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14 - 16 June 2017, Chicago, USA

Abstracts:
Oral Presentations
Abstract: O_01

Single- and multiple-ascending doses (SAD/MAD) and food effect of orally administered JNJ-64155806 in healthy volunteers

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Background: Despite the availability of vaccines and antivirals, influenza remains a significant global healthcare challenge that results in significant morbidity and mortality, particularly in the event of a pandemic. JNJ-64155806 (AL-794) is an ester prodrug of ALS-033719, a novel potent endonuclease inhibitor of influenza A and B including strains resistant to neuraminidase inhibitors.(OPTIONS IX; O-97) Antiviral activity has been previously demonstrated in a human challenge model.(OPTIONS IX 2016; LBO-2) First-in-human experience is presented herein.

Methods: A Phase 1, multi-Part study of JNJ-64155806 (AL-794; NCT025888521) was conducted in healthy volunteers (HVs) using a suspension formulation (0.5% methylcellulose in water). Part 1: Single-dose JNJ-64155806 (50 to 2000 mg) administered fasted in 8 HVs (6:2 active:placebo (A:P))/cohort; Part 2: JNJ-64155806 50 mg twice daily (BID) with food (standard meal), 200 or 600 mg BID administered fasted for 7 days in 10 HVs (8:2 A:P)/cohort; and Part 3: single 450 mg dose food effect in 8 HVs (6:2 A:P). Plasma samples for pharmacokinetics (PK) were collected over 120 hours after a single dose in Parts 1 and 3 and over 24 hours (AM and PM dose) on Days 1 and 7 in Part 2. Samples were analyzed for ALS-033719 and ALS-033927 (inactive glucuronide metabolite) with a validated LC-MS/MS method. PK parameters were calculated using non-compartmental analysis. ECGs, laboratory and other safety parameters were routinely collected.

Doses were escalated only after a review of safety and available PK data.

Results: In Part 1, ALS-033719 PK increased in a dose proportional manner up to 150 mg but less than dose proportionally beyond 150 mg. ALS-033719 terminal elimination half-life was from 6 to 10 hours. A high-fat meal significantly increased ALS-033719 exposure (~3-fold). In Part 2, BID dosing was selected for MAD cohorts to achieve trough concentrations above the protein-binding adjusted EC90. Accumulation was observed between the first and second dose but steady-state was generally achieved by the second dose. Trough concentrations above the EC90 were achieved with 50 mg BID (with food) and EC90 x 3 with 200 mg BID (fasted). A standard meal with a lower dose of JNJ-64155806 (50 mg BID) had minimal effect on ALS-033719 exposure. Treatment-emergent adverse events (TEAEs) were mostly mild. There were no SAEs. The most common TEAEs reported were headache and dizziness (lightheadedness); dizziness occurred at high exposures of ALS-033719 (in 2, 4 and 6 subjects receiving JNJ-64155806 1000 mg, 450 mg with high-fat meal, and 600 mg BID), respectively. There were no clinically significant laboratory abnormalities across all Parts.

Conclusion: JNJ-64155806 was generally well tolerated when given to HVs at doses that demonstrated antiviral activity (50 and 150 mg BID) in an influenza human challenge study. Further studies of JNJ-64155806 are ongoing.
Abstract: 0_02

Effects of cobicistat on tenofovir durability: is it time to rethink at TAF trials?

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Background: The dose of tenofovir alafenamide (TAF) is reduced from 25 to 10 mg daily when given with boosting agents. However, such dose reduction has never been adopted for tenofovir disoproxil fumarate (TDF). Here we aimed to investigate the potential effect of cobicistat both on tenofovir concentrations and TDF durability in real life setting.

Methods: HIV-positive patients receiving TDF-containing antiretroviral therapies with at least one assessment of tenofovir plasma trough concentrations were included in the study. Uni- and multivariate regression analyses were carried out considering tenofovir concentration as the dependent variable and clinical characteristics as independent covariates. Subsequently, survival and Cox analyses were carried out considering as the primary outcome TDF discontinuation.

Results: Patients were given TDF with PIs/ritonavir (n=207), NNRTIs (n=178), INIs (dolutegravir or raltegravir, n=49) or with elvitegravir/cobicistat (n=76). By multivariate analysis, concomitant antiretroviral therapies resulted significantly associated with tenofovir concentration as the dependent variable and clinical characteristics as independent covariates. Important differences on tenofovir exposure were found between the class of PIs/r, with atazanavir and lopinavir showing the highest tenofovir concentrations compared with amprenavir or darunavir, respectively (163±145 and 164±120 ng/mL versus 112±96 or 107±68 ng/mL, respectively). Overall, a total of 149 cases of TDF discontinuation were recorded during a mean period of 1149±3537 days of follow-up, of whom 75/207, 41/178, 13/49 and 20/76 cases were detected in the PIs/r, NNRTIs, INIs and ELV/COBI groups, respectively. The Kaplan Meyer survival analysis revealed a significant difference between ELV/COBI and other ARV regimens (Log-Rank p=0.0002), which resulted particularly evident in the first 1-2 years after starting treatment, with a number of events of TDF discontinuations resulting 3-fold higher compared with PIs/r, NNRTIs and INIs. Results of a multivariable Cox regression analysis assessing the time fixed factors at baseline associated with the risk to experience TDF discontinuation showed that ELV/COBI concomitant therapy and tenofovir plasma trough concentrations were both associated with a significantly higher risk to develop TDF toxicity (ELV/COBI: hazard ratio=2.284; tenofovir trough levels: hazard ratio=1.002 per 1 ng/mL increment of tenofovir concentrations).

Discussion: Coadministration with cobicistat resulted in significantly higher tenofovir concentrations and lower TDF tolerability compared with other antiretroviral regimens. Indeed, despite the lower follow-up due to the more recent introduction on the market of the ELV/COBI/TDF/FTC coformulation, patients treated concomitantly with cobicistat experienced a 3-fold higher rate to of TDF discontinuation in the first 1-2 years of therapy compared with other ARV regimens. These findings add further evidence that the dose of TDF should be reduced when combined with boosting agents. This concept is important not only when considering the tolerability of TDF per se, but also when comparing it with that from TAF. Indeed, according to our findings, it cannot be excluded that the lack of proper dose adjustment for TDF when given with cobicistat (or ritonavir) might have biased the safety results between TAF and TDF during registrative trials.
Abstract: O_03

Pharmacokinetics of darunavir/cobicistat and etravirine alone and coadministered in HIV-infected patients

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Objective: Based on prior experience with dual antiretroviral therapy with darunavir/ritonavir plus etravirine, there is a growing interest in combining etravirine with the recently developed fixed-dose combination of darunavir/cobicistat tablet. However, data on drug-drug interactions between darunavir/cobicistat and etravirine are lacking. Our objective was, therefore, to determine the effect of etravirine on the pharmacokinetics of darunavir/cobicistat and vice versa. The safety and tolerability of this drug combination were also evaluated.

Methods: Single-centre, open-label, fixed-sequence, phase I clinical trial in two cohorts of HIV-infected patients who were receiving stable antiretroviral therapy including darunavir/cobicistat (800/150 mg once daily; DRV cohort) or etravirine (400 mg once daily; ETR cohort). All participants continued taking their antiretroviral therapy during the study, and etravirine (400 mg once daily) or darunavir/cobicistat (800/150 mg once daily) were added on days 1-14 and 1-7 in participants included in the DRV or in the ETR cohort, respectively. Full pharmacokinetic profiles were obtained from each participant on days 0 and 14 in the DRV cohort, and on days 0 and 7 in the ETR cohort. Drug concentrations in plasma were determined using validated LC-MS/MS methods. Darunavir, cobicistat and etravirine pharmacokinetic parameters were calculated for each individual using a non-compartmental approach (Winnonlin, Phoenix, version 7.0). Geometric mean ratios (GMRs) and 90% confidence intervals (CI) were derived from the log transformed AUC0-24, Cmax and C24 using linear mixed-effects models. Adverse events (AEs) and HIV-1 RNA load in plasma were monitored throughout the study.

Results: Fifteen patients were included in each study cohort. The plasma concentration-time profile and pharmacokinetics for etravirine were unchanged by darunavir/cobicistat. Conversely, the GMRs (90% CI) for darunavir/cobicistat coadministered with etravirine relative to darunavir/cobicistat alone were 0.70 (0.56-0.87) for cobicistat AUC0-24, 0.86 (0.75-0.98) for cobicistat Cmax, 0.34 (0.23-0.50) for cobicistat C24, 0.99 (0.86-1.13) for darunavir AUC0-24, 1.11 (0.99-1.24) for darunavir Cmax, and 0.44 (0.33-0.58) for darunavir C24. Study treatments were well tolerated. The majority of AEs were grade 1 or 2, and there were no serious AEs or discontinuations in the study. HIV-1 RNA in plasma remained undetectable in all participants during the study.

Conclusion: While etravirine pharmacokinetics are unchanged by darunavir/cobicistat, there is a marked decrease in cobicistat exposure and in darunavir C24 when darunavir/cobicistat is coadministered with etravirine. Based on this drug interaction, boosting darunavir with ritonavir instead of with cobicistat may be preferred if dual therapy with darunavir plus etravirine is to be used in clinical practice.
Abstract: O_04

Evaluation of the Drug-Drug Interaction Potential between Cobicistat-Boosted Protease Inhibitors and Statins

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Background: Cobicistat (COBI; TYBOST®) is a pharmacokinetic (PK) enhancer that boosts exposures of HIV protease inhibitors, atazanavir (ATV) or darunavir (DRV) to treat HIV-1 infection. COBI is an inhibitor of CYP3A, P-gp, BCRP, and OATP1B1/1B3. ATV inhibits CYP3A, UGT1A1, P-gp, BCRP, and OATP1B1/1B3. DRV inhibits CYP3A and P-gp. HMG-CoA reductase inhibitors, atorvastatin (ATOR; Lipitor®) and rosuvastatin (ROS; Crestor®), are substrates for P-gp, BCRP, and OATP1B1/1B3 and ATOR is also metabolized by CYP3A. As ROS and ATOR are commonly prescribed to treat hypercholesterolemia in HIV-infected individuals, we evaluated the safety, tolerability, and drug-drug interaction (DDI) potential between COBI-boosted DRV (DRV+COBI) and COBI-boosted ATV (ATV+COBI) when administered with ROS or ATOR. We hypothesized that the DDI would increase exposures of ROS and ATOR.

Materials & Methods: This was a randomized, fixed sequence, three periods, multiple cohort, open label, single center study. Healthy subjects (n=16/cohort) received the following treatments: ATOR or ROS (10 mg) on Day 1; DRV+COBI (800 mg+150mg) on Days 4-15 or ATV+COBI (300 mg+150mg) on Days 4-13; DRV+COBI (800 mg+150mg) plus ATOR, or ROS (10 mg) on Day 16; ATV+COBI (300mg+150mg) plus ATOR, or ROS (10mg) on Day 14. PK assessments were performed on the final day of each treatment period. Statistical comparisons of exposures were made using geometric least-squares mean (GLSM) ratios and associated 90% confidence intervals (CI) and compared to no-effect bounds of 70-143% for all analytes and parameters with the exception of Cmax for ATOR and ROS that had bounds of 50-200%. ATV+COBI plus ATOR, ATV+COBI plus ROS, DRV+COBI plus ATOR or DRV+COBI plus ROS were designated as test, and ATOR, ROS, ATV+COBI or DRV+COBI alone as reference treatment.

Results: The GLSM ratios and 90% CIs for all statistical comparisons fell outside of the prespecified no-effect boundaries. When coadministered with DRV+COBI, AUCinf and Cmax were increased by 93% and 277% for ROS, and 290% and 319% for ATOR, respectively. The AUCinf and Cmax were increased by 242% and 958% for ROS, and 822% and 1785% for ATOR, respectively when administered with ATV+COBI. These results are consistent with the potent inhibitory effect of ATV on OATP1B1/1B3, and inhibition of CYP3A and BCRP by ATV+COBI and DRV+COBI. ATOR and ROS did not affect DRV, ATV or COBI exposures. All subjects completed the study, and treatments were generally well tolerated. The majority of adverse events (AEs) that were related to study drug were mild in severity and no Grade 3 or 4 AEs were observed.

Conclusions: The study findings are consistent with the current dosing recommendation for ATOR and ROS with COBI-boosted DRV or ATV. When DRV+COBI is coadministered with ROS or ATOR, it is recommended to initiate ROS or ATOR treatment with the lowest dose, and titrate to desired response while monitoring for safety. For ATV+COBI when coadministered with ROS, the lowest ROS dose is recommended while monitoring for safety. With respect to ATV+COBI, it is recommended not to exceed a single dose of 10 mg ATOR daily and monitor for safety.
Abstract: O_05

Confirmation of the drug-drug interaction (DDI) potential between cobicistat-boosted antiretroviral regimens and hormonal contraceptives

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Introduction: Cobicistat (COBI; TYBOST\(^\textregistered\)) is a pharmacokinetic (PK) enhancer that boosts exposures of HIV protease inhibitors, atazanavir (ATV) or darunavir ( DRV) to treat HIV-1 infection. COBI is a PK enhancer of the integrase strand transfer inhibitor elvitegravir (EVG) within the approved single tablet regimens EVG/COBI/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) (Striibld\(^\textregistered\)) or EVG/COBI/FTC/tenofovir alafenamide (Genvoya\(^\textregistered\)). COBI is a CYP3A inhibitor. Hormonal (“oral”) contraceptives (OCs) are extensively metabolized by CYP enzymes, including CYP3A and CYP2C9, and glucuronidation. The effect of COBI boosted ATV (ATV+COBI), COBI boosted DRV (DRV+COBI), or EVG/COBI/FTC/TDF on OC PK was evaluated in two clinical studies.

Materials & Methods: Study 1 was an open-label, two cohort (n=18/cohort), fixed sequence Phase 1 study in healthy female subjects that evaluated the DDI potential between multiple dose ATV+COBI(300 mg+150 mg) or DRV+COBI(800 mg+150 mg) and single dose OC drospirenone/ethinyl estradiol (EE). Statistical comparisons of the primary PK parameters of drospirenone and EE, coadministration with COBI-containing regimens. The majority of AEs were mild; no Grade 3 or 4 AEs were observed. In Study 2, coadministration of OCs with EVG/COBI/FTC/TDF in HIV-infected women resulted in norgestrel AUC and Cmax that were 2-fold and 1.6-fold higher, respectively, compared to historical data of levonorgestrel/EE administered alone. All subjects completed the substudy and all treatments were generally well tolerated.

Conclusions: Consistent with COBI-mediated CYP3A inhibition, an increase in exposure of the OC progestin component (drospirenone or norgestrel) was observed following co-administration with COBI-containing regimens. The decrease in EE exposure with DRV+COBI+drospirenone/EE was consistent with previous data with DRV+ritonavir+OCs. These findings were expected and aligned with the prescribing information of EVG/COBI/FTC/TDF and EVG/COBI/FTC/TAF. For drospirenone/EE, clinical monitoring is recommended when coadministered with COBI-containing regimens due to potential for hyperkalemia. This recommendation is aligned with the prescribing information of drospirenone/EE.

Reviews in Antiviral Therapy & Infectious Diseases 2017_5
Abstract: O_06

Darunavir concentrations in CSF of HIV-infected individuals when boosted with cobicistat versus ritonavir

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Background: Cobicistat (COBI) and ritonavir (RTV) have different inhibitory profiles on drug transporters which could impact the distribution of co-administered drugs. This study compared in the same patients darunavir (DRV) concentrations in cerebrospinal fluid (CSF) when boosted by COBI versus RTV relative to plasma concentrations and assessed whether the DRV levels remained above the established target concentration inhibiting wild-type HIV-1 virus replication by 50% (IC50) and 90% (IC90).

Methods: We performed an open, one-armed, sequential clinical trial (NCT02503462) where paired CSF and blood samples were taken from seven HIV-infected patients presenting with HIV-associated neurocognitive disorders (HAND) and treated with a DRV/RTV (800/100 mg) QD regimen (study period 1). RTV was subsequently replaced by COBI and paired CSF and blood samples were obtained from the same patients after treatment with the DRV/COBI (800/150 mg) QD regimen (study period 2). DRV concentrations measured at the end of the dosing interval were quantified by liquid chromatography coupled to tandem mass spectrometry. The Wilcoxon signed rank test was used to compare DRV concentrations between study periods.

Results: The median (IQR) DRV concentrations in CSF with RTV and COBI boosting were 16.4 (8.6-20.3) and 15.9 (6.7-31.6) ng/ml, respectively (P = 0.58). The corresponding median (IQR) DRV concentrations in the plasma were 1761 (1614-2473) ng/ml and 1275 (657-3240) ng/ml with RTV and COBI boosting, respectively, (P = 0.94). The median (IQR) DRV CSF-to-plasma ratios with RTV and COBI boosting were 0.007 (0.006-0.012) and 0.011 (0.007-0.015), respectively (P = 0.16). All DRV concentrations in CSF exceeded DRV IC50 and IC90 by a median of 9.2 and 6.7-fold with RTV boosting, and by 8.9 and 6.5-fold with COBI boosting, respectively. All patients remained virologically suppressed both in the CSF and plasma throughout the study.

Conclusions: COBI and RTV give comparable effective DRV concentrations in CSF and therefore can be used interchangeably as boosters in patients with HAND.
Abstract: O_07

A Comparison of the Pharmacokinetics of Dolutegravir during Pregnancy and Postpartum

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Background: It is important to achieve effective blood concentrations of antiretroviral drugs to achieve treatment efficacy and to prevent development of resistance. During pregnancy physiological changes take place, influencing the pharmacokinetics of medicines. In most cases, the net effect will be a decreased exposure during pregnancy. Dolutegravir is an integrase inhibitor recommended to be used in first line of ARV treatment. Very limited data is available about the pharmacokinetics of dolutegravir during pregnancy and the placental passage of dolutegravir. In 2008, a European network was established to study the pharmacokinetics of newly developed antiretroviral drugs during pregnancy (PANNA). We present preliminary data on third trimester exposure to dolutegravir.

Materials & Methods: An open-label, multicentre phase IV study in HIV infected pregnant women recruited in HIV treatment centers in Europe (PANNA Network). Patients treated with dolutegravir 50mg once daily during pregnancy had intensive steady-state 24-hour PK profiling in the third trimester and at least 2 weeks postpartum. When possible a cord blood (CB) and matching maternal blood (MB) samples were taken at delivery to assess placental transfer. Safety and virological efficacy were evaluated. Dolutegravir plasma concentrations were determined with a validated LCMSMS method with an LLOQ of 0.01mg/L. The minimum effective concentration of dolutegravir was defined as 0.10 mg/L based on an exposure-response relationship of dolutegravir (Min, 2011). Pharmacokinetic parameters were calculated with WinNonlin 6.3.

Results: Eight patients (6 black, 2 white) with a median (range) age of 28 (21-42) years were included in the analysis. Three patients dropped out of the study and one patient did not yet deliver, hence only third trimester data is available. All patients used 50mg dolutegravir once daily. Median (range) gestational age at delivery was 38 weeks (34-40); birth weight was 3030 (2120-3530) gr. Approaching delivery all patients had a VL <50 cps/mL. One intrauterine fetal death (34 weeks of pregnancy) was reported due to cholestasis pregnancy syndrome. 4/6 children were HIV un-infected (2 unknown status) and no birth defects were reported. Eight third trimester PK curves and four during postpartum were available. The results are presented as medians (range). AUC0-24h (mg*h/L) was 48 (24-73) in the third trimester and 71 (29-106) post-partum. Cmax (mg/L) was 4.0 (2.1-5.1) in the third trimester and 4.4 (2.0-5.9) post-partum. Cthrough (mg/L) was 0.93 (0.11-1.80) in the 3rd trimester and 2.07 (0.67-3.37) post-partum. Ratios of PK parameters third trimester/post-partum (median (range)) were: 0.50 (0.45-0.99) for AUC0-24; 0.74 (0.60-1.13) for Cmax; 0.45 (0.28-0.69) for Cthrough. None of the patients had a subtherapeutic Cthrough in the third trimester. The median (range) CB:MB dolutegravir plasma concentration ratio was 1.4 (0.35-1.6; n=5).

Conclusions: In this small population (n=8) exposure to dolutegravir seems to be lower during pregnancy (third trimester) than postpartum although remaining always above the minimum effective concentration. This is in line with the behaviour of most antiretroviral agents used in pregnancy. Dolutegravir efficiently crosses the placenta and therefore may have potential for pre-exposure prophylaxis. These results need to be confirmed in a larger group of patients.
Abstract: O_08

Relationship between dolutegravir plasma exposure, quality of sleep and its functional outcome in patients living with HIV over the age of 60 years.

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Background: Dolutegravir (DTG) a potent second generation HIV integrase inhibitor is increasingly being prescribed to people living with HIV (PLWH). DTG-related central nervous system (CNS) adverse events (AEs) have been shown to: 1. Occur less frequently than when prescribing efavirenz; 2. Occur in up to 5% of PLWH enrolled in prospective clinical trials with low discontinuation rates; 3. Lead to discontinuation in up to 5% of PLWH in observational cohorts. Whether DTG systemic exposure correlates with the development of CNS AEs remains unclear. We conducted a PK/PD study in PLWH ≥60 years following a combination antiretroviral therapy (cART) switch to abacavir (ABC)/lamivudine (3TC)/DTG fixed dose combination (FDC).

Materials & Methods: The study protocol required the enrolment of PLWH aged ≥60 years (30%) and ≥65 years (70%), with HIV-RNA<50 copies/mL on any cART, HLAB5701 negative. All participants switched to ABC/3TC/DTG (from different cART, 43% from efavirenz-containing regimens) on Day 1 and, on day 28, intensive PK sampling over 24 hours was undertaken in a fasted state. DTG steady-state PK parameters were compared to those obtained from the PK sub-study of SPRING-1, where PLWH younger than 50 years underwent full DTG PK determination following ABC/3TC/DTG intake in a fasted state (control group). Sleep questionnaires (Pittsburgh Sleep Quality Index, PSQI, and Functional Outcomes of Sleep Questionnaire, FOSQ) were administered at baseline (before switching to ABC/3TC/DTG) and 28 days following ABC/3TC/DTG initiation. Non-parametric testing (Mann–Whitney U test) was used to compare DTG exposure in the two groups and to compare questionnaire outcomes at baseline versus day 28 to investigate whether there was a correlation between DTG PK parameters and sleep questionnaire results.

Results: PK and sleep data were obtained from 40 PLWH, median/range age: 65.5/60-78 years; 1 female. and PK data alone from 16 younger controls (median/range age: 37/22-50 years; 1 female). Geometric mean (GM) and 95%CI DTG Cmax, Ctrough and AUC0-24 for the studied PLWH versus the controls were 4250 (3966-4819) and 3409 (2854-4184) ng/mL (p=0.004), 1055 (992-1358) versus 1130 (780-1480) ng/mL (p=0.769), and 51856 (48789-59637) versus 51124 (40461-61784) ng.h/mL (p=0.568).

At day 28, global PSQI and FOSQ scores were not significantly different compared with baseline in the over 60 group; no significant differences were observed in individual domains in both assessments. Change in global PSQI and FOSQ scores were not associated with DTG Cmax, Ctrough and AUC0-24. However, higher DTG Cmax and AUC were associated with shorter sleep duration (PSQI domain) (p=0.05 and 0.03, respectively). Overall, the studied FDC was well tolerated, with no grade 3 or 4 side effects or laboratory abnormalities and no virological failures at week 4 post-switch.

Conclusions: Although total DTG exposure (AUC) was not different between the two groups, Cmax was significantly higher in older PLWH, which may represent differences in drug absorption. ABC/3TC/DTG was well tolerated by PLWH over the age of 60 during the first month of treatment, with no change in sleep scores observed from baseline. An association between DTG exposure and sleep duration was seen but this needs further investigation.
Abstract: O_09

Adherence biomarker measurements in older HIV-infected adults receiving tenofovir-based therapy

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Background: Concentrations of tenofovir (TFV) accumulate in hair and have been shown to reflect cumulative adherence and exposure in younger, HIV-negative individuals taking TFV disoproxil fumarate (TDF)/emtricitabine (FTC) for pre-exposure prophylaxis (PrEP). We sought to evaluate TFV concentrations in hair from virally suppressed, HIV-infected adults aged 18-35 and >60 years. Additionally, we compared TFV drug concentrations in hair to another measure of cumulative adherence, TFV-DP in dried blood spots (DBS), in the same participants.

Methods: Whole blood and hair samples were collected from virally suppressed (<48 copies/mL on consecutive visits), HIV-infected adults aged either 18-35 or >60 years. Additionally, we compared TFV drug concentrations in hair to another measure of cumulative adherence, TFV-DP in dried blood spots (DBS), in the same participants.

Conclusions: This study evaluated two objective adherence measures in a unique population of older and younger HIV-infected individuals, including 6 with grey hair. The correlation between TFV in hair and TFV-DP in DBS indicates that both measures assess cumulative drug exposure across a wide age range. The reason for higher drug concentrations with age may be due to better adherence, as has been observed in other studies, as well as slower systemic clearance among older individuals. Additional research is needed to define the mechanism of these findings and to define the potential role of DBS and hair as adherence biomarkers in older and younger HIV-infected individuals.
Abstract: O_10

Pharmacokinetics of Dolutegravir and Rilpivirine after Switching to the Two-Drug Regimen from an Efavirenz- or Nevirapine-Based Antiretroviral Regimen: SWORD-1/2 Pooled PK Analysis

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Background: Dolutegravir (DTG) is metabolized primarily by uridine diphosphate glucuronosyltransferase-1A1 (UGT1A1) with minor contribution of cytochrome P450-3A4 (CYP3A4). Rilpivirine (RPV) primarily undergoes oxidative metabolism by CYP3A4. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz (EFV) and nevirapine (NVP) both induce CYP3A4 and UGT1A1 and can result in decreased concentrations of DTG and RPV. A secondary objective of the SWORD 1&2 studies was to evaluate the pharmacokinetics of DTG + RPV when virologically suppressed patients were switched from an EFV- or NVP-based regimen to the DTG/RPV two-drug regimen.

Materials & Methods: SWORD 1&2 are identically designed Phase III, randomized, non-inferiority studies evaluating the efficacy, safety, and tolerability of switching to DTG+RPV from an INI-, NNRTI-, or PI-based current antiretroviral regimen (CAR) in virologically-suppressed (HIV-1 RNA < 50 c/mL) HIV-1 infected adults. Enrolled subjects were randomized 1:1 to DTG 50mg + RPV 25mg once-daily with a meal or to continue CAR through week 52. Blood samples were collected pre-dose at weeks 4, 24, and 48 in all subjects randomized to DTG+RPV for measurement of DTG and RPV plasma concentrations (C0). The first ~20 subjects per study switching from an EFV- or NVP-based regimen to DTG+RPV had additional pre-dose samples taken at week 2 and 8 for DTG and RPV and at week 2 and 4 to measure residual EFV or NVP concentrations (NNRTI subset with extra PK sampling population). Plasma concentrations were measured by validated LC/MS/MS methods and observed C0 were summarized across both studies.

Results: The pooled-study primary endpoint analysis indicated that DTG+RPV is non-inferior to CAR with a similar proportion of subjects in the DTG + RPV group (95%) achieving plasma HIV-1 RNA<50c/mL at Week 48 (Snapshot) compared with the CAR group (95%). No significant differences were observed in the proportion of subjects achieving <50 c/mL when stratified by switched drug class (NNRTI/PI/INI). In the NNRTI subset with extra PK sampling (n=54), the geometric mean (CV%) DTG C0 were 0.685(67%), 0.919(71%), 1.24(80%), 1.31(89%), and 1.03(81%) µg/mL at Weeks 2, 4, 8, 24, and 48, respectively. The corresponding geometric mean RPV C0 were 53.9(55%), 66.8(47%), 69.3(59%), 76.2(49%), 75.6(56%) ng/mL. At all sample times, DTG and RPV concentrations were above their respective PA IC90 values. From Week 2 to 4, median EFV concentrations decreased from 82.6 to 7.95 ng/mL and NVP from 2.92 ng/mL to non-quantifiable. In the overall population (n=481), DTG C0 were 1.26(78%), 1.36(72%), and 1.34(72%) µg/mL and RPV C0 were 71.8(57%), 79.8(50%), and 82.9(53%) ng/mL at Weeks 4, 24, and 48.

Conclusions: After switching to DTG+RPV, residual NVP and EFV plasma concentrations decreased to negligible levels by Weeks 2 and 4, respectively. The DTG and RPV C0 in the NNRTI subset increased between Week 2 and 4, and by Week 4 concentrations were comparable to those for the overall SWORD study population and to previously observed steady-state trough concentrations. The efficacy and virology results, overall and in the NNRTI subgroup, demonstrate that the exposure to DTG and RPV during the switch stage was sufficient to maintain virologic response.
Abstract: O_11

HIV-1-infected Males and Females under Less-Drug Regimens Achieve Antiretroviral Levels above the Inhibitory Concentration in the Genital Tract.


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Background: There is a growing interest for antiretroviral (ARV) less-drug regimens (LDR) to decrease side effects, toxicity and drug-drug interactions. A recent study from our group showed that LDR showed no evidence of a deleterious impact on residual replication in both blood and genital tract compartments. However, it is important to verify that each ARV penetrates well into the genital tract in order to achieve level above inhibitory concentration (IC). Otherwise LDR could jeopardize long-term virologic suppression and lead to the emergence of drug resistance in the genital sanctuary. Therefore, our objective was to describe plasma (PC) and genital (GC) concentrations of ARVs in HIV-1-infected patients under LDR versus triple therapy.

Materials & Methods: HIV-1-infected adults with sustained plasma viral suppression (i.e. HIV-RNA <50 copies/ml) receiving one among four evaluated LDR (cases) or classic triple therapy (i.e.: 2 nucleoside reverse transcriptase inhibitors (NRTI) - either abacavir (ABC) + lamivudine (3TC) or tenofovir diproxil fumarate (TDF) + emtricitabine (FTC) - plus a Non-NRTI or a boosted protease inhibitor or an integrase strand transfer inhibitor; controls) were prospectively enrolled. Seventy-one patients (37 males; 34 females) were included (LDR group, n= 55; control group, n=16). LDR consisted of: dolutegravir (DTG) monotherapy, n=19; TDF + FTC, n=15; DTG + unboosted atazanavir (uATV), n=10; uATV + TDF/FTC or ABC/3TC, n=11; triple therapy, n=16. Concomitant genital (i.e. sperm or cervico-vaginal lavage) and blood samples were collected to measure ARV trough concentrations. Trough concentrations (C24h) were measured using liquid chromatography-tandem mass spectrometry. Vaginal concentrations were corrected by the method of urea dilution. The GC/PC total drug concentration ratios were calculated and expressed as means +/- standard deviation.

Results: In the LDR group, C24h measured in blood were in therapeutic ranges for all drugs ARV, although in a low range for ATV (172+/−196ng/mL).
For males under LDR, mean GC/PC ratios were 0.18+/−0.15 for uATV, 0.03+/−0.03 for DTG, 0.81+/−1.36 for FTC, 1.92+/−2.60 for TDF and 0.28 for 3TC (only one patient). Under triple therapy, GC/PC ratios were not significantly different from those under LDR.
For females under LDR, GC/PC ratios were 0.20+/−0.38 for uATV, 0.01+/−0.02 for DTG, 3.11+/−5.23 for FTC, 2.17+/−4.90 for TDF, 0.22+/−0.23 for 3TC and 0.23+/−0.24 for ABC. Under triple therapy, GC/PC ratios were not significantly different from those under LDR, except for 3TC (3.61+/−5.50) and ABC (3.14+/−5.00). Overall, in the LDR group, genital concentrations exceeded for both males and females the IC50 of ATV (12 fold), DTG (137 fold), FTC (167 fold) and TDF (14 fold). There were not enough data to conclude for ABC and 3TC.

Conclusions: We found that patients under LDR achieved good genital tract to blood concentration ratios for uATV, DTG, TDF or FTC. Moreover, genital and plasma exposures for these ARV drugs were considered efficient, as compared with the IC50, and likely contributed to the virologic control seen in both compartments.
Abstract: O_12

Examining the Basis of Drug-Drug Interaction Labeling Recommendations for Antiviral Approvals from 1998 to 2015

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Background: Drug-drug interactions (DDIs) constitute a major cause of adverse drug events (ADEs), which result in morbidity, mortality, and increased healthcare expenditure. Although the development of more effective antiviral medications has greatly improved patient outcomes in diseases like HIV and Hepatitis C infection, the therapeutic benefit of these medications may be limited by the potential for ADEs based on significant DDIs with these agents. To mitigate the clinical burden of DDIs, it is essential that the potential for DDIs be investigated during drug development and that obtained DDI information be effectively utilized to inform actionable drug labeling recommendations to practitioners. Accordingly, the objective of this research was to characterize the sources and types of information, including drug exposure changes in clinical DDI studies, that formed the basis for antiviral DDI label recommendations from 1998 to 2015.

Methods: The most recent versions of drug labels and clinical pharmacology reviews for antiviral new molecular entities (NMEs) approved from 1998 to 2015 were accessed through the Drugs@FDA database (https://www.accessdata.fda.gov/scripts/cder/drugsatfda/). Labels and review documents were scanned for drug exposure data from clinical DDI studies, population based PK (POPPK) modeling predictions, and physiologically based PK (PBPK) modelling predictions. Information to inform drug labeling obtained from predictions based on metabolic pathways or from observed ADE and toxicity profiles in clinical trials and/or clinical practice with drugs from similar therapeutic classes was also collected. Trial design characteristics (types of patients, dosing schemes, etc.) were also collected. When available, point estimates of the actual or predicted geometric mean ratio (GMR) of the difference in victim drug maximum concentration (Cmax) and area-under-the-curve (AUC) during individual and co-administration were used to assess DDI severity.

Results: A total of 922 DDI label recommendations were analyzed from the 34 antivirals that were approved during the period. Of these label recommendations, 59.3% were based on clinical DDI studies, 39.8% were based on predictions based on metabolic pathways, and the remaining 0.9% were based on clinical experience. POPPK and PBPK analyses did not inform antiviral label recommendations during the period. Nearly 75% of recommendations contained interacting drugs affecting major CYP isoenzymes or transporters, with CYP3A and OATP1B1 being most common. The distribution of labeling recommendations was as follows: Contraindication-20.8%; Co-administration Not Recommended-13.3%; Dose Adjustment-10.0%; Use With Caution-20.6%; No Dose Adjustment-35.3%.

A total of 547 clinical DDI studies were conducted, most prior to initial NME approval (~93%). DDI studies resulted in positive changes in drug exposure, defined by Cmax and/or AUC GMRs outside of the conventional bioequivalence range of 0.8 to 1.25, in 51% of cases. Positive DDIs based on drug exposure informed actionable label recommendations in 67.5% of cases, and clinical DDI studies with changes in drug exposure deemed to be severe, defined as changes in Cmax and/or AUC GMR <0.5 or >2.0, informed actionable label recommendations in 77.9% of cases.

Conclusion: Clinical DDI studies are the most common source of DDI label recommendations, and positive DDI studies inform actionable recommendations in most cases.
Abstract: O_13

CYP3A induction data can predict other P450 and drug transporter DDI liability: An example of carbamazepine and rifabutin with sofosbuvir and P-gp

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Background: Sofosbuvir (SOF) is a potent nucleotide analog approved for the treatment of HCV infection. SOF is sensitive to P-gp efflux in vivo, but not CYP3A metabolism. Unlike rifampin (rif, prototypical pan-inducer), the antiepileptic, carbamazepine (CBZ), and antibiotic, rifabutin (RBT), are pregnane X receptor (PXR) agonists that induce CYP3A in vivo, but their effect on P-gp is unclear. The primary objective of this study was to determine if CBZ or RBT decrease the exposure of SOF in vivo to inform concomitant medication use recommendations. As a secondary objective, RBT- and CBZ-dependent induction of P-gp, OATP, BCRP, CYP3A, CYP2C9 and CYP1A2, was also evaluated to thoroughly characterize and rank order the inductive effect of these agents on P450s and drug transporters.

Materials and Methods: Forty-four healthy volunteers received 400 mg SOF, 75 mg dabigatran etexilate (DE, P-gp probe), 20 mg pravastatin (PRA, OATP probe), 10 mg rosvastatin (ROS, OATP/BCRP probe) and a 2 mg midazolam (MDZ, CYP3A probe) + 500 mg tolbutamide (TOL, CYP2C9 probe) + 200 mg caffeine (CAF, CYP1A2 probe) cocktail orally in the morning (separated by 48 hr) before and after a minimum of 10 days of 300 mg PO QD RBT or 300 mg PO BID CBZ. Inducer dosing was continued through probe administration. Plasma samples were collected for up to 72 hrs post dose for pharmacokinetic analysis. Observed decrease in exposure of SOF and probe drugs after RBT or CBZ administration was compared to their predicted change in exposure (based on previously established RIF induction relationships) to verify induction model and offer useful alternative to dedicated clinical studies.

Results: RBT and CBZ are moderate and moderate-to-strong inducers of CYP3A, respectively [MDZ AU(C)inf %GMR (90% CI) of 31.0 % (27.3, 35.1 %) and 21.1 % (18.3, 24.4 %)]. Previous RIF dose escalation data indicated that P-gp induction is always one DDI category less than CYP3A induction. This relationship predicts weak and weak-to-moderate SOF induction after RBT and CBZ administration, respectively. Results of this study confirmed this prediction as the inductive effect of RBT or CBZ on SOF AU(C)inf %GMR (90% CI) were weak [75.7 % (63.3, 90.7 %)] and weak-to-moderate [52.3 % (46.2, 59.3 %)], respectively. Induction of P-gp (DE) and CYP2C9 (TOL) by RBT and CBZ were accurately predicted as one DDI category lower than CYP3A induction. Moderate and weak induction of OATP/BCRP (PRA/ROS) and CYP1A2 (CAF), respectively, by CBZ was under-predicted by CYP3A induction.

Conclusions: RBT and CBZ demonstrated weak and weak-to-moderate P-gp-mediated induction. SOF exposure was only modestly reduced by these agents. Given the known exposure-response relationship for efficacy, RBT and CBZ are not expected to result in reduced therapeutic effect of SOF. The results of this study demonstrate that CYP3A induction data can be leveraged to accurately predict induction of other PXR-regulated P450s/transporters and to decrease the number of discrete induction studies needed in new drug development.
Pharmacokinetics of Co-encapsulated Truvada® with Ingestible Sensor to Assess Adherence

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Background: High medication adherence is critical to successful HIV pre-exposure prophylaxis (PrEP). However, most methods used to measure adherence have significant limitations. A novel technology has been developed that employs an ingestible sensor (IS) to detect medication ingestion and accurately determine adherence. The technology in this FDA-approved system includes an ingestible micro-sensor, a monitor patch worn on the torso and a paired mobile device. The patch detects the ingested micro-sensor and transmits this to the paired mobile device allowing continuous real-time data monitoring and discernment of longitudinal patterns of oral medication adherence. Since the co-formulation of the IS with approved FDA formulations may impact drug absorption, pharmacokinetic studies are needed with the co-formulated product.

Materials & Methods: This is a prospective single arm open label intervention study over 12 weeks using the digital health feedback system (DHFS) with 60 adult participants initiating or continuing HIV PrEP to assess adherence to Truvada® (tenofovir disoproxil fumarate/emtricitabine). A subset of 12 participants received IS-Truvada® for PrEP were enrolled in a PK sub-study to provide data on the co-encapsulated IS–Truvada® formulation. Serum PK specimens for emtricitabine and tenofovir were collected on Day 14 of treatment. Following an observed dose of IS-Truvada® given in a fasting state, PK specimens were collected at predose, 2, 4, 6, 8, & 24-hours post-dose. On Day 15, participants returned to clinic and were given an observed dose of native Truvada®, with PK sampling occurring at 2 (C2) and 4 (C4) hours post ingestion. Plasma specimens were analyzed using a validated LC-MS/MS method. Non-compartmental PK analysis for IS-Truvada® was performed using Phoenix (Certara). The statistical comparison of C2 for tenofovir and emtricitabine in IS-Truvada® and native Truvada® dosage forms was achieved using the Wilcoxon rank-sum test for paired samples.

Results: The ratio of the median (IS/Native) C2, a surrogate of Cmax, for tenofovir and emtricitabine were 0.90 (p = 0.84) and 1.09 (p = 0.48), respectively. PK parameters, Median (IQR), for Tmax, AUC(0-24), CL/F, and T1/2 for emtricitabine in the IS-Truvada® formulation were 2 (2, 2) hr, 10498 (8458, 12530) ng*hr/mL, 18009 (14715, 22304) L, & 6.8 (6.4, 7.0) hr, respectively. Values for Tmax, AUC(0-24), CL/F, and T1/2 for tenofovir in the IS-Truvada® formulation were 2 (2, 2) hr, 2610 (2007, 2997) ng*hr/mL, 72094 (50277, 11760) L and 14.4 (11.3, 18.1) hr. The pharmacokinetics of emtricitabine and tenofovir following IS-Truvada® dosing are in good agreement with literature values for healthy participants dosed with native Truvada®.

Conclusions: Our study has shown that co-encapsulation of IS with Truvada® produces emtricitabine and tenofovir pharmacokinetics that are equivalent to the traditional Truvada® formulation alone. This IS technology will allow for definitive determination of medication ingestion times to accurately assess adherence while not altering the pharmacokinetics of emtricitabine or tenofovir.
Abstract: O_15

Identification of long-acting NRTI candidates through in silico modelling

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Background: Long-acting (LA) antiretrovirals (ARVs) simplify dosing regimens, with potential to improve adherence and reduce costs. Currently only a limited number of LA drugs exist and development of complimentary LA formulations of multiple ARV classes will expand regimens to better manage therapy and prevention. The aim of this study was to identify potential nucleoside reverse transcriptase inhibitor (NRTI) LA candidates from the ‘Division of AIDS Anti-HIV/OI/TB Therapeutics Database’ (http://chemdb.niaid.nih.gov), integrating quantitative structure–activity relationship (QSAR) models into physiologically-based pharmacokinetic (PBPK) modelling to predict LA pharmacokinetics.

Methods: NRTIs were shortlisted based on chemical class and cell-based anti-HIV activity against HIV-1 IIIB strain in MT-4 cells. Twenty-five candidates with the highest therapeutic index were then progressed. Drug parameters including blood-to-plasma ratio, logP and protein binding were derived from validated computational models. Molecular descriptors obtained using Dragon 7 (Kode srl) and PaDEL (CSU, China) were used to compute metabolism and elimination from a published QSAR model. The drug specific parameters were integrated into PBPK models, and drug distribution was simulated for 100 virtual individuals using MATLAB, R2013b. A single injectable intramuscular dose of 2000 mg was set and drug release rate was kept constant at 0.0015 and 0.0005 h^-1 for monthly and quarterly formulations, respectively. The ratio of simulated plasma trough concentration (C_{trough}) and reported HIV IIIB effective concentration (EC50) was used to identify compounds with potential for future formulation development.

Results: The table shows shortlisted compounds including therapeutic index, 50% effective concentration (EC50), simulated C_{trough} and relative ratio for monthly and quarterly LA injections. AIDS #343656, 343654, 168658, 168640, 105830, 105173, 168620, 168614, 168635 and 105173 had high relative ratio indicating potential for LA administration (non-proprietary chemical names will be given at the presentation).

Conclusion: Integrated PBPK / QSAR models assisted in identifying potential NRTI candidates for LA delivery, which may now be explored through advanced reformulation strategies. This rational approach for the selection of suitable candidates may prove useful to support the development of additional LA formulations across multiple ARV classes.
Abstract: O_16

A mathematical model that predicts virological failure and elucidates the impact of lymph node drug penetration

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Background: Predicting virological failure following HIV treatment remains a difficult task. Efavirenz, a non-nucleoside reverse transcriptase inhibitor, is an example for which clinical outcomes differ from results obtained in tissue culture infection assays. Although viral growth is significantly inhibited in vitro when drug concentrations are similar to those observed in the plasma of patients, resistance to efavirenz is frequently observed by clinicians. Unfortunately, efavirenz is not an exception and clinical studies may be the only reliable way to provide information about the clinical efficacy of antiretroviral treatments.

Materials and Methods: We have developed a mathematical model able to explain and predict HIV virological failure and resistance for various compounds and patients’ drug intake patterns. The approach we adopted complies with the integrative vision advocated in Quantitative Systems Pharmacology. In particular, the most up-to-date knowledge in immune physiology, antiretroviral pharmacology and viral kinetics was incorporated into a model that describes the processes linking drug use to treatment effect. Compared to current approaches, this model considers, altogether, drug penetration into lymph nodes, a refined adherence representation accounting for the propensity for long drug holidays, population pharmacokinetic and pharmacodynamic variability drug interaction and cross-resistance. The model was mathematically translated and numerically implemented to produce virological outcomes. We compared these in silico predictions to clinical observations in order to judge the plausibility of hypotheses regarding the pathogenesis of undesirable virological outcomes.

Results: In silico results are consistent with clinical observations for treatment with efavirenz, efavirenz in association with tenofovir DF and emtricitabine, or boosted darunavir. In particular, lymph node drug penetration can account for a large proportion of cases of virological failure and drug resistance for these drugs.

Conclusions: Our findings suggest that a high drug concentration inside lymph node T-cells is desirable, although not observed for many drugs. The findings also suggest that the main cause of virological failure is likely insufficient drug exposure in one or more physiological compartments hosting a large number of CD4+ T-cells infections, hence allowing viral replication for some of the strains. Additional HIV compounds and combinations could be investigated using the developed model. Moreover, the current model can readily be adapted to predict virological failure occurrences in specific patients. Indeed, targeted predictions are possible through involvement in the model of patient drug adherence, immunity, viral quasispecies’ susceptibility, viral setpoint and drug disposition, all assigned to different model parameters. Since a limited amount of information is required by the model, it can be of use in the process of drug discovery and to guide clinical treatment strategies.
Abstract: O_17

Early Safety, Tolerability, and Pharmacokinetic Profile of GSK2838232, a Novel 2nd Generation HIV Maturation Inhibitor, as Assessed in Healthy Subjects

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Background: GSK2838232 is an investigational HIV maturation inhibitor with a preclinical virological profile amenable for use in HIV treatment, as part of combination antiretroviral therapy. In preclinical studies, GSK2838232 demonstrated low to moderate oral bioavailability (6-40% across species) and was metabolized primarily via CYP3A4 and UGT.

Materials & Methods: Four Phase I dose-escalation studies (NCT01802918, NCT02289482, NCT 02289495, NCT02795754) were carried out in healthy adult subjects to ascertain the safety, tolerability, and single and repeat-dose pharmacokinetics (PK) of GSK2838232 with and without ritonavir (RTV) as well as the relative bioavailability of suspension and solid oral dosage formulations and the impact of food. Serial PK samples were collected and intensive safety assessments (including continuous cardiovascular monitoring) were performed throughout each study. Plasma was analyzed by HPLC-MS/MS and PK parameters were determined by NCA (Phoenix WinNonlin 6.3).

Results: A total of 124 healthy subjects were enrolled across four studies, which assessed doses of 5 mg to 250 mg GSK2838232 as single doses with or without 100 mg RTV, and as repeated doses for 11 days of up to 200 mg QD with 100 mg RTV QD, and 200 mg BID without RTV. The studies were placebo controlled with the exception of relative bioavailability assessments. Four subjects were withdrawn in NCT02795754 due to AEs considered unlikely to be related to GSK2838232. Sporadic cardiovascular events (including NSVT) were seen on active and placebo arms, and none were definitively related to GSK2838232. Infrequently reported AEs assessed with a reasonable likelihood of being drug-related were headache and dizziness while skin rash, consistent with the wearing of ECG electrodes, was also reported. There were no clinically significant changes in hematology or clinical chemistry laboratories observed in any study. Following single and once-daily repeat dose oral administration, non-boosted repeated doses from capsules of 200 mg twice-daily (BID), given with food (normal 30% fat), exceeded the target trough concentration (5 ng/mL); however, in preliminary studies, once daily (QD) single (up to 100 mg) and repeated doses (up to 50 mg) from an unoptimized suspension formulation did not achieve the target trough concentration. Co-administration of RTV significantly altered the PK profile of GSK2838232, increasing single dose GSK2838232 plasma AUC and Cmax by 10-fold and 3-fold, respectively, compared to administration of GSK2838232 alone. A prolongation of half-life from ~20 hr non-boosted to ~34 hr with RTV was also observed. This boosting effect was also seen in repeat-dose GSK2838232 studies which achieved optimal plasma exposure with GSK2838232 as once-daily regimen of up to 200 mg with RTV. A moderate food effect (~60% increase in AUC and Cmax) was seen with a capsule formulation. Mean projected inhibitory quotient (IQ) values are in the range of 20 30 following RTV-boosted GSK2838232 doses of 100-200 mg QD and 8 following 200 mg BID non-boosted.

Conclusions: GSK2838232 with or without RTV was safe with no pattern of adverse events or problems with tolerability across these four studies in healthy subjects. The PK and safety data support continued investigation of antiviral activity (boosted or non-boosted) in HIV patients.
Abstract: O_18

Drug-drug interactions of glecaprevir and pibrentasvir with pravastatin, rosuvastatin, or dabigatran etexilate

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Background: The combination of glecaprevir (GLE; formerly ABT-493, a NS3/4A protease inhibitor discovered by AbbVie and Enanta) and pibrentasvir (PIB; formerly ABT-530, a NS5A inhibitor) is being developed as a combination therapy for the treatment for all major genotypes of hepatitis C virus (HCV) infection. Phase 1 drug-drug interaction studies were conducted with the transporter substrates pravastatin (OATP1B1/3), rosuvastatin (BCRP, OATP1B1/3), and dabigatran etexilate (P-gp) in healthy subjects to evaluate the potential drug-drug interactions with GLE and PIB.

Methods: Phase 1 studies evaluated the pharmacokinetics and safety of pravastatin 10 mg QD alone and with GLE 400 mg + PIB 120 mg QD, rosuvastatin 5 mg QD alone and with PIB 400 mg + PIB 120 mg QD, or single doses of dabigatran etexilate 150 mg alone and with GLE 300 mg + PIB 120 mg QD. N=12 healthy subjects participated in each of the three study arms. Blood samples were collected and pharmacokinetic parameters (maximum concentration [Cmax], area under the concentration-time curve [AUCinf or AUC24], and/or trough concentration [C24]) were estimated. Pharmacokinetic interactions of GLE + PIB with pravastatin, rosuvastatin, or dabigatran were assessed by a repeated-measures analysis using SAS. Safety and tolerability were assessed throughout the studies. All subjects provided informed consent and study protocols were approved by an appropriate IRB.

Results: Coadministration with multiple GLE + PIB doses increased exposures of pravastatin (↑2.2-fold Cmax, ↑2.3-fold AUC24), rosuvastatin (↑5.6-fold Cmax, ↑2.2-fold AUC24), and dabigatran (↑2.0-fold Cmax, ↑2.4-fold AUCinf). GLE exposure was higher (↑Cmax 59%, ↑AUC24 44%) with pravastatin, but PIB exposure was unaffected (≤24% difference). GLE and PIB exposures were similar (≤25% difference) with rosuvastatin or dabigatran etexilate. One subject was discontinued from the rosuvastatin study arm after receiving a single dose of GLE + PIB alone due to the event of panic attack (Grade 2), which was assessed by the investigator as having no reasonable possibility of being related to study drug. One subject discontinued from the dabigatran study arm due to chemical exposure (Grade 1) assessed by the investigator as having no reasonable possibility of being related to study drug. All other adverse events were mild in severity. No clinically significant vital signs, ECG or laboratory measurements were observed during the course of the study.

Conclusions: GLE + PIB significantly increased the exposure of pravastatin, rosuvastatin and dabigatran. Given the magnitude of the interaction and therapeutic index of the drugs, pravastatin and rosuvastatin can be used with GLE and PIB at reduced doses. Pravastatin dose should be reduced by 50% and rosuvastatin dose should be limited to 10 mg QD when administered with GLE and PIB. Use of dabigatran etexilate with GLE and PIB is not recommended.

Disclosures: These studies were funded by AbbVie. AbbVie contributed to the study designs, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.
Abstract: O_19

Influences on Pharmacokinetics of ledipasvir, sofosbuvir and GS-331007 in patients with decompensated cirrhosis – results from the UK Expanded Access programme.

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Background: With the availability of interferon-free direct acting antiviral therapy (DAA) for hepatitis C (HCV), patients with decompensated cirrhosis can now be considered for therapy. The combination of ledipasvir/sofosbuvir + ribavirin (RBV) was associated with high sustained virologic response rates (SVR) in decompensated cirrhosis in phase 3 clinical trials, as well as real world cohorts such as the NHS England expanded access programme.

Materials & Methods: Steady-state pharmacokinetic sampling was prospectively conducted in 314 patients with decompensated cirrhosis receiving 12 weeks of therapy with ledipasvir/sofosbuvir ± RBV as part of the HCV Research UK-NHS England expanded access programme. Sofosbuvir, GS-331007 (major circulating metabolite of sofosbuvir) and ledipasvir plasma samples were collected at 3-4 occasions across random time-points during therapy, and measured using a validated LC-MS/MS bioanalytical assay. The relationship between baseline patient characteristics and DAA concentrations was examined.

Results: The overall SVR rate was 83.1% (Genotype 1 – 93.5%; Genotype 3 – 56.6%). Mean age was 55 ± 8 years and mean weight was 82 ±16.6 Kg. The median MELD score was 11 (range 6-35), and the majority of patients were Child-Pugh-Turcot (CPT) class B (67.2%) at baseline. Median platelet count was 79 x 10⁹ (range 18-450 x 10⁹). 46.8% of patients were receiving low-dose PPI therapy at the beginning of therapy. The geometric mean of ledipasvir and GS-331007 concentrations were 254.1 ng/ml (90% CI 199.4-226.8 ng/ml), and 558.3 ng/ml (90% CI 524.9-592 ng/ml) respectively. In multivariate analysis, weight, platelet count, baseline PPI use, albumin and time-post dose, but not CPT score were significant predictors of ledipasvir concentrations. However, there was no significant difference in SVR rates between patients receiving PPI therapy (82.4%) vs no PPI therapy at baseline (83.6%) (p=0.88).

Conclusion: In a real world cohort of patients with decompensated cirrhosis, weight, platelet count, albumin and baseline PPI use were significant predictors of ledipasvir concentrations. Weight has previously been shown to be a statistically significant, but not clinically meaningful covariate for ledipasvir exposure. While albumin and platelet count would not be expected to directly affect the pharmacokinetics of ledipasvir, they may reflect an indirect marker of disease severity. A population pharmacokinetic model is being developed using this real-world data to further examine the effects of covariates on DAA exposure in patients with decompensated cirrhosis and portal hypertension.
Abstract: O_20

Evaluation of Drug-Drug Interactions between Sofosbuvir/Velpatasvir/Voxilaprevir and Boosted or Unboosted HIV Antiretroviral Regimens

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Background: A once-daily fixed-dose combination of sofosbuvir (SOF; pangenotypic nucleotide analog HCV NS5B inhibitor), velpatasvir (VEL; pangenotypic HCV NS5A inhibitor), and voxilaprevir (VOX; pangenotypic HCV NS3/4A protease inhibitor) is being developed for the treatment of chronic HCV infection. Phase 1 studies were conducted in healthy volunteers to evaluate potential for drug-drug interactions (DDIs) between SOF/VEL/VOX and boosted or unboosted HIV antiretroviral (ARV) regimens to inform coadministration in HCV/HIV coinfected patients.

Methods: The DDI studies were multiple-dose, randomized, and cross-over in design. Subjects received HIV ARV regimens including bictegravir (BIC; an investigational integrase inhibitor)/emtricitabine (FTC)/tenofovir alafenamide (TAF) 50/200/25 mg, FTC/rilpivirine (RPV)/TAF 200/25/25 mg, elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF 150/150/200/10 mg, or darunavir (DRV) 800 mg + ritonavir (RTV) 100 mg + FTC/tenofovir disoproxil fumarate (TDF) 200/300 mg and HCV DAAs SOF/VEL/VOX (400/100/100 mg) + VOX (100 mg), alone or in combination. The additional 100 mg of VOX was administered to the healthy subjects to approximate systemic VOX exposures observed in the HCV-infected population. Steady-state plasma concentrations of SOF, its predominant circulating nucleoside metabolite GS-331007, VEL, VOX, and ARVs were analyzed and PK parameters were calculated. Geometric least-squares means ratios and 90% confidence intervals (combination vs alone) for PK parameters (AUC, Cmax, and Ctau [as applicable]) were estimated and compared against lack of PK alteration boundaries of 70% to 143% for all analytes. Safety assessments were conducted throughout the study.

Results: 116 of 120 enrolled subjects (n=30/cohort) completed the studies; overall, 4 subjects discontinued due to withdrawal of consent. The majority of adverse events (AEs) were Grade 1 or 2 and there were no discontinuations due to AEs and no serious AEs.

Overall exposure (AUC) of BIC, FTC, RPV, DRV, and EVG was unaltered by coadministration with SOF/VEL/VOX. COBI and RTV AUC were 50% and 45% higher, respectively, when administered with SOF/VEL/VOX. TAF and TFV AUC were 53% to 61% higher and 63% to 79% higher, respectively, when the unboosted regimens were administered with SOF/VEL/VOX. TAF and TFV AUC from EVG/COBI/FTC/TAF were unaltered when coadministered with SOF/VEL/VOX. TFV AUC from DRV+RTV+FTC/TDF was 39% higher when administered with SOF/VEL/VOX.

Overall exposure (AUC) of SOF and VEL were unaltered following administration of SOF/VEL/VOX with the ARV regimens. GS-331007 was 43% higher when EVG/COBI/FTC/TAF was administered with SOF/VEL/VOX. VOX AUC was unaffected by administration with unboosted regimens, but higher VOX AUC (143% to 171%) was observed with boosted ARV regimens.

Conclusion: Study treatments were well tolerated. There were no clinically relevant changes in the PK of ARVs, SOF, GS-331007, or VEL with coadministration. Unboosted regimens did not impact VOX PK; higher VOX exposures were observed with boosted ARV regimens.
Abstract

The Potential Role of PK-Based Drug Interactions in FAERS-Reported Rhabdomyolysis Cases in Patients Receiving a DAA Regimen and a Statin

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Background: Several cases of rhabdomyolysis associated with the use of HCV direct-acting antiviral (DAA) regimens in combination with HMG-CoA reductase inhibitors (statins) have been reported to the FDA Adverse Event Reporting System (FAERS). Given the serious nature of rhabdomyolysis and the known association with the use of statins, it is important to evaluate whether reported cases could potentially have been precipitated by a PK-based (CYP enzyme/transporter-mediated) drug interaction between DAA(s) and statins. The aim of this project was to evaluate each rhabdomyolysis case reported to FAERS and determine if there is a mechanistic basis for a PK-based drug interaction that would lead to increased exposure of the statin.

Methods: The FAERS database was searched for cases of rhabdomyolysis associated with the use of currently marketed FDA approved DAA regimens from approval to 2016. FAERS contains over 13 million spontaneous reports submitted to FDA by healthcare professionals, general public, and drug manufacturers. We defined a “case” as any report of clinical diagnosis of rhabdomyolysis temporally associated with DAA therapy with or without use of a statin. For cases associated with statin use, the potential for drug interactions between DAA regimens and statins were assessed based on available in vivo drug interaction information in the respective US prescribing information (USPI) or predicted based on metabolic enzyme/transporter-mediated interaction potential.

Results: Fourteen cases of rhabdomyolysis have been reported to FAERS in patients receiving a DAA regimen and a statin. Based on the potential for drug interactions between a DAA regimen and a statin, these cases were categorized into one of the following scenarios:
1. A drug interaction resulting in a significant increase in statin plasma concentrations is known or anticipated and the co-administration is contraindicated or not recommended in USPIs (e.g., ombitasvir/paritaprevir/ritonavir/dasabuvir and simvastatin, n=4).
2. A drug interaction resulting in a significant increase in statin plasma concentrations is known or anticipated and a specific dose cap is recommended in USPIs (e.g., simeprevir-atorvastatin, n=5).
3. A drug interaction resulting in an increase in statin plasma concentrations is known or anticipated but no specific dosing recommendation is available in USPIs (e.g., daclatasvir-atorvastatin, n=2).
4. No significant interaction is expected based on in vitro or in vivo study results (e.g., sofosbuvir/ledipasvir-atorvastatin, n=3).

Conclusions: Through 2016, fourteen cases of rhabdomyolysis have been reported to FAERS in patients receiving a DAA regimen and a statin. For most cases, there is a mechanistic basis for a PK-based interaction, thus increased statin exposures caused by a DAA regimen could potentially have increased the risk of rhabdomyolysis. Many patients also had at least one other contributing factor that could increase the risk of rhabdomyolysis. There were three rhabdomyolysis cases observed in patients receiving a concomitant DAA regimen and a statin where a PK-based interaction was not anticipated. For these cases, due to non-availability of PK data, it is unknown whether higher statin concentrations due to PK changes or other intrinsic/extrinsic factors precipitated the rhabdomyolysis event. Furthermore, it is unknown if statin exposure alone could cause the observed rhabdomyolysis in these cases.
18th International Workshop on Clinical Pharmacology of Antiviral Therapy

14 - 16 June 2017, Chicago, USA

Abstracts:
Poster Presentations
Abstract: P_22

Effects of food and formulation on the pharmacokinetics of orally administered JNJ-64155806 in healthy volunteers

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Background: Despite the availability of vaccines and antivirals, influenza remains a significant global healthcare challenge that results in significant morbidity and mortality, particularly in the event of a pandemic. JNJ-64155806 (AL-794) is an ester prodrug of ALS-033719, a novel potent endonuclease inhibitor of influenza A and B including strains resistant to neuraminidase inhibitors. Antiviral activity has been previously demonstrated in a human challenge model. Ongoing efforts in formulation improvement and evaluating food effect are presented.

Methods: A Phase 1, 2-Part, open-label, single-dose, crossover study (AL-794-803; NCT02877160) to assess the relative oral bioavailability of JNJ-64155806 was conducted in healthy volunteers (HVs). In Part 1, 15 HVs received JNJ-64155806 150 mg (batch 2), in random order, suspension fasted, tablets fasted, and tablets with standard meal. In Part 2, 16 HVs received JNJ-64155806 100 mg, in random order, tablets (batch 2 and 3) fasted and tablets (batch 3) with a standard or high-fat meal. The suspension was prepared as 0.5% methylcellulose in water and 50-mg tablets were manufactured from two different batches. Plasma samples for ALS-033719 and ALS-033927 (inactive glucuronide metabolite) were collected over 72 hours after each treatment and analyzed using a validated LC-MS-MS method. PK parameters were calculated using non-compartmental analysis and compared using least squares means ratio (LSMR) and 90% confidence intervals (CI). Safety and tolerability were monitored throughout.

Results: All subjects completed Parts 1 and 2; subjects were all male and mostly white. In Part 1, tablets (fasted) were significantly more bioavailable compared to suspension (fasted) with LSMR (90% CI) for Cmax and AUC of 3.02 (2.58-3.53) and 2.42 (2.15-2.73), respectively; there was also a significant food effect: 1.80 (1.53-2.11) and 1.90 (1.68-2.15), respectively, when comparing tablets fasted vs standard meal. In Part 2, tablets from batch 3 were comparable to batch 2 with LSMR (90% CI) for Cmax and AUC of 1.05 (0.92-1.22) and 0.98 (0.88-1.08), respectively. Food increased both Cmax and AUC: 1.51 (1.32-1.73) and 1.77 (1.60-1.96), respectively, with a standard meal and 1.89 (1.65-2.17) and 2.04 (1.85-2.25), respectively, with a high-fat meal. Adverse events were all mild (Grade 1) or moderate (Grade 2) and occurred in 32% of subjects with the most common being headache (N=4) and dizziness (N=3); there were no clinically significant safety evaluation findings.

Conclusion: JNJ-64155806 has improved bioavailability when administered as tablets compared to suspension. No difference was observed between manufacturing batches (2 vs 3). A significant food effect was also observed. Single dose administration of JNJ-64155806 was generally safe and well tolerated. Clinical studies of JNJ-64155806 are ongoing.
Abstract: P_23

The Effect of Food on the Pharmacokinetics of the HIV-1 Attachment Inhibitor Temsavir, the Active Moiety of the Prodrug Fostemsavir

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Background: Fostemsavir is a prodrug of temsavir, a first-in-class attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into host CD4+ T cells. The impact of food on the pharmacokinetics (PK) of temsavir relative to fasted conditions was assessed in healthy subjects. Fostemsavir was administered using the extended release (ER) tablet formulation and dose being evaluated in the ongoing Phase 3 trial, where it is being administered without regard to food.

Materials and Methods: AI438042 (NCT 02164045) was an open-label, randomized, 2-period, 2-treatment, crossover study that assessed the impact of a standard meal (~423 kcal, 36% fat) on the multiple dose PK of temsavir. Eligible subjects received fostemsavir 600 mg twice daily on Days 1-3 and a single dose on Day 4 in each period, with a 3-day washout between periods. Fostemsavir was administered fasted or within 5 minutes of completing a standard meal. Serial blood samples for temsavir PK were collected up to 12 hours post-dose on Day 4 of each period. AI438071 (NCT02666053) was an open-label, randomized, single dose, 3-treatment, 3-period, 6-sequence, crossover study that assessed the impact of a high fat meal (985 kcal, 59.9% fat) or famotidine on the single dose PK of temsavir. Eligible subjects received fostemsavir 600 mg fasted, within 5 minutes of completing a high fat meal, or ~2 hours after a single dose of famotidine 40 mg (results not shown), with a 4-day washout between periods. PK parameters were derived by noncompartmental methods. Geometric mean ratios (GMR) and 90% confidence intervals (CI) were derived using linear mixed-effects models. Subjects were monitored for adverse events (AEs) throughout the studies.

Results: In Studies AI438042 and AI438071, 17 and 24 healthy subjects, respectively, were randomized, received study drug and completed the study. Relative to fasted conditions, a standard meal increased steady state temsavir C12 68% (90% CI: 1.36-2.07) with no meaningful impact on temsavir Cmax (GMR: 0.96, 90% CI: 0.83-1.10) or AUC(0-tau) (GMR: 1.10, 90% CI: 0.95-1.26). The median (range) temsavir Tmax increased from 2.00 (1.00-6.00) hours under fasted conditions to 4.00 (2.00-8.00) hours with a standard meal. Relative to fasted conditions, a high fat meal increased temsavir AUC(0-inf) 81% (90% CI: 1.54-2.12) and C12 5.66-fold (90% CI: 4.43-7.24), with no meaningful impact on temsavir Cmax (GMR: 0.97, 90% CI: 0.81-1.17). Following administration of fostemsavir with a high fat meal, the mean temsavir plasma concentration time profile contained two peaks with similar concentrations - at 4 hours (1020 ng/mL) and 10 hours (1050 ng/mL). There were no deaths, serious AEs, or discontinuations in either study.

Conclusions: The impact of food on temsavir PK following administration of fostemsavir ER is dependent on meal type. Temsavir absorption rate is prolonged and C12 values are higher with food. Temsavir bioavailability is enhanced with a high fat meal but not with a standard meal; there is no meaningful impact on Cmax. The increase in temsavir exposure with a high fat meal is not anticipated to impact the safety profile of fostemsavir.
Abstract: P_24

Population Pharmacokinetic Analysis of Voxilaprevir, a Pan-Genotypic HCV NS3/4A Protease Inhibitor in Hepatitis C Virus-Infected Subjects

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Background: A fixed-dose combination (FDC) of voxilaprevir (VOX, GS-9857), a potent pan-genotypic HCV NS3/4A protease inhibitor, sofosbuvir (SOF), a nucleotide analog HCV NS5B inhibitor and velpatasvir (VEL), a potent pan-genotypic HCV NS5A inhibitor, has demonstrated high efficacy in Phase 2 and 3 clinical trials and is under regulatory review for the treatment of chronic HCV infection. A population-based pharmacokinetic (PopPK) model was developed to understand the clinical covariates of the PK of VOX in subjects with chronic HCV infection when administered as VOX 100 mg in combination with SOF/VEL 400/100 mg or as the SOF/VEL VOX 400/100/100 mg FDC.

Methods: The PopPK model for VOX was developed using VOX plasma concentration data from pooled intensive and sparse samples from 8 phase II and III studies in patients with chronic HCV infection (n=1597). A nonlinear mixed effects modeling approach using first-order conditional estimation with interaction (FOCE-I) method in NONMEM 7.3 was used for PopPK analysis. Covariates including age, sex, body weight, race, ethnicity, creatinine clearance, cirrhosis status, and concomitant medications including anti-coagulants, selective serotonin reuptake inhibitors, statins, calcium channel blockers (CCB), H2 receptor antagonists, diuretics, proton pump inhibitor and P-gp inhibitors were evaluated using a stepwise forward addition followed by backward elimination methodology for their effect on VOX PK. Clinical significance of statistically significant covariates was determined by a sensitivity analysis of their impact on the steady-state VOX exposure parameters AUCtau, Cmax and Ctau relative to the available clinical safety and efficacy data.

Results: Voxilaprevir plasma PK was best described by a two-compartment model with first-order absorption, first-order elimination from the central compartment and an absorption lag time. The PK model was parameterized in clearance (CL), central volume (Vc), distribution clearance (Q), peripheral volume (Vp), absorption rate constant (ka), and lag time (Tlag).

Statistically significant parameter-covariate relationships were identified for sex and cirrhosis on CL and Vc, and concomitant CCB use on CL. For a typical male HCV-infected subject without cirrhosis or CCB use, CL was 65.8 L/hr, Vc was 707 L, Q was 11.0 L/hr, Vp was 259 L, ka was 0.401 1/hr, and Tlag was 0.462 hr. Interindividual variability was 70.1% for CL, 109% for Vc, and 83.6% for ka. The sensitivity analysis identified cirrhosis as the most influential covariate resulting in 74%, 76% and 79% higher VOX AUCtau, Cmax and Ctau, respectively compared with subjects without cirrhosis. Additionally, the combined effect of sex, cirrhosis and CCB use on VOX steady-state exposure resulted in 126%, 107% and 187% higher VOX AUCtau, Cmax and Ctau, respectively, compared with male subjects without cirrhosis or CCB use. None of these relationships were considered to have a clinically meaningful impact on VOX PK in HCV-infected subjects relative to the clinical safety and efficacy profile of the regimen across VOX exposures.

Conclusions: Demographic variables such as age, sex, body weight, race, ethnicity, creatinine clearance, cirrhosis status, and concomitant medications do not have a clinically relevant impact on VOX exposures in HCV-infected subjects.
Abstract: P_25

Bioequivalence of a Fixed Dose Combination Tablet of Dolutegravir and Rilpivirine in Healthy Subjects

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Background: Clinical development of a 2-drug regimen of the integrase inhibitor dolutegravir (DTG, Tivicay®) and the non-nucleoside reverse transcriptase inhibitor rilpivirine (RPV, Edurant®) as a once-daily treatment option for maintenance of HIV suppression is ongoing. The objective of Study 201676 (NCT02741557) was to evaluate bioequivalence (BE) of a fixed-dose combination (FDC) tablet containing DTG 50 mg and RPV 25 mg (DTG/ RPV FDC, test treatment) compared to co-administration of the separate agents (reference treatment) under fed conditions.

Materials & Methods: This was a single-dose, open-label, randomized, 2-way crossover study in 118 healthy subjects. Test and reference treatments were administered in a random order after consumption of a moderate-fat meal with a 21-day between-treatment washout period. Serial pharmacokinetic (PK) samples were collected prior to dosing and for 120 h or 264 h post-dose for DTG and RPV, respectively. Plasma concentrations of DTG and RPV were assessed using validated LC/MS/MS methods and PK parameters were estimated using noncompartmental methods. The test/reference geometric least squares (GLS) means ratio and associated 90% confidence intervals (CI) of key PK parameters (ln-transformed) were determined using a mixed effects model for DTG and RPV.

Results: A total of 113 subjects completed both treatment periods. Bioequivalence of the DTG/RPV tablet was established with the 90%CI for the GLS means ratios for AUC and Cmax within the 0.80-1.25 BE criteria for both DTG and RPV: GLS means ratios (90%CI) for AUC(0-inf), AUC(0-t) and Cmax were 1.037 (1.010, 1.064), 1.038 (1.011, 1.066) and 1.050 (1.022, 1.078) for DTG and 1.108 (1.045, 1.174), 1.107 (1.042, 1.176) and 1.124 (1.047, 1.207) for RPV. The tolerability profile was comparable between treatments with no observed serious or DAIDS grade 3/4 adverse events. The most common AEs were headache (7 events) and upper respiratory tract infection (2 events).

Conclusions: The DTG/RPV FDC tablet is bioequivalent to co-administration of the DTG + RPV tablets under fed conditions and was well-tolerated. This study establishes a pharmacokinetic bridge for the DTG/RPV FDC tablet to the SWORD Phase 3 trials of the DTG+RPV 2-drug regimen, in which HIV-infected patients took the individual DTG and RPV tablets together with a meal.

Abstract: P_26

Tenofovir-diphosphate (TFV-DP) in dried blood spots (DBS) is inversely correlated with body mass index (BMI)

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Background: Previously, a high body mass index (BMI) has been associated with lower plasma levels of tenofovir (TFV). The clinical impact of this is unknown, although no studies have shown any impact on human immunodeficiency virus (HIV) viral suppression at 12 months. Using tenofovir-phosphate (TFV-DP) in dried blood spots (DBS) has emerged as an objective biomarker of cumulative exposure and adherence to TFV-based regimens, given its long half-life (17 days) in this matrix compared to...
Abstract

TFV in plasma (15 hours). Whether levels of TFV-DP in DBS differ in obese vs non-obese has yet to be determined.

Materials and Methods: DBS from 102 virologically-suppressed (<50 copies/mL), HIV-infected individuals on chronic (at least 3 months) tenofovir disoproxil fumarate (TDF)-based antiretroviral therapy (ART) enrolled in a longitudinal cohort of adherence, were studied. Variables including age, gender, race, ART regimen, and BMI were recorded. BMI was evaluated as a continuous variable and then as categorical, divided into normal (18-25 kg/m²), overweight (25.1-30 kg/m²), and obese (>30 kg/m²) groups. Quantification of TFV-DP in DBS was performed using a previously-validated LC/MS-MS method and reported as fmol/punch. Pearson correlation was used to measure the relationship between TFV-DP in DBS and BMI (as a continuous variable). ANOVA was used to measure the relationship between TFV-DP in DBS and BMI (as a categorical variable) in addition to TFV-DP in DBS by race and ART regimen. Pairwise comparisons were run on the ANOVA analysis. The TFV-DP levels were log transformed in all analyses to normalize the data.

Results: A total of 102 patients were studied. 87.2% were males and 12.7% were females. 70.6% reported being white (13 Hispanics), 20.6% reported being black (2 Hispanics), and 8.8% reported “other”. Median age was 48 years (range 23-70). ART included: 32.4% on an integrase strand transfer inhibitor (INSTI), 36.3% on a non-nucleoside reverse transcriptase inhibitor (NNRTI), 15.7% on a boosted protease inhibitor (PI), and 15.7% on a mixed regimen of three or more drug classes. BMI was distributed as follows: 40.2% normal, 40.2% overweight, and 19.6% obese. In an unadjusted model, BMI was inversely correlated with TFV-DP levels (rho=-0.3 [95% CI; -0.48 to -0.20, p=0.0012]). When evaluating mean TFV-DP levels with categorical BMI there were significant differences between the normal and obese groups (2398 vs 1459 fmol/punch, p=0.0001) and the overweight and obese groups (2493 vs 1459 fmol/punch, p<0.0001) but not between the normal and overweight group (2398 vs 2493 fmol/punch, p=0.9699). No differences in TFV-DP concentrations by race or ART regimen were observed.

Conclusion: In an unadjusted model, TFV-DP in DBS were inversely associated with BMI. This is expected given previous findings of lower plasma TFV levels in obese compared to non-obese individuals. When BMI was evaluated as a categorical variable the difference in TFV-DP levels in DBS were driven by the obese patients. There were no significant differences in the TFV-DP levels between the normal and overweight BMI category groups. Further studies aiming to evaluate the mechanism(s) driving this difference and the long-term clinical significance of these findings are needed.

Abstract: P_27

The Effect of Hepatic or Renal Impairment on Bictegravir Pharmacokinetics

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Background: Bictegravir (BIC) is a novel, potent, HIV integrase strand transfer inhibitor (INSTI) with a high barrier to resistance and low potential for DDIs. BIC is currently in development for treatment of HIV-1 infection coformulated with emtricitabine and tenofovir alafenamide as a single tablet regimen. BIC is primarily eliminated through hepatic metabolism with similar contribution by CYP3A4 and UGT1A1. Renal elimination of unchanged BIC is negligible. The pharmacokinetics (PK) and safety of BIC were evaluated across two studies in HIV-uninfected subjects with moderate hepatic (HI) or severe renal impairment (RI).

Materials and Methods: Two open-label, parallel-group studies were conducted using a single dose of BIC 75 mg. Subjects with moderate hepatic impairment (n=10) had a baseline Child-Pugh-Turcotte score of 7-9. Subjects with severe renal impairment (n=10) had a baseline creatinine clearance (CLcr) of 15-29 mL/min based on Cockcroft-Gault equation. Subjects in the control groups, matched for
Abstract

gender, age (± 10 years) and body mass index (± 20%), had normal hepatic (n=10) or renal function (CLcr ≥90 mL/min) (n=8). Intensive PK sampling was performed over 144 hour post-dose. BIC unbound fraction in plasma was assessed. Statistical comparisons for BIC exposures were evaluated using geometric least-squares mean (GLSM) ratios and 90% confidence intervals (CIs) with subjects in HI or RI group serving at the test and subjects in the matched control group as the reference. An increase of ≥100% in 90% CI for exposures was considered potentially clinically significant. Safety was monitored throughout the study and follow-up.

**Results:** Total BIC exposure was approximately 41% lower in HI relative to the normal matched control group (AUCinf %GLSM ratio [CI%]: 58.7 [41.3, 83.5]). However, the higher free fraction (% unbound BIC) (0.81% HI vs. 0.61% controls), resulted in free BIC exposure (the moiety associated with therapeutic effect) 23% lower in HI than controls (%GLSM ratio [CI%]: 76.5 [56.5 -103.7]). Total BIC exposure was approximately 27% lower in RI relative to the normal matched control group (AUCinf %GLSM ratio [CI%]: 72.6 [48.8, 108.1] and free BIC exposure was comparable between both groups (AUCinf %GLSM ratio [CI%] 99.3 [79.5 -124.0]) due to a higher BIC free fraction in the RI subjects (0.75% RI vs. 0.49% controls). All adverse events observed were mild (Grade 1) in severity. No clinically meaningful changes in laboratory values, vital signs, or ECGs occurred.

**Conclusion:** Moderate hepatic impairment or severe renal impairment did not result in clinically relevant changes in BIC exposure. Bictegravir was well tolerated in these studies. Dose adjustment of BIC is not necessary in patients with mild or moderate hepatic impairment or in patients with mild to severe renal impairment.

Abstract: P_28

**Inflammation and gene expression of drug transporters and metabolizing enzymes in the female genital tract.**

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**Background:** Systemically, inflammatory cytokines regulate the expression and activity of drug metabolizing enzymes and transporters (DMET), often leading to altered pharmacokinetics. However, while adequate drug exposure in the female genital tract (FGT) is critical to effective HIV prophylaxis for women, the effect of local inflammation on drug exposure in the FGT is unknown. In populations of women where prophylactic HIV interventions have been tested, elevated proinflammatory cytokines in the FGT were observed; whether this contributed to reduced drug efficacy is unknown. Here, we examined the role of FGT inflammation in regulating local DMET gene expression.

**Materials and Methods:** Thirty-one DMET genes were selected a priori based on known distribution and metabolism pathways of antiretrovirals. RNAseq was performed on RNA extracted (Qiagen RNeasy kits) from cervical tissues of 24 donors undergoing gynecologic surgeries in Chapel Hill, NC. A cDNA library was prepared using Illumina TruSeq RNA Access kit and sequencing performed using Illumina’s Hiseq 2500 on a 50bp paired end read. FPKM (fragments per kilobase of transcript per million mapped reads) values were generated using Cufflinks software and compared between tissues with (n=13) and without (n=11) cervicitis as documented on clinical pathology reports. Candidate genes selected from RNAseq analysis were measured using qPCR in cervical RNA from 27 donors (Minneapolis, MN). cDNA synthesis and quantitative PCR were performed using Superscript ® Vilo ™ cDNA Synthesis Kit.
and Taqman ® Gene Expression Assays. The 2^-ΔCt method was used to determine expression relative to endogenous control GAPDH. The association of each gene with IL-6 expression was tested using Spearman rank correlation test.

**Results:** Five genes were initially identified from RNAseq using a 5% false discovery rate. An additional four genes were identified using t-test without adjusting for multiple comparisons. ABCB1, ABCG2 (efflux transporters), and SLC29A3 (uptake transporter) were upregulated in tissues with cervicitis while (ABCC1, ABCC5 (efflux transporters), CYP3A5 (metabolizing enzyme), NME1, NME2, and PGK1 (nucleotide kinases)) were downregulated. These nine genes were quantified via qPCR in a separate tissue cohort; ABCB1 (p<0.05), ABCG2 (p<0.01), and NME1 (p<0.01) were positively correlated with IL-6 expression.

**Conclusions:** Using two unique tissue cohorts and two gene quantification methods, we have identified components of drug metabolism and transport processes subject to inflammatory regulation in the FGT. ABCB1, ABCG2, and NME1 were identified in both analyses although interestingly, NME1 was downregulated in tissues with cervicitis in RNAseq analysis yet positively correlated with IL-6 in qPCR analysis. Further validation is ongoing to determine whether altered expression results in altered local drug exposure. Implications of these findings suggest that, in the setting of inflammatory conditions, substrates for efflux transporters ABCB1 or ABCG2 may achieve decreased local exposure. NME1, a diphosphate kinase, plays a significant role in the intracellular phosphorylation of nucleotide analogues to their active metabolites; therefore altered expression or activity may modulate the efficacy of nucleotide analogues such as tenofovir and emtricitabine, currently used for HIV prevention. In summary, these findings can guide the development and evaluation of HIV prevention interventions that will be effective in women regardless of inflammatory status.

**Abstract: P_29**

**Dose-selection of odalasvir for use in combination with AL-335 and simeprevir in a phase 2A study using a population pharmacokinetic modelling and simulation approach**

**Background:** Hepatitis C virus (HCV) infection is a leading cause of liver disease and an estimated 130-150 million people are infected worldwide. A combination therapy of direct-acting antivirals (DAAs) AL-335 (uridine nucleotide analog nonstructural (NS)5B polymerase inhibitor), odalasvir (ODV; NS5A protein inhibitor) and simeprevir (SMV; NS3/4A protease inhibitor) is currently under investigation for the treatment of HCV infection. The objective of this population pharmacokinetic (Pop-PK) modelling and simulation analysis was to guide dose-selection of ODV in a Phase 2a study.

**Materials and Methods:** The pop-PK model for ODV in monotherapy was developed using data from three Phase 1 studies (ACH102-001, -002 and -020) and one Phase 2 study (ACH102-017). Subsequently the effect of co-administering SMV and AL-335 with ODV on the exposure of ODV was quantified. This interaction model was developed using data in healthy volunteers from a Phase 1 interaction study (AL-335-602) and the preliminary data from the first cohorts of non-cirrhotic patients from a Phase 2a study (AL-335-604), in which different AL-335, ODV ± SMV regimens are investigated in patients with chronic HCV infection.

**Results:** The resulting pop-PK model was a three-compartmental model with lagged dual first order absorption and first order elimination. The
significant effect of SMV on ODV exposure was quantified. In contrast, co-administering AL-335 did not significantly affect the exposure of ODV. The resulting model was used to simulate different dosing regimens with and without co-administration of SMV to match the ODV exposure, observed in the PROXY-study (ACH102-017). The PROXY-study, in which ODV was co-administered with sofosbuvir (a nucleotide analog NS5B polymerase inhibitor), demonstrated 100% sustained virologic response following six weeks treatment in non-cirrhotic HCV genotype-1 infected patients without clinically relevant adverse events. These simulations resulted in guiding the selection of efficacious and safe dosing regimens of 2- or 3-DAA (ODV+AL-335±SMV) combinations for subsequent cohorts in study AL-335-604. A daily dose of 25mg ODV (50mg every other day, until the 25mg formulation became available) was selected to be combined with daily dosing of 800mg AL-335 ± 75mg SMV.

**Conclusion:** The pop-PK model for ODV in monotherapy and in combination with AL-335 with or without SMV was used successfully to guide dose selection in Phase 2a. This model will be updated when additional data from Phase 2a becomes available and will be used to support PK parameter estimation from sparse PK sampling designs in future Phase 2b and Phase 3 trials.

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**Abstract: P_30**

**Pharmacokinetics of daclatasvir in cirrhotic patients: challenges in PBPK modelling**

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**Introduction:** Daclatasvir is an NS5A-inhibitor which is used for the treatment of a chronic hepatitis C virus (HCV) infection. Since HCV infection eventually leads to liver cirrhosis, it is necessary to study safety, efficacy and pharmacokinetics (PK) of daclatasvir in cirrhotic patients. An in silico approach using physiology-based pharmacokinetic (PBPK) modeling can be of help to design these studies, or even predict the influence of cirrhosis on PK. PBPK modeling is a mechanistic approach used for the prediction of the PK of a compound by combining physicochemical and in vitro data, with human anatomical and (patho) physiological information in a mathematical model. The aim of this study was to describe daclatasvir PK in healthy volunteers and cirrhotic patients using a PBPK model.

**Material & Methods:** We modified a PBPK model of daclatasvir (Wang et al.) for which the Simcyp simulator (Version 15, release 1) was used. The daclatasvir model incorporated hepatic metabolism by CYP3A4, CYP3A5 and CYP2C8. In addition, passive diffusion and active transport were added using sinusoidal uptake in the liver by an unknown transporter and canalicular efflux by P-gp.

The performance of the model was tested simulating daclatasvir PK for single (10, 30, 100mg) and multiple (30, 60mg) dosages in healthy volunteers. In addition, daclatasvir PK was simulated with strong CYP3A4 inhibitors darunavir/ritonavir and atazanavir/ritonavir. Simulated data were compared with in vivo data.
from literature using the area under the time curves (AUC) and maximal plasma concentration (C\text{max}). Subsequently, single dosages of 30mg daclatasvir were simulated in Simcyp special populations of Child-Pugh (CP) A, B, and C patients.

**Results:** The AUC ratios (simulated/observed) of single dose daclatasvir 10, 30, and 100mg in healthy volunteers varied from 0.74-0.89 and C\text{max} ratios varied from 0.93-1.13. Also, the multiple dose simulations and the simulations with the CYP3A4 inhibitors resulted in AUC and C\text{max} ratios which were considered acceptable. We were not able to mimic in vivo exposure with the model in cirrhotic patients. In CP-A patients AUC and C\text{max} were predicted to be 7.74 mg/L*h and 0.66 mg/L*h (reference 4.14 mg/L*h and 0.38 mg/L) respectively and for CP-B 14.69 mg/L*h and 0.72 mg/L (reference 4.55 mg/L*h and 0.38 mg/L), and for CP-C 19.85 mg/L*h and 0.63 mg/L (reference 4.65 mg/L*h and 0.317 mg/L), respectively. The predicted exposure is in line with the decreasing apparent clearance (CL/F) from the simulated data starting 24 mL/min (reference 120 mL/min) to 9 mL/min (reference 108 mL/min) in CP-A and CP-C patients, respectively.

**Conclusion:** We were able to accurately model daclatasvir PK in healthy volunteers using a PBPK model including mechanistic hepatic metabolism and hepatic drug-transport data. However, a discrepancy remained between the observed and simulated daclatasvir exposure in cirrhotic patients. This warrants further studies into the pathophysiologic changes that take place in cirrhotic patients and influence drug disposition.

**Abstract: P_31**

**Population pharmacokinetics of romidepsin as a latency reactivating agent in HIV-infected adults**


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**Background:** The combined use of therapeutic vaccination and specific drugs that can reactivate latent reservoir virus (Kick and kill strategies) may be required to achieve a functional cure for HIV infection. Romidepsin has been shown to induce HIV-1 transcription in vivo in previous studies, demonstrating that reversal of HIV-1 latency is possible. To date, no information regarding the pharmacokinetics of romidepsin in HIV infected individuals is available. Thus, the objective of the present study was to develop a population pharmacokinetic model for romidepsin in HIV-infected adults under antiretroviral treatment. The model sought to incorporate patient characteristics that influence variability in romidepsin concentrations.

**Methods:** BCN02-\neg Romi (NCT02616874) is an ongoing single \neg arm proof-of-concept study with 15 HIV-infected individuals who started antiretroviral treatment with an integrase strand transfer inhibitor-based antiretroviral regimen.
early (<6 months) from HIV acquisition, and who were rolled over from the past BCN01 trial (NCT01712425). After 3 years with viral suppression, all participants were immunized with MVA.HIVconsv (2x108 pfu), followed by three doses of romidepsin (RMD1-2-3, 5 mg/m2 BSA as a 4-hour infusion/every week), and by a second MVA.HIVconsv vaccination. Romidepsin concentrations in plasma were determined by HPLC MS/MS before and at the end of each infusion, as well as 0.5, 1, 2, 4, 8, 10 and 20 hours after RMD1, and 4 and 8 hours after RMD2 and RMD3. A population analysis was performed using non-linear mixed effects modelling (NONMEN, version 73). Two- and three-compartment models were tested. Pharmacokinetic parameters, inter-individual and inter-occasion variability, and residual error were estimated. In addition, the influence of different patient characteristics on the pharmacokinetics of romidepsin was explored. The visual predictive check was used to validate the final model.

Results: Romidepsin concentrations were best described by a three-compartment model with first order elimination. Body weight influenced clearance (CL) and central volume of distribution (V). The estimated population CL and V, expressed for an individual weighing 70 kg, were 21.19 L/h (inter-individual variability 25%) and 7.33 L, respectively. No other covariates influenced the pharmacokinetics of romidepsin. The final model appropriately predicted romidepsin concentrations, with no systematic bias and with adequate precision.

Conclusions: Our population pharmacokinetic model adequately described the pharmacokinetic parameters of romidepsin when used as a viral latency reversal agent in virologically suppressed HIV-infected individuals. Both CL and V were influenced by body weight. Bayesian estimates of the individual parameters may prove helpful to optimize romidepsin dosing strategies once the therapeutic range of romidepsin in this setting has been properly defined.

Abstract: P_32

Population Pharmacokinetics of Dolutegravir in HIV-1 Infected Adults from Clinical Practice

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Background: Higher rate of discontinuation due to neuropsychiatric adverse events has been observed with dolutegravir compared with other integrase strand transfer inhibitors, especially amongst women, older patients and abacavir-receiving subjects. Moreover, a positive correlation between dolutegravir concentrations and neuropsychiatric adverse events has been suggested. The objective of the present study was therefore to develop a population pharmacokinetic model for dolutegravir, and to identify characteristics that might explain variability in the pharmacokinetic parameters of this drug in a population of HIV-infected adults from routine clinical practice, with special focus on gender, age and concomitant antiretroviral drugs.

Methods: A population analysis was performed using non-linear mixed effects modelling (NONMEN, version 7.3) with 378 plasma samples from 176 of HIV-infected adults on antiretroviral therapy including dolutegravir (50 mg once daily) in clinical practice. Dolutegravir concentrations in plasma were determined by LC-MS/MS. Single and multiple compartmental models with different absorption models (i.e., first-order absorption with and without lag time and a more flexible transit compartment absorption) were tested. Pharmacokinetic parameters, interindividual and interoccasion
variability and residual error were estimated. In addition, the influence of gender, age, and other patient characteristics on dolutegravir pharmacokinetics was explored. The visual predictive check was used to validate the final model.

**Results:** Patients characteristics were as follow: gender (n) M/F 120/56, age (mean±SD) 51.6±9.3 years, body weight 70.5±13.8 kg. Dolutegravir concentrations were best described by a one-compartment model with first order elimination. Body weight influenced clearance (CL/F) and central volume of distribution (V/F). The estimated population CL/F and V/F, expressed for an individual weighting 70 kg, were 1.4 L/h and 13.7 L, respectively. Interoccasion variability in dolutegravir CL/F was 36%. There was an inverse relationship between bilirubin concentrations and CL/F. Concomitant treatment with atazanavir reduced CL/F by 32%, whereas no significant effect of other antiretroviral medications was observed.

**Conclusions:** Our population pharmacokinetic model adequately described dolutegravir concentrations from clinical practice in HIV-infected patients. Body weight, concomitant use of atazanavir and bilirubin concentrations, but neither gender nor age, influenced dolutegravir exposure. Wide interoccasion variability in dolutegravir pharmacokinetics in clinical practice deserves attention, especially if TDM programs are to be implemented.

**Abstract: P_33**

**Modeling of the Effects of Food and Enterohepatic Circulation on the Pharmacokinetics of Orally Administered JNJ-64155806 (AL-794) in Healthy Volunteers**

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**Background:** JNJ-64155806 (AL-794) is a potent endonuclease inhibitor of influenza A and B including strains resistant to neuraminidase inhibitors (OPTIONS IX; O-97). Following oral administration, JNJ 64155806, a prodrug, is rapidly hydrolyzed to ALS-033719. The major circulating metabolite is an inactive glucuronide, ALS-033927, which undergoes enterohepatic circulation (EHC). We developed a model to account for the metabolism, EHC, renal and other elimination using single-and multiple-dose (twice daily [BID]) data from study 801 (NCT02588521).

**Methods:** Of the 89 subjects included in this analysis, 25 received a single dose 50-2000 mg fasted (of which 6 received a single 450 mg dose both fasted and with high fat meal), 56 received BID dosing (50 to 200 mg) for 5-7 days, and 8 received 600 mg BID up to 3 doses. Plasma ALS-033719 and ALS-033927 were collected from all subjects for up to 7 days postdose, whereas urine ALS-033719 and ALS-033927 were collected from subjects receiving single 1000 mg dose (N=6) for up to 60 hours. Bioavailability (F) was estimated as a decreasing function with dose, and a factor increase when administered with food. Presence of diurnal variation was also evaluated on the absorption parameters. One- or two-compartment models were tested. EHC was described using a gallbladder compartment that empties into the gut compartment following a periodic sine function. Data were pooled and analyzed using NONMEM version 7.3. Values below the lower
limit of quantification were included as censored data using M3 method. Visual predictive check was performed to evaluate the model predictive performance.

**Results:** The complex JNJ-64155806 pharmacokinetics was adequately described by a two-compartment model with EHC. F for 450-1000 mg was estimated to be around half that of 50 mg. Only 1 subject received 2000 mg and F was estimated to be 19% that of 50 mg. High-fat meal doubles the bioavailability of 450 mg, and compared to morning doses, evening doses had higher bioavailability with a factor that increases with dose. Absorption lag time was 0.206 h and the first-order rate constant was 0.145 h⁻¹. Central volumes of distribution were 66 L for ALS-033719 and 1.67 L for ALS-033927. The peripheral volume of distribution for ALS-033719 was 34.5 L and the distributional clearance was 0.819 L/h. Metabolic clearance was 46.3 L/h, the renal clearance estimates were 0.183 L/h for ALS-033719 and 3.1 L/h for ALS-033927. The biliary rate constant was 1.93 h⁻¹ and gallbladder emptying peaked at 9:00 AM and 6:50 PM daily. Other elimination (eg fecal clearance) was 17.8 L/h. All parameters were estimated with good precision (<25% RSE). The effective half-life of drug accumulation for BID dosing is around 9 h, and over time, with multiple doses and as dose level increases, the terminal half-life is prolonged due to EHC.

**Conclusion:** A PK model with EHC was successfully developed and it can describe the plasma and urine concentration of ALS-033719 and ALS-033927 in healthy volunteers. The model will be used to further evaluate between and within subject variabilities, covariates, and assessment of PKPD relationships.

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**Abstract: P_34**

**Exposure to sofosbuvir and daclatasvir is unchanged in liver transplant patients on cyclosporine or tacrolimus based immunosuppression**

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**Background:** HCV recurrence is a main complication following liver transplantation (LT) impacting graft and patient survival. The recent approval of IFN -free regimen using direct antiviral agents (DAA) has radically changed the management of liver transplant recipients. However, the optimal strategy remains to be determined. The aim of this study was to assess the drug-drug interaction and tolerance between immunosuppressive therapy and DAA, sofosbuvir (SOF) and daclatasvir (DCV).

**Methods:** The ANRS CO23 CUPILT study is a prospective cohort including currently 699 patients (pts) with HCV recurrence and treated with 2nd generation DAA. Sixty-seven pts treated with SOF + DCV ± ribavirin (RBV) between Jul. 2013 and Nov. 2015 were included in this pharmacokinetic substudy. Patients should be on stable tacrolimus or cyclosporine–based immunosuppressive therapy at DAA initiation. Blood samples collected at week 2, 4, 12 and 24 were used to assay SOF, SOF main metabolite GS331007 and DCV using a validated LC-MS/MS method. Variation of quality controls inserted in all analytical runs were
<15%. All results are expressed as mean and SD.

**Results:** This substudy enrolled 67 liver recipients (male: 79%, mean age 57.4 ± 7.7 years), with an active HCV recurrence (G1: 51, G3: 9, G4: 7), in 14 centers. Treatment duration was 24 weeks (wk) in 92.5% of pts. RBV was given in 35 (52%) pts. All pts received cyclosporine (26%) or tacrolimus (74%). At baseline, HCV viral load, GGT, creatinine clearance and hemoglobin levels were 6.4 ± 0.7 log10 IU/mL, 447.4 ± 743.8 IU/L, 73.3 ± 30.7 mL/min-1 and 13.4 ± 2.2 g/dL respectively. Concentrations of DAA were measured at least once in all patients. One hundred forty five blood collections were assayed during DAA treatment, with an average 2.5 samples per patient. Intra-individual variability over the follow-up was 19% for SOF, GS331007 and 33% for DCV. SOF and GS331007 trough concentrations (99 blood collections) were 1.0 ± 1.5 ng/mL and 643.4 ± 406.9 ng/mL, respectively. Though a 40% increase in DCV exposure was expected when co-administrated with cyclosporine, no difference in DCV trough concentrations was observed: 619.0 ± 578.4 ng/mL in cyclosporine treated patients (n=8) and 444.3 ± 498.4 ng/mL in tacrolimus treated patients.

**Conclusion:** SOF, GS and DCV concentrations in liver transplant patients were in the range of previously published study whether patients were on tacrolimus or cyclosporine based immunosuppressive therapy.

**Abstract: P_35**

**Low rate of drug-drug interaction management during interferon-free simeprevir therapy - An integrated analysis of interventional and observational clinical studies**

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**Introduction:** The widespread use of direct acting antivirals (DAA) for chronic hepatitis C has raised the question of the clinical relevance of drug-drug interactions (DDI) with frequently prescribed medications. The aim of this analysis was to investigate the impact of known or potential pharmacokinetic (PK) interactions between the hepatitis C virus (HCV) protease inhibitor simeprevir (SMV) and concomitant medications on DDI management and safety profile.

**Methods:** We pooled data across 9 prospective clinical studies of SMV in interferon-free combinations in HCV patients treated for ≥12 weeks (n=876). Subjects who started antihypertensive (AHD), anxiolytic (AXD), or lipid-lowering drugs (LLD) prior to SMV therapy were grouped based on known DDI profiles of the concomitant drug relative to SMV (Liverpool DDI database, SMV Summary of Product Characteristics): “green” (no interaction) or “amber” (known/potential interaction). Safety was investigated during SMV treatment (12 weeks). Outcomes of co-administration were assessed during screening and SMV treatment (12 weeks) using a composite endpoint of discontinuation,
interruption, or dose modification of the concomitant medication.

**Results:** 409 (47%), 153 (17%), and 96 (11%) subjects were on any AHD, AXD, or LLD, respectively. Subjects represented a diverse population (female 34% -41%; black/African American 14% -27%; cirrhosis 37% -49%) with high numbers of concomitant medications (10+: 22% -46%). The rate of meeting the composite endpoint was generally low. Subjects on green and amber AHDs had similar outcomes. Numerical differences were seen between green and amber AXD and LLD. Discontinuations of amber drugs often occurred prior to or on day 1 of SMV therapy (7/14 amber AHD; 6/15 amber AXD; 3/7 amber LLD). Most amber AHD dose modifications were single changes (6/10) with subsequent discontinuation in 1 patient. Dose changes of amber LLDs were single dose reductions of statins which mostly (5/7) occurred prior to or on day 1 of SMV therapy with 1 subsequent discontinuation. SMV treatment was generally well tolerated with very low rates of discontinuations. No relevant differences in the frequency of AEs and SAEs at least possibly related to SMV were observed.

**Conclusion:** In this large pooled analysis co-administration of SMV with commonly prescribed medications with known or potential PK interactions with SMV was feasible and resulted in few cases of adjustments of concomitant medications.

**Abstract: P_36**

**Treating the “untreatable”: Adjusted doses of daclatasvir with the anti-epileptic drug carbamazepine (HepNED study 003)**

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**Background and Aims:** Drug-drug interactions between direct-acting antivirals (DAAs) and co-medication occur frequently. They have clinical consequences because this necessitates dose modification, intensified monitoring and/or drug substitution. The anti-epileptic drug carbamazepine, which is a strong inducer of CYP450 enzymes and membrane transporters, may be an exception to this rule because it may decrease exposure of DAAs such as daclatasvir. In rare cases, patients and or neurologists are unable to stop carbamazepine and there are currently no DAA regimens that can be combined with carbamazepine. We hypothesize that treatment with sofosbuvir (SOF) and an adjusted dose of daclatasvir (DAC) plus intensive pharmacokinetic (PK) monitoring could be an effective approach in these difficult to treat patients.

**Methods:** This is an ongoing cohort of HCV infected patients referred to us because of carbamazepine treatment that cannot be stopped. Patients have intensive PK monitoring with dose-adaptation as appropriate.

**Results:** We currently have intensive PK data on three patients. The first patient was a treatment-naive 56-year-old male with GT 1, METAVIR F0, treated with 12 weeks of standard dose SOF + DAC 60 mg twice daily (BID) who achieved
sustained virologic response (SVR). The patient had a Cmax of 0.46 mg/L and a CLast of 3.9mg/L. The AUC0-24 was 4.72 h*mg/L. The second patient was a 71-year-old male, pretreated with peg-interferon and ribavirin, HCV GT1b, METAVIR F3 who started on standard dose SOF + DAC 60 mg BID. After PK evaluation showed suboptimal DAC levels (Cmax: 0.37 mg/L; CLast: 0.093 mg/L; AUC0-24: 4.41 h*mg/L), therefore the DAC dose was increased to 60 mg trice daily (TID) and PK evaluation was repeated and judged adequate (Cmax: 0.15 mg/L; CLast: 0.035 mg/L; AUC0-24: 1.48 h*mg/L). He is now on a 24-week course and SVR results are pending. The third patient is a 45-year treatment-naïve patient HCV GT3a with METAVIR F4 who started standard dose SOF + DAC 60 mg TID + ribavirin. He is also on a 24-weeks course and SVR results are pending. The patient had a Cmax of 0.32mg/L, Clast of 0.101mg/L, and an AUC0-24 of 3.90 h*mg/L.

Conclusions: This cohort study using an adaptive dosing strategy demonstrates the feasibility of studying DAA combinations with the contra-indicated drug carbamazepine. We invite physicians to contact us at IDPharmacology@radboudumc.nl if they have HCV infected patients on antiepileptic therapy who would benefit from this intensive PK approach.

Abstract: P_37

The Effect of Increased Gastric pH on the Bioavailability of Extended Release Tablet of Fostemsavir in Healthy Subjects

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Background: Fostemsavir is a prodrug of temsavir, a first-in-class attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into host CD4+ T cells. Fostemsavir has been developed as an extended-release (ER) tablet. This study was conducted to evaluate the effect of increased gastric pH on the bioavailability of an ER tablet of fostemsavir using the same dose and formulation as employed in the ongoing Phase III clinical trial.

Methods: AI438071 (NCT02666053) was a Phase I, open-label, randomized, single-dose, 3-treatment, 3-period, crossover study in 24 healthy male and female subjects. Eligible subjects received a single ER oral dose of 600 mg fostemsavir either fasted, within 5 minutes of completing a high-fat meal (results not shown), or approximately 2 hours after a single oral dose of 40 mg famotidine in a randomized crossover fashion. Serial blood samples were collected for 72 hours post-dose following fostemsavir dosing in each period. Plasma concentrations of temsavir were quantified by validated LC/MS/MS methods. PK parameters were derived by noncompartmental methods. Geometric mean ratios (GMRs) and 90% confidence intervals (CI) were derived using linear mixed-effects models. Adverse events (AEs) were monitored throughout the study.

Results: Twenty-four healthy subjects were randomized, received study drug and completed the study. Compared to administration of fostemsavir alone under fasted conditions, Cmax and AUC(0-inf) of temsavir were similar to when fostemsavir was administered fasted at approximately 2 hours after a single oral dose of 40 mg famotidine (AUC(0-inf) GMR: 1.039, 90% CI: 0.867 to 1.245; Cmax GMR: 1.011, 90% CI: 0.845 to 1.208). The 90% CIs of Cmax and AUC were contained within the bioequivalence boundaries of 80-125%. Temsavir C12 was reduced by approximately 10% (GMR: 0.903; 90%CI: 0.636 to 1.282) when dosed after famotidine compared to alone under fasted conditions. The median Tmax and mean half-life were unchanged (Tmax: 2 hours; half-life: 11 hours, with or without famotidine). There were no deaths, serious AEs, or discontinuations in the study.

Conclusion: Administration of a single ER oral dose fostemsavir under increased gastric pH conditions did not affect the pharmacokinetics of temsavir in healthy subjects.
Abstract: P_38

Lack of clinically significant pharmacokinetic interaction between the 3-DAA combination of AL-335, odalasvir and simeprevir for the treatment of chronic HCV infection and an oral contraceptive containing ethinylestradiol and drospirenone

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Background: The combination of 3-direct acting antivirals (3-DAA), AL-335 (uridine nucleotide analog NS5B polymerase inhibitor), odalasvir (ODV; NS5A protein inhibitor) and simeprevir (SMV; NS3/4A protease inhibitor) is under investigation for the treatment of chronic hepatitis C virus (HCV) infection. Here, an oral contraceptive [OC] containing 3 mg drospirenone and 0.02 mg ethinylestradiol (EE) as betadex clathrate was administered with the 3-DAA combination.

Methods: This open-label, Phase I study investigated the effect of steady-state concentrations of both AL-335 and ODV as single agents, and the combination of AL-335, ODV and SMV on the single-dose pharmacokinetics (PK) of drospirenone and EE. A single-sequence trial was performed in 24 healthy, female subjects. All subjects received a single dose of OC on Day 1 followed by AL-335 800 mg once daily (QD) on Days 5−7. On Day 7, a single dose of OC was coadministered with AL-335. ODV 25 mg QD was administered on Days 12−25 and on Day 25 a single dose of OC was coadministered with ODV. On Days 26−32 the 3-DAA combination (ODV 25 mg QD, AL-335 800 mg QD and SMV 75 mg QD) was administered as single agents. On Day 32, a single dose of OC was coadministered with the 3-DAA combination. Full PK profiles for drospirenone and EE were determined on Days 1 (OC alone), 7 (OC in the presence of AL-335), 25 (OC in the presence of ODV) and 32 (OC in the presence of the 3-DAA combination) using a validated LC-MS-MS method. PK parameters were calculated using non-compartmental analysis. AL-335, ODV and SMV were measured at tmax to confirm exposure. Safety and tolerability were monitored throughout.

Results: All subjects completed the study. Drospirenone PK profiles were not affected by coadministration with AL-335 or ODV as single agents or with the 3-DAA combination. The least squares means (LSM) (90% confidence interval [CI]) for Cmax and AUClast for drospirenone were 1.08 (0.94−1.23) and 1.09 (1.03−1.15) in the presence of AL-335 alone, 1.07 (0.94−1.22) and 1.01 (0.96−1.07) in the presence of ODV alone, and 1.09 (0.96−1.25) and 1.14 (1.08−1.21) in the presence of the 3-DAA combination, respectively.

Conclusion: The 3-DAA combination comprising AL-335, ODV and SMV had no effect on the PK profile of drospirenone and a mild, clinically insignificant increase in EE exposure was observed. The coadministration was safe and well-tolerated. Systemic hormonal OCs can be used concomitantly with the 3-DAA combination for the treatment of chronic HCV infection.
Abstract: P_39

Doravirine Does Not Have a Clinically Meaningful Pharmacokinetic Interaction with Ledipasvir/Sofosbuvir (Harvoni®)

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Background: Approximately 25% of HIV infected individuals are coinfected with HCV. Since medications to treat HIV and HCV may have clinically significant drug-drug interactions (DDI), it is important to evaluate the DDI potential of these medications. Doravirine is a novel, potent HIV-1 non-nucleoside reverse transcriptase inhibitor eliminated primarily by CYP3A-mediated metabolism. Harvoni® is a once-daily, oral, fixed-dose combination of ledipasvir (90 mg), an inhibitor of the non-structural-5A protein, and sofosbuvir (400 mg), an inhibitor of HCV NS5B RNA-dependent RNA polymerase, for the treatment of chronic hepatitis C genotype 1, 4, 5, or 6 infection. Doravirine is a weak BCRP inhibitor and may increase the exposure of BCRP substrates such as ledipasvir and sofosbuvir by inhibiting gut BCRP. Doravirine is a P-gp substrate and although P-gp does not appear to have a significant involvement in the disposition of doravirine, ledipasvir could potentially affect its PK. A two-way DDI study of doravirine with ledipasvir/sofosbuvir was conducted in healthy subjects to inform coadministration in HIV/HCV coinfected individuals.

Materials and Methods: This was an open-label, single dose, 3-period randomized crossover study in healthy males and females aged 25 to 60. Treatments were a single dose of 100 mg doravirine, a single dose of 90 mg ledipasvir/400 mg sofosbuvir, or all three drugs coadministered. Plasma PK samples were collected for evaluation of doravirine, ledipasvir, sofosbuvir and its metabolite GS 331007. A linear mixed-effects model was used for the analysis of the natural log (ln)-transformed AUC0-inf, Cmax, and C24 and evaluated separately using a linear mixed effects model with fixed effects terms for treatment and period. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each subject.

Results: Fourteen subjects were enrolled (2 female, 12 male); all subjects completed the study. The PK of all four analytes was not meaningfully altered by coadministration of doravirine with ledipasvir/sofosbuvir. For the comparison of (doravirine + ledipasvir/sofosbuvir) / (ledipasvir/sofosbuvir alone), the geometric mean ratios (GMRs) (90% confidence intervals (CIs)) for ledipasvir AUC0-inf and Cmax were 0.92 (0.80, 1.06) and 0.91 (0.80, 1.02), respectively; for sofosbuvir the GMRs (90% CI) for AUC0-inf and Cmax were 1.04 (0.91, 1.18) and 0.89 (0.79, 1.00), respectively; and for GS-331007, the GMRs (90% CI) for AUC0-inf and Cmax were 1.03 (0.98, 1.09) and 1.03 (0.97, 1.09), respectively. For the comparison of (doravirine + ledipasvir/sofosbuvir) / (doravirine alone), the GMRs (90% CIs) for doravirine AUC0-inf, Cmax, and C24 were 1.15 (1.07, 1.24), 1.11 (0.97, 1.27), and 1.24 (1.13, 1.36), respectively. Six subjects (43%) reported ≥1 AE during treatment. Coadministration of all three drugs was generally well tolerated.

Conclusions: There was no meaningful effect on doravirine, ledipasvir, sofosbuvir or GS-331007 PK when doravirine and ledipasvir/sofosbuvir were coadministered. The results of this study suggest that doravirine and ledipasvir/sofosbuvir may be co-administered in patients coinfected with HIV and HCV without dose adjustment.

Note: This abstract is related to separate abstract “Doravirine Does Not Have a Clinically Meaningful Pharmacokinetic Interaction with Elbasvir Plus Grazoprevir”.

Reviews in Antiviral Therapy & Infectious Diseases 2017_5
Abstract: P_40

Lack of Pharmacokinetic Drug-Drug Interaction between Norgestimate/Ethinyl Estradiol and Sofosbuvir/Velpatasvir/Voxilaprevir

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Background: A once-daily fixed-dose combination of sofosbuvir (SOF; pan-genotypic nucleotide analog HCV NS5B inhibitor), velpatasvir (VEL; pan-genotypic HCV NS5A inhibitor), and voxilaprevir (VOX; pan-genotypic HCV NS3/4A protease inhibitor) is being developed for the treatment of chronic HCV infection. Since HCV-infected female patients on oral hormonal contraceptives (OC) may be treated with SOF/VEL/VOX, this study evaluated the potential for a drug-drug interaction between SOF/VEL/VOX and norgestimate/ethinyl estradiol (NGM/EE, Ortho Tri-Cyclen Lo®), a representative hormonal OC.

Methods: This was an open-label, fixed-sequence, Phase 1 study in healthy (HCV-uninfected) female subjects. Subjects not using NGM/EE were enrolled into Part A (lead-in) and received NGM/EE for 1 menstrual cycle prior to enrollment into Part B of the study. Subjects on NGM/EE could enroll into Part B directly. In Part B, subjects received NGM/EE for 2 sequential cycles. In cycle 1, NGM/EE was administered alone. In cycle 2, SOF/VEL/VOX (400/100/100 mg) + VOX (100 mg) was coadministered with NGM/EE for 7 days (Days 8-14) of the cycle, where the largest change in follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH) would be observed if contraceptive efficacy were compromised. The additional 100 mg of VOX was administered to the healthy subjects to approximate systemic VOX exposures observed in the HCV-infected population. Safety assessments were conducted throughout the study. Plasma concentrations of norgestimate, norelgestromin (NGMN), norgestrel (NG), EE, SOF and GS-331007 (predominant circulating metabolite), VEL, and VOX were analyzed on Day 14 of each cycle (as appropriate). Geometric least squares mean ratios (GLSM) and 90% confidence intervals (CIs) for AUCtau, Cmax and Ctau were estimated with lack of PK alteration bounds of 70 to 143%. Quantitation of pharmacodynamic (PD) markers, including follicle-stimulating hormone (FSH; Day 14), luteinizing hormone (LH; Day 14), and progesterone (Day 21) was conducted in both cycles.

Results: Fifteen subjects were enrolled in the lead-in part of the study and all 15 subjects continued to and completed Part B of the study. Study treatments were generally well tolerated. Headache was reported at similar frequencies during both treatments (each 40%), while gastrointestinal disorders were more frequently reported during treatment with NGM/EE + SOF/VEL/VOX (67%) compared with NGM/EE alone (20%). All treatment-emergent AEs were mild (Grade 1) or moderate (Grade 2).

Similar systemic exposures (AUCtau, Cmax, and Ctau) of NGMN and NG (active metabolites of NGM) and EE were observed following administration of NGM/EE alone or in combination with SOF/VEL/VOX. The 90% CIs of the GLSM ratios for AUCtau, Cmax, and Ctau of NGMN, NG, and EE were all within the lack of PK alteration boundaries of 70% to 143%. Norgestimate was not quantifiable for all subjects at most time points. FSH, LH, and progesterone values were similar in both cycles.

Conclusion: Coadministration of SOF/VEL/VOX with NGM/EE was safe and well tolerated. Based on PK and PD results, no loss in contraceptive efficacy is expected upon administration of oral contraceptives containing NGM/EE with SOF/VEL/VOX.
Abstract: P_41

No clinically significant interaction of the proton pump inhibitor omeprazole with the components of MK-3682B

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Background: Grazoprevir (GZR, MK-5172), ruzasvir (RZR, MK-8408), and uprifosbuvir (UPR, MK-3682) are novel, small molecule inhibitors of different HCV proteins and enzymes being developed as an all-oral fixed-dose combination (FDC) tablet MK-3682B for the treatment of chronic hepatitis C virus (HCV) infection. A real-world observational cohort of ~1600 HCV-infected patients (HCV-TARGET) found that approximately 40% in the cohort was on a chronic acid-reducing medication. Therefore, it is important to determine whether acid-reducing agents have the potential to alter the pharmacokinetics of the MK-3682B FDC. This study evaluated the effect of omeprazole on the single-dose pharmacokinetics (PK) of MK-3682B (GZR/RZR/UPR FDC) when administered to healthy adult subjects.

Materials & Methods: This was a 2-period, fixed-sequence, open-label drug-interaction study. On Day 1 of Period 1, a single oral dose of MK-3682B (2 x [50 mg GZR/30 mg RZR/225 mg UPR] FDC tablets) was administered. In Period 2, multiple oral once-daily doses of omeprazole (1 x 40 mg omeprazole capsule) were administered for 5 consecutive days; on Day 5, the single oral dose of omeprazole was administered 2 hours prior to a single oral dose of MK-3682B. The washout period was 7 days between the last dose of MK-3682B in Period 1 and the first dose of omeprazole in Period 2. Blood samples were collected for PK analysis of MK-3682B components. PK parameter values were calculated for all analytes by non-compartmental analysis. Geometric mean ratios (GMR) and 90% confidence intervals (CI) were calculated from the log transformed AUC0–∞, AUC0-24, Cmax, and C24 using linear mixed effect modelling. Safety was monitored throughout the study.

Results: 14 healthy male and female subjects were enrolled. Co-administration of omeprazole with MK-3682B did not meaningfully affect the PK of components of MK-3682B. Mean GZR and RZR AUC0–∞ increased ~25%. UPR AUC0–∞, Cmax, and C24 remained unchanged (<5% decrease). Exposures of M6, the major circulating metabolite of UPR, remained unchanged (<10% difference in AUC, Cmax, and C24). The co-administration of omeprazole with MK-3682B in this study was generally well tolerated.

Conclusions: Multiple doses of omeprazole did not meaningfully affect the pharmacokinetics of a single dose of MK-3682B. These results support co-administration of MK-3682B with omeprazole.

Abstract: P_42

Doravirine Does Not Have a Clinically Meaningful Pharmacokinetic Interaction with Elbasvir Plus Grazoprevir

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Background: Approximately 25% of HIV infected individuals are coinfected with HCV. Since medications to treat HIV and HCV may have clinically significant drug-drug interactions (DDI), it is important to evaluate the DDI potential of these medications. Doravirine is a novel, potent HIV-1 non-nucleoside reverse transcriptase inhibitor eliminated primarily by CYP3A-mediated metabolism. ZEPATIER™ is a fixed-dose combination of 50 mg elbasvir, an HCV nonstructural protein 5A inhibitor, and 100 mg grazoprevir, an HCV nonstructural protein 3/4A protease inhibitor, indicated for treatment of
chronic HCV genotype 1 or 4 infection. Based on the elimination pathways of elbasvir and grazoprevir, doravirine was unlikely to affect PK of either drug. Grazoprevir is a weak CYP3A inhibitor with potential to affect doravirine PK. A two-way DDI study of doravirine with elbasvir + grazoprevir was conducted to inform coadministration in HIV/HCV coinfected individuals.

Materials and Methods: This was an open-label, multiple-dose, fixed-sequence study in healthy males and females aged 19 to 64. In Period 1, 100 mg doravirine was administered once daily (QD) for 5 days, followed by a 5 day washout. In Period 2, 200 mg grazoprevir + 50 mg elbasvir was administered QD for 10 days; Period 3 began immediately following Period 2. In Period 3, 100 mg doravirine was coadministered with 200 mg grazoprevir + 50 mg elbasvir QD for 5 days. Plasma PK samples for all drugs were collected following the last dose in each period when all three drugs had reached near steady-state exposures. The dose of grazoprevir was selected to match the PK in HCV-infected individuals at the approved 100 mg dose. The PK (AUC0-24, Cmax, C24) for each analyte was natural log-transformed and evaluated separately using a linear mixed effects model with fixed effects terms for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each subject.

Results: Twelve subjects enrolled (5 female, 7 male); all completed the study. Coadministration of doravirine with elbasvir + grazoprevir did not meaningfully alter the PK of any drug. For the comparison of doravirine + elbasvir + grazoprevir/elbasvir + grazoprevir alone, the geometric mean ratios (GMRs) (90% confidence intervals (CIs)) of elbasvir AUC0-24, Cmax, and C24 for were 0.96 (0.90, 1.02), 0.96 (0.91, 1.01), and 0.96 (0.89, 1.04), respectively, and for grazoprevir they were 1.07 (0.94, 1.23), 1.22 (1.01, 1.47), and 0.90 (0.83, 0.96), respectively. The GMRs (90% CI) of doravirine AUC0-24, Cmax, and C24 for the doravirine + elbasvir + grazoprevir / doravirine alone comparison were 1.56 (1.45, 1.68), 1.41 (1.25, 1.58), and 1.61 (1.45, 1.79), respectively. Six subjects (50%) reported ≥1 adverse event (AE) during treatment. Four (33%) subjects reported a drug related AE. Coadministration of all three drugs was generally well tolerated.

Conclusions: There was no meaningful effect on doravirine, elbasvir or grazoprevir PK when these drugs were coadministered. The results of this study suggest that doravirine and elbasvir + grazoprevir may be co-administered in patients coinfected with HIV and HCV without a dose adjustment.

Abstract: P_43
Daclatasvir (DCV) pharmacokinetics and appropriate dosing in HCV/HIV patients co-administered with antiretroviral drugs

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Background: Due to potential drug-drug interaction, DCV dosing requires different adjustment when co-administered with CYP3A4 inducers [efavirenz (EFV), nevirapine, etravirine (ETV), or strong CYP3A4 inhibitors, mainly with atazanavir/ritonavir (ATV/r). Scanty data or none are currently available on DCV dosing when unboosted atazanavir (ATV), rilpivirine and cobicistat (COBI) boosted regimens are co-administered with international guidelines suggesting a reduced 30 mg dose when the latter is prescribed. Nevertheless available data suggest that main boosting effect is provided by ATV rather than boosting of ritonavir or cobicistat. Aim of our study was to describe DCV pharmacokinetics when co-administered with different antiretroviral drugs (ARVs) in our real-life cohort of HIV/HCV positive patients.

Materials and Methods: HIV/HCV co-infected patients treated with DCV plus sofosbuvir (SOF)
for at least 4 weeks and receiving antiretroviral therapy (ART) were enrolled. DCV was dosed 30 mg with ATV assuming a comparable effect of ATV and ATV/r, 60 mg with ETV, due to lack of data at the time of prescription and 60 mg with RPV. One patient treated with elvitegravir/cobicistat/emtricitabine/tenofovir (E/C/F/TDF) received DCV 60 mg. DCV plasmatic levels (DCVpl) (22±2 hours after last intake) were measured using UPLC-MS/MS validated method and reported as ng/mL. Data are expressed as numbers (percentage) and median (IQR).

**Results:** 44 patients were enrolled: 79.5% males, age 52 (48;54), BMI 25 kg/m2 (20;27). Metavir score was 4, 3 and 1 in 30, 9 and 1 patients respectively. Child-Pugh score was A and B in 98% and 2%, respectively. HCV genotype was 3, 1a and 1b in 35, 4 and 1 respectively. Patients received ART containing following drugs: protease inhibithor (PI) in 18 (7 ATV/r, 3 ATV, 5 DRV/r, 3 LPV/r), RPV in 10, raltegravir or dolutegravir in 12, EFV in 1, ETV in 2. One patient received E/C/F/TDF. Total 233 DCV determinations were obtained. Median DCVpl in study population was 215 ng/ml (118;383). Two patients treated with ETV and DCV 60 mg showed DCVpl 45 ng/mL (42;45), significantly lower (p= 0.018) compared to other patients. DCVpl was 294 ng/mL (62;294) and 225 ng/mL (181;250) in patients treated with ATV and ATV/r, respectively, with no statistical difference between two group considered; DCVpl was 188 ng/mL (60;301) in those receiving RPV without significant statistical difference with those receiving other ARVs. One patient treated with E/C/F/TDF and DCV 60 mg showed DCVpl 415 ng/mL with no statistical difference with other ARVs (p= 0.201) or with DCVpl with ritonavir boosted or unboosted PIs (p= 0.358).

**Conclusions:** This is the first report on DCV exposure in HIV/HCV patients according to different ARV regimens in the clinical setting. Our findings confirm the appropriateness of 30 mg reduced DCV dose not only with ATV/r but also with unboosted ATV and the need to increase DCV to 90 mg when co-administered with ETV without PIs. Moreover, in the first case so far reported of coadministration with E/C/F/TDF, standard 60 mg DCV dose provides adequate DCV levels.

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**Abstract: P_44**

**MK-3682B is not a clinically significant CYP3A inhibitor or inducer**

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**Background and Aims:** Grazoprevir (GZR, MK-5172), ruzasvir (RZR, MK-8408), and uprifosbuvir (UPR, MK-3682) are novel, small molecule inhibitors of different HCV proteins/enzymes that are being developed as an all-oral fixed-dose combination (FDC) tablet MK-3682B for the treatment of chronic hepatitis C virus (HCV) infection. Each component of MK-3682B carries either a known or possible liability of CYP3A inhibition either in the gut and/or liver with no evidence of CYP3A induction potential. This study evaluated the effect of multiple doses of co-administered GZR, RZR, and UPR on the single-dose pharmacokinetics of midazolam, a sensitive CYP3A substrate.

**Methods:** This was an open-label, two-period, fixed-sequence pharmacokinetic (PK) drug interaction study in healthy male and female subjects. On Study Day 1 (Period 1), a single oral dose of 2 mg midazolam was administered. On Study Days 2 to 8 (Period 2), multiple once daily oral doses of two (2) fixed dose combination (FDC) MK-3682B tablets (corresponding to 100 mg GZR, 60 mg RZR, and 450 mg UPR) and one (1) GZR 100 mg tablet were administered for seven (7) days, with co-administration of 2 mg midazolam on Study Day 8. Plasma was collected prior to midazolam administration and at specified time points up to 24 hours after midazolam administration for measurement of midazolam and midazolam 1-OH concentrations. PK parameter values were calculated for both analytes by non-compartmental analysis. Geometric mean ratios (GMR) and 90% confidence intervals (CI) were calculated from the log transformed AUC0-inf.
and Cmax using linear mixed effect modelling. Safety and tolerability were monitored.

Results: 14 healthy male and female subjects were enrolled. Co-administration of MK-3682B with midazolam did not meaningfully affect the PK parameters of midazolam. The GMR and 90% CIs [midazolam co-administered with GZR, RZR, and UPR / midazolam alone] of AUC0-inf and Cmax for midazolam were 1.09 (0.98, 1.20) and 1.00 (0.89, 1.13), respectively, and for midazolam 1-OH were 0.87 (0.80, 0.96) and 0.77 (0.69, 0.87), respectively. Multiple doses of GZR, RZR, and UPR when co-administered with single-dose midazolam were generally well-tolerated.

Conclusions: Steady state co-administration of GZR, RZR, and UPR had no meaningful impact on the PK of the CYP3A substrate midazolam. Data support the co-administration of MK-3682B with other CYP3A substrates without the need for dose adjustment.

Abstract: P_45

Plasma population pharmacokinetics of dolutegravir in HIV-1 infected patients in a real-life setting and impact of drug-drug interactions

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Background: Dolutegravir, as one of the most prescribed integrase inhibitor, is mainly metabolized by UGT1A1 with some contribution of CYP3A4. In HAART regimen, its association with PI or NNRTI, or even rifampin (during tuberculosis co-infection), highlights the potential Drug-Drug Interactions on dolutegravir disposition. The objectives of this analysis were to build a population pharmacokinetics model of dolutegravir in a real-life setting and to evaluate the effects of different co-medications on the pharmacokinetic parameters.

Materials & Methods: A multicenter and observational study was conducted in HIV-1 infected adults receiving dolutegravir containing regimen. Therapeutic Drug Monitoring was performed at least 4 weeks (steady-state) after starting dolutegravir. Time between last drug intake and sampling was recorded. Dolutegravir plasma concentrations was determined using UPLC-MS/MS (LOQ <10ng/mL). A population pharmacokinetic model was developed using
Results: Plasma pharmacokinetics of dolutegravir were adequately described by a linear one compartment model with first order absorption and first order elimination in a cohort of 1,759 patients (median age 51 years [IQR 43-58], 66% men) corresponding to 2,479 samples. Population estimates (RSE%) for CL/F, V/F, ka and absorption lag-time (ALAG) were 0.849L.h\(^{-1}\) (1%), 15.8L (3%), 1.65h\(^{-1}\) (26%) and 0.328h (43%), respectively. Inter-individual variabilities expressed as CV% (RSE%) of CL/F, V/F, ka and ALAG were 26.6%(4%), 14.2%(62%), 125%(21%) and 175%(20%), respectively. Modified CL/F(L.h\(^{-1}\)) with associated drugs were: DRVQD 1.050, ATVr 0.525, ATV400 0.483, ATV300 0.554, DRVBiD 1.270, EFV 2.11, NVP 1.49, ETR 1.660 and RIF 3.080. The estimated half-lives (%modification/REF) were: REF 14.1h, DRVQD 11.4h(-19%), ATVr 22.7h(+61%), ATV400 24.7h(+75%), ATV300 21.5h(53%), DRVBiD 9.4h(-33%), EFV 5.7h(-60%), NVP 8.0h(-43%), ETR 7.2h(-49%), RIF 3.9h(-73%). No effect of RPV or ETrr was found on CL/F. Finally, no effect of the associated drugs was reported on V/F.

Conclusions: Our population model successfully described dolutegravir plasma pharmacokinetics and the interaction between dolutegravir and major associated drugs, and were consistent with historical data. The decrease of dolutegravir clearance associated with atazanavir and its increase with darunavir (regardless of the dosing regimen) confirm the previous findings. As expected, the association with strong or mild CYP inducers significantly affected dolutegravir clearance.

Abstract: P_46

Pharmacokinetic interaction between ledipasvir/sofosbuvir and etravirine containing regimen

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Background: Treatment of HCV-HIV co-infection raises the question of drug-drug interaction between DAAs and ARV. Ledipasvir/sofosbuvir is one of the recommended single-tablet-regimen for 1 and 4 genotype HCV. The use of etravirine is less predominant, however remains interesting in dual maintenance therapy or in patients harboring reverse transcriptase resistance associated substitutions preventing the use of simpler drugs. Respective ledipasvir and etravirine disposition pathways allow its association among HCV-HIV co-infected adults, considering that the P-gp and BCRP transporters appear to be their only known common ties. The
objective of this analysis was to look for a possible interaction between ledipasvir and etravirine by two different approaches: comparison of ledipasvir plasma concentrations and non-linear mixed effect modeling method.

**Materials & Methods:** Multicenter and observational study was conducted in HCV-infected and HCV-HIV co-infected adults receiving ledipasvir/sofosbuvir (90/400mg QD) and etravirine (daily 400mg) containing regimen (boosted PI excluded). Time between last drug intake and sampling were recorded. Steady-state (at W4) average ledipasvir plasma concentrations (CLDV) was determined using UPLC-MS/MS (LOQ <10ng/mL). Results are presented as median (IQR25-75%) and compared using Mann-Whitney tests between patients receiving etravirine (LDV-ETR) or not (LDV). Then, a population pharmacokinetic model (non-linear mixed effect modeling approach) was developed using SAEM algorithm (Monolix Suite 2016R1). Effect of etravirine on ledipasvir pharmacokinetic parameters was assessed on each model parameter following an ascending procedure.

**Results:** 141 patients were eligible (median age 53 years old [IQR 48-58], 75% men), including 17 HCV-HIV co-infected adults. CLDV were significantly higher in LDV group than in LDV-ETR: 262 ng/mL (162-468; n=151 samples) and 119 (81-214; n=25 samples), respectively (p<0.0001). Ledipasvir plasma pharmacokinetics were adequately described by a linear one compartment model with first order absorption and first order elimination. Population estimates for elimination rate constant (kel) and V/F, (RSE %) were 0.031h⁻¹ (25%), 360L (25%), respectively. Due to sparseness of data, the absorption rate constant (ka) and absorption lag-time (ALAG) were fixed at 0.32h⁻¹ and 0.42h, respectively as previously published (German P et al., AASLD 2014). Inter-individual variabilities expressed as CV% (RSE%) of kel and V/F were 26.6%(4%) and 14.2%(62%), respectively. Modified kel with etravirine was 0.059h⁻¹ corresponding to an elimination half-life of 11.5h (versus 23.0h in LDV group) (p<0.001). No effect of ETR was found on V/F.

**Conclusions:** Using both descriptive and population modeling method, etravirine presented similar and significant effect on ledipasvir pharmacokinetics. Indeed, a 50% decrease of CLDV and 50% decrease of elimination half-life were observed in LDV-ETR group, mediated through efflux transporters (P-gp or BCRP) interaction. Despite the magnitude of the interaction, etravirine might be coadministered with ledipasvir/sofosbuvir without any dose adjustment, due to the long half-life of phosphorylated metabolites.

**Abstract: P_47**

Lack of effect of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate on glomerular filtration rate (GFR) in HIV-infected patients


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**Introduction:** Cobicistat (COBI), a pharmacokinetic (PK) enhancer and component of the single tablet regimen elvitegravir/COBI/emtricitabine /tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF; Striibild®) reversibly inhibits the renal transporters, multidrug and toxin extrusion protein 1 (MATE1) and organic cation transporter 2 (OCT2), which play a role in the proximal tubular secretion of creatinine in the kidney. In healthy subjects, COBI was shown to increase serum creatinine without affecting actual glomerular filtration rate (aGFR). This study in HIV-infected patients assessed glomerular function before and during treatment with EVG/COBI/FTC/TDF, ritonavir-boosted atazanavir (ATV+RTV)+FTC/TDF, or efavirenz (EFV)/FTC/TDF, versus the non-COBI, non-TDF containing regimen ATV+RTV+abacavir/ lamivudine (ABC/3TC).

**Materials & Methods:** This was a randomized, open-label, parallel, 4-group (n=16/group) study that assessed glomerular function via determination of aGFR as measured by iohexol
clearance before and during treatment with EVG/COBI/FTC/TDF, ATV+RTV+FTC/TDF, EFV/FTC/TDF, or ATV+RTV+ABC/3TC in treatment-naive, HIV-infected adults with baseline eGFR ≥70 mL/min. Actual and estimated GFR (eGFR) were determined at baseline (Week -1 and Day 1), and during treatment (Weeks 4, 8, 16, and 24). Intensive PK sampling was performed at on-treatment visits. Statistical comparisons of aGFR and eGFR (by Cockcroft-Gault [CG] or Modification of Diet in Renal Disease [MDRD]) while on treatment (test) relative to baseline (reference) within each treatment and between treatments at any postbaseline visit were made using geometric mean ratios (GMR) and associated 90% confidence intervals (CI) with a no-effect boundary of 80-125%. PK parameters of COBI, RTV and the TDF-metabolite TFV were compared to historical data. Safety and efficacy were assessed throughout the study.

**Results:** There was a maximum change in eGFR_CG from baseline of -9.3, -8.8, -2.8 and -5.0 mL/min/1.73 m² in the EVG/COBI/FTC/TDF, ATV+RTV+FTC/TDF, EFV/FTC/TDF, and ATV+RTV+ABC/3TC groups, respectively, between Weeks 4 and 16. At Week 24, change from baseline in mean eGFR_CG was −4.7, +2.2, -1.0 and +0.2 mL/min/1.73 m² in the EVG/COBI/FTC/TDF, ATV+RTV+FTC/TDF, EFV/FTC/TDF, and ATV+RTV+ABC/3TC groups, respectively. Actual GFR was stable from Weeks 4 to 24. At Week 24, EVG/COBI/FTC/TDF had no effect on aGFR; the GMR and associated 90% CI were within the prespecified no-effect boundary (GMR% [90% CI]: 93.8 [86.7, 101.4]). ATV+RTV+FTC/TDF reduced aGFR by 7.4% (90% CI: [79.9, 107.4]). The 90% CIs of the GMRs for EFV/FTC/TDF (GMR% [90% CI]: 115.1 [94.7, 139.9]) and ATV+RTV+ABC/3TC (GMR% [90% CI]: 111.2 [89.2, 138.8]) exceeded the upper boundary.

None of the changes in aGFR were considered clinically relevant. All treatments were generally well tolerated and most adverse events (AEs) were mild.

**Conclusions:** Consistent with COBIIs inhibitory effect on tubular secretion of creatinine through MATE1 and OCT2 inhibition, administration of EVG/COBI/FTC/TDF affected the estimated GFR (calculated using serum creatinine) and did not impact the actual GFR (as measured by iohexol clearance) in HIV-infected patients. These results were expected based on previous data in healthy subjects.

**Abstract: P_48**

**Small increase in dolutegravir trough, but equivalent total exposure with simeprevir**

**Background:** Treatment of HIV/hepatitis C virus (HCV) coinfected patients necessitates minimizing unfavorable drug interactions. Dolutegravir (DTG), an HIV integrase inhibitor, and simeprevir (SMV), an HCV NS3/4A protease inhibitor, have the potential to interact as DTG is a P-glycoprotein (P-gp), uridine glucuronosyl transferase 1A1 (UGT1A1), and CYP3A substrate and SMV has been shown to mildly inhibit these. The primary objective of this study was to compare DTG and SMV pharmacokinetics (PK) when given alone vs. in combination.

**Methods:** This was a prospective, single center, open-label, three arm, three-period, crossover study to evaluate the drug interaction potential between DTG and SMV in healthy volunteers ages 18-60 years. Subjects received (1) SMV 150mg once daily for 7 days, (2) DTG 50mg once daily for 7 days, and (3) SMV 150mg once daily plus DTG 50mg once daily for 7 days with ≥14-day “washout” between sequences. Subjects were randomized to sequence order. Intensive PK sampling was performed on day 7 of each sequence following observed dosing and a standardized meal. SMV and DTG were quantified using a validated, simultaneous LC/MS/MS assay. PK parameters were determined using non-compartmental methods.
Abstract

log-transformed, and compared using paired t-tests. There were no adjustments for multiple comparisons. Bioequivalence for area under the curve (AUCtau) and maximum concentration (Cmax) were also assessed. Bioequivalence was declared when the 90% CI for the geometric mean ratio (GMR) of combination vs. individual drug fell within 80%-125%.

Results: Twenty-four subjects completed all 3 sequences (15 female, 21 Caucasian/3 Hispanic, mean age 35 yrs and weight 69.4 kg). DTG trough was increased 24% (p=0.0003) with SMV. DTG AUCtau was increased 15% (p=0.002), but was deemed bioequivalent as the 90% CI for the GMR was 107%-123%. DTG Cmax was bioequivalent (GMR 106%; 90% CI 100%-114%). DTG Tmax increased by 0.5 hours while DTG CL/F decreased by ~100mL/hr. SMV AUCtau (GMR 99%; 90% CI 82%-119%) and Cmax (GMR 105%; 90% CI 88% to 125%) were bioequivalent with DTG. There were no significant differences in any other SMV PK parameters with DTG. There were no discontinuations due to adverse events and all adverse events were mild to moderate in severity. The most common clinical adverse events were gastrointestinal upset and headache reported by 7/24 (29.2%) of participants. The most common laboratory abnormality was a decline in creatinine clearance (CrCl) due to an increase in serum creatinine by an average of 18.2 mL/min (average baseline CrCl was 113.8 mL/min for all participants) which occurred in 6/24 (25%) of participants while taking DTG, consistent with DTG’s inhibition of renal creatinine transporters.

Conclusions: DTG trough was increased slightly with SMV, but AUC was bioequivalent. The delayed DTG Tmax suggests SMV may inhibit P-gp in the gut, but this alone cannot account for the increased DTG trough so there may be additional inhibition of hepatic clearance via either UGT1A1 or CYP3A. Despite the increase in trough, DTG concentrations were well within the range with established safety data. Thus, SMV and DTG can be safely co-administered.

Abstract: P_49

Evaluation of Drug-Drug Interaction Potential between Sofosbuvir/Velpatasvir and Atorvastatin

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Introduction: Sofosbuvir/velpatasvir (SOF/VEL, Epclusa®) 400/100 mg is an approved, pan-genotypic, fixed dose combination for the treatment of chronic HCV infection. Sofosbuvir does not inhibit or induce CYP450 enzymes or drug transporters. Velpatasvir does not affect CYP450 enzymes; however, VEL inhibits OATP, P-gp, and BCRP transporters. Atorvastatin is a substrate of CYP3A, and atorvastatin and its metabolites are substrates of the drug transporters OATP3A, and atorvastatin and its metabolites are substrates of the drug transporters OATP and/or P-gp. As SOF/VEL inhibits drug transporters, but not CYP3A, a modest drug interaction (<2-fold) was anticipated upon coadministration with SOF/VEL. This Phase 1 study characterized the drug-drug interaction potential between SOF/VEL and atorvastatin.

Methods: This was an open-label, randomized, two-way crossover study in healthy subjects. Subjects received a single dose of atorvastatin (40 mg) alone (Treatment A), or in combination with multiple-dose SOF/VEL (400/100 mg; Treatment B). PK sampling was performed for 72 hours following administration of atorvastatin, and safety was assessed throughout the study. Geometric-least squares means ratios (GLSM) and 90% confidence intervals (90%CI) were estimated for atorvastatin, and were compared against pre-specified lack of PK alteration boundaries of 70 to 143% (AUC) and 50-200% (Cmax). Exploratory PK analyses were performed for atorvastatin metabolites (atorvastatin lactone, o-hydroxyatorvastatin, p-hydroxyatorvastatin), SOF and its metabolites (GS-566500 and GS-331007) and VEL.
Results: The study enrolled 26 subjects into 2 treatment sequences. All subjects completed study treatments, but 1 subject was lost to follow up. The mean (range) age of subjects was 31(24-44) years; 15 (58%) subjects were male, 14 (54%) were black or African American, and 21 (81%) were of non-Hispanic ethnicity.

Study treatments were generally well tolerated; 3 (12%) and 4 (15%) of subjects experienced an AE during Treatments A and B, respectively. No serious or severe AEs occurred, and no Grade 4 AEs occurred. Grade 1 AEs of arthralgia (N=2 [8%] during Treatment B) and nausea (N=1[4%] and N=3 [12%] during Treatments A and B, respectively) occurred; nausea was considered related to study treatment for 1 subject in each of Treatments A and B. One Grade 2 AE of myalgia occurred (related to study treatment; Treatment A). One Grade 3 laboratory abnormality (occult blood in the urine; Treatment B) was assessed as not clinically significant by the investigator, and occurred in a patient who reported no symptoms or AEs throughout the study. No treatment emergent laboratory abnormalities of creatine phosphokinase (CPK) occurred during this study.

Co-administration of SOF/VEL with atorvastatin resulted in higher atorvastatin AUC (↑59%) and Cmax (↑68%); similarly higher exposure of atorvastatin metabolites was also observed (o-hydroxyatorvastatin AUC: ↑37%, Cmax: ↑11%; p-hydroxyatorvastatin AUC: ↑77%, Cmax: ↑41%; atorvastatin lactone AUC: ↑60%, Cmax: ↑82%). These results are consistent with inhibition of OATP and P-gp by VEL. Steady-state exposures of SOF, its metabolites and VEL were similar to historical values.

Conclusions: Consistent with the previous characterization of VEL as an inhibitor of OATP and P-gp transporters, co-administration of SOF/VEL resulted in a ~60% increase in exposure of atorvastatin. All study treatments were well-tolerated.

Abstract: P_50

Lack of Clinically Relevant Effect of Bictegravir on Metformin Pharmacokinetics and Pharmacodynamics

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Background: Bictegravir (BIC) is a novel, potent, HIV integrase strand transfer inhibitor (INSTI) with a high barrier to resistance and low potential for DDIs. BIC is currently in development for treatment of HIV-1 infection coformulated with emtricitabine (FTC, F)/ and tenofovir alafenamide (TAF) as a single tablet regimen (STR). Metformin is first-line therapy in diabetic HIV-infected patients. In vitro, BIC inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1), which are known to contribute to the disposition of metformin. This study evaluated the effect of BIC on the pharmacokinetics (PK) and pharmacodynamics (PD) of metformin following coadministration of the B/F/TAF STR.

Materials and Methods: This was a Phase 1, blinded, placebo-controlled, multiple-dose, 2-period, crossover study in healthy subjects. Thirty-two subjects were randomized in a 1:1 ratio to receive either B/F/TAF or placebo once daily for 9 days followed by a 3 days of washout. Following 4 days of B/F/TAF or placebo, subjects received 850 mg metformin at 12 hours postdose of B/F/TAF or placebo, and 500 mg twice daily for an additional 4 days. The evening dose of metformin on the last day was not given. Plasma and urine PK of metformin were assessed on the last day of treatment (Days 9 and 21 for B/F/TAF or placebo). Oral glucose tolerance test (OGTT) was performed before metformin (Days 5 and 17) and after the last dose of metformin (Days 9 and 21). Metformin PD endpoints including plasma glucose, active Glucagon-Like Peptide 1 (GLP-1) and lactate following OGTT were assessed. Safety was monitored throughout the study. Geometric least-squares mean (GLSM)
ratios and 90% confidence intervals (CIs) for metformin plasma exposure were calculated for B/F/TAF vs placebo treatments. Comparisons of PD responses within a treatment (before vs after metformin) as well as comparisons between treatments (B/F/TAF vs placebo) were evaluated using the nonparametric Wilcoxon signed-rank test (p > 0.05 denotes non-significance).

Results: Metformin plasma exposure (AUCtau) was increased by approximately 39% (%GLSM ratio [90% CI]: 139 [131, 148]) when coadministered with B/F/TAF relative to placebo. Median plasma t1/2 was similar between B/F/TAF (6.36 hrs) and placebo (7.06 hrs) treatments. Metformin renal clearance (CLR) decreased approximately 31% when coadministered with B/F/TAF vs placebo. Following metformin administration, statistically significant reduction of plasma glucose, and increase of plasma active GLP-1 and lactate levels relative to baseline were observed (p < 0.001) confirming their utility as PD endpoints for metformin. Importantly, clinically-relevant PD responses were not statistically different when metformin was administered with B/F/TAF vs placebo (p >0.05). Coadministration of metformin with B/F/TAF was generally safe and well tolerated.

Conclusions: Inhibition of renal transporters OCT2 and/or MATE1 by BIC led to a modest increase of metformin plasma exposure following coadministration with B/F/TAF; however, the PD characteristics of metformin, such as glucose reduction, and active GLP-1 and lactate increases after OGTT were not significantly affected by B/F/TAF relative to placebo. Based on these findings, prospective dose adjustment or dose restriction of metformin is not required when it is coadministered with B/F/TAF.

Abstract: P_51

Pharmacokinetics of generic Ritonavir tablets with low-dose Atazanavir in HIV-infected Asian adults

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Background: Low-dose atazanavir (ATV) / ritonavir (RTV) (200/100 mg/day) has shown non-inferior results to standard dose ATV/ RTV (300/100 mg/day) in HIV-infected Thai adults. Generic RTV tablets manufactured by Thai Government Pharmaceutical Organization can be stored at room temperature which offered a more convenient alternative than RTV soft gel capsules (RTV-SGC). Here we evaluated the pharmacokinetics of generic RTV tablet as a part of boosted low-dose ATV-based antiretroviral regimens in virologically suppressed patients.

Methods: Sixteen treatment-experienced HIV-infected Thai adults with HIV-RNA < 50 copies/ml who were currently treated with ATV 200 mg / RTV-SGC 100 mg with 2NRTIs were partly enrolled to the prospective, open-label, 48-week single-arm study (N=100). RTV-SGC was switched to generic RTV 100 mg/tablet and intensive steady-state 24-hour pharmacokinetic profiles were performed at week 4 by LC-MS/MS method. CD4, HIV-RNA, ALT, total bilirubin, direct bilirubin, serum creatinine (Cr), and CrCl estimated by Cockcroft-Gault equation were performed at week 24 and 48.

Results: Totally 15 participants (60% female) were included in this analysis (1 excluded due to omeprazole used); median age was 44.5 (range: 31.1-50) years, body weight was 62 kg. The geometric mean (95% CI) of ATV concentrations: AUC_{tau}^{0-24 h}, C-max, and C_{trough} were 28.8 mg/L*h (95%CI 22.5-36.8), 3.0 mg/L (95%CI 2.4-3.8), and 0.46 mg/L (95%CI 0.3-0.7),
respectively. Whereas, the geometric mean (95% CI) of generic RTV concentrations: AUC₀-₂₄h, C-max, and Ctrough were 12.7 mg*L⁻¹*h⁻¹ (95%CI 10.5-15.4), 1.8 mg/L (95%CI 1.5-2.2), and 0.08 mg/L (95%CI 0.06-0.1), respectively. Thirteen participants (87%) had ATV AUC₀-₂₄h above target level (>15 mg*L⁻¹*h⁻¹) and 14 participants (93%) had ATV Ctrough above target level (>0.15 mg/L). At week 48, all had HIV-RNA < 50 copies/ml. The median (IQR) changed from baseline of safety lab were following: ALT +3 (0, +8) IU/L, total bilirubin -0.2 (-1.3, +0.2) mg/dL, direct bilirubin 0 (-0.2, 0) mg/dL, serum Cr +0.01 (-0.02, +0.07) mg/dL, and CrCl -1.6 (-4.3, +6.4) mL/min. No participants had total bilirubin concentration of grade 3 or higher toxicity (≥3.12 mg/dL). No severe adverse event was reported.

Conclusion: Generic RTV tablets with low-dose ATV showed adequate levels and had good efficacy and safety at week 48. These findings suggested that low-dose ATV can be safely used with generic RTV tablet among HIV-infected Thai adults.

Abstract: P_52

Pharmacokinetics, pharmacology, preclinical safety and clinical efficacy of nucleic acid polymers in chronic HBV and HDV infections

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Nucleic acid polymers (NAPs) are novel antiviral agents currently in clinical development for the treatment of chronic HBV and HDV infections. Several proof-of-concept clinical trials have demonstrated that NAPs reliably clear serum HBsAg and HDV RNA in different patient populations, which appears to facilitate the ability of immunotherapy to achieve functional control over HBV and HDV infection.

The inactivity of NAPs in rodent models of HBV infection or the lack of post-entry effects in tissue culture systems have hampered mechanistic studies. However, recent establishment of an experimental system (electroporation of NAPs in HepG2.2.15 cells) which recovers a post-entry effect of NAPs in vitro is now allowing mechanistic investigations to proceed. Initial results indicate that NAPs act at a post-translational step to block the release of HBsAg but not virions (HBV DNA) suggesting a selective targeting of subviral particle (SVP) assembly and or secretion, consistent with the observations of NAP activity pre-clinically in the duck model and in human trials. Inhibition of HBsAg release is not accompanied by an increase in intracellular HBsAg. Cell free binding studies demonstrate that NAPs do not interact with HBsAg, suggesting a host protein involved in subviral particle assembly may be targeted by NAPs.

Evaluation of NAP pharmacokinetics and biodistribution in 6-month exposure studies in CD-1 mice and cynomolgus monkeys demonstrates that the clinically active NAPs, REP 2139 and REP 2165, are rapidly cleared from the circulation within 1 hour post-dosing with simultaneous accumulation primarily in the
liver and kidney, consistent with the clinical effectiveness of these agents with a once weekly dosing regimen. NAP accumulation throughout dosing is more pronounced in the liver but tissue accumulation is significantly reduced and elimination is significantly accelerated after withdrawal of therapy with REP 2165, a REP 2139 analog with increased lability.

Despite these accumulation phenomena with NAPs, in the 6-month exposure studies as well as in safety pharmacology studies in monkeys, both REP 2139 and REP 2165 were remarkably well tolerated at doses substantially higher than clinically active doses with no significant perturbations of cardiovascular, respiratory, liver and kidney function or hematological abnormalities, consistent with the good safety profile of NAPs in clinical studies.

Recent and evolving data from clinical studies in HBV / HDV co-infected patients (REP 301 / REP 301-LTF studies) and HBV monoinfected patients (REP 401 study) demonstrate that NAPs used in chronic combination dosing regimens with TDF and peg-IFN are well tolerated and that the activity of these agents is not inhibited by the presence of NAPs. In both patient populations, NAPs are able to achieve rapid clearance of HBsAg which is frequently associated with therapeutic transaminase flares in the presence of peg-IFN. These antiviral effects have led to profound functional control of HDV infection (HDV RNA target not detected) in 7 / 12 patients and of HBV infection (HBsAg 0.00 IU / ml, HBV DNA target not detected, HBcAg < LLOD, HBV RNA target not detected) in 5/12 patients in the REP 301 trial one year after withdrawal from antiviral therapy.

**Abstract:**

**Intracellular pharmacokinetics evaluation and accumulation rates of the new direct-acting antiviral agents for the treatment of hepatitis C**

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**Background:** In the last few years, the development and introduction of the new direct-acting antiviral agents (DAAs) have significantly improved the management of chronic hepatitis C. New therapies have been associated with an increased virological response rate, a shorter treatment duration and, sometimes, a convenient single-tablet formulation. Although new regimens show high levels of efficacy, adverse events and treatment failures are reported. Few data are available concerning new drugs pharmacokinetics in “real life” setting. Since these drugs explicate their activity inside the cells, it could be useful to evaluate their concentrations in the intracellular compartment. Peripheral blood mononuclear cells (PBMCs) may represent a valid and easier available surrogate for hepatocyte cells, since the biopsy is an invasive technique. The aim of this study was to evaluate the intracellular (PBMCs) concentrations and the accumulation rates, respect to plasma, of DAAs.

**Methods:** HCV+ mono-infected patients were enrolled in the “Kineti-C study” at the Amedeo di Savoia Hospital, Turin (Italy); they were treated with different regimens which included sofosbuvir (SOF), daclatasvir (DAC), ledipasvir (LDV), simeprevir (SMV) and the co-formulation of ombitasvir (OMB)-paritaprevir (PAR) with/without dasabuvir (DBV). PBMCs were collected following a previous validated protocol including automated PBMC count and evaluation the mean cellular volume for each patient.

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*Reviews in Antiviral Therapy & Infectious Diseases 2017_5*
A gradient of ammonium-acetate 5 mM/pH 9.5 and acetonitrile at flow rate of 0.4 mL/min was used for the chromatographic separation. Detection was carried out with a triple-quadrupole-tandem mass spectrometer coupled with electrospray ionization (ESI). PMBC samples were treated with acid phosphatase for GS-331007 (SOF metabolite) analysis. Calibration curve and quality controls were prepared using PBMCs from healthy donors spiked with standards. Quinoxaline, DAC-D8, OMB-D6 were used as internal standards.

**Results:** We analyzed 38 plasma and PMBCs samples at 1 day and 189 ones at one month of treatment. Inter and intra-day accuracy and precision of the developed method were both below 15%, as required by FDA guidelines. Recovery was above the 50% for all drugs. Median PBMC/plasma ratio concentration values at one month of therapy were: 4.60 for GS-331007 (SOF was not detectable neither in plasma, nor in cells), 2.51 for SMV, 4.12 for DAC, 16.92 for LDV, 34.07 for OMB, 3.77 for DBV and 1.95 for PAR. We observed a significant correlation between plasma and PBMC concentrations (p<0.05) for all drugs, except for OMB and DBV. Moreover, data showed an increased trend of intracellular concentrations from one day to one month of therapy.

**Conclusions:** LDV and OMB showed higher intracellular accumulation compared to other DAAs, otherwise PAR showed the lowest accumulation rate. These preliminary “real life” data on intracellular DAAs concentrations could better clarify these drugs pharmacokinetics, helping clinicians in the patient’s management. In future, our aim will be to confirm our preliminary results in larger cohorts of patients, and evaluate the impact on therapy outcome and/or toxicity.

**Abstract: P_54**

**Effect of a high fat meal on the pharmacokinetics of the HIV integrase inhibitor, cabotegravir**

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**Background:** Cabotegravir (CAB, GSK1265744) is an integrase inhibitor in late stage development for the treatment and prevention of HIV. The treatment regimen includes a tablet product for oral administration followed by a long acting injectable suspension for intramuscular injection. Studies with early prototype tablet formulations demonstrated a modest increase in CAB exposure following a moderate-fat meal. The objective of this study was to evaluate the effect of a high-fat, high-calorie meal on CAB pharmacokinetics following administration of the tablet formulation to be used in Phase 3 clinical trials in healthy adults.

**Methods:** This was a single-center, randomized, open-label, 2x2 crossover study in healthy adult male and female subjects. Subjects were randomized to receive CAB 30 mg as a single dose on two separate occasions either fasting or fed with a high fat (870 kcal, 53% fat) meal. There was a washout of 14 days between doses. Safety evaluations and serial PK samples were collected after each dose and subjects had a follow-up visit within 14 days after the last dose. Non-compartmental PK analysis was performed with WinNonlin 6.3. Fed vs fasting geometric least squares mean ratios (GLS-MR) and 90% confidence intervals (CI) were generated by the mixed effect model for within-subject treatment comparison.

**Results:** Twenty-four subjects enrolled and 22 completed the study. Two subjects withdrew consent during the study and one subject had un evaluable PK concentrations. Co-administration of CAB with a high-fat, high-calorie meal led to a significant increase in CAB exposure.
A high-fat, high-calorie meal modestly increased the exposure of CAB and is not considered clinically significant. Therefore, CAB can be given with or without food and without regard to fat content.

Abstract: P_55

High prevalence and long duration of nervous system and psychiatric adverse drug reactions in Ugandan patients taking efavirenz 600mg daily

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Background: Efavirenz (EFV) is now classed as an ‘alternative’ in European and US guidelines, however it remains a mainstay of first-line therapy in Africa. Patients of black ethnicity treated with EFV were found to have 59% higher EFV exposure, associated with a higher population prevalence of CYP2B6 polymorphisms which cause loss of function. Such CYP2B6 polymorphisms were found in 22-39% of Ugandans, depending on tribe. A South African study demonstrated that increased exposure to EFV in CYP2B6*6 homozygotes was significantly associated with increased central nervous system (CNS) side effects, however symptoms resolved within one month. Recent WHO guidelines recommend a lower dose of 400mg EFV daily, as an alternative to the 600mg dose based on the ENCORE studies, where the lower dose was found to improve toxicity, while maintaining efficacy, regardless of genotype. However, EFV 400mg is not widely used. We report the prevalence, type, severity and duration of CNS adverse drug reactions (ADRs) in a Ugandan outpatient cohort taking EFV 600mg daily.

Materials & Methods: During a prospective longitudinal observational study, Ugandan HIV-positive patients on antiretrovirals (of any duration) were asked to detail current side effects, and rate their perceived severity on a scale of 1-10. Reported side effects were classified using the Medical Dictionary for Regulatory Activities (MedDRA), capturing the different aspects of CNS toxicity in detail. All ADRs were evaluated using the Liverpool Adverse Drug Reaction Causality Assessment Tool (L-CAT), by at least 2 members of the study team, which comprised pharmacists and clinicians.

Results: Of 174 consecutive patients, 100 were taking an EFV-based regimen (72% female, mean weight 62kg). 38% (95%CI 28-48%) of patients taking EFV reported currently experiencing a side effect classified as a nervous system disorder (NSD) or psychiatric disorder (PD). A total of 59 NSD/PD ADRs were reported with 56 (95%) considered either possibly or probably related to EFV. These comprised: Dizziness (34); Somnolence/drowsiness (9); Nightmares/Abnormal dreams (4); Hypoaesthesia/Parasthesia (3); Memory impairment (2); Headache (2); Anxiety (1); Blurred vision (1). 17 (30%) of these were rated by patients to have severity of >5/10; 42 (75%) were rated ‘Minor’ by the study team, and 14 (25%) ‘Moderate’ in severity. The median duration of the NSD/PD ADRs was 37.5 months (range <1-120 months, IQR: 22.5 (20.25-42.75)). All but one ADR had been experienced for >3 months. Only 6 (11%) of the ADRs detected were recorded in the patients’ clinical files.

Conclusion: More than a third of these patients reported NSD or PD ADRs, 75% of CNS symptoms were experienced for 20.25 months or greater, with symptoms ongoing at the point of analysis. In contrast, current literature and manufacturers’ guidance consider CNS symptoms to be transient, resolving within a
month of continued therapy. Patients rated the severity of their symptoms highly, demonstrating an impact on quality of life, however symptoms were rarely documented, suggesting a hidden burden. Patients in this cohort may benefit from the alternative regimen in the WHO antiretroviral guidelines, containing EFV 400mg daily, if alternatives to EFV are unavailable or not tolerated.

Abstract: P_56

Characteristics of dolutegravir protein binding in human and nonhuman primate: a first approach for the study of pharmacologic sanctuaries

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

Materials & Methods: DTG protein binding was measured in plasma samples of 2 NHP (n=5 for each NHP) who received DTG (20 mg/kg per os) as well as in vitro in blank human plasma from the Blood Bank and in blank NHP plasma which were spiked with DTG to final concentrations of 800 and 1,600ng/mL. DTG HSA binding was measured using a 40-g/L HSA solution prepared in pH 7.4 phosphate-buffered saline and spiked with DTG to yield 8 final concentrations from 25 to 25,000ng/mL. The influence of pH on DTG binding was studied in a 40-g/L HSA solution spiked with DTG at 800 and 1,600ng/mL at pHs ranging from 7.0 to 7.8. Each experiment was run in triplicate. Bound and unbound fractions were separated by ultrafiltration (Centrifree devices). Total and unbound DTG concentrations were measured by quality controls validated assays (LC–MS/MS). A graphical Scatchard plot method was used to estimate the albumin binding characteristics.

Results: In the 2 NHP, mean predose trough total and unbound DTG were 576.2 ng/mL and 7.9 ng/mL, respectively corresponding to a mean bound fraction of DTG of 98.6% (CV, 58.4%). In vitro, at the 800 and 1,600ng/mL DTG total concentrations, mean DTG plasma protein bindings were 99.4% (CV, 4.4%) and 99.1% (CV, 6.6%) respectively in human plasma and 98.9% (CV, 8.5%) and 98.5% (CV, 3.1%) respectively in NHP plasma. The mean binding of DTG to HSA was 89.6% (range, 83.2%-94.7%), and independent of DTG total concentration. DTG was found to bind to two classes of albumin sites: one with high affinity and one nonsaturable with low affinity. Interestingly in the pH range from 7.0 to 7.8, a 0.2U decrease in pH led to a 2% decrease in DTG albumin binding (P<0.0001).

Conclusions: Unbound dolutegravir concentrations were above the IC50 (0.08 ng/mL) in both NHP. DTG binding is high mainly with HSA and is pH sensitive that could influence diffusion in some biological fluid and cells. As characterization of binding of DTG is similar in human and in NHP, the NHP model could be an adequate model for studying tissue distribution, particularly in inaccessible human tissues.
Abstract: **P_57**

**Tenofovir pharmacokinetics and drug-associated tubular impairment in patients switching to rilpivirine/emtricitabine/tenofovir disoproxil fumarate**

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**Background:** Tenofovir disoproxil fumarate (TDF) has been associated with renal impairment and with clinical and subclinical tubular toxicity. A direct correlation between tenofovir (TFV) concentrations and tubular impairment has been reported. Rilpivirine/Emtricitabine/Tenofovir Disoproxil Fumarate (R/F/TDF) is a single tablet regimen that showed excellent efficacy and tolerability but TFV exposure and renal safety are incompletely known.

**Materials and methods:** Adult HIV-positive patients switching from TDF-containing regimens to R/F/TDF with plasma HIV RNA <50 copies/mL were included. Plasma and urinary TFV 12-hour concentrations (pTFV C12 and uTFV C12) were measured at baseline and 48 weeks through validated methods. Urinary retinol binding protein corrected by urinary creatinine (RBP/Cr µg/g) and 24-hour urine tubular markers were concomitantly measured. RBP/Cr normality ranges were <130 µg/g (patients <50 years) and <172 µg/g (patients aged ≥50 years). Data are expressed as median values (interquartile ranges).

**Results:** Seventy-one patients were enrolled. 56 were male (78.9%), age and BMI were 48 years (40-52) and 24 Kg/m2 (22-26). 10 patients (14%) were HCV-positive (1 with compensated cirrhosis); estimated creatinine clearance (eCrCl, estimated through the MDRD equation) and CD4+ cells were 83 mL/min (73-93) and 561 (453-729) respectively. Last regimen before switching included NNRTIs [47 (66%), 46 on efavirenz and 1 on nevirapine], boosted or unboosted PIs (22, 31%) or raltegravir (RAL) (2, 2.8%). Baseline pTFV C12 and urinary/plasma ratio (upR) were 58 ng/mL (46-77), and 402 (239-519) respectively; pTFV C12 was 80 ng/mL (57-109) at week 48. A significant increase in pTFV C12 from baseline was observed in patients switching from NNRTIs (p <0.01) but not in those switching from PIs or RAL. A concomitant decrease in TFV upR was observed at week 48 (p=0.002) in patients switching from NNRTIs. RBP/Cr was abnormally high in 51 patients (72%) at BL and no significant change was observed through week 48 (34, 77%, p=0.402); this difference was not significant even stratifying for baseline treatment. A significant correlation was observed at week 48 between pTFV C12 and RBP/Cr (p=0.002, rho =0.480). 24-hours proteinuria and eCrCl remained stable with no significant changes through week 48 (p=0.244 and p=0.267, respectively).

**Conclusions:** Switching to Tenofovir Disoproxil Fumarate/Emtricitabine/Rilpivirine was not associated with improvements in tubular safety, independently from baseline treatment. Tenofovir plasma concentrations increased over time in patients switching from NNRTI-containing regimens while no difference was observed in patients with pre-switch PI-based therapy; RPV inhibition of P-glycoprotein might explain this finding.
Abstract: P_58

Impaired absorption of dolutegravir and tenofovir DF, but not emtricitabine, following oral and jejunostomy-tube administration in a patient with advanced HIV infection

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Background: The paucity of pharmacokinetic (PK) data comparing oral and enteral feeding tube (EFT) administration of antiretroviral (ARV) medications poses challenges when EFT administration is necessary. Here, the PK of dolutegravir (DTG) 50 mg, tenofovir (TFV) disoproxil fumarate (TDF) 300 mg, and emtricitabine (FTC) 200 mg after oral and jejunostomy (J)-tube administration are described in a 47-year-old male with advanced HIV infection, failure to thrive, and ARV treatment failure who required medication administration via a Roux-en-Y J-tube due to intractable nausea/vomiting. PK assessments were performed to rule out decreased ARV drug absorption as a cause of virologic failure, and to compare differences in ARV exposure following oral and J-tube administration.

Materials & Methods: PK assessments were performed under a clinical study for patients with virologic failure (NCT01976715). HIV viral loads (HIV-VL) were performed at Days 1, 3, 5, and 8. He received his ARV medications via J-tube (after crushing whole tablets and mixing with water) throughout the hospitalization, except for Day 4 when ARV medications were given orally. Blood for PK analysis was drawn at time 0 (pre-dose), 1, 2, 4, and 24 hours post-dose following J-tube (Day 3) and oral (Day 4) administration. DTG, TFV, and FTC plasma concentrations were measured using validated LC-MS/MS methods. PK parameters were determined via noncompartmental analysis with linear-up/log-down trapezoidal rule (Phoenix WinNonlin v6.4, Certara, Inc.) and were compared between administration routes and against steady-state PK data in HIV-infected patients following oral administration (reference).

Results: Patient-specific DTG and TFV exposures were comparable between J-tube vs. oral administration (DTG ratio 1.04; TFV ratio 0.86). In comparison to reference PK, DTG AUC0-τ was 75-76% lower (J-tube: 13680, oral: 13211 vs. reference: 55026 ng*hr/mL) and Cτ was 71-78% lower (J-tube: 219, oral: 163 vs. reference: 753 ng/mL); and TFV AUC0-τ was 55-61% lower (J-tube: 1237, oral: 1436 vs. reference: 3179 ng*hr/mL) and Cτ was 43% lower (J-tube and oral: 28, reference: 50 ng/mL). FTC exposure was lower for J-tube vs. oral administration (ratio 0.62). FTC AUC0-τ was 5 and 71% higher, respectively in comparison to reference data (J-tube: 10532; oral: 17087; reference: 10000 ng*hr/mL). Despite the lower DTG and TFV concentrations, HIV-VL decreased by 1.57 log₁₀, from 37,620 (Day 1) to 1,011 copies/mL (Day 8).
Conclusions: In this patient, plasma exposures to DTG and TFV following J-tube and oral administration did not differ, but were markedly lower than reference data. This decreased exposure was mostly likely due to impaired absorption. FTC exposure was similar or higher following J-tube and oral administration, respectively. Though >1.0 log₁₀ decline in HIV-VL was achieved after 7 days, the reduced DTG exposure was concerning for potential ARV failure based on exposure-response data and the proximity of Cτ to DTG's PA-IC₉₀ (64 ng/mL). Increasing DTG to 50 mg twice-daily with follow-up TDM was considered, but the patient died before this could be done. These data highlight the clinical utility of TDM in patients where reduced ARV drug absorption may be of concern.

Abstract: P_59

Higher Dolutegravir Plasma Trough Concentration (Ctrough) in patients presenting side effects: Interest of Therapeutic Drug Monitoring?

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Background: Dolutegravir (DTG), a potent next-generation HIV integrase inhibitor, widely prescribed in association with other antiretrovirals presents a specific pharmacokinetic profile. Although mainly metabolized through UGT1A1, contributing to a better drug-drug interaction profile, DTG exposure decreases with di- or trivalent cation-containing drugs and is recommended to be administered 2-hours before or 6-hours after. DTG bioavailability is increased by a high fat meal but there is no recommendation regarding food intake. A pharmacokinetic-pharmacodynamic relationship has been described and the DTG plasma trough concentration (Ctrough) identified as a parameter significantly correlated with virologic response. Recently, in various cohort studies, DTG has been associated with a higher rate of adverse events (AEs), in particular neuropsychiatrics (NP), than reported in phase 3 trials. As part of therapeutic drug monitoring (TDM), we assessed the factors of variability of DTG exposure and the relationship between DTG Ctrough and tolerance.

Material and Methods: DTG Ctrough, measured by a liquid-chromatography coupled with tandem mass spectrometry method, was collected at steady-state, one month after initiation (W4) in patients initiating a 50mg QD DTG-containing regimen. Patients’ demographic, therapeutic and immuno-virologic data were collected at baseline from their electronic medical records. Adherence, co-medications and tolerance were prospectively monitored at W4 and W12. Results are presented by median (IQR; n). Statistical analysis was performed using non-parametric tests (Mann-Whitney test) and Pearson correlation (PASW Statistics v.17).

Results: Data of 48 HIV-infected patients [60% male, median age: 50.5 years], receiving DTG 50 mg QD in combination with ABC+3TC (58.3%), TDF+FTC (31.2%), RPV (6.3%), 3TC (2.1%) or TDF+DRV/r (2.1%) were available. DTG was taken mainly on the evening (37.5%), during meals (72.9%) and 29.2% of patients were receiving polyvalent cation-containing drugs. A treatment adherence of 100% was reported in 87.5% and 84% of patients at W4 and W12, respectively. Median DTG exposure was 1281 ng/ml (810-2037; CV=69%) on the whole population and the median DTG Ctrough was 1192 ng/ml (818-1789; 42; CV=59%). DTG Ctrough was not significantly affected by food (p=0.62), use of polyvalent cation-containing drugs (p=0.50), sex (p=0.40) nor by age (p=0.31). At W4, 17/48 (35%) of patients reported AEs: NP (41.2%), asthenia (23.5%), gastro-intestinal (23.5%), cutaneous (5.9%), others (5.9%). DTG Ctrough was statistically higher in patients presenting AEs: 1562 ng/ml
Abstract: P_60

**Abstract: P_60**

**Determination of Dolutegravir, Darunavir and Atazanavir unbound fraction in HIV patients by equilibrium dialysis and ultrafiltration using a liquid chromatography mass spectrometry**

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Unbound fraction (fu) is considered as the pharmacologically active form of a drug. This parameter could be an alternative of interest to therapeutic drug monitoring for patients experiencing virological failure, mostly with low level viremia, and toxicity, despite normal total concentrations. Indeed, for antiretroviral highly bound to plasma proteins, inter-individual variability of fu could explain differences in efficacy or toxicity response with optimal total concentration. Ultrafiltration (UF) is often used to evaluate antiretrovirals unbound fraction, while firstly sparse data are available on both the pre-analytical process and secondly comparison is occasionally performed with the gold standard method, equilibrium dialysis (ED). As a consequence, published values of unbound fraction are different without clear explanation. In this obscure context, we aimed to establish a protocol to evaluate the unbound fraction of dolutegravir (DTG), darunavir (DRV) and atazanavir (ATV) by ED and UF on HIV+ patients samples. Spiked plasma, with DTG, DRV or ATV were used to study unbound fraction by ED and UF. Time to reach binding equilibrium, non-specific binding (NSB) and binding saturation were explored with ED. Additionally, different parameters like temperature, hemolysis and drug-drug interaction were tested on unbound fraction. In a second time, different combinations of UF conditions, including temperature, duration and centrifugal force were compared with ED performed at 37°C. Once pre-analytical conditions were established for UF, patients’ fu (n=110) were determined using both ED and UF. Whatever the process (ED vs UF), samples were analysis by a validated LC-MS/MS method. Albumin and alpha-1-acid-glycoprotein (AAG), two variability factors of fu, were measured. Analysis of variance, followed by a Dunnetts test if necessary (p<0.05 for statistical significance), were used for interpretation. Results of patients’ fu were expressed as median and InterQuartileRange (IQR[25%;75%]). Equilibrium was reached after 4h at 37°C on ED device for each drug. Proteins binding of the 3 antiretroviral were stable at least 5 days at +4°C or after 2 thaw cycles. With the exception of DTG during UF (<15%), NSB were <10%. Protein binding was saturated at 20mg/L for DRV and 10mg/L for both DTG and ATV (p<0.01). Only DTG binding equilibrium was influenced by hemolysis (p<0.01) and interaction with other antiretrovirals (ATV, DRV, rilpivirine and etravirine; p<0.01). Only one combination of UF temperature (37°C), time (20min) and centrifugal
force (1000g) conditions allowed identical results with ED for DTG and DRV, but none for ATV (p<0.01). Patients' fu showed a wide inter-individual variability for DTG (fu=0.45%; IQR[0.37; 0.55]), DRV(fu=5.09%; IQR[3.85; 6.51]) and ATV (fu=7.59%; IQR[5.66; 8.73]), unexplained by albumin (43.1g/L; IQR[39.60; 45.15]) or AAG levels (0.79g/L; IQR[0.60 ; 0.92]). As only few UF conditions yielded comparable results with ED, it is necessary to establish preanalytical conditions leading to the same results with ED, before analyzing patients' samples. Moreover, as unbound fraction evaluation in HIV patients has shown a large inter-individual variability for the tested drugs, the following step will consist in exploring the pharmacokinetic (fu) –pharmacodynamic (LLV) relationship.
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Author Index
<table>
<thead>
<tr>
<th>Author</th>
<th>Abstract Title</th>
<th>Abst #</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kakuda, T.</td>
<td>Single- and multiple-ascending doses (SAD/MAD) and food effect of orally</td>
<td>O_01</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>administered JNJ-64155806 in healthy volunteers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattaneo, D.</td>
<td>Effects of cobicistat on tenofovir durability: is it time to rethink at TAF</td>
<td>O_02</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>trials?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molto, J.</td>
<td>Pharmacokinetics of darunavir/cobicistat and etravirine alone and</td>
<td>O_03</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>coadministered in HIV-infected patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Boosted Protease Inhibitors and Statins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Majeed, S.</td>
<td>Confirmation of the drug-drug interaction (DDI) potential between</td>
<td>O_05</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>cobicistat-boosted antiretroviral regimens and hormonal contraceptives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marzolini, C.</td>
<td>Darunavir concentrations in CSF of HIV-infected individuals when boosted</td>
<td>O_06</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>with cobicistat versus ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bollen, P.</td>
<td>A Comparison of the Pharmacokinetics of Dolutegravir during Pregnancy and</td>
<td>O_07</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Postpartum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boffito, M.</td>
<td>Relationship between dolutegravir plasma exposure, quality of sleep and its</td>
<td>O_08</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>functional outcome in patients living with HIV over the age of 60 years.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kiser, J.</td>
<td>Adherence biomarker measurements in older HIV-infected adults receiving</td>
<td>O_09</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>tenofovir-based therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adkison, K.</td>
<td>Pharmacokinetics of Dolutegravir and Rilpivirine after Switching to the Two-</td>
<td>O_10</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Drug Regimen from an Efavirenz- or Nevirapine-Based Antiretroviral Regimen:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SWORD-1/2 Pooled PK Analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lefevre, S.</td>
<td>HIV-1-infected Males and Females under Less-Drug Regimens Achieve</td>
<td>O_11</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Antiretroviral Levels above the Inhibitory Concentration in the Genital Tract.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shugg, T.</td>
<td>Examining the Basis of Drug-Drug Interaction Labeling Recommendations for</td>
<td>O_12</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Antiviral Approvals from 1998 to 2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kirby, B.</td>
<td>CYP3A induction data can predict other P450 and drug transporter DDI liability:</td>
<td>O_13</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>An example of carbamazepine and rifabutin with sofosbuvir and P-gp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanan, N.</td>
<td>Pharmacokinetics of Co-encapsulated Truvada® with Ingestible Sensor to</td>
<td>O_14</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Assess Adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siccardi, M.</td>
<td>Identification of long-acting NRTI candidates through in silico modelling</td>
<td>O_15</td>
<td>17</td>
</tr>
<tr>
<td>Sanche, S.</td>
<td>A mathematical model that predicts virological failure and elucidates the</td>
<td>O_16</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>impact of lymph node drug penetration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson, M.</td>
<td>Early Safety, Tolerability, and Pharmacokinetic Profile of GSK2838232, a</td>
<td>O_17</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Novel 2nd Generation HIV Maturation Inhibitor, as Assessed in Healthy Subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kosloski, M.</td>
<td>Drug-drug interactions of glecaprevir and pibrentasvir with pravastatin,</td>
<td>O_18</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>rosvastatin, or dabigatran etexilate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Abstract Title</td>
<td>Abst #</td>
<td>Page #</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Elsherif, O.</td>
<td>Influences on Pharmacokinetics of ledipasvir, sofosbuvir and GS-331007 in patients with decompensated cirrhosis – results from the UK Expanded Access programme.</td>
<td>O_19</td>
<td>21</td>
</tr>
<tr>
<td>Garrison, K.</td>
<td>Evaluation of Drug-Drug Interactions between Sofosbuvir/Velpatasvir/Voxilaprevir and Boosted or Unboosted HIV Antiretroviral Regimens</td>
<td>O_20</td>
<td>22</td>
</tr>
<tr>
<td>Choi, S.</td>
<td>The Potential Role of PK-Based Drug Interactions in FAERS-Reported Rhabdomyolysis Cases in Patients Receiving a DAA Regimen and a Statin</td>
<td>O_21</td>
<td>23</td>
</tr>
<tr>
<td>Kakuda, T.</td>
<td>Effects of food and formulation on the pharmacokinetics of orally administered JNJ-64155806 in healthy volunteers</td>
<td>P_22</td>
<td>26</td>
</tr>
<tr>
<td>Sevinsky, H.</td>
<td>The Effect of Food on the Pharmacokinetics of the HIV-1 Attachment Inhibitor Temsavir, the Active Moiety of the Prodrug Fostemsavir</td>
<td>P_23</td>
<td>27</td>
</tr>
<tr>
<td>Kirby, B.</td>
<td>Population Pharmacokinetic Analysis of Voxilaprevir, a Pan-Genotypic HCV NS3/4A Protease Inhibitor in Hepatitis C Virus-Infected Subjects</td>
<td>P_24</td>
<td>28</td>
</tr>
<tr>
<td>Mehta R.</td>
<td>Bioequivalence of a Fixed Dose Combination Tablet of Dolutegravir and Rilpivirine in Healthy Subjects</td>
<td>P_25</td>
<td>29</td>
</tr>
<tr>
<td>Hawkins, K.</td>
<td>Tenofovir-diphosphate (TFV-DP) in dried blood spots (DBS) is inversely correlated with body mass index (BMI)</td>
<td>P_26</td>
<td>29</td>
</tr>
<tr>
<td>Zhang, H.</td>
<td>The Effect of Hepatic or Renal Impairment on Bictegravir Pharmacokinetics and Inflammation and gene expression of drug transporters and metabolizing enzymes in the female genital tract.</td>
<td>P_27</td>
<td>30</td>
</tr>
<tr>
<td>Nicol, M.</td>
<td>Dose-selection of odalasvir for use in combination with AL-335 and simeprevir in a phase 2A study using a population pharmacokinetic modelling and simulation approach</td>
<td>P_28</td>
<td>31</td>
</tr>
<tr>
<td>Ackaert, O.</td>
<td>Pharmacokinetics of daclatasvir in cirrhotic patients: challenges in PBPK modeling</td>
<td>P_29</td>
<td>32</td>
</tr>
<tr>
<td>Smolders, E.</td>
<td>Population pharmacokinetics of romidepsin as a latency-reactivating agent in HIV-infected adults</td>
<td>P_30</td>
<td>33</td>
</tr>
<tr>
<td>Molto, J.</td>
<td>Population Pharmacokinetics of Dolutegravir in HIV-1 Infected Adults from Clinical Practice</td>
<td>P_31</td>
<td>34</td>
</tr>
<tr>
<td>Wu, L.</td>
<td>Modeling of the Effects of Food and Enterohepatic Circulation on the Pharmacokinetics of Orally Administered JNJ-64155806 (AL-794) in Healthy Volunteers</td>
<td>P_32</td>
<td>35</td>
</tr>
<tr>
<td>Goldwirt, L.</td>
<td>Exposure to sofosbuvir and daclatasvir is unchanged in liver transplant patients on cyclosporine or tacrolimus based immunosuppression</td>
<td>P_33</td>
<td>36</td>
</tr>
<tr>
<td>Back, D.</td>
<td>Low rate of drug-drug interaction management during interferon-free simeprevir therapy - An integrated analysis of interventional and observational clinical studies</td>
<td>P_34</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P_35</td>
<td>38</td>
</tr>
<tr>
<td>Author</td>
<td>Abstract Title</td>
<td>Abst #</td>
<td>Page #</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Smolders, E.</td>
<td>Treating the “untreatable”: Adjusted doses of daclatasvir with the anti-epileptic drug carbamazepine (HepNED study 003)</td>
<td>P_36</td>
<td>39</td>
</tr>
<tr>
<td>Magee, M.</td>
<td>The Effect of Increased Gastric pH on the Bioavailability of Extended Release Tablet of Fostemsavir in Healthy Subjects</td>
<td>P_37</td>
<td>40</td>
</tr>
<tr>
<td>Kakuda, T.</td>
<td>Lack of clinically significant pharmacokinetic interaction between the 3-DAA combination of AL-335, odalasvir and simeprevir for the treatment of chronic HCV infection and an oral contraceptive containing ethinylestradiol and drospirenone</td>
<td>P_38</td>
<td>41</td>
</tr>
<tr>
<td>Ankrom, W.</td>
<td>Doravirine Does Not Have a Clinically Meaningful Pharmacokinetic Interaction with Ledipasvir/Sofosbuvir (Harvoni®)</td>
<td>P_39</td>
<td>42</td>
</tr>
<tr>
<td>Garrison, K.</td>
<td>Lack of Pharmacokinetic Drug-Drug Interaction between Norgestimate/Ethinyl Estradiol and Sofosbuvir/Velpatasvir/Voxilaprevir</td>
<td>P_40</td>
<td>43</td>
</tr>
<tr>
<td>Arrington, L.</td>
<td>No clinically significant interaction of the proton pump inhibitor omeprazole with the components of MK-3682B</td>
<td>P_41</td>
<td>44</td>
</tr>
<tr>
<td>Ankrom, W.</td>
<td>Doravirine Does Not Have a Clinically Meaningful Pharmacokinetic Interaction with Elbasvir Plus Grazoprevir</td>
<td>P_42</td>
<td>44</td>
</tr>
<tr>
<td>Bonora, S.</td>
<td>Daclatasvir (DCV) pharmacokinetics and appropriate dosing in HCV/HIV patients co-administered with antiretroviral drugs</td>
<td>P_43</td>
<td>45</td>
</tr>
<tr>
<td>Kim, N.</td>
<td>MK-3682B is not a clinically significant CYP3A inhibitor or inducer</td>
<td>P_44</td>
<td>46</td>
</tr>
<tr>
<td>Le, M.</td>
<td>Plasma population pharmacokinetics of dolutegravir in HIV-1 infected patients in a real-life setting and impact of drug-drug interactions</td>
<td>P_45</td>
<td>47</td>
</tr>
<tr>
<td>Le, M.</td>
<td>Pharmacokinetic interaction between ledipasvir/sofosbuvir and etravirine containing regimen</td>
<td>P_46</td>
<td>48</td>
</tr>
<tr>
<td>Majeed, S.</td>
<td>Lack of effect of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate on glomerular filtration rate (GFR) in HIV-infected patients</td>
<td>P_47</td>
<td>49</td>
</tr>
<tr>
<td>Macbrayne, C.</td>
<td>Small increase in dolutegravir trough, but equivalent total exposure with simeprevir</td>
<td>P_48</td>
<td>50</td>
</tr>
<tr>
<td>Begley, R.</td>
<td>Evaluation of Drug-Drug Interaction Potential between Sofosbuvir/Velpatasvir and Atorvastatin</td>
<td>P_49</td>
<td>51</td>
</tr>
<tr>
<td>Zhang, H.</td>
<td>Lack of Clinically Relevant Effect of Bictegravir on Metformin Pharmacokinetics and Pharmacodynamics</td>
<td>P_50</td>
<td>52</td>
</tr>
<tr>
<td>Dalodom, T.</td>
<td>Pharmacokinetics of generic Ritonavir tablets with low-dose Atazanavir in HIV-infected Asian adults</td>
<td>P_51</td>
<td>53</td>
</tr>
<tr>
<td>Vaillant, A.</td>
<td>Pharmacokinetics, pharmacology, preclinical safety and clinical efficacy of nucleic acid polymers in chronic HBV and HDV infections</td>
<td>P_52</td>
<td>54</td>
</tr>
<tr>
<td>D'Avolio, A.</td>
<td>Intracellular pharmacokinetics evaluation and accumulation rates of the new direct-acting antiviral agents for the treatment of hepatitis C.</td>
<td>P_53</td>
<td>55</td>
</tr>
<tr>
<td>Author</td>
<td>Abstract Title</td>
<td>Abst #</td>
<td>Page #</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Patel, P.</td>
<td>Effect of a high fat meal on the pharmacokinetics of the HIV integrase inhibitor, cabotegravir</td>
<td>P_54</td>
<td>56</td>
</tr>
<tr>
<td>Seden, K.</td>
<td>High prevalence and long duration of nervous system and psychiatric adverse drug reactions in Ugandan patients taking efavirenz 600mg daily</td>
<td>P_55</td>
<td>57</td>
</tr>
<tr>
<td>Gelé, T.</td>
<td>Characteristics of dolutegravir protein binding in human and nonhuman primate: a first approach for the study of pharmacologic sanctuaries.</td>
<td>P_56</td>
<td>58</td>
</tr>
<tr>
<td>Bonora, S.</td>
<td>Tenofovir pharmacokinetics and drug-associated tubular impairment in patients switching to rilpivirine/emtricitabine/tenofovir disoproxil fumarate</td>
<td>P_57</td>
<td>59</td>
</tr>
<tr>
<td>Brooks, K.</td>
<td>Impaired absorption of dolutegravir and tenofovir DF, but not emtricitabine, following oral and jejunostomy-tube administration in a patient with advanced HIV infection</td>
<td>P_58</td>
<td>60</td>
</tr>
<tr>
<td>Solas, C.</td>
<td>Higher Dolutegravir Plasma Trough Concentration (C&lt;sub&gt;t&lt;/sub&gt;rough) in patients presenting side effects: Interest of Therapeutic Drug Monitoring?</td>
<td>P_59</td>
<td>61</td>
</tr>
<tr>
<td>Metsu, D.</td>
<td>Determination of Dolutegravir, Darunavir and Atazanavir unbound fraction in HIV patients by equilibrium dialysis and ultrafiltration using a liquid chromatography mass spectrometry.</td>
<td>P_60</td>
<td>62</td>
</tr>
</tbody>
</table>