg Q12H, B: BMS-663068 1200 mg QHS + RTV 100 mg QHS, C: BMS-663068 1200 mg Q12H + RTV 100 mg Q12H, D: BMS-663068 1200 mg Q12H + RTV 100 mg QAM, or E: BMS-663068 1200 mg Q12H, all with a standard meal, for 8 days. Steady-state plasma samples for BMS-626529 (active moiety of the BMS-663068 produrg) were collected on Day 8. HIV-1 RNA was measured at baseline, daily through Day 11 and at discharge. CD4+ and safety parameters were collected throughout the study. Phenosense Entry assay was used to determine baseline viral susceptibility from which protein binding adjusted EC90 was derived. A population pharmacokinetic model was developed using mixed-effect modeling. The relationships between HIV-1 RNA decline, CD4+ cell increase and safety parameters and baseline EC90, BMS-626529 Css.av (AUC/TAU), Cmin and each pharmacokinetic parameter normalized for EC90 were explored graphically and using nonlinear regression analysis. Model based simulations were conducted for various BMS-663068 dosing regimens, ±RTV and varying EC90 thresholds.

Results: In the BMS-663068 1200 mg BID arms, coadministration with RTV 100 mg once or twice daily resulted in 17-48% and 30-42% higher BMS-626529 Cmin and AUC, respectively, than BMS-663068 alone. A two-compartment model with sequential 0 and 1st order absorption adequately described BMS-626529 concentration time profiles. Baseline viral susceptibility to BMS-663068 is diverse with median EC90 = 9.6 ng/mL (range 0.33 to >1860 ng/mL (upper limit of assay), n=46). The distributions of Css.av/EC90 and Cmin/EC90 are consequently considerably wider than the range observed in the corresponding pharmacokinetic exposures. Maximum change in HIV-1 RNA from baseline was correlated with EC90 (p<0.0001) and both Css.av/EC90 and Cmin/EC90 (p<0.0001) but not with BMS-626529 exposures alone (p>0.15). An inhibitory sigmoid Emax model was used to describe the relationships between maximum change in HIV-1 RNA and Css.av/EC90 or Cmin/EC90; correlations were similar (r²=0.54) for both ratios. No significant correlations were noted between BMS-626529 exposures and CD4+ cell increases (p>0.37) and selected safety parameters (p>0.3). Cmin/EC90 ≥0.63 (95% C.I. 0.12-1.15) and Css.av/EC90 ≥2.3 (0.78-3.78) were each associated with a HIV RNA decrease of at least 1.0 log10.

Conclusions: E-R analysis from this monotherapy study indicate that baseline EC90 appears to be the most influential factor in determining the magnitude of decline in HIV RNA. Both Css.av/EC90 and Cmin/EC90 are correlated with antiviral activity; PK exposures alone are not predictive. These results and corresponding simulations support further development of BMS-663068 in a virologically sensitive population at lower doses than those used in this study, given once or twice daily, without the requirement for RTV coadministration.

Financial relationship(s): Employee of Bristol-Myers Squibb

Abstract: O_09

PK/PD analyses for QDMRK, a phase III study of the safety & efficacy of once versus twice daily Raltegravir in treatment-naïve HIV-infected patients

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Introduction: QDMRK was a study to evaluate 800 mg once-daily (QD) versus 400 mg twice-daily (BID) raltegravir (RAL) regimens, both in combination with tenofovir and emtricitabine in treatment-naive HIV-infected patients. Both regimens achieved high virologic response rates; however, QD RAL was inferior compared to BID in terms of HIV RNA suppression at Week 48 of treatment. Pharmacokinetic/pharmacodynamic (PK/PD) analyses were performed to examine potential relationships between RAL PK and viral response.

Material & Methods: Sparse plasma samples were collected during visits at Weeks 2 through 48 of treatment (1 sample per visit; 7 samples per patient). Intensive PK profiles were collected in a subset of patients at Week 4 and analyzed via non-compartmental analysis. A population PK model could not be developed due to interoccasion variability in absorption, and so 3 measures of observed sparse concentrations were reported for each patient: Geometric Mean (GM) C_{trough} (GM of all samples collected between 11 and 13 hrs postdose for BID dosing or 22 to 26 hrs postdose for QD); C_{all} (GM of all samples) and C_{min} (minimum of all samples). Efficacy parameters HIV RNA <50 c/mL, HIV RNA <400 c/mL, protocol defined virologic failure, and resistance mutations at amino acid 143, 148 and/or 155 following 48 weeks of treatment were used for the PK/PD analyses. Statistical analyses of potential relationships between RAL PK and efficacy outcomes were performed using logistic regression models. An odds ratio (95% CI) was determined, which represents the fold change in probability of the event occurring versus not occurring for each 10-fold increase in PK parameter value.

Results: From the intensive PK data, exposure over 24 hours (AUC24) was similar for 800 mg QD versus 400 mg BID RAL [GMR (90% CI) AUC24 for QD/BID = 1.17 (0.80, 1.72)]. GM C_{trough} values were lower for QD [GM (%CV) = 83 (140%) nM] compared to BID [380 (126%) nM]. Consistent with prior analyses, no significant PK/PD associations were observed using data from only the BID dosing arm. Using data from the QD and BID arms pooled together, statistically significant PK/PD associations were observed between almost all combinations of the examined sparse PK parameters (C_{trough}, C_{all}, and C_{min}) and efficacy parameters (HIV RNA <50, <400, and virologic failure). For example, for the binary outcome of virologic failure, the odds ratio (95% CI) was 0.50 (0.29, 0.86); p=0.012; N=537 for C_{trough} and 0.56 (0.34, 0.92); p=0.023; N=738 for C_{all}, indicating that the probability of virologic failure significantly decreased with increasing RAL PK. Other factors, such as high baseline HIV RNA, were also significant predictors of treatment failure.

Conclusions: Statistically significant relationships were observed between RAL C_{trough}, C_{all} and C_{min} and efficacy parameters at Week 48, while AUC24 was similar for 800 mg QD vs 400 mg BID. This implies that shape of the raltegravir concentration-time profile is important for long-term efficacy. Patients with low RAL PK and high baseline viral load were at highest risk of treatment failure.

Financial relationship(s): Employee of Merck and own stock and stock options in Merck. This study was sponsored by Merck

Abstract: O_10
Pharmacokinetics of increased dose atazanavir with and without tenofovir during pregnancy


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Introduction: Plasma exposure of ritonavir-boosted atazanavir (ATV) is decreased by ~30% during pregnancy and by an additional ~30% when coadministered with tenofovir (TDF).

Materials & Methods: IMPAACT P1026s is an on-going, prospective, non-blinded study of ARV pharmacokinetics (PK) in HIV-infected pregnant women that includes 2 cohorts receiving ATV/r 300/100mg once daily during the 2nd trimester (2nd trim), 400/100 mg during the 3rd trimester (3rd trim) and 300/100 mg from delivery through 2 weeks postpartum (PP) as part of a combination ARV regimen either with or without TDF. Intensive steady-state 24-hour PK profiles were performed during 2nd trim, 3rd trim and PP. Maternal and umbilical cord blood samples were obtained at delivery. ATV concentrations were measured by HPLC with a detection limit of 0.047 mcg/mL. PK targets were the estimated 10th percentile ATV AUC (29.4 mcg*hr/mL) in non-pregnant adults taking the standard dose (mean AUC=57 mcg*hr/mL) and 0.15 mcg/mL, the suggested minimum target trough concentration. Infant bilirubin concentrations were measured at 24-48 hours and 4-6 days after birth.

Results: ATV PK data were available for 58 women (30 without TDF, 28 with TDF; ethnicity: 15 Black, 25 Hispanic, 3 White, 15 Asian. Median maternal age at delivery was 29.7 years, median maternal weight at delivery was 74 kg, median gestational age at delivery was 39.4 weeks, median birth weight was 3100 gm. PK parameters are presented below for 2nd trim, 3rd trim and PP as median (range) and number who met target/total. Values with * indicate p<.01 compared to PP.

For the women who received ATV without TDF: AUC was 19.4 (9.2-41.1), 45.7 (14.9-88.3), and 57.8 (9.9-99.5) mcg-hr/mL, and 2/5, 19/25 and 20/23 met the AUC target. CI/F was 15.5 (7.3-32.6), 8.8 (4.5-26.9)*, 5.2 (3.0-30.3) L/hr. C24h was 0.28 (0.09-0.64), 0.71 (0.22-2.09), and 0.99 (0.05-2.73) mcg/mL, and 4/5, 25/25 and 18/23 met the C24h concentration target.

For the women who received ATV with TDF: AUC was 25.1 (11.3-60.9)*, 39.9 (9.3-88.2)*, and 56.8 (7.5-134.9) mcg-hr/mL, and 4/12, 18/23 and 17/19 met the AUC target. CI/F was 12.0 (4.9-26.5)*, 10.0 (4.5-43.0)*, and 5.3 (2.2-40.0) L/hr. C24h was 0.40 (0.17-1.06)*, 0.73 (0.17-2.06)*, and 1.18 (0.24-3.65) mcg/mL, and 12/12, 23/23 and 19/19 met the C24h target.

Median cord blood ATV concentration was 0.22 (0.05-1.33) mcg/mL and median ratio of cord blood/maternal delivery ATV concentration was 0.18 (0.03-4.08). All newborn bilirubin concentrations were normal.

Conclusions: Compared to nonpregnant adults, ATV CI/F is increased during both 2nd trim and 3rd trim. ATV exposure with or without tenofovir is low with standard dosing during the 2nd trim but improved during the 3rd trim with the dose increase to 400/100mg. ATV exposure PP on the standard dose equalled or exceeded that in the 3rd trim on the increased dose. ATV/r 400/100 mg provides adequate ATV exposure during the 3rd trim and should be considered during the 2nd trim as well.

No conflict of interest

Abstract: O_11

Transport of antiretrovirals by ABCB5: the elusive non-nucleoside reverse transcriptase efflux pump?

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Background: Antiretrovirals exhibit marked inter-patient variability in pharmacokinetics. ATP-dependent efflux transporters of protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors have been
reported, but less is known about efflux of non-nucleoside reverse transcriptase inhibitors (NNRTIs). ABCB5 (ATP-binding cassette, sub-family B member 5) is an efflux transporter belonging to the same family as P-glycoprotein and is widely expressed in epithelia. ABCB5 is thought to play an active role in drug extrusion and shares some substrate overlap with P-glycoprotein, known to transport PIs. The aim of this study was to investigate ABCB5-mediated transport of PIs and NNRTIs.

Materials & Methods: ABCB5-mediated transport of 1 µM ³H lopinavir, ³H atazanavir, ³H nevirapine and ¹⁴C efavirenz was investigated in MDCKII-ABCB5 and parental MDCKII cells. Cells were cultured on Transwell™ membranes for seven days and bi-directional transport across both basolateral (B) and apical (A) membranes were assessed. Only cultures with a transepithelial electrical resistance (TER) > 300 ohms were used. Drugs were added to the donor compartment (either apical or basolateral) and the receiver compartment was sampled at 10, 20, 40, 60 and 120 min. Radioactivity in the sampled aliquots was then quantified by scintillation counting. The apparent permeability coefficient (Papp) was calculated as Papp = (dQ/dt)(1/ACo) and sink conditions were maintained throughout. Differences in Papp values were tested for significance using a paired t-test (SPSS).

Results: Transport of lopinavir, nevirapine and efavirenz in the MDCK-ABCB5 cell line was greater in the A to B direction than in the B to A direction. Transport of atazanavir was similar in both directions, suggesting that atazanavir is not an ABCB5 substrate. The transport ratio (A to B/B to A) was also calculated. Differences in Papp values were tested for significance using a paired t-test (SPSS).

Conclusion: This is the first study to show ABCB5-mediated transport of lopinavir, nevirapine and efavirenz. Importantly, ABCB5 has been identified as the first efflux transporter for NNRTIs. ABCB5-mediated efflux may constitute an additional factor for the inter-patient variability in lopinavir, nevirapine and efavirenz pharmacokinetics. The direction of ABCB5 mediated transport suggests localisation of ABCB5 to the basolateral membrane, in contrast to P-glycoprotein which is localised to the apical membrane. Pharmacogenetic studies to determine whether functional variants in the ABCB5 gene contribute to this variability are now warranted.

No conflict of interest

Abstract: O_12

Population pharmacokinetic modelling of plasma and intracellular once daily ritonavir-boosted darunavir in HIV-infected patients

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Purpose of Study: Once daily ritonavir-boosted darunavir (DRV/RTV) is a preferred antiretroviral regimen for treatment-naive patients. As antiretrovirals act within cells it is of potential interest to determine intracellular (IC) concentrations as numerous factors may influence drug distribution between plasma and IC compartments and ultimately impact efficacy. Population pharmacokinetic modelling is a useful tool that can be used to simultaneously describe plasma and IC concentrations and evaluate potential
covariates influencing important pharmacokinetic parameters in both compartments.

**Methods:** Data were pooled from 3 DRV/RTV studies (with one study having both plasma and IC concentrations). In total 51 HIV-infected patients (7 female) stable on DRV/RTV [800/100mg or 900/100mg once daily; n=32 (n=24 plasma and IC) and 19, respectively] were included. Median age, weight, BMI, plasma RTV area under the curve over 24h (AUC_{0-24}), IC RTV AUC_{0-24} and baseline CD4 cell count were 39yr (21-63), 74kg (57-105), 24kg/m^2 (18-31), 4.35mg.h/L (2.27-10.99), 31.01mg.h/L (10.79-123.46) and 500cells/mm^3 (227-1129), respectively; 49 patients had undetectable viral load at baseline. PK sampling was performed at steady-state with between 1-3 profiles available per patient. Nonlinear mixed effects modelling (NONMEM v. VI 2.0) was applied to determine DRV PK parameters, interindividual and interoccasion variability and residual error. IC DRV was modelled as a proportion of plasma concentration using an accumulation ratio as a proportionality constant (ACC). This ratio will be dependent on the method of cell collection (here, CPT tubes) and cell processing (here, no washes). The following covariates were evaluated: age, weight, BMI, sex, ethnicity, plasma and IC RTV AUC_{0-24} and raltegravir co-medication (400mg twice daily and 800 mg once daily). The model was validated by means of simulation and visual predictive check.

**Summary of Results:** A 2-compartment model with first-order absorption (k_a 0.89h^{-1}) and lag-time (0.37h) best described the data. Inclusion of a different apparent oral clearance (CL/F) and volume of distribution (V2/F) for one of the studies improved the fit (Study 1,2 vs. Study 3 CL/F: 12.5 vs. 15.6L/h; V2/F 125 vs. 186L). DRV ACC was estimated as 4.8. RTV AUC_{0-24} and age were significantly associated with DRV CL/F resulting in a 14% reduction in DRV CL/F with every 10yr increase in age. IC RTV AUC_{0-24} was significantly related to DRV ACC with a higher DRV ACC associated with higher IC RTV AUC_{0-24}. Based on the visual predictive check 89% and 97% of observed DRV plasma and IC concentrations, respectively were within the 90% prediction interval, indicative of an adequate model.

**Conclusions:** A population model simultaneously describing plasma and IC pharmacokinetics of once daily RTV-boosted DRV has been developed and validated. IC DRV concentrations were approximately 5-times that of plasma and RTV AUC_{0-24} and age were significantly related to DRV CL/F; however the impact of age requires further clarification over a wide age range. IC RTV AUC_{0-24} was significantly associated with DRV ACC suggesting IC RTV has a role in preventing the loss of DRV from cells. Identification of covariates to help understand IC DRV pharmacokinetics and its relationship with efficacies are now needed.

No conflict of interest

**Abstract: O_13**

**Pharmacokinetic interaction between Maraviroc and Etravirine: a multicentre study in HIV-patients receiving an antiretroviral regimen without PI**

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**Introduction:** Etravirine (ETR) is a next-generation NNRTI designed to have a high genetic barrier to the development of resistance and also maintains an activity
despite common NNRTI mutations. ETR is a substrate and inducer of CYP3A4, a substrate and inhibitor of CYP2C9 and CYP2C19 and also an inhibitor of Pgp. Maraviroc (MVC) is an antagonist of the CCR5 receptor, recently approved for use in treatment-experienced patients infected with CCR5-tropic HIV-1. MVC is a substrate for both CYP3A4 and Pgp. Specific drug interaction studies showing the effects of CYP3A4/Pgp inhibitors and inducers have been conducted in healthy volunteers but few data are available between ETR and MVC in HIV+ patients. The objective of our study was to determine ETR and MVC steady-state plasma concentrations in HIV+ patients receiving ETR and MVC containing regimen without any protease inhibitor (PI).

Patients and Methods: a multicentre study was conducted to collect data regarding patient’s characteristics (age, gender), treatment (daily doses, associated antiretrovirals) and respective plasma concentrations. LC-MS/MS was used to measure ETR and MVC concentrations and to check the absence of associated PI/r on samples. Patients taking drugs susceptible to interact or respective values below the LOQ were excluded from the final analysis. Results of Ctrough and Cave (any time post dose) are presented as median (IQR). Interpretation was done regarding the target plasma concentration from Pfizer of 75 ng/ml.

Results: 64 HIV-patients (18W/46M), with a median age of 59 yrs (range: 33-74) and receiving MVC + ETR ± RAL ± 1 or 2 NR(t)TI were enrolled. Overall, 100 plasma concentrations were collected corresponding to 77 Ctrough, drawn 12 hours (12-14h) post dose. The respective daily dose were 300mg bid (n=28) and 600mg bid (n=36) for MVC and 200 mg bid for ETR. MVC Cave and Ctrough were respectively: 59 ng/ml (29-112; n=37) and 53 ng/ml (27-75; n=28) at 300 mg bid and 64 ng/ml (36-92; n=63) and 60 ng/ml (36-85; n=49) at 600 mg bid. In the whole population, 62% of Cave and 67% of Ctrough were <75 ng/ml. According to the MVC dose, 62% of Cave and 75% of Ctrough were <75 ng/ml at 300 mg bid and 62% of Cave and 63% of Ctrough were <75ng/ml at 600 mg bid, respectively. Corresponding ETR Ctrough was 723 ng/ml (478-1055; n=76) and approximately 180-fold higher than the protein binding-adjusted EC50 for wild-type virus.

Conclusion: Surprisingly, MVC Ctrough were very similar between both doses and quite lower compared with a PI boosted containing regimen, suggesting a modest effect by increasing MVC doses on the induction of ETR. A very high proportion (around 65-70 %) of concentrations was below the proposed target of 75 ng/ml, whatever the parameter chosen Cave or Ctrough.

No conflict of interest

Abstract: O_14

Pharmacokinetic evaluation of Rifabutin and its active metabolite LM565 coadministered with Lopinavir/r in HIV-infected patients

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Introduction: HIV infection has contributed to a significant increase in the worldwide incidence of tuberculosis (TB). Combination ART containing lopinavir/ritonavir (LPV/r) is commonly used in patients with HIV infection. Because rifabutin is metabolized by CYP3A4, its plasma levels are increased during concomitant ritonavir administration; thus, current HIV treatment guidelines recommend the use of a dose adjustment of RFB of 150 mg thrice weekly in patients receiving LPV/r. The major RFB metabolite is the 25-O-desacetyl (LM565), with activity almost equivalent to that of RFB. This preliminary study was performed to explore RFB and LM565 exposures in a 3 times weekly regimen when coadministered with LPV/r in patients with HIV-associated TB.
Materials & Methods: 14 HIV-infected subjects with mycobacterial disease were included in this analysis. All patients received LPV/r(standard-dose)+RFB(150mg thrice weekly). Full pharmacokinetic LPV/r+RFB+LM565 curves were obtained, during the dosing interval, at week 2 (T1) and week 6 (T2) after starting combined therapy. A control curve for RFB alone (at 300mg dose daily) was performed before starting LPV therapy (T0). A control curve for LPV/r was performed 10 weeks after stopping RFB therapy (T3). Plasma samples were collected at 0, 1, 2, 3, 4, 6, 8, and 12 hours after drugs administration. LPV, RFB and LM565 levels were measured by validated HPLC-UV/MS methods. PK parameters were calculated by standard non-compartmental methods (Kinetica V4, Innphase).

Results: Median (range) RFB PK values at T0, T1, and T2 were, respectively: AUC₀-24h (µg.h/mL) 3.01 (1.4-10.5), 4.2 (1.9-5.5), 2.4 (1.3-6.4); Cₚ (ng/mL) 91 (11-152), 87 (20-104), 42 (8-114); Cₘₚ (ng/mL) 330 (106-1950), 309 (106-564), 239 (151-526). Median (range) LM565 PK values at T0, T1, and T2 were, respectively: AUC₀-24h (µg.h/mL) 0.7 (0.18-2.4), 1.6 (0.35-2.6), 1.6 (0.79-2.4); Cₚ (ng/mL) 4 (3-10), 33 (10-71), 30 (13-75); Cₘₚ (ng/mL) 52 (32-72), 115 (90-190), 122 (40-221). Median (range) LPV PK values at T1, T2, and T3 were, respectively: AUC₀-24h (µg.h/mL) 143.4 (86.3-278), 137 (46.8-303), 124.3 (74.7-139.4); Cₚ (µg/mL) 10 (5.6-20), 8.8 (1-17.6), 7.8 (5.1-9); Cₘₚ (µg/mL) 14.4 (9.2-34), 16.3 (15.4-33), 13.7 (7.8-20.9); CL/F (L/h/kg) 0.044 (0.021-0.077), 0.048 (0.018-0.11), 0.04 (0.027-0.12). If we consider the suggested RFB AUC₀-24h target value of 4.5 µg.h/mL, 42% and 28% of patients were below this value at T1 and T2, respectively.

Conclusions. In patients receiving LPV/r, the change in LM565 exposure reported from the study was significantly greater than the change observed in the rifabutin area under the concentration-time curve. The results confirm that RFB 150mg/thrice weekly with LPV/rtv may produce low RFB plasma concentrations, as reported in other studies. RFB regimens in HIV-TB infection need to be further studied and patients may benefit from the measurement of RFB and its metabolite concentrations.

No conflict of interest

Abstract: O_15

Population Pharmacokinetic Analysis and Effects of Raltegravir In HIV positive and Healthy Individuals

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Background: Raltegravir (RAL) pharmacokinetics (PK) was reported to exhibit large inter and intra-individual variability, thus resulting in heterogeneous concentration exposure under standard dosage regimens. The aims of the study were (i) to quantify the variability affecting RAL PK parameters, (ii) to identify potential demographic and environmental factors that could influence drug concentration exposure, (iii) to explore the correlations between PK exposure and markers of efficacy and toxicity, and (iv) to simulate different dosage regimens for predicting and comparing drug levels at trough.

Methods: A total of 544 RAL plasma concentration measurements were collected in 145 HIV+ participants from the Swiss HIV cohort study followed routinely by therapeutic drug monitoring. Another 19 healthy volunteers underwent extensive pharmacokinetic sampling under standardized food intake. One and two compartments with various absorption models were tested using NONMEM. A relative bioavailability (Fᵢₑ) was introduced in the model to capture a scale shift in the PK parameters observed in HIV+ patients.
compared to healthy individuals. Distinct absorption rate constants (ka) were allowed as well between both populations. Demographic characteristics, environmental factors and concomitant medications were evaluated as covariates. Posterior Bayesian individual estimates of $C_{\text{min}}$ and $AUC_{0-24}$ were correlated with CD4+ count, HIV viral load, total bilirubin, AST and ALT concentrations using linear regression analyses.

Results: A 2 compartment model with first order absorption adequately described the data. $F_{\text{HIV}+}$ amounted to 80% of RAL bioavailability in healthy subjects (CV=86.4%). Average apparent clearance was $98.7 \text{ Lh}^{-1}$, volumes of distribution 393 L for the central compartment (CV=76.8%), and 182 L for the peripheral compartment, $ka$ 0.2 h$^{-1}$ and 0.8 h$^{-1}$ (CV = 100%) in HIV+ and healthy individuals, respectively. Among the covariates evaluated, atazanavir, female gender and hyperbilirubinemia (stade 1 or higher) affected $F_{\text{HIV}+}$, yielding an increase of 40%, 60% and 400% in RAL bioavailability, respectively. No obvious correlations were detected between RAL exposure and efficacy (CD4+ and HIV RNA count) or toxicity (AST, ALT, total bilirubin). Model-based simulations predicted average trough concentrations of 124 ng/ml (95% prediction range 9.7 - 1381) for the 400 mg b.i.d. regimen and of 52.2 ng/ml (4.2 - 817) for the 800 mg q.d. dosage regimen.

Conclusion: RAL PK confirmed a large interpatient variability, of which only 6% was explained by atazanavir intake, female gender and by the association with high total bilirubin levels. A large proportion of the variability yet remains unexplained. The smaller relative bioavailability in HIV+ patients could result from pathophysiological differences related to HIV infection, compliance issues or food effects. Once daily dosing with 800 mg yielded average trough predictions 50% lower than 400 mg twice daily, which might impact on treatment efficacy. No clear correlation between RAL exposure and efficacy or toxicity markers could nevertheless be detected in this limited study population.

No conflict of interest

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Abstract: O_16

**Tenofovir Population Pharmacokinetics in Children and Adults**

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Introduction: Tenofovir (TFV) is often prescribed in HIV-infected adolescents and adults, but in children less than 12 yrs of age the provisional dose of 8 mg/kg results in lower exposure than in adults. We present a unified adult and pediatric TFV population PK model.

Material & Methods: Intensive PK samples were prospectively collected from children and adults over 12 to 24 hrs. We measured plasma TFV concentrations with a validated LC-MS assay and analyzed these data by non-parametric population PK and simulation methods as implemented in the MM-USCPACK software. For simulations, we log-transformed model parameters and used the full parameter covariance matrix. AGE, weight (WT) for AGE>18 yrs, and creatinine clearance (CRCL) were simulated as random variables each with a uniform distribution between an appropriate study population ranges. WT for AGE<18 yrs was simulated as the AGE-specific median from CDC growth curves, adjusted randomly by +/- 25%.

Results: There were 32 participants with a median age of 33.8 yrs (range 8.3 to 58); 13 (41%) were female. The TFV disoproxil fumarate (TDF) dose was 300 mg daily, except for the 3 subjects <12 yrs who had a daily dose of 150 mg. The median (range) CRCL and WT were 118.9 (84.7 to 351.0) ml/min/1.73m$^2$ and 68.2 (28.1 to 123.6) kg.
A 2-compartment model with linear absorption after a delay fitted the data best. TFV transfer to the peripheral compartment decreased with increasing WT. TFV elimination from the central compartment was scaled allometrically to WT with further dependence on CRCL and AGE. Volume of the central compartment was proportional to WT. The observed vs. individual model-predicted concentration regression had a slope of 1.02 (95% confidence interval [CI] 1 to 1.05), intercept of 0 (95% CI -0.01 to 0.01) and an $R^2$ of 0.96. Visual and numerical predictive checks showed no major discrepancies. After doses of 12 mg/kg, 225 mg, and 300 mg once daily from 0-2, 2-12, and >12 yrs, respectively, geometric mean steady-state TFV AUC 0-24h was 3.6, 2.2, 2.8, and 3.1 mg*h/L in 1000 simulated 0-2, >2-12, >12-18, and >18 yr olds. At a higher dose of 300 mg, 2-12 yr olds had a correspondingly higher AUC 0-24h of 2.5 mg*h/L. Apparent TFV clearance was 3.3, 4.5, 2.0, and 1.2 L/kg/h in the same age groups, respectively.

**Conclusions**: TFV PK parameters depend on age, weight and creatinine clearance in children and adults. TFV AUCs are within the range reported in the TDF package insert for patients >12 years of age. Children 2-12 yrs of age may require a TDF daily dose up to 300 mg, and in young children 0-2 yrs a dose of 12 mg/kg daily might be required in order to achieve TFV exposure similar to older children and adults.

*No conflict of interest*

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**Abstract: O_17**

**Drug Interactions**

**Pharmacokinetic interaction between Norgestimate/Ethinyl Estradiol and EVG/COBI/FTC/TDF single tablet regimen**

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**Introduction**: Cobicistat (COBI) - boosted elvitegravir (EVG), an inhibitor of HIV-1 integrase, has been co-formulated with the standard of care NRTI backbone FTC/TDF into a EVG/COBI/FTC/TDF (Quad) single tablet regimen for the treatment of HIV-1 infection. Norgestimate/ethinyl estradiol (NGM/EE 25 µg, OrthoTri-Cyclen Lo®) is a representative hormonal oral contraceptive (OC) that may be co-administered with EVG/COBI/FTC/TDF in HIV-1 infected female patients. This study evaluated the effect of EVG/COBI/FTC/TDF on the pharmacokinetics (PK), pharmacodynamics (PD) and safety of NGM/EE in healthy female subjects.

**Methods**: This open-label, fixed-sequence Phase 1 study consisted of two parts. HIV-1 uninfected female subjects using OC other than NGM/EE 25µg were enrolled into Part A (lead-in) and received NGM/EE for one menstrual cycle prior to enrolling into Part B (main study). Subjects using NGM/EE were enrolled into Part B directly. In Part B, all subjects received NGM/EE for two sequential 28-day cycles. EVG/COBI/FTC/TDF was administered for the last 10 days of active OC dosing (Days 12-21) in the second cycle in combination with NGM/EE.

In Part B, serial PK samples were collected over 24 hours on Day 21 of each cycle for the analysis of norelgestromin (NGMN: active NGM metabolite) and EE and on Day 21 of the second cycle for the analysis of...
EVG and COBI. Plasma concentrations were measured using LC/MS/MS. PK parameters were calculated using non-compartmental analysis. Geometric least squares mean ratios and 90% CIs for $AUC_{\text{tau}}$ and $C_{\text{max}}$ were estimated using ANOVA with PK equivalence boundaries of 80-125%. The effect of NGM/EE alone and in combination with EVG/COBI/FTC/TDF on PD parameters, progesterone, FSH and LH, was explored using descriptive statistics.

Results: Twelve evaluable subjects were needed to complete Part B. Eighteen subjects received NGM/EE and 16 received NGM/EE + Quad in Part B; 15 subjects completed the study. NGM/EE administered alone, and with EVG/COBI/FTC/TDF, was well tolerated. There were no adverse events (AEs) that led to study discontinuation. Nausea and headache were the most frequently reported AEs and were seen in more subjects with NGM/EE + Quad than with NGM/EE alone. All treatment-emergent AEs were mild (Grade 1) or moderate (Grade 2). More treatment-emergent AEs were seen during co-administration of NGM/EE and EVG/COBI/FTC/TDF than with NGM/EE alone.

Co-administration of Quad with NGM/EE resulted in a ~25% decrease in EE $AUC_{\text{tau}}$ and ~2-fold increases in NGMN $AUC_{\text{tau}}$ and $C_{\text{max}}$ relative to NGM/EE administration alone. EVG and COBI exposures achieved in this study were within the range of values observed in previous clinical studies. No changes from baseline in progesterone and similar decreases from baseline in FSH were observed after both treatments. A larger reduction from baseline in LH was noted during treatment of EVG/COBI/FTC/TDF + NGM/EE vs. with NGM/EE alone.

Conclusion: Concurrent administration of EVG/COBI/FTC/TDF with NGM/EE was safe and well tolerated. Co-administration resulted in EE $AUC_{\text{tau}}$ decreases, NGMN $AUC_{\text{tau}}$ and $C_{\text{max}}$ increases and a larger reduction in LH relative to NGM/EE alone. These results suggest that negative feedback inhibition for the secretion of LH and FSH was maintained in spite of an observed reduction in EE plasma concentrations. In light of the EE exposure decrease with EVG/COBI/FTC/TDF, it is recommended that an OC contain at least 30 µg of EE when administered with EVG/COBI/FTC/TDF.

Financial relationship(s): all authors are employees of Gilead Sciences, Inc.
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Abstracts Poster Presentations
Abstract: P_01

Advanced Investigations in Pharmacology: Protein Binding, Intracellular Drug Concentrations, and Compartmental Pharmacokinetics

Investigating variability in reported intracellular Raltegravir concentrations: contribution of PBMC isolation methodology.

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Background: Most antiretroviral drugs act within cells and therefore knowledge of cellular penetration and intracellular (IC) pharmacokinetics should aid understanding of virological response and toxicity. Recently Bazzoli et al (Clinical Pharmacokinetics 2010; 49: 18-45) summarised findings from studies on IC concentrations of antiretrovirals and highlighted clear limitations, eg small numbers, poor design and methodological. We have addressed methodological issues particularly cell collection and washing procedures. The impetus was the observation of marked differences in raltegravir (RAL) disposition in 4 publications – ranging from undetectable to IC/plasma ratios of 0.05, 0.07 and 5.11 (ie a difference of > 100-fold). Since our laboratory was involved in two studies (cell collection in Barcelona and London) generating different data it seemed prudent to investigate the underlying causes of the disparity.

Materials and Methods: We initially performed analysis of methodology used in each publication. In three studies, blood collection was in CPT tubes and in one study blood was layered over Ficoll. The number of cell washes varied from no washes through two washes (either PBS or 0.9% NaCl) to 3 washes with PBS. The critical issue was therefore to compare a) CPT and Ficoll cell separation and b) the number of cell washes. We did this in two ways. Firstly blood samples were collected from healthy volunteers and spiked with RAL [1000ng/mL] followed by mixing for 1 hour (ex-vivo). 8 mL of blood was then placed into CPT tubes or layered over Ficoll. The number of wash steps (PBS) varied from zero to five and both cells and supernatant were analysed for RAL. The second approach was in-vivo with blood samples from HIV+ patients on a regimen containing RAL (n=2; 4 time points). RAL was determined by LC-MS/MS. Cell counts were taken to calculate IC concentration, assuming a PBMC to be 0.4pL.

Results: Cell counts following the CPT and Ficoll methods of cell separation were comparable. However, the number of washes markedly impacted the final intracellular RAL concentration. Results from both the ex-vivo and in-vivo samples show a decrease in the IC concentration of RAL as the number of washes increases. The greatest difference was seen between no wash and the first wash (eg. ex-vivo in CPT tubes – loss of ~ 95%; in Ficoll, loss of ~95%). In the in-vivo collection there was a greater reduction in IC concentration after the first wash with samples collected over Ficoll (> 95% reduction) than with CPT tubes (~70% loss). Cells from CPT tubes showed a greater loss after the second wash in comparison with cells from the Ficoll collection.

Conclusions: The number of washes has a marked impact on the quantification of IC RAL. The absence of a wash step potentially over-estimates IC RAL by inclusion of residual plasma drug contamination and drug bound to cell membrane. On the other hand RAL rapidly effluxes from the cell during washing. Currently the ‘optimal’ numbers of washes for IC determination of RAL is unclear. It is important to have consensus if studies are to be compared.

No conflict of interest
Abstract: P_02

Advanced Investigations in Pharmacology: Protein Binding, Intracellular Drug Concentrations, and Compartmental Pharmacokinetics

Modeling of Raltegravir Intracellular Accumulation in Healthy Volunteers

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Introduction: Raltegravir (RAL) is a potent inhibitor of HIV integrase. Despite demonstrating large pharmacokinetic (PK) variability, RAL is highly efficacious in most patients. Since there are limited data available on RAL intracellular (IC) levels, we performed a pilot study to investigate the association of the plasma concentrations with IC accumulation of RAL for 48 hours after a single RAL dose.

Material & Methods: This was a pharmacokinetic study in 6 healthy volunteers. Paired blood samples for plasma and peripheral blood mononuclear cells (PBMCs) were collected at pre-dose (0h) and 4, 8, 12, 24 and 48 hours, after a single 400 mg dose of RAL given in the fasting state. Concentrations of RAL were determined using a validated liquid chromatography/mass spectrometry method. The lower limit of quantitation for plasma RAL and intracellular RAL were 2 nmol/L and 0.225 nmol/L respectively. Non-compartmental analyses were performed using WinNonLin. Population pharmacokinetic analysis was performed using NONMEM. Intracellular accumulation ratio was derived from observed intracellular concentrations, predicted plasma concentrations, and the individual error.

Results: Six male subjects were included in the study; median weight was 67.4 kg (range 56.5 to 87.1 kg), and median age was 33.5 years (range 31 to 36 years). The geometric mean (GM) (95% confidence interval) RAL plasma $C_{\text{max}}$ (nmol/L), AUC$_{0-12}$ and AUC$_{\text{inf}}$ (nmol/L*h) were 2246 (1175 to 4294), 10776 (5770 to 20126), and 13119 (7235 to 23788) respectively. Apparent plasma RAL half life was 7.8 (5.5 to 11.3) h. RAL IC $C_{\text{max}}$, AUC$_{0-12}$ and AUC$_{\text{inf}}$ were 383 (114 to 1281), 2073 (683 to 6290), and 2435 (808 to 7337). Apparent IC RAL half life was 4.5 (3.3 to 6.0) h. IC RAL was 24.0% (6.7 to 58.1%) of plasma concentrations. Concentration-time curves for IC and plasma RAL were parallel, with IC/plasma ratios remaining stable for each patient without significant time-related trends over 48 hours. RAL IC and plasma concentrations were closely correlated, and the time course of IC and plasma RAL was similar. NONMEM analysis showed that the IC to plasma ratio for RAL was 11.2%, and the relative standard error of this estimate was 35%.

Conclusions: Non-compartmental and compartmental modeling of plasma and intracellular RAL concentrations suggest that there is no intracellular concentration or persistence of RAL within PBMCs.

No conflict of interest

Abstract: P_03

Advanced Investigations in Pharmacology: Protein Binding, Intracellular Drug Concentrations, and Compartmental Pharmacokinetics

Effect of ritonavir concentrations on atazanavir pharmacokinetics: population pharmacokinetic analysis

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Background: Atazanavir (ATV) is a protease inhibitor indicated for the treatment of HIV infection, with approved doses of unboosted 400mg (2 capsules, approved in the USA) or 300mg boosted with 100mg of ritonavir (2 capsules, approved in the EU and USA), both qd. The aim of this study was to develop a population pharmacokinetic (pk) model for atazanavir and ritonavir in a population of HIV-infected adults. The model sought was to detect possible pk differences in ATV when administered unboosted or boosted with ritonavir (RTV), and to incorporate patient characteristics influencing variability in ATV and/or RTV concentrations.

Methods: HIV-infected adults on stable therapy with oral atazanavir unboosted (400mg qd) or boosted (400mg/100mg rRTV, qd) in routine clinical practice for at least 4 weeks were included. A concentration–time profile was obtained for each patient, and serial blood samples were collected immediately before and over 24h after a morning-dose or between 12 and 24h after a night-dose. ATV and RTV concentrations in plasma were determined by high performance liquid chromatography. A population pharmacokinetic model was developed for ATV and RTV. Pharmacokinetic parameters, interindividuial variability and residual error were estimated, and the influence of different patient characteristics on the pharmacokinetics of ATV and RTV was explored. The final model incorporated the effect of RTV exposure on ATV oral clearance (CL/F). Population analysis was performed using non-linear mixed effects modeling (NONMEM, version VI).

Results: A total of 29 Caucasian patients were included in the study. Atazanavir and ritonavir pharmacokinetics were described with one-compartment models with first order absorption and elimination. An absorption lag-time was needed to describe ATV absorption phase. Atazanavir CL/F was inhibited by RTV concentrations following an exponential model. The model predicted a 30% decrease in ATV oral CL/F at a 0.63mg/mL of RTV in plasma. This concentration represents the average observed concentration of RTV in the dosing interval. The final model appropriately predicted plasma concentrations, with no systematic bias and adequate precision.

Conclusions: A population model has been developed to quantify the effect of RTV exposure on ATV pharmacokinetics in HIV-infected patients. No differences in the pharmacokinetics of atazanavir were found apart from a decrease in plasma clearance when co-administered with ritonavir. Bayesian estimates of the individual parameters of ritonavir and atazanavir could be useful to predict boosted and unboosted atazanavir exposure in an individual manner.

No conflict of interest

Abstract: P_04

Advanced Investigations in Pharmacology: Protein Binding, Intracellular Drug Concentrations, and Compartmental Pharmacokinetics

Intracellular mono-, di-, and tri-phosphate levels of tenofovir/emtricitabine in human peripheral blood mononuclear (hPBMC) vs red blood cells (RBC)

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**Background:** Tenofovir (TFV) disoproxil fumarate (TDF) and emtricitabine (FTC) are the preferred nucleos(t)ide analog backbone for HIV treatment, and were shown to prevent HIV infection in humans. These drugs require successive intracellular phosphorylation to a pharmacologically active tri-phosphate (TP) analog. TFV requires two steps to TFV-diphosphate, the TP analog for TFV, whereas FTC requires three steps to the TP. Little is known about the pattern of intermediate phosphates (mono- (MP) and di- (DP)) in various cell types in humans. This study examined relationships among the different drug phosphates in hPBMCs and RBCs.

**Methods:** Single samples were obtained from HIV infected subjects who were stabilized on antiretroviral regimens with TDF/FTC backbones. Eight milliliters of blood were collected into a heparin Cell Preparation Tube at various times post dose. hPBMCs and RBCs were harvested, counted with a Countess Automated Cell Counter (Invitrogen), lysed with cold 70% methanol, and stored at -70°C. Drug was quantified with a validated LC-MS/MS assay using approximately 2 million cells per sample. Samples below the lower limit of quantification (2.5 fmol/sample for TFV-phosphates and 0.1 pmol/sample for FTC-phosphates) were reported as BLQ. Analyses were by paired, two-sided t tests. Units for TFV-phosphates were fmol/10^6 cells versus pmol/10^6 cells for FTC-phosphates.

**Results:** Five subjects (2 male) participated. HIV-RNA values were 127, 250 and three were <48 copies/mL. CD4 counts were between 425-1092 cells/µL. Reported times post dose ranged from 2 to 37 hours. The average (range) TFV, TFV-MP, TFV-DP in hPBMC were 11.4 (BLQ - 19.4), 16.6 (2.7 - 28.1), and 53.3 (3.7 - 100). The same values in the paired RBCs were 6.37 (3.0 - 12.7), 99.8 (29.1 - 171), and 91.0 (21.2 - 184). For FTC, the average (range) MP, DP, TP in hPBMCs were 1.18 (BLQ - 1.7), 5.99 (BLQ - 8.1), and 4.71 (BLQ - 6.2). FTC-DP and FTC-TP were BLQ in the paired RBC samples, but FTC-MP was quantifiable in two samples (0.27 and 0.09). One participant with low intracellular TFV-phosphates and BLQ FTC in hPBMC had detectable HIV-RNA (250 copies/mL), suggesting non-adherence. The patterns of TFV phosphates differed in hPBMCs and RBCs. TFV-DP levels in hPBMCs were significantly higher than TFV (6.1 fold, p=0.02) and TFV-MP (3.6 fold, p=0.03). In RBCs, TFV-DP levels were similar to TFV-MP levels and both were approximately 15 fold higher than TFV levels (p≤0.03). TFV-DP was higher in RBCs versus hPBMCs by 1.7-fold (p=0.04) and correlated significantly in the two cell types (p=0.007). In hPBMCs, FTC-DP and TP levels were similar, and higher than FTC-MP (p=0.04 and 0.03, respectively).

**Conclusions:** These novel human data show that TFV and FTC phosphates accumulate with different patterns in hPBMCs and RBCs, suggesting unique transport and enzyme characteristics in these two cell types. These findings enhance our understanding of drug distribution and activation in the human body, and provide a basis for future pharmacokinetic-pharmacodynamic analyses.

No conflict of interest

**Abstract:** P_05

**Drug Development Science**

**Modeling of Maraviroc pharmacokinetics in the presence of Atazanavir/ritonavir in healthy volunteers and HIV-1-infected patients**

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**Background:** Maraviroc (MVC) concentrations are increased by atazanavir/ritonavir (ATV/r) through CYP3A4/transporter inhibition. Modeling of sparse MVC pharmacokinetic (PK) data from treatment-experienced HIV-infected...
patients suggested lower exposures than predicted by a drug interaction study in healthy volunteers (A4001025, MVC 300 mg BID). The present analysis uses a semi-physiological MVC PK model to explore the interaction of MVC with ATV/r, using data from volunteers (A4001025) and a 2-drug pilot study (A4001078) in which treatment-naïve (TN) patients received once-daily MVC 150 mg + ATV/r 300/100 mg.

**Materials and Methods:** Nonlinear mixed effects modeling (NONMEM®) was used to apply a model with 2 absorption and 4 disposition compartments, using certain fixed disposition parameters from previous modeling. Absorbed drug was introduced into a liver compartment with metabolic clearance and absorption transporters inhibited by ATV/r. Renal clearance was scaled using baseline creatinine clearance centered on 120 mL/min. The data from volunteers (n=12, samples=192) were used to estimate the ATV/r effect on intrinsic clearance and extent of absorption. These values were applied to the rich (n=15, samples=145) and sparse (n=57, samples=138) data from TN patients. This was followed by sensitivity analyses including estimation of these effects independently for patient data.

**Results:** In volunteers, ATV/r reduced population intrinsic clearance of MVC from 90 to 14 L/h and increased absorption from 83.3% to 98.5% (300 mg dose), leading to a 2.5-fold increase in \( C_{\text{max}} \), a 4.6-fold increase in AUC/Cavg, a 10-fold increase in \( C_{\text{min}} \), and an 8.2-fold increase in effective constant concentration (ECC). For the same intrinsic clearance, MVC 150 mg QD in patients produced 93.5% absorption. Patient profiles with MVC 150 mg QD+ATV/r were flatter than those in volunteers at the recommended dose of 300 mg BID (without inhibitors), with \( C_{\text{max}} \) lower at 591 vs 933 ng/mL, Cavg lower at 170 vs 213 ng/mL, but \( C_{\text{min}} \) higher at 43 vs 38 ng/mL, and ECC at 95 vs 89 ng/mL. Sensitivity using patient-rich data gave similar results: \( C_{\text{max}} \) 614 ng/mL, Cavg 170 ng/mL, \( C_{\text{min}} \) 44 ng/mL, and ECC 96 ng/mL. However, this analysis produced an intrinsic clearance of 9 L/h and 69% absorption of MVC 150 mg.

**Conclusions:** The volunteer and HIV-infected patient populations are consistent in ATV/r effects on MVC exposure. In patients, MVC 150 mg QD +ATV/r produced less peak-trough fluctuation with lower \( C_{\text{max}} \) and Cavg, but similar \( C_{\text{min}} \) and ECC to volunteers given MVC 300 mg BID in the absence of ATV/r.

**Financial relationship(s):** M. Vourvahis and L. McFadyen are employees of Pfizer, and hold stock in Pfizer. B. Weatherley is a contractor employed by Pfizer.

**Abstract: P_06**

**Drug Development Science**

**GSK2248761 development; formulation and food effect**

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**Background.** GSK2248761 (761) is a once daily, next generation NNRTI with activity against EFV-resistant strains and the potential for future fixed dose combinations with other HIV treatments. Early human studies utilized *gelucire (GEL) capsules, which is unsuitable as a final marketed form due to long-term stability and storage issues. Two bioavailability studies were conducted to evaluate the relative bioavailability and effect of food on a capsule solid dosage form for use in Phase 2b studies and then tablets for Phase 3 and to enable the final marketed product.

*Gelucire*® 44/14 is a semi-solid excipient is a mixture of glycerol and PEG1500 esters of long fatty acids.

**Methods.** Two cross-over design studies in healthy adult subjects were conducted to evaluate the relative bioavailability and the effect of food on a capsule solid dosage form for use in Phase 2b studies and then tablets for Phase 3 and to enable the final marketed product.
micronized or wet bead milled (WBM) 761, in 24 subjects. Part 2 studied the effect of a moderate (30%) fat meal (MFAT). Then, in Part 1 (24 subjects) of Protocol SGN114435 compared 200mg doses of three wet bead milled (WBM) tablets (direct compression (DC), roller compaction (RC) and continuous granulation (CG)) to WBM capsule from SGN113391 (2x100mg). Part 2 studied the effect of a MFAT on the tablet that showed the best performance from Part 1. There was a washout period of 7 days between treatments. Serial PK samples and safety assessments were obtained throughout. Non-compartmental PK analysis was performed and geometric least squares (GLS) mean ratios and 90% confidence intervals (CI) were generated by a mixed effect model for within-subject treatment comparisons of key PK parameters.

Results. 761 was well tolerated with no deaths, SAEs, withdrawals due to 761-related AEs or clinically significant trends in clinical laboratory values, vital signs, or ECGs. Compared to the gelucire formulation (given with food), standard milled, WBM and micronized 761 dosage forms had similar or better AUCinf and Cmax, given fasted. When administered with MFAT, all three test formulations achieved higher Cmax and AUCinf compared to the GEL capsule with negligible impact on C24. The WBM capsule showed the lowest food-effect (increase in Cmax of 28%) and was chosen for Phase II studies. Relative to the WBM capsule, all of the WBM tablet formulations performed reasonably well however the RC formulation had almost identical values for AUCinf, Cmax and C24 and was chosen based on ease of future manufacturing. A moderate food effect was observed in Part 2 (57% increase in Cmax, 33% in AUCinf, no change in C24). This formulation will serve as the basis for the dosage form used in Phase 3 trials.

Conclusions. The WBM tablet formulation of 761 represents the best option for phase III, pending review of virology, safety and PK data from on-going Phase II studies. The modest food effect is not thought likely to be clinically significant or require food restrictions for dosing.

No conflict of interest

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Abstract: P_07

Drug Development Science

Population pharmacokinetics of lersivirine using Phase I/IIa pharmacokinetic data after suspension and tablet administration

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Background: This study was conducted to explore the relationship between the population pharmacokinetics of lersivirine and covariates (dose, suspension/tablet, food effects, weight, race, subject/patient status) utilizing data from eight healthy volunteer studies and one lersivirine monotherapy study in HIV-positive subjects.

Material and methods: A total of 285 concentration-time profiles (4307 samples) from 199 subjects (42 HIV-positive) were analyzed using nonlinear mixed-effects modeling, NONMEM VI. All subjects were male. Seventy-four percent were White and 21% were Asian. The median (range) for age and weight were 32 (19-53) years and 76 (53-99) kg, respectively. The base model was a two-compartment model with first-order absorption and a lag time, fit to the log-transformed data. Three levels of random effects (interindividual (IIV), interoccasion (IOV), and residual variability) were investigated. Race and weight were explored after incorporation of dose, food, and formulation effects in the model.

Results: The typical (reference) subject was a 76 kg, healthy subject taking the lersivirine 500 mg tablet formulation. The absorption rate constant (Ka) was 1.20 h\(^{-1}\) and the absorption lag was 0.227 h. Ka was reduced with dose (Dose \^0.305) and food (to 44% of the reference fasted). The suspension formulation was absorbed more slowly (Kα
60% of reference tablet) in HIV subjects but was marginally faster in healthy volunteers (106% of tablet). Ka for tablet in HIV subjects was similar (97%) to that in volunteers. IIV (percentage standard deviation) for Ka was 49% and IOV was 66%. Relative bioavailability (F1) was fixed at 1 for the 500 mg tablet in volunteers, fasted. There was a small increase with dose (Dose1.0283) and food (to 103%). F1 was reduced in HIV-positive subjects by 40% for suspension and by 14% for tablet. IIV and IOV for F1 were 15% and 10%, respectively. Apparent (CL/F) and intercompartmental (Q/F) clearances of lersivirine were 94.0 L/h (IIV 14%) and 43.3 L/h (IIV 44%), respectively. Apparent central (V1/F) and peripheral (V2/F) volumes of distribution of lersivirine were 440 L (IIV 39%) and 210 L (IIV 29%), respectively. The residual error was 31.3%. Standard allometric scaling (CL/F, Q/F ~Weight0.75 and V1/F and V2/F ~Weight1) was applied subsequently to testing with power models for weight and was found to be statistically significant. Race was not significant once weight had been included.

Conclusions: Although dose, food, and formulation effects were statistically significantly associated with changes in lersivirine PK, these effects were small and unlikely to be clinically relevant. However, F1 in HIV-positive subjects was 40% less than in healthy subjects for the suspension and 14% less for the tablet. This study/patient/formulation effect is being investigated further, including in a lersivirine pharmacokinetic Phase IIb sub study. Lersivirine showed low IIV and IOV for relative bioavailability. Residual variability was also low. Weight was the only identified demographic covariate associated with changes in lersivirine PK.

Financial relationship(s): L. McFadyen, G. Langdon and M. Vourvahis are employees of Pfizer and own stock in Pfizer. B. Weatherley is a contractor employed by Pfizer.

Abstract: P_08

Drug Interactions

Effect of rifabutin on the pharmacokinetics (PK) of lersivirine, and lersivirine on the PK of rifabutin/25-O-desacetyl-rifabutin, in healthy subjects

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Introduction: Lersivirine (UK-453,061) is a non-nucleoside inhibitor of HIV-1 reverse transcriptase (NNRTI) that displays potent anti-viral activity against both wild-type virus and certain clinically significant NNRTI-resistant viruses. Lersivirine is a modest inducer of CYP3A4 activity at clinical doses. A third of people with HIV are co-infected with tuberculosis and rifabutin is used as an alternative to rifampicin as it is a less potent inducer of CYP3A4. Rifabutin may decrease lersivirine exposures by a lesser extent than that observed with rifampicin (87%). This study investigated the effect of co-administration of lersivirine and rifabutin on lersivirine, rifabutin, and rifabutin active metabolite exposure.

Materials and methods: In this open-label, randomized, 3-way crossover study, 18 subjects participated in three 11-day treatment periods separated by 14-day washout periods. During the 11-day treatment period subjects received one of three treatments following breakfast: lersivirine (1000 mg QD), rifabutin (300 mg QD) or lersivirine (1000 mg QD) and rifabutin (300 mg QD) in combination. Blood samples for pharmacokinetic (PK) profiling were collected serially up to 24 hours following dosing on Day 10. AUC24, Cmax, Tmax, and C24h were determined for each drug. Safety and tolerability were assessed by reporting of adverse events (AEs), vital
Results: The lersivirine PK (co-administration/alone) ratios (90% CI) for lersivirine and rifabutin compared with lersivirine alone were 0.66 (0.61–0.71), 0.75 (0.67–0.84), and 0.42 (0.36–0.48) for AUC24, Cmax, and C24h, respectively. No difference was observed for lersivirine Tmax between treatment groups. The rifabutin concentration profile or overall exposure did not change following co-administration with lersivirine; the rifabutin PK ratios (90% CI) for lersivirine and rifabutin compared with rifabutin alone were 1.01 (0.96–1.08), 1.10 (0.98–1.25), and 1.00 (0.94–1.06) for AUC24, Cmax, and C24h, respectively. Following co-administration of lersivirine and rifabutin, lower exposure of the rifabutin metabolite, 25-O-desacetyl-rifabutin, was observed when compared to administration of rifabutin alone: PK ratios (90% CI) for 25-O-desacetyl-rifabutin comparing lersivirine and rifabutin to rifabutin alone were 0.73 (0.68–0.79), 0.73 (0.66–0.81), and 0.85 (0.73–0.98) for AUC24, Cmax, and C24h, respectively. No unexpected AEs or clinically significant laboratory abnormalities were observed in this study. One subject discontinued due to pyrexia while receiving lersivirine plus rifabutin.

Conclusions: Lersivirine total exposure was reduced by 34% in the presence of rifabutin which may therefore necessitate lersivirine dose modification. Co-administration of lersivirine with rifabutin decreased the total exposure to the rifabutin active metabolite by 27%. However this is unlikely to be clinically relevant given that 25-O-desacetyl-rifabutin contributes only up to 10% of the total antimicrobial activity of rifabutin treatment. The exposure of rifabutin was unaffected and therefore no rifabutin dose adjustment is necessary. Lersivirine showed an acceptable safety profile when co-administered with rifabutin.

Financial relationship(s): authors are employees of Pfizer and own stock in Pfizer.
200mg QD. Twelve subjects completed all treatments. Plasma simvastatin, simvastatin acid, atorvastatin, ortho-hydroxy-atorvastatin, and rosuvastatin concentrations were determined by LC-MS/MS. Plasma PK parameters were determined by noncompartmental methods in WinNonlin 5.2. The ratios of geometric least squares (GLS) means (90% CI) comparing selected PK parameters with and without GSK2248761 were estimated by analysis of variance (ANOVA) using the SAS Mixed Linear Models procedure.

**Results:** The study medication was well tolerated. One subject withdrew consent for personal reasons, and another was withdrawn by the principal investigator for elevated CPK. Coadministration of GSK2248761 200mg QD increased simvastatin AUC(0-48h) and Cmax 3.7- and 4.3-fold; increased simvastatin acid AUC(0-48h) and Cmax 3.0- and 3.9-fold; increased atorvastatin AUC(0-48h) and Cmax 47% and 25%; decreased ortho-hydroxy-atorvastatin AUC(0-48h) and Cmax 24% and 59%; and increased rosuvastatin AUC(0-48h) and Cmax 26% and 32%.

**Conclusions:** Simvastatin and its active ring-open acid form generated via esterase hydrolysis of the parent lactone were the most sensitive to inhibition by GSK2248761 with increases of 3-4-fold in PK parameters for the combination relative to simvastatin alone. Simvastatin is known to be a CYP3A4 substrate sensitive to inhibition and is contraindicated in combination with many HIV therapies including RTV-boosted protease inhibitors. Atorvastatin, typically less sensitive to inhibition of CYP3A4 than simvastatin, was increased 25-47%, with a commensurate decrease in CYP3A4 mediated production of active ortho-hydroxy-atorvastatin, for a minimal impact on total atorvastatin+metabolite exposure. Rosuvastatin, a substrate for OATP1B1 uptake into the liver, was increased 26-32%, suggesting that GSK2248761 does inhibit OATP1B1 somewhat in vivo which likely resulted in decreased biliary excretion of rosuvastatin. Based on the results of this study, atorvastatin and rosuvastatin would be preferable to simvastatin for treatment of hyperlipidemia in patients receiving GSK2248761 for HIV-1 infection.

**Abstract: P_10**

**Drug Interactions**

**Effect of fosamprenavir/ritonavir on the pharmacokinetics of single-dose olanzapine in healthy volunteers**

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**Introduction:** Psychosis and other mental illnesses are common in HIV-infected patients. Olanzapine (OLZ) is one of the preferred antipsychotic agents for the treatment of schizophrenia. OLZ is primarily metabolized by CYP1A2 and UGT. High-dose ritonavir (RTV) has been shown to increase OLZ elimination through induction of CYP1A2 and/or UGT, but the effect of low-dose RTV on OLZ pharmacokinetics (PK) is unknown. Fosamprenavir (FPV) is an HIV protease inhibitor that is boosted by low-dose RTV. We hypothesized that OLZ AUC of OLZ 15 mg with FPV/RTV would lead to a similar OLZ AUC of OLZ 10 mg alone.

**Material & Methods:** This was an open-label, randomized, 2-period, cross-over, single-centre trial in 24 healthy volunteers. All subjects were randomized to one of the following treatments: a) FPV/RTV 700/100 mg BID for 16 days with a single-dose of OLZ 15 mg on day 13, a wash-out period of 30 days and subsequently a single-dose of OLZ 10 mg on day 48, or b) same medication in reversed order. OLZ was taken with a standardized breakfast. Blood was collected after OLZ intake for up to 96
Reviewed articles

Abstracts

No effect of ritonavir or timing of food intake on etravirine pharmacokinetics in HIV-negative volunteers

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Background: The non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine is approved for use in treatment-experienced, HIV-1-infected patients, including those with NNRTI resistance. A previous food-effect study has demonstrated that etravirine exposure is 51% lower when administered under fasted conditions compared to when administered with food. In-vitro and in-vivo studies have shown that etravirine is metabolized by cytochrome (CYP)3A, CYP2C9 and CYP2C19. Ritonavir is a potent inhibitor of CYP3A and, as such, is used at low doses as a pharmacokinetic enhancer. The mechanistic effect of a single-dose of ritonavir on etravirine pharmacokinetics was investigated by separating drug administrations by time and by food intake.

Materials and methods: In an open-label, randomized, 4-way crossover trial, volunteers were divided equally into two panels and received four different treatments per panel, all administered as a single dose, as follows: Panel 1: A: simultaneous etravirine 200mg/ritonavir 100mg after a standard breakfast (reference); B: simultaneous etravirine 200mg/ritonavir 400mg after a standard breakfast; C: etravirine 200mg after a standard breakfast plus ritonavir 100mg 4 hours after etravirine intake; D: etravirine 200mg after a standard breakfast plus ritonavir 100mg 4 hours before etravirine intake. Panel 2: E: as for A; F: etravirine 200mg alone after a standard breakfast; G: etravirine 200mg alone before a standard breakfast.
breakfast; H: etravirine 200mg before a standard breakfast plus ritonavir 100mg after the breakfast. There was a wash-out period of 14 days between subsequent etravirine intakes. Full pharmacokinetic profiles of etravirine and ritonavir were determined. Data were compared using least square means (LSM) of C_max and AUC_last. Safety and tolerability were also assessed.

**Results:** 40 volunteers (90% male) participated. In Panel 1 (n=20), relative to reference, etravirine/ritonavir 200/400mg after breakfast did not affect etravirine AUC_last or C_max [LSM ratio (90% CI): AUC_last 0.92 (0.84, 1.01); C_max 0.91 (0.82, 1.02). Similarly, relative to reference, etravirine AUC_last/C_max were not affected by administration of ritonavir 100mg 4 hours after [1.03 (0.94, 1.13); 1.00 (0.89, 1.13), respectively] or 4 hours before [1.00 (0.94, 1.07); 0.98 (0.88, 1.11), respectively] etravirine intake. In Panel 2 (n=20), relative to etravirine 200mg after breakfast alone, co-administration with ritonavir 100mg did not affect etravirine AUC_last or C_max [1.03 (0.90, 1.16); 1.00 (0.89, 1.12), respectively]. Treatment with etravirine 200mg alone before breakfast resulted in 17% and 23% reductions in etravirine AUC_last and C_max, respectively, relative to etravirine treatment after breakfast [0.83 (0.76, 0.90); 0.77 (0.67, 0.87)]. Treatment with etravirine 200mg before breakfast and ritonavir 100mg after breakfast did not affect etravirine AUC_last relative to reference [0.95 (0.84, 1.08)], however etravirine C_max was reduced by 17% [0.83 (0.72, 0.96)]. Co-administration of etravirine and ritonavir was generally well tolerated. Most adverse events were grade 1 and there were no grade 3 or 4 adverse events.

**Conclusions:** No evidence of a pharmacokinetic interaction between single-dose etravirine and single-dose ritonavir was observed. Separation of etravirine and ritonavir administration by time or food intake is not expected to result in clinically relevant changes to etravirine pharmacokinetics in multiple dose trials. The combination was generally well tolerated.

*Financial relationship(s): Employee of Tibotec, Inc. and stock holder of Johnson & Johnson*

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**Abstract: P_12**

**Drug Interactions**

**Effect of food on the pharmacokinetics of the integrase inhibitor, dolutegravir (S/GSK1349572)**

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**Introduction.** Dolutegravir (DTG, S/GSK1349572) is an unboosted, once daily integrase inhibitor (INI) currently in late stage development for the treatment of HIV infection which demonstrates a unique resistance profile distinct from other INIs. The objective of this study was to evaluate the effect of meals with varying fat and calorie content on DTG pharmacokinetics.

**Methods.** This was a single-center, randomized, open-label, crossover study in healthy adult male and female subjects. 18 subjects received DTG 50 mg as a single dose on four separate occasions either fasting or with a low (300 kcal, 7% fat), moderate (600 kcal, 30% fat) or high fat (870 kcal, 53% fat) meal. There was a washout of 7 days between doses. Safety evaluations and serial PK samples were collected after each dose and subjects had a follow-up visit within 7-14 days after the last dose. Non-compartmental PK analysis was performed and geometric least squares mean ratios (GLS-MR) and 90% confidence intervals (CI) were generated by the mixed effect model for within-subject treatment comparison.

**Results.** Co-administration of DTG with food increased plasma DTG exposures and...
reduced the rate of absorption as evidenced by a longer t<sub>max</sub>. The increases in exposure were modest and were observed with increasing fat content, with AUC<sub>(0-∞)</sub> increased by 33%, 41% and 66% when DTG was administered with low, moderate or high fat meal, respectively, compared to the fasting state. Plasma DTG C<sub>max</sub> increased by 46%, 52%, and 67% when DTG was administered with low fat, moderate fat and high fat food, respectively. The median t<sub>max</sub> when DTG was administered fasting was 2.1 hours. This increased to 3.0 with a low fat meal, 4.0 hours for a moderate fat meal and 5.0 hours for a high fat meal. Elimination half-life was not affected by food. DTG was generally well tolerated with few, primarily minor adverse events (AEs) reported. No, grade 3/4 AEs or withdrawals due to AEs were reported. No clinically significant trends in clinical laboratory values, vital signs, or ECGs were observed.

**Conclusion.** Food modestly increases the exposure of DTG. The effect of food observed in this study is not considered clinically significant. Thus, DTG can be given with or without food and without regard to fat content.

**Financial relationship(s):** Employee of GlaxoSmithKline

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**Abstract: P_13**

**Drug Interactions**

**Effect of acid reducing agents on the relative bioavailability and pharmacokinetics of Cobicistat-boosted Elvitegravir**

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**Introduction:** Cobicistat boosted elvitegravir (EVG/co) as part of a single tablet regimen containing elvitegravir/cobicistat/emtricitabine/tenofovir DF is in Phase 3 development for the treatment of HIV infection in treatment-naive subjects. The intrinsic solubility of cobicistat (COBI) is high (6.5 mg/mL) at normal gastric pH (2.2) but decreases with increasing pH. Because the ability of COBI to effectively boost CYP3A substrates like EVG depends on the concentrations that are achieved pre-systemic and/or systemically to reduce first-pass effects, this study evaluated the effect of representative H2-receptor antagonists (H2RA: famotidine, FAM, 40 mg QD) and Proton Pump Inhibitors (PPI: omeprazole OME, 20 mg QD) on the pharmacokinetics of COBI and EVG.

**Methods:** Two Phase 1 multiple dose studies were conducted, in healthy subjects, to evaluate the concomitant use of acid reducing agents with EVG/co. Each study had two dosing periods (8 days each); study 1, subjects were randomized to one of three sequences (n=11/sequence) to the order in which they received Reference treatment A (EVG/co, 150 mg) followed by one of the following test treatments; Test treatment B (EVG/co and FAM staggered 12 hours), Test Treatment C (EVG/co and OME 2 hours prior to EVG/co) or Test Treatment D (EVG/co and OME staggered 12 hours). Study 2 (n=16) evaluated simultaneous co-administration of EVG/co with FAM in a two-way crossover design. COBI and EVG PK were assessed on Day 8 of each period. The studies concluded lack of a PK interaction (reduction in exposure) if the lower bound the 90% confidence interval (CI) of the geometric mean ratios (GMR) of Test vs. Reference were greater than 0.7 for EVG and COBI AUC<sub>tau</sub> and C<sub>max</sub>.

**Results:** Thirty-three subjects enrolled, and 32 completed Study 1; one subject discontinued prematurely due to pregnancy. Sixteen enrolled and completed Study 2. All treatments were generally well tolerated. In both studies the predefined lack of interaction criteria were met for both EVG and COBI all test vs. reference assessments,
specifically, the GMR (%) (lower bound of the 90% CI) for $\text{AUC}_{\text{tau}}$ and $C_{\text{max}}$ were as follows:

**Study 1 EVG**: H2RA 12 hr stagger: 103 (94.9) and 102 (89.4); PPI 2 hr stagger: 110 (102) and 116 (104) and PPI 12 hr stagger: 105 (92.9) and 103 (91.9).

**Study 1 COBI**: H2RA 12 hr stagger: 105 (102) and 104 (99.1); PPI 2 hr stagger: 92.4 (84.8) and 90.2 (81.8) and PPI 12 hr stagger: 98.7 (89.0) and 94.4 (85.1).

**Study 2 EVG**: 103 (98.1) and 100 (91.7).

**Study 2 COBI**: 103 (96.8) and 106 (99.4), respectively.

**Conclusion**: No dosing restrictions are necessary on the administration of EVG with COBI with PPIs. Based on the available data, EVG and COBI should be administered simultaneously with, and/or 12 hours after, dosing of H2-receptor antagonists.

**Financial relationship(s)**: The authors are employees of Gilead Sciences

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**Abstract: P_14**

**Drug Interactions**

**Lack of a clinically relevant effect of Maraviroc on the pharmacokinetics of digoxin in healthy volunteers**

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**Background**: Maraviroc is a potent CCR5 antagonist approved for the treatment of patients infected with CCR5-tropic HIV, and is also a substrate for CYP3A4 and P-glycoprotein (P-gp). Maraviroc does not inhibit any of the major P450 enzymes at clinically relevant concentrations; however, in vitro data suggest that maraviroc could inhibit P-gp ($IC_{50} = 183 \mu M$) in the gut, thus affecting the bioavailability of certain drugs that are P-gp substrates. Therefore, we sought to assess the effect that maraviroc has on P-gp, utilizing digoxin as a probe for P-gp.

**Materials and methods**: This was an open-label, fixed-sequence, crossover study in 12 healthy volunteers conducted in Singapore. In Period 1, all subjects received a single dose of digoxin 0.25 mg on Day 1. In Period 2, all subjects received maraviroc 300 mg BID for 6 days (Days 1-6), with a single dose of digoxin 0.25 mg on Day 5. Blood samples were collected over 48 hours following each single dose of digoxin. Safety and tolerability were also assessed.

**Results**: The ratios of the adjusted geometric means for digoxin $\text{AUC}_{\text{last}}$ and $C_{\text{max}}$ (steady-state maraviroc + digoxin:digoxin alone) were 1.00 (90% confidence interval [CI]: 0.88, 1.14) and 1.04 (90% CI: 0.84, 1.29), respectively. There were no serious or severe adverse events and no clinically significant laboratory abnormalities.

**Conclusions**: No clinically relevant effect on the exposures of digoxin was observed in the presence of maraviroc, suggesting that maraviroc is not a clinically significant inhibitor of P-gp. Therefore, no dose adjustment is warranted with P-gp substrates when co-administered with maraviroc. Co-administration of maraviroc with digoxin was well tolerated.

**Financial relationship(s)**: M. Vourvahis, J. Fang, H.W. Choo and J. Heera are employees of Pfizer and own stock in Pfizer
Abstract: P_15

Drug Interactions

Lack of pharmacokinetic interaction between doxycycline and protease inhibitors or non-nucleoside reverse transcriptase inhibitors in HIV patients

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Introduction: Very few data are available on potential interactions between antiretroviral and antimalarial drugs. The VIHVO is an open-label study designed to include HIV-infected patients on antiretroviral therapy (ARV) native from sub-Saharan Africa before a travel in a sub-Saharan country lasting between 15 days and 6 months. Objective was to evaluate the pharmacokinetic (PK) interaction between antimalarial and ARV drugs in these patients.

Material & Methods: This PK study focused on the interaction of doxycycline on four ARV: 2 protease inhibitors (PI), atazanavir (ATV and ATV/r) and lopinavir (LPV/r), and 2 non-nucleoside reverse transcriptase inhibitors (NNRTI), efavirenz (EFV) and nevirapine (NVP) administered at standard and respective daily doses. Lack of impact of doxycycline on ARV trough plasma concentrations (Cp) was tested separately and by therapeutic class. ARV Cp were measured using UPLC-MS/MS at enrolment visit (V0) during the month preceding the travel before doxycycline introduction and in the week following the return to France (V1) when patients were taking doxycycline for at least 15 days. Inclusion criteria were a plasma HIV-RNA < 50 c/ml at both V0 and V1 and good declared treatment adherence (auto-questionnaire) to both ARV and doxycycline. Lack of PK interaction was tested based on differences of log ARV Cp between V1 and V0. The Schuirmann TOST adapted to the Wilcoxon test was used. Median and CI90% for the differences of log Cp were estimated with the Hodges-Lehmann estimator. Limit of equivalence was fixed at 20% as usual.

Results: Sixty-five patients (male 37%, median age 41 yrs) receiving ATV (n=1), ATV/r (n=14), LPV/r (n=23), EFV (n=17), NVP (n=10) containing regimen were included. No patient got infected with malaria. Lack of PK interaction was statistically significant by therapeutic class: PI (p=0.02) and NNRTI (p=0.005) while it was not demonstrated for each ARV separately tested although differences of log Cp between V0 and V1 were small. Exponential of median and CI90% for the differences of log Cp were 0.96 [0.82-1.15] and 1.01 [0.90-1.09], for PI and NNRTI, respectively.

Conclusions: This study was the first to assess the interaction of doxycycline on PI and NNRTI. Lack of PK interaction was only demonstrated by therapeutic class but support the choice of doxycycline as antimalarial in patients treated with PI or NNRTI. Further studies, with control of drug intake, would be useful to confirm these results.

No conflict of interest

Abstract: P_16

Ethno-Pharmacology

Pharmacokinetics of the non-nucleoside reverse transcriptase inhibitor Efavirenz among HIV Infected Ugandans

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Introduction: Pharmacokinetic variability of non-nucleoside reverse transcriptase inhibitor efavirenz has been documented and great variation in trough concentrations or clearance is cited as a risk for virological failure while high plasma concentrations is a risk for adverse drug reactions. The African population has been shown to exhibit greater variability in efavirenz concentrations and a better understanding of the pharmacokinetics of the drug and their relationship to clinical outcome is needed. This study aimed at characterizing the pharmacokinetics of non-nucleoside reverse transcriptase inhibitor efavirenz among HIV infected Ugandans.

Materials and Methods: Data were collected from 66 (female 42 and male 22) HIV sero-positive Ugandan patients initiating on efavirenz- based regimens between September 2007 and March 2009. An intensive pharmacokinetic study was done on days 1 and 14 of antiretroviral therapy. Blood samples were collected at 9 time points over 24hrs and analysed using a reverse phase high performance liquid chromatography (HPLC) with ultra violet-detection, yielding 924 efavirenz concentration data points. Non-compartmental analysis was used to describe efavirenz pharmacokinetics on both days.

Results: We observed mean efavirenz steady-state $C_{min}$ of 2.9$\mu$/mL, AUC was 278.5 $h\times\mu$/mL, half life of 27.2 h, and $V_t$ of 247L. Average $C_{max}$ increased from 4.1$\mu$/mL on day 1 to 7.4 on day 14, while the average half life and $V_t$ did not change significantly within the two weeks of treatment. Though overall mean clearance did not change significantly between day 1; 7.5L/h and day 14; 7.4L/h, 41.9% of the participants showed an average 95.8% (range 1 - 423%) increase in clearance between the two study days while the other participants either experienced no change or had a reduction in clearance. More than half (52.7%) of the samples collected over the 24hr period on d14 and 96.6% of the maximum concentrations were above therapeutic range while only three minimum concentrations were below therapeutic range. Two of the three patients with subtherapeutic $C_{min}$ had experienced an increase in clearance that was above 95% within the two weeks of treatment.

Conclusion: We conclude from these results that patients of the same population may exhibit autoinduction to different extents or at different stages of treatment and this need to be taken into consideration during clinical management of individual patients. The proportion of efavirenz plasma concentrations above the therapeutic range indicates that many patients may be at risk for efavirenz central nervous system toxicity during the early phase of treatment. Further investigation is needed to determine the mechanism that contributes to toxicity in patients with and without autoinduction.

No conflict of interest

Abstract: P_17

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

TDM of Antiretroviral Drugs in HIV-infected Pregnant Women: pharmacokinetics, compartmental diffusion, efficacy and safety


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Background: The aim was to evaluate antiretroviral (ARV) drugs levels during three trimesters of pregnancy, transplacental and
amniotic fluid diffusion and clinical maternal and newborn outcome.

**Methods:** Antiretroviral concentrations were determined in mother and cord blood and in amniotic fluid by high-performance liquid chromatography (HPLC-UV). Cord-to-mother ratio (C:M) was calculated to estimate the ARVs placental passage. HIV viral load and CD4 cell count values were recorded in first, second, third trimester and at delivery. Newborn gestational age, weight, Apgar score and complications were recorded at birth.

**Results:** Seventy-three HIV-infected pregnant women were enrolled. Maternal nevirapine (NVP, n=14) mean $C_{\text{trough}}$ was $3629\pm956$ ng/mL with a mean C:M ratio of 0.68±0.1 and amniotic fluid level of 1257 ng/mL obtained from one sample; maternal nelfinavir (NFV, n=7) $C_{\text{trough}}$ was $837\pm673$ ng/mL with a mean C:M ratio of 0.58±0.18; maternal atazanavir (ATV, n=8) $C_{\text{trough}}$ was $1309\pm609$ ng/mL with a mean C:M ratio of 0.20±0.17 and mean amniotic fluid level of 286±47 ng/mL; maternal saquinavir (SQV, n=2) $C_{\text{trough}}$ was $903\pm137$ ng/mL with a mean C:M ratio of 0.13±0.03; maternal fosanprenavir (FPV, n=6) $C_{\text{trough}}$ was $696\pm401$ ng/mL with a mean C:M ratio of 0.18 ±0.09 and mean amniotic fluid level of 468±58 ng/mL; maternal lopinavir (LPV, n=31) $C_{\text{trough}}$ was $4113\pm2465$ ng/mL with a mean C:M ratio of 0.1±0.2 and mean amniotic fluid level of 198±125 ng/mL; maternal darunavir (DRV, n=5) $C_{\text{trough}}$ was $2014\pm1549$ ng/mL with a mean C:M ratio of 0.12±0.04 and mean amniotic fluid level of 403±437 ng/mL. $C_{\text{trough}} < MEC$ was reported in 19% (n=14) of women. ATV, DRV and FPV were more concentrated in amniotic fluid than in cord blood. All children were HIV negative, no birth defects were reported. The observed prevalence rate of neonatal low birth weight (LBW, <2500g) and preterm delivery (PTD, <37 week) was 22% (n=16) and 17.8 % (n=13), respectively. All women treated during pregnancy only for prevention of HIV vertical transmission maintained an immunological set-point at follow-up above the nadir CD4 cell count. $C_{\text{trough}}$ below recommended drug $C_{\text{min}}$ was not significantly associated to virological failure during follow-up (p=0.01).

**Conclusions:** Measurement of antiretroviral exposure in different compartments during pregnancy may be needed to identify sub- or supra-therapeutic drug exposure. Further, larger study population data on PK, safety and maternal viro-immunological are warranted to assist in selecting optimal drug regimens and to justify implementation of antiretroviral dose adjustment during pregnancy.

**No conflict of interest**

**Abstract: P_18**

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

A comparison of the pharmacokinetics of Raltegravir during pregnancy and post-partum

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**Introduction:** It is important to achieve effective concentrations of antiretroviral drugs in the blood to prevent treatment failure and the development of resistance. During pregnancy, physiological changes take place, influencing the pharmacokinetics of medicines. In most cases, the net effect will be a decreased exposure during pregnancy. Only very limited data are available about the pharmacokinetic behaviour of raltegravir during pregnancy and whether the drug passes the placenta. In 2008, a European network was established to study the pharmacokinetics of
newly developed antiretroviral drugs during pregnancy (PANNA). We present preliminary data on third trimester exposure to raltegravir.

**Material & Methods**: Patients treated with raltegravir (400mg BID) during pregnancy were screened and a 12h pharmacokinetic curve ($t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12h$) after supervised intake of 400mg raltegravir after a standardised breakfast took place in the third trimester and at least 2 weeks post-partum. Where possible a cord blood sample and matching maternal blood sample were taken at delivery. Safety and antiviral efficacy were evaluated. Raltegravir plasma concentrations were determined with a validated HPLC method with fluorescence detection and an LLOQ of 0.014 mg/L. Pharmacokinetic parameters were calculated with WinNonlin 5.2.

**Results**: Raltegravir plasma concentrations are available from 5 patients. The results are presented as medians (range). $\text{AUC}_{0-12h} (\text{mg}\cdot\text{h}/\text{L})$ was 10.3 (1.9-28.3) in the 3rd trimester and 7.4 (3.3-16.0) post-partum. $\text{C}_{\text{max}} (\text{mg}/\text{L})$ was 1.13 (0.38-9.67) in the 3rd trimester and 1.78 (0.78-4.03) post-partum. $\text{C}_{12h} (\text{mg}/\text{L})$ was 0.10 (0.02-0.33) in the 3rd trimester and 0.10 (0.05-0.23) post-partum. Ratios of PK parameters 3rd trimester/post-partum (median (range)) were: 1.50 (0.66-1.77) for $\text{AUC}_{0-12h}$; 1.53 (0.44-2.40) for $\text{C}_{\text{max}}$ and 1.76 (1.46-2.33) for $\text{C}_{12h}$.

The ratio of cord blood / maternal plasma raltegravir concentrations, determined in two patients, was 1.02 and 1.16 respectively. All children were HIV uninfected, no birth defects were reported.

**Conclusions**: In this small population (n=5) exposure to raltegravir was no lower during pregnancy (third trimester) than post-partum. This is in contrast to a number of other antiretroviral agents, especially protease inhibitors. Raltegravir efficiently crosses the placenta. These results need to be confirmed in a larger group of patients.

Financial relationship(s): The PANNA project gets a research grant from Merck.
performed at baseline and at 12 and 24 weeks.

Results: Twelve children were enrolled. Median (range) age was 13.1 (9.3-17.7) yrs, weight 40.8 (26.8-50.3) kg, CD4 cell count was 699 (456-1,239) cells/mm³, CD4 percentage 23 (16-31) %. Six children were concomitantly receiving efavirenz (EFV). Eleven children completed both PK evaluations.

For children receiving 2xNRTIs plus LPV/r twice daily the median LPV dose was 270 (255-283) mg/m² and the LPV AUC₀₋₁₂h, Cmax and C₁₂h were 86.1 (62.4-100.4) mcg.hr/mL, 8.8 (7.4-9.9) mcg/mL and 4.2 (2.0-6.5) mcg/mL, respectively; and after switching to LPV/r once daily the LPV dose was 533 (514-569) mg/m², AUC₀₋₂₄h, Cmax and C₄₈h were 199 (95-228) mcg.hr/mL, 12.1 (8.5-15.0) mcg/mL and 3.9 (0.2-4.2) mcg/mL, respectively. For those children receiving LPV/r twice daily coadministered with EFV, the median LPV dose was 303 (273-338) mg/m² and the LPV AUC₀₋₁₂h, Cmax and C₁₂h were 84.0 (62.0-94.5) mcg.hr/mL, 10.3 (9.5-12.9) mcg/mL and 3.1 (1.2-3.4) mcg/mL, respectively; and after switching to LPV/r once daily the LPV dose was 612 (538-645) mg/m², and the LPV AUC₀₋₂₄h, Cmax and C₄₈h were 154 (145-182) mcg.hr/mL 13.5 (11.4-15.6) mcg/mL and 0.17 (0.08-0.43) mcg/mL, respectively. Geometric mean ratio (90% CI) of LPV AUC QD/BID was 1.01 (0.83-1.22). With LPV/r once daily, the efavirenz AUC₀₋₂₄h, Cmax and C₄₈h were 62.6 (36.2-197.2) mcg.hr/mL, 4.1 (3.1-10.8) mcg/mL and 1.7 (0.9-6.0) mcg/mL, respectively.

While receiving LPV/r twice daily all children had a LPV C₁₂h >1.0 mcg/mL; however, while receiving LPV/r once daily 4/5 and 0/6 children had a LPV C₁₂h >1.0 mcg/mL when administered with and without EFV, respectively. Children with a LPV C₂₄h <1.0 mcg/mL had a 20-30% dose increase after 12 weeks. All children maintained a HIV-1 VL <40 copies/mL after 24 weeks of once daily LPV/r (n=11). No adverse events related to the LPV/r once daily dosing schedule were reported.

Conclusion: LPV/r exposure was comparable between once and twice daily administration, with and without EFV; however, with concomitant EFV use LPV/r once daily had significantly lower trough concentrations. Short-term virologic suppression was maintained with once daily LPV/r dosing.

No conflict of interest

Abstract: P_20

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Atazanavir dosing conversion and pharmacokinetics in HIV-infected children switching from atazanavir powder to capsules

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Introduction: Children with HIV may advance from taking liquid or powder formulations of a drug to solid formulations as they become better able to swallow tablets and capsules. However, differences may exist in antiretroviral pharmacokinetics and thus dosing requirements between drug formulations. The objective of this work is to describe the dosing conversion and atazanavir pharmacokinetics in children who had a formulation change from atazanavir...
powder to capsules in IMPAACT study P1020A.

**Material & Methods:** P1020A was an open label, multicenter study of once daily atazanavir and atazanavir/ritonavir pharmacokinetics, dosing, and safety in children 91 days to 21 years in the US and South Africa. Two formulations of atazanavir, an orange-vanilla flavored powder and capsules, were evaluated in this study. Children underwent intensive pharmacokinetic sampling 7 days and 56 weeks after starting atazanavir or atazanavir/ritonavir-based antiretroviral regimens and 2 weeks following any pharmacokinetic-guided dose adjustments. Children older than 2 years receiving atazanavir powder could change to capsules if they had a week 56 atazanavir area under the concentration curve from 0-24 hours (AUC0-24) between 30-90 mcg*hr/mL. A 24-hour intensive pharmacokinetic visit was conducted 2 weeks following the formulation change.

**Results:** In comparing day 7 atazanavir pharmacokinetics in children of similar age who received powder vs. capsules, the powder was found to be 40% less bioavailable at the same BSA-based dose, thus powder doses were multiplied by 0.6 and then rounded to the nearest 50 mg to arrive at the new capsule dose. 11 children converted from powder to capsules after a median (range) 232 (136-392) weeks on study. In the 8 children on atazanavir/ritonavir, median (range) age, BSA, and capsule dose were 9.2 (6-14.5) years, 1.11 (0.79-1.21) m², and 200 (100-300) mg, respectively. Two weeks following the change in formulation, median (range) atazanavir AUC0-24, concentration at 24 hours post dose (C24), and maximum concentration (Cmax) were 40.7 (24.1-82.6) mcg*hr/mL, 454 (254-1946) ng/mL, and 4440 (2464-8666) ng/mL, respectively. The three children on unboosted atazanavir were 8, 9, and 14.5 years old and had BSAs of 0.85, 1.33, and 1.52 m², respectively. On capsule doses of 300, 700, and 600 mg, respectively, atazanavir AUC0-24 were 2.5, 62.9, and 48.6 mcg*hr/mL, C24 were <20, 540, and 334 ng/mL, and Cmax were 321, 8379, and 4465 ng/mL, respectively. Direct comparisons between powder and capsule pharmacokinetics were not performed since a minimum of 2.6 years had passed since the last intensive profile before the formulation change. 10/11 children were virologically suppressed at least 2 months following the formulation change. One subject had detectable viremia prior to the formulation change, but suppressed 7 months later.

**Conclusions:** Most children (and all of those atazanavir/ritonavir) who switched from atazanavir powder to capsules had atazanavir AUC0-24 greater than 20 mcg*hr/mL and C24 greater than 150 ng/mL. There are insufficient data to provide recommendations about conversion of unboosted atazanavir. While additional study is needed, these data suggest children greater than 2 years who are virologically suppressed on atazanavir/ritonavir powder may be converted to atazanavir capsules by multiplying the powder dose by 0.6.

No conflict of interest

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**Abstract: P_21**

**Pharmacogenetics**

**No influence of CYP3A5 and ABCB1 polymorphisms on darunavir and ritonavir pharmacokinetics in HIV-negative Caucasian volunteers**

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**Background:** Darunavir (DRV) is a substrate for CYP3A and P-glycoprotein (ABCB1). Ritonavir (r) is both a substrate and inhibitor of CYP3A and P-glycoprotein. The objective of this retrospective
investigation was to determine if CYP3A5 and ABCB1 polymorphisms were associated with variability in DRV/r pharmacokinetics (PK) in healthy volunteers.

Materials & Methods: The study included 23 HIV-negative Caucasian volunteers who had previously participated in a pravastatin/DRV/r drug-drug interaction study. Participants received pravastatin 40 mg once daily on days 1-4, a washout on days 5-11, DRV/r 600/100 mg twice daily on days 12-18, with pravastatin 40 mg once daily added back on days 15-18. Blood was collected over 12 hours after the morning dose of DRV/r on day 18. Stored human genomic DNA samples were genotyped for CYP3A5 *3, *6, *7 and ABCB1 1236 C>T, 2677 G>T/A, and 3435 C>T polymorphisms. Genetically-determined CYP3A5 expressor status was defined as: “expressor” (at least one copy of the wild-type *1 allele) or “non-expressor” (*3/*3 or *6/*6 genotypes). ABCB1 haplotypes were computationally assigned. DRV/r plasma concentrations were determined by HPLC/UV and PK parameters were determined using non-compartmental methods. PK parameters were compared between CYP3A5 expressors versus non-expressors using unpaired t tests, and between ABCB1 1236T/2677T/3435T (TTT) haplotype groups (i.e., 0 versus 1 versus 2 copies of the TTT haplotype) using ANOVA.

Results: The study population consisted of 13 women and 10 men [age (mean ± SD) = 38 ± 11 years; weight (mean ± SD) = 72.5 ± 12.1 kg]. Genetic make-ups included: n=5 CYP3A5 expressors, n=18 CYP3A5 non-expressors, and n=6, n=12, and n=5 subjects with 0, 1, or 2 copies, respectively, of the ABCB1 TTT haplotype. DRV weight-adjusted oral clearance (CL/kg) did not differ significantly between CYP3A5 expressors versus non-expressors (0.157 ± 0.039 L/hr/kg versus 0.156 ± 0.049 L/hr/kg; p=0.84) or by number of copies of the ABCB1 TTT haplotype (0 copies=0.131 ± 0.027 L/hr/kg; 1 copy=0.157 ± 0.045 L/hr/kg; 2 copies=0.174 ± 0.058 L/hr/kg; overall p=0.38). No other DRV PK parameters (AUC$_{max}$, $C_{max}$, $C_{12}$) nor ritonavir PK parameters (CL/kg, AUC$_{taut}$, $C_{max}$, or $C_{12}$) differed significantly by CYP3A5 expressor status, or by the number of copies of the ABCB1 TTT haplotype.

Conclusions: These data suggest that CYP3A5 expressor status and the number of copies of the ABCB1 TTT haplotype do not influence DRV/r PK in the presence of pravastatin in HIV-negative Caucasian volunteers. However, given the small sample size, these data merit further study in larger cohorts.

Financial relationship(s): Grant from Tibotec Therapeutics.

Abstract: P_22

Pharmacogenetics

Pharmacogenetics of low plasma Efavirenz (EFV) concentrations in AIDS Clinical Trials Group (ACTG) studies: Analysis NWCS 301

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Introduction: Single nucleotide polymorphisms (SNPs) in CYP2B6 (516T and 983C alleles) predict increased plasma concentrations of EFV (cEFV). Data are scant regarding genetic predictors of low cEFV. We used a large clinical trials cohort to characterize associations between low cEFV and SNPs in CYP2B6, selected other genes, and targeted SNPs implicated in recent studies (rs36118214, rs1872121 and rs12721649).

Materials & Methods: Analyses included patients with ≥1 timed cEFV during participation in randomized ACTG studies.
Each cEFV was assigned a percentile (%-ile) rank using simulated cEFV-time curves. We excluded values >24 hrs post-dose or <2 weeks after initiating EFV, and patients with exactly 2 cEFV values if %-iles differed by >50%. An estimated C24h value was derived for each patient based on their median %-ile. We defined low C24h as the bottom 25th %-ile (<1025 ng/mL). Genotyping for 73 SNPs in CYP2B6 (47), CYP2A6 (21), CYP3A4 (1), CYP3A5 (1) and ABCB1 (3) was by MassARRAY iPLEX Gold. Each SNP was tested for association with low C24h in univariate analyses adjusted for age and body mass index. Contrast tests assessed for dominant and recessive effects. All SNPs with P<0.05 (adjusted for false discovery rate) were tested for independent associations by stepwise selection logistic regression. Analyses were performed separately in whites, blacks, and Hispanics.

**Results:** A total of 1150 EFV recipients who were genotyped (573 white, 353 black, 224 Hispanic) had cEFV data available and met inclusion criteria. These evaluable patients represented 10 ACTG studies, including A5202 (556), ACTG384 (293) and A5095 (153). Univariate analyses identified low C24h associations with 29 SNPs, many in strong linkage disequilibrium (LD). By multivariate analyses, after controlling for CYP2B6 516G>T, SNPs in CYP2B6 remained associated with low C24h (rs1987236 in whites, Odds Ratio [95% confidence interval] 3.7 [2.2-6.2], P<0.0001; rs2099361 in Hispanics, 4.5, [2.1-9.4], P<0.0001). These 2 SNPs are in LD at r2>0.65. In blacks, only CYP2B6 516G and 983T alleles were independently associated with low C24h. No associations were seen with rs36118214, rs1872121 or rs12721649 (nominal P>0.1).

**Conclusions:** In whites and Hispanics, CYP2B6 SNPs were associated with low EFV C24h independent of CYP2B6 516G>T. We do not yet know if these represent CYP2B6*4 haplotypes. In blacks, no SNPs other than 516G and 983T alleles were independently associated with low EFV C24h.

**Financial relationship(s):** David Haas has received research grants from Boehringer Ingelheim, Gilead Sciences, and Merck. He is been a consultant to Boehringer Ingelheim.

**Abstract: P_23**

**Pharmacogenetics, pharmacokinetics, and pharmacodynamics (PG/PK/PD) of central nervous system effects with single-dose efavirenz**

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**Background:** Efavirenz (EFV), an extensively prescribed antiretroviral, often causes central nervous system (CNS) side effects during initial dosing. Increased plasma EFV exposure is associated with increased CNS adverse events, and CYP2B6 variants that are frequent in populations of African descent (516G>T and 983T>C) predict increased plasma EFV exposure. However, relationships between CYP2B6 genotype and CNS adverse events have been inconsistent. For example, in a recent report CYP2B6 516/983 genotype predicted graded CNS adverse events in whites but not in blacks (J Inf Dis 202:717, 2010). Such inconsistencies may reflect incomplete understanding of PG/PK/PD relationships. To better define the relationships between EFV concentrations, CYP2B6 genotype and CNS effects we performed serial evaluations following EFV administration.

**Materials & Methods:** A single 600 mg dose of EFV was administered in the morning to 34 healthy, HIV-negative African Americans (10 extensive, 17 rapid, and 7 slow metabolizer CYP2B6 516/983 genotypes). Plasma EFV concentrations were determined 0.5, 1, 2, 4, 6, 8, 12 and 24 hours post-dose (PG/PK findings previously reported in J Inf Dis 198:972, 2009). Neuropsychometric (NP) tests [dominant and non-dominant hand grooved pegboard
(GPB\textsubscript{D} and GPB\textsubscript{ND}, respectively), symbol digit matching (SDM), and drowsiness visual analogue scale (VAS)] were administered pre-dose and 0, 1, 2, 3, 4 and 6 hours post-dose. All NP tests were corrected for baseline responses. A 19-item EFV CNS symptom questionnaire was completed 6 hours post-dose to capture symptoms at or before 6 hours, and a total score for CNS symptoms calculated. Associations between CYP2B6 genotype, PK parameters, NP test results, and EFV symptom scores were assessed by multivariable regression analysis, adjusting for BMI, gender and age.

Results: Maximum concentration (C\textsubscript{max}) occurred at a median of 2.6 hrs (T\textsubscript{max}). Higher C\textsubscript{max} was associated with worse GPB\textsubscript{ND} performance at 1 hr (p=0.027), 2 hr (p=0.051), and 4 hr (p=0.030), and less VAS drowsiness at 6 hr (p=0.033). Shorter time to reach C\textsubscript{max} (i.e. T\textsubscript{max}) correlated with worse GPB\textsubscript{ND} performance at 1 hr (p=0.007) but not at later times. CYP2B6 516/983 genotype predicted EFV clearance (p=0.0027) and AUC\textsubscript{0-48h} (p=0.033), but not C\textsubscript{max} (p=0.37). CYP2B6 516/983 genotype tended to predict worse GPB\textsubscript{ND} performance at 4 hours (p=0.066) and 6 hours (p=0.070) but not at earlier times. Neither CYP2B6 genotype nor PK correlated with other NP test results or EFV symptom questionnaire scores.

Conclusions: PG/PK/PD relationships for CNS effects of EFV are complex and time-dependent. C\textsubscript{max}, but not genotype, was associated with CNS effects at earlier timepoints. This reflects the lack of association between C\textsubscript{max} and genotype. In contrast, genotype was associated with CNS effects at later timepoints, perhaps reflecting the association of genotype with delayed clearance. These finding helps to explain inconsistent associations reported between genotype and CNS side effects. GPB\textsubscript{ND}, an objective measure of fine motor speed that requires high-level motor processing, may be more sensitive to EFV CNS effects than other less objective measures. These findings will inform the design of future EFV PG/PK/PD studies, including optimal measurement tools and sampling times.

No conflict of interest

Abstract: P_24

Pharmacogenetics

In vitro-in vivo extrapolation of CYP2B6 genotype-based efavirenz dose reduction.

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Background: The pharmacokinetics of efavirenz (EFV) is characterized by large inter-patient variability. CYP2B6 is the main enzyme responsible for EFV metabolism. CYP2B6 polymorphisms can markedly affect EFV exposure, with 516G>T considered to be the main genetic variant. In vitro-in vivo extrapolation (IVIVE) can be used to predict drug absorption, distribution, clearance, and metabolic drug-drug interactions from in vitro data. The aim of this study was to develop an IVIVE model to simulate EFV pharmacokinetics in virtual human subjects, which could then be used to investigate dose reduction strategies driven by 516G>T genotype.

Methods: In vitro data describing the physiochemical properties, absorption and metabolism of EFV and the effect of CYP2B6 516 genotype on CYP2B6 protein expression in liver tissue were obtained from published literature*. These data were used to simulate EFV (600mg once daily) pharmacokinetics in a virtual population of 100 patients using Simcyp Population-based Simulator. Simulated pharmacokinetic parameters, such as C\textsubscript{trough}, C\textsubscript{max}, AUC, and the impact of 516G>T genotype were compared with observed values available in the literature*. Two dosing strategies were then simulated in 100 virtual patients for each genotype. Firstly, dose reduction to 400mg once daily and secondly a regimen where subjects received 600 mg once daily for 5 days followed by 2 days without EFV therapy (5 days on and 2 days off; FOTO study) were simulated.
Results: Simulated pharmacokinetic variables at steady state (mean ± SD), C_{trough} (2424 ± 2247 ng/ml), C_{max} (4112 ± 2484 ng/ml), AUC (80819 ± 58807 ng/mL.h) were in agreement with previously published pharmacokinetic data* (mean ± SD) C_{trough} (1764 ± 1008 ng/ml), C_{max} (4063 ± 1165 ng/ml), AUC (57960 ± 22995 ng/mL.h). The effect of 516G>T on simulated EFV clearance (GT = -24% and TT = -58%) was comparable to previous published population pharmacokinetics studies (GT = -36%, TT = -66%)*. For a dose reduction of 400 mg once daily, the mean simulated C_{trough} was 1380 ng/ml (90% CI, 360-2946) for GG homozygotes, 1391 ng/ml (90% CI, 55-1798) for heterozygotes and 2837 ng/ml (90% CI, 392-1798) for TT homozygotes. Simulation of FOTO-like administration resulted in a mean simulated C_{trough} at the end of two days without EFV administration of 610 ng/ml (90% CI, 17-1798) for GG homozygotes, 1391 ng/ml (90% CI, 55-1798) for heterozygotes and 2837 ng/ml (90% CI, 392-1798) for TT homozygotes.

Discussion: The developed IVIVE model predicted the in vivo pharmacokinetics of EFV in individuals with different CYP2B6 genotypes. Inclusion of other genetic variants and a more detailed description of absorption, metabolism and induction of enzyme expression could improve the accuracy of IVIVE models. This simulation approach can be used to investigate clinically relevant ‘what-if’ questions, such as whether genotype-based dose reduction strategies are feasible to manage inter individual differences in exposure. This information can now be used to design prospective clinical studies.

*All published literature used to develop the model is available on request from the authors.

No conflict of interest

Abstract: P_25

Pharmacogenetics

Single-nucleotide polymorphism PXR 7635G>A influences plasma concentrations of Efavirenz in CYP2B6 516G>T carriers

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Background: Efavirenz (EFV) is mainly metabolised by cytochrome P450 2B6 (CYP2B6) and diminished-function alleles in the CYP2B6 gene significantly affect EFV pharmacokinetics. Some studies indicate that neuropsychiatric side effects are associated with high plasma concentrations, particularly in the first weeks of treatment, and 4000 ng/mL has been suggested as a toxicity cut-off. Nuclear receptor PXR is one of the main regulator of CYP450s expression and PXR 7635A>G SNP has been recently associated with an alteration of CYP2B6 activity. The objective of our study was to investigate the effect of PXR 7635A>G on EFV plasma concentrations in HIV infected patients.

Materials and Methods: Patients of our centre administered with 2 N(t)RTIs plus EFV since at least 3 months were included in this study. Sampling was performed after written informed consent which was obtained in accordance with local ethics committee indications. Main inclusion criteria were no concomitant interacting drugs, no hepatic or renal function impairment, self-reported adherence > 95%. Plasma concentrations were measured in samples collected 9-15 h after dosing by a validated HPLC-PDA method. Genotyping was conducted by RT-PCR based allelic discrimination using standard methodology. Statistical analysis was conducted by Mann Whitney or Spearman Rank to assess the effects of weight, age, gender, and genotype on EFV concentrations. Results for
continuous data were expressed as median with interquartile range (IQR).

**Results:** 176 patients were included providing 270 samples for analysis, with a mean number of plasma measurement of 1.53. No associations between patient demographics (weight, age, gender) or NRTIs co-administration with EFV concentrations were observed. All the patients were CYP2B6 983 wild-type. EFV concentrations were significantly associated with CYP2B6 516 genotype (GG, n=100; GT=65, TT=11) [2294 ng/mL (1718-3034) vs 3121 ng/mL (2383-3907) vs 6004 ng/mL (4078-9185), p < 0.001]. For PXR 7635A>G, no differences were observed (AA, n=48; AG=95, GG=33) [2959 ng/mL (1914-4572) vs 2657 ng/mL (2116-3482) vs 2461 ng/mL (1906-3137), p = 0.308]. However, in subjects carrying 516 T allele PXR 7635A>G genotype was associated with significant lower plasmatic concentrations (AA, n=23; AG=36, GG=17) [4078 ng/mL (3146-6457) vs 3031 ng/mL (2372-4089) vs 2562 ng/mL (2188-3378), p = 0.004]. Moreover, efavirenz exposure in 2B6 516GT/TT-PXR 7635AA patients were more frequently above to the toxicity cut-off considered (4000 ng/mL) respect 2B6 516GT/TT-PXR 7635AG/GG patients (χ² = 8.34; p = 0.004).

**Conclusions:** Our findings confirm the effect of CYP2B6 516G>T and indicate a significant influence of PXR 7635A>G in 516T carriers on efavirenz plasma concentrations. These data suggest an influence of PXR in the regulation of CYP2B6 and consequently of EFV metabolism for 516T carriers. Although further studies are now required to confirm these associations, characterization of PXR polymorphisms could help to identify patients with a higher risk of reaching potential toxic concentrations (>4000 ng/mL).

No conflict of interest

**Abstract: P-26**

**Pharmacogenetics**

**Pharmacogenomics of Plasma Nevirapine Clearance among HIV-infected Cambodians**

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**Introduction:** Nevirapine (NVP) is metabolized by CYP2B6 and CYP3A. Expression of these genes is regulated by NR1I2 (PXR), and functional single nucleotide polymorphisms (SNPs) of these genes vary in frequency among populations. In a previous study, focused genotyping of CYP2B6 516G>T in HIV-infected Cambodians in the ANRS12154 study showed its association with steady-state NVP clearance (Cl/F). The present study more thoroughly investigated CYP2B6 and other genes to better understand the genetics of NVP Cl/F.

**Material & Methods:** Analyses included patients from the Phnom Penh Esther cohort who consented to genetic testing. All received standard dose NVP plus two nucleoside analogs. Mean individual NVP Cl/F estimates were derived from a population model developed on month 18 and 36 NVP concentrations in ANRS12154. Genotyping was with MassARRAY iPLEX Gold. Association tests were performed using mean individual Cl/F as the phenotype. SNP associations were identified based on linear regressions on minor allele dosage. A FDR correction was used. Analyses were performed in PLINK, and haplotype blocks defined with the D’ confidence intervals method in Haploview.
Results: Genotypes were obtained in 129 patients. Patient characteristics at months 18 and 36, respectively, were (mean [range]): weight 53.2 kg [25-79] and 56.8 kg [39-82]; age 36 years [19-57] and 37 years [21-59]). Estimated NVP CI/F was 2.72 L/h [1.06-0.781]. Of 196 SNPs assayed in CYP2B6, CYP3A4, CYP3A5, NR1I2 (PXR) and ABCB1, 126 were polymorphic in this population. Minor allele frequencies of CYP2B6 516G>T and CYP3A5 6986A>G (loss-of-function variant) were 0.34 and 0.37, respectively. In univariate analyses corrected for multiple comparisons, 17 SNPs in CYP2B6 and 1 in CYP3A4 as well as 6 haplotypes in CYP2B6 were associated with CI/F (range of P-values 0.03 to 4.6x10^{−5}). In multivariate analyses conditioned on 516G>T, no other SNP was independently associated to CI/F. CYP2B6 516 TT homozygosity predicted a 36% reduction in CI/F. The 516T allele represented a single large (≥32.9 kb) haplotype block starting ≥8.2 kb 3’ of CYP2B6 and spanning the first 8 (of 9) exons.

Conclusions: Among HIV-infected Cambodians the strong association between CYP2B6 516G>T and decreased steady-state NVP CI/F may represent the effect of an extended CYP2B6 haplotype block that encompasses promoter regions and multiple exons. Individual SNPs beyond this haplotype block did not independently predict NVP CI/F.

No conflict of interest

Abstract: P_27

Pharmacogenetics

Pharmacogenetics-based population pharmacokinetic analysis of Lopinavir in HIV-infected individuals

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Background: Wide interindividual variability in lopinavir exposure is observed in HIV-infected individuals. Lopinavir is a known substrate for ABCB1 and ABCC2 transporters that are transcriptionally regulated by PXR and CAR. Recently, lopinavir was also shown to be a substrate for SLCO1A2, SLCO1B1 and SLCO1B3. Furthermore, a relationship between some SLCO1B1 single nucleotide polymorphisms (SNPs) and lopinavir pharmacokinetics was previously described. The aim of this study was to screen SNPs across the entire SLCO family for their potential impact on lopinavir pharmacokinetics using a population pharmacokinetic (popPK) analysis.

Methods: A popPK was performed with 413 plasma samples from 50 Caucasian individuals receiving a lopinavir/ritonavir containing regimen for at least 4 weeks, had DNA available and were able to provide informed consent. Lopinavir concentrations in plasma were determined by high performance liquid chromatography. Genotyping for SLCO, PXR, CAR, ABCB1 and ABCC2 (total of 148 SNPs) was performed using a combination of sequenom mass array and real-time PCR based allelic discrimination. The effect of SNPs on the PK parameters of lopinavir was first explored using analysis of the variance with log-transformed data. Those SNPs related to changes in lopinavir PK parameters were then further evaluated using non-linear mixed effects modelling (NONMEM vVI).

Results: Patient demographics were: 76% male, mean age 45.2 ± 7.9 years and mean body weight 68.4 ± 9.8 kg. Lopinavir plasma concentrations ranged between 234 and 20,917 ng/mL. A one compartment model with first-order absorption and elimination best described the data. Population lopinavir clearance (CL) was 4.24 L/h with an interindividual variability (IVI) of 28%. The volume of distribution was 98.1 L (IVI 52%)
and the absorption rate constant (Ka) was 0.98 h\(^{-1}\). Two SNPs, rs4149034 (SLCO1B1) and rs5488 (SLCO1A2) explained 21% of the IIV on CL. Lopinavir CL was 4.2 L/h in patients carrying rs4149034 GG or GA alleles compared with 6.6 L/h in patients with AA allele. In addition, lopinavir CL was 4.5 L/h in patients carrying rs5488 TT allele compared with 3.6 L/h in patients with AA or AT alleles.

**Conclusion:** These data show an association between SLCO1B1 and SLCO1A2 polymorphisms and lopinavir CL. This association is likely to be mediated by altered uptake of lopinavir into hepatocytes. Further studies with larger sample sizes aimed at confirming these associations are now warranted.

No conflict of interest

**Abstract: P_28**

**Pharmacogenetics**

**Human genetic polymorphisms and virologic response to protease inhibitor-containing regimens in African Americans and European Americans**

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**Introduction:** A previous analysis by our group found that African Americans (AA) were significantly less likely than European Americans (EA) to achieve viral suppression with protease inhibitor (PI)-based highly active antiretroviral therapy (HAART). We evaluated whether different frequencies of single nucleotide polymorphisms (SNPs) in selected genes relevant to PI disposition could explain, at least in part, this population difference in virologic response to PI-based HAART.

**Materials and Methods:** Analyses included 735 patients (377 EA and 358 AA) enrolled in a longitudinal US military cohort who initiated PI-containing HAART and had viral load (VL) data at HAART initiation and 6 months later. We genotyped 168 SNPs in CYP3A4 (44), NR112 (PXR, 50), ABCB1 (71), CYP3A5 (1), CYP2C19 (1), and SLCO1B1 (1) using MassARRAY iPLEX Gold and Taqman. Allele frequencies were calculated by ethnicity and compared using Pearson \(\chi^2\) test. Logistic regression explored associations between SNPs, haplotypes, and virologic suppression (VS, defined as VL < 400 c/ml) after adjusting for age, sex, baseline VL and CD4, prior antiretroviral use, and year of HAART initiation. Haplotype blocks were estimated using 95% confidence bounds on D'. Pairwise linkage disequilibrium was calculated for SNPs within 200kb and logistic regression was applied in PLINK to perform the haplotype-based association analysis. Analyses were stratified by population and PI use. Using a Bonferroni correction, \(P < 3 \times 10^{-4}\) was considered significant.

**Results:** Of the 735 patients, 38% were on indinavir (IDV) containing regimens, 29% nelfinavir (NFV) containing regimens, and 33% other PIs. Allelic frequencies of 61 SNPs (36%) differed significantly \((P<3\times10^{-4})\) between AA and EA. In the multivariate analyses, no SNP or haplotype was significantly associated with VS at \(P<3\times10^{-4}\).

In exploratory analyses uncorrected for multiple comparisons \((P<0.05)\), VS in AA on IDV was associated with 7 SNPs (5 in PXR, 1 in ABCB1, 1 in CYP3A4) and with a haplotype in ABCB1; VS in AA on NFV was associated with 17 SNPs (5 in CYP3A4, 11 in ABCB1, 1 in CYP2C19); VS in EA on IDV was associated with 3 SNPs (1 each in CYP3A4, ABCB1, CYP3A5); and VS in EA on NFV was associated with 4 haplotypes (3 in ABCB1, 1 in CYP3A4).

**Conclusions:** In a cohort of AA and EA who initiated PI-containing HAART, no SNP or
haplotype in CYP3A4, NR1I2, ABCB1, CYP3A5, CYP2C19 or SLCO1B1 was associated with VS at P<3x10^{-4}. SNPs with trends (P<0.05) toward significance warrant replication in other patients.

No conflict of interest

Abstract: P_29

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Clinical pharmacology of complex regimen of antiretroviral therapy including Etravirine, Maraviroc and Raltegravir.

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Background: Guidelines suggest to treat HIV-experienced patients with at least two active drugs in order to obtain viral suppression and CD4 recovery. Innovative options were introduced in antiretroviral treatment. Most of these therapies involve Raltegravir, thanks to its excellent short-term tolerability and efficacy. The co-administration of Raltegravir, Etravirine and Maraviroc seemed to be a very interesting therapy, but pharmacokinetic and tolerability data are not available by now. The aim of this study was evaluating the Pk/Pd aspects of coadministration, the efficacy, toxicity and tolerability of this treatment.

Material & Methods: Eligible patients were HIV-1 infected patients over 18 years old and treated with at least one of the drugs mentioned above. Among the 59 enrolled patients, 30 were being treated with Raltegravir (Group 1) combined with other antiretrovirals and 29 with all three new drugs (Group 2). Three evaluations of C_{min} have been made for each patient: the average concentration has been calculated based on these evaluations. The samples were drawn 10-14 hours after the last dose administered and they were misured by means of an HPLC-MS/MS validated methods. Patient's parameters were evaluated at baseline, 24 weeks and 48 weeks.

Results: At weeks 24 and 48, CD4 cell counts were higher for Group 2 (166 cell/mm^3 vs 197 cell/mm^3 and 94 cell/mm^3 vs 225 cell/mm^3; p=0,020 and p=0,27; 3% vs 5,8%; p=0,05). Group 2 achieved viral suppression sooner (92% vs 82%; p>0,05 weeks 48). At week 48, an increase of the cholesterol level was observed in Group 1 (Tot Chol.: 23mg/dl vs 11 mg/dl; p0,008 and LDL 18,5 mg/dl vs 0,9 mg/dl; p=0,01). The increase of CD4 cells in patients treated with a Maraviroc-based therapy was nearly twice higher than in patients who had not been treated with that drug (189 cell/mm^3 vs 52 cell/mm^3 24 weeks p=0,034; 214 cell/mm^3 vs 27,2 cell/mm^3 48 weeks p=0,009). Levels of Maraviroc C_{trough} were significantly higher in Group 1 than in Group 2 (173,5 ng/ml vs 57 ng/ml; p=0,01).

Conclusion: The study showed that NNRTIs and PIs sparing regimens had a better short-term tolerability. Patients treated with Maraviroc experienced a significant CD4 cells increase. Even with a 600 mg dose of Maraviroc instead of 150 bd, coadministration of Maraviroc and Etravirine in Group 2 determined a decrease in Maraviroc concentration (Cmin) due to Etravirine's CYP3A4 inductive activity. This protease inhibitor and nucleoside analogue-sparing regimen showed sustained efficacy and tolerability. Further long-term studies are needed in order to evaluate if the drugs concentrations of the more recent ARVs are correlated with the therapeutic success and if a two drugs regimen instead of three would maintain the suppression and decrease the costs.

No conflict of interest
Abstract: P_30

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Pilot pharmacokinetic study of dual therapy with Raltegravir 400 mg BID and Darunavir/r 800/100 mg QD in HIV-1 infected patients

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Background: While 3-antiretroviral drug regimens remain standard of care for HIV-1 infected patients, nucleoside reverse transcriptase inhibitors (NRTIs)-sparing regimens are attractive options to avoid NRTIs associated toxicity and to provide a full active regimen in patients with some extent of NRTIs resistance. Raltegravir (RAL) and Darunavir (DRV) are potent “third drugs” and they provide a synergistic inhibition of 2 different steps in HIV replication. We hypothesized that RAL/DRV/r would be a well-tolerated and effective regimen for those patients who are failing NRTIs based regimens, due to poor tolerability, nucleoside toxicity or resistance. We explore plasma pharmacokinetics (PK) of RAL 400mg BID and DRV/r 800/100 mg QD in these patients.

Methods: This is a prospective, single center, open-label, fixed-sequence, single-arm PK study. 15 HIV-1 positive patients receiving a NRTIs based regimens were included. Treating physician decided a NRTI-sparing regimen which included DRV/r 800/100mg QD plus RAL 400mg BID. All patients were naïve to RAL and DRV and had no evidence of PI mutations. After at least 15 days on therapy, patients were admitted for a PK study. Blood samples were drawn before the mooring dose and 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours after. DRV and RAL plasma concentrations were analyzed by validated high performance liquid chromatography methods adapted to ultraviolet and fluorescence detectors, respectively. PK parameters were calculated using Win Nolin software version 4.1.

Results: 13 patients were males, median age 44 years, median body mass index 25.08 kg/m². Antirretroviral therapy was changed in 8 patients due to toxicities or side effects to NRTIs. 7 patients were changed due to virological failure to previous treatment. Geometric mean values for DRV were AUC_0-24: 69,280 ng.h/mL (95% CI: 59,580-86,960), C_trough: 1,330 ng/mL (95% CI: 1,110-1,760), C_max: 7630 ng/mL, (95% CI: 6740-9000), and t_1/2: 10.93h (95% CI: 9.20-14.05). Geometric mean values for RAL were AUC_0-12: 4,050 ng.h/mL, (95% CI: 3,220-6,540), C_trough: 80 ng/mL (95% CI: 60-160), C_max: 970 ng/mL (95% CI: 850-2,270), t_1/2 : 7.66 h, (95% CI: 4.82-14.70). No side effects including rash or lab abnormalities were described. At week 24 all patients had HIV-1 viral load below 37 copies/mL.

Conclusions: According to our study, dual therapy with RAL 400mg BID plus DRV/r 800/100mg QD had a favorable PK profile and the efficacy and tolerability were adequate.

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Abstract: P_31

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

No changes in atazanavir exposure when boosted with 100mg or 50mg of ritonavir in healthy volunteers.

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Background: There is a growing interest in evaluating whether protease inhibitors could be boosted with lower doses of ritonavir (RTV). The aim of this study was to evaluate the pharmacokinetics, tolerability and safety of 300mg of atazanavir (ATV) with ritonavir 100mg or 50mg, both once-daily, at steady-state.

Methods: Thirteen healthy adult men were included in this cross-over, single-blind, two-period study. Participants received once-daily witnessed doses of ATV (300mg) boosted with ritonavir 100mg (Treatment A) or 50mg (Treatment B) for 10 days. 15 day apart. ATV was administered as 300mg capsules and RTV as oral solution. ATV and RTV plasma concentrations were determined on day 10 prior to drugs administration and at 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24h after dosing. Gastrointestinal effects, lipid profile and billirrubin plasma levels were measured at the beginning and end of each period. Individual pharmacokinetic parameters (Cmax, Ctrough and AUC0-24) were calculated by a noncompartmental approach (WinNonlin), and log-transformed. Cmax and AUC0-24 were compared between treatments using an ANOVA and the 90% confidence intervals (CIs) of the ratio between treatments. Ctrough were compared between treatments by the Student t-test. Total-, LDL- and HDL-cholesterol, triglycerides and billirrubin plasma levels were compared between baseline and end-of-period by the Wilcoxon signed-rank test.

Results: Twelve participants, mean age 29 (range: 19-51) years completed the study. Medication was well tolerated, although one subject was excluded and replaced due to a non-drug related adverse event (local hand inflammation). RTV Cmax and AUC0-24 were lower after Treatment B than after Treatment A (Cmax: 0.75 vs 1.82mg/L, p<0.001; AUC0-24: 4.50 vs 12.54mg×h/L, p<0.001). Ctrough for RTV could not be calculated since all and the majority of the observations were bellow the limit of quantification after Treatment B and A, respectively. ATV concentrations vs time profiles were almost super-imposable and no differences were observed in ATV total systemic exposure when boosted with RTV 50 or 100mg (Cmax: 5.07 vs 5.19mg/L, p=0.98; AUC0-24: 47.09 vs 50.62mg×h/L, p=0.86). The 90% CIs of the ratio (TreatmentB/TreatmentA) was 82.38-122.14 for Cmax and 82.50-116.38 for AUC0-24. ATV Ctrough was above 0.15mg/L in all volunteers and no differences were found between treatments (Treatment B: 0.59 vs Treatment A: 0.79mg/L, p=0.132).

Compared with day 0, total- and LDL-cholesterol on day 10 increased 0.40mm/L (p=0.01) and 0.37mmol/L (p=0.003) in Treatment A, while there were no significant variations in Treatment B. No other significant differences in safety or tolerability were observed between treatments, although small increases in billirrubin were observed on day 10 after the two treatments.

Conclusions: In conclusion, atazanavir exposure was not affected by its co-administration with 100 or 50mg of ritonavir, in spite of a higher exposure to ritonavir when using a 100mg; however, the lower ritonavir dose was associated with a lower impact in the lipid profile.

No conflict of interest
Abstract: P_32

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Variability of Darunavir plasma concentrations and relationships with adherence and virological response in the MONOI-ANRS136 trial

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Introduction: MONOI is a prospective, open-label, non-inferiority, 96-week safety and efficacy trial in virologically suppressed patients on triple therapy who were randomized to DRV/r mono- or continuing a triple-drug DRV/r-containing regimen. Virologic failure was defined as 2 consecutive plasma HIV-RNA (pVL)>400c/mL by W48. PK analysis was performed at each visit to investigate relationship between trough plasma concentrations (Cpl) and adherence and virological response.

Material & Methods: 225 patients were randomized after 8 weeks run-in period with DRV/r triple therapy and switched to either DRV/r (600/100mg bid) monotherapy (n=113) or DRV/r + 2NRTI (n=112). Patient’s adherence to study-drug regimen was assessed by self-report questionnaires at D0, W4, W24 and W48. DRV and RTV Cpl were measured at steady-state at D0, W4, W8, W16, W24, W32, W40 and W48 using UPLC-MS/MS assay. Results are presented as median (IQR). Spearman correlation was estimated at each study visit. Fisher’s exact test and Wilcoxon rank sum test were used for discrete and continuous variables, respectively.

Results: Overall 1608 measures of both DRV and RTV Cpl were available for the 8 study visits. In the whole population, DRV and RTV Cpl were 2609ng/mL (1725-3769) and 345ng/ml (205-646), respectively. There was no significant difference between the 2 treatment arms. Overall, DRV and RTV Cpl were well correlated (Spearman correlation from 0.46 to 0.60). Between and within patients variability of DRV Cpl calculated on 8 study visits were 61% (60%-64%) and 64% (60%-65%) and 41% (31%-61%) and 43% (31%-58%) in mono- and tri-therapy arms, respectively. There was no significant association between DRV or RTV Cpl and the occurrence of pVL>50c/mL at each patient visit and no significant difference was observed between the 2 treatment arms. No statistical correlation was found between DRV Cpl and adherence at the 4 visits measuring adherence. However, at D0, 67% of patients with DRV Cpl<=550ng/ml declared at least one missing dose compared with 13% in patients with DRV Cpl>550ng/ml (p=0.02).

Conclusions: DRV Cpl was similar in the 2 studied arms. Adequate DRV Cpl was consistent with the good efficacy of this strategy in patients with suppressed pVL. Between and within variability of DRV Cpl were similar between arms suggesting the lack of impact of the TDF backbone. Finally we did not found any relationship between DRV Cpl and episodes of low level pVL and only a weak association with adherence levels.

No conflict of interest
Abstract: P_33

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Pharmacokinetics of reduced dose Darunavir/ritonavir in Asian HIV-1 infected adults

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Background: Darunavir/ritonavir (DRV/r) is an essential HIV drug for salvage regimen but it is expensive in resource limited settings (RLS). There is extensive evidence that Asians have higher protease inhibitor plasma concentrations than Caucasians while taking the same dose. It is currently unknown whether this is also true for DRV/r in Asian population. We therefore evaluated the pharmacokinetic (PK) profiles of reduced dosed DRV/r in well-suppressed HIV-1 infected Thai adults.

Material & Methods: Thai HIV-1 infected adults aged ≥ 18 years with HIV RNA < 50 copies/mL who were on DRV/r 600/100 mg twice daily (BID) as a part of their second line or salvage regimens for ≥ 4 weeks underwent 12-hour PK sampling before, and at 1, 2, 4, 6, 8, 10 and 12 hours post dosing. After 12-hour PK, DRV/r dose was reduced to DRV/r 600/100 mg once daily (QD) dose for another 4 weeks and then 24-hour PK was performed. Plasma concentrations were measured by validated HPLC method. PK parameters were calculated using WinNonlin software. Statistical analysis was carried out using Stata version 10. To accommodate both within-patient and between-patient variability, a repeated-measures generalized estimating equation/random effects model was used for comparing the PK parameters of the two dose groups.

Results: Twenty-one subjects were enrolled (67% male) with a median (IQR) age of 40 (37-44) years and median (IQR) body weight (BW) and BMI of 58.1 (53.5-61) kg and 21.5 (19.8-23.5) kg/m², respectively. The median duration of DRV/r use was 16 months. All subjects took tenofovir disoproxil fumarate (TDF) plus either lamivudine or zidovudine as a backbone. Mean (SD) values for DRV/r 600/100 mg BID were 46.9 (29.8) h.mg/L for AUC0-12, 6.8 (1.3) mg/L for Cmax and 2.2 (1.0) mg/L for Ctrough. For DRV/r 600/100 mg QD mean (SD) AUC0-24, Cmax, Ctrough were 62.49 (19.4) h.mg/L, 7.2 (2.1) mg/L and 0.9 (0.5) mg/L, respectively. None of the subjects on 600/100mg BID vs. 4 subjects(19%) on 600/100mg QD had Ctrough values below the protein-binding adjusted IC50 of PI-resistant virus (0.55 mg/L). In multivariate analysis, there was statistically non significant association of age, sex, BW, and RTV concentrations on AUC, Cmax, and Ctrough of DRV/r. Compared to Caucasian study data (n=14 for DRV/r 600/100 BID and n=7 for DRV/r 800/100 QD), the PK profiles of our subjects were comparable to those data. All subjects had HIV RNA <50 copies/mL at 1 months after low dose DRV/r and no any grade II-IV AEs reported.

Conclusions: Thai HIV-infected adult who were on standard DRV dosing with 100mg ritonavir boosting had adequate DRV AUC0-12, Cmax and Ctrough. Furthermore, the PK of DRV/r 600/100 mg QD from our subjects seem to be similar to those Caucasian on DRV/r 800/100 QD. The regimen was well tolerated. Our data suggest that Asian adults may have slightly higher DRV concentrations for once daily dose.

No conflict of interest
Abstract: P_34

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

The influence of tobacco smoking on Atazanavir pharmacokinetics

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Background: Conflicting data have been reported on the potential negative effects of tobacco use on atazanavir pharmacokinetics (Ma et al. 49th ICAAC, abstract H-231; Guilleni et al. 18th IAS Conference, WEPE0095). The consequence of reduced exposure to atazanavir could be virological failure and the development of resistance. If the negative effect of tobacco smoking on atazanavir concentrations were true, this would be another incentive to motivate patients to stop smoking. Both studies were hampered by a cross-sectional design, unobserved intake of atazanavir, measurement of only atazanavir C\textsubscript{min}, and no adjustment for potential confounders such as food intake, age, body weight, gender, race, etc. The objective of our study was to evaluate the impact of smoking behaviour on atazanavir pharmacokinetic parameters in subjects that previously participated in two of our studies.

Materials & Methods: Data were collected on healthy subjects taking either atazanavir 400mg QD or atazanavir/ritonavir 300/100mg QD, both with a standardized breakfast. Subjects participated in one of the following studies: ARRIVO (Burger et al. AAC 2006) or ELLA (Burger et al. CP&T 2008). Only data on atazanavir pharmacokinetics without interacting agent were used. Smoking was allowed up to a maximum of 10 cigarettes per day. Subject demographics, smoking behaviour and atazanavir pharmacokinetics (AUC, C\textsubscript{max}, C\textsubscript{min}) were extracted from the study databases. Comparison between smokers and non-smokers were made for each atazanavir dose for all study subjects combined. A subtherapeutic atazanavir C\textsubscript{min} was defined as < 0.12 mg/L. SPSS version 16.0 was used for statistical analyses.

Results: Atazanavir pharmacokinetic data were available from 68 subjects taking 400mg QD (18 smokers) and from 64 subjects taking 300/100mg QD (15 smokers). The median (+IQR) atazanavir AUC\textsubscript{0-24h}, C\textsubscript{max} and C\textsubscript{min} in non-smoking vs. smoking subjects taking atazanavir 400mg QD were 28.8 (22.4-35.6) vs. 27.3 (21.6-35.3) h.mg/L, 5.1 (4.3-6.4) vs. 5.4 (4.4-6.2) mg/L, and 0.17 (0.13-0.30) vs. 0.16 (0.10-0.26) mg/L, respectively. For atazanavir/ritonavir 300/100mg QD, the median (+IQR) atazanavir AUC\textsubscript{0-24h}, C\textsubscript{max} and C\textsubscript{min} in non-smoking vs. smoking subjects were 47.9 (39.3-53.7) vs. 40.4 (33.7-58.3) h.mg/L, 5.3 (4.4-6.2) vs. 5.4 (4.0-5.8) mg/L, and 0.72 (0.58-0.91) vs. 0.55 (0.37-0.95) mg/L, respectively. None of these differences were statistically significant (Mann-Whitney test; p>0.226). None of the patients on atazanavir/ritonavir had a subtherapeutic atazanavir C\textsubscript{min}. For atazanavir 400mg QD, this was the case in 7/50 non-smokers vs. 6/18 smokers (p=0.09; Fisher's Exact Test).

Conclusions: Moderate tobacco use (up to 10 cigarettes per day) was not associated with a significant difference in atazanavir pharmacokinetics in healthy volunteers taking either atazanavir 400mg QD or atazanavir/ritonavir 300/100mg QD.

No conflict of interest
Abstract: P_35

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Etravirine pharmacokinetics after switch from ETR twice daily to once daily regimen in treatment-experienced HIV-infected patients: MONETRA Sub-study

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Introduction: Etravirine (ETR) is a next-generation NNRTI designed to have a high genetic barrier to the development of resistance and also maintains an activity despite common NNRTI mutations. With a terminal half-life of 30-40 hours, ETR is a candidate for once daily (qd) dosing. Previous studies in healthy volunteers (C168 and C178) have demonstrated that the daily systemic exposure to ETR was similar for qd and bid administrations. MONETRA is a prospective, pilote and monocenter study to assess the safety and efficacy of a switch from ETR (200 mg bid) to ETR (400 mg qd) in virologically suppressed (<50 c/ml) and treatment stable for at least 6 months HIV-1-infected patients.

Objectives: Determination of ETR trough plasma concentrations and description of intra- and inter-patients variability before and after the switch (at D0) from bid to qd Regimen.

Material and Methods: ETR trough Plasma Concentrations (C12h and C24h) were determined using an UPLC-MS/MS method (Acquity UPLC®-Acquity TQD®) after samples extraction (LOQ<5mg/mL), 12 ± 2 and 24 ± 4 hours after the last drug intake, respectively. Blood Plasma was collected at Screening (W-4) and D0 (bid period) and at W4, W12, W24, W36 and W48 (qd period).

Results: 24 treatment experienced patients were enrolled. Median (range) patients characteristics were: age 50 yrs (34-64), 23 males, 14 yrs of previous treatment duration, 14 (3-22) antiretroviral drugs previously received (5 PI, 6 NRTI and 1 NNRTI), 50% at SIDA Stage, CD4=40 (1-454)/mm3 (Nadir), CD4=478 (187-963)/mm3 (Baseline). Eleven patients received a DRV/r and ETR containing regimen. In the whole population, median (IQR, n) ETR C12h and C24h were 515 ng/ml (340-758, 46) and 422 ng/ml (264-655, 103), respectively (p=NS). Median intra- and inter-patients variability of ETR C12h were 14% and 55% (2 visits, 23 patients, 46 samples) and intra- and inter-patients variability of ETR C24h were 36% and 77% (5 visits, 22 patients, 103 samples). ETR C12h and C24h were not statistically different with and without DRV combination.

Conclusions: ETR C12h and C24h for bid and qd regimen were as expected. ETR C24h was slightly lower for qd ETR relative to bid ETR in that population of treatment-experienced patients and approximately 100-fold higher than the protein binding-adjusted EC50 for wild-type HIV. Median intra- and inter-patient variability were lower in bid regimen (14% and 55%) than in qd regimen (36% and 77%) probably due to the lower variability of the intestinal absorption consecutive to the twice daily division of the total dose.

No conflict of interest
Abstract: P_36

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

A population pharmacokinetic (PK) analysis of candidate genes associated with atazanavir disposition

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Background: Atazanavir (ATV) is a once-daily, first-line protease inhibitor with variable PK. Sources of PK variability may include demographic factors and functional/expression differences in transporters (e.g. ABCB1, OATP1B1), metabolizing enzymes (e.g. CYP3A4, CYP3A5), and transcriptional/regulatory mechanisms that control drug elimination systems (e.g. Pregnane X Receptor, PXR). Previous studies identified genetically-determined CYP3A5 expression and a PXR genotype (63396C>T) as factors associated with ATV CL/F (without ritonavir), but no studies have evaluated these factors together in the same model. The objective of this study was to evaluate genetically-determined CYP3A5 expression, PXR (63396C>T), as well as CYP3A4*1B (-392 A>G) for relationships with atazanavir disposition using a population pharmacokinetic approach.

Methods: This study included HIV-negative subjects who participated in a previous atazanavir PK study and who consented for additional genetic analyses. The previous study pre-screened and recruited 15 genetically-determined CYP3A5 expressors and 16 CYP3A5 non-expressors balanced by gender and African-American race. Subjects received 400mg of ATV daily for 7 days with a 24-hour PK profile on day 7 after a standardized breakfast. ATV was measured with a validated HPLC-UV method. Genetics were determined with PCR-pyrosequencing. Pharmacokinetic analysis was performed using first-order conditional estimation with interaction in NONMEM (version 7.1, Icon Inc). Genetic variants of interest were identified using graphical analysis of collected genes interacted with CYP3A5.

Results: Fourteen CYP3A5 expressor (7 male, 6 African-American) and 16 CYP3A5 non-expressor (7 male, 6 African-American) were included. CYP3A5 expressors had 1.3-fold faster ATV CL/F compared with non-expressors (P=0.03) and CYP3A4*1B=AA carriers had 1.4-fold faster CL/F versus CYP3A4*1B=AG or GG (P=0.007). CYP3A5 expressors with CYP3A4*1B=AA (n=7) demonstrated 1.66-fold faster clearance (24.5 L/hr, 95% CI: 10.5 to 38.5) than all others (14.8 L/hr, 95% CI: 12.6 to 17.0), p=0.0014. PXR was not associated with ATV CL/F in univariate analyses, but a significant interaction was observed between CYP3A5 and P396. CYP3A5 expressors with PXR=CC (n=7) showed a 1.7-fold faster CL/F (25.0 L/hr, 95% CI: 18.9 to 31.1) than all others (14.7 L/hr, 95% CI: 12.8 to 16.6), p=0.0008. However, CYP3A5 non-expressors with PXR=CC (n=4) showed a 43% slower CL/F (10.2 L/hr, 95% CI: 8.06 to 12.3) than all others (17.9 L/hr, 95% CI:15.1 to 20.7), p=0.0044.

Conclusions: This study found interactions between CYP3A5 with CYP3A4*1B and CYP3A5 with PXR. The CYP3A5 – PXR interaction showed a slower ATV CL/F in CYP3A5 non-expressors with PXR=CC, which is consistent with publications that reported slower ATV CL/F for PXR=CC versus PXR=TT in mainly Caucasian subjects, a high percentage of whom were likely CYP3A5 non-expressors. Although this study’s main limitation was its small sample size, which restricted the ability to separate confounded effects, these new findings nonetheless provide hypotheses for larger studies to replicate and extend these findings in diverse populations.

No conflict of interest
Abstract: P_37

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Once Daily (OD) maraviroc (MVC) in combination with ritonavir-boosted darunavir (DRV/r) (800/100mg): What is the optimal MVC dose? 300mg OD or 150mg OD?

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Introduction: The licensed dosing of MVC is 300mg BD in the absence of enzyme inducers or inhibitors or 150mg BD when combined with most boosted protease inhibitors (bPIs). Pilot studies have suggested that [MVC]s when dosed at 150mg OD with ATV/r 300/100 OD are equivalent to [MVC]s achieved with 300mg BD without bPIs. The OD option for MVC is desirable for patients but the pharmacokinetics with different bPIs is yet to be ascertained. [MVC]s >25ng/ml have been associated with good viral response in non bPI regimens. The aim of this study was to investigate the effect of dose and ethnicity on MVC plasma exposure when dosed with DRV/r compared to standardised BD regimens.

Materials & Methods: A retrospective case-notes review of HIV-infected adults from two UK treatment centres. Standardised protocols were followed for novel MVC use including [MVC] drug level monitoring. Patients were grouped according to MVC dose: 1) MVC 300mg BD with Truvada (TVD). 2) 300mg OD and 3) 150mg OD (both with DRV/r 800/100 OD). Ctrough and Cpeak were collected where possible (150mg OD Ctrough only). Categorical data was analysed using a Mann–Whitney or Kruskal–Wallis statistical test. Spearman rank correlation was used for continuous data. Univariate and stepwise multivariate linear regression analyses were conducted on log transformed data to identify factors associated with [MVC]s. Statistical analyses were conducted using SPSS 16.

Results: 54 patients providing 100 samples were included. Median (IQR) Cpeak was 384ng/ml (340-743) for group 1 (n=8), 773ng/ml (395-982) for group 2 (n=37) and 364ng/ml (n=2) for group 3, p = 0.166. Median (IQR) Ctrough was 48ng/ml (38-66) for group 1 (n=10), 70ng/ml (48-102) group 2 (n=36) and 50ng/ml (39-56) for group 3 (n=16), p=0.015, MVC Ctrough in patients treated with 300mg OD + DRV/r were higher than patients treated with 150mg OD + DRV/r, p = 0.021 and 300mg BD + TVD, p = 0.023. No differences were observed for Cpeak. Black patients had higher Cpeak [MVC] compared to White patients; 801ng/ml, IQR 414-1063 vs 383ng/ml, IQR 301-817, p = 0.012. Ctrough [MVC]s (n=35) in black pts were 92ng/ml, IQR 56-147 vs. (whites n=27) 49ng/ml, IQR 44-70, p = 0.034, respectively. Ethnicity was the only factor independently associated with Cpeak (β = 0.21, 95% CI 0.04-0.39, p = 0.019) while dose and ethnicity were independently associated with Ctrough (β = 0.16, 95% CI 0.06-0.27, p = 0.003 and β = 0.15, 95% CI 0.04-0.25, p = 0.007, respectively).

Conclusion: 300mg MVC OD with DRV/r achieved comparable Cpeaks and higher Ctroughs compared to either MVC 300 mg BD with NRTIs or 150mg OD with DRV/r. As all regimens were well tolerated, further work on the longer-term effects of low vs high concentrations levels and the effects of ethnicity are warranted.

No conflict of interest
Abstract: P_38

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Lack of relevant pharmacokinetic interaction between raltegravir and ribavirin in HIV/HCV coinfected patients

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Introduction: Raltegravir (RAL) is a novel antiretroviral agent. The current treatment schedule of hepatitis C virus (HCV) infection associates ribavirin (RBV) with pegylated-interferon (peg-IFN). Scarce data document their safe co-administration with RAL. We aimed to describe the safety and the lack of pharmacokinetic interactions in patients treated with RAL and RBV/peg-IFN.

Method: Data of 12 HIV/HCV-coinfected patients who underwent a therapy associating RAL with RBV were retrospectively analysed, with respect to baseline/follow-up treatment characteristics, efficacy/toxicity outcomes, and evolution of RAL/RBV plasma concentrations.

Results: Three patients had compensated and one patient decompensated liver cirrhosis. RAL was introduced prior to anti-HCV therapy in 11/12 patients at a dosage of 400 mg bid. RBV dosage at treatment initiation was 400-1600 mg/day. HIV viral load remained undetectable during anti-HCV therapy in all patients. HCV early virological response was achieved in 8/12 patients. No patient experienced major hepatic toxicity. Median (range) RBV through concentration was 1.98 (1.09-4.49) mg/L, RBV dosage ranged 100-2000 mg/day. When RAL was associated or not with RBV, median through plasma concentration were 0.071 (0.037-0.243) mg/L and 0.051 (0.021-0.254) mg/L, respectively (p=0.98).

Conclusion: This real-life situation report highlights the safe coadministration of RAL and RBV/peg-IFN in patients with various liver-damage stages. The treatment tolerance in these patients did not differ from that usually observed during anti-HCV treatment, without premature RAL or RBV/peg-IFN discontinuation due to adverse effects. Distributions of RAL and RBV plasma concentrations were similar to those previously described. Our results have to be confirmed in prospective studies.

No conflict of interest

Abstract: P_39

Effect of food on the steady-state pharmacokinetics of a fixed-dose combination tablet containing tenofovir, emtricitabine and efavirenz in HIV-positive Ugandan patients

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Introduction: A proprietary fixed-dose combination (FDC) tablet containing tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) plus efavirenz (EFV) was introduced in 2006. Food intake was shown to influence the pharmacokinetics of single-drug formulations of TDF and EFV without affecting FTC exposure; however,
the food effect has not been investigated using the new FDC formulation.

Methods: An open-label, two-phase, crossover study was conducted in 15 Ugandan HIV-1 infected patients receiving TDF/FTC/EFV (Atripla®) one tablet daily for >1 month. Blood sampling was performed on Day1 in the fasted state and repeated seven days later (Day8) when TDF/FTC/EFV was administered with a local meal (650 kcal, 19g fat content). On each occasion, venous samples were collected pre-dose and 0.5,1,2,3,4,6,8,12 and 24 hours post-TDF/FTC/EFV dosing. Plasma concentrations of tenofovir (TFV), FTC and EFV were determined by validated LC-MS/MS assays. Pharmacokinetic parameters (AUC<sub>0-24</sub>, C<sub>24</sub>, C<sub>max</sub>) were calculated by non-compartmental methods (WinNonlin). Geometric means (GM), GM ratios (GMR) with Day1 data as reference, and 90% confidence intervals (CI) were calculated.

Results: Fifteen participants (4 female) completed the study. Median (interquartile range) age and weight were 43 (40–50) years and 74 (61–80) kg, respectively. On Day1, for TFV, FTC and EFV AUC<sub>0-24</sub> (GM, 90% CI) were 1316 ng.h/mL, 7029 ng.h/mL and 46299 ng.h/mL, respectively. On Day8, corresponding values were 1568 ng.h/mL, 6115 ng.h/mL and 52194 ng.h/mL, respectively. Five patients on Day1 and four patients on Day8 had EFV C<sub>24</sub> concentrations below 1000 ng/mL. For EFV, C<sub>max</sub>, AUC<sub>0-24</sub>, and C<sub>24</sub>, (GMRs,90% CIs) were 1.47 (1.24–1.75), 1.13 (1.03–1.23) and 1.01 (0.91–1.11) respectively. Corresponding values for TFV and FTC were 1.04 (0.84 – 1.27), 1.19 (1.10–1.29), 0.99 (0.82-1.19); and 0.83 (0.76-0.92), 0.87 (0.78 – 0.97) and 0.91 (0.73-1.14).

Conclusions: Efavirenz peak concentration was significantly increased with a local Ugandan (moderate fat) meal while the effect of food on TDF and FTC pharmacokinetics was consistent with data previously reported with a light meal. For patients experiencing EFV concentration-dependent toxicity (e.g. central nervous system side effects), this FDC formulation should be taken without food.

No conflict of interest

Abstract: P_40

Therapeutic Drug Monitoring

Interest of Ribavirin therapeutic drug monitoring in chronic hepatitis C treatment outcome for HIV/HCV coinfected patients

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Introduction: Chronic infection with hepatitis C virus (HCV) is frequent in HIV-infected persons. Treatment with peginterferon (peg-IFN) plus ribavirin (RBV) leads to sustained virological response (SVR) in 14%-29% of patients coinfected with genotype 1 or 4 HCV (G1/4) and in 44%-73% of patients coinfected with HCV genotype 2 or 3 (G2/3). However, SVR is reached in 40–45% (G1/4) and 80% (G2/3) of HCV-monoinfected patients. As RBV displays high interindividual variability, and as higher RBV exposure is associated with SVR, RBV therapeutic drug monitoring (RBV<sub>TDM</sub>) appears relevant. Our study aimed to describe the influence of RBV<sub>TDM</sub> on RBV/peg-IFN treatment response in HIV/HCV-coinfected patients.

Method: Data from patients whose RBV concentration had been assessed during treatment were retrospectively analysed. RBV<sub>TDM</sub> was considered as being properly performed if RBV concentration was assessed before week 12 (W12), and if RBV dosage was modified when the required RBV concentration cut-off (1.60 mg/L for G2/3 and 2.50 mg/L for G1/4 patients) was not achieved.

Results: There were 11 G2/3 and 25 G1/4 patients. Rates of poor response factors (age, gender, baseline HCV viral load, liver
fibrosis stage, previous unsuccessful treatment) and antiretroviral treatments were similar to literature. SVR, relapse and non-response rates were 73%, 9% and 52%, respectively, in G1/4 patients. RBV_{TDM} was performed in 64% (G2/3) and 76% (G1/4) patients. At treatment initiation, RBV dosage was 800, 1000, and 1200 mg/day in 73%, 18% and 9% of G2/3 patients, and 0%, 44% and 56% of G1/4 patients, respectively. RBV dosages were modified in 18% (G2/3) and 72% (G1/4) of patients, leading to RBV dosage of 600-800, 1000, and >= 1200 mg/day in 64%, 4% and 28% of G2/3 patients, and 4% and 80% of G1/4 patients, respectively. The median (IQR) RBV steady-state plasma concentrations before any dosage modification were 1.53 (0.99-2.15) and 1.43 (1.23-2.34) mg/L in G2/3 and G1/4 patients, respectively. At W12, levels were 1.60 (0.99-2.10) and 2.24 (1.30-2.62) mg/L in G2/3 and G1/4 patients, respectively. 55% (G2/3) and 48% (G1/4) of patients achieved the concentration cut-off at W12. The haemoglobin drop at W12 was > 3 g/dL in 55% (G2/3) and 60% (G1/4) of patients. Epoetin beta was used in 46% (G2/3) and 40% (G1/4) of patients.

**Conclusion:** SVR rates for these HIV/HCV-coinfected patients are higher than those usually described, and come close to those of HCV-monoinfected patients. RBV_{TDM} was performed in most of patients, leading to numerous RBV dosage modifications and increased concentrations in G1/4 patients. Thus, the recommended body-weight adjusted RBV dosage seems to be adequate for G2/3 patients, but could be insufficient for G1/4 patients. Haematological toxicity was comparable between G2/3 and G1/4 patients despite of different RBV concentrations, suggesting that host-related factors such as genotypic variants in the gene encoding for IL-28 might be involved. RBV remains a cornerstone in the new schedules based on HCV-protease inhibitors, and therapeutic drug monitoring is thus still a going concern to improve treatment adherence and manage drug-drug interactions.

*No conflict of interest*

Abstract: P_41

**Therapeutic Drug Monitoring**

**Retrospective analysis of Atazanavir therapeutic drug monitoring: is boosting with ritonavir necessary if Atazanavir is used with Tenofovir?**

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**Background:** Tenofovir (TDF) is known to decrease atazanavir (ATZ) exposure and minimum concentrations by 25 and 40%, respectively. The recommendation to overcome this interaction is to give ATZ/ritonavir(RTV) when taken with TDF. For tolerability, unboosted ATZ is sometimes administered with TDF. This study examined whether unboosted ATZ with TDF provided therapeutic ATZ concentrations.

**Materials and Methods:** The database of the Quebec Antiretroviral Therapeutic Drug Monitoring (TDM) Program was screened to find every ATZ TDM performed between June 2006 and September 2010 in patients ≥ 18 years old and receiving standard doses of ATZ. Any sample not taken between 12h and 26h post-dose or with missing data regarding nucleoside reverse transcriptase inhibitor intake was excluded, as were patients with documented pregnancy, hepatic insufficiency, non-adherence, and ATZ drug interactions. C_{t\text{rough}} was calculated by using the product monograph half-lives. Genotypic inhibitory quotient (GIQ) was calculated by dividing C_{t\text{rough}} by
the number of protease mutations as defined by Gonzalez de Requena et al. Ctrough and GIQ targets were >0.15mg/L and 0.10mg/L/mutation, respectively. Viral load was also available for a subgroup of patients. Group comparisons were done with Mann-Whitney U, χ² or Fisher’s exact test.

Results: 379 Ctrough and 108 GIQs were analyzed for 284 patients. Mean patient age was 44 years, mean weight 72.9kg, and 18.2% had past protease inhibitor (PI) failure. The median Ctrough for ATZ/RTV/TDF (n=95 patients/115 samples) and ATZ/TDF without RTV (n=33 patients/51 samples) were 0.5 and 0.14 mg/L (p<0.001). The proportion of therapeutic Ctrough in these two groups were 82.6% and 49.0%, respectively (p<0.001). In the absence of TDF, the proportion of therapeutic Ctrough was also higher in the ATZ/RTV group (n=91 patients/122 samples; 84.4%) than in the ATZ without RTV group (n=65 patients/91 samples; 47.3%) (p < 0.001).

When used without RTV, the difference between the proportion of therapeutic Ctrough for ATZ/TDF versus ATZ without TDF was not statistically significant (p = 0.840). The median GIQ for ATZ/RTV/TDF (n=51 results) and ATZ/TDF without RTV (n=16 results) were 0.25 and 0.12 mg/L/mutation (p=0.049). The difference in the proportion of therapeutic GIQs between these two groups was not statistically significant (76.5% versus 68.8%, p=0.528).

When used without RTV, the median GIQ for ATZ/RTV (n=26 results) and ATZ without RTV (n=15 results) were 0.26 and 0.08 mg/L/mutation, respectively (p=0.033) and the proportion of therapeutic GIQs significantly differed (73.1% versus 40.0%, p=0.036). There were no statistical differences when comparing the viral loads between the groups.

Conclusions: In our study, the absence of RTV and not the presence of TDF determined the proportion of cases with subtherapeutic Ctrough. Selection bias may have influenced these results; that is, patients receiving ATZ and TDF without RTV might be selected differently and educated differently regarding adherence. Patients with virus harbouring protease mutations should receive RTV boosted ATZ regardless of TDF co-administration and TDM using GIQs is recommended in this population. For PI-naïve patients, it remains unclear if the low ATZ concentrations seen with unboosted ATZ regimens with or without TDF are clinically significant.

Financial relationship(s): ViiV HealthCare

Abstract: P_42

Therapeutic Drug Monitoring

Increased darunavir doses for heavily treatment experienced patients with low level viremia

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Introduction: Frequently used salvage regimens contain boosted darunavir (DRV) with etravirine (ETV) and raltegravir (RAL) plus a backbone. Sparse real life data is available on the options if such treatments fail. We present 4 cases of heavily treatment-experienced HIV-infected Caucasian males on such salvage regimens to determine if an increase of DRV or ritonavir (RTV) doses can improve the weighted score genotypic inhibitory quotient (gIQ WS) and viral suppression.

Materials & Methods: Summary of four case reports, data were collected form charts, DRV levels were analyzed using HPLC tandem mass spectrometry.

Results: Case 1: 52 y.o. male using AZT, 3TC, TDF, RAL, ETV, DRV 600mg BID, RTV 100mg BID with a pVL of 470 copies/mL (8 months on ARVs). Baseline DRV trough level and gIQ WS were 2.2 mg/L and 314 and remained the same after
increasing RTV dose to 200mg BID. When dosage was changed to DRV 900mg BID + RTV 100mg BID the DRV trough level and gIQ WS were 2.6 mg/L and 371. Patient had no adverse effects and pVL dropped to 46 copies/mL.

Case 2: 46 y.o. male using 3TC, TDF, RAL, ETV, DRV 600mg BID, RTV 100mg BID with a pVL of 240 copies/mL (> 4 months on ARVs). Baseline DRV trough level and gIQ WS were 2.2 mg/L and 550 and dropped to 1.8 mg/L and 450 after increasing RTV dose to 200 mg BID. When dosage was changed to DRV 900mg BID + RTV 100mg BID the DRV trough level and gIQ WS were 2.6 mg/L and 371. Patient had no adverse effects and pVL dropped to <40 copies/mL.

Case 3: 48 y.o. male using RAL, ETV, DRV 600mg BID, RTV 100mg BID with a pVL of 9700 copies/mL (4 months on ARVs). Baseline DRV peak level was 6.9 mg/L. DRV trough level and gIQ WS were 4.2 mg/L and 600 after increasing RTV dose to 200 mg BID. When dosage was changed to DRV 900mg BID + RTV 100mg BID the DRV trough level and gIQ WS were 6.9 mg/L and 857. Patient had no adverse effects and pVL dropped to <40 copies/mL.

Case 4: 53 y.o. male using 3TC, RAL, ETV, DRV 600mg BID, RTV 100mg BID with pVL of 420 copies/mL (9 months on ARVs). Baseline DRV trough level and gIQ WS were 0.84 mg/L and 70. When dosage was changed to DRV 900mg BID + RTV 100mg BID the DRV trough level and gIQ WS were 2.9 mg/L and 241. Patient had no adverse effects and pVL increased to 1500 copies/mL; non-adherence may have contributed (developed integrase mutations).

Conclusions: Heavily treatment-experienced patients on boosted DRV and an unsuppressed VL may benefit from an increase in DRV dose to 900 mg BID with RTV 100 mg BID to improve gIQ WS.

Increasing RTV to 200 mg BID did not improve DRV levels or VL response. Higher doses of DRV appear to be well tolerated. Our last case suggests adherence remains of high importance.

No conflict of interest

**Abstract: P_43**

**Therapeutic Drug Monitoring**

**Proficiency program supports the accuracy of antiretroviral concentrations used in HIV Clinical Trial Networks**

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**Introduction:** The DAIDS Clinical Pharmacology Quality Assurance and Quality Control (CPQA) program provides multiple programs for international Clinical HIV Clinical Trial Networks. The laboratory-focused programs include an assay review program that ensures that all drug assay methods applied to clinical trial samples meet FDA bioanalytical method requirements, laboratory training programs, and a proficiency testing program. The proficiency testing (PT) program ascertains accuracy of antiretroviral (ARV) concentrations measured in trial samples. This evaluation of the first four CPQA rounds of PT and their longitudinal outcomes provides an assessment of the quality of the values reported by laboratories and identifies variables associated with quality.

**Materials and Methods:** Every six months, the CPQA PT program offered prepared plasma samples containing prespecified concentrations (unknown to laboratories) of up to 21 ARV analytes; five concentrations of each ARV were provided. During two rounds, concentrations of some ARVs were duplicated to assess laboratories’ reproducibility. Criterion for measurement accuracy was within ±20%. The US Clinical Laboratory Improvement Act (CLIA) PT
regulations were imposed to assess the laboratories’ performance. Four testing rounds have been completed. The results were tabulated to determine the prominent characteristics of participating labs and ARV analytes. For duplicate assessments, a % difference between the two reported values was determined. Performance variables were determined by participant and analyte as well as comprehensively. Among candidate factors (lab, analyte, round, nominal concentration and prior participation), regression models were used to identify those associated with bias and variability in reported concentrations.

Results: Of 1706 concentrations submitted, efavirenz, lopinavir, and ritonavir represented 27% as these were tested by all 10 participating laboratories. The least participation was found in newly marketed drugs such as etravirine (2 labs) and maraviroc (3 labs) or in older drugs such as the nucleoside reverse transcriptase inhibitors ddI and D4T (3 labs each). 97% of reported concentrations were within 20% of the final target value and 3% were outside these limits. Less than 1% of scored results corresponded to missing results for analytes the lab intended to report. In addition, 5 concentrations (false positives) were reported for blank samples. The laboratories’ performance for blinded duplication ranged from 0-13% difference with a median performance measure of 2%. Over the four rounds, 6 laboratories were below 80% accuracy (unsatisfactory) for one or more analytes. Of the 21 analytes, tenofovir, emtricitabine and nelfinavir had the greatest unsatisfactory incidence. Systematic bias was detected at 2 labs. Increased variability in reported concentrations was detected for 3 labs, 5 analytes and at the lowest nominal concentrations.

Conclusions: The CPQA proficiency testing program has demonstrated the competence of the laboratories that assay plasma samples for ARV concentrations for HIV clinical trial plasma samples. The program provides assurance that ARV concentrations used for DAIDS-sponsored clinical trials were accurate, and when necessary works with labs to solve performance problems.

No conflict of interest
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Author Index
<table>
<thead>
<tr>
<th>Author Name</th>
<th>Abstract Title</th>
<th>Abstract #</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson, P.</td>
<td>The cellular pharmacology of zidovudine and lamivudine according to HIV-status and gender</td>
<td>O_06</td>
<td>8</td>
</tr>
<tr>
<td>Avihingsanon, A.</td>
<td>Pharmacokinetics of reduced dose Darunavir/ritonavir in Asian HIV-1 infected adults</td>
<td>P_33</td>
<td>53</td>
</tr>
<tr>
<td>Blonk, M.</td>
<td>The influence of tobacco smoking on Atazanavir pharmacokinetics</td>
<td>P_34</td>
<td>54</td>
</tr>
<tr>
<td>Burger, D.</td>
<td>Effect of fosamprenavir/ritonavir on the pharmacokinetics of single-dose olanzapine in healthy volunteers</td>
<td>P_10</td>
<td>31</td>
</tr>
<tr>
<td>Chen, J.</td>
<td>Use of accelerator mass spectrometry (AMS) to determine the pharmacokinetic profile of intracellular tenofovir diphosphate (TFV-dp)</td>
<td>O_07</td>
<td>9</td>
</tr>
<tr>
<td>Colbers, A.</td>
<td>A comparison of the pharmacokinetics of Raltegravir during pregnancy and post-partum</td>
<td>P_18</td>
<td>38</td>
</tr>
<tr>
<td>Corcione, S.</td>
<td>Clinical pharmacology of complex regimen of antiretroviral therapy including Etravirine, Maraviroc and Raltegravir.</td>
<td>P_29</td>
<td>49</td>
</tr>
<tr>
<td>Cressey, T.</td>
<td>Pharmacokinetics of Lopinavir/r tablets administered once versus twice daily with/without Efavirenz in antiretroviral treatment experienced children</td>
<td>P_19</td>
<td>39</td>
</tr>
<tr>
<td>Csajka, C.</td>
<td>Population Pharmacokinetic Analysis and Effects of Raltegravir In HIV positive and Healthy Individuals</td>
<td>O_15</td>
<td>16</td>
</tr>
<tr>
<td>Cusato, M.</td>
<td>Pharmacokinetic evaluation of Rifabutin and its active metabolite LM565 coadministerd with Lopinavir/r in HIV-infected patients</td>
<td>O_14</td>
<td>15</td>
</tr>
<tr>
<td>D'Avolio, A.</td>
<td>Single-nucleotide polymorphism PXR 7635G&gt;A influences plasma concentrations of Efavirenz in CYP2B6 516G&gt;T carriers.</td>
<td>P_25</td>
<td>45</td>
</tr>
<tr>
<td>Dickinson, L.</td>
<td>Population pharmacokinetic modelling of plasma and intracellular once daily ritonavir-boosted darunavir in HIV-infected patients</td>
<td>O_12</td>
<td>13</td>
</tr>
<tr>
<td>DiFrancesco, R.</td>
<td>Proficiency program supports the accuracy of antiretroviral concentrations used in HIV Clinical Trial Networks</td>
<td>P_43</td>
<td>62</td>
</tr>
<tr>
<td>Else, L.</td>
<td>Pharmacokinetics of plasma lamivudine (3TC), and its active intracellular anabolite 3TC-triphosphate (3TC-TP) over a 24 hour dosing interval following administration of 3TC 300 mg and 150 mg once daily (od) to HIV-negative healthy volunteers. The ENCORE2 Study</td>
<td>O_05</td>
<td>7</td>
</tr>
<tr>
<td>Ford, S.</td>
<td>Inhibition potential for GSK2248761, a next-generation NNRTI, on HMG-CoA Reductase inhibitors Simvastatin, Atorvastatin and Rosuvastatin</td>
<td>P_09</td>
<td>30</td>
</tr>
<tr>
<td>German, P.</td>
<td>The effect of Cobicistat on Cytochrome P450 2D6, 2B6 and P-glycoprotein using phenotypic probes</td>
<td>O_01</td>
<td>3</td>
</tr>
<tr>
<td>German, P.</td>
<td>Pharmacokinetic interaction between Norgestimate/Ethynyl Estradiol and EVG/CObI/FTC/TDF single tablet regimen</td>
<td>O_17</td>
<td>18</td>
</tr>
<tr>
<td>Haas, D.</td>
<td>Pharmacogenetics of low plasma Efavirenz (EFV) concentrations in AIDS Clinical Trials Group (ACTG) studies: Analysis NWCS 301</td>
<td>P_22</td>
<td>42</td>
</tr>
<tr>
<td>Haas, D.</td>
<td>Pharmacogenomics of Plasma Nevirapine Clearance among HIV-infected Cambodians</td>
<td>P_26</td>
<td>46</td>
</tr>
<tr>
<td>Haas, D.</td>
<td>Human genetic polymorphisms and virologic response to protease inhibitor-containing regimens in African Americans and European Americans</td>
<td>P_28</td>
<td>48</td>
</tr>
<tr>
<td>Ivanovic, J.</td>
<td>TDM of Antiretroviral Drugs in HIV-infected Pregnant Women: pharmacokinetics, compartmental diffusion, efficacy and safety</td>
<td>P_17</td>
<td>37</td>
</tr>
<tr>
<td>Johnson, D.</td>
<td>Pharmacogenetics, pharmacokinetics, and pharmacodynamics (PG/PK/PD) of central nervous system effects with single-dose efavirenz</td>
<td>P_23</td>
<td>43</td>
</tr>
<tr>
<td>Johnson, M.</td>
<td>GSK2248761 development; formulation and food effect</td>
<td>P_06</td>
<td>27</td>
</tr>
<tr>
<td>Author Name</td>
<td>Abstract Title</td>
<td>Abstract #</td>
<td>Page #</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Kakuda, T.</td>
<td>No effect of ritonavir or timing of food intake on etravirine pharmacokinetics in HIV-negative volunteers</td>
<td>P_11</td>
<td>32</td>
</tr>
<tr>
<td>Kile, D.</td>
<td>A population pharmacokinetic (PK) analysis of candidate genes associated with atazanavir disposition</td>
<td>P_36</td>
<td>56</td>
</tr>
<tr>
<td>Kiser, J.</td>
<td>Atazanavir dosing conversion and pharmacokinetics in HIV-infected children switching from atazanavir powder to capsules</td>
<td>P_20</td>
<td>40</td>
</tr>
<tr>
<td>la Porte, C.</td>
<td>Increased darunavir doses for heavily treatment experienced patients with low level viremia</td>
<td>P_42</td>
<td>61</td>
</tr>
<tr>
<td>Lamorde, M.</td>
<td>Effect of food on the steady-state pharmacokinetics of a fixed-dose combination tablet containing tenofovir, emtricitabine and efavirenz in HIV-positive Ugandan patients</td>
<td>P_39</td>
<td>58</td>
</tr>
<tr>
<td>Lee, L.</td>
<td>Modeling of Raltegravir Intracellular Accumulation in Healthy Volunteers</td>
<td>P_02</td>
<td>24</td>
</tr>
<tr>
<td>Lou, Y.</td>
<td>Using Adaptive/Bayesian methodology to evaluate four different formulations of GSK2248761 in a relative bioavailability and food effect study</td>
<td>O_03</td>
<td>5</td>
</tr>
<tr>
<td>Mallolas, J.</td>
<td>Pilot pharmacokinetic study of dual therapy with Raltegravir 400 mg BID and Darunavir/r 800/100 mg QD in HIV-1 infected patients</td>
<td>P_30</td>
<td>50</td>
</tr>
<tr>
<td>Mathias, A.</td>
<td>Effect of acid reducing agents on the relative bioavailability and pharmacokinetics of Cobicistat-boosted Elvitegravir</td>
<td>P_13</td>
<td>34</td>
</tr>
<tr>
<td>McFadyen, L.</td>
<td>Modeling of Maraviroc Pharmacokinetics in the Presence of Atazanavir/Ritonavir in Healthy Volunteers and HIV-1-Infected Patients</td>
<td>P_05</td>
<td>26</td>
</tr>
<tr>
<td>McFadyen, L.</td>
<td>Population pharmacokinetics of lersivirine using Phase I/IIa pharmacokinetic data after suspension and tablet administration</td>
<td>P_07</td>
<td>28</td>
</tr>
<tr>
<td>Mirochnick, M.</td>
<td>Pharmacokinetics of increased dose atazanavir with and without tenofovir during pregnancy</td>
<td>O_10</td>
<td>11</td>
</tr>
<tr>
<td>Moltó, J.</td>
<td>Pharmacogenetics-based population pharmacokinetic analysis of Lopinavir in HIV-infected individuals</td>
<td>P_27</td>
<td>47</td>
</tr>
<tr>
<td>Muret, P.</td>
<td>Lack of relevant pharmacokinetic interaction between raltegravir and ribavirin in HIV/HCV coinfected patients</td>
<td>P_38</td>
<td>58</td>
</tr>
<tr>
<td>Muret, P.</td>
<td>Interest of Ribavirin therapeutic drug monitoring in chronic hepatitis C treatment outcome for HIV/HCV coinfected patients</td>
<td>P_40</td>
<td>59</td>
</tr>
<tr>
<td>Nanzigu, S.</td>
<td>Pharmacokinetics of the non-nucleoside reverse transcriptase inhibitor Efavirenz among HIV Infected Ugandans</td>
<td>P_16</td>
<td>36</td>
</tr>
<tr>
<td>Nettles, R.</td>
<td>Single and multiple dose pharmacokinetics and safety in non-HIV-infected healthy subjects dosed with BMS-663068, an oral HIV attachment inhibitor</td>
<td>O_04</td>
<td>6</td>
</tr>
<tr>
<td>Okoli, C.</td>
<td>Once Daily(OD) maraviroc(MVC) in combination with ritonavir-boosted darunavir(DRV/r)(800/100mg): What is the optimal MVC dose?300mg OD or 150mg OD?</td>
<td>P_37</td>
<td>57</td>
</tr>
<tr>
<td>Owen, A.</td>
<td>Transport of antiretrovirals by ABCB5: the elusive non-nucleoside reverse transcriptase efflux pump?</td>
<td>O_11</td>
<td>12</td>
</tr>
<tr>
<td>Peytavin, G.</td>
<td>Lack of pharmacokinetic interaction between doxycycline and protease inhibitors or non-nucleoside reverse transcriptase inhibitors in HIV patients</td>
<td>P_15</td>
<td>36</td>
</tr>
<tr>
<td>Peytavin, G.</td>
<td>Variability of Darunavir plasma concentrations and relationships with adherence and virological response in the MONO1-ANRS136 trial</td>
<td>P_32</td>
<td>52</td>
</tr>
<tr>
<td>Peytavin, G.</td>
<td>Etravirine pharmacokinetics after switch from ETR twice daily to once daily regimen in treatment-experienced HIV-infected patients: MONETRA Sub-study</td>
<td>P_35</td>
<td>55</td>
</tr>
<tr>
<td>Piscitelli, S.</td>
<td>Effects of enzyme inducers, tipranavir and efavirenz, on the pharmacokinetics of the integrase inhibitor, Dolutegravir (S/GSK1349572)</td>
<td>O_02</td>
<td>4</td>
</tr>
<tr>
<td>Author Name</td>
<td>Abstract Title</td>
<td>Abstract #</td>
<td>Page #</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Piscitelli, S.</td>
<td>Effect of food on the pharmacokinetics of the integrase inhibitor, dolutegravir (S/GSK1349572)</td>
<td>P_12</td>
<td>33</td>
</tr>
<tr>
<td>Rakhmanina, N.</td>
<td>Tenofovir Population Pharmacokinetics in Children and Adults</td>
<td>O_16</td>
<td>17</td>
</tr>
<tr>
<td>Rower, J.</td>
<td>Intracellular mono-, di-, and tri-phosphate levels of tenofovir/emtricitabine in human peripheral blood mononuclear (tPBMC) vs red blood cells (RBC)</td>
<td>P_04</td>
<td>25</td>
</tr>
<tr>
<td>Sheehan, N.</td>
<td>Retrospective analysis of Atazanavir therapeutic drug monitoring: is boosting with ritonavir necessary if Atazanavir is used with Tenofovir?</td>
<td>P_41</td>
<td>60</td>
</tr>
<tr>
<td>Siccardi, M.</td>
<td>In vitro-in vivo extrapolation of CYP2B6 genotype-based efavirenz dose reduction.</td>
<td>P_24</td>
<td>44</td>
</tr>
<tr>
<td>Solas, C.</td>
<td>Pharmacokinetic interaction between Maraviroc and Etravirine: a multicentre study in HIV-patients receiving an antiretroviral regimen without PI</td>
<td>O_13</td>
<td>14</td>
</tr>
<tr>
<td>Torres, R.</td>
<td>No influence of CYP3A5 and ABCB1 polymorphisms on darunavir and ritonavir pharmacokinetics in HIV-negative Caucasian volunteers</td>
<td>P_21</td>
<td>41</td>
</tr>
<tr>
<td>Valle, M.</td>
<td>Effect of ritonavir concentrations on atazanavir pharmacokinetics: population pharmacokinetic analysis</td>
<td>P_03</td>
<td>24</td>
</tr>
<tr>
<td>Valle, M.</td>
<td>No changes in atazanavir exposure when boosted with 100mg or 50mg of ritonavir in healthy volunteers.</td>
<td>P_31</td>
<td>51</td>
</tr>
<tr>
<td>Vourvahis, M.</td>
<td>Effect of rifabutin on the pharmacokinetics (PK) of lersivirine, and lersivirine on the PK of rifabutin/25-O-desacetyl-rifabutin, in healthy subjects</td>
<td>P_08</td>
<td>29</td>
</tr>
<tr>
<td>Vourvahis, M.</td>
<td>Lack of a clinically relevant effect of Maraviroc on the pharmacokinetics of digoxin in healthy volunteers</td>
<td>P_14</td>
<td>35</td>
</tr>
<tr>
<td>Watson, V.</td>
<td>Investigating variability in reported intracellular Raltegravir concentrations: contribution of PBMC isolation methodology.</td>
<td>P_01</td>
<td>26</td>
</tr>
<tr>
<td>Wenning, L.</td>
<td>PK/PD analyses for QDMRK, a phase III study of the safety &amp; efficacy of once versus twice daily Raltegravir in treatment-naive HIV-infected patients</td>
<td>O_09</td>
<td>10</td>
</tr>
<tr>
<td>Zhu, L.</td>
<td>Exposure-response analyses of an oral HIV attachment inhibitor BMS-663068 following 8 days of monotherapy in HIV-infected patients</td>
<td>O_08</td>
<td>9</td>
</tr>
</tbody>
</table>
Abstract Book
12th International Workshop on Clinical Pharmacology of HIV Therapy
13 - 15 April, 2011, Miami, Florida, USA