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Abstracts
Oral Presentations
Abstract: O_01

Rifampicin-based antituberculosis treatment is not associated with reduced efavirenz concentrations in children

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Background: Efavirenz with 2 NRTIs is the preferred ART regimen for children over 3 years-old with tuberculosis. However, rifampicin may alter efavirenz concentrations. There is scant pharmacokinetic information on efavirenz in children with tuberculosis, and concern that efavirenz concentrations may be reduced, particularly in younger children.

Materials & Methods: Children with tuberculosis underwent pharmacokinetic evaluation after at least 2 weeks of combined treatment with an efavirenz-based regimen and antituberculosis treatment containing rifampicin. Up to 4 blood samples were drawn per visit at 1-2 visits, 11-24 h after the evening dose of efavirenz. Pharmacokinetic evaluation was repeated at least 1 month after antituberculosis treatment. Children without tuberculosis and established on efavirenz-based ART served as controls. Efavirenz was dosed according to WHO-recommended weight bands. Plasma concentrations of efavirenz were measured using LC-MS/MS. Composite CYP2B6 516/983 genotype was determined. Average mid-dose-interval concentrations (aveMDI; average concentration during a single dose interval 12-20 h after the dose) were compared between groups using Wilcoxon rank-sum and matched-pairs signed-ranks tests for unmatched and paired data, respectively. Multilevel linear mixed-effects (MLME) regression was used to examine the effects of antituberculosis treatment, genotype, time after dose, and weight on the log-transformed efavirenz concentrations. The model included random effects for individual and visit to account for within subject and visit correlations. Missing genotype values were imputed by a chained equations approach, with estimation results combined by Rubin’s rules.

Results: Forty children with tuberculosis (median[IQR]: age 7.5[4.6,10.9] y; weight 19.6[15.1,25.4] kg; height 114[99,125] cm) and 41 control children without tuberculosis (age 8.1[6.4,9.6], weight 22.2[17.6,26.8] kg, height 120[106,129] cm) were included in the pharmacokinetic analysis. Genotype data was available for 64 children; 17(27%), 36(56%) and 11(17%) of whom had extensive, intermediate and slow CYP2B6 metabolizer genotypes, respectively.

The median (IQR) aveMDI during antituberculosis treatment was 1.64 (1.21, 4.40) mg/L, compared with 1.96 (1.32, 2.93) mg/L after antituberculosis treatment (p=0.640, for 32 children with paired data), and 1.7 (1.14, 2.27) mg/L in controls (p=0.626, vs. on rifampicin). Children in the lower weight bands (<20 kg) were more likely to have aveMDI <1mg/L (5/26 [19%] vs. 2/48 [4%], p=0.024). The MLME model described 5.05 (95% CI: 3.67,6.89)-fold and 1.52(95% CI: 1.18,1.97)-fold increases in efavirenz concentrations for slow and intermediate metabolizer genotypes, respectively, compared with children wild-type for CYP2B6 516/983. While efavirenz concentrations declined by 4.6%(95% CI: 4.5,2) for each hour during the observed portion of the dosing interval, and weight tended to slightly increase efavirenz concentrations (1% [95% CI: 0.3,2.5] for each kg), antituberculosis treatment did not significantly affect efavirenz concentrations. However, when children with slow composite genotype for CYP2B6 only were included, TB treatment increased efavirenz concentrations by 35% (95% CI: 8,62).

Conclusions: Our findings do not support the use of increased efavirenz doses in children with tuberculosis. Paradoxically children with slow CYP2B6 genotype appear to have increased efavirenz concentrations during antituberculosis treatment, probably due to inhibition by isoniazid of accessory metabolizing pathways. Children in the lower weight bands are at increased risk of subtherapeutic efavirenz concentrations irrespective of co-administration with antituberculosis drugs.

No conflict of interest
Abstract: O_02

Pharmacokinetics of efavirenz in combination with rifampin in HIV-infected adults: results of the PECAN (ANRS 12154) study


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Introduction: Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor, is widely used in combination with nucleoside inhibitors as first-line treatment of type I human immunodeficiency virus (HIV-1) infection, specially in patients (pts) coinfected with tuberculosis (TB). The objectives of this descriptive study were: i) to characterize EFV pharmacokinetics (PK) with and without rifampin (R) co-administration, and ii) to identify environmental and genetic factors of EFV variability in pts enrolled in the CAMELIA (ANRS1295-CIPRA KH001) clinical trial who volunteered to enter this pharmacogenetic (PG) sub study called PECAN.

Material and methods: PECAN study was conducted in pts coinfected with TB and HIV-1. EFV 600 mg was administered od with stavudine+lamivudine bid. TB treatment, including R, was administered from week (wk) 0 to wk 26. EFV plasma concentrations were measured approximately 14h after drug intake at wks 2 and 6 after the onset of antiretroviral therapy and at wks 22 and 50 after the onset of TB treatment along with rich PK profile (6 samples) in 10 pts after wk 50. CYP2B6 G516T, CYP2B6 C1459T, CYP3A4*1B, CYP3A5 A6986G, CYP2A6*9, ABCB1 C3435T, OATP-C T521C and PXR A7635G polymorphisms were genotyped. EFV was assayed in plasma by HPLC. EFV concentrations versus time at all occasions were modelled using a one compartment model with delayed (1.5h) first-order absorption (0.8/h) and linear elimination. The estimate of the apparent volume of distribution (V/F) and clearance (CL/F) were 227L and 7.69L/h, respectively. BSV and WSV variabilities were 37% and 15% on CL/F and 53% and 14% on the bioavailability parameter F (fixed to 1), respectively. The CYP2B6 G516T polymorphism was strongly associated to EFV PK and explained 34% and 6% of EFV CL/F and F BSV, respectively. Frequency of loss of function CYP2B6 516T allele was 32%.

Conclusions: The PECAN study showed that CYP2B6 G516T genetic polymorphism was a strong genetic factor associated with EFV CL/F. Neither R nor body weight were found to significantly affect the PG model.

No conflict of interest
Abstract: O_03

Pharmacokinetics and drug interaction profile of cobicistat boosted-EVG with atazanavir, rosvuastatin or rifabutin

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Background: The single tablet regimen of elvitegravir (EVG)/cobicistat (COBI)/emtricitabine/tenofovir disoproxil fumarate (QUAD STR) has demonstrated durable efficacy and a favorable safety profile in Phase 3 studies. The drug interaction between COBI-boosted EVG (EVG/co) and a representative non-CYP3A metabolized lipid lowering agent (due to the known inhibitory effect of COBI on CYP3A), rosvuastatin, and an antimycobacterial agent, rifabutin, was evaluated to provide dosing recommendations for the QUAD STR. In addition, the interaction between EVG/co and atazanavir (ATV) was evaluated.

Methods: This crossover study enrolled healthy subjects across three cohorts. Cohort 1 (n=12) entailed sequential dosing rosvuastatin (single dose), 10-day dosing of EVG/co 85/150 mg plus ATV 300 mg once-daily (QD), 10-day dosing of EVG/co 150/150 mg QD, and EVG/co 150/150 mg plus rosvuastatin 10 mg. Cohort 2 (n=10) sequentially dosed EVG/co 85/150 mg plus ATV 300 mg QD followed by ATV 300 mg plus ritonavir 100 mg (ATV/r) QD, each for 10 days. Cohort 3 (n=12) dosed EVG/co for 10 days QD followed sequentially by 13-day dosing of EVG/co plus rifabutin 150 mg every other day (QOD), 10-day washout, and 13-day dosing of rifabutin 300 mg QD. Statistical comparisons of exposure for all analytes were made using geometric mean ratios (%GMR), with 90% confidence interval (CI) bounds of 70-143%, except rosvuastatin Cmax (70-175%). Safety assessments were performed throughout dosing and during 7-day follow-up.

Results: Of the 34 enrolled subjects, 5 discontinued due to adverse events (AEs): n=2 in Cohort 1 and n=3 in Cohort 2, all while receiving EVG/co + ATV (3 due to Grade 3 hyperbilirubinemia (a known ATV-related AE); 1 each due to Grade 3 rash and Grade 2 abdominal pain, with both subjects also having Grade 2 or 3 laboratory abnormality of hyperbilirubinemia). The most common treatment emergent AEs were headache, hyperbilirubinemia (in ATV treatments), and constipation. Upon EVG/co plus rosvuastatin dosing, EVG exposures were unaffected, but rosvuastatin Cmax (GMR (90% CI): 189 (148, 242)) and AUCref (138 (114, 167)) were higher. EVG/co 85/150 mg plus ATV resulted comparable AUCtau and Cmax, but higher Ctrough (192 (163, 225)) relative to EVG/co 150/150 mg. ATV Cmax (76.1 (59.1, 96.9)) and Ctrough (80.5 (55.6, 117)) were modestly lower, but many-fold above ATV protein-binding adjusted IC95, and these changes are not considered to be clinically relevant. EVG/co plus rifabutin resulted in lower EVG Ctrough (32.9 (26.9, 40.10)) versus EVG/co. With EVG/co, rifabutin exposures were comparable to reference, while metabolite 25-O-desacetylrifabutin exposures were 4.8 to 6.3-fold higher, resulting in 21% higher total antimycobacterial activity.

Conclusions: Administration with COBI-boosted EVG resulted in a modest increase in rosvuastatin exposure, which is not considered clinically relevant and does not require dose modification. No clinically relevant changes in ATV or dose-reduced rifabutin exposure were seen with EVG/co. COBI-boosted EVG exposures were unaffected by rosvuastatin or atazanavir. Coadministration of EVG with dose-reduced rifabutin is not recommended due to a reduction in EVG Ctrough.

Conflict of interest financial relationship(s): employee and stock holder of Gilead Sciences
Abstract: O_04

Therapeutic Drug Monitoring

Impact of Efavirenz (Efv) and N-Glucuronide efavirenz (N-Gln-Efv) plasma concentrations on premature discontinuation of efavirenz treatment

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Introduction: Poor tolerance and adverse drug reactions are the main reasons for Efv treatment discontinuation. An association study on the pharmacogenetic basis of ART discontinuation revealed that patients on Efv with CYP2B6 Loss of Function (LOF) were not more likely to discontinue their Efv treatment as compared to the reference genotype composite as long as they had functional accessory pathways (i.e. CYP2A6 and CYP3A). Only patients with all pathways impaired (major and accessory i.e. CYP2B6, CYP2A6 and CYP3A LOF) showed a remarkable early increase in the probability of Efv discontinuation1. Additionally, we observed a relative increase of Efv metabolites plasma levels, especially N-gln-Efv, in patients having all metabolic pathways impaired2.

In that context, we measured Efv and its metabolites in the plasma of genotyped patients included in this study, to determine whether Efv exposure and/or metabolites pattern may be a better predictor of treatment discontinuation than the Pharmacogenetic Score.

Materials & Methods: This is an observational cohort study including 89 patients under Efv in the first year of treatment, included in a pharmacogenetics association study for whom blood samples were collected during cohort visits. Genotyped Patients were classified according to a genetic score based on CYP2B6, CYP2A6 and CYP3A, with scores 1 to 6 corresponding to patients with all common functional to all LOF variants, respectively.

Plasma concentrations of Efv and metabolites were determined by liquid chromatography coupled to tandem mass spectrometry. N-gln-Efv levels were expressed in arbitrary units (a.u) using signal peak area. The rates of Efv treatment discontinuation rates were analysed amongst groups according to Efv and N-gln-Efv levels and genetic scores, by survival analysis using Cox regression models.

Results: Efv plasma concentrations ranged from 466 to 19037 ng/mL and increased progressively across the genetic score groups, with mean Efv and N-gln-Efv levels of 1470 ng/ml and 9361 a.u, and 6601 ng/ml and 28022 a.u, in the extreme scores 1 and 6, respectively (p<0.0001). A total of 36 (40%) patients discontinued Efv during the first year of treatment. No significant differences were observed in Efv and N-gln-Efv plasma concentrations between the population remaining on treatment and those discontinuing the Efv treatment (p= 0.75). The Cox regression model did not find any association between discontinuation rate and either Efv plasma concentration (p=0.83) or N-gln-Efv (p=0.90).

Conclusions: Blood concentration analysis confirms higher plasma levels of Efv and N-gln-Efv in patients with impaired metabolic pathways, as compared to patients with functional proteins. However, in this limited set of patients, neither Efv plasma levels nor N-glu-Efv levels were found to predict per se the early interruption of Efv treatment. Thus, other phenotypic markers of toxicity (i.e. other yet unstudied Efv metabolites or secondary biomarkers) remain to be identified in patients with all CYP2B6-, CYP2A6- and CYP3A-mediated pathways impaired. Meanwhile, the previously proposed pharmacogenetic score enables the best prediction of premature Efv discontinuation.

References:
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No conflict of interest
Abstract: O_05

Pharmacokinetic interaction between etravirine or darunavir/ritonavir and artemether/lumefantrine in healthy volunteers: a randomised trial.


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Background: Etravirine is a substrate and inducer of CYP3A and a substrate and inhibitor of CYP2C9 and CYP2C19. Darunavir/ritonavir is a substrate and inhibitor of CYP3A. Artemether and lumefantrine are primarily metabolised by CYP3A; artemether is also metabolized to a lesser extent by CYP2B6, CYP2C9 and CYP2C19. Artemether has an active metabolite, dihydroartemisinin. Interactions between artemether/lumefantrine and darunavir/ritonavir or etravirine were evaluated.

Methods: This single-centre, randomised, two-way, two-period cross-over study included 33 healthy volunteers. In Panel 1, 17 healthy volunteers received two treatments (A and B), with a washout period of 4 weeks between treatment: Treatment A: artemether/lumefantrine 80/480mg alone, three day course; Treatment B: etravirine 200mg BID for 21 days with artemether/lumefantrine 80/480mg from Day 8 (three day treatment course). In Panel 2, another 16 volunteers received two treatments (A and B), similar as in Panel 1 but instead of etravirine, darunavir/ritonavir 600/100 mg BID was given. Pharmacokinetics of darunavir/ritonavir and etravirine over 12 hours were made at Day 8 and Day 11. Pharmacokinetics of artemether, dihydroartemisinin and lumefantrine were performed after first and last intake of artemether/lumefantrine. Plasma concentrations of artemether, dihydroartemisinin, lumefantrine and etravirine or darunavir and ritonavir, as applicable, were assayed using validated liquid chromatography tandem mass spectrometry methods. Cmax and area under the plasma concentration-time curve (AUC) of each drug were obtained using non-compartmental analysis (WinNonlin) and compared using least square mean (LSM) ratios and associated 90% confidence intervals (CI).

Results: Overall 28 of 33 volunteers completed the study, 14 in each panel. Co-administration of etravirine led to reductions in the AUC of artemether (38%, 90% CI 0.48-0.80), dihydroartemisinin (15%, 90% C. 0.75-0.97) and lumefantrine (13%, 90% CI 0.77-0.98). Co-administration of darunavir/ritonavir led to reductions in the AUC of artemether (16%, 90% CI 0.69-1.02) and dihydroartemisinin (18%, 90% CI 0.74-0.91) with an increase in lumefantrine (2.75-fold, 90% CI 2.46-3.08). Co-administration of artemether/lumefantrine had no effect on etravirine, darunavir or ritonavir AUC. No relevant differences in the incidence of adverse events were observed when artemether/lumefantrine was co-administered with either etravirine or darunavir/ritonavir, compared with either drug used alone. No drug-related serious adverse events were reported during the study.

Conclusions: Co-administration of etravirine with artemether/lumefantrine may lower the antimalarial activity of artemether and therefore, should be used with caution. Co-administration of darunavir/ritonavir with artemether/lumefantrine increased lumefantrine exposure by 2.75-fold. Darunavir/ritonavir can be co-administered with artemether/lumefantrine without dose adjustment however co-administration is not recommended with other drugs that may cause QTc prolongation. No effect of artemether/lumefantrine on etravirine, darunavir or ritonavir pharmacokinetics were observed. The treatments were generally safe and well tolerated in healthy volunteers.

Conflict of interest financial relationship(s): TK, RD, YD and PM are employees of Janssen. KJ was funded by Janssen to conduct the trial. AH has received consultancy payments from Janssen
Abstract: O_06

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Antiviral activity, exposure-response, and resistance analyses of monotherapy with the novel HIV NRTI BMS-986001 in ART-experienced subjects

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Background: BMS-986001 is a novel potent HIV NRTI with a favourable in vitro mitochondrial safety profile. Monotherapy with BMS-986001 100 to 600 mg QD for 10 days in antiretroviral-experienced subjects was found to be generally safe and well tolerated, with significant reductions in plasma HIV-1 RNA observed for all doses. The purpose of this analysis was to evaluate further the antiviral activity, exposure-response relationship, and resistance profile of BMS-986001 monotherapy.

Materials and Methods: This was a double-blind, placebo-controlled, dose-escalating multicenter study in 32 antiretroviral-experienced HIV-1 infected subjects who were off therapy for ≥3 months. Sequential 8 subject cohorts (100, 200, 300, and 600 mg) were randomized 3:1 to receive BMS-986001 or placebo once daily for 10 days. Serial PK samples were collected over a 24 h dosing interval on Days 1 and 10 as well as pre-dose on Days 3 and 5 and post-dose on Day 12. BMS-986001 was assayed by validated LC-MS/MS. PK parameters were derived from plasma concentration versus time data using noncompartmental methods. Plasma HIV-1 RNA was determined at screening, Day 1 (pre-dose), Days 3, 5, 11, and during follow-up on Day 17 and 24. HIV-1 drug resistance genotype was assessed on Day 1 (pre-dose), 11, and 17. Mann-Whitney U-test was used for exploratory analysis of changes from baseline to compare each active dose to placebo. Exposure-response (E-R) analysis was performed to explore the relationship between overall plasma exposures (AUC) of BMS-986001 and Day 11 change from Day 1 in log_{10} plasma HIV-1 RNA levels. A nonlinear Emax model was fitted to the data using WinNonlin®.

Results: PK parameters were similar on Days 1 and 10 with no significant accumulation at all doses tested. Median declines from baseline in plasma HIV-1 RNA of 0.97, 1.15, 1.28, and 1.15 log_{10} copies/mL were observed on Day 11 in the 100, 200, 300, and 600 mg cohorts, respectively. Increases in median CD4+ T-cell counts from baseline on Day 11 (71-178.5 cell/mm³) were observed in all groups. An Emax model adequately described the relationship between BMS-986001 plasma AUC(TAU) on Day 10 versus change in log_{10} plasma HIV-1 RNA on Day 11 from Day 1. Doses of 100, 200, and 400 mg are expected to cover the range of exposures that have demonstrated antiviral activity ≥1 log_{10} based on the E-R analysis, with minimal overlap in AUC. Despite treatment experience with NRTIs in all subjects, no NRTI-associated mutations were selected on HIV-1 genotype resistance testing.

Conclusions: Significant decline in plasma HIV-1 RNA comparable to currently marketed NRTIs was observed in all dose groups, with no selection of NRTI resistance mutations after 10 days of monotherapy in this antiretroviral-experienced population. E-R analysis suggested a correlation between BMS-986001 plasma AUC and antiviral activity, with doses from 100 to 600 mg demonstrating ≥1 log_{10} decline in plasma HIV-1 RNA. Continued clinical development of BMS-986001 at ≥100 mg daily is warranted.

Conflict of interest: I am an employee of Bristol-Myers Squibb.
Abstract: O_07

Metabolism and drug-drug interaction profile of dolutegravir(DTG, S/GSK1349572)

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Introduction: DTG is a once-daily, unboosted, integrase inhibitor(INI) in late stage clinical development in HIV-1 infected adults and children. A comprehensive clinical pharmacology program has assessed the potential interactions between DTG and various drugs. Herein, we summarize the results from both clinical and non-clinical evaluations of DTG metabolism and drug-drug interaction profile including associated clinical implications.

Methods: In vitro experiments were performed to determine DTG’s metabolic enzymology, its interaction with transporters, and its potential to cause and be subject to drug interactions. A human mass balance study using radiolabeled DTG in 6 healthy subjects was performed to quantify recovery of DTG in urine and feces as well as profile metabolites in plasma, urine, and feces. Forteen Phase 1 studies in healthy subjects have been performed to assess the interaction between DTG and various drugs, including midazolam (CYP3A probe), antiretroviral (ART) and non-ART medications expected to be used concomitantly with DTG.

Results: DTG is primarily metabolized by UGT1A1 with CYP3A as a minor route (~10-15%). Renal excretion of unchanged DTG is minimal (<1% dose administered). In vitro, DTG is not a CYP inducer and at clinically relevant concentrations is not an inhibitor of CYP, UGT, or major transporters (except for OCT2). In vivo, DTG had no effect on the pharmacokinetics of midazolam, tenofovir, or methadone. DTG is not anticipated to be a perpetrator of drug-drug interactions except for sensitive substrates of OCT2 with a narrow therapeutic window, e.g. dofetilide. DTG exposure is affected by clinically manageable drug-drug interactions. UGT1A1 inhibitor, atazanavir and atazanavir/ritonavir, increased DTG exposure by 62-91% for AUC and 33-49% for Cmax. UGT/CYP3A inducers decreased DTG exposure at variable degrees, with the reduction in DTG Cτ by some ritonavir-boosted protease inhibitors (darunavir, tipranavir, fosamprenavir), rifabutin, and efavirenz ranging from 30% to 76%. These changes in DTG exposure are not considered clinically significant in INI-naive patients given the safety/tolerability profile of DTG as well as the fact that DTG exposures with these enzyme inducers remain above those showing durable antiviral activity in Phase 2 dose ranging trials in HIV-infected subjects. Efavirine (alone) reduced DTG Cτ by 88%, however, this effect was attenuated by lopinavir/ritonavir (LPV/r) and darunavir/ritonavir (DRV/r) coadministration; DTG may therefore be co-administered with etravirine without a dosage adjustment if the subject is receiving concomitant LPV/r or DRV/r. DTG should be given twice daily if co-administered with rifampin in INI-naive patients. Antacid (Maalox) decreased DTG exposure by >70% when given concomitantly due to metal cation chelation rather than pH effect; dosing separation by at least 2 hours attenuated the impact. LPV/r, prednisone, and omeprazole had no significant effect on DTG exposure.

Conclusions: DTG has demonstrated a limited number of clinically significant drug-drug interactions without dose adjustment for most antiretroviral (ART) and other commonly co-administered drugs in INI-naive subjects. Based on long-term data (>48 weeks) from phase2b dose-ranging studies, a dose of DTG 50mg once daily in the face of modest drug interactions is anticipated to achieve adequate drug exposure to maintain good tolerability and antiviral activity in INI-naive subjects.

Conflict of interest financial relationship(s): I am currently an employee with GlaxoSmithKline
Abstract: O_08

CYP2C19 genotype-dependent pharmacokinetic drug interaction between voriconazole and ritonavir boosted atazanavir in healthy subjects

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Introduction: Voriconazole, a broad-spectrum triazole antifungal agent, is mainly metabolized by CYP2C19 and to a lesser extent by CYP3A4 and CYP2C9. Due to genetic polymorphism of CYP2C19, voriconazole AUC is on average 2-4 fold higher in CYP2C19 poor metabolizers (PM) than in extensive metabolizers (EM). Ritonavir 100 mg BID was shown to decrease voriconazole steady-state AUC by 39% in a majority CYP2C19 EM population, likely due to induction of CYP2C19 by ritonavir. This study assessed the two-way drug interactions when adding voriconazole to ritonavir-boosted atazanavir in both CYP2C19 EM and PM healthy subjects.

Material & Methods: This was an open-label, three periods, two-center, non-randomized, trial in healthy volunteers. 24 subjects with at least 1 functional CYP2C19 allele and 8 subjects without functional CYP2C19 allele were dosed. Each received voriconazole alone on Days 1-3 followed by a 7-day washout. Atazanavir/ritonavir 300/100mg QD was given on Days 11-20 and then coadministered with voriconazole on Days 21-30. The voriconazole doses were 200mg BID (400 mg BID on Days 1 and 21) for EM subjects and 50mg BID (100mg BID on Days 1 and 21) for PM subjects. Serial pharmacokinetic samples for atazanavir, ritonavir and voriconazole were collected on Days 3, 20 and 30. Pharmacokinetic analyses were conducted using noncompartmental methods. General linear models for treatment comparison were performed for EM subjects; interim summary statistics were provided for PM subjects.

Results: 20 EM and 7 PM subjects completed the study. 3 EM subjects dropped out due to rash and 1 EM subject withdrew consent. 1 PM subject withdrew consent but provided complete pharmacokinetic data. In EMs, upon coadministration, voriconazole AUC and Cmin decreased 33% (90% CI: 22%-42%) and 39% (28%-49%), respectively; atazanavir AUC and Cmin decreased 12% (5%-18%) and 20% (10%-28%), respectively. In PM subjects, coadministration of atazanavir/ritonavir with voriconazole 50mg BID increased voriconazole Cmax and AUC by 4-6 fold; atazanavir AUC and Cmin decreased by 20% and 31%, respectively. Ritonavir Cmax and AUC were generally unchanged in either population. There were no deaths or SAEs. In EM subjects, headache (50%) and blurred vision (33%) were most frequent reported AEs (all grades) when receiving voriconazole; hyperbilirubinaemia (63%) was most frequent while receiving atazanavir/ritonavir. In PM subjects, the most frequent reported AEs were increased blood bilirubin (13%).

Conclusions: Results of this study indicated that the effect of atazanavir/ritonavir on voriconazole exposure is highly dependent on CYP2C19 genotype. In EM subjects, atazanavir/ritonavir decreased voriconazole AUC by 33%, similar to the historical observation of 39% when voriconazole was given with ritonavir 100mg BID. In PM subjects, atazanavir/ritonavir markedly increased voriconazole exposure, likely through inhibition of CYP3A4. Voriconazole resulted in a 20-30% decrease in atazanavir Cmin in both EM and PM subjects. The safety and tolerability profiles of the combination were comparable with atazanavir/ritonavir and voriconazole administered alone. These results support the current recommendation that coadministration of voriconazole and atazanavir/ritonavir is not recommended unless an assessment of the benefit/risk justifies the use of voriconazole.

Conflict of interest financial relationship(s): LZ, JU, EC, IC, XX, BV, MH, RBertz are employees of Bristol-Myers Squibb RBrüggemann, AC, RS, DB are contracted service providers
Abstract: O_09

CYP2B6 activity in HIV-infected children and adolescents: Pharmacokinetic evaluation of efavirenz and its 8-hydroxymetabolite

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Background: Efavirenz (EFV) is a substrate of CYP2B6 and the 8-hydroxylation of EFV has been proposed as a phenotypic probe to evaluate CYP2B6 activity in humans. Functional polymorphisms in CYP2B6 result in large variability in EFV exposure among infants, children and adolescents. EFV concentrations are often sub-therapeutic with currently recommended pediatric EFV dosing. Developmental changes in the metabolism of EFV may also have a potential role in sub-therapeutic pediatric exposure. This study was aimed to evaluate EFV metabolism and CYP2B6 activity in HIV-infected children and adolescents.

Methods: This was a cross-sectional study of pediatric and adolescent patients with HIV-infection receiving EFV-based antiretroviral therapy. CYP2B6 genotyping was performed at enrollment using the ABI TaqMan assay. The concentrations of EFV and its metabolites 8-hydroxy-EFV (E8F) and 8-hydroxy-EFV glucuronide (E8G), were measured at steady-state during a 24 hour pharmacokinetic (PK) study at time points 0, 1, 2, 4, 6, 8, 12 and 24 hours after an observed standard recommended EFV dose and were quantitated by a published validated HPLC-MS/MS method using the Sciex APT-2000. PK analyses were performed using non-compartmental methods. Non-parametric methods were used to analyze the association between the different CYP2B6 516 genotypes and EFV, E8F and E8F+E8G exposures.

Results: 13 children and adolescents (7 girls/6 boys; 12 Black/1 Hispanic) with a median age of 12.8 yrs (range: 8.2-17.4 yrs) were enrolled. CYP2B6 516 genotype distribution was GG=6, GT=4, TT=3 (HWE p-value=0.207). Median EFV AUC was 62.3 (range: 21.6-271.6) mcg*hr/mL and CL/F was 0.21 (0.0466-0.460) L/h/kg. The subjects with CYP2B6 516 TT genotype had the 3 highest EFV AUCs (96.3-271.6) and lowest CL/F (0.0466-0.113) values. Sub-therapeutic C24 (<1 mg/L) was observed in 2 subjects with CYP2B6 516 GG genotype. The median ratio of (E8F+E8G)/EFV was comparable across the three genotypes. (E8F+E8G)/EFV was associated with GG genotype being greatest and TT genotype being lowest, 8.97 (2.68 – 14.41) and 1.04 (0.93 – 1.60), respectively (p=0.013). With GT and TT genotypes combined into one group, a significant difference for both E8F/EFV and E8F+E8G/EFV was observed with the GG genotype having a greater median than the GT and TT genotype, p=0.046 and p=0.046, respectively. E8G concentrations were greater than E8F in all but one subject and had a trend to decreasing E8G/EFV median values from 3.43 (0.00-9.45) to 2.83 (1.48-6.04) to 1.03 (0.61-1.38) with GG, GT and TT genotypes, respectively (p=0.075). The E8G/EFV ratio was correlated with EFV CL/F (r=0.79) while the E8F/EFV ratio was not (r=0.27). No age effects on EFV CL/F were apparent given the impact of CYP2B6 genotype.

Conclusions: EFV pharmacokinetics were highly variable among children and adolescents in our study cohort. CYP2B6 genotype was directly related to the AUC and CL/F of EFV. Extensive conversion of E8F to E8G limited the usefulness of E8F as a phenotypic probe for CYP2B6 activity in our study. Ongoing study with repeated within-subject sampling will allow us to better investigate the impact of developmental changes on the metabolism of EFV in children and adolescents.

No conflict of interest
Abstract: O_10

Can Tenofovir diphosphate and Emtricitabine triphosphate concentrations in total blood cells be used to measure adherence?

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Introduction: Intracellular tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) are measurable in peripheral blood mononuclear cells (PBMCs), have a half-life 5-8 fold longer than the plasma half-life of TFV and FTC and have been proposed as markers of long-term antiretroviral (ARV) adherence. However, isolating PBMCs is expensive, complex, and not feasible in many research settings. The FEM-PrEP trial collected the upper layer packed cells (ULPC) obtained after centrifuging anticoagulated blood and removing the plasma. We compared concentrations of TFV-DP and FTC-TP between these ULPCs and PBMCs as a possible surrogate marker of adherence.

Material & Methods: 10 HIV+ adults with HIV RNA <50c/mL on a TFV/FTC-containing regimen provided 5 paired PBMC and ULPC samples over 6h. To simulate FEM-PrEP conditions, the ULPC samples were split; one was immediately frozen, and one refrigerated for 14h prior to freezing. TFV-DP and FTC-TP concentrations were analyzed by LC-MS/MS. Partial areas under the curve (AUC) were calculated using WinNonlin and Spearman Rank Correlations (rho) between PBMC and ULPC were determined using SAS. Median values and interquartile ranges are reported.

Results: The concentration of TFV-DP in PBMCs was 143(103-248)fmol/10⁶ cells and in ULPC was 663 (481-1110)fmol/10⁶ cells (rho=0.64; p <0.0001). The concentration of FTC-TP in PBMCs was 6660 (5650-10000)fmol/10⁶ cells and in ULPC was 36.3 (22.6-52.9)fmol/10⁶ cells (rho 0.56;p<0.0001). The TFV-DP AUC correlation was 0.98 (p<0.0001) and the FTC-TP correlation was 0.52 (p=0.15). Compared to PBMCs, ULPC TFV-DP was 450% higher and FTC-TP was 99.5% lower. Refrigeration did not result in degradation for TFV-DP (increase of 6% (9-21%)) or FTC-TP (increase of 54% (11-91%)). ULPC concentrations for TFV-DP and FTC-TP in 1 additional subject receiving a single dose of TFV/FTC were only 0.7% and 29%, of the other 10 subjects, respectively.

Conclusions: In ULPCs, TFV-DP concentrations were 450% higher than in PBMCs while FTC-TP concentrations were 99.5% lower. ULPC concentrations significantly correlated with PBMC concentrations, and TFV-DP AUCs were highly correlated. ULPC samples refrigerated prior to freezing did not show significant drug degradation. Preliminary single-dose data suggest good discrimination between intermittent vs. consistent dosing. Based on these data, ULPC concentrations of TFV-DP and FTC-TP may be a good surrogate for PBMC concentrations as a measure of ARV adherence. This is currently being investigated in the FEM-PrEP study.

No conflict of interest
Abstract: O_11

Antiretrovirals for prevention: pharmacokinetics of raltegravir in gut-associated lymphoid tissue (GALT) of healthy male volunteers


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Background: The integrase inhibitor raltegravir (RAL) is an extremely potent ARV that may have applications beyond treatment of chronic HIV. The extent to which RAL penetrates into the gastrointestinal tract, particularly gut-associated lymphoid tissue (GALT), is not known but important to understand as primary HIV infection results in rapid viral migration to GALT.

Methods: An open-label pharmacokinetic (PK) study was performed in 14 HIV-negative men receiving RAL 400mg twice daily for 7 days. Seven blood plasma (BP) samples were collected over a 12 hr interval on Day 1 (PK1) and Day 7 (PK2). Subjects underwent colonoscopy during PK1 and PK2. Tissue samples were obtained from the terminal ileum (TI), splenic flexure (SF) and rectal tissue (RT). RAL concentrations were measured by validated LC/MS assays with a 1ng/mL LLD. Data were analyzed by noncompartmental methods (WinNonlin 6). A RT density of 1.05 g/mL was assumed for comparisons. Demographics are reported as median (range). PK parameters are reported as mean using composite data.

Results: Subject age was 24 (19-49) yrs and BMI was 25 (19-31) kg/m². Nine were Caucasian. After a single dose, the AUC12h was 594, 258 and 143 mg*hr/g in the TI, SF, and RT, respectively, and increased to 530, 2240, and 788 mg*hr/g in the TI, SF, and RT, respectively, following multiple dosing. When compared to BP AUC, the RAL AUCs was 99-fold, 70-fold and 39-fold higher in the TI, SF, and RT, respectively after single dose. After multiple doses, RAL AUC decreased slightly to 84-fold in the TI, but increased to 679-fold at the SF and 239-fold in the RT as compared to BP AUC. The RAL accumulation ratio (PK2 AUC12h/ PK1 AUC12h) was 0.9 for TI, 8.7 for SF and 5.5 for RT. RAL was quantifiable throughout the GI tract within 1 hr post-dose.

Conclusions: RAL rapidly disseminates and maintains high exposure throughout the GI tract. Following the initial dose, exposure is especially high in the terminal ileum, where GALT is prominent. After multiple dosing, concentrations in the GI tract increase disproportionately to plasma. Concentrations of RAL in these tissues are much higher than what is required for full viral suppression in plasma, and may result in full suppression of local viral replication. These data also suggest that RAL may have a role in pre- or post-exposure prophylaxis and treatment of primary HIV infection.

No conflict of interest
Abstract: O_12

Pharmacokinetics of long-acting rilpivirine in plasma, genital tract and rectum of HIV-negative females and males administered a single 600 mg dose.

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Introduction: Pre-exposure prophylaxis (PrEP) is an experimental approach using antiretroviral agents to prevent HIV transmission. Studies on HIV PrEP have yielded mixed results, indicating that efficacy of oral PrEP may be dependent on treatment adherence. A long acting injectable formulation of rilpivirine (RPV-LA) has been developed, which, given its prolonged apparent elimination half-life, may represent a PrEP agent that can be administered at intervals ≥1 month. In this study we determined the pharmacokinetics (PK) of RPV-LA in the plasma, female genital tract (cervicovaginal fluid & tissue; CVF & VT) and male rectal compartment (rectal fluid & tissue; RF & RT) up to 84 days after a single 600 mg IM injection in HIV-negative subjects.

Methods: As part of a prospective, open-label, exploratory PK trial, 10 female and 6 male HIV-negative volunteers with low behavioural risk for HIV were administered 600 mg RPV-LA (G001 formulation) intramuscularly (gluteus maximus) at day 0. Plasma RPV concentrations were determined on days 0 (pre-dose, 4, 8 hr), 1, 3, 7, 11, 14, 21, 28, 42, 56 and 84. CVF, self-collected by direct aspiration, and RF, collected via intra-rectal aspiration using Weck Cel® spears, were determined at similar times from day 0, at 8 hr postdose onwards. Biopsies of VT were taken at days 14 and 7 or 28, and RT biopsies were collected at days 7 and 14. RPV concentrations [RPV] were determined by LC-MS/MS (range 0.2–200 ng/mL). PK parameters (AUC \textsubscript{84d}, C\textsubscript{84d}, C\textsubscript{max}, T\textsubscript{max} and t\textsubscript{1/2}) were calculated using WinNonLin.

Results: Following a single 600 mg IM injection, [RPV] persisted in plasma over 84 days postdose in both sexes.
Abstract: O_13

Pharmacokinetics of a novel EVG/COBI/FTC/GS-7340 single tablet regimen

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Background: GS-7340, a novel prodrug of tenofovir (TFV) with enhanced lymphatic delivery, has demonstrated significantly greater decreases in HIV-1 RNA at lower doses versus tenofovir disoproxil fumarate (TDF), provides higher intracellular TFV diphosphate in peripheral blood mononuclear cells (PBMCs), and substantially lower circulating TFV exposures. GS-7340 has been coformulated with elvitegravir (EVG), cobicistat (COBI), and emtricitabine (FTC) into a single tablet regimen (STR). Across three healthy subject studies, the multiple dose pharmacokinetics (PK) of EVG/COBI/FTC/GS-7340 STR and/or interaction potential between GS-7340 and COBI were evaluated to facilitate GS-7340 dose selection for STR clinical development.

Methods: In Study 1 (n=20), subjects received EVG/COBI/FTC/GS-7340 (150/150/200/40 or 150/150/200/25 mg), EVG/COBI/FTC/TDF (150/150/200/300mg) or GS-7340 25 mg stand alone (SA), 12 days/treatment in a balanced Williams 4x4 design. In Study 2 (n=12), subjects sequentially received GS-7340 8 mg SA (Reference) for 12 days and GS-7340 plus COBI 8/150 mg (Test) for 10 days. In Study 3 (n=34), across two cohorts (each 2x2 crossover design), subjects received EVG/COBI/FTC/GS-7340 (150/150/200/10 mg) (Test, both cohorts), EVG plus COBI 150/150 mg (Reference, Cohort 1), and FTC plus GS-7340 200/25 mg (Reference, Cohort 2), each treatment dosed for 12 days. Statistical comparisons of GS-7340 and TFV were made using geometric mean ratios (GMR), with 90% confidence intervals (CI) of 70-143% (Study 1: Test= EVG/COBI/FTC/GS-7340, Reference= GS-7340 SA). Safety assessments were performed throughout dosing and follow-up.

Results: All treatments were generally well tolerated. Study 1 entailed 19/20 completers with one discontinuation from adverse events (AEs) (rhabdomyolysis (Grade 2) while receiving GS-7340 SA). All subjects completed Study 2, while 33 of 34 subjects completed Study 3. No Grade 3 or 4 AEs were observed in the studies. In Study 1, when dosed as EVG/COBI/FTC/GS-7340 , GS-7340 (25 mg) and resulting TFV exposures were substantially higher versus GS-7340 SA (GMR (90% CI) GS-7340 AUClast: 222 (200, 246) and Cmax: 223 (187, 265); TFV AUCtau: 307 (290, 324), Cmax: 368 (320, 423)). In Study 2, when dosed as GS-7340 plus COBI versus GS-7340 SA, GS-7340 exposures were similarly high, suggesting that the interaction observed in Study 1 was COBI-mediated (GMR (90% CI) GS-7340 AUClast: 265 (229, 307) and Cmax: 283 (220, 365), TFV AUCtau: 331 (310, 353), Cmax: 334 (302, 370), and Ctau: 335 (312, 359)). In Study 3, upon dose adjustment of GS-7340 to 10 mg, EVG/COBI/FTC/GS-7340 (150/150/200/10 mg) versus Reference resulted in comparable GS-7340 and TFV exposures. (GMR (90% CI) GS-7340 AUClast: 91.4 (84.1, 99.4) and Cmax: 98.7 (84.6, 115), TFV AUCtau: 124 (117, 131), Cmax: 114 (97.5, 134), and Ctau: 125 (117, 134)). EVG/COBI/FTC/GS-7340 STR provided similar EVG, COBI, and FTC exposures versus reference treatments and historical data.

Conclusions: GS-7340 and TFV exposures increase ~2-3-fold following coadministration with COBI or as EVG/COBI/FTC/GS-7340 dosing, which may be due to COBI inhibition of intestinal Pgp-mediated intestinal secretion of GS-7340. With a GS-7340 10 mg dose, EVG/COBI/FTC/GS-7340 provided comparable GS-7340 and TFV exposures as GS-7340 25 mg and ~90% lower TFV exposure versus EVG/COBI/FTC/TDF. A Phase 2 study comparing these STRs is ongoing.

Conflict of interest

financial relationship(s): employee and stockholder of Gilead
Abstract: O_14

Pharmacokinetic modeling of Efavirenz (EFV), Atazanavir (ATV), Lamivudine (3TC), and Tenofovir (TFV) in the female genital tract of HIV-infected women

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Introduction: Understanding disposition of antiretrovirals (ARVs) in the female genital tract using pharmacokinetic (PK) modeling is critical to designing effective oral drug regimens for HIV prevention. Here, we mathematically describe the relationship between ARV concentrations in blood plasma (BP) and cervicovaginal fluid (CVF) for 4 ARVs demonstrating high CVF exposure (lamivudine-3TC), CVF exposure similar to BP (tenofovir-TFV), moderate CVF exposure (atazanavir-ATV), and low CVF exposure (efavirenz-EFV) from published data.

Materials and Methods: Paired BP and CVF samples were taken at 6 time-points over 24 hours in an unblinded, open-label PK study in HIV-infected women at first-dose (FD) and after multiple doses (MD) of a provider-selected ARV regimen. Drug concentrations were determined using validated analytical methods. For each drug, the appropriate compartmental model was fit to individual subject BP concentration-time profiles using Bayesian estimation within ADAPT5. CVF concentrations were co-modeled with BP and the model was further optimized. The final model was chosen based on residual plots, Akaike Information Criterion, and visual inspection of observed vs. fitted concentration-time profiles. After fitting individual profiles to obtain initial estimates for parameters, nonlinear mixed effects modeling was performed using S-ADAPT (MCPEM) to obtain mean parameter estimates, precision, and inter-individual variability. Model-predicated area-under-the-time-concentration curve over the dosing interval at steady state (AUC0-t) was calculated for each subject using post-hoc estimates, and exposure ratios of CVF AUC0-t:BP AUC0-t calculated for each drug, using both total and fitted free BP AUC.

Results: 25/27 women in the published analysis contributed data for the 4 drugs (n = 10 for EFV, n = 8 for ATV, n = 19 for 3TC, n = 15 for TFV). 17/25 women were African-American, and median age was 35 years. The basic model for all drugs utilizes first-order absorption with an absorption delay, a central blood compartment with 1 peripheral compartment, and a series of transit compartments to describe the transfer of drug from BP to CVF. Only protein-unbound drug was assumed to transfer into the CVF for EFV and ATV (protein binding >85%); total drug was transferred for 3TC and TFV (protein binding <50%). Drug in the CVF was modeled as a single compartment with an implied volume of 1 L for EFV and ATV, and 2 compartments with an estimated volume for 3TC and TFV. In order to characterize variability between visits, certain parameters were allowed to vary between visits, including total BP clearance and CVF clearance, absorption rate, and transfer rate between blood and CVF. Inter-individual variability is high, as expected for ARVs, particularly in the female genital tract. Model-predicted CVF AUC0-t:BP AUC0-t ratios are consistent with published results.

Conclusions: This is the first PK modeling of antiretroviral disposition between blood and the female genital tract, using data from a comprehensive study of CVF concentrations in HIV-infected women. This model will help inform future studies designed to determine optimal ARV CVF concentrations for effective HIV transmission prevention and suppression of genital tract viral load in women, as well as provide a framework for optimal sampling design in prevention studies.

Conflict of interest: financial relationship(s): ADMK has received research grants and honoraria from GlaxoSmithKline, Bristol-Myers Squibb, and Gilead. KBP has received research grants from GlaxoSmithKline.
Abstract: O_15

Pharmacokinetic interaction between boceprevir and etravirine in HIV/HCV seronegative volunteers

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Abstract: O_15

Pharmacokinetic interaction between boceprevir and etravirine in HIV/HCV seronegative volunteers

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Background: A critical consideration in the treatment of HIV/HCV coinfection is the potential for drug interactions. The HCV protease inhibitor, boceprevir, may be administered to treatment-experienced patients on an antiretroviral regimen which includes the non-nucleoside reverse transcriptase inhibitor, etravirine. These drugs have overlapping pharmacology; both are CYP3A substrates, etravirine is a CYP3A inducer, and boceprevir is a CYP3A inhibitor. The objective of this study was to estimate the bioequivalence of boceprevir and etravirine area-under-the concentration time curve over the dosing interval (AUCtau), maximum concentration (Cmax), and trough concentration (Cmin or C8hr) in combination vs. alone.

Materials & Methods: In this open-label, cross-over study, HIV/HCV seronegative volunteers received (1) boceprevir 800mg every 8 hours, (2) etravirine 200mg every 12 hours, and (3) boceprevir 800mg every 8 hours plus etravirine 200mg every 12 hours for 11-14 days with at least a 14 day “washout” between sequences. Subjects were randomized to sequence order and intensive pharmacokinetic sampling was performed on day 11-14 of each sequence following observed dosing and a standardized meal. Boceprevir and etravirine were quantified using validated LC/MS/MS and HPLC/UV assays, respectively and pharmacokinetic parameters determined using non-compartmental methods (WinNonLin). Geometric mean ratios (GMR) and 90% CI for the combination sequence vs. alone were evaluated using two one-sided t tests (TOST). The hypothesis of equivalence was rejected if the lower confidence limit was <0.8 or the upper confidence limit was >1.25.

Results: Thirty four subjects consented for study, 26 enrolled, and 20 (10 female, 14 Caucasian/3 Hispanic/3 Black, mean age and weight 36.4 years and 72.41 kg) completed all three sequences. Geometric mean (%CV) etravirine AUCtau, Cmax, and Cmin were 7698 ng/hr/mL (33), 890 ng/mL (29), and 439 ng/mL (46), respectively when given alone vs. 5957 ng/hr/mL (54), 686 ng/mL (45), and 313 ng/mL (60) when combined with boceprevir. The GMR (90% CI) for etravirine AUCtau, Cmax, and Cmin were 0.77 (0.66-0.91), 0.76 (0.68-0.85), and 0.71 (0.54-0.95), respectively. Geometric mean (%CV) boceprevir AUCtau, Cmax, and C8hr were 4600 ng/hr/mL (47), 1423 ng/mL (43), and 106 ng/mL (64), respectively when given alone vs. 5047 ng/hr/mL (30), 1565 ng/mL (28), and 94 ng/mL (98) when combined with etravirine. The boceprevir GMR (90% CI) for AUCtau, Cmax, and C8hr were 1.10 (0.94-1.28), 1.10 (0.94-1.29), and 0.88 (0.66-1.17), respectively. All adverse events were mild or moderate. Six subjects discontinued study; 4 due to grade 2 rash (3 on combination, 1 on etravirine only); 1 due to increased energy, anxiety, nervousness, and insomnia while on the combination; and 1 due to presumed viral illness while on the combination, causing her to miss three days’ of study medications.

Conclusions: Etravirine AUCtau, Cmax, and Cmin were decreased 23%, 24%, and 29%, respectively in the presence of boceprevir. Boceprevir AUCtau and Cmax were increased 10%, while C8hr was decreased 12% by etravirine. The observed interactions were not predicted based on our current knowledge of the pharmacology of these drugs. Interactions between boceprevir and antiretroviral drugs are complex and additional research is needed to elucidate their mechanism(s) and therapeutic implications.

Conflict of interest

financial relationship(s): Investigator funded project by Merck
Abstract: O_16

Darunavir and ritonavir total and unbound plasmatic concentrations in HIV-HCV coinfected patients with hepatic cirrhosis.

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Background: Ritonavir (RTV)-boosted Darunavir (DRV/r) is mainly metabolized in the liver. Hepatic cirrhosis can impair liver function and decrease plasmatic proteins, potentially modifying DRV/RTV pharmacokinetics (PK). With other protease inhibitors (eg fosamprenavir) dose adjustments have been recommended in cirrhotic patients. Unbound rather than total concentrations may be more reliable in these patients, but there is scarce data on DRV unbound concentrations.

Methods: HIV-HCV coinfected patients with compensated cirrhosis (defined by biopsy, clinical or radiological findings or elastography>14 kPa) were included. DRV/r was given 800/100 mg once-daily or 600/100 mg twice-daily as appropriate. A complete steady-state 12-hours PK study was performed, with pre-dose, 1, 2, 3, 4, 6, 8 and 12 hours after dose samples. Drug concentrations were determined by mass spectrometry. AUC and CL/F were assessed by non-compartmental model and linear/log trapezoidal rule with WinNonlin 3.3. Descriptive values are expressed as medians and interquartile ranges. Mann-Whitney U test has been used to compare concentrations between groups and Spearman test for studying correlations.

Results: Nineteen patients (15 once-daily, 4 twice-daily) were included. Baseline characteristics were: 68% men, age 48 (43-49) years, BMI 23.4 (20.2-26.6) kg/m², CD4 350 (249-677) cel/mm³. HCV genotypes were: 1 (74%), 3 (21%) and unknown (5%). Eight patients had had prior clinical descompensations, median MELD was 9 (8-12) and the patient’s worse Child-Pough score was C in 3 cases, B in 2 and A in 14. Median elastography values were 22 (13-35) kPa.

Darunavir total and unbound PK parameters for 800/100 mg once-daily were Cmin 1299 (915-4920) and 153 (113-317) ng/mL, Cmax 6445 (5631-11863) and 1131 (985-1382) ng/mL, Tmax 4 (2-4) and 2 (2-4) hours, AUC0-12 63732 (56045-153704) and 12753 (8472-16002) ng·h/mL, CL/F 10.1 (4.5-14.1) and 62.7 (49.9-94.9) L/h. Ritonavir total and unbound PK parameters for 800/100 mg once-daily were Cmin 82 (54-168) and 1 (0.4-1.5) ng/mL, Cmax 6445 (5631-11863) and 1131 (985-1382) ng/mL, Tmax 4 (2-4) and 2 (2-4) hours, AUC0-12 63732 (56045-153704) and 12753 (8472-16002) ng·h/mL, CL/F 10.1 (4.5-14.1) and 62.7 (49.9-94.9) L/h.

Darunavir total and unbound PK parameters for 600/100 mg twice-daily were Cmin 957 (74-1707) and 2566 (1290-4260) ng/mL, Cmax 6775 (4545-7135) and 944 (429-1308) ng/mL, Tmax 4 (2-4) and 3 (2-4) hours, AUC0-12 63732 (56045-153704) and 12753 (8472-16002) ng·h/mL, CL/F 9.2 (8.5-26.7) and 87.8 (60.5-216.5) L/h. Ritonavir total and unbound PK parameters for 600/100 mg twice-daily were Cmin 222 (95-707) and 3.4 (1.3-5.8) ng/mL, Cmax 915 (267-1366) and 9.5 (4.4-24.9) ng/mL, Tmax 4 (2-6) and 3 (2-5) hours, AUC0-12 7973 (2580-12444) and 80.3 (36.2-161.49) ng·h/mL, CL/F 13.9 (8.1-50.4) and 1320.7 (663.2-3099.8) L/h.

There were no differences in PK parameters depending on Child-Pough score, gender or concomitant medications. There was a significant correlation between total DRV Cmax and AAG (rho=0.53, p=0.03); also between unbound DRV Cmax, AUC, CL/F and albumin (rho=-0.48, p=0.03, rho=-0.58, p=0.01 and rho=0.60 p= 0.007, respectively).

Conclusions: In HIV-HCV patients with compensated cirrhosis, DRV/r total and unbound concentrations are well above the IC50 for wild-type HIV. DRV total concentrations are similar to those observed in prior studies in non-cirrhotic patients, and dose adjustments are not necessary.

Conflict of interest financial relationship(s): Study supported in part by a grant from the Spanish Ministry of Health (Proyecto de Investigación sanitaria PS09/02123 FIS Convocatoria 2009)

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Abstract: O_17

Ribavirin PBMC accumulation and ribavirin plasma concentration as determinants of anemia after one month of anti-HCV therapy.

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Background: Standard of care (SOC) therapy for chronic hepatitis C (CHC) is the combination of pegylated interferon-α (Peg-IFNα) and ribavirin (RBV). Despite its effectiveness, a major cause of treatment failure is RBV-induced hemolytic anemia which occurs in about 30% of patients. Supportive care with erythropoietin increases therapy costs. Moreover, the rate of accumulation of RBV and phosphorilated-RBV (RBV-P) within the nucleate cells is still not published, probably due to methodological limitations. Therefore, our aim was to measure peripheral blood mononuclear cells (PBMCs)-associated concentration of RBV and RBV-P in patients in order to verify the intracellular concentrations and evaluate the relationship with the onset of anemia.

Materials and Methods: Thirty-eight naïve HCV-positive chronic hepatitis patients undergoing Peg-IFNα+RBV treatment were included in this study. Main inclusion criteria were no concomitant interacting drugs, no hepatic or renal function impairment, and self-reported adherence >95%. Blood sampling at the end of dosing interval (Ctough) was performed at week 4 on therapy after written informed consent given. PBMCs-associatesd (RBV-P and RBV) and plasma RBV concentrations were measured by validated HPLC-MS/MS and HPLC-UV methods, respectively. Cell count and mean cell volume were performed by a Coulter Counter instrument and those data were used to calculate the total PBMC volume for each patient. Statistical analysis was performed by Mann-Whitney and Spearman-Rank tests. Values are expressed as median (interquartile range).

Results: At 1 month of therapy, 12/26 (31.6%) patients developed anemia (Hgb < 10 g/dL and/or Hgb decline > 3 g/dL). Plasma RBV concentration 1584 ng/mL (1095-2072), PBMC RBV 3781 ng/mL (2391-5138) and PBMC RBV-P 42630 ng/mL (27384-56156) concentrations were significantly correlated with anemia (p<0.001, p=0.003 and p=0.027, respectively). Median RBV and RBV-P intracellular/plasma concentrations ratios were 2.68 and 27.74, respectively. Moreover, a significant (p=0.001) correlation between plasma and PBMC concentrations was observed only for RBV-P and not (p=0.074) for RBV.

Conclusions: This is, to our knowledge, the first study reporting RBV concentrations in PBMCs. An high rate of RBV intracellular accumulation in PBMC was showed. Plasma RBV concentration and PBMC-RBV/RBV-P concentrations were associated with onset of anemia in CHC patients receiving SOC therapy. This approach warrant further evaluation to test if intracellular concentrations can predict RBV-induced anemia and treatment outcome in current and future ribavirin containing regimens.

No conflict of interest
Abstract: O_18

Pharmacokinetic interaction between etravirine or rilpivirine and telaprevir in healthy volunteers: a randomised, two-way crossover trial.

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Background: Patients co-infected with HIV and HCV may require concurrent treatment with antiretrovirals and anti-HCV protease inhibitors such as telaprevir. Etravirine is a substrate and inducer of CYP3A and a substrate and inhibitor of CYP2C9 and CYP2C19; etravirine is also an inhibitor of P-glycoprotein. Rilpivirine is a substrate of CYP3A. Telaprevir is a substrate and inhibitor of CYP3A and P-glycoprotein.

Methods: This was a randomised 2-way crossover study in 33 healthy volunteers, divided into two panels. Panel 1 (n=17) received Treatment A: etravirine 200mg BID from Day 1 to Day 10 followed by a single dose in the morning of Day 11; then Treatment B: telaprevir 750mg TID from Day 1 to Day 17 followed by two doses on Day 18, and etravirine 200mg BID from Day 8 to Day 17 followed by a single dose on Day 18. Panel 2 (n=16) received Treatment C: rilpivirine 25mg QD from Day 1 to Day 11, then Treatment D: telaprevir 750mg TID from Day 1 to Day 18 and rilpivirine 25mg QD from Day 8 to Day 18. Volunteers were randomised to sequence AB or BA (Panel 1) or CD or DC (Panel 2). There was a washout period of two weeks between treatments. Serial pharmacokinetic assessments for etravirine (12 hours) and rilpivirine (24 hours) were done on Day 11 of Treatment A or C, respectively and Day 18 of Treatment B or D, respectively. Pharmacokinetic assessments for telaprevir (8 hours) were done on Days 7 and 18 of Treatments B and D. Plasma concentrations of telaprevir and etravirine or rilpivirine, as applicable, were assayed using validated liquid chromatography tandem mass spectrometry. C\(_{max}\), C\(_{min}\) and area under the plasma concentration-time curve (AUC) were obtained using non-compartmental analysis and compared using least square mean (LSM) ratios and associated 90% confidence intervals (CI).

Results: Co-administration of telaprevir had no effect on the pharmacokinetics of etravirine: LSM and 90% CI of etravirine C\(_{max}\), C\(_{min}\) and AUC\(_{12h}\) etravirine levels, with versus without telaprevir, were all within 80%-125%. Etravirine lowered telaprevir C\(_{min}\), C\(_{max}\) and AUC\(_{8h}\) by 25%, 10% and 16%, respectively. Rilpivirine exposure was significantly higher when co-administered with telaprevir: C\(_{min}\), C\(_{max}\) and AUC\(_{24h}\) increased by 1.93-, 1.49- and 1.78-fold, respectively. Telaprevir C\(_{min}\), C\(_{max}\) and AUC\(_{8h}\) were, respectively, 11%, 3% and 5% lower when coadministered with rilpivirine. The most common Grade 1 clinical adverse event was headache, observed in both panels of the two treatment arms (n=18/33 patients, 55%). One patient in the Treatment A arm discontinued for myocardial ischaemia (Grade 2, not related to etravirine or telaprevir). No clinically significant laboratory abnormalities were observed.

Conclusions: Co-administration of etravirine or rilpivirine with telaprevir resulted in lower telaprevir exposure but not to a clinically relevant extent. Telaprevir had no effect on etravirine and significantly increased rilpivirine exposure. The increase in rilpivirine is not considered to be clinically relevant. Dose adjustment is not considered necessary when co-administering etravirine or rilpivirine with telaprevir. Short-term co-administration was generally safe and well tolerated. No new or clinically significant safety issues were identified.

Conflict of interest
financial relationship(s): All authors are employees of Janssen. AH has received consultancy payments from Janssen
Abstract: O_19

Novel mechanism for rapid pharmacokinetic drug interaction data evaluation for NIH clinical trials

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Background: The concurrent development of new drugs for the treatment of human immunodeficiency virus type 1 (HIV-1), hepatitis B virus (HBV), hepatitis C virus (HCV), and tuberculosis (TB) poses a challenge for the review of rapidly emerging pharmacokinetic (PK) data. Many of these new drugs are metabolized, at least in part, by the cytochrome-P 450 (CYP 450) system and are substrates or inhibitors of efflux transporters. The potential for drug-drug interactions among each other as well as other commonly prescribed drug classes (including statins, oral contraceptives, anti-depressants, antibiotics, and anti-seizure agents) is significant. Due to the high volume of information, a comprehensive resource was developed by the AIDS Clinical Trials Group (ACTG) to facilitate rapid peer review and create a compilation of data in a searchable format to facilitate clinical trials.

Materials & Methods: A previously developed, static document was transitioned to a searchable, web-based database containing drug-drug interaction data on antiretrovirals (ARVs) for HIV-1. The content has begun to expand to include PK data for agents for HBV, HCV, and TB. New data presented in abstracts at research conferences, as well as emerging information from drug manufacturers and/or the United States Food and Drug Administration, is summarized and uploaded directly to the database for review by an expert panel. An international peer review system has been established to evaluate submitted data for accuracy and clinical significance. Following submission approval, the entry becomes searchable on the database, which includes a printable report feature that may be used by investigators creating research protocols.

Results: The database features 16 approved ARVs: 10 protease inhibitors (PIs), 4 non-nucleoside reverse transcriptase inhibitors (NNRTIs), one integrase inhibitor (InSTI), and one entry inhibitor. Four agents, including two newly approved directly acting agents (DAAs), for HCV are included. Two HBV agents and four TB medications are also incorporated into the database. Of these classes, the PIs, NNRTIs, entry inhibitor, DAAs, and anti-TB agents have been shown to have moderate to significant metabolic interactions with medications via the CYP 450 system, including statins, macrolide antibiotics, estrogens, certain benzodiazepines and selective serotonin reuptake inhibitors, tri-cyclic antidepressants, and some complimentary medicines. There are over 30 anti-HCV drugs currently in development; several require CYP 450 metabolism. Of seven TB drugs currently in development, 2 are known CYP 450 substrates, 2 may have limited CYP 450 inhibition properties, 2 have shown no significant CYP 450 interactions, and one has not been fully described in terms of its PK profile. Drug-drug interactions related to alternative mechanisms have also been described, including gastric pH and transporter (including p-glycoprotein and organic anion-transporting polypeptide) related interactions.

Conclusions: The ACTG drug interactions database is a resource that facilitates the collection of new PK data for rapid peer review prior to publication and accelerates clinical research protocol development. Future plans include the continued expansion of new HIV, HCV and TB investigational agents and the inclusion of PK parameters and drug concentration ranges to assist clinical pharmacology research.

No conflict of interest
Abstract: O_20

Bioavailability of two FDC formulations of darunavir/cobicistat 800/150mg compared with darunavir/ritonavir 800/100mg co-administered as single agents

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Background: Cobicistat is an investigational pharmacoenhancer of CYP3A substrates with no intrinsic antiviral activity. It has the potential for coformulation with darunavir. A previous trial, GS-US-216-0115, demonstrated comparable darunavir pharmacokinetics (C₀h, Cmax, and AUC24h) for darunavir/cobicistat 800/150mg qd compared to darunavir 800mg and ritonavir 100mg qd in healthy adult volunteers under fed and steady-state conditions. The objective of this study is to compare the oral bioavailability, short-term safety, and tolerability of two investigational FDCs of darunavir/cobicistat (formulation G003 and G004) with that of darunavir/ritonavir given as single agents, under fed, and steady-state conditions.

Methods: Thirty-six HIV-negative, healthy adult volunteers were recruited to this open-label, randomised, crossover study. Volunteers received darunavir 800mg plus ritonavir 100mg qd, darunavir/cobicistat 800/150mg qd (G003), and darunavir/cobicistat 800/150mg qd (G004). Each treatment was given for 10 days and was separated by a wash-out period of at least 7 days. Blood samples were collected over 24 hours on Day 10 for the determination of darunavir, and ritonavir or cobicistat (as applicable) plasma concentrations. Samples were assayed using validated LC-MS/MS methods. Pharmacokinetic parameters were obtained using non-compartmental analysis (WinNonlin) and evaluated using least square means (LSM) ratio and 90% confidence intervals (CI). Safety assessments were performed throughout the study until at least 7 days after the last dose.

Results: Pharmacokinetics were available for 32 (G003), 33 (G004) and 31 volunteers (darunavir/ritonavir), and safety data for 34 (darunavir/ritonavir and G004) and 35 volunteers (G003). For darunavir Cmax and AUC24h, least square means (LSM) ratios were 0.97 and 0.97, respectively, for G003 vs darunavir/ritonavir and 1.00 and 0.99, respectively, for G004 vs darunavir/ritonavir. The 90% confidence intervals (CI) were all within 80.00% to 125.00%. For DRV Cmin, LSM ratios were 0.69 for G003 (90% CI: 0.60–0.81%) and 0.74 for G004 (90% CI: 0.63–0.86%). No serious adverse events (AEs) were reported. Five volunteers discontinued for an AE, all for rash (two each for darunavir/ritonavir and G003, and one for G004). Most AEs were grade 1 or 2 in severity. Nausea and diarrhea occurred at similar incidences between all three treatments. Three incidences of Grade 3 AEs were reported (fatigue during darunavir intake and rash during both sessions with darunavir/cobicistat [G003 and G004]). Changes in laboratory parameters, vital signs and ECG parameters were generally small and not considered clinically relevant. No laboratory abnormalities were reported as AEs.

Conclusions: Two FDC tablets of darunavir/cobicistat 800/150mg have been developed. Comparable bioavailability of both formulation concepts to darunavir/ritonavir was demonstrated for darunavir Cmax and AUC24h. Darunavir Cmin is moderately lower with darunavir/cobicistat relative to darunavir/ritonavir irrespective of FDC but is not considered to be clinically relevant. Darunavir with cobicistat or ritonavir was generally well tolerated in this short-term study with no relevant differences in safety between groups.

Conflict of interest financial relationship(s): employee of Janssen
Abstract: O_21

Pharmacokinetics of EVG/COBI/FTC/TDF single tablet regimen following treatment with EFV/FTC/TDF (Atripla®) in healthy subjects

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Background: Elvitegravir (EVG), the HIV integrase inhibitor in EVG/cobicistat (COBI)/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) single tablet regimen (STR), primarily undergoes CYP3A metabolism, and secondarily glucurononidation (UGT1A1/3; metabolite M4); COBI is a potent mechanism-based CYP3A inhibitor. Efavirenz (EFV), the NNRTI component of EFV/FTC/TDF STR (Atripla®; ATR) induces CYP3A and UGT, with residual effects after discontinuation due to long T1/2 (40-55 hours). EFV exposures are increased in CYP2B6 poor metabolizers (PMs), prolonging induction effects. Due to overlapping metabolic pathways and lower potential for CNS side effects by EVG, this study evaluated the impact of EFV/FTC/TDF on EVG/COBI/FTC/TDF pharmacokinetics (PK).

Methods: This was a healthy subject study (n=32) that included CYP2B6 poor metabolizers (n=8). Subjects received EVG/COBI/FTC/TDF (150/150/200/300mg) for one week (Days 1-7) followed by washout. Subjects were then treated with EFV/FTC/TDF (600/200/300mg) for 2 weeks (Days 15-28) and switched to EVG/COBI/FTC/TDF (150/150/200/300mg) for 5 weeks (Days 29-62). Intensive PK assessments occurred on Days 7, 28, 35, and 42, with trough samples (Ctough) collected throughout the study. Statistical comparisons of EVG and COBI were made using EVG/COBI/FTC/TDF PK from Days 35 and 42 (post-switch; test) against Day 7 (pre-switch; reference). EFV PK was compared against historical data. Safety assessments were performed throughout dosing and follow-up.

Results: Twenty-nine subject completed with 3 adverse event-driven (AE) discontinuations. Two subjects discontinued while receiving EVG/COBI/FTC/TDF, one due to flank pain and abdominal pain lower (Grade 3), one due to vomiting (Grade 1). One subject discontinued due to rash (Grade 2) while receiving EFV/FTC/TDF. No Grade 4 or other Grade 3 AEs were noted. Post-ATR-switch, EVG exposures were lower (GMR (90% CI) Day 35: AUCtough: 63.1 (59.8, 66.6), Cmax: 81.5 (76.0, 87.4), Ctough: 32.8 (28.3, 38.1); Day 42 AUCtough: 70.8 (67.2, 74.7), Cmax: 88.7 (82.7, 95.1), Ctough: 44.5 (38.6, 54.4)), while COBI exposures were within the lack of interaction boundary by 2 weeks post-switch except for Ctough (35% lower). Exposures (AUCtough) of EVG glucurononidated metabolite, GS-9200, were higher (46% and 32% on Days 35 and 42, respectively) post-switch. Mean EVG Ctough was ~3-fold and ~5-fold greater than the protein-binding adjusted IC95 (45 ng/mL) on Days 35 and 42, respectively, and 7-8-fold above IC95 by 5 weeks post switch (~25% lower versus reference). EFV exposures were comparable to historical data, while PMs displayed higher AUCtough and Cmax (125% and 91%, respectively) versus non-PMs, with lower EVG and COBI exposures. EFV Ctough in all subjects was above 1000 ng/ml for three days post switch and above the IC90 (10 ng/ml) through 4 weeks post switch. FTC and TFV exposures were comparable before and after ATR treatment.

Conclusions: Following switch from EFV/FTC/TDF to EVG/COBI/FTC/TDF, EVG exposures were lower due to CYP3A and UGT induction by EFV. However, EVG and/or EVF exposures were in a range associated with potent antiviral activity throughout the study, while FTC and TFV levels were unaffected. A Phase 3b study evaluating this regimen-switch in HIV-1 patients is ongoing.

Conflict of interest financial relationship(s): employee and stockholder of Gilead
**Abstract: O_22**

*Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations*

**Raltegravir (RAL) pharmacokinetics (PK) and safety in neonates: washout PK of transplacental RAL (IMPAACT P1097)**

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**Background:** There is limited safety and dosing information for antiretroviral drugs (ARVs) in neonates. Raltegravir (RAL) has the potential for use as prophylaxis to prevent transmission in infants at high risk of infection and for treatment of HIV-infected infants. RAL is primarily metabolized by the UGT1A1 enzyme. UGT enzyme activity is low at birth and increases exponentially over the first weeks to months of life. To assist in the development of a neonatal dosing regimen, we studied in neonates the washout PK of transplacentally acquired RAL via maternal dosing.

**Materials and Methods:** IMPAACT P1097 is an ongoing phase IV multicenter trial to determine the washout PK and safety of in utero/intrapartum exposure to RAL in infants born to HIV-1-infected pregnant women who received at least two weeks of RAL (400 mg twice daily) prior to study entry and through labor. Cord blood and single maternal blood samples were obtained within one hour of delivery along with infant blood samples (1-5, 8-14, 18-24, and 30-36 hrs after birth). Samples were analyzed for RAL concentrations using a validated HPLC-MS-MS method. The half-life (t1/2) in infants was estimated using the terminal 3 concentration-time points. Safety of in utero/intrapartum exposure to RAL was evaluated through 6 months of age. The geometric mean (%CV) was used to summarize the PK data.

**Results:** Evaluable PK data was obtained in 8 mother-infant pairs. Mean maternal RAL concentration at delivery was 1270 ng/mL (108.3%). Mean cord blood RAL concentration was 1284 ng/mL (70.5%). Mean cord blood to maternal delivery concentration ratio was 1.01 (44.8%). Mean last infant RAL concentration at 32.5 hrs (5.8%) was 424 ng/mL (76.7%). Mean infant RAL t1/2 was 23.2 hours (88.8%) and ranged from 9.3-87.8 hrs. There were no adverse effects noted in the infants via drug acquisition from the mother.

**Conclusions:** Maternal RAL concentrations at delivery were similar to those in cord blood. Infant RAL plasma t1/2 was highly variable. These data suggest that it may be possible to initially dose RAL once daily in newborns, but more PK data are needed before a neonatal RAL dosing regimen can be established.

**Conflict of interest financial relationship(s):** J Butterton, H Tepller, and C Welebob are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., who may potentially own stock and/or hold stock options in the Company.
Abstract: O_23

Impact of body weight on the risk of low lopinavir/r concentrations during the third trimester of pregnancy in HIV-infected Thai and US Women


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Background: Lopinavir-boosted with ritonavir (LPV/r)-based Highly Active Antiretroviral Therapy (HAART) is one of the preferred options for HIV-infected pregnant women. Pregnancy impacts LPV/r pharmacokinetics causing a reduction in drug exposure during the third trimester compared with non-pregnant adults. However, this reduction with standard dosing was found to be less pronounced in Thai women than in US women, 25% versus 50%, respectively. Our aim was to develop a population pharmacokinetic model to describe LPV/r concentrations in HIV-infected pregnant women during the third trimester of pregnancy and identify patient characteristics which explain the variation in exposure observed across different populations.

Materials and Methods: LPV/r plasma concentration data from two prospective clinical trials were pooled for this analysis: (Study 1) PHPT-5, a phase III trial for the prevention of mother-to-child-transmission of HIV in Thailand (ClinicalTrials.gov Identifier: NCT00409591); and (Study 2) IMPAACT Network Protocol 1026s, a prospective study evaluating the pharmacokinetics of antiretrovirals among pregnant HIV-infected women [NCT00042289]. A total of 1,268 LPV/r concentrations were available (69 women with full pharmacokinetic curves and 85 with sparse evaluations). Population means and variances of lopinavir and ritonavir pharmacokinetic parameters were estimated using non-linear mixed effects regression models (Monolix Version 3.2). Monte Carlo simulations were performed to estimate the probability of achieving target lopinavir trough concentrations across the weight range of the study population.

Results: 154 HIV-infected pregnant women (123 Thai and 31 American) were included: at third trimester PK evaluations the median (range) age was 28 years (18-43), weight was 62 kg (45-123) and gestational age was 33 (29 to 38) weeks. Both LPV and RTV concentrations were best described by a one compartment model; however, the LPV PK model included an absorption lag, while the RTV model was coupled with a single transit compartment absorption model. The influence of body weight, body mass index and fat free mass on LPV/r pharmacokinetic parameters were evaluated for their inclusion in the models. Body weight influenced lopinavir and ritonavir apparent oral clearance (CL/F) and volume of distribution (Vd/F), and allometric scaling significantly reduced the interindividual variability. Simultaneously modeling LPV and RTV concentrations significantly improved the LPV model fit with LPV CL/F inhibited by RTV concentrations following a maximum-effects model. Population estimates of lopinavir CL/F and Vd/F were 8.4 L/h/70kg (calculated for a median RTV conc. of 0.17 mcg/mL 12 hours post-dose) and 147 L/70kg, respectively. Probability to achieve an LPV trough concentration >1.0 mcg/mL was >93% for 400/100 mg and >99% for 600/150 mg, twice daily, in patients 40 to 129 kg. As body weight increases from 40 to 129 kg the probability of achieving the target trough of 4.0 mcg/mL for treatment-experienced women decreased from 57% to 15% with 400/100 mg compared to 88% to 54% with 600/150 mg.

Conclusions: The majority of pregnant women attain LPV trough concentrations above the target for ARV-naive women with standard dosing; however, the risk of concentrations below target increases with higher body weight. A 600/150 mg dose may be preferable for women with high body weight and/or ARV-treatment experienced.

No conflict of interest
Abstract: O_24

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Pharmacokinetics of atazanavir/ritonavir 300/100mg or 400/100mg qd when co-administered with etravirine 200 mg bid in HIV-infected patients

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Background: In healthy volunteers, co-administration of atazanavir/ritonavir 300/100mg once-daily with etravirine 800 mg twice-daily (phase II formulation) resulted in atazanavir AUC24h and Cmin decreasing 14% and 38%, respectively. Etravirine exposure increased 1.3-fold. TEACH (clinical trials.gov ID NCT00896051) is a study to assess this interaction in HIV-infected patients.

Methods: TEACH is a randomized, open-label trial to investigate the pharmacokinetics, safety, tolerability and antiviral activity of etravirine in combination with atazanavir/ritonavir and 1 NRTI in treatment-experienced HIV-1-infected patients. Patients had to have previously received at least 1 antiretroviral regimen but no more than 2 HIV protease inhibitor-containing regimens with HIV-RNA >500 copies/mL. Patients were treated with atazanavir/ritonavir 300/100mg once-daily with 2 NRTIs (excluding tenofovir as tenofovir decreases atazanavir and etravirine exposure) for 2 weeks then randomized (on Day 1) to remain on atazanavir/ritonavir 300/100mg or increase to 400/100mg once-daily; in addition 1 of 2 NRTIs was switched to etravirine 200mg (commercial formulation) twice-daily. Blood samples for atazanavir and ritonavir plasma concentrations were collected over 24 hours on Day -1 (reference) and Day 14 (test); blood samples for etravirine plasma concentrations were also collected on Day 14. Samples were assayed using validated LC-MS/MS methods. Pharmacokinetic parameters were obtained using non-compartmental analysis (WinNonlin) and evaluated using least square means (LSM) ratios and 90% confidence intervals (CI). For the assessment of etravirine pharmacokinetics, a comparison with historic control (etravirine 200mg twice daily combined with darunavir/ritonavir 600/100mg twice-daily and other antiretrovirals in the DUET pharmacokinetic substudies) was made.

Results: 44 patients were treated with atazanavir/ritonavir and etravirine (22 patients at each atazanavir dose). Median baseline HIV-RNA and CD4 cell count was 4.1 log_{10} copies/mL and 223 cells/mm^3, respectively. For patients randomized to continue atazanavir/ritonavir 300/100mg, the switch of 1 NRTI to etravirine resulted in a decrease in atazanavir AUC24h and Cmin of 4% and 18%, respectively. For patients randomized to increase their atazanavir/ritonavir dose to 400/100mg, the switch of 1 NRTI to etravirine resulted in no change in atazanavir AUC24h and a 9% decrease in Cmin. Ritonavir pharmacokinetics were in general lower among patients continuing atazanavir/ritonavir 300/100mg compared to 400/100mg. Etravirine AUC_{12h} when co-administered with atazanavir/ritonavir 300/100mg was 1.24-fold higher in comparison to historic control. For patients receiving atazanavir/ritonavir 400/100mg, etravirine AUC_{12h} was 16% lower than historic control. At week 12, 59.1% of patients in both atazanavir dose groups were <50 copies/mL and CD4 cell count increased on average 51 cells/mm^3. Co-administration of atazanavir/ritonavir and etravirine was generally safe and well tolerated in both atazanavir dose groups.

Conclusions: Adding etravirine to an atazanavir/ritonavir-containing regimen in HIV-infected patients resulted in a smaller interaction on atazanavir than observed in healthy volunteers. Increasing the atazanavir dose to 400mg did not substantially increase atazanavir exposure. In contrast, increasing the dose of atazanavir decreased etravirine exposure. Atazanavir/ritonavir with etravirine and 1 NRTI demonstrated potent antiviral activity in this patient population and was generally safe and well tolerated. This trial is ongoing to further assess the long-term antiviral activity, safety, tolerability and population pharmacokinetics of the combination.

Conflict of interest
financial relationship(s): Janssen employee
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Abstracts
Poster Presentations
Abstract: P_01

Drug Development Science

Long-acting parenteral nanoformulated antiretroviral therapy: Patient interest and attitudes

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Background: Parenteral administration of long-acting nanoformulated antiretroviral therapy (nanoART) given by injection weekly, every other week or monthly has the potential to optimize adherence to treatment and decrease adverse effects. Patient acceptance of, and interest in, this method of drug delivery is currently unknown.

Methods: Adult HIV-infected patients attending two HIV clinics and currently receiving ART were surveyed. Information collected included demographics, self-reported adherence to ART, history of substance abuse, and interest in receiving periodic injections instead of daily oral dosing. Concerns about cost and side effects were also assessed. Chi-squared tests were used for comparisons of interest across groups.

Results: Four hundred patients completed the survey; one was ineligible and was excluded from the analysis. Respondents were 68% male, 53% African American, and the mean age was 47 years. Reported drug use in the last six months was 24% for marijuana, 7% for cocaine, 4% for heroin and 2% for amphetamines. Fifteen percent reported a history of intravenous drug use. 75% indicated not missing doses of ART in the past four days. Overall, 73% (95% CI 68-77) of patients indicated they would definitely or probably try nanoART given once a week or less frequently. For weekly dosing, 61% indicated interest (95% CI 55-66); for every 2 week dosing 72% (95% CI 67-78); and for monthly dosing 84% (95% CI 80-89). When queried about cost, 47% would probably still try the new method if it cost a little more than their current regimen, and 28% if much more.

Overall, 177 (48%) indicated they were very concerned about possible side effects and 35% were very concerned about needle use. There were no differences in enthusiasm by race or gender, but younger respondents were more willing to try the new method compared to older (p=0.03). No differences were observed by drug use history except 100% of intravenous drug users would definitely try it if dosed monthly (p=0.04). Respondents who had missed ART doses were more likely to try the new method if dosed weekly (p=0.03), every 2 weeks (p<0.01), and monthly (p=0.04). When compared to males, female respondents were more concerned about side effects (p<0.01), about using needles (p=0.01), and about change in routine (p<0.01). African Americans were also concerned about needle use and change in routine compared to whites (p<0.01 for both).

Conclusions: The majority of respondents indicated that they definitely or probably would try nanoART. Longer dosing intervals attracted greater interest than shorter intervals. Patients who reported missed ART doses and intravenous drug users indicated increased interest, and may represent those who would benefit most from this strategy to optimize adherence to therapy.

No conflict of interest

Abstract: P_02

Drug Development Science

Population pharmacokinetics of Cobicistat-boosted Elvitegravir in adult healthy subjects and HIV-infected patients

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Background: Elvitegravir (E VG) is an HIV integrase inhibitor for the treatment of HIV-1 infection. EVG is being developed as a stand alone agent and as a component of an investigational single tablet regimen (STR) including cobicistat (COBI), emtricitabine...
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(FTC), and tenofovir disoproxil fumarate (TDF). The population pharmacokinetics (PK) of COBI-boosted-EVG and the effects of demographic and formulation characteristics on EVG PK were determined.

Methods: Pooled intensive and sparse data from COBI-boosted EVG from a total of nine studies were used (6 studies in healthy subjects (n = 161) and 3 studies in HIV-1 infected patients (n = 419). A mixed effect modeling approach using NONMEM version 7.2 was applied using the Stochastic Approximation Expectation Maximization (SAEM). The effect of covariates was assessed including age, gender, race, HIV status (positive or negative), formulation (administered as STR or EVG plus COBI), body weight, body mass index, body surface area (BSA), creatinine clearance (estimated GFR), COBI AUC and COBI C_{trough}, and HBV and/or HCV coinfection. Graphical assessments, accuracy and meaningfulness of parameter estimates, significant decrease in the objective function value provided by NONMEM, and predictive checks were used as model selection criteria.

Results: A two-compartment PK model with first-order absorption rate constant and absorption lag-time provided a good description of the PK of EVG in both healthy subjects and HIV infected patients. The typical apparent systemic clearance of EVG (CL/F) was estimated to be 6.55 L/h (relative standard error (RSE)=2.0%) with an interindividual variability (IIV) of 31.6% (8.0%). The apparent volume of the central compartment (Vc/F) was estimated to be 12.9 L (6.4%) with an IIV of 49.1% (22.7%). EVG was absorbed at a rate of 0.134 h^{-1} (3.5%) (IIV=22.1% (25.4%)) with a lag-time of 1.55 (4.3%) hours (IIV=64.8% (11.1%)]. Different error terms were estimated for the early (<2.5 hours) and late (>2.5 hours) sampling time points, with corresponding estimated proportional errors of 0.309 (6.8%) and 0.563 (8.2%), respectively. Following covariate analysis, BSA was shown to have a statistically significant effect on EVG CL/F. However, the effect was modest and the range of observed BSA of 1.62 m^2 – 2.92 m^2 (5th to 95th percentile) corresponded to minor differences of -15% and +18% in EVG CL/F, respectively. Hence, BSA is not deemed to be a clinically relevant covariate. No other relevant effects of demographic covariates, HIV status (positive or negative), formulation characteristics (i.e., administered as STR or EVG plus COBI), or COBI 150 mg exposure (as a covariate) were observed on EVG PK.

Conclusions: A two-compartment PK model with first-order absorption rate constant and absorption lag-time and including the effect of BSA on EVG CL/F adequately described the PK of EVG in both healthy volunteers and HIV infected patients. No clinically relevant effects of any covariate were observed on EVG PK.

Conflict of interest financial relationship(s): employee and stock holder of Gilead

Abstract: P_03

Drug Interactions

Interaction between echinacea purpurea and etravirine in HIV-infected patients.

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Objective: to investigate the potential of a commonly used botanical supplement, Echinacea purpurea, to interact with the non-nucleoside reverse transcriptase inhibitor etravirine.

Methods: open-label, fixed-sequence study in 15 HIV-infected patients receiving antiretroviral therapy including etravirine (400 mg once daily) for at least 4 weeks. Echinacea purpurea root extract-containing capsules were added to the antiretroviral treatment (500 mg every 8 hours) from days 1 to 14. Etravirine concentrations in plasma were determined by HPLC immediately before and 1, 2, 4, 6, 8, 10, 12 and 24 hours after a morning dose of etravirine on days 0 (ETR) and 14 (ETR + echinacea). Individual etravirine pharmacokinetic parameters were calculated by non-compartmental analysis, and were compared between days 0 and 14 with the geometric mean ratio (GMR) and its 90% confidence interval (90% CI).

Results: Median (IQR) age was 46 (41-50) years, and body weight was 76 (68-92) kg. Echinacea was well tolerated and all
participants completed the study. The GMR for etravirine coadministered with echinacea relative to etravirine alone was 1.03 (90% CI, 0.68-1.56) for the concentration at the end of the dosing interval, 1.04 (90% CI, 0.73-1.47) for the area under the concentration-time curve from 0 to 24 hours, and 1.03 (90% CI, 0.74-1.43) for the maximum concentration. All subjects had etravirine concentrations well above the median protein binding adjusted EC50 of 4 ng/mL.

Conclusion: Coadministration of Echinacea purpurea with etravirine was safe and well tolerated in HIV-infected patients; data suggest that no dose adjustment for etravirine is necessary.

No conflict of interest

Abstract: P_04

Drug Interactions

Effect of milk thistle on the pharmacokinetics of darunavir/ritonavir in HIV-infected patients.

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Objective: to investigate the potential of the botanical supplement milk thistle (silymarin) to interact with the boosted protease inhibitor darunavir/ritonavir.

Methods: open-label, fixed-sequence study in 15 HIV-infected patients receiving antiretroviral therapy including darunavir/ritonavir (600/100 mg twice daily) for at least 4 weeks. Silymarin-containing capsules were added to the antiretroviral treatment (150 mg every 8 hours) from days 1 to 14. Darunavir concentrations in plasma were determined by HPLC immediately before and 1, 2, 4, 6, 8, 10 and 12 hours after a morning dose of darunavir/ritonavir on days 0 (DRV/r) and 14 (DRV/r + silymarin). Individual darunavir pharmacokinetic parameters were calculated by non-compartmental analysis, and were compared between days 0 and 14 by using the geometric mean ratio (GMR) and its 90% confidence interval (90% CI).

Results: Median (IQR) age was 48 (44-50) years, and body weight was 70 (65-84) kg. Silymarin was well tolerated and all participants completed the study. The GMR for darunavir/ritonavir coadministered with silymarin relative to darunavir/ritonavir alone was 0.94 (90% CI, 0.70-1.26) for the concentration at the end of the dosing interval, 0.86 (90% CI, 0.67-1.10) for the area under the concentration-time curve from 0 to 12 hours, and 0.83 (90% CI, 0.68-1.02) for the maximum concentration. All subjects had darunavir concentrations well above the median protein-binding-adjusted IC50 of 550 ng/mL.

Conclusion: Coadministration of silymarin with darunavir/ritonavir was safe and well tolerated in HIV-infected patients; data suggest that no dose adjustment for darunavir/ritonavir seems to be necessary.

No conflict of interest

Abstract: P_05

Drug Interactions

Pharmacokinetics of Raltegravir 400 mg once-daily in combination with Atazanavir/ritonavir plus two NRTIs

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Background: Current dosing for raltegravir (RAL) is 400 mg twice daily; nevertheless a dose-finding phase II study, where naïve patients were administered with 100 mg, 200 mg, 400 mg or 600 mg twice daily, previously reported equivalent 48-weeks immunovirological efficacy in all the groups, irrespectively of the dosing. These findings suggest that PK/PD relationship of RAL have to be still elucidated and a possible use of lower RAL doses warrant further evaluation. In this context, atazanavir, known to increase
RAL exposure by 40-72% probably through UGT1A1 inhibition, could be a good candidate as a companion drug. Therefore we performed a pharmacological pilot phase II study of RAL 400 mg qd in patients administered with atazanavir/ritonavir (ATV/r)-based regimens.

Materials and Methods: Patients on 2 NRTIs plus ATV/r were intensified for ten days with RAL 400 mg, after informed consent given. Serial plasma samples for pharmacokinetic analysis were collected on day 10 at predose (0 h), and 1.5, 3, 4.5, 6, 8, 12 and 24 h after the morning dose. Plasma concentrations were measured by validated HPLC-PDA method (limit of detection LOD, 11 ng/mL). Estimated glomerular filtration rates (eGFR) were calculated by the Cockrauft-gault formula. Steady-state pharmacokinetic parameters were derived by non-compartmental analysis using the validated computer programme Kinetica and they are expressed as medians and interquartile ranges.

Results: Eight patients were enrolled but two were excluded because they missed either ritonavir or NRTIs during the study. The six included patients were male, middle-aged [48.5 years (48-62)] and of BMI of 21.8 Kg/m² (19.3-24.4). Three were on tenofovir/emtricitabine and three on abacavir/lamivudine as a backbone. Plasma creatinine and eGFR were 1.01 mg/dL (0.97-1.32) and 69.3 mL/min/24h (67.7-72.8) respectively. Raltegravir AUC, Cmax, C24, half-life and clearance were respectively 14497 ng*h/mL (13845-28325), 3984 ng/mL (3863-6703), 40 ng/mL (22-51), 2.8 hours (2.7-3.6) and 27.1 L/h (15.7-28.9). Raltegravir pre-dose and C24 were below the LOD in one patient. Atazanavir AUC, Cmax, C24, half-life and clearance were respectively 26414 ng*h/mL (23037-33109), 2284 ng/mL (1706-2666), 526 ng/mL (397-604), 11.3 hours (9.4-13.6) and 11.4 L/h (9.2-13.1). Ritonavir AUC, Cmax, C24, half-life and clearance were respectively 9147 ng*h/mL (8052-12860), 1107 ng/mL (983-1244), 99 ng/mL (61-183), 5.5 hours (4.8-6.1) and 11 L/h (7.9-12).

Conclusions: This pilot study shows that half-dose RAL exposure, when combined with ATV/r, seems to be adequate in the majority of patients, with only one trough value below the IC95 (15 ng/mL). AUCO<sub>24</sub> of RAL 400 mg qd showed to be similar to the AUCO<sub>24</sub> of the 800 mg once-daily dosage in the QDMARK study (14895 ng*h/mL), and resulted two-fold higher than the reported AUCO<sub>12</sub> values with standard 400 mg twice-daily dosage (6340 to 6910 ng*h/mL). Atazanavir concentrations are comparable to historical data and Ctroughs are above the target level (150 ng/mL) in all patients. RAL 400 mg qd associated with ATV/r warrants further investigation as a potential strategy in selected patients.

Conflict of interest:
financial relationship(s): Speaker's honoraria and travel grants from MSD and BMS

Abstract: P_06

Drug Interactions

A multidisciplinary staff for the optimisation of therapy in HIV-infected patients treated for cancer

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Background: With the improvement of HAART, life expectancy of HIV-infected patients sharply increased. The incidence of cancerous diseases is therefore increasing in this population. This raises the problem of drug-drug interactions between HIV treatment and cancer chemotherapy poorly understood because few data are available. However, the potential risk of interactions is important because of the involvement of similar metabolic enzymes and transporters between these drugs and due to the inhibitory and/or inducer effects on different cytochrome P450 (CYP450) isoforms of the protease inhibitor (PI) and non nucleoside reverse transcriptase inhibitors (NNRTI). These interactions may both lead to inefficiency and/or an increased risk of toxicity of the chemotherapy which can be life-threatening for the patient.

Materials and methods: We set up since January 2010 a monthly multidisciplinary staff “AIDS-cancer-transplantation” to optimize the
management of HIV-infected patients diagnosed for a tumour disease and for whom chemotherapy is planned. Demographic, virological and immunological characteristics were collected from the patients’ file. Therapeutic decision issued from the staff and the reasons of the adjustment proposed if required for these patients have been retrospectively analyzed.

Results: As of today, data of 28 patients have been evaluated. A therapeutic adjustment had to be proposed for 14 patients (50%), mainly corresponding to a modification of the antiretroviral therapy (11/14). The new cART therapeutic option was defined according to HIV resistance profile, ART history and after additional biological analyzes (such as genotropism) if requested. In few cases (4/14), the cancer chemotherapy was adjusted according to the different therapeutic options proposed. The main reasons for such therapeutic adjustment were, for 57% (8/14), related to a potential metabolic interaction through the CYP3A4 because of the presence of a boosted PI or NNRTI and for 36% (5/14) to an increased risk of nephrotoxicity due to the concomitant administration of tenofovir with a potent nephrotoxic anticancer drug, such as cis-platin. For all patients, opportunistic infections prophylaxis (PCP) and screening for PCR CMV have been prescribed according to French recommendations.

Conclusion: The implementation of the multidisciplinary staff “AIDS-cancer-transplantation” highlights a high frequency of the risk of drug interactions between antiretrovirals and antitumoral agents. This staff allows us to optimize the management of HIV patients treated for malignant diseases by apprehending the risk of drug interactions and to avoid the occurrence of severe toxicities potentially impacting the issue of the anticancer treatment.

No conflict of interest

Abstract: P_07

Drug Interactions

Induction and Inhibition of Raltegravir metabolism in Healthy Volunteers

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Introduction: Raltegravir is a potent inhibitor of HIV integrase. Raltegravir is primarily metabolized by the glucuronidation pathway via the UGT1A1 enzyme. Therefore the clearance of raltegravir may be increased by UGT1A1 inducers such as rifampin, and reduced by UGT1A1 inhibitors such as ketoconazole.

Material & Methods: We conducted a pharmacokinetic study in 12 healthy volunteers. Subjects underwent 4 periods of treatments - Baseline period; Period 1: either ketoconazole 200 mg or ritonavir 100 mg twice daily given for 3 days; Period 2: either ritonavir or ketoconazole given for 3 days (periods 1 and 2 in a randomized crossover design); Period 3: rifampin 600 mg given nightly for 2 weeks. There was a washout period of 3 days after each period.

At the end of each period, blood samples for plasma were collected at pre-dose and up to 12 hours (21 timepoints total), after a single oral 400 mg dose of raltegravir and intravenous midazolam 0.75 mg, given in the fasting state. Concentrations of raltegravir and raltegravir glucuronide were determined using a validated liquid chromatography/mass spectrometry method. The lower limit of quantitation for plasma raltegravir and raltegravir glucuronide was 22.5 nmol/L and 16.1 nmol/L respectively. Non-compartmental analyses were performed using Phoenix WinNonLin.

Results: Twelve subjects were included in the study, 11 male. Raltegravir coadministered with rifampin resulted in lower plasma raltegravir concentrations. The geometric mean ratios (GMRs) and 90% confidence intervals (90% CIs) for plasma raltegravir concentrations determined 12 h postdose (C(12)), area under the concentration-time curve from 0 h to infinity (AUC(0-infinity)), and
maximum concentration of drug in plasma (C(max)) (400-mg raltegravir plus rifampin / 400-mg raltegravir) were 0.45 (0.22, 0.91), 0.60 (0.28, 1.31), and 0.75 (0.32, 1.76), respectively. Raltegravir coadministered with ketoconazole resulted in higher plasma raltegravir concentrations. GMRs for 400-mg raltegravir plus ketoconazole / 400-mg raltegravir C(12), AUC(0-infinity) and Cmax were 3.35 (1.65, 6.78), 1.94 (0.89, 4.25) and 1.75 (0.74, 4.12). There was no consistent pattern for raltegravir coadministered with ritonavir. GMRs for 400-mg raltegravir plus ritonavir / 400-mg raltegravir C(12), AUC(0-infinity) and Cmax were 3.57 (1.76, 7.23), 1.22 (0.56, 2.66) and 0.80 (0.34, 1.89). Raltegravir glucuronide to raltegravir AUC ratios were increased after coadministration with rifampicin (GMR 1.60 (1.14, 2.23)) but were not significantly decreased after coadministration with ketoconazole (GMR 0.86 (0.62, 1.20). There was no change in glucuronide ratio after ritonavir (GMR 1.00 (0.72, 1.40)).

Conclusions: Rifampin increased the metabolism of raltegravir, resulting in lower plasma exposure and increase in glucuronide production. This is likely to be due to induction of UGT1A1 activity. Ketoconazole reduced the clearance of raltegravir leading to increased plasma exposure. However, the glucuronide ratio were not significantly reduced, implying that ketoconazole may also be inhibiting other pathways such as transporters. There was no consistent pattern with ritonavir. This is possibly due to mixed induction / inhibition caused by ritonavir after 3 days of treatment. The raltegravir glucuronide ratio should be investigated further as a tool for measuring UGT1A1 activity.

No conflict of interest

Abstract: P_08

Drug Interactions

Safety/tolerability, pharmacokinetics, and boosting of twice-daily cobicistat administered alone or in combination with darunavir or tipranavir

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Background: Cobicistat (COBI; 150 mg once-daily (QD)), a potent mechanism-based CYP3A inhibitor, is an investigational pharmacoenhancer (booster) which provides comparable boosting with ritonavir (RTV) 100 mg QD when coadministered with the HIV protease inhibitors atazanavir (ATV) or darunavir (DRV) dosed QD. The once-daily regimen of COBI-boosted ATV (ATV/co) plus emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) has demonstrated comparable efficacy and favorable safety in long-term Phase 2 and 3 studies versus RTV-boosted ATV plus FTC/TDF. The current study evaluated the pharmacokinetics (PK), boosting, and drug interaction of COBI 150 mg twice-daily (BID) administered alone, in combination with tipranavir (TPV) or DRV BID, and the interaction of DRV/co with antiretroviral agents (ARVs) elvitegravir (EVG) or etravirine (ETR).

Methods: This was a crossover study in healthy subjects with three cohorts, with all study treatments administered for 10 days followed by pharmacokinetic (PK) assessment. Cohort 1 (n=12) studied COBI 150 mg BID followed by safety evaluation based on pre-defined treatment-stopping criteria. Cohort 2 (n=24) sequentially dosed RTV-boosted DRV (DRV/r 600/100 mg) BID, and after a 7-day washout, COBI-boosted DRV (DRV/co 600/150 mg) BID. Two subsets of Cohort 2 subjects (n=12/each) then randomly received DRV/co 600/150 mg BID plus EVG 150 mg QD or ETR 200 mg BID. Cohort 3 (n=12) evaluated RTV-boosted TPV (TPV/r 500/200 mg) BID, and after a 7-day washout, COBI-boosted TPV (TPV/co 500/150 mg) BID. Initiation of DRV/co or TPV/co were contingent on supportive Cohort 1 safety/tolerability data. DRV and TPV exposures were assessed using geometric mean ratios (GMR%), with 90% confidence interval (CI) bounds of 80-125% and 70-143%, respectively; EVG and ETR PK were compared against historical data. Safety was assessed during dosing and follow-up.

Results: In Cohort 1, COBI 150 mg BID was well tolerated with no discontinuations due to adverse events (AEs) and no pre-defined stopping criteria being met, allowing DRV/co and TPV/co dosing in Cohorts 2 and 3, respectively. All Cohort 2 subjects completed the study; In Cohort 3, one discontinuation due to AE (rash while receiving TPV/r) was observed. In general, AEs were generally of mild severity. In Cohort 1, COBI 150 mg BID
provided AUC_{tau}: 23100 ng.h/ml, corresponding to daily exposures ~4-fold above COBI 150 mg QD; C_{max} was correspondingly 87% higher. In Cohort 2, DRV exposures were bioequivalent between DRV/co and DRV/r (GMR (90% CI) AUC_{tau}: 101 (93.7, 108), C_{max}: 101 (94.8, 108), and C_{tau}: 95.0 (84.5, 107)); coadministration of EVG or ETR did not affect DRV or EVG/ETR PK. In Cohort 3, TPV exposures were markedly lower with TPV/co versus TPV/r (GMR (90% CI) AUC_{tau}: 46.2 (40.0, 53.4), C_{max}: 62.2 (54.9, 70.5), C_{tau}: 14.4 (11.7, 17.6)). COBI AUC with TPV/co was 90% lower versus COBI alone.

Conclusions: COBI 150 mg BID administration provided ~4-fold higher exposure versus QD and was well tolerated when administered alone or with DRV or TPV. DRV/co was bioequivalent to DRV/r BID and unaffected by coadministration with EVG or ETR. TPV and COBI exposures were markedly lower with TPV/co versus TPV/r. No long-term safety data are available with COBI BID.

Conflict of interest
financial relationship(s): employee and stockholder of Gilead

Abstract: P_09
Drug Interactions
Lack of clinically relevant drug interactions between GS-7340 and efavirenz
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Background: GS-7340, a novel second generation prodrug of tenofovir (TFV) with enhanced lymphatic delivery, provides greater decreases in HIV-1 RNA at lower doses versus tenofovir disoproxil fumarate (TDF), provides higher intracellular TFV diphosphate concentrations in peripheral blood mononuclear cells (PBMCs), and substantially lower plasma TFV exposures. The role of the CYP3A pathway in GS-7340 metabolism is minor. Efavirenz (EFV) is a known inducer of CYP enzymes, specifically CYP3A4. This study evaluated the potential for clinically relevant pharmacokinetic (PK) drug interactions between EFV and GS-7340, coformulated with emtricitabine (FTC) into a fixed dose combination (FDC) tablet, to inform dosing recommendations regarding coadministration of these agents in HIV patients.

Methods: This was a fixed sequence, crossover study (n=12) in healthy subjects with two treatment periods. Subjects sequentially received FTC/GS-7340 FDC (200/40 mg) for 12 days followed by FTC/GS-7340 FDC plus EFV (600 mg) for 14 days. PK assessments were performed on Days 12 and 26. Statistical comparisons of FTC, GS-7340, and TFV exposures were made using geometric mean ratios (GMR) and associated 90% confidence interval (CI) bounds of 70-143%, with FTC/GS-7340 plus EFV as the test treatment and FTC/GS-7340 administered alone serving as the reference. Safety assessments were performed throughout dosing and during follow-up.

Results: All study treatments were generally well tolerated. Eleven of the 12 enrolled subjects completed the study with one discontinuation due to adverse events (AEs) (anxiety (Grade 2 moderate AE) while receiving FTC/GS-7340 plus EFV). No Grade 3 or 4 AEs or Grade 3 or 4 laboratory abnormalities were observed. Following once-daily administration of FTC/GS-7340 plus EFV relative to FTC/GS-7340 alone, FTC exposures were within the protocol-defined lack of interaction boundary (GMR (90% CI) AUC_{tau}: 91.6 (87.4, 96.1), C_{max}: 89.7 (81.3, 99.9), and C_{tau}: 91.9 (86.1, 98.2)). GS-7340 and corresponding TFV exposures were modestly lower upon coadministration with EFV (GMR (90% CI) GS-7340 - AUC_{last}: 85.5 (72.1, 102) and C_{max}: 77.9 (57.7, 105); TFV - AUC_{last}: 79.7 (73.3, 86.7), C_{max}: 75.5 (66.7, 85.5), and C_{tau}: 81.6 (74.7, 89.1)). These changes are not considered to be clinically relevant. EFV exposures (mean (%CV) AUC_{tau}: 67155 (26) ng.h/ml, C_{max}: 4484 (24) ng/ml, and C_{tau}: 2075 (40) ng/ml) were comparable to historical data.

Conclusions: There are no clinically relevant drug interactions between efavirenz (EFV) and the FTC/GS-7340 fixed dose combination. No dose adjustment is needed when EFV is co-administered with FTC/GS-7340 FDC or GS-7340 stand alone agent.

Conflict of interest
financial relationship(s): employee and stockholder of Gilead
Abstract: P_10

Drug Interactions

Simulation of the interaction between SSRIs and efavirenz using in vitro in vivo extrapolation.

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Background: Rates of depression in patients with HIV is higher than in the general population and up to 40-60% of HIV positive subjects can report depressive symptoms. The selective serotonin reuptake inhibitors (SSRIs) are often used first line in the treatment of depression due to their efficacy, good tolerability and relative safety. Antiretroviral and antidepressant treatment are long-term and can therefore lead to complex polypharmacy. Efavirenz (EFV) is classified as an inducer and inhibitor of several CYPs which are responsible for SSRIs metabolism and potential drug-drug interactions can occur. However there is a lack of clinical data concerning these potential interactions on which to base clinical decisions and therapy choices. The aim of this study was to simulate the interaction between SSRIs and EFV in virtual human subjects using in vitro in vivo extrapolation (IVIVE).

Methods: In vitro data describing the physiochemical properties, absorption, metabolism, induction and inhibitory potential of efavirenz and three SSRIs were obtained from published literature. Interactions between EFV and SSRIs was evaluated using the full PBPK model implemented in the Simcyp Population-based Simulator (Version 10.1, Simcyp Limited, UK) and virtual clinical studies were simulated on 50 Caucasian subjects receiving 600 mg once daily of EFV for 35 days plus sertraline (20 mg once daily), citalopram (40mg once daily), fluoxetine (20mg once daily) from day 21-35. Simulated pharmacokinetic (PK) parameters, such as C_{trough}, C_{max}, AUC, were compared with observed values available in the literature.

Results: The simulated PK parameters of EFV, sertraline, citalopram and fluoxetine at standard dosage were similar to reference values obtain from published clinical studies. The effect of simulated EFV co-administration on sertraline exposure was comparable to published studies, mean (90% CI) AUC ratio was 0.6 (0.57-0.64) vs 0.61 (0.5-0.73), C\textsubscript{max} was 0.69 (0.66-0.72) vs 0.71 (0.6-0.85) and C\textsubscript{trough} was 0.51 (0.47-0.54) vs 0.54 (0.42-0.69). For citalopram (no published DDI data) AUC ratio was 0.54 (0.50-0.57), C\textsubscript{max} ratio was 0.66 (0.63-0.69) and C\textsubscript{trough} ratio was 0.45 (0.41-0.70). The exposure of fluoxetine (no published DDI data) was minimally affected by EFV, the AUC ratio was 1.11 (1.09-1.13), C\textsubscript{max} ratio was 1.07 (1.06-1.08) and C\textsubscript{trough} ratio was 1.13 (1.11-1.15).

Discussion: The developed IVIVE model predicted the in vivo pharmacokinetics of efavirenz and SSRIs and the simulated interaction between efavirenz and sertraline was comparable with available clinical data. The significant decrease in sertraline and citalopram exposure indicates the need for close monitoring of patients also receiving EFV. Although fluoxetine represents a better candidate for patients on EFV from a pharmacokinetic point of view, there are many considerations in seeking to optimize antidepressant therapy. IVIVE is a useful tool for both prediction of drug-drug interactions and design of prospective clinical trials, giving insight into optimal sample size, time dependent induction or inhibition, selection of doses and structure of the studies.

No conflict of interest

Abstract: P_11

Drug Interactions

Pharmacokinetics, safety, and tolerability of the HIV integrase inhibitor dolutegravir co-administered with rifabutin in healthy subjects

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**Background:** Dolutegravir (DTG) is an investigational HIV integrase inhibitor currently in Phase 3 trials. Among patients with HIV, tuberculosis (TB) is common and is a leading cause of death. Treating TB and HIV concurrently rather than waiting to start antiretroviral treatment until after TB treatment is complete reduces mortality and is now the standard of care in most settings. Rifabutin (RBT) is a first-line anti-tuberculosis drug that can be used instead of rifampin because it is a less potent inducer of cytochrome P450 drug-metabolizing enzymes. DTG is metabolized primarily by UGT1A1, with CYP3A4 as a minor route. This study evaluated the effect of RBT on the pharmacokinetics of DTG and assessed short-term safety and tolerability of concomitant use.

**Methods:** Phase I, open label, two-period, fixed-sequence, single site pharmacokinetic (PK) drug interaction study. Healthy HIV-seronegative subjects received DTG 50 mg once daily for seven days (Period 1) and co-administered with RBT 300mg once daily for 14 days (Period 2). Subjects were admitted for 24-hour plasma PK sampling on the final day of each dosing period. Safety assessments were performed at multiple timepoints. Plasma DTG concentrations were quantified using LC-MS/MS. A non-compartmental PK analysis was performed. Geometric least squares mean ratios (GMR) and 90% confidence intervals (CI) were generated for treatment comparison.

**Results:** Fifteen subjects were enrolled and nine completed both PK sampling periods. Median age was 43 years, median weight was 82 kg, 67% were male, and 73% were African-American. Comparing Period 2 to Period 1, the GMR for the area under the time-concentration curve (AUC0-24) was 0.95 (90% CI 0.82 to 1.09) and the GMR for the maximum concentration (Cmax) was 1.15 (90% CI 0.97 to 1.36). The trough concentration at the end of the dosing interval (Ct) in Period 2 was less than that of Period 1, with a GMR of 0.70 (90% CI 0.57 to 0.86). One subject was discontinued before starting study drug because of abnormal baseline laboratory values; another was discontinued for inadvertently taking extra doses of DTG. Two subjects dropped out for personal reasons (marital conflict leading to arrest, scheduling issue related to change in employment hours). Overall, study drugs were well-tolerated. There were two discontinuations for adverse events (AEs). One subject was discontinued for a grade 3 lymphopenia (asymptomatic) and the other for a grade 4 drug reaction (fever, hypotension, lymphopenia) after the first dose of RBT.

**Conclusions:** DTG 50 mg with RBT 300 mg once daily resulted in overall plasma DTG AUC similar to DTG 50 mg once daily alone. Trough concentrations were reduced by about 30%, a decrease unlikely to be clinically-significant given the known PK/PD relationships and data from Phase 2b dose-ranging studies. The AEs documented in this study are consistent with known adverse reactions to RBT; it is unclear whether or not these AEs may be more or less common among healthy volunteers than among patients with TB and/or HIV. With proper safety monitoring, DTG plus RBT may be a reasonable option for the concomitant treatment of HIV and TB.

**Conflict of interest** financial relationship(s): Support for this study was provided by GlaxoSmithKline to Johns Hopkins University.

**Abstract: P_12**

**Drug Interactions**

**Pharmacokinetic interaction between maraviroc and fosamprenavir/ritonavir: an open-label, fixed-sequence study in healthy volunteers**

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**Background:** Maraviroc (MVC) is a CCR5 antagonist indicated for the treatment of CCR5-tropic HIV-1 infection, and is a substrate for CYP3A4/P-gp. When dosed with most ritonavir (RTV)-boosted protease inhibitors, which inhibit CYP3A4/P-gp, MVC exposure is increased. This study evaluated the two-way pharmacokinetic (PK) interaction between multiple doses of MVC and fosamprenavir, a pro-drug of amprenavir (APV), boosted with RTV (FPV/r) in healthy volunteers.
Materials & Methods: This open-label, single-center, fixed-sequence, Phase I study enrolled healthy adults aged 18-55 years. In Period 1, volunteers received MVC 300 mg twice daily (BID) [Cohort 1] or MVC 300 mg once daily (QD) [Cohort 2] for 5 days. In Period 2, Cohort 1 received FPV/r 700/100 mg BID on Days 1-10 then FPV/r 700/100 mg BID plus MVC 300 mg BID on Days 11-20, and Cohort 2 received FPV/r 1400/100 mg QD on Days 1-10 then FPV/r 1400/100 mg QD plus MVC 300 mg QD on Days 11-20. On Day 5 of Period 1, and Days 10 and 20 of Period 2, Cohort 1 received only a single dose of study treatment. Blood samples were collected over 12 hours (Cohort 1) and 24 hours (Cohort 2) on these days for PK analysis. Parameters included: maximum plasma concentration (Cmax), concentration at end of dosing interval (Cτ), and area under the curve over dosing interval (AUCτ). Safety and tolerability were also assessed.

Results: Fourteen volunteers were enrolled in each cohort: all were male, mean age was 35.7 years, and the majority (82.1%) were white. For MVC, the ratios of the geometric means (90% confidence intervals) for AUCτ, Cmax, and Cτ (MVC + FPV/r versus MVC alone) were 2.49 (2.19-2.82), 1.52 (1.27-1.82), and 4.74 (4.03-5.57), respectively, for BID administration, and 2.26 (1.99-2.58), 1.45 (1.20-1.74), and 1.80 (1.53-2.13), respectively, for QD administration. For APV, the ratios for AUCτ, Cmax, and Cτ (FPV/r + MVC versus FPV/r alone) were 0.65 (0.59-0.71), 0.66 (0.59-0.75), and 0.64 (0.57-0.73), respectively, for BID administration, and 0.70 (0.64-0.77), 0.71 (0.62-0.80), and 0.85 (0.75-0.97), respectively, for QD administration. For RTV, the ratios for AUCτ, Cmax, and Cτ (FPV/r + MVC versus FPV/r alone) were 0.66 (0.58-0.76), 0.61 (0.50-0.73), and 0.86 (0.14-5.28), respectively, for BID administration, and 0.70 (0.61-0.80), 0.69 (0.57-0.84), and 2.66 (0.41-17.23), respectively, for QD administration. The average MVC plasma concentration achieved with MVC 300 mg QD + FPV/r was comparable to MVC 300 mg BID alone (235 ng/mL versus 217 ng/mL). Overall adverse event (AE) incidence was 96.4% (n=27/28); all were mild-to-moderate in severity. Diarrhea (53.6%) and fatigue (42.9%) were most common. One volunteer in Cohort 2 discontinued due to an AE (Grade 2 rash, Period 2). No serious AEs or deaths occurred.

Conclusions: These findings confirm that MVC exposure is increased when administered with FPV/r. In the presence of MVC, APV and RTV exposure was decreased. MVC co-administered with FPV/r was generally well-tolerated in this population with no unexpected safety findings. Further exploration for QD dosing of MVC 300 mg with FPV/r 1400/100 mg as a treatment option for HIV-1 is warranted.

Conflict of interest financial relationship(s): Employee of Pfizer Inc, and holds stock/stock options in Pfizer Inc.

Abstract: P_13

Drug Interactions

No clinically significant drug interaction when BMS-663068, a novel HIV-1 attachment inhibitor, is coadministered with tenofovir disoproxil fumarate

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Introduction: BMS-663068 is a phosphate prodrug of BMS-625629, and represents a novel class of oral antiretroviral agents that blocks the attachment of HIV-1 envelope gp120 to its host receptor CD4. BMS-625629 is metabolized by both the esterase-mediated hydrolysis pathway and by the cytochrome p450 mediated oxidative pathway. BMS-663068 and BMS-625629 have not been shown to be inhibitors or inducers of major cytochrome p450 enzymes. This study investigated the two-way drug interaction between BMS-663068 and tenofovir disoproxil fumarate (TDF), a commonly used nucleotide reverse transcriptase inhibitor.

Materials & Methods: 18 healthy subjects were dosed; all completed the study. Subjects received BMS-663068 600 mg BID on Days 1-5, TDF 300 mg QD on Days 6-12, followed by coadministration of BMS-663068 600 mg BID and TDF 300 mg QD on Days 13-19. All morning doses were given with a standard meal and evening doses after a snack. Serial blood samples were collected on Days 5 and 19 for 12 h post-AM dose for BMS-625629 and on Days 12 and 19 for 24 h for tenofovir. PK

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parameters were derived using noncompartmental methods. General linear models were used for exposure comparisons.

**Results:** The overall exposures of BMS-626529 (Cmax and AUC) were similar when administered as BMS-663068 with or without TDF. The geometric mean ratio and associated 90% CI for Cmax and AUC of BMS-626529 were 0.986 (0.861, 1.130) and 1.004 (0.910, 1.107), respectively, when coadministered with TDF vs BMS-663068 alone. Upon coadministration, BMS-663068 increased tenofovir geometric mean Cmax, AUC by 18% (90% CI: 11.6%, 24.9%) and 19% (12.3%, 25.1%), respectively. All adverse events (AE) were mild in intensity. There were no clinically relevant laboratory abnormalities.

**Conclusions:** No clinically significant interaction was observed on overall BMS-626529 exposures when BMS-663068 and TDF were coadministered at steady state. Coadministration of BMS-663068 600 mg BID with TDF resulted in a modest increase in tenofovir Cmax and AUC by approximately 20%. Similar or greater magnitude of increase in tenofovir exposure has been observed when TDF was coadministered with ritonavir-boosted protease inhibitors, with no apparent effects on safety or tolerability. Taken together, these data suggest that BMS-663068 and TDF may be coadministered without change in dose of either drug.

**Conflict of interest financial relationship(s):** Employees of Bristol-Myers Squibb

**Abstract: P_14**

**Drug Interactions**

An increase in atazanavir to 400 mg mitigates the effects of famotidine when given with ritonavir and tenofovir DF in HIV-infected patients

**Introduction:** Atazanavir (ATV) is a potent protease inhibitor widely used in HIV-infected patients. ATV exhibits pH-dependent solubility and the pharmacokinetic (PK) interaction between ATV/ritonavir (RTV) and H2-receptor antagonist famotidine (FAM) has been studied in healthy subjects and HIV-infected patients. The purpose of this study was to assess the steady-state PK of a higher dose of ATV 400 mg with RTV 100 mg once-daily (QD) in HIV-infected patients on highly active antiretroviral therapy (HAART) containing ATV/RTV and tenofovir disoproxil fumarate (TDF) and ≥1 nucleoside reverse transcriptase inhibitor(s) (NRTI(s)) co-administered with multiple-dose FAM 20 and 40 mg twice-daily (BID) relative to ATV/RTV 300/100 mg QD and TDF in the absence of FAM in those same patients.

**Materials and Methods:** This was an open-label, 3-period, multiple-dose, sequential crossover, drug interaction study in 24 HIV-infected patients well-controlled on HAART containing ATV/RTV 300/100 mg, TDF 300 mg, and ≥1 NRTI(s). Subjects continued on TDF and NRTI(s) throughout the study and ATV/RTV and FAM were dosed as follows: ATV/RTV 300/100 mg QD on Days 1-10, ATV/RTV 400/100 mg QD and FAM 20 mg BID on Days 11-17, and ATV/RTV 400/100 mg QD and FAM 40 mg BID on Days 18-24. FAM was dosed simultaneously with ATV in the morning after a meal. Serial blood samples were collected up to 24 hours after the morning dose on Days 10, 17, and 24. ATV and RTV were analyzed by LC/MS/MS. Steady-state PK parameters for ATV and RTV were derived from plasma concentration versus time data. Adjusted geometric mean ratios (GMR) and 90% confidence intervals (CI) for Cmax, AUC, and Ctrough were estimated using linear mixed model.

**Results:** FAM 40 mg BID co-administered with ATV/RTV 400/100 mg QD resulted in similar ATV exposures [GMR (90% CI): Cmax 0.95 (0.83-1.08), AUC(TAU) 0.98 (0.87-1.10), Ctrough 1.01 (0.90-1.15)] when compared to the clinical dose of ATV/RTV 300/100 mg in the absence of FAM in HIV-infected patients taking TDF and ≥1 NRTI(s). FAM 20 mg BID co-administered with ATV/RTV 400/100 mg QD resulted in slightly higher (approximately 20%) ATV exposure [GMR (90% CI): Cmax 1.18 (1.07-1.31), AUC(TAU) 1.18 (1.07-1.30), Ctrough 1.24 (1.10-1.39)] relative to the clinical dose of ATV/RTV 300/100 mg QD without
FAM. RTV exposures were similar following administration of ATV/RTV 400/100 mg with TDF and FAM (20 mg and 40 mg BID) and ATV/RTV 300/100 mg without FAM. The most frequent AEs were headache (20%) and diarrhea (12%). There were no clinically meaningful trends in hyperbilirubinaemia, HIV RNA levels, or CD4 T-cell counts across groups.

Conclusion: ATV/RTV was safe and generally well-tolerated by HIV-infected patients when co-administered with FAM 20 mg or 40 mg BID in the presence of TDF and ≥1 NRTI(s) in this study. The results from this study in HIV-infected patients confirm that increasing the dose of ATV to ATV/RTV 400/100 mg QD in combination with an H2-receptor antagonist such as FAM and TDF will produce similar ATV concentrations to that of ATV/RTV 300/100 mg QD in the absence of an H2-receptor antagonist.


Abstract: P_15

Drug Interactions

Etravirine has no effect on the pharmacokinetics of S/GSK1265744, a novel HIV Integrase inhibitor

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Introduction: S/GSK1265744 is an HIV integrase inhibitor (INI) with potent antiviral activity following short-term once daily oral dosing in HIV-infected subjects and is also under development as a long-acting depot injection. Etravirine (ETR), a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), is an inhibitor of CYP3A4 and an inhibitor of CYP2C9, CYP2C19, and P-gp, and has demonstrated significant drug interactions with other antiretroviral agents. S/GSK1265744 is neither an inducer nor inhibitor of CYP or UGT enzymes, and thus is unlikely to affect ETR. This study evaluated the one-way drug-interaction effect of ETR on S/GSK1265744 pharmacokinetics (PK).

Materials and Methods: In this open label, two-period, single-sequence crossover study, 12 healthy adults received S/GSK1265744 30mg q24h orally for ten days in Period 1 followed by S/GSK1265744 30mg q24h + ETR 200mg q12h orally for an additional 14 days with no washout prior to Period 2. All doses were administered following a moderate fat meal. Serial PK sampling was performed on Day 10 of Period 1 and Day 14 of Period 2. Plasma S/GSK1265744 and ETR concentrations were measured by LC/MS/MS, and plasma PK parameters were determined by non-compartmental analysis. Geometric least squares mean ratios (GMR) and 90% confidence intervals (CI) were generated for treatment comparison of GSK1265744 PK parameters.

Results: The combination of S/GSK1265744 + ETR was generally well-tolerated; no Grade 3 or 4 AEs were observed and no subject discontinued due to AEs. Geometric mean (CVb%) plasma S/GSK1265744 AUC(0-τ), Cmax and Ct were 183μg·h/mL (13%), 9.47μg/mL (11%), and 6.50μg/mL (14%), respectively, following administration of S/GSK1265744 alone and were 184μg·h/mL (9%), 9.83μg/mL (11%), and 6.49μg/mL (12%), respectively, following co-administration of S/GSK1265744 with ETR. GMR (90% CI) for S/GSK1265744 AUC(0-τ), Cmax and Ct were 1.01 (0.956, 1.06), 1.04 (0.987, 1.09) and 0.999 (0.942, 1.06), respectively, following co-administration of S/GSK1265744 with ETR. Geometric mean (CVb%) plasma ETR AUC(0-τ), Cmax and Ct were 9176ng·h/mL (25%), 975ng/mL (24%), 597ng/mL (28%) following co-administration with GSK1265744.

Conclusion: S/GSK1265744 30mg q24h for 10 days alone, or in combination with ETR 200mg q12h for 14 days, was well tolerated in healthy subjects. ETR does not affect S/GSK1265744 pharmacokinetics.

Conflict of interest financial relationship(s): employee of GlaxoSmithKline
Abstract: P_16

Drug Interactions

Nevirapine and Rifampicin pharmacokinetic profiles in the treatment of South African HIV-infected patients with tuberculosis.

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Background: Rifampicin (RFM), may reduce blood levels of nevirapine (NVP), hampering the treatment of TB/HIV coinfected patients. Moreover, NVP must be given at a lower dose for the first two weeks of treatment in order to reduce the risk of toxicities, further increasing the risk of sub-therapeutic drug levels when co-administered with RFM. NVP is widely used in antiretroviral therapy in resource-limited settings, due to its low cost and availability in a wide range of fixed-dose combinations. We report the results of our study in Burkina Faso, conducted in HIV/TB co-infected patients receiving NVP-containing therapy and RFM-based anti-TB treatment.

Patients and Methods: From January-09 to July-10, we enrolled 20 patients with documented HIV-1 infection, CD4+ T lymphocyte < 100 cells /cm³ and TB diagnosis according to national guidelines. Patients received RFM in bodyweight-adjusted fixed dose combination (2 months RHZE/4 months RH) and standard HAART (fixed dose combination of NVP, 3TC and D4T). HAART was started within 30 days from anti-TB therapy; NVP was given as 200 mg OD for 2 weeks, then 200 mg BID. Three NVP/RFM pharmacokinetic curves were obtained: after 4 weeks of RFM+NVP combined therapy (T0) and after 16 weeks of RFM+NVP (T1). A third pharmacokinetic curve for NVP evaluation (without RFM) was obtained 30 days after termination of anti-tuberculosis therapy (T2). Blood samples were taken at 0, 1, 2, 4, 6, 8, 12 hours after drugs intake. Steady-state NVP and RFM plasma concentrations were quantified by using validated HLPC assays and pharmacokinetic parameters were determined by non compartmental methods. Statistical analysis was performed by Wilcoxon signed-rank and Friedman tests.

Results: Median (IQR) values of NVP AUC0-12 at T0, T1 and T2 were, respectively: 65.79 (52.53-94.92), 53.59 (39.45-75.3) and 91.22 (67.94-112) mcg.h/mL. Median Ctrough were, respectively: 4.6 (3.2-5.9), 3.5 (2.4-5.1) and 6.5 (4.1-9.5) mcg/mL. Values of Ctrough < 3 mcg/mL (minimum recommended cutoff value) were observed in 15% of patients at T0 and 35% at T1. No patients had sub-therapeutic concentrations at T3 (NVP alone). Median CL/F values were: 0.061 (0.039-0.089), 0.07 (0.052-0.095) and 0.04 (0.028-0.046) L/h/kg, respectively. Median RFM AUC and CL/F were, respectively: 24.32 (16.9-29.69) mcg.h/mL and 0.43 (0.35-0.59) L/h/kg at T0 and 14.21 (7.84-27.32) mcg.h/mL and 0.72 (0.39-1.27) L/h/kg at T1. Median Cmax (2h) was 4.1 (1.33-5.35) mcg/mL at T0 and 2.3 (1.5-4.3) at T1.

Conclusions: After 16 weeks of NVP/RFM combination therapy we observed a decrease in NVP AUC and Ctrough of borderline significance, due to an increase patients weight, as CL/F (L/h/kg) did not vary. The interruption of RFM determined a significant reduction of NVP CL/F (40%), ranging from 4.8% to 76.6%, with a 28% increase of AUC values. Our results confirm that RFM reduces serum exposure to NVP, even though the clinical implications for this reduction remain to be established. RFM CL/F (L/h/kg) values did not significantly change during concomitant NVP treatment.

No conflict of interest

Abstract: P_17

Drug Interactions

Use of in vitro to in vivo extrapolation to choose the best strategy for patients switching from efavirenz to maraviroc

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Reviews in Antiviral Therapy & Infectious Diseases – Volume 3: 2012
Background: Efavirenz (EFV) in combination with two NRTIs is recommended for first line combined antiretroviral therapy (cART). However, CNS toxicity can be a significant limitation to its use in some patients. Maraviroc (MVC) is an option for those intolerant of EFV, but the long and variable half-life (40-55 h) of EFV and its inducing effect on cytochrome P450 makes optimal dosing of MVC post switch uncertain. Persisting enzyme induction may lower MVC exposure and increase the risk for treatment failure.

Objectives: The objective of this study was to develop an in vitro–in vivo extrapolation (IVIVE) model to describe the pharmacokinetics (PK) of MVC administered in HIV-infected individuals switching from EFV-containing therapy. MVC concentration-time profiles were simulated from 4 dosing scenarios:
1. MVC at 600 mg BID for 2 weeks followed by standard 300 mg BID dosing
2. MVC at 600 mg BID for 1 week followed by standard 300 mg BID dosing
3. MVC at 600 mg BID (week 1) followed by 450 mg BID (week 2), and standard 300 mg BID dosing thereafter
4. MVC at 450 mg BID for 2 weeks followed by standard 300 mg BID dosing

Methods: In vitro data describing the chemical and ADME characteristics of EFV and MVC were obtained from published literature, and used to simulate plasma exposures of EFV and MVC using Simcyp (Version 11). The waning induction of CYP450 metabolism following EFV discontinuation was also simulated. The predicted MVC exposures were compared with data from a clinical study (Waters et al; EACS 2011; Abs. PS6/3) evaluating MVC exposures following a switch from EFV (Scenario 1; 11 patients).

Results: Model predictions for MVC exposure for Scenario 1 were in agreement with the clinically observed data. The simulations suggest that geometric mean MVC C\text{trough} concentrations after 1 week of MVC 600mg bid (Scenario 2) were equivalent to standard 300mg dosing. Similar geometric mean C\text{trough} values were observed at the end of week 1 and week 2 (Scenario 3) and similar geometric mean C\text{trough} values were observed after 2 weeks of MVC 450mg bid (Scenario 4) compared with 2 weeks of MVC 600mg bid (Scenario 1).

Conclusion: IVIVE modelling successfully predicted patient exposure in Scenario 1. Based on predictions for alternative dosing schemes, similar MVC exposures could be achieved following a switch from EFV therapy with Scenario 2 and Scenario 4, both at lower drug cost. This modelling technique may inform better design of clinical studies, and allow assessment of pragmatic dosing strategies under complex therapeutic scenarios.

No conflict of interest

Abstract: P_18

Drug Interactions

The clinical implications of antiretroviral drug interactions with warfarin: a case-control study

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Background: Warfarin is highly susceptible to interactions with antiretroviral therapy (ART), specifically with non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI), mediated through cytochrome P450 (CYP) 2C9, 2C19, and/or 3A4. Data characterizing these interactions are limited to inconclusive case reports and one boosted PI-warfarin pharmacokinetic study that describes a 22% reduction in warfarin exposure when given with lopinavir/ritonavir. Clinical guidance to manage these interactions is lacking. The primary objective of this study was to compare the warfarin maintenance dose, defined as the dose required to maintain goal international normalized ratio (INR), between patients receiving PI- and/or NNRTI-based ART and patients not on ART. The secondary objective was to identify predictors of warfarin maintenance dose in these patients.
Materials & Methods: This was a retrospective, case-control (1:2) study conducted in adult patients (≥18 years) at outpatient clinics affiliated with an academic, tertiary medical center. Cases were defined as HIV-infected patients receiving warfarin and PI- and/or NNRTI-based ART. Controls were randomly selected HIV-uninfected patients receiving warfarin without ART. The goal INR in all patients was 2-3. Key variables collected included patient age, race, weight, gender, and warfarin indication. The warfarin maintenance dose was compared between cases and controls, as well as between cases on varying ART regimens. Patients were excluded if a stable warfarin dose was not achieved during clinic follow-up. Bivariate comparisons were performed, as appropriate, and a backward stepwise linear regression model was developed to identify predictors of the required warfarin maintenance dose.

Results: We identified 18 eligible HIV-infected patients receiving warfarin and ART as cases and 36 control patients on warfarin without ART. Controls were older than cases (mean age: 63.1 vs 45.8 years, p<0.01) and more likely to be female (63.9% vs 27.8%, p=0.01). A higher proportion of cases versus controls were African American (50% vs 22%, p=0.04). Among the 18 cases, ART was classified as PI-based (n=9), NNRTI-based (n=7), and PI+NNRTI-based (n=2). The most commonly used PI and NNRTI was lopinavir/ritonavir (n=7) and efavirenz (n=8), respectively. The warfarin maintenance dose (mean±SD) differed significantly between cases and controls (8.6±3.4mg vs 5.1±1.5mg, p=0.01), but not across ART regimens (PI: 8.8±4.6mg; NNRTI: 8.6±1.8mg; PI+NNRTI: 7.3±3.3mg; p=0.86). Race and ritonavir dose were identified as independent predictors of warfarin dose; the warfarin maintenance dose is expected to increase by 3.9mg ([95%CI: 0.88-7.0], p=0.02) or 3.7mg ([95%CI: 0.53-6.9], p=0.03) if the patient is African American or if the total daily ritonavir dose is 200mg, respectively.

Conclusions: This is the first systematic evaluation of warfarin dose requirements in HIV-infected patients receiving warfarin and ART as compared with patients not receiving ART. The warfarin dose required to maintain goal INR was significantly higher (mean difference: 3.5mg) in patients receiving ART. Importantly, we identified total ritonavir daily dose of 200mg to be an independent predictor of increased warfarin dose, which is likely explained by ritonavir-mediated CYP2C9 induction, the isoenzyme largely responsible for metabolism of the potent S-warfarin isomer. Higher empiric warfarin doses and/or more vigilant monitoring and dosage adjustments may be required in these patients.

No conflict of interest

Abstract: P_19

Drug Interactions

Pharmacokinetics of amodiaquine and desethylamodiaqine in HIV-infected patients with and without nevirapine-containing antiretroviral therapy

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Introduction: Amodiaquine plus artesunate (AQ-AS) is an artemisinin-based combination therapy frequently used for malaria treatment in regions with overlapping HIV endemicity. Coadministration of AQ-AS with antiretroviral therapy (ART) may result in drug-interactions, but there is minimal information to guide concomitant therapy. One study evaluating efavirenz plus AQ-AS was prematurely interrupted when clinically significant transaminase elevations occurred in the first two subjects. Pharmacokinetic evaluation revealed significantly higher AQ exposure and lower desethylamodiaquine (DEAQ) exposure, the active metabolite formed via CYP2C8. The purpose of the current study was to evaluate the impact of nevirapine (NVP)-based ART on the disposition of AQ-AS. AS data were previously reported, and although pharmacokinetic changes occurred, there was similar overall exposure to AS and its active metabolite.
Materials & Methods: This was an open-label, parallel-group pharmacokinetic comparison between HIV-infected, adult Nigerian subjects receiving steady state NVP-based ART (n=10) and ART-naïve controls (n=11). AQ-AS 600/200mg was given as a single daily dose for three days, with pharmacokinetic sampling after the final dose on day 3 (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72 and 96 hours). AQ and DEAQ were quantified using validated LC-MS/MS procedures, with a lower limit of quantification of 5 ng/mL. Pharmacokinetic parameters [Cmin (ng/L), AUC0-24 (ng/ml*h), and t1/2 (hours)] were determined using WinNonLin® and standard non-compartmental methods for analysis. Liver function tests (LFTs) were monitored prior to initiating AQ-AS, days 7 and 14. All data are presented as mean±standard deviation.

Results: Participants were predominately female (71%). The control group was relatively younger than the NVP group (35.8±6.4 vs 39.7±13.5 years, p<0.01), but the mean body mass index was similar between groups (22.8±4.6 vs 23.2±2.9 kg/m2, p=0.60). The NVP group received NVP-based ART for a mean duration of 1.65 years with the shortest duration of exposure being 6 months. Mean CD4 counts for the control and NVP groups were 438±219 and 415±229 cells/mm3, respectively (p=0.82). No significant differences in AQ or DEAQ pharmacokinetics were identified between groups, however considerable interpatient variability was observed. Comparing the control to NVP group, the AQ and DEAQ AUC0-24 were 242±78 vs 197±94, p=0.26, and 21,311±21,012 vs 13,121±7947, p=0.26, respectively. Similarly, AQ and DEAQ t1/2 were unchanged (7.1±4.5 vs 10.9±6.3, p=0.14, and 3.2±2.3 vs 3.1±2.7, p=0.90). Finally, the DEAQ Cmin did not differ between groups (137±65 vs 124±52, p=0.26). Notably, four individuals in the control group discontinued the study protocol due to weakness, vomiting, diarrhea, and dizziness, while no subjects in the NVP group experienced treatment-limiting adverse effects. In patients who continued on protocol, moderate to severe weakness was reported similarly in both the control and NVP groups [1/11 (9%) vs 2/10 (20%), p=0.93]. LFTs remained within normal limits through study day 14.

Conclusions: Initial non-compartmental pharmacokinetic analyses indicate no statistically significant impact of NVP on the disposition of AQ or DEAQ. Reassuringly, AQ-AS in combination with NVP-containing ART was well tolerated by HIV-infected, adult Nigerian patients involved in this study.

No conflict of interest

Abstract: P_20

Ethno-Pharmacology

Allelic variants of SLC01B1 gene in the Serbian population

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Introduction: Organic-anion-transporting-polypeptides (OATP), coded for by the SLC01 genes, are a family of membrane-transport-proteins which influx numerous endogenous and xenobiotic compounds. OATP1B1 and OATP1B3 are major hepatic drug transporters whilst OATP1A2 is mainly located in the brain and liver. These transporters have been reported to have functional single nucleotide polymorphisms (SNPs) at the SLC01B1 gene. So far, there are a very few data about it and therefore, we aimed to investigate frequency distribution of allelic variants of SLC01B1 gene in the Serbian Caucasian population.

Material & Methods: Blood samples were collected at the HIV/AIDS Center, Institute of Infectious and Tropical Disease, University teaching hospital, Belgrade, Serbia. While the genotyping was carried out by polymerase-chain-reaction (PCR) and allele-specific-real-time-PCR assays with fluorescent probes at the Department of Pharmacology and Therapeutics, University of Liverpool, UK. SNPs rs4149032, which is located in intron 2 of the SLC01B1 gene was amplified. Written consent was obtained.

Results: Genotyping was carried out in 79 unrelated Serbian Caucasian derived from Belgrade and Central Serbia volunteers. Genotype frequencies for SLC01B1 gene rs4149032, were 40 wild-type homozygous, 22
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wild-type heterozygous and 17 mutant-homozygous variants; CC 40 (50.63%), CT 22 (27.85%) and TT 17 (21.52%), respectively.

**Conclusion:** Our results contribute to better understanding of the molecular basis of ethnic differences in drug response, which may help to improve individualization of antiretroviral therapy and offer a preliminary basis for more rational use of drugs that are substrates for OATP family members in the Serbian Caucasian population.

**No conflict of interest**

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**Abstract: P_21**

**Pharmacogenetics**

**Genetic predictors of plasma efavirenz exposure among HIV-infected South Africans**

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**Background:** Some CYP2B6 polymorphisms are known to predict efavirenz concentrations. There is an increased frequency of both CYP2B6 516T and 983C, which decrease efavirenz clearance, among individuals of African ancestry. There is limited data on the effect of CYP2B6 polymorphisms on efavirenz plasma concentrations in the South African population. The aim of the study is to characterize relationships between genetic polymorphisms and plasma efavirenz concentrations in HIV-infected South African adults and children.

**Methods:** We assayed 241 single nucleotide polymorphisms (SNPs) across ABCB1, CYP2B6, CYP2C19, CYP3A4, CYP3A5, NR1I2 and NR1I3, were genotyped from 119 HIV infected black South African participants (63 adults and 56 children) in whom steady state mid-dosing interval (between 10 and 20 hours post-dose) efavirenz concentrations were measured. Plasma concentrations were measured using liquid chromatography with tandem mass spectrometry. Primary analyses involved 2 CYP2B6 SNPs (rs3745274, 516G>T; rs28399499, 983T>C) known to predict increased plasma efavirenz concentrations. Linear regression using PLINK was done to identify associations between genetic predictors and log-transformed efavirenz concentrations. For exploratory SNPs the Bonferroni p-value threshold for significance was 0.0002.

**Results:** Among 63 adults (49 female) median (IQR) age, weight, body mass index, and time after last efavirenz dose were 38 (36-45) years, 67.3 (59.8-78.9) kg, 26.4 (23.3 to 29.4) kg/m², and 12.5 (11.7 to 12.9) hours, respectively. All adults received 600mg evening dosing. Among 56 children (27 female) the median efavirenz dose was 250mg, and median (IQR) age, weight, height, and time after last efavirenz dose were 8.2 (5.8 to 10.7) years, 22.3 (18.4-28.6) kg, 1.20 (1.07 to 1.29) metres, and 16.0 (15.3 to 16.7) hours, respectively. Among all 119 participants, minor allele frequencies for rs3745274 and rs28399499 were 0.37 and 0.07, respectively. No individual was homozygous for rs28399499 CC. Based on composite CYP2B6 516/983 genotype, there were 36 extensive metabolizers (neither SNP), 63 intermediate metabolizers (heterozygous for one of these SNPs), and 20 slow metabolizers (homozygous for either SNP or homozygous for both SNPs). Median (IQR) mid-dose efavirenz concentrations were 1.48 (1.16-2.22) µg/mL, 2.03 (1.65-2.94) µg/mL and 7.00 (3.92-8.18) µg/mL for extensive, intermediate, and slow metabolizers, respectively. A model that included composite genotype best predicted efavirenz concentrations (ß coefficient =0.27, p=3.17x10⁻¹¹). Among individual SNPs, rs3745274 best predicted efavirenz concentrations (ß coefficient=0.21,p=9.53x10⁻¹⁰), as did 8 CYP2B6 SNPs in linkage disequilibrium. There was also an association with rs28399499 (ß coefficient=0.27, p=0.0013). Several CYP2B6 SNPs tended toward association with lower efavirenz concentrations (ß coefficient = -0.17, p=0.002), but were not significant after correcting for multiple comparisons.

**Conclusions:** Composite CYP2B6 516/983 genotype best described efavirenz exposure in HIV-infected black South African participants. Additional CYP2B6 polymorphisms may be associated with decreased plasma efavirenz exposure.

**No conflict of interest**
Abstract: P_22

Pharmacogenetics

Effect of CYP3A5 polymorphisms on the metabolism of atazanavir in HIV-infected patients: a sub-study of AIDS Clinical Trials Group A5175 (NWCS 342).

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Introduction: Atazanavir (ATV) is partially metabolized via the CYP3A5 pathway. A multinational, randomized clinical trial (PEARLS) conducted in resource-limited settings found significantly greater risk of treatment failure in the ATV + didanosine (ddI-EC) + emtricitabine (FTC) arm compared to lamivudine (3TC)/zidovudine (ZDV) + efavirenz (EFV). A population pharmacokinetic study from PEARLS found geographic associations with ATV clearance, raising the question whether genetic variations modified ATV exposure. The objective of this study was to evaluate the effect of CYP3A5 polymorphisms on the pharmacokinetics of unboosted ATV in patients enrolled in PEARLS.

Methods: HIV-infected individuals randomized to ddI-EC (250 or 400 mg) PO QD + FTC 200 mg PO QD + ATV 400 mg PO QD in the United States (US), South Africa (SA) and Peru were included in the analysis. A single ATV plasma sample was drawn at any time during weeks 4 to 8. ATV was assayed by a validated high performance liquid chromatography method. A population pharmacokinetic model using non-linear mixed effects was previously built to obtain individual subject estimates of predicted concentrations and ATV pharmacokinetic parameters, which included area under the curve (AUC0-24), oral clearance (CL/F) and concentration at 24 hrs (C24). Stored human DNA samples were genotyped for CYP3A5 *3, *6 and *7 polymorphisms using PCR-pyrosequencing. CYP3A5 expressor status was defined as “expressor” (at least one copy of the *1 allele) or “non-expressor” (*3/*3 or *6/*6 genotypes). ATV mono-oxidation metabolites M1 and M2 were determined via a validated method using liquid chromatography/tandem mass spectrometry and M1/ATV and M2/ATV ratios were calculated. Pharmacokinetic parameters and metabolite ratios were loge transformed; statistical analysis was conducted using unpaired t tests between CYP3A5 expressors vs. non-expressors. Data are presented as absolute value mean ± standard deviation.

Results: Eighty-four HIV-infected patients (28 women) were available for CYP3A5 genotypic analysis (54 US, 24 SA, 6 Peru). Mean age was 35 ± 9 years. Racial distribution was: Black Africans/African Americans (BAA) 52.3%, Whites (W) 32%, other/unknown 15%. We identified 56 CYP3A5 expressors (40 BAA, 11 W, 5 other/unknown) and 28 non-expressors (4 BAA, 16 W, 8 other/unknown). AUC0-24, CL/F and C24 were available in 69 patients. These pharmacokinetic parameters did not differ significantly between CYP3A5 expressors vs. non-expressors (AUC0-24 31823 ±11340 vs. 32068 ± 6659 ng*hr/mL, p=0.62; CL/F 13.70 ± 3.52 vs. 13.03 ± 2.87 L/hr, p=0.61; and C24 198 ± 353.8 vs.193 ± 158.4 ng/mL, p=0.14). However, M1/ATV and M2/ATV ratios were significantly higher in CYP3A5 expressors vs. non-expressors (M1/ATV 0.00905 ± 0.00365 vs. 0.00706 ± 0.00416 ng/mL, p=0.008 and M2/ATV 0.00701 ± 0.00261 vs. 0.00576 ± 0.00351 ng/mL, p=0.02).

Conclusions: Genetic polymorphisms in CYP3A5 modify the metabolite profile of ATV but did not influence the pharmacokinetics of the parent drug in this study. The differences in M1/ATV and M2/ATV ratios among expressors vs. non-expressors indicate a unique metabolite phenotype for ATV in CYP3A5 expressors, which has unknown clinical implications. Further investigation of demographic, pharmacologic and pharmacogenetic factors that influence the effect of CYP3A5 expression on ATV pharmacokinetics is warranted.

No conflict of interest
Abstract: P_23

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

**Intracellular accumulation of atazanavir/ritonavir according to ABCB1, OATP1B1 and PXR genetic polymorphisms.**

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**Background:** Atazanavir (ATV) boosted with ritonavir (RTV) is a widely used drug combination in HIV therapy. *In vivo* and *in vitro* tests have shown that both plasma and intracellular concentrations of ATV and RTV are under the functional influence of p-glycoprotein (ABCB1), organic anion transporters (OATs) and nuclear factors (PXR). However, the rate of accumulation of ATV and RTV within the cells is still debated due to scarce data and methodological limitations. Therefore, our aim was to measure the peripheral blood mononuclear cell (PBMC) concentration of ATV and RTV in clinical samples in order to verify whether single-nucleotide-polymorphisms (SNPs) in the genome regions coding for p-glycoprotein, OATP1B1 and PXR play any consistent role in intracellular drug penetration.

**Materials and Methods:** Patients administered with standard dose of boosted Atazanavir (ATV/RTV) (300/100 qd) were considered. Main inclusion criteria were no concomitant interacting drugs, no hepatic or renal function impairment, and self-reported adherence >95%. Blood sampling at the end of dosing interval (Ctough) was performed after written informed consent given. PBMCs-associated and plasma ATV and RTV concentrations were measured by validated methods in HPLC-MS and HPLC-PDA, respectively. Cell count and mean cell volume were performed by a Coulter Counter instrument and those data were used to calculate the total PBMC volume. Median value of individual measurements was considered. Genotyping was conducted by Real-Time-PCR based allelic discrimination using standard methodology. Statistical analysis was performed by Mann-Whitney and Spearman-Rank tests. Values were expressed as ng/mL.

**Results:** 35 patients were enrolled. Median (IQR) ATV and RTV intracellular concentrations were 1844 (973-3334) ng/mL and 716 (502-1028) ng/mL, respectively. Median (IQR) ATV and RTV plasma concentrations were 645 (469-991) ng/mL and 75 (46-164) ng/mL, while median intracellular/plasma concentrations ratios were 2.43 and 9.19, respectively. The average (IQR) RTV intracellular concentrations in individuals with mutant allele (TC or CC, n=8) for OATP1B1-521 (rs4149056) was significantly higher as compared to patients wild-type genotype (TT, n=27) [1439 (808-1701) vs 860 (431-1007), respectively, p=0.010]. Similarly, the average (IQR) RTV intracellular concentrations in individuals with mutant allele (AG or GG, n=29) for PXR-44477 (rs1523130) was higher in patients with GG genotype (n=17) in ABCB1 at position 2677 (rs4165124) compared to GT (n=13) and TT (n=5) groups [4.10 (1.99-5.18) vs 2.43 (1.65-5.40) vs 0.75 (0.47-1.99), respectively, p=0.025].

**Conclusions:** Our study showed a general rate of RTV intracellular accumulation higher as previously reported, probably due to the more accurate calculation of intracellular concentrations (use of mean individual PBMCs volume). These concentrations showed to vary according to OATP1B1-512 and PXR-44477 SNPs, suggesting a role of the latter in RTV penetration. ATV intracellular/plasma ratio showed to be influenced by p-glycoprotein transporter. Further clinical studies are warranted in order to elucidate and confirm inter-individual differences and clinical implications of ATV and RTV intracellular penetration.

No conflict of interest
Abstract: P_24

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

Comparative PK analysis of maraviroc, darunavir, raltegravir, etravirine and ritonavir between blood and seminal plasma in HIV infected patients

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Background: Several studies have confirmed that the male genital tract is a viral reservoir in which HIV replication occurs. Although there have been several studies describing the distribution of various antiretroviral drugs into this compartment, the extent of pharmacokinetic evidence is limited, particularly for the recently marketed antiretrovirals. In this study, we determined the concentrations of maraviroc, darunavir, etravirine, raltegravir and ritonavir in semen versus blood, and determined the seminal plasma to blood plasma ratios (SP/BP) of these drugs. We also evaluated the variability between SP/BP ratios of the aforementioned drugs throughout the dosing period by collecting samples from multiple time points post-ingestion.

Materials & Methods: HIV-positive men using twice daily (BID) maraviroc as a part of their antiretroviral regimen for at least 3 months prior to the study were eligible for the study. Multiple sampling was carried out over the entire dosing interval, while staggering sampling days. Blood and seminal plasma samples were taken 1 hour pre-dosing, and 1,2,4,8 and 12 hours post-dose. Cmin, Cmax, Tmax, AUC0-12h and coefficient of variation (CV) between mean SP/BP ratios were calculated.

Results: Of the 14 enrolled subjects, 10 completed the study and were included in the analysis. Of the 10 individuals, all were using maraviroc (150mg BID) and raltegravir (400mg BID), 8 were using etravirine (200mg BID), and 8 were using darunavir/ritonavir (600/100mg BID). The median Cmin for maraviroc in semen was 0.08mg/L, which is 36-fold higher than the upper limit of the EC50 (0.0023mg/L) and 8-fold higher than the upper limit of EC90 (0.0107mg/L) for HIV. The median Cmax value of maraviroc in semen was 0.62mg/L, with a median Tmax of 3.78 hours. The median Cmin and Cmax values for maraviroc in blood were 0.083mg/L and 0.42mg/L respectively. The median maraviroc AUC0-12h values were 2.76 hours*mg/L in blood and 3.43 hours*mg/L in semen. The median and average (CV) AUC0-12h SP/BP ratios for maraviroc were 0.93 and 2.16 (123%) respectively. The median and average (CV) SP/BP ratios for darunavir, raltegravir, etravirine and ritonavir were 0.25 (48%), 3.19 (41%), 0.18 (38%) and 0.09 (46%) respectively.

Conclusions: Our findings indicate that maraviroc and raltegravir accumulate in the seminal plasma, whereas darunavir, etravirine and ritonavir distribute into the male genital tract to a lesser extent. However, we observed considerable variability in the degree of distribution into this compartment by maraviroc.

Conflict of interest financial relationship(s): study support by Pfizer

Abstract: P_25

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

Tenofovir diphosphate (TFV-DP) and Emtricitabine triphosphate (FTC-TP) pharmacokinetics (PK) in older HIV+ patients

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Background: TFV and FTC are phosphorylated within cells to their active forms. Aging may affect cell activation states, and thus metabolism in older HIV+ patients. To inform design of a larger population PK study, we determined TFV-DP and FTC-TP PK in peripheral blood mononuclear cells (PBMCs) of older HIV+ adults.

Materials and Methods: In this open-label pilot PK study, 12 non-frail (by phenotype) HIV+ adults >55 years of age receiving tenofovir/emtricitabine (TFV/FTC) with either efavirenz (EFV; n = 6) or atazanavir/ritonavir (ATV/r; n = 6) for clinical care for >2 weeks each provided 11 PBMC samples over a 24hr visit. Concentrations were analyzed with validated LC-MS/MS methods. Noncompartmental PK was used to calculate area under the curve (AUC); the Wilcoxon signed-rank test was used for comparisons to published values in subjects aged 25-60 years (historic controls).

Results: Mean ± SD age was 59.7 ± 3.9 years, BMI was 29.9 ± 5.4 kg/m2, CrCL was 70.1 ± 17.6 ml/min and CD4+ lymphocytes were 818 ± 370 cells/mm3 (1). 3 Caucasians and 3 African Americans were enrolled on each regimen; 6/12 were female. 11/12 had undetectable HIV RNA with 100% self-reported adherence. TFV/TFV-TP concentrations were similar between regimens, while FTC concentrations were higher for subject receiving EFV. Median (25th, 75th percentile) TFV AUC was 3330 (2920, 4230) hr*ug/L, compared with 3710 hr*ug/L, yielding ~10% lower values than historic controls. FTC AUC was 14100 (10300, 19100) hr*ug/L in EFV subjects, and 10050 (8540, 12400) hr*ug/L in ATV/r subjects. Compared with 8010 hr*ug/L, older subjects had ~31-75% higher exposures than historic controls. However, the mean TFV-DP concentration over the 24 hour dosing interval of 121 fmol/10^6 cells is 33% higher and median FTC-TP concentrations at 4hrs post-dose of 3110 (2100, 4120) (EFV subjects) and 3110 (2389, 3346) (ATV/r subjects) fmol/10^6 cells were 22% lower compared to historic controls. FTC-TP concentrations at 4hrs were significantly different from historic control for ATV/r subjects (p=0.03); for all other comparisons of concentrations between older subjects and controls, p>0.05.

Conclusions: In these HIV+ subjects >55 years, TFV-DP concentrations were higher while FTC-TP concentrations were lower than historic controls 25-60 years. These results are consistent with increased cellular activation in older patients, as FTC is preferentially metabolized in resting cells and FTC-TP concentrations were lower, despite increased FTC exposure. Increased TFV-DP concentrations may be due to the effects of chronic inflammation on drug transporters, and may increase toxicity. PK modeling of the relationship between parent and metabolite is ongoing, and these results will inform design of a larger population PK study including both younger and frail HIV+ patients. The results from this first report of intensive TFV-DP and FTC-TP PK in HIV+ subjects >55 years support further investigations defining the relationship between nucleos(t)ides and their metabolites.

The tenofovir and emtricitabine parent PK were originally presented at the 2nd International Workshop on HIV and Aging, Baltimore, MD, October 27-28, 2011. They are included here as a reference point for the metabolite behavior.

No conflict of interest

Abstract: P_26

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

Development and validation of a LC-MS/MS assay to quantify 10 anti-retroviral (ARV) drugs in cerebral spinal fluid (CSF).

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Background: Combination antiretroviral therapy (cART) has resulted in a dramatic decline in HIV morbidity and mortality. However, in an ageing HIV-infected population, HIV-associated neurocognitive disorders (HAND) remain a concern. HIV may reside outside of the systemic circulation in anatomical sanctuary sites, including the central nervous system (CNS). There is some
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Evidence that anti-retrovirals (ARV) exhibiting high CNS penetration effectiveness suppress compartmentalised viral replication and improve neurocognitive functioning. Ineffective penetration of antiretroviral agents (ARV) into the CNS can result in sub-therapeutic concentrations and the possibility of viral resistance, whereas excessive levels can potentially lead to neurotoxicity. A greater understanding of ARV pharmacokinetics (PK) in the CNS may influence the timing of cART initiation, in order to preserve neurocognitive functioning. In order to gain better understanding of ARV penetration into anatomical sanctuary sites we need sensitive and specific analytical methods. Here we describe the validation of a LC-MS/MS method for the quantification of 10 ARV agents in CSF.

Materials and Methods: Artificial CSF was spiked with nevirapine (NVP), rilpivirine (RPV), etravirine (ETV), atazanavir (ATV), amprenavir (APV), darunavir (DRV), lopinavir (LPV), ritonavir (RTV), raltegravir (RAL) and maraviroc (MVC). Human serum albumin [0.2 g/L] was added for stabilisation of the drugs. A nine point standard curve was produced by serial dilution. Internal standards quinoxaline and 13C6-RPV were added and samples were extracted via protein precipitation (acetonitrile: 0.1% formic acid [50/50]). Samples were analysed by LC-MS/MS. Gradient chromatographic separation on a reverse-phase C18 column, with detection by selective reaction monitoring in positive mode was applied. Accuracy of the methodology was monitored using quality controls at low, medium and high points on the calibration curve.

Results: All drugs eluted within a 10 minute run time. Calibration curves were validated over the following concentration ranges; LPV, MVC, RTV = 0.78-100 ng/mL, RAL, APV, ATV, RPV, ETV, DRV = 1.95-250 ng/mL and NVP = 19.5-2500 ng/mL (r² values >0.99; quadratic 1/x). Intra and inter assay variation ranged between 1.59-15% for precision and -10.5-6.4% for accuracy. Carryover was <20% of the lower limit of quantification for all drugs. The recovery was >70% and the CV% at low, medium and high concentrations was less than 20% for all drugs.

Conclusions: The developed assay can be applied to CSF samples collected in clinical PK trials. The methodology is robust, accurate and highly sensitive for the simultaneous measurement of ten ARV’s, enabling greater insight into compartmentalised ARV concentrations within this sanctuary site. The direct quantification of an ARV in CSF is one important aspect of seeking a greater understanding of why some patients develop HIV–associated neurocognitive disorders despite having optimal ARV plasma levels.

No conflict of interest

Abstract: P_27

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

The interplay between raltegravir solubility, metal binding, charge state and cell permeability: Unravelling the interactions with antacids and food

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Introduction: Raltegravir exhibits marked inter-patient pharmacokinetic variability that is potentially influenced by gastrointestinal pH and divalent metal binding. Previous investigations suggest that influx and efflux transporters are unlikely to play a major role in raltegravir disposition. We have investigated raltegravir solubility, pKa and permeability in vitro to better understand interactions with acid reducing agents (omeprazole, antacids), and food, which increase gastric pH.

Materials and Methods: Solubility of raltegravir was determined between pH 1 to 8 using buffered solutions. Predicted solubility and logD for raltegravir was calculated using ACD/Labs Online (i-Lab). Raltegravir pKa was determined using UV-Vis spectroscopy. The effects of divalent (Mg2+, Ca2+) and monovalent (K+) metal salts on the extent of raltegravir cellular permeability were determined using cultured Caco-2 monolayers and efflux ratios (basolateral-to-apical versus apical-to-basolateral raltegravir permeability) calculated. Lopinavir was used as a negative control since
it is unable to bind to divalent metals. To confirm any induction/inhibition effects of omeprazole on raltegravir cellular permeability, Caco-2 monolayers were pre-incubated (3 days) in the presence of 10µM omeprazole and used in raltegravir permeability experiments with and without the addition of 20µM omeprazole. Samples were analysed using LC-MS/MS or scintillation counting.

**Results:** Raltegravir (10mM) was determined to be only partly soluble at pH 6.6 and below. The predicted solubility of raltegravir was greatly reduced (423-fold decrease, 110mM to 0.26mM) as pH was reduced from 8 to 1. Raltegravir appeared to be monoprotic at physiological pH and the pKa was determined as 6.7. Raltegravir cellular permeability was influenced by changes in divalent metal concentrations: cellular permeability was reduced in the presence of 25mM magnesium chloride (66% decrease, p<0.05) and 25mM calcium chloride (36% decrease, p<0.05), whereas 25mM potassium chloride did not significantly alter raltegravir cellular permeability (p=0.83). Lopinavir efflux ratio was unaltered with the addition of 25mM magnesium (p = 0.83), illustrating that the effect of magnesium on raltegravir cellular permeability was not a result of general changes in monolayer integrity. Omeprazole did not significantly alter raltegravir cellular permeability in induction or inhibition experiments.

**Conclusions:** Gastrointestinal pH and polyvalent metals may alter the disposition of raltegravir and the present data provide a rational basis for some of the variability in raltegravir exposure in patients. The lack of a direct effect of omeprazole on raltegravir cellular permeability suggests that the gastric pH-boosting effect of omeprazole is responsible for increasing raltegravir absorption in vivo. The evaluation of how polyvalent metal-containing products (such as multivitamins) alter raltegravir pharmacokinetics in patients is now warranted.

No conflict of interest

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**Abstract: P_28**

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

**Simultaneous population pharmacokinetic modelling of atazanavir/ritonavir in HIV-infected adults and assessment of different dose reduction strategies**

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**Background:** Atazanavir (ATV) is a protease inhibitor (PI) used as part of combination HIV therapy. ATV is metabolised by CYP3A4/3A5 and is an inhibitor of CYP3A4, p-glycoprotein and UDP-glucuronosyltransferase 1A1. A target minimum effective concentration (MEC) of 0.15 mg/L at trough has been recommended for optimal viral suppression. ATV is co-administered with ritonavir (RTV) and licensed at a dose of ATV/RTV 300/100 mg once daily, but is also approved in the USA unboosted at 400 mg once daily for treatment-naive patients. The concentration of RTV maximal inhibition of CYP3A4 may occur with a lower RTV dose than 100 mg. There are clear advantages to lower doses of RTV (better tolerated, cheaper to manufacture, easier to co-formulate), but current there are also obstacles.

**Objectives:** The objective of this study was to develop a simultaneous population PK model to describe ATV/RTV PK (300/100 mg) and to assess the effect of RTV dose reduction on ATV PK. Simulations of ATV concentration-time profiles were performed at doses of ATV/RTV 300/50 mg, 200/50 mg and 200/100 mg once daily.

**Methods:** A total of 288 ATV and 312 RTV plasma concentrations from 30 patients were included to build a population pharmacokinetic model using the stochastic approximation maximization algorithm implemented in MONOLIX 3.2 software.
Results: A maximum-effect model in which RTV inhibited the elimination of ATV was used to describe the relationship between RTV concentrations and ATV clearance (CL/F). A RTV concentration of 0.22 mg/liter was associated with 50% maximum inhibition of ATV CL/F. The population prediction of ATV CL/F in the absence of RTV was 16.6 liters/h (relative standard error, 7.0%), and the apparent volume of distribution and absorption rate constant were 106 liters (relative standard error, 8%) and 0.87 h^\textsuperscript{-1} (fixed), respectively. Simulated average ATV trough concentrations at ATV/RTV 300/50 mg, 200/50 mg and 200/100 mg once daily were 45%, 63% and 33% lower, respectively, than that of the standard dose.

Conclusion: A population model to simultaneously describe the pharmacokinetics of ATV and RTV was developed and validated in HIV-infected individuals. The simulated median ATV trough concentrations following dose reductions were reduced compared to the licensed dose but were still above the ATV MEC (2.9, 1.9 and 3.6 fold for ATV/RTV 300/50 mg, 200/50 mg and 200/100 mg, respectively). Simulated data for the 300/50 mg regimen are consistent with the clinical data. This modelling approach aids our understanding of the interaction between ATV and RTV and informs the design of dose reduction strategies, particularly in relation to RTV.

No conflict of interest

Abstract: P_29

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Therapeutic drug monitoring and clinical outcome after acute atazanavir overdose in an HIV-positive adult male

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Introduction: There are limited data on the pharmacokinetics and safety of atazanavir after acute overdose. No specific antidote exists and management includes general supportive measures such as monitoring ECG, vital signs and clinical status. Here we report clinical and pharmacokinetic findings in an HIV-infected adult male after acute ingestion of atazanavir 8700mg (300mg x29 capsules) in an attempted suicide.

Materials & Methods: The patient was identified through referral to the B.C. Centre for Excellence in HIV/AIDS Therapeutic Drug Monitoring (TDM) Program. Plasma antiretroviral concentrations were determined by a validated high-performance liquid chromatography method with tandem mass spectroscopy. Limits of quantification for both atazanavir and ritonavir were 50-10,000ng/mL. Concomitant medications and clinical and laboratory data were abstracted from pharmacy and health records.

Results: A 37-year-old HIV/HCV co-infected male was brought to hospital by ambulance 3.5 hours after ingesting atazanavir 8700mg without ritonavir. The subject was 60kg with CD4 270 cells/µL and HIV viral load <40 copies/mL. Co-medications were atazanavir 300mg, ritonavir 100mg, abacavir/lamivudine 600mg/300mg, citalopram 40mg, quetiapine 200mg (all once daily) and ferrous sulfate 300mg po BID. Last ritonavir 100mg dose was reportedly taken 24 hours prior to the overdose. There was no vomiting and gastric decontamination was not performed. At admission, vital signs were as follows: blood pressure 109/64 mmHg, heart rate 88 bpm, respiratory rate 18, temperature 37.7 degrees Celsius. No jaundice, dermatologic, musculoskeletal or genitourinary symptoms were present. Abacavir/lamivudine was continued and atazanavir and ritonavir were re-initiated 62 hours after overdose. Laboratory values 14 days before and 24 and 48 hours after the ingestion respectively were AST 66, 37, 42 U/L, ALT 111, 73, 70 U/L, total bilirubin 10, 40, 18 μmol/L and SCr 63, 107, 74 μmol/L. ECG was normal 4 hours post-ingestion, with no significant change compared to ECG 8 days prior. However, at 22 hours post-overdose (compared to 4 hours), prolonged PR interval (204 from 144ms) and QTc interval (493 from 471ms) were observed. These values returned to baseline at one-month follow-up. The patient remained under psychiatric observation for 8 days, after which he was discharged.
Atazanavir plasma concentrations (C) were 5400ng/mL and 594ng/mL at 22 and 62 hours post-overdose (recommended C_{trough} >150ng/mL). Ritonavir was not detected in either sample. Assuming one-compartment model in the postabsorption, postdistribution phase, estimated plasma t_{1/2} was 12.6 hours, exceeding reference plasma t_{1/2} of 8.6 hours for atazanavir/ritonavir 300/100mg daily and t_{1/2} of 6.5 hours for atazanavir 400mg daily. Estimated patient atazanavir C_{max} at 2.5 hours post-dose was 15837ng/mL (C_{max} 4422ng/mL for atazanavir/ritonavir 300/100mg daily and 2298ng/mL for atazanavir 400mg daily) and estimated atazanavir C_{24h} was 5104ng/mL (C_{min} 636ng/mL for atazanavir/ritonavir 300/100mg daily and 120ng/mL for 400mg daily). Estimated AUC_{0-24} was 237361ng*h/mL compared to 48073ng*h/mL (atazanavir/ritonavir 300/100mg) and 14874ng*h/mL (atazanavir 400mg).

Conclusions: Limited clinical toxicity was observed after acute ingestion of atazanavir 8700mg. Transient elevation in total bilirubin and SCr and asymptomatic increases in PR and QTc intervals were observed. Antiretroviral TDM was beneficial in guiding when to re-initiate treatment after acute overdose of atazanavir.

No conflict of interest

Abstract: P_30

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Raltegravir penetration into the cerebrospinal fluid: Impact of co-administered antiretrovirals and rifampin.

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Background: Raltegravir (RAL) concentrations in the CSF have been recognized to be 3-5% of plasma concentrations even if a wide inter-patient variability has been described (CSF-to-plasma ratios ranged from 1 to 61%). Determinants of blood-brain-barrier (BBB) passage are not completely defined and co-medications have the potential to modulate transporters responsible for drugs transportation. Therefore our aim was to evaluate RAL penetration in the CSF according to the different co-administered drugs.

Materials and Methods: RAL-administered patients undergoing lumbar punctures for clinical reasons were included after having given signed informed consent. Plasma and CSF samples were concomitantly obtained and RAL concentrations were measured through a validated HPLC-PDA method with a limit of detection (LOD) of 12 ng/ml (plasma) and a UPLC-MS/MS method with a LOD of 0.25 ng/ml (CSF). Data are expressed as median (IQ range).

Results: 27 patients (66.7% male, 90.9% caucasians) were included; age and BMI were 45 years (38.3-53) and 22.1 kg/m² (20-25.1), respectively. Diagnostic spinal taps were performed in patients with neurological or neurocognitive complains (42.9%), opportunistic infections (38.1%) or tubercular meningitis (19%). Most frequent co-administered drugs were PIs (66.7 %), NNRTIs (15.2%), NRTIs (6.1%), and rifampin-NRTIs (12.1%). Median RAL plasma and CSF concentrations on 33 samples were respectively 150 ng/ml (77-291) and 33 ng/ml (22-57); CSF-to-plasma ratios ranged from 0.05 to 1.32 [median 0.25, IQR (0.10-0.42)]. At the end of the dosing interval patients on concomitant boosted PIs (22 samples) showed non-significant higher CSF trough concentrations [34 ng/ml (23-57)] but lower CSF-to-plasma ratios [0.21 (0.11-0.44)] compared to other drugs [n=5, CSF RAL 21 ng/ml (15-42), ratio 0.36 (0.31-0.89)] (p=0.24 and 0.06, respectively). 11 patients (40.7%) presented an altered BBB (CSAR > 6.5) and higher CSF-to-plasma ratios (0.57 vs. 0.18, p=0.01). In the subgroup of 4 patients co-treated with rifampin, 3 of whom taking RAL at 800 mg twice daily dosing associated with 2 NRTIs, CSF RAL concentrations were 41.5 ng/ml (ranging from 8 to 187 ng/ml) with CSF-to-plasma ratio of 0.31 (from 0.09 to 0.92).

Conclusions: RAL passage into the CSF showed a large inter-patient variability but cerebrospinal concentrations were above the in vitro IC50 (3.2 ng/ml) in all cases, including in patients treated with double-dose raltegravir and rifampin. The role of BBB damage and concomitant drugs interactions (and potentially pharmacogenetics) in affecting RAL...
penetration in the CSF deserve further investigation in larger clinical studies.

Conflict of interest
financial relationship(s): Speaker's honoraria and travel grants from MSD.

Abstract: P_31

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Circadian variations of darunavir plasma concentrations in HIV-infected patients receiving DRV/r qd containing regimen.

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Background: Circadian Rhythm causes physiological and metabolic changes therefore influencing drug pharmacokinetic (PK). Studies show that anti-HIV drugs, protease inhibitors (PI), can be affected by the circadian rhythm. Ritonavir boosted darunavir (DRV/r) can be administered once daily and its plasma exposure is increased by 30% when administered with food. The objective of our study is to compare morning and evening 800/100 mg qd DRV/r dose on DRV plasma concentration.

Materials & Methods: A cross-sectional study was performed on our TDM database in non-pregnant adult HIV-infected patients receiving DRV/r (800/100 mg qd) containing regimen. DRV plasma concentrations were determined using UPLC-MS/MS (LOQ<5 ng/ml). Interval between last drug intake and sampling were recorded. DRV plasma concentrations (C24H) were extrapolated to 24 hours post-dose based on a 12hrs half-life. A cut-off of 550ng/ml, corresponding to a ten fold half maximal effective concentration of DRV (EC50), was established to exclude potential adherence difficulties. Interpretation of morning and evening DRV C24H were performed on the whole population and on restricted populations. Circadian variation was defined as the difference between C24H post-morning and post-evening doses. DRV C24H were also compared in a restricted range of drug intake (8±2hrs am and 8±2hrs pm). In another subgroup, the impact of co-variables (age, gender, origin, viral failure defined as two successive plasma viral load (pVL)>50 c/ml, CD4-cell count, BMI) was analyzed regarding their availability in our database. All results are presented as median (IQR25–75%). Statistical analysis was performed using ANOVA and Spearman tests.

Results: In that study, 1164 patients (67% male, 47 (40–54) years) corresponding to 1671 DRV C24H were enrolled. After excluding potential adherence difficulties (C24H<550ng/ml), 1431 DRV C24H remained and among them, 611 were post-morning. DRV C24H were 1568ng/ml (991–2306) and 1390ng/ml (956–2037) (p<0.0001) for post-morning and post-evening doses, respectively. Females are significantly more subject to circadian variation than males (p<0.0001). There was a statistical difference in the subgroup of restricted range of drug intake (1058 C24H and 432 post-morning) (p<0.0001), persisting in the co-variable subgroup (675 C24H and 263 post-morning) (p<0.001). In this subgroup, 27% of virological failure was found whatever the morning and evening doses. Treatment-experienced patients (79%) were as sensible to circadian variation as naïve patients. No correlation between BMI and PK has been found. In obese patient, C24H are slightly higher in females in the post-morning dose (p=0.045), but there is no difference in the post-evening dose.

Conclusion: A significant difference was observed in the DRV C24H in favour of post-morning dose. Circadian variation was higher in females than in males, but there is no influence of treatment experience. PK was independent of BMI, however, there is a higher C24H in obese females than in males in the morning. Statistical difference between morning and evening can be explained by diurnal/nocturnal physiological difference that can affect PK, for example CYP3A4 variation with circadian rhythm. Also it may be explained by a difference in regimen between the two periods.

No conflict of interest
Abstract: P_32

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Bioequivalence of the 800-mg tablet formulation of darunavir compared with the commercially available 400-mg tablet formulation

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Background: Darunavir/ritonavir 800/100mg once daily (qd) has been studied in treatment-naïve and-experienced adults with no darunavir resistance-associated mutations. At this dose, darunavir is currently administered as two 400-mg tablets. Given that dosing convenience is a key driver for adherence, with resultant reduced risk for resistance development, an 800-mg darunavir tablet was developed. The 400-mg and 800-mg tablets differ in excipient composition. Bioequivalence of the 800-mg tablet and current 400-mg tablet was assessed in a Phase I study, both under fed and fasted conditions and both in the presence of low-dose ritonavir.

Methods: This was an open-label, randomised, two-panel, two-way crossover study in HIV-negative, healthy adult volunteers (TMC114-TiDP3-C176; NCT01308658). A classical two-sequence, two-period Williams design was used. In Panel 1 (fasted state), 83 volunteers received a single oral 800-mg dose of darunavir as either two 400-mg tablets, or one 800-mg tablet. In Panel 2 (fed state), 45 volunteers similarly received two 400-mg tablets, or one 800-mg tablet. Each session was separated by a ≥7-day wash-out period. A single darunavir dose was administered on Day 3 in each treatment session. All volunteers received 100-mg ritonavir qd (Days 1–5) which was given under fed conditions, except on Day 3 in Panel 1 where it was administered under fasted conditions. Full pharmacokinetic profiles were determined up to 72 hours after administration for darunavir and over 24 hours for ritonavir. Safety and tolerability were assessed at regular intervals throughout. Follow-up period was for 30–32 days.

Results: 121 volunteers (62% male, 99% white) completed the study. In Panel 1 (fasted), the mean ± SD darunavir Cmax was 4914 ± 1332 vs. 4866 ± 1441 ng/mL and AUClast was 91,140 ± 40,250 vs. 96,120 ± 54,820 ng.h/mL for 800-mg and 2x400-mg tablets, respectively. In Panel 2 (fed), Cmax was 6773 ± 1668 vs. 7031 ± 1669 ng/mL and AUClast was 105,100 ± 37,880 vs. 105,900 ± 32,530 ng.h/mL for 800-mg and 2x400-mg tablets, respectively. Least-squares means ratio of darunavir Cmax, AUClast and AUC were 1.02, 0.99 and 1.00, respectively for Panel 1, and 0.96, 0.98 and 0.98, respectively, for Panel 2; the 90% confidence intervals were all within 80.00% to 125.00%. All adverse events (AEs) were grade 1 or 2 with no grade 3 or 4 AEs. One volunteer experienced a serious AE (bone fractures), leading to discontinuation (not considered drug related). In addition, one volunteer discontinued due to abdominal pain and diarrhea, also not considered drug related. AEs considered possibly related to darunavir were reported in 24.2% of volunteers (mostly headache or fatigue). Laboratory abnormalities were mostly grade 1 or 2. There were no relevant differences in AEs or laboratory abnormalities between formulations.

Conclusions: The 800-mg tablet of darunavir was bioequivalent to two tablets of the commercially available 400-mg tablet, both co-administered with low-dose ritonavir regardless whether participants were in a fed or fasted state. Short-term administration of darunavir/ritonavir 800/100-mg was generally safe and well tolerated.

Conflict of interest financial relationship(s): employee of Janssen

Abstract: P_33

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Population pharmacokinetics of antiretroviral drugs in HCV/HIV or HBV/HIV coinfected individuals

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Introduction The human immunodeficiency virus (HIV) infection affects more than 40 million individuals worldwide. Currently, the antiretroviral therapy is based on three or more antiretroviral drugs of two or three therapeutic groups. The availability of these drugs converted the fatal HIV infection into a chronic, slow progressive disease. About one quarter of every HIV-infected individual in developed world is also HCV infected and about one tenth HIV-infected individuals are HBV infected. This co-infection leads to a faster progression of both HCV/HBV liver damage and HIV immune system deterioration. Thus it is necessary to be aware of the factors that affect the efficacy of anti-HIV, anti-HBV and anti-HCV drugs. This study was designed to assess the influence of viral hepatitis co-infection and liver damage in the antiretroviral drug pharmacokinetics.

Material & Methods Sixty HIV-infected patients on triple antiretroviral therapy from the Clinical Ward of Infectious Diseases of Santa Maria Hospital (Lisbon) were enrolled for this study of which twenty eight were HCV co-infected (33.3%) and two are HBV co-infected (3.3%). Samples of six milliliters of blood were collected between 8 to 24 hours post-dose (trough concentration / Cmin) and analyzed by an HPLC-UV validated method. Individual demographic and clinical data were retrieved. Aboottbase PKS software was used to estimate adjusted pharmacokinetic parameters (clearance, distribution volume, etc.). All results were analyzed in IBM SPSS 17.0 by Mann-Whitney (MW-test) or t-Student tests (t-test).

Results The statistical analysis between co-infected and non co-infected groups showed a significant difference in lopinavir Cmin (MW-test, p < 0.05) with higher mean±SD Cmin values for co-infected patients (3953±679 ng/mL versus 2383±1389 ng/mL). The adjusted pharmacokinetic parameters obtained showed no statistically significant differences except for a trend in the half-life (t-test, p = 0.07). Other drugs showed no differences in all analyzed variables. A clear association between hepatic enzymes (GPT, GOT, GGT) and co-infection was found (p < 0.05). Also urea plasma levels showed correlation with the presence of viral hepatitis (t-test, p = 0.009).

Conclusions This preliminary study reveals a small association between some pharmacokinetic parameters of antiretroviral drugs and the presence of HCV or HBV co-infection in HIV-infected patients. The lopinavir Cmin was significantly influenced by the presence of viral hepatitis, however the statistical association of lopinavir adjusted pharmacokinetic parameters is not so clear. To disclose further association between the presence of HIV-HCV or HIV-HBV co-infection, more robust data are needed.

No conflict of interest

Abstract: P_34

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

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

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Background: Combination antiretroviral therapy (cART) has been shown to reduce HIV mother to child transmission (MTCT) from 15-40% to <2%. The most commonly used nucleoside reverse transcriptase inhibitors are zidovudine and lamivudine. However, an overview of antiretroviral use during pregnancy between 1995 and 2009 showed an increase of tenofovir (TDF)/emtricitabine use to approximately 30% whereas zidovudine/lamivudine use decreased from 90% to 70%.

It is important to achieve effective concentrations of antiretroviral drugs to prevent treatment failure and the development of
resistance. During pregnancy, physiological changes take place influencing the pharmacokinetics of medicines and in most cases, the net effect will be a decreased exposure. Sparse publications on pharmacokinetic parameters of chronic exposure to tenofovir concluded that exposure during pregnancy is lower, but not below the threshold target for most women.

In 2008, a European network was established to study the pharmacokinetics of newly developed antiretroviral drugs during pregnancy (PANNA). We present data on third trimester exposure to tenofovir.

**Materials & Methods:** Pregnant women taking TDF (245mg QD) as part of their cART were screened and blood was collected for a 24h pharmacokinetic curve ($t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24h$) after supervised intake of TDF 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. Tenofovir plasma concentrations were determined with a validated HPLC method with fluorescence detection (lower limit of quantification of 0.015 mg/L). Pharmacokinetic parameters were calculated with WinNonlin 5.3.

**Results:** Paired tenofovir plasma concentration curves were available from 19 women (14 also used a boosted protease inhibitor). Geometric mean (95% confidence interval (CI)) for $AUC_{0-24h}$ (mg*h/L) was 2.37 (2.13-2.64) in the 3rd trimester and 3.17 (2.74-3.65) post-partum. For $C_{max}$ (mg/L) this was 0.270 (0.223-0.328) in the 3rd trimester and 0.350 (0.289-0.424) post-partum and for $C_{24h}$ (mg/L) this was 0.049 (0.043-0.057) in the 3rd trimester and 0.065 (0.053-0.079) post-partum. The GM (95% CI) for $t_{1/2}$ (h) was 14.4 (12.6-16.4) in the 3rd trimester and 13.5 (11.8-15.5) post-partum.

Ratios of PK parameters 3rd trimester/post-partum (geometric mean ratio (90% CI)) were: 0.75 (0.67-0.83) for $AUC_{0-24h}$; 0.77 (0.69-0.87) for $C_{max}$; 0.76 (0.63-0.92) for $C_{24h}$; 1.06 (0.91-1.25) for $t_{1/2}$. These results are independent of concomitant use of boosted protease inhibitor. The ratio of cord blood/maternal plasma tenofovir concentrations, determined in 11 patients, ranged from 0.66 to 1.03. All children were HIV uninfected, no birth defects were reported.

**Conclusions:** During pregnancy (third trimester) exposure to tenofovir is approximately 25% lower than post-partum, which does not appear to be caused by (renal) clearance because $t_{1/2}$ did not change. Potential causes for the decreased exposure are reduced absorption and/or increased volume of distribution. Despite this decrease in exposure, no children were infected. Tenofovir efficiently crosses the placenta.

No conflict of interest

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**Abstract: P_35**

**Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations**

**Use of population pharmacokinetics bridging from adult data to predict ritonavir-boosted saquinavir exposures in HIV-infected children aged 2-15 years**

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**Background:** Although boosted saquinavir is an important HIV treatment in resource-limited settings, particularly in children failing NNRTI-based therapy, pharmacokinetic data in paediatric patients are lacking. For inferences to be made regarding paediatric dosing one approach is to perform a population pharmacokinetic bridging analysis using data from adults and available paediatric data with the aim of simulating saquinavir exposures of HIV-infected patients for whom pharmacokinetic data are lacking but clinical data are available (e.g. demographics).

**Materials & Methods:** Nonlinear mixed effects modelling (NONMEM v. VI 2.0) was applied to saquinavir/ritonavir (1000/100mg twice daily) pharmacokinetic data from 48 HIV-infected adults (10 female) median (range) age 44years (22-63) to estimate saquinavir pharmacokinetic parameters, interindividual variability (IVIV), interoccasion variability (IOV) and residual error. Pharmacokinetic data from 13 HIV-infected paediatric patients (8 female) median
(range) age 4 years (2-5) were available. Prior information from the adult model was used to constrain some parameter estimates in the paediatric model. Pharmacokinetic parameters for the paediatric population and the final paediatric model was used to simulate saquinavir exposures and pharmacokinetic parameters of HIV-infected paediatric patients for whom saquinavir pharmacokinetic data were unavailable [median (range) age 9 years (4-15); n=50].

Results: A one-compartment model with sequential first and zero-order absorption best described the adult data. The paediatric model was simplified to a one-compartment model with first-order absorption parameterised by apparent oral clearance (CL/F), volume of distribution (V/F) and absorption rate constant (ka) with IIV and IOV on CL/F. The use of prior information from the adult model on ka and IOV CL/F provided reliable parameter estimates; using ritonavir AUC0-12 as a covariate on CL/F also improved the fit. Saquinavir pharmacokinetic parameters (RSE%) from the final model were: CL/F, 18.9 L/h (10.3%); V/F, 169 L (17.1%); ka, 2.35 h-1 (24.5%); IIV CL/F, 50.1% (18.7%); IOV CL/F, 21.4% (41.1%); proportional error, 52.9% (18.0%). Using the model 100 simulations were performed for patients without saquinavir pharmacokinetic data. Ritonavir data were lacking and were therefore simulated from the distribution of the original dataset. Median (range) simulated saquinavir AUC0-12, Cmax, Ctrough, Tmax, half-life and ritonavir AUC0-12 were: 49.1 mg.h/L (13.1-133.4), 7.0 mg/L (3.2-13.8), 2.0 mg/L (0.2-8.6), 1.2 h (1.0-1.3), 6.1 h (2.5-15.6) and 8.6 mg.h/L (0.7-15.8), respectively. The typical value of saquinavir CL/F obtained with the median ritonavir AUC0-12 (8.8 mg.h/L) was 18.9 L/h. The simulated distribution of ritonavir AUC0-12 (PS-P95) was 2.43-14.43 mg.h/L which was equivalent to a typical value of saquinavir CL/F of 26.14 L/h and 14.19 L/h, respectively. This corresponded to a 38% increase and 25% decrease in saquinavir CL/F compared to the typical value obtained with the median ritonavir AUC0-12.

Conclusions: A model describing saquinavir pharmacokinetics in HIV-infected paediatric patients has been developed and validated using a bridging approach stabilising the model with prior information from adult HIV-infected patients. The model was successfully applied to determine saquinavir exposures in HIV-infected paediatric patients for whom pharmacokinetic data were unavailable. This approach could be used to inform the design of clinical trials to aid dosage selection of other antiretrovirals in children.

Conflict of interest financial relationship(s): Some support for this work was provided by Roche

Abstract: P_36

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Preliminary pharmacokinetic data for maraviroc tablet dosing in treatment-experienced paediatric patients (6-18 years) on boosted protease inhibitors

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Background: A4001031 is an ongoing 2-stage, open-label, multicentre, pharmacokinetic (PK)/dose-finding, safety and efficacy study of maraviroc (MVC) in CCR5-tropic HIV-1-infected, antiretroviral (ARV)-treatment-experienced children (aged 2-18 years). Patients were stratified by age and MVC formulation into one of 4 cohorts receiving optimised background therapy (OBT; 3-5 ARV) + MVC either in solution (cohort 1: ≥2 years; cohort 3: ≥6-<12 years) or tablet formulation (cohort 2: ≥6-<12 years; cohort 4: ≥12 years). Initial paediatric MVC doses were based on adult doses scaled by body surface area (BSA) and adjusted for concomitant medications affecting CYP3A4. Stage 1 consists of an intensive MVC PK dose-adjustment period with a minimum of 10 patients/cohort. When dose has been determined in Stage 1, patients continue into Stage 2 (where sparse PK sampling is undertaken); Stage 2-only patients are enrolled for treatment with the Stage 1-determined dose. The aim of the present analysis was to use a population PK model developed with adult and interim paediatric data to determine
the average concentration (C<sub>avg</sub>) for Stage 2-only patients in Cohorts 2 and 4 who received ritonavir-boosted protease inhibitors (bPI), and compare these results with Stage 1 patients and adult data on similar bPIs.

**Materials and Methods:** Stage 1 patients had full MVC PK profiles at Week 2. If the average MVC concentration (C<sub>avg</sub>=area under curve/12) was \(\geq 100\) ng/mL, patients entered Stage 2, otherwise dose-adjustment with further PK evaluation occurred. Patients in Stage 2-only had single PK samples taken (5-12 hours post-dose) at all visits ≤Week 48. For Stage 2-only patients, the concentration/dose check was performed after the 6th patient in that cohort made their 8-week visit; a mechanistic NONMEM population PK model developed with extensive adult and paediatric data was applied to sparse data. Post hoc Empirical Bayesian PK parameters were used to calculate individual C<sub>avg</sub> values.

**Results:** Data were available for patients on bPI-containing OBT (darunavir and lopinavir) as follows: • Cohort 2: n=8 and n=7 for Stages 1 and 2, respectively • Cohort 4: n=9 and n=6 for Stages 1 and 2, respectively Stage 2-only, Cohort 2 patients with a median BSA of 0.89 m² (50-100 mg doses) had a median (range) C<sub>avg</sub> of 384 (148-474) ng/mL. This is comparable with Stage 1, Cohort 2 patients who had a median (range) C<sub>avg</sub> of 275 (120-398) ng/mL with a median BSA of 1.06 m² (75-100 mg doses). Stage 2-only, Cohort 4 patients with a median BSA of 1.225 m² achieved a median (range) C<sub>avg</sub> of 311 (164-461) ng/mL (75-150 mg doses). All patients in Stage 1, except one in Cohort 4, achieved C<sub>avg</sub> >100 ng/mL on the initial BSA scaled MVC doses.

**Conclusions:** A BSA-scaled twice-daily (BID) tablet dose of MVC in paediatric patients (≥6 years) in Stage 1 and Stage 2-only concomitantly receiving bPIs (darunavir and lopinavir) achieved concentrations similar to those in adults receiving 150 mg MVC BID with bPI.

**Conflict of interest** financial relationship(s): employee of Pfizer Inc. and owns Pfizer stock.

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**Abstract: P_37**

**Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations**

**Effect of pregnancy on pharmacokinetics of indinavir boosted ritonavir**

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**Background:** Indinavir/ritonavir (IDV/r) remains one of the few protease inhibitors available in Thailand and other resource-limited settings. Pregnancy greatly reduces unboosted IDV exposure and the recommended adult IDV/r dose of 800/100 mg twice daily has not been studied during pregnancy. IDV/r 400/100mg twice daily provides adequate exposure and minimal toxicity in non-pregnant Thai women. The impact of pregnancy on IDV exposure with the 400/100 mg dose is unknown.

**Methods:** IMPAACT P1026s is an on-going, prospective, non-blinded study of antiretroviral pharmacokinetics (PK) in HIV-infected pregnant women with a Thai cohort receiving IDV/r 400/100 mg twice daily during pregnancy through 6-12 weeks postpartum (PP). Intensive steady-state 24-hour PK profiles were performed during the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters and at 6-12 weeks PP. Plasma IDV/r concentrations were measured by reverse-phase HPLC. PK targets were the estimated 10<sup>th</sup> percentile IDV AUC (12.9 mcg.h/mL) in

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*Abstracts*
non-pregnant historical Thai controls (mean AUC=19.1 mcg.hr/mL) and a trough concentration of 0.1 mcg/mL, the suggested minimum target C12h trough conc.

**Results:** IDV/r PK data were available for 26 women. At 3rd trimester PK evaluation median (range) age was 30.4 (18.9 to 37.5) years, weight 61.3 (50.0 to 85.0) kg, gestational age 31.1 (29.3 to 37.0) weeks. Median infant birth weight was 2830 (2200 to 3548) gm. IDV was well tolerated. Median (range) indinavir AUC, Cmax and Cmin (mcg.hr/mL) during the 2nd trimester were 14.9 (10.4 to 38.7, n=13), 3.9 (2.4 to 10.3), 0.13 (0.07 to 0.23); during the 3rd trimester were 16.1 (7.5 to 39.9, n=25), 3.5 (1.3 to 7.4), 0.13 (0.07 to 0.6); and postpartum were 27.1 (18.6 to 44.7, n=26), 5.5 (3.8 to 9.4) and 0.28 (0.14 to 0.71), respectively. 10/13 (77%) women, 18/26 (69%) and 26/26 (100%) met the AUC target, while 9/13 (69%), 17/24 (71%) 26/26 (100%) met the C12h target during the 2nd, 3rd trimester and postpartum. Median (range) 2nd trimester/PP AUC ratio was 0.55 (0.35-1.35) and 3rd trimester/PP AUC ratio was 0.63 (0.29-1.37) in subjects with both evaluations. IDV/r dose was increased to 600/100 in 2 subjects with low pregnancy IDV AUC.

**Conclusions:** Median IDV exposure during the 2nd and 3rd trimesters is reduced by ~40% compared to postpartum and ~30% of pregnant women receiving IDV/r 400/100 mg failed to achieve the trough concentration target of 0.1 mcg/mL. Use of an increased dose of IDV/r in pregnancy may be preferable to ensure adequate exposure throughout pregnancy.

**No conflict of interest**

**Abstract: P_38**

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

pharmacokinetics of elvitegravir and cobicistat in subjects with severe renal impairment

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**Introduction:** Cobicistat-boosted elvitegravir (EVG/COBI), as a component of a single tablet regimen EVG/COBI/emtricitabine/tenofovir DF, has been evaluated in Phase 3 clinical trials for the treatment of HIV-1 infection. Unboosted EVG and COBI are subject to extensive hepatic metabolism; renal excretion is a minor elimination pathway. However, since kidney disease is an important complication of HIV infection, we evaluated the effect of renal impairment on the pharmacokinetics of EVG/COBI. In previous Phase 1 and 2 studies, small decreases in estimated creatinine clearance (eGFR) were observed with COBI. The decreases occurred within the first few days of dosing and reversed upon discontinuation of study drugs. Thus, the effect of EVG/COBI on eGFR was also explored in this study.

**Methods:** Two groups of HIV-uninfected subjects with severe renal impairment (RI) not on dialysis (screening eGFR <30 ml/min using Cockcroft-Gault [CG]) and with normal renal function (NF) (screening eGFRCG > 90 ml/min, matched for age (±10 years), sex, and BMI (±15%)) were enrolled. Both groups received EVG150 mg/COBI150 mg daily for 7 days. Day 7 EVG and COBI concentrations were analyzed and PK parameters were calculated. Geometric least squares mean ratios and 90% CIs for EVG and COBI AUCtau, Cmax and Ctau were calculated using ANOVA model between RI and NF subjects. Since plasma protein binding is often altered in RI, EVG and COBI fraction unbound was determined. eGFRCG and eGFRMDRD (MDRD: modification of diet in renal disease) were calculated on Days -1, 7 and 14. A paired t-test was used to evaluate if eGFR changes on Days 7 and 14 from Day -1 were significantly different from 0 for both groups.

**Results:** Thirteen RI and 11 NF subjects were enrolled, 12 RI and 11 NF completed the study. All adverse events (AEs) were Grade 1 (mild) and no subject discontinued due to an AE. One serious (not drug-related) AE (diabetic foot ulcer) was reported in a RI subject with pre-existing diabetes and polyneuropathy. EVG AUCtau, Cmax and Ctau were ~ 25%, 33% and 31% lower in RI subjects than in NF controls. Notably, EVG exposures in NF subjects in this study were higher than previously observed. COBI AUCtau, Cmax and Ctau were ~ 25%, 22% and 13% higher in RI subjects than in NF controls. EVG mean (SD) % free fraction was 1.42 (0.17) in RI and 1.16 (0.16) in NF subjects. Mean eGFR changes
were approximately -3 ml/min (-11%) in RI group and - 9 ml/min (-9%) in NF group at Day 7, relative to Day -1. Mean eGFR returned to baseline by Day 14 (p>0.05).

**Conclusion:** Since no clinically relevant changes in EVG or COBI pharmacokinetics were observed at the extremes of renal function, dose adjustment of EVG or COBI is not warranted in renal impairment. Small reversible decreases in eGFR were observed at Day 7 with EVG/COBI. These decreases are consistent with those observed in Phase 2 and 3 studies in HIV-infected patients and are attributed to transient inhibition of proximal tubular secretion of creatinine by COBI.

Conflict of interest
Financial relationship(s): The authors are employees of Gilead Sciences, Inc. Gilead Sciences employees potentially own stock and/or hold stock options in the company.

**Abstract:** P_39

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

**Impact of HIV infected patient’s obesity on antiretroviral pharmacokinetics and immuno-virological response.**

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**Background:** Prevalence of obesity among HIV-infected patients is increasing in European countries. Previous data suggest that excess weight and obesity might affect immune system and pharmacokinetics of several lipophilic drugs. Our objectives were to evaluate the impact of HIV-infected patient’s obesity on immuno-virological response and antiretroviral (ARV) plasma exposures.

**Material & Methods:** A cross sectional study was performed from 2009 to 2011. Eligibility criteria were: obesity defined by BMI>30 kg/m², HIV-infected patients receiving ARV at approved daily dose, with plasma viral load (pVL), CD4 cell count, ARV plasma concentration and demographic characteristics available. Patients were excluded if pregnancy, HCV co-infection or lack of biological data. Blood samples were collected 12 or 24 hours post-dose (C12h or C24h) according to bid or qd regimen, respectively. Virological failure was defined by two successive pVL>50c/ml. ARV plasma concentrations were determined using UPLC-MS/MS and presented as median (IQR25th-75th), n, inter-patient variability as CV %). Statistical analysis was performed using Khi-2 test.

**Results:** According to eligibility criteria, 315 patients (61% female, 74% African, 45 years (38-52)) were enrolled corresponding to a prevalence of obesity in our active file of approximately 7%. Other patients' characteristics are: 72% 30<BMI<35 kg/m², 20% 35<BMI<40 and 8% BMI>40; 82% pVL<50 c/ml; 6% CD4<200/mm³, 53% CD4>500/mm³ and 86% were treatment-experienced. In the whole population, only 5 patients had a C12h or C24h<LOQ. HIV infection and ARV treatment durations were 8 (6-13) and 6 (3-11) years, respectively. C12h for ETR=808 ng/ml (474-1070, 19, 62%); NVP=4681 ng/ml (3480-7257, 21, 58%); DRV=2982 ng/ml (2274-3816, 23, 46%); LPV=4595 ng/ml (3446-6136, 45, 55%); RAL=114 ng/ml (57-245, 29, 148%). Among PI/r and NNRTI, adequate C12h and C24h were observed in 75% and 80% of patients, respectively. Proportion of patients with pVL<50 c/ml were 84% and 95% for PI/r and NNRTI groups, respectively (p<0.01). Among the 43 patients (18%) with virological failure, only 18 had an available HIV genotype. In male, a trend of statistical relationship between BMI and pVL was observed, however a statistical relationship between higher BMI and CD4>500/mm³ was found (p<0.01). In male and female, no deleterious impact of obesity on ARV concentrations or virological response was found. Overall patients, CD4 cell count and pVL were not correlated with BMI.

**Conclusion:** In our population of obese experienced HIV-infected patients, virological response was consistent with historical data showing no impact of obesity, confirming the lack of modification of ARV concentrations. As previously reported in HAART era, despite our results on males, no influence of obesity on CD4 cell count has been observed in the whole population.

No conflict of interest
Abstract: P_40

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Pharmacokinetics and safety of boosted-Elvitegravir in subjects with hepatic impairment

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Background: Elvitegravir (EVG), an HIV strand transfer integrase inhibitor metabolized primarily via CYP3A and secondarily via glucuronidation, displays substantially higher systemic levels when coadministered (i.e., is boosted) with low doses of the potent mechanism-based CYP3A inhibitors ritonavir or cobicistat (COBI). Due to the predominant hepatic metabolism pathway, the present study evaluated the effect of impaired liver function on the clinical pharmacokinetics of boosted-EVG in HIV negative subjects versus matched control subjects.

Methods: The enrolled subjects had stable hepatic impairment (N=10) with Child-Pugh-Turcotte (CPT) classification B (moderate liver impairment; score: 7 to 9), with no clinically significant changes within 120 days of screening. The control group (N=10) consisted of healthy subjects with normal liver function, with each subject matched for age (± 5 years), gender and body mass index (± 15%) with a subject in the impairment group. COBI-boosted EVG (EVG/co; 150/150 mg) was administered once-daily for 10 days, followed by intensive pharmacokinetic (PK) sampling. Safety evaluations were performed throughout dosing and during a 11-day follow-up period. Statistical analyses entailed 90% confidence interval (CI) assessment for the ratio of geometric means of EVG and COBI exposures in the impairment versus control group, with an increase in exposure of at least 100% considered to be clinically relevant, consistent with US FDA guidance. Protein binding measurements for EVG and COBI were made using equilibrium dialysis.

Results: All 20 (10/group) enrolled subjects completed the study. Overall incidence of treatment-emergent adverse events (AEs) was comparable between the two groups, with all study-drug related AEs being of mild severity and no hepatobiliary AEs noted. Subjects in the impairment group had CPT scores of 7 (n=3), 8 (n=4), or 9 (n=3). Mean age and BMI in both groups were 56 years and ~28 kg/m², respectively, and subjects were mostly male (n=9/group). The geometric mean ratio (%) (90% CI) for EVG AUCₜₐᵤ, Cₘₐₓ, and Cₜₐᵤ were 135 (103, 177), 141 (109, 183), and 180 (111, 290), indicating that the increase in AUC was well below the pre-specified clinical relevance threshold of 100%. Corresponding values for COBI were 99.8 (76.0, 131), 86.1 (65.4, 113), 208 (117, 368), indicating minimal/modest change in exposure of no clinical significance. No correlations were observed between EVG or COBI exposures versus CPT score or individual laboratory components of CPT classification (albumin, total bilirubin, prothrombin time, or INR). Mean (SD) free fraction (%) of EVG in the control and impairment group were 1.2 (0.1) and 1.2 (0.2); corresponding values for COBI were 2.7 (0.6) and 3.2 (0.6), indicating the lack of effect of hepatic impairment on EVG or COBI protein binding.

Conclusions: No clinically relevant changes in EVG or COBI exposures were observed in subjects with moderate hepatic impairment relative to normal matched control subjects following once-daily administration of EVG/co. Accordingly, no dose adjustment of EVG or COBI is necessary in subjects with moderate or mild hepatic impairment. No PK or safety data are available for EVG or COBI in subjects with severe hepatic impairment.

Conflict of interest financial relationship(s): employee and stockholder of Gilead

Abstract: P_41

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Impact of menstrual cycle on single dose pharmacokinetics of tenofovir, emtricitabine, atazanavir and ritonavir in healthy volunteers

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Abstract: P_42

Therapeutic Drug Monitoring

Lack of correlation between UGT1A1*6, *28 genotypes, and plasma raltegravir concentrations in Japanese HIV-1-infected patients


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Background: Raltegravir is metabolized by glucuronidation via UGT1A1. Among the genetic polymorphisms of UGT1A1, the *6, *27 and *28 alleles are associated with reduced levels of UGT1A1. In particular, the *28 allele accounts for most of the UGT1A1 polymorphisms, and the level of UGT1A1 activity has been the focus of most studies. On the other hand, among Asians, the *6 and *27 alleles are more commonly found in comparison with white populations. In this study, we aimed to clarify the contribution of UGT1A1 polymorphisms (*6, *27) to plasma raltegravir concentrations in Japanese HIV-1-infected patients.

Methods: We analyzed the presence of genotypic variants (*6, *27 and *28) among the 64 patients recruited at the National Hospital Organization Nagoya Medical Center. Genotyping of *6 and *27 in UGT1A1 was performed using the TaqMan Drug Metabolism Genotyping Assay. Genotyping of *28 in
**UGT1A1** was performed using the primers described by Ehmer et al. Plasma raltegravir concentrations were determined by a LC-MS method.

**Results:** Among the 64 patients, the **UGT1A1** genotype in 2 patients (one male, one female) was *6 homozygote. Heterozygous variants were found in 18 patients for *6, and in 11 patients for *28, while all of the patients were found to carry wild-type sequences at the position corresponding to the *27 allele. The male *6 homozygote patient had modestly higher plasma raltegravir concentration (0.53 μg/ml) than other patients who were wild type (0.12 μg/ml) or heterozygous (0.16 μg/ml) for the *6 polymorphism. The female **UGT1A1** *6 homozygote had a lower plasma raltegravir concentration (0.03 μg/ml). On the other hand, plasma raltegravir concentrations were 0.12 μg/ml (*6-/- *28-/-; n=33), 0.11 μg/ml (*6-/- *28-/+; n=11), 0.16 μg/ml (*6-/+ *28-/-; n=19).

**Conclusions:** There were no statistically significant differences in the plasma raltegravir concentrations between patients carrying wild-type alleles and those heterozygous for *6 or *28. In this study, we showed that heterozygosity for the reduced-function *6 and *28 alleles had no significant effect on plasma raltegravir concentrations in Japanese HIV-1-infected patients.

*No conflict of interest*

**Abstract:** P_43

**Therapeutic Drug Monitoring**

**Determination of specific indications for antiretroviral therapeutic drug monitoring using an evidence based approach - the Québec TDM guidelines**

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**Background:** Therapeutic drug monitoring (TDM) of antiretrovirals (ARV) remains controversial for some clinicians, mainly due to the lack of randomized controlled trials with newer ARV regimens. The province of Quebec (Canada) ministry of health mandated a working group to develop a practice guide on ARV TDM. The primary objective was to recommend the specific indications for ARV TDM supported by the literature.

**Methods:** A thorough review of the literature was done using PubMed and Medline (until March 2011). Studies presented at HIV conferences were also included. Indication categories studied were routine controls in patients without past treatment failure and with resistant virus, virologic failure, specific adverse effects, drug interactions, special populations (dialysis, hepatic and renal impairment, geriatrics, pediatrics, pregnancy), malabsorption, obesity and low body weight, validation post dose adjustments, validation of non traditional doses and non adherence to dosing requirements. Specific indications for TDM for each ARV (except NRTIs and enfuvirtide) were recommended using a classification code for the strength of the recommendation (A: strongly recommended, B: moderately recommended, C: optional; D: not recommended) and for the quality of the evidence (recommendation supported by: I, at least one prospective clinical study based on clinical or biological parameters; II, retrospective, observational or pharmacokinetic studies; III, expert opinion). Working group members consisted of HIV specialized pharmacists and physicians (general practitioners and specialists), a pharmacologist, a clinical biochemist and a government representative. Consensus was reached amongst the working group members.

**Results:** Over 700 references were consulted and reviewed. Based on analysis of the data, TDM is strongly recommended for the following indications and ARVs: routine controls in patients without past treatment failure (nelfinavir, indinavir, AI); routine controls in patients with resistant virus (atazanavir, indinavir/ritonavir(r), AI); central nervous system side effects (efavirenz, AI); hyperbilirubinemia (atazanavir/r, AI); nephrotoxicity (indinavir/r, AI); drug-drug interactions (all ARVs, AI); dialysis (atazanavir, atazanavir/r, darunavir/r, AI);
moderate or severe hepatic impairment (atazanavir/r, fosamprenavir/r, indinavir/r AII); pediatrics (lopinavir/r and efavirenz AII, other ARVs AIII); validating non traditional doses (all ARVs, AIII), validating dose adjustments (nelfinavir and indinavir AI, other ARVs AIII). TDM is moderately recommended (BII or BIII depending on the ARV) for virologic failure (all ARVs), dialysis (protease inhibitors, except as above), moderate or severe hepatic impairment (all ARVs, except as above), suspected malabsorption, and non adherence to dosing requirements. TDM is also moderately recommended for pregnancy (atazanavir, atazanavir/r, indinavir/r, nelfinavir, saquinavir/r, nevirapine, BII; other ARVs BIII). TDM is moderately recommended (BII) for the following adverse effects: dermatologic effects with indinavir, hyperbilirubinemia with atazanavir and indinavir/r, nephrotoxicity / nephrolithiasis with atazanavir and atazanavir/r, lipodystrophy with nelfinavir, and hepatotoxicity with efavirenz and nevirapine.

Conclusions: ARV TDM is strongly or moderately recommended for numerous indications based on scientific evidence and expert opinion. ARV TDM could be beneficial for patient care when used for these specific indications.

Conflict of interest financial relationship(s): Funding was received from the ministère de la Santé et des Services Sociaux du Québec to develop these guidelines. No funding was received from pharmaceutical companies.

Abstract: P_44

Therapeutic Drug Monitoring

A reappraisal of efavirenz phase I and phase II metabolites profiles in plasma and urine from HIV patients

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Background: Efavirenz, remains an important component of first-line antiretroviral therapy despite poor tolerance in some patients which constitutes the main reason for treatment discontinuation, and this has a genetic basis1. We hypothesized that some EFV metabolites may be incriminated for the premature treatment discontinuation of patients with the high risk genetics factors (all CYP2B6-, CYP2A6- and CYP3A-mediated pathways impaired)1. Pursuing our search of possible phenotypic markers of efavirenz toxicity, we are performing general metabolites profiles analysis not only in plasma but also in urine from unselected patients under efavirenz.

Materials & Methods: Plasma and urine samples were obtained from consenting patients under stable efavirenz regimen, collected at the occasion of their regular follow-up visit which includes TDM. Detailed metabolites profiles analysis were carried-out by LC tandem MS in paired (plasma and urine) samples before and after enzymatic hydrolysis by sulfatase during 18h at 37 °C. The reaction was terminated by MeOH and the incubation extracts were diluted with suitable buffer prior to LC tandem MS analysis.

The phase II metabolites were identified by detailed mass fragmentation analysis and comparison with previously published mass spectra data2, as well as by enzymatic conversion to the corresponding hydroxylated efavirenz metabolites.

Results: We have been able to identify for the first time the sulfate conjugate of 8-hydroxy-efavirenz, a metabolite reportedly not present in humans2. The 8-hydroxy-efavirenz sulfate was differentiated from the known 7-hydroxy-efavirenz sulfate by comparison of their mass spectral fragmentation pattern. Whereas the ESI- MS/MS showed a signal [M+H] at m/z 410 for the sulfate conjugates of both 8-hydroxy-efavirenz and 7-hydroxy-efavirenz, the fragment ion at m/z 330 (expectedly missing in the sulfate conjugate of 7-hydroxy-efavirenz, that shows instead a signal at m/z 258)2, is the characteristic signature for 8-hydroxylated analogues of efavirenz. Enzymatic hydrolysis of plasma and urine by sulfatase results in a corresponding increase in the respective 8-hydroxy-efavirenz and 7-hydroxy-efavirenz species. Interestingly, the principal 8-hydroxy-efavirenz sulfate was found at much higher level than 7-hydroxy-efavirenz sulfate in plasma, whereas in urine the relative proportion was opposite with 7-hydroxy-efavirenz sulfate being consistently the principal urinary sulfate conjugate. Moreover,
the previously reported 8,14 di-hydroxy-
metabolite of efavirenz was barely detectable
in plasma, but was found in significant amount
in urine.

**Conclusion:** The inverse relative proportion of
sulfate conjugates of 8-hydroxy-efavirenz and
7-hydroxy-efavirenz in plasma and urine is
intriguing. It is unclear whether this is due to a
possible difference in renal clearance of 8-
hydroxylated and 7-hydroxylated sulfate
conjugates, or because of alternate pathways
possibly driving further metabolism for only one
of the substituted metabolite. Alternately, a
possible renal involvement for CYP450-
mediated oxidation and sulfation of efavirenz
cannot be excluded. This study demonstrates
that power of LC-MS/MS for drug metabolites
profiles analysis that has made possible the
identification of a new metabolite for a drug
that was approved about fourteen years ago.

**References**

No conflict of interest
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