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Abstract Book

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Abstracts

Oral Presentations

Abstract: O_1

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Pharmacokinetic, Safety and Efficacy of Darunavir/Ritonavir in HIV+ Pregnant Women

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Introduction: Darunavir/ritonavir (DRV/r) is the most popular protease inhibitor recommended to prevent the risk of HIV mother-to-child transmission. However, a decrease of DRV plasma exposure during the 3rd trimester which might put at risk the efficacy of the ARV strategy. The objectives were to assess maternal DRV plasma concentrations and to describe the safety and efficacy of DRV/r containing regimen.

Materials & Methods: A multicentre, cross-sectional, cohort was conducted from 2006 to 2015. HIV pregnant women receiving DRV/r (800/100mg QD or 600/100mg BID) containing regimen, with available demographics characteristics, plasma HIV-RNA (pVL) and CD4 count were enrolled. Switch from DRV/r QD to BID was recommended during pregnancy. Total and unbound DRV C24h and C12h were determined by UPLC-MS/MS at the three trimesters (Tn) of pregnancy and at delivery. Safety assessments and newborn data (weight, gestational age, APGAR score) were collected. Results are presented as medians (IQR).

Results: 220 pregnant women were included: aged 32 years old (28-36), 89% from sub-Saharan Africa, with HIV diagnosis since 7 years (6-12), 98% HIV-1 infected, 12% HBV+ and 4% HCV+ co-infected, 84% cART-experienced; ART backbone: 60% FTC/TDF, 15% ABC/3TC, 10% NRTIs+RAL, 5% ZDV/3TC, 5% DRV/r monotherapy. Before pregnancy, 149 women received DRV/r 800/100mg QD (among them,61 women switched to DRV/r 600/100mg BID during pregnancy) and 71 women received DRV/r 600/100mg BID ante-partum, throughout the period of pregnancy and post-partum. Before pregnancy (>6 months), BMI was 27 (23-30) kg/m² and CD4 nadir 270 (164-391) cells/mm^3. DRV plasma concentrations during pregnancy were: at T1, DRV C24h 1,574 ng/mL (1,101-2,033; n=33) and DRV C12h 2,088 (1,219-2,835; n=13); at T2, DRV C24h 1,144 ng/mL (743-1,605; n=81) and DRV C12h 2,174 ng/mL(1,534-2,812; n=49); at T3, DRV C24h 934 ng/mL (707-1,160; n=81) and DRV C12h 2,134 ng/mL (1,560-2,893; n=98); and at delivery, DRV C24h 853 ng/mL (479-1,617; n=30) and DRV C12h 2,033 ng/mL (1,081-2,793; n=53). DRV C24h was significantly lower at T2 and T3 than in T1 (-28%, p<0.05 and -41%, p<0.0001, respectively). DRV C12h was similar between T1, T2 and T3 (p=NS). At T3, 2% of DRV C12h and 12% of DRV C24h were < 550 ng/mL (10 fold protein adjusted EC_{50} for Wild-Type HIV). Cord blood/maternal ratio of DRV plasma concentration was 0.16 (0.07-0.42, n=91), consistently with previous studies. RTV C24h and C12h remained similar between the 3 trimesters. At birth, gestational age was 36 weeks (37-40): 20% <37 weeks and 4% <32 weeks, newborns' weight 2,910 gr (2,600-3,190; n=37), and APGAR score 10, and 84% of women presented pVL ≤50 copies/mL: 13% with 50<pVL≤400 copies/mL (69% receiving DRV/r 800/100mg QD) and 3% with pVL >400 copies/mL (40% receiving DRV/r 800/100mg QD). To date, no case of mother-to-child HIV transmission was observed.

Conclusions: In this population of mostly African HIV+ pregnant women, DRV/r containing regimen demonstrated a good virological efficacy at delivery. No significant impact of the pregnancy term was found on DRV C12h in contrast with DRV C24h, lower at T2 and T3.

No conflict of interest

Abstract: O_2

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Raltegravir (RAL) Pharmacokinetics (PK) and Safety in HIV-1 Exposed Neonates at High Risk of Infection (IMPAACT P1110)

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Background: Safety and dosing information for antiretroviral drugs (ARVs) in neonates are limited. Raltegravir (RAL) has potential for use as prophylaxis to prevent mother to child transmission and as early intensive treatment of HIV-infected neonates. RAL is primarily metabolized by UGT1A1 enzyme. UGT enzyme activity is low at birth and increases exponentially over the first weeks to months of life. The objectives of IMPAACT P1110 study are to evaluate safety and pharmacokinetics of RAL and to determine the appropriate neonatal dose of RAL oral granules for suspension during the first 6 weeks of life.

Materials and Methods: IMPAACT P1110 is a phase I multicenter trial enrolling full-term HIV-1 exposed neonates at high risk of acquiring HIV-1-infection, with or without in utero RAL exposure. Study design includes two cohorts: cohort 1 infants receive 2 single RAL doses 1 week apart; cohort 2 infants receive daily RAL dosing for first 6 weeks of life. PK results from Cohort 1 (previously reported) were combined with that from older infants and children receiving daily dosing in a population PK model and simulations performed to develop a daily RAL dosing regimen to be evaluated in 20 infants in Cohort 2. The RAL dosing regimen under investigation in Cohort 2 for infants unexposed to RAL in utero is: 1.5 mg/kg daily starting within 48 hours of life through day 7; 3 mg/kg twice daily on days 8-28 of life; 6 mg/kg twice daily after 4 weeks of age. Four plasma samples were collected after the initial dose and on the increased dose between 15-18 days of life; sparse sampling was obtained when doses were changed. Samples were analyzed for RAL concentrations using a validated HPLC-MS-MS method. AUC was estimated after the first dose and for twice daily dose of 3 mg/kg using the trapezoidal method. Protocol exposure targets for each subject are AUC_{24} 12-40mgxh/L, AUC_{12} 6-20 mgxh/L, C_{min}> 33ng/mL.

Results: PK results and 6 week safety data are available for the first 8 infants. After the first dose of 1.5 mg/kg, geometric mean RAL AUC_{24} was 41 mgxh/L (4/8 met target; range18.6-78.3 mgxh/L). On 3 mg/kg twice daily the geometric mean for RAL AUC_{12} was 12.2 mgxh/L (6/8 met target; range 4.7-24.5 mgxh/L) and C_{min} estimated to be 136 ng/mL. Sparse sampling confirmed that RAL plasma concentrations were within the expected range. There were no safety concerns associated with daily RAL administration based on safety data through 6 weeks of life.

Conclusions: Daily RAL was well tolerated in infants receiving this regimen during the first 6 weeks' of life. AUC_{24} following the initial dose was slightly above the target range, but given the rapid increase in RAL metabolism over the first week of life, this exposure was considered acceptable. AUC_{24} and C_{min} on day 15-18 were within the target range. The PK targets and the safety guidelines have been met for the first 8 RAL-unexposed infants in cohort 2. IMPAACT P1110 Cohort 2 enrollment is ongoing to reach our target of 20 PK evaluable infants.

No conflict of interest

Abstract: O_3

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Timing of the postpartum curve in pharmacokinetic studies in pregnancy should not be too early

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Introduction: To study the effect of pregnancy on pharmacokinetics of antiretroviral agents, it is common practice to perform an intra-subject comparison during and after pregnancy. These postpartum pharmacokinetic parameters serve as the control for the non-pregnant situation, and are preferably taken between 4 and 6 weeks after delivery. Due to circumstances, sometimes, pharmacokinetic curves are taken prior to this preferred period with a minimum of two weeks, assuming normalization of pregnancy-induced physiological changes. According to our knowledge, the choice for the 2-6 weeks postpartum period has not been validated, but is widely used in pharmacokinetic studies in pregnancy.We aim to assess the timing of the postpartum control curve with respect to the effect of pregnancy on the pharmacokinetics of several antiretroviral agents and to evaluate the 2-6 weeks criteria for the postpartum control curve.

Materials & Methods: Data were derived from an open-label, multi-centre phase IV study in HIV infected pregnant women recruited in HIV treatment centers in Europe (PANNA study). Patients who had paired PK profiles taken in the PANNA study for the antiretrovirals for which lower exposure in pregnancy was observed (emtricitabine, tenofovir, atazanavir/ritonavir, darunavir/ritonavir, raltegravir and maraviroc) were included in the analysis.To generalize over agents, relative ratios (RelRatio) for AUC and C_{max} were calculated for each subject and antiretroviral agent. The ratio of the AUC in the third trimester/postpartum for each individual patient and antiretroviral agent was divided by the geometric mean ratio of the third trimester/ postpartum in the study population for that anti-retroviral agent. The time-point of the postpartum curve was grouped per week. Kruskal Wallis test with weeks postpartum as grouping variable was used for statistical analysis.

Results: 157 paired PK parameters, from 62 unique patients, generated in the PANNA study were included in this analysis. The median (range) age at delivery was 32 years (19-45); 61% was black, 37% white and 2% of other race; weight at postpartum PK sampling was 71 kg (43-126), whereas the weight at third trimester PK sampling was 76 kg (48-139).Six RelRatios were reported for <4 weeks postpartum, 21 in week 4, 39 in week 5; 35 in week 6; 27 in week 7 and 29 >week 7. No statistically significant difference was observed for AUC (p=0.116), but C_{max} showed a significant difference (p=0.028), mainly driven by a higher RelRatio prior to week 5. This could indicate that pregnancy-induced pharmacokinetic changes were not fully normalized at 2-4 weeks postpartum. Posthoc analysis per drug class showed no statistically significant effect over time postpartum.

Conclusions: To assess pregnancy induced pharmacokinetic changes, timing of the post-partum control curve >4 weeks post delivery is most valid, >2 weeks post delivery can be acceptable in some cases.

Conflict of interest
financial relationship(s): The PANNA network is financially supported by the "European AIDS Treatment Network (NEAT)", EC, DG Research, 6th Framework program, BMS, MSD, Janssen Pharmaceuticals N.V. and ViiV.

Abstract: O_4

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Evaluation of efavirenz and lopinavir concentrations in Plasma and prediction of uptake by nursed infants in Mali.

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Background: Breastfeeding increases risk of HIV transmission by 14 %, with an additional 1% risk per month for the first six months of breastfeeding. Currently, limited data are available on antiretroviral pharmacokinetics in breast milk as well as in breastfed infants' plasma. Similarly, sparse information is available on the relationship between drug levels in milk or breastfed infants' plasma and the virological response. In this work, we measured plasma antiretroviral levels in HIV infected Malian mothers and their infants during breastfeeding. The second objective was to evaluate the correlation between plasma concentrations and viral load.

Materials & Methods: The included patients were HIV-positive pregnant women receiving antiretroviral prophylaxis from gestational week 25 until 6 months after delivery and their breastfed infants. Blood samples were collected at delivery and at month 1, 3 and 6 postpartum. Efavirenz and lopinavir concentrations were measured by liquid chromatography tandem mass spectrometry method. The detection limit of quantification was 0.216 mg /L for efavirenz and 0.264 mg /L for lopinavir. The viral load was detected with nucleic acid sequenced-based amplication (M2000RT, Abbott). The detection limit of viral quantification was 40 copies/mL. The viral load was determined at birth and at 6 months post-partum for mothers and at 3 and 6 months post-partum for children. All children received nevirapine for 6 weeks after birth.

Results: A total of 41 coupled women and breastfed newborns were included: 32 mothers received tenofovir (TDF)), lamivudine (3TC) and efavirenz (EFV) while 9 received zidovudine (ZDV), lamivudine (3TC) and lopinavir/ritonavir (LPV/r). During pregnancy, mothers were given a combination of three antiretroviral that was continued also during breastfeeding (up to 6 months) and thereafter. Median (range) mothers' age was 29 (19-40) years.
At delivery, 36/41 patients had an HIV viral load <50 copies/mL. Mean CD4+ Cell Count at delivery (cells/mm3) was 589.31. Median (IQR) EFV maternal plasma concentration was 2930 ng/mL (2450, 6595) at month 1; 2960 ng/mL (2060, 6685) at month 3; 2740 ng/mL (2150, 8080) at month 6. Median (IQR) EFV infant plasma concentration was 391 ng/mL (282, 572.5) at month 1; 263 ng/mL (142, 464.5) at month 3; and 165 ng/mL (89.7, 331) at month 6. The Median (IQR) ratio (infant plasma/maternal plasma) was 0.057 (0.031, 0.113) at month 1; 0.072 (0.051, 0.091) at month 3 and 0.048(0.033, 0.070) at month 6. Median (IQR) LPV maternal plasma concentration was 1870 ng/mL (586, 4190) at month 1; 10900 ng/mL (5495, 15750) at month 3; 5790 ng/mL (1230, 10600) at month 6. All LPV infants' plasma concentrations were undetectable. No drug-related adverse reaction or toxicity was observed in any of the infants. The two women who presented a viral load > 50 copies/mL at 6 month, had undetectable plasma drug concentrations at the seime period.

Conclusions: Maternal administration of antiretroviral therapy at 3 to 6 months of post-partum was effective and safe for both mothers and infants. Breastfeeding infants were exposed to low concentrations of efavirenz while LPV was undetectable.

No conflict of interest

Abstract: O_5

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Effect of Renal Impairment on Drugs Primarily Eliminated by Metabolism or Biliary Excretion: Review of Data from HCV DAA Drugs and Literature

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Introduction: Several reports in the literature demonstrate that renal impairment (RI) can lead to alterations in non-renal clearance of drugs by affecting drug-metabolizing enzymes and transporters even if primarily eliminated by non-renal pathways.

Methods: The effect of RI on HCV Direct Acting Antiviral (DAA) drugs which are primarily eliminated by the liver via metabolism or biliary excretion, including those developed by Bristol-Myers Squibb (BMS), and the impact of study design on dosing recommendations was evaluated (e.g., reduced design studying severe RI patients with or without hemodialysis [HD]). Based on the influence of design on interpretation, we performed a literature review (using a combination of the following key words: renal impairment study, reduced design, hepatic clearance and metabolism.) to assess the impact of RI on drugs primarily eliminated by non-renal route, and compared the results to drugs that are primarily renally cleared. The review identified a total of 75 drugs, of which 27 drugs were primarily eliminated by renal clearance, 38 by metabolism or transport and 10 by mixed mechanisms.

Results: Several of the recently developed DAA's (boceprevir, telaprevir, simeprevir, sofosbuvir, ledipasvir, ombitasvir, parateprevir, dasabuvir, daclatasvir (DCV), asunaprevir (ASV) and beclabuvir [BCV]) are represented. Seven of the above DAA's evaluated the effect of RI using a full study design (i.e., the entire range of renal function) and four used a reduced design limited to subjects with severe RI or with end stage renal disease (ESRD). For DCV and ASV, a reduced design in ESRD subjects on HD was used initially and results indicated only small differences in total exposure between controls and ESRD. A subsequent full design for DCV in RI patients demonstrated a 51% increase in unbound AUC(INF). Although neither case warrant a dose adjustment, the observed differences were striking. A study of the DCV 3DAA regimen (DCV+ASV+BCV) using a full design demonstrated 99% and 2.3-fold increases in ASV AUC(TAU) in moderate and severe RI, respectively, which demonstrated a need for dose adjustment in subjects with severe RI unlike ESRD subjects on HD.
Literature review indicated that for a majority (22/27) of drugs with a significant component of renal elimination (fe ≥ 30%), Sponsors used a full RI study design. Dosage adjustment in RI subjects was frequently recommended for such compounds. In contrast, full RI studies were conducted in 68% of drugs eliminated by non-renal mechanisms. In almost all cases for which full RI studies were conducted, RI resulted in altered PK; dose adjustments were recommended in 13/38 (34%) cases.

Conclusions: Literature review and in-house BMS results indicate that subjects with RI can have significantly higher exposures of drugs with elimination primarily via metabolism or via transporter-mediated pathways. Sponsors should carefully consider subgroups included in a reduced study design; using only ESRD subjects on HD may not sufficiently characterize exposures and any needed dose adjustments in RI subjects.

Conflict of interest
financial relationship(s): Employee and stock holder of BMS

Abstract: O_6

Drug Drug Interactions

Effect of daclatasvir/ asunaprevir/beclabuvir in fixed-dose combination on the pharmacokinetics of CYP450/ transporter substrates in healthy subjects

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Introduction: Daclatasvir (DCV; NS5A inhibitor), asunaprevir (ASV; NS3 inhibitor), and beclabuvir (BCV; non-nucleoside NS5B inhibitor), in a fixed-dose combination (FDC) of DCV 30 mg, ASV 200 mg, and BCV 75 mg administered twice daily (BID), have been evaluated in phase 3 studies for the treatment of chronic hepatitis C infection. This open-label, single-sequence, five-period study assessed the effect of steady-state DCV/ASV/BCV FDC ± additional BCV 75mg BID (adjustment for differential exposure in HCV patients) on the single-dose pharmacokinetics of probe cytochrome P450 (CYP) and transporter substrates administered in a validated combination cocktail in healthy subjects.

Materials & Methods: Subjects (N=20; age 18–43 years; BMI 19.1–30.9 kg/m^2) received the probe substrate cocktail (caffeine 200 mg [CYP1A2], metoprolol 50 mg [CYP2D6], montelukast 10 mg [CYP2C8], flurbiprofen 50 mg [CYP2C9], omeprazole 40 mg [CYP2C19], midazolam 5 mg [CYP3A4], digoxin 0.25 mg [P-glycoprotein], and pravastatin 40 mg [OATP]) on Days 1 (alone), 16 (with FDC), and 31 (with FDC and additional BCV 75 mg). DCV/ASV/BCV was administered on Days 6–20 and 21–35 (+ BCV 75 mg BID). Serial pharmacokinetic sampling was conducted for 6 days after each probe dose. Treatment effects were assessed by point estimates and 90% confidence intervals (90% CI) for the ratio of geometric means (GMR) for standard pharmacokinetic parameters, including maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve extrapolated to infinity (AUC_{inf}), or to the last quantifiable concentration (AUC_T) using linear mixed models on log-transformed data.

Results: Coadministration of DCV/ASV/BCV did not have a meaningful effect on CYP1A2, CYP2C8, or CYP2C9, as indicated by the respective probe C_{max} and AUC_{inf} GMRs and 90% CIs being contained entirely within the 0.8–1.25 boundary: caffeine, 0.97 (0.93–1.02) and 0.96 (0.90–1.01); montelukast, 1.01 (0.95–1.08) and 0.92 (0.88–0.97); flurbiprofen 0.94 (0.88–0.99) and 0.90 (0.87–0.93), respectively. BCV was associated with dose-dependent moderate induction of CYP2C19 (omeprazole C_{max} and AUC_T were lower when administered with DCV/ASV/BCV + BCV 75 mg [0.36 (0.23–0.55) and 0.34 (0.25–0.46)] than with DCV/ASV/BCV [0.57 (0.42–0.78) and 0.48 (0.39–0.59)], respectively). Additional BCV 75 mg BID had no further meaningful impact on CYP1A2, CYP2C9, CYP2C8, CYP2D6, CYP3A4, P-glycoprotein, or OATP probe exposure. In concurrence with prior findings, weak-to-moderate induction of CYP3A4 was observed (midazolam C_{max}, 0.57 [0.50–0.65]; AUC_{inf}, 0.53 [0.47–0.60]), as was weak-to-moderate inhibition of CYP2D6 (metoprolol C_{max}, 1.40 [1.20–1.64]; AUC_{inf}, 1.71 [1.49–1.97]), weak inhibition of P-glycoprotein (digoxin C_{max}, 1.23 [1.12–1.35]; AUC_{inf}, 1.23 [1.17–1.29]), and inhibition of OATP (pravastatin C_{max}, 2.01 [1.63–2.47]; AUC_{inf}, 1.68 [1.43–1.97]). Study medications were generally well tolerated. One subject withdrew due to an adverse event (hemorrhoidal hemorrhage) considered related to flurbiprofen.

Conclusions: No dose adjustments are required during coadministration of DCV/ASV/BCV FDC with substrates of CYP1A2, CYP2C9, CYP2C8, or P-glycoprotein; substrates of CYP3A4, CYP2D6, and OATP should be coadministered with caution. It is not recommended to coadminister drugs solely eliminated by CYP2C19 with the DCV/ASV/BCV FDC regimen.

Conflict of interest
financial relationship(s): I am an employee of Bristol-Myers Squibb.

Abstract: O_7

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Steady state ribavirin pharmacokinetics in chronic hepatitis C infected patients with moderate renal impairment taking modern DAA combinations: are we dosing too high?

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Background and aim: Direct-acting antivirals (DAAs) are used for the treatment of chronic hepatitis C virus infection (HCV) to which ribavirin is added. In certain clinical situations ribavirin causes a concentration dependent anemia. Therefore, our aim was to identity variables which affect steady state plasma concentration of ribavirin in the context of modern DAA therapy.

Methods: In this prospective multicenter study we enrolled HCV patients treated with any DAA regimen and ribavirin. Ribavirin plasma concentrations were determined at treatment week 8. All sites were instructed to centrifuge the samples within two hours of blood collection, to prevent ribavirin leakage from the erythrocyte. The leakage could potentially cause false high ribavirin drug levels. Therefore we checked and removed outliers. Mean week 8 ribavirin concentrations were analyzed using a t-test for gender and body weight (<75kg or ≥75kg). DAA treatment and renal function were compared using ANOVA. Target range for ribavirin concentration was 2.2-3.6 mg/L and anemia was defined as a hemoglobin serum concentration <10g/dL.

Results: The cohort included 100 HCV patients (78% male) treated in 4 hospitals in The Netherlands. The majority was infected with genotype 1 (65%), had liver cirrhosis (55%), and was treated for 12 weeks (77%). The estimated glomerular filtration rate (eGFR) ranged from 17 to >90 mL/min, though 55% of the patients included had eGFR >90mL/min. Used DAA regimes were: sofosbuvir/daclatasvir (45%), sofosbuvir/simeprevir (32%), sofosbuvir alone (23%). The median ribavirin start dose (min; max) and week 8 ribavirin plasma concentration were 13.6 (5.0;19.1) mg/kg/day and 2.61 (0.4;6.0) mg/L, respectively. Ribavirin concentration below, in or above the target range was identified in 29%, 45% and, 26% of the patients, respectively. No significant differences in ribavirin concentrations were seen for gender, DAA regimen, or body weight. Despite the reduced doses (6.4, 10.1, 13.3mg/kg resp.), significantly different ribavirin concentrations were measured in patients with baseline eGFR <50, ≥50 <90, and ≥90 mL/min: 2.62, 3.49, and 2.46 mg/L, respectively (p=0.001). This is in line with the hemoglobin levels of these subgroups: 9.3, 11.0, 12.8 g/dL. Patients with eGFR ≥50 <90 mL/min had more frequently elevated week 8 ribavirin plasma concentrations (46%), more anemia (41%), and more dose reductions (57%) than patients without renal impairment (16%, 4%, and 31% resp.).

Conclusion: At steady-state, there was high variation in ribavirin concentrations. Additionally, the majority of patients had increased or decreased ribavirin plasma concentrations compared with target rage. This implies, that therapeutic drug monitoring (TDM) could be beneficial to improve ribavirin concentrations during DAA treatment. Especially in patients with mildly to moderately decreased renal function (eGFR ≥50 <90 mL/min). To date, no dose reductions are recommended by interactional guidelines. However, we expect these patients should receive a lower starting dosage of ribavirin, so SVR can be achieved without unnecessary toxicity.

No conflict of interest

Abstract: O_8

Drug Drug Interactions

Evaluation of Drug-Drug Interaction Between Sofosbuvir/Velpatasvir and Rifaximin in HCV-Infected Subjects with Moderate Hepatic Impairment

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Introduction: A fixed-dose combination of sofosbuvir (SOF), a nucleotide analog NS5B inhibitor, and velpatasvir (VEL; GS-5816), a pangenotypic NS5A inhibitor, is under regulatory review for the treatment of chronic HCV infection. In subjects with hepatic encephalopathy, rifaximin, a structural analog of rifampin, is commonly used at a dose of 550 mg twice-daily. Unlike rifampin, conflicting data exists on the potential of rifaximin to be a clinically-relevant P-gp/CYP inducer due to its poor bioavailability. Preclinical characterization of rifaximin demonstrates intestinal PXR agonism, though administration of rifaximin with midazolam, a selective CYP3A substrate, resulted in little change in the PK of midazolam. The effect of rifaximin on P-gp substrates, and particularly substrates of intestinal P-gp, is unknown. SOF and VEL are both substrates of P-gp and VEL is a substrate for CYP3A4, CYP2B6, and CYP2C8, and thus may be sensitive to induction of these pathways. Taking this into consideration, as well as the increased exposures of rifaximin seen with hepatic impairment (Child-Pugh Class A, B, or C: ~10, 14, and 21-fold increases in exposure, respectively), an analysis was conducted to understand the impact of rifaximin on the PK of SOF/VEL.

Methods: HCV-infected subjects with moderate (Child-Pugh B) hepatic impairment (HI) enrolled into the ASTRAL-4 study (N=268) received SOF/VEL once-daily ± ribavirin for 12 weeks or SOF/VEL once-daily for 24 weeks. Pharmacokinetic sampling to assess concentrations of SOF, its primary circulating metabolite GS-331007 and VEL occurred throughout the study. A population PK model was developed using Phase 1, 2, and 3 data and population PK-derived exposure was reported for SOF, GS-331007, and VEL. Rifaximin use and duration were recorded for each subject. Geometric least squares mean ratios (GMR[%]) and 90% confidence intervals (CIs) for AUC_{tau}, C_{max}, and C_{tau} (as applicable) were estimated comparing HCV-infected subjects with moderate HI concomitantly using rifaximin versus not using rifaximin.

Results: Two hundred sixty eight subjects were enrolled in the ASTRAL-4 study for the treatment of HCV infection, and 267 subjects received study drug. Amongst the study population, rifaximin use was reported in 92 of the 267 subjects. Of subjects reporting rifaximin use, 81/92 (88%) used rifaximin throughout the entire course of SOF/VEL treatment and 90/92 (98%) used rifaximin chronically (≥14 days during treatment with SOF/VEL). The exposure of SOF (GMR% for AUC: 102%; C_{max}: 98%), GS-331007 (GMR% for AUC: 102%; C_{max}: 103%), and VEL (GMR% for AUC: 89%; C_{max}: 88%; and C_{tau}: 91%) were not significantly altered by rifaximin. These data suggest limited potential for P-gp or CYP induction by rifaximin, even in subjects with hepatic impairment were rifaximin systemic exposure is higher.

Conclusions: The concomitant use of rifaximin with SOF/VEL±RBV in HCV-infected subjects with moderate hepatic impairment did not impact the PK of SOF/VEL, supporting coadministration of rifaximin with SOF/VEL.

Conflict of interest
financial relationship(s): All authors are employees of Gilead Sciences, Inc.

Abstract: O_9

PK-PD of Drug Efficacy and Toxicity

Cumulative tenofovir exposure is associated with decreased BMD in young and old HIV-infected adults on tenofovir based regimens

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Background: Decreased bone mineral density (BMD) is an established side effect of tenofovir disoproxil fumarate (TDF). Overall exposure to TDF is difficult to assess and cannot be quantified with plasma concentrations alone. Due to its long intracellular half-life in dried blood spots (DBS), tenofovir-diphosphate (TFV-DP) offers an objective and quantitative measure of cumulative dosing indicative of TDF exposure over a 1-2 month period. This study aimed to investigate the association between concentrations of TFV-DP in DBS and BMD in young versus older HIV-infected adults.

Methods: Blood samples were collected from fasting, virally suppressed, HIV-infected adults aged either 18-35 years or >60 years with ≥1 year of consistent tenofovir-based antiretroviral therapy. Whole blood was spotted onto Protein Saver Cards for DBS analysis. Validated LC/MS-MS methods were used to quantify TFV-DP in a 3-mm DBS punch. All participants underwent a dual-energy x-ray absorptiometry (DXA) scan of the lumbar spine, hip, and whole body. Steady-state concentrations (Css) of TFV-DP were log transformed prior to statistical analysis. Univariate and multivariable regression models were used to assess the association of TFV-DP in DBS with spine and hip BMD.

Results: The study included 45 subjects (23 young/22 older, 4 female, 6 African-American, 14 taking a protease inhibitor (PI)). Mean duration of TDF therapy was 3.8 and 4.9 years in the young and older cohorts, respectively. Mean (95% confidence interval) TFV-DP Css in DBS was 2136 (1777, 2495) fmol/punch in the young and 2341 (1919, 2763) fmol/punch in the older cohort. One participant in the older cohort had a TFV-DP Css in DBS of 43,614 fmol/punch and was excluded. Univariate regression analysis indicated that TFV-DP Css in DBS was negatively associated with lumbar spine BMD in the young cohort (p=0.03). In a multivariable model, the relationship between spine BMD and TFV-DP differed significantly by age (p=0.014). Spine BMD decreased an average of 0.007 g/cm^2 (-0.002, 0.013) per 100 fmol/punch increase in TFV-DP in the young cohort (p=0.009) and increased 0.002 g/cm^2 (-0.003, 0.007) per 100 fmol/punch in the older cohort (p=0.407). Univariate regression analysis in hip BMD found a decrease of 0.0042 g/cm^2 (-0.0081, -0.0004) per 100 fmol/punch increase in TFV-DP (p=0.032); although this result was attenuated after adjusting for lean mass and age (-0.0061, 0.0007). Exploratory analyses suggested the effect of PI-use on hip BMD varied by age (p=0.024). In a model adjusted for lean mass and TFV-DP, older participants taking a PI had lower hip BMD by 0.11 g/cm^2 (0.03, 0.19, p=0.008) relative to those not taking a PI, while younger participants taking a PI did not differ significantly from those not taking a PI (-0.03 g/cm^2, -0.12, 0.06, p=0.51).

Conclusions: Cumulative TFV therapy was associated with lower spine BMD in young participants, and PI-use was associated with lower hip BMD in older participants. Measures of cumulative TFV exposure may predict the degree of BMD decline in HIV-infected patients.

No conflict of interest

Abstract: O_10

PK-PD of Drug Efficacy and Toxicity

Intracellular Metabolism of Tenofovir Alafenamide in Cervical and Vaginal Epithelial Cells

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Background: Tenofovir alafenamide(TAF), a prodrug of tenofovir diphosphate(TFVdp), exhibits favorable intracellular metabolism in PBMCs compared to tenofovir disoproxil fumarate(TDF). Thus TAF's potential utility in HIV pre-exposure prophylaxis is being investigated. We have previously shown lower TFVdp concentrations in tissue homogenates from women dosed with TAF compared to TDF. However, it's unknown whether epithelial cells confound TFVdp concentrations in tissue homogenates by phosphorylating TAF to a lesser extent than HIV target cells.

Materials & Methods: To describe intracellular metabolism in epithelial cells compared to peripheral blood mononuclear cells(PBMCs), ectocervical(Ect1/E6E7) and vaginal(VK2/E6E7) cell lines were obtained from ATCC® and sub-cultured for >4 passes after initial thaw. $2X10^5$ Ect1/E6E7 and VK2/E6E7 cells/well were incubated overnight in 12-well culture plates with supplemented Gibco™ Keratinocyte medium. Freshly isolated PBMCs, from a single human donor, were incubated overnight at $2X10^6$ cells/well with supplemented RPMI 1640 medium. Cells were incubated with 0.5 and 10μM TAF or TFV for 3, 12, 24, 48 and 72hrs prior to harvesting and counting on a Muse™ Cell Analyzer. TFVdp was quantified in 3 replicate experiments using LC-MS/MS (lower limit of quantification= 0.02ng/ml) and reported as pmol/10^6 cells. $AUC_{0\text{-}72hr}$ was calculated with the linear trapezoidal rule using WinNonlin® version6.3. Pearson correlation was used to quantify the relationship among cell types for dose-normalized, log_{10} TFVdp concentrations from dose and time matched samples in SAS version9.3.

Results: TFVdp exposure was 1.7-17-fold higher in epithelial cells compared to PBMCs and 192-1309-fold higher with TAF versus TFV. Mean(SE) TFVdp $AUC_{0\text{-}72hr}$ (pmol*hr/10^6 cells) is as follows for Ect1/E6E7: 0.5μM TAF=10036(989) and TFV=26.66(1.783), 10μM TAF=210382(18701) and TFV=468.8(28.12); VK2/E6E7: 0.5μM TAF=3587(826) and TFV=18.62(1.598), 10μM TAF=60604(35751) and TFV=256.2(11.06); and PBMCs: 0.5μM TAF=2122(209) and TFV=1.626(0.1734), 10μM TAF=12646(702) and TFV=33.51(5.607). TFVdp concentrations plateaued by 48hrs in TAF and TFV treated PBMCs and Ect1/E6E7 cells and by 24hrs in VK2/E6E7 cells. During the linear phase of accumulation, TFVdp's rate of formation in PBMCs, Ect1/E6E7 and VK2/E6E7 was 0.765, 8.574 and 6.013pmol/10^6 cells/hr with 0.5μM TAF and 0.00058, 0.018 and 0.040pmol/10^6 cells/hr for 0.5μM TFV, respectively. TFVdp concentrations were strongly correlated among all cell types for both TAF (Pearson's r=0.42-0.90, $p<0.05$) and TFV (Pearson's r=0.45-0.71, $p<0.05$).

Conclusions: Consistent with previous *in vitro* investigations, equivalent molar doses of TAF compared to TFV achieved higher TFVdp exposure (>100-fold) in all cell types. These data demonstrate cervical and vaginal epithelial cells efficiently metabolize TAF achieving >1.7-fold higher TFVdp exposure relative to PBMCs. Therefore, it is unlikely that a high proportion of epithelial cells dilute TFVdp concentrations in tissue homogenates. The strong correlation between TFVdp concentrations in these cell types further supports tissue homogenates providing a qualitative measure of TFVdp in HIV target cells within mucosal tissues. Assuming dose proportionality, TFVdp concentrations in our Ect1/E6E7 cell line were only 1.7-fold higher than previous reports in primary ectocervical cells treated with TFV. Thus it is reasonable to extrapolate our findings in immortalized cells to primary epithelial cells. These data support the use of tissue homogenates to investigate TAF's mucosal tissue pharmacokinetics.

No conflict of interest

Abstract: O_11

PK-PD of Drug Efficacy and Toxicity

Pharmacogenetics of Efavirenz Discontinuation for Central Nervous System Symptoms at a Southeastern United States Clinic May Differ by Race

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Introduction: Efavirenz (EFV) is known to cause treatment-limiting central nervous system (CNS) symptoms. Single nucleotide polymorphisms (SNPs) in *CYP2B6* and *CYP2A6* predict increased plasma EFV exposure. We evaluated genetic associations with EFV discontinuation for CNS symptoms during the first year of antiretroviral therapy (ART).

Material & Methods: Eligible participants had initiated EFV-containing ART at the Vanderbilt Comprehensive Care Clinic (formerly called Comprehensive Care Center), had at least 12 months of follow-up data, and consented for genetic research. Clinical data were abstracted from electronic medical records. Reasons for EFV discontinuation were ascertained from provider notes. Four SNPs (*CYP2B6* rs3745274, rs28399499, rs4803419; *CYP2A6* rs28399433 by MassARRAY iPLEX Gold and TaqMan) were genotyped to assign EFV metabolizer status, and >500K SNPs (Illumina HumanCore Exome assay) to adjust for population stratification by multidimensional scaling (MDS). We used Cox models to examine genetic associations in all participants after adjusting for two MDS vectors, and separately by race after censoring individuals whose self-identified race/ethnicity varied from MDS clustering.

Results: A total of 563 individuals who initiated EFV from 1998 to 2012 were eligible. Median age was 37.9 years, 86% were male, 335 were White, 198 were Black, 25 were Hispanic and 5 were Asian. Self-identified race/ethnicity generally agreed with MDS clustering. Of the 563 individuals, 99 (17.5%) permanently discontinued EFV within 1 year, including 29 (5% overall) for CNS symptoms, while 464 continued EFV for at least 1 year. Among all individuals, in comparison to extensive metabolizers, the adjusted hazard ratio (HR) for EFV discontinuation for CNS symptoms in slow metabolizers was 4.87 (95% CI: 2.73 to 12.40; p=0.001), and in intermediate metabolizers was 1.09 (95% CI: 0.44 to 2.73; p=0.84). Among Whites with slow (n=24) or intermediate (n=126) metabolizer genotypes, HR for EFV discontinuation for CNS symptoms were 6.50 (95% CI: 2.25 to 18.75; p=0.001), and 1.11 (95% CI: 0.38 to 3.20; p=0.85), respectively. Among Blacks with slow (n=45) or intermediate (n=95) metabolizer genotypes, HR for EFV discontinuation for CNS symptoms were 2.59 (95% C.I. 0.47 to 14.13; p=0.27) and 0.90 (95% CI: 0.15 to 5.40; p=0.91), respectively. Within each metabolizer genotype group, we examined whether EFV discontinuation for CNS symptoms differed by race. Among individuals with slow metabolizer genotypes, the HR for EFV discontinuation for CNS symptoms in Whites versus Blacks was 3.08 (95% C.I. 0.87 to 10.95 p=0.08). Among intermediate metabolizers this HR in Whites versus Blacks was 1.52 (95% C.I. 0.38 to 6.06; p=0.55), and among extensive metabolizers this HR in Whites versus Blacks was 1.23 (95% C.I. 0.26 to 5.78; p=0.79).

Conclusions: At an HIV primary care clinic in the Southeastern United States, genotypes that are known to predict increased plasma EFV exposure were significantly associated with increased likelihood of EFV discontinuation for reported CNS symptoms in Whites but not in Blacks, despite these genotypes being more frequent in Blacks. This apparent difference by race, which is consistent with a previous report by Ribaudo et al (PMC2919241), may be due to biological and/or behavioral factors.

No conflict of interest

Abstract: O_12

PK-PD of Drug Efficacy and Toxicity

Virologic and Immunologic Responses to Raltegravir and Dolutegravir in GALT of HIV+ Men and Women

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Introduction: Persistent HIV replication during highly active antiretroviral therapy (HAART) has been noted in tissue reservoirs such as gut-associated lymphoid tissue (GALT). We have previously described differing GALT distribution of two integrase strand transfer inhibitors: raltegravir (RAL) exposure is >100-fold higher than blood plasma (BP) while dolutegravir (DTG) exposure is >5-fold less. It's unknown if this difference affects local virologic replication or immune activation. The primary objectives of this study were to compare HIV RNA, HIV DNA, and immunological markers in the GALT of HIV+ participants receiving RAL or DTG, with a backbone of tenofovir disoproxyl fumarate (TDF) + emtricitabine (FTC).

Material & Methods: In this Phase IV, open label study, HIV+ adults with BP viral load <50 copies/mL and treated with TDF 300mg + FTC 200mg once daily in combination with RAL (400mg) twice daily (n=10) or DTG (50mg) once daily (n=10) for >90 days were enrolled. BP was collected 2 hours post-dose and GALT specimens from terminal ileum (TI), splenic flexure (SF), and rectum (RT) were obtained by colonoscopy 2-6 hours post-dose. Flow cytometry for immunological markers was done using TI and SF tissues, drug concentrations were measured in RT, and HIV RNA and DNA were quantified using Droplet Digital PCR on combined tissues of all three types. During flow cytometry, CD4+ and CD8+ T-cells were tested for the γδTCR, markers of T-cell activation (e.g. CCR5, CD69, CD38+HLA-DR+), exhaustion (PD1), and type of memory T-cell (e.g. T(N), T(CM), T(EM), T(Eff)). Quantification of RAL and DTG concentrations in homogenates were measured using validated LC-MS/MS methods. All results are presented as median (range).

Results: Fifteen men and 5 women [age 52(32-64)yr; 15 African American, 6 Caucasian)] completed the study. Time since HIV diagnosis did not differ significantly between RAL [9.5(4-22)yr] and DTG [17(1-24)yr] (p=0.5) groups, although time on RAL 5.3(2.3-6.7)yr and DTG 1.0(0.25-1.5)yr was significantly different (p≤0.001). Current CD4+ T-cell count, and CD4+ nadir did not significantly differ between groups: 811(594-956) and 356(9-476)cells/mm^3 for RAL, 620(223-1300) and 74(2-458)cells/mm^3 for DTG (p≥0.2). Concentrations of DTG and RAL in RT were 810(490-5,927)ng/g and 5,307(2,025-33,654)ng/g, respectively, with tissue:plasma ratios of 0.44 (0.25-2.2) for DTG and 11.3 (2.0-85.2) for RAL. RNA and DNA concentrations did not significantly differ between groups: 7(0-144) and 3(0-78)copies/mg for DTG, 11(0-182) and 11(0-84)copies/mg for RAL (p≥0.4). 40% of DTG participants had undetectable DNA and/or RNA compared to 20% for RAL. No differences between CD4+ (43% vs 31%) and CD8+ (46% vs 52%) T-cells were found (p≥0.1). CCR5 expression on CD8+ T-cells was significantly lower in participants treated with RAL [0.15(0.03-1.73)%] vs DTG [0.63(0.1-9.22)%](p=0.03).

Conclusions: This study is the first to compare virologic and immunologic responses in GALT of RAL and DTG-treated participants using a backbone of TDF+FTC. Even though RAL produced higher tissue exposures than DTG consistent with previous studies, no significant differences in tissue HIV RNA, DNA, or most immunologic markers were observed. RAL-treated subjects had significantly lower CCR5 expression on CD8+ cells. Tissue imaging is ongoing to determine drug concentrations and viral expression in cell subtypes.

No conflict of interest

Abstract: O_13

PK-PD of Drug Efficacy and Toxicity

Efficacy of once-weekly MK-8591 in SIV infected rhesus macaques

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Background: MK-8591 is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) in early clinical development for the treatment and prophylaxis of HIV-1. A single 10 mg dose of MK-8591 demonstrated robust efficacy in HIV-1 infected subjects for a ten day period, with a viral load (VL) reduction of 1.78 $\log_{10}$. In vitro, MK-8591 exhibits similar antiviral activity against both HIV-1 and SIV. Here we describe the evaluation of MK-8591 dosed orally once-weekly in an SIV-infected rhesus macaque model of HIV-1 infection. Our study provides the first proof-of-concept for the extended duration dosing potential of MK-8591 and suggests the intracellular MK-8591 tri-phosphate concentration targets required for efficacy in the clinic.

Materials & Methods: Rhesus macaques were inoculated with SIVmac251. Six or twelve weeks later, treatments were administered in a 2-arm adaptive study design. Macaques were administered either two sequential once-weekly oral doses of vehicle, 1.3, 3.9, 13 or 18.2 mg/kg MK-8591 or a once-daily oral doses of 0.19 mg/kg QD for 14 days. VL was monitored through study day 35. All samples were sequenced to monitor for the emergence of resistance mutations. To evaluate efficacy against SIV variants harboring M184 resistance mutations, macaques inoculated with wild-type virus were administered 3TC daily until viral rebound was observed, treated with two once-weekly doses of MK-8591, and monitored as described.

Results: Maximal rates of VL decline were observed in groups dosed with 3.9 to 18.2 mg/kg MK-8591 administered once-weekly, corresponding to an intracellular MK-8591 triphosphate concentrations of greater than or equal to 0.53 pmol/million peripheral blood mononuclear cells. At these doses, the rate and extent in the decline of viremia was similar to that observed with once-daily administration of MK-8591. Viral suppression was maintained for at least 7 days from the last dose, however, the time to recrudescence in VL correlated with the dose. While M184I and M184V were detected intermittently at various time points in the study, it was not associated with viral rebound, suggesting the ability of MK-8591 to suppress this variant at the concentrations achieved. When administered to SIV infected animals harboring M184 mutations, MK-8591 suppressed these variants at concentrations achieved in clinical studies.

Conclusions: MK-8591 is a potent inhibitor of SIV replication in a macaque model of HIV infection. Our data provide the first proof-of-concept for once-weekly administration of 0.19 mg/kg MK-8591, establish an intracellular compound concentration target for efficacy in humans, and demonstrate efficacy against variants harboring M184 mutations in reverse transcriptase.

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

Abstract: O_14

PK/PD modeling

In silico pharmacokinetic/ pharmacodynamic simulation of long acting tenofovir injectable formulation for pre exposure prophylaxis strategies.

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Introduction: Oral tenofovir (TFV) disoproxil fumarate has been effectively used in pre-exposure prophylaxis (PrEP) strategies to protect against HIV acquisition in high-risk populations. Maintenance of sufficient antiretroviral drug concentrations is critical for prevention, and PreP efficacy is limited by patient adherence. Development of long-acting (LA) injectable formulations of TFV presents opportunities to mitigate problems associated with patient non-adherence. The aim of this study was to utilise physiologically-based pharmacokinetic/ pharmacodynamic (PBPK-PD) modelling to provide a quantitative framework for development of NRTI-based LA PrEP.

Materials & Methods: In vitro or population PK data for TDF were integrated into PBPK models and PK was simulated for 500 individuals (MATLAB, R2013b).
The models included mathematical descriptions of covariance between demographics and tissue size, expression of metabolic enzymes and processes regulating absorption, distribution and elimination, which are drug-specific.
The models were validated against clinical data for oral administration of standard regimens. The PD concentration cut-offs for oral PrEP efficacy were then included in the models.
Validated models were used for the prediction of PK and PD following intramuscular administration of theoretical LA formulations.

Results: The simulated PK parameters for oral administration were in agreement with previously published clinical data. Following simulation of LA-TFV the following dose and release rates were identified to provide suitable exposure for 1 (750mg, release rate 0.002) and 3 months (1000mg, release rate 0.001). Minimum plasma concentrations (C_{min}; mean ± SD) following 1 month and 3 month injections were predicted to be 29.4 ng/ml ± 16.1 and 9.5 ng/ml ± 5.1 respectively. Predicted intracellular C_{min} for tenofovir diphosphate (TFV-DP) were 45.7 fmol/10^6 cells ± 16.4 and 41.2 fmol/10^6 cells ± 15.1 following 1 month and 3 month injections, respectively. The simulated intracellular concentrations were above the concentrations associated with 90% reduction in HIV acquisition in 96.6% and 96% of patients following 1 month and 3 month simulated injections respectively, indicating LA-TFV may be a suitable candidate for monthly or quarterly IM LA if pharmaceutical challenges can be met.

Conclusions: The pharmacokinetics of TFV following intramuscular injection were predicted using a validated in silico modelling approach. The simulation of PreP PD assumed that the TFV distribution into key tissues and mucosa is comparable between the traditional oral formulations and intramuscular injections as would be expected for a solid drug nanoparticle formulation. Importantly, the concentration cut-offs used were those generated in combination with emtricitabine and are likely to be different for monotherapy. These data may be useful to inform development of TFV LA PreP.

Conflict of interest
financial relationship(s): Andrew Owen has received research funding from Merck, Pfizer and AstraZeneca, consultancy from Merck and Norgine, and is a co-inventor of patents relating to HIV nanomedicines. Marco Siccardi has received research funding from ViiV and Janssen Charles Flexner received consulting or advisor fees from Abbvie, Boehringer Ingelheim, Bristol Myers-Squibb, Gilead, GlaxoSmithKline, Merck and ViiV.

Abstract: O_15

Novel Drugs and Formulations

MK-3682, a HCV NS5B Inhibitor with a Broad Spectrum of HCV Genotypic Activity, Demonstrates Potent Antiviral Activity in Genotypes -1,-2, and -3 HCV-Infected Patients

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Background: MK-3682 is a potent, pan-genotypic inhibitor of Hepatitis C Virus (HCV) non-structural protein 5B (NS5B) that is being developed for the treatment of HCV infection. A Phase 1b, randomized, placebo-controlled study was conducted to assess the safety, pharmacokinetics and antiviral activity of MK-3682 administered as 7 days of monotherapy in non-cirrhotic patients with genotype (GT) -1, -2, or -3 HCV infection and in HCV GT1-infected patients with mild hepatic impairment.

Materials & Methods: Eighty (80) adults, with HCV GT-1, -2, or -3 infection (HCV RNA ≥ 5.0 $\log_{10}$ IU/mL) without clinical evidence of cirrhosis, were randomized to receive placebo or MK-3682 from 50 to 400 mg (GT1) or were randomized to receive open-label MK-3682 300 to 450 mg (GT-1) or 50 to 300 mg (GT-2 or GT-3) once daily for 7 days, followed by pharmacokinetic (PK) and viral load sampling for 14 and 35 days, respectively. Safety and tolerability were evaluated using laboratory values, ECGs, and evaluation of adverse events (AEs). After review of safety, antiviral activity, and pharmacokinetic (PK) data, eleven (11) adults with HCV GT1 infection and mild hepatic impairment (Child-Pugh Score A) received open-label MK-3682 300 or 450 mg once daily for 7 days, followed by collection of safety, efficacy, and PK data.

Results: Data from seventy-three (73) subjects were analyzed as the per-protocol population. Plasma HCV RNA declined rapidly after dosing with mean maximum reductions from baseline of 4.3 $\log_{10}$ IU/mL in non-cirrhotic GT-1 HCV-infected patients, reflecting 4.9 and 4.1 $\log_{10}$ IU/mL reductions for GT-1a (n=2) and GT-1b subjects (n=5), respectively, following 450 mg QD for 7 days (tablets). In non-cirrhotic GT-2 (n=2) and GT-3 (n=7) HCV-infected patients, the mean maximum viral load reductions from baseline were 4.7 and 4.1 $\log_{10}$ IU/mL, respectively, following 300 mg QD for 7 days (capsules). In GT-1 HCV-infected patients with mild hepatic impairment (n=7), viral load reductions from baseline were 3.1 $\log_{10}$ IU/mL following 450 mg QD for 7 days (tablets). In all treatment groups, MK-3682 and its major circulating metabolite M6 had median Tmax of 0.5-2 hours and 2-4 hours, respectively, with mean apparent terminal $t_{1/2}$ of ~2-3 hours and 26-30 hours, respectively. MK-3682 exposures were approximately dose-proportional, while M6 was slightly less than dose-proportional. Decreases in viral load were dose-proportional, and exposure-response analyses suggest that antiviral activity of MK-3682 at a 450 mg dose of the tablet formulation is largely maintained at the plateau level. MK-3682 was generally well-tolerated, with all AEs transient and mild in intensity. The most common AE was headache. There were no clinically significant laboratory abnormalities, changes in vital signs or ECG readings.

Conclusions: MK-3682 exhibits potent antiviral activity during 7 days of monotherapy in non-cirrhotic patients with GT-1, -2, and GT-3 chronic HCV infection and in patients with mild hepatic impairment with GT-1 chronic HCV infection. The safety, pharmacokinetics, and antiviral data support the continued clinical investigation of MK-3682 at a dose of 450 mg as a once-daily component of an all-oral, interferon-free regimen for the treatment of chronic HCV-infection.

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

Abstract: O_16

PK/PD modeling

PBPK/PD Modeling and Simulations to Guide Dose Recommendation of Amlodipine after Co-administration with Viekirax or Viekira Pak

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Introduction: Amlodipine is a commonly used calcium channel blocker (CCB) prescribed as an anti-hypertensive drug. Based on the amlodipine label, moderate and strong CYP3A inhibitors result in increased systemic exposure to amlodipine and may require dose reduction with recommendations to monitor for symptoms of hypotension and edema. Ritonavir (RTV) is a known potent CYP3A4 inhibitor and part of the 2- and 3-DAA HCV regimen of ombitasvir/ paritaprevir/ ritonavir ± dasabuvir. Using physio-logicallybased pharmacokinetic & pharma-codynamic (PBPK/PD) modeling, the magnitude and time course of RTV effect on amlodipine exposures and PD responses (systolic blood pressure) were evaluated to provide guidance on dose adjustment of amlodipine when dosed with the 2- and 3-DAA regimen.

Materials and Methods: A PBPK model was developed in Simcyp® for amlodipine using data from literature. The model was validated against published clinical PK and DDI data from studies in healthy volunteers. An initial PBPK model for RTV was available in Simcyp®, and was optimized/validated using internal and published data. Assuming a full dose of amlodipine of 5 mg QD prior to co-administration with RTV, a 50% dose reduction of amlodipine (2.5 mg QD) with RTV (100 mg QD) co-administration at steady state was simulated using the developed PBPK models.

Amlodipine PBPK model was combined with a PD linear model to describe changes in systolic blood pressure (BP) during and after co-administration with RTV.

Results: PBPK modeling accurately predicted the increase (157% higher AUC and 26% higher C_{max}) in amlodipine exposure following co-administration with RTV containing 3-DAA regimen. PBPK simulations revealed that the net effect (inhibition) of RTV on CYP3A4 in liver reached a steady-state in about 3 days. After stopping RTV co-administration, hepatic CYP3A4 levels returned to baseline in about 10 days and amlodipine plasma exposure returned to approximately baseline in about 5 days. Simulations suggest that continuing amlodipine reduced dosage of 2.5 mg QD for 5 days after RTV was stopped, results in a slight increase in the daily average systolic BP to a maximum of 2.3 mmHg above the steady-state levels. In contrast, resuming amlodipine full dose of 5 mg QD immediately after RTV was stopped results in a decrease of daily average systolic BP by a maximum of 3.2 mmHg below steady-state levels.

Conclusions: PBPK/PD modeling strategy was used to investigate dose adjustment recommendations for amlodipine during and after co-administration of RTV containing 2- or 3-DAA regimens. Based on the model simulations, amlodipine at reduced dose of 2.5 mg QD may be continued for 5 days after RTV is stopped, followed by a return to the full dose of 5 mg QD. Alternatively, the full dose of amlodipine may resume immediately the day after last dose of RTV. The developed strategy utilizing PBPK/PD modeling of amlodipine can be utilized to explore dosing recommendations of amlodipine with other CYP3A4 modulators.

*** AbbVie contributed to the research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options.*

Conflict of interest
financial relationship(s): AbbVie contributed to the 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_17

PK-PD of Drug Efficacy and Toxicity

Effects of Sofosbuvir/Ribavirin Treatment and ITPA Phenotype on Endogenous Purines

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Background: Ribavirin (RBV) is a purine nucleoside analog used to treat hepatitis C (HCV) and other viruses. *In-vitro* studies suggest the triphosphate form of RBV (RBV-TP) may affect adenosine and guanosine triphosphate (ATP, GTP) concentrations in red blood cells (RBC), but there are limited data *in-vivo*. Single nucleotide polymorphisms in the gene encoding the inosine triphosphatase enzyme (ITPA) are associated with protection from RBV-induced anemia and increased inosine triphosphate (ITP) levels in RBC. ITPA activity may also modify the association between RBV treatment and changes in ATP and GTP. We estimate the effect of RBV treatment, RBV-TP concentrations, and ITPA activity on ATP, GTP and ITP concentrations in RBC of HCV-infected individuals.

Materials and Methods: Whole blood was collected in PAXgene® RNA tubes from HCV-infected genotype 1 patients receiving low dose (600 mg/day) or weight-based (1000 or 1200mg daily) RBV and sofosbuvir (SOF) (400 mg/day) at baseline, days 3, 28 and 84. Separation, isolation, and quantification of triphosphates for all analytes was achieved with a validated, LC-MS/MS method. ITPA genotyping of rs1127354 and rs7270101 was performed and ITPA activity phenotype assigned as 100% (wild type, WT) or ≤60% (non-WT). Mixed-effects models were used.

Results: Forty-seven subjects (66% male, 81% black, 74% WT, mean (SD) age 54 (9.0) years and weight 89.5 (20.8) kg) from the NIH SPARE trial were included. Mean (SD) ATP, GTP and ITP concentrations at baseline were 103 (35.1), 5.43 (2.5) and 0.709 (3.2) pmol/10^6cells, respectively. By day 84 of treatment, ATP levels were reduced by 38.6% (95% CI 25.0%, 49.6%, p<0.0001). However, the effect of RBV-TP on ATP levels differed by ITPA status (p=0.006). Given RBV-TP concentration of 120 pmol/10^6 cells at day 84, ATP decreased by 29.4% (-39.9%, -17.1%, p<0.001) in non-WT vs. 9.6% (-20%, 2.9%, p=0.13) in WT.

GTP did not significantly decrease over time (p=0.47), but RBV-TP effect differed by ITPA status (p=0.02). GTP increased 16.5% (3.3%, 31.4%) for every 100 pmol/10^6cells RBV-TP increase in WT (p=0.01) with corresponding 1.0% decrease (-12.1%, 12.5%) in non WT (p=0.88). ITP was not significantly decreased over time (p=0.08) and the effect of RBV-TP on ITP did not differ by ITPA status (p=0.13). ITP increased in WT 22.7% (-1.2%, 52.4%) for every 100 pmol/10^6cells RBV-TP (p=0.06), with corresponding 1.5% increase (-18.4%, 26.2%) for non-WT (p=0.89).

Conclusions: SOF/RBV treatment decreased ATP levels in humans, and this change remained after controlling for RBV-TP levels and ITPA activity. Surprisingly, ITPA non-WT subjects had larger reductions in ATP suggesting that protection from RBV-induced anemia is due to a different mechanism than predicted from *in-vitro* studies. Additionally, there was little effect of SOF/RBV on GTP in RBC, but this may be explained by the fact that *de-novo* purine synthesis is not occurring in RBC and thus RBV does not impact GTP production. While ITPA non-WT subjects were expected to have higher ITP levels, this was not observed. These results underscore the importance of characterizing the impact of nucleos(t)ide analog treatment on endogenous purines *in vivo*.

No conflict of interest

Abstract: O_18

Drug Drug Interactions

Rifampin (RIF) Decreases Cabotegravir (CAB) Exposure following Oral Coadministration

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Introduction: CAB is an integrase strand transfer inhibitor (ISTI) in development as a long-acting (LA) injectable formulation for the treatment and prevention of HIV. Drug-drug interactions with oral CAB have been conducted to support coadministration of other agents with CAB LA. CAB is metabolized primarily by UGT1A1, with minor contribution by UGT1A9. RIF, a potent inducer of UGT and CYP enzymes, reduces exposure to the ISTIs raltegravir, elvitegravir and dolutegravir, which are metabolized by these pathways. This study was conducted to determine the impact of RIF on oral CAB.

Materials and Methods: This Phase I, open label, fixed-sequence cross-over study was conducted to evaluate the effect of RIF on the pharmacokinetics (PK) of oral CAB in healthy adult subjects. Subjects received a single dose of oral CAB 30mg on Day 1 with PK sampling to Day 7, oral RIF 600mg once daily x 13d from Day 8 to Day 20, and a single dose of oral CAB 30mg on Day 21 with RIF 600mg once daily continuing through PK sample collection to Day 28. Plasma CAB PK parameters were determined by noncompartmental analysis. Geometric least squares (GLS) mean ratios with associated 90% confidence intervals for CAB PK parameters were calculated to compare CAB+RIF versus CAB treatments.

Results: Fifteen subjects enrolled and completed all treatments. All AEs were mild (Grade 1), and all subjects reported experiencing chromaturia while receiving RIF. Geometric mean CAB AUC(0-∞), Cmax, t1/2 and CL/F were 146mg•h/mL, 3.61mg/mL, 38.6h, and 0.21L/h prior to RIF administration and were 59.7mg•h/mL, 3.39mg/mL, 16.4h, and 0.50L/h when CAB was administered 2 weeks after initiating RIF once daily dosing. RIF increased CAB oral clearance 2.4-fold and reduced CAB AUC(0-∞) and terminal phase t1/2 by 59% and 57%, respectively. RIF had no effect on CAB Cmax, and the observed reduction in exposure can be attributed to increased elimination rather than decreased absorption.

Conclusions: RIF increased CAB clearance and decreased CAB exposure following oral coadministration. Concomitant administration of RIF with CAB LA IM injections is likely to decrease plasma CAB concentrations and, therefore, is not recommended without further investigation.

Conflict of interest
financial relationship(s): Employee of GlaxoSmithKline at the time of the study. Current employee of PARAXEL

Abstract: O_19

Drug Drug Interactions

Increased Tenofovir Diphosphate in Red Blood Cells, but Not Tenofovir in Plasma, with Sofosbuvir and Ribavirin

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Background: ACTG 5327 (SWIFT-C) is a two cohort study assessing sofosbuvir (SOF)-containing direct acting antiviral therapies for the treatment of acute Hepatitis C virus (HCV) in patients with chronic HIV-infection. Cohort I assessed the efficacy of SOF and weight-based ribavirin (RBV; 1000 or 1200mg daily) for 12 weeks. The sustained virologic response (SVR) rate was 59% with a high rate of relapse (41%). We previously reported that individuals with relapse had lower RBV plasma concentrations, which may reflect reduced adherence to RBV. Thus, we sought to quantify antiretroviral (ARV) adherence in the study participants. Tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots (DBS) are reflective of cumulative drug dosing and long-term adherence, whereas tenofovir (TFV) concentrations in plasma reflect recent dosing and short-term adherence. The primary aim of this study was to compare TFV-DP concentrations in DBS and TFV concentrations in plasma before, during, and after SOF/RBV treatment.

Methods: Plasma and DBS were obtained from participants at entry, week 12 of SOF/RBV treatment (WK12) and 12 weeks following the end of SOF/RBV treatment (EOT+12). Validated LC/MS-MS methods were used to quantify TFV in plasma and TFV-DP in a 3-mm DBS punch. TFV and TFV-DP concentrations were compared across the three visits using repeated measures ANOVA with Tukey's post-hoc test for individual comparisons.

Results: Seventeen HIV-infected male participants entered Cohort I of SWIFT-C and all completed 12 weeks of SOF/RBV treatment for acute HCV. All 17 were on antiretroviral (ARV) therapy and 15 were taking tenofovir disoproxil fumarate (TDF) as part of their ARV regimen. Among these 15, 11 were Hispanic, 4 Caucasian non-Hispanic and mean (±SD) age was 44.3 (±9.5) years and weight 76.5 (±10.3) kg. TFV-DP concentrations in DBS differed between entry, WK12, and EOT+12 (p=0.002). At entry, mean (±SD) TFV-DP in DBS was 1767.8 (±543.1) fmol/punch; consistent with historical data in HIV-infected individuals with good adherence. However, at WK12 of SOF/RBV treatment, TFV-DP concentrations were 6.8-fold higher vs. entry (range 1.43-18.3, p=0.0043), with a mean (±SD) TFV-DP in DBS of 10,055.6 (±7678.6) fmol/punch. By EOT+12, TFV-DP in DBS was similar to entry with a mean (±SD) of 2237.5 (±814.3) fmol/punch. TFV concentrations in plasma were similar to historical data and unchanged across visits. At entry, WK12 and EOT+12, mean (±SD) TFV was 113.2 (±70.9), 109.9 (±62.9), and 110.5 (±87.1) ng/mL, respectively. Renal function was unchanged between entry and wk12; mean (±SD) CrCl was 123.88 (±24.34) mL/min and 118.05 (±20.54) mL/min, respectively. TFV-DP in DBS at WK12 did not differ in those that achieved SVR vs. relapsed.

Conclusions: The intent of this work was to assess ARV adherence, however these data suggest a new type of drug interaction at the cellular level. After 12 weeks of SOF/RBV treatment, TFV-DP concentrations in DBS were increased 6.8-fold despite no change in TFV plasma levels. Additional studies are needed to determine the perpetrator (SOF vs. RBV) and mechanism, presence in other cell types, and clinical significance.

No conflict of interest

Abstract: O_20

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Pharmacokinetics of Darunavir, Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir and Ribavirin in Adults Infected with Hepatitis C Virus (HCV) Genotype (GT) 1 and Human Immunodeficiency Virus Type 1 (HIV-1)

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Background: The three-direct acting antiviral (3-DAA) regimen containing ombitasvir, paritaprevir, ritonavir and dasabuvir with or without ribavirin (RBV) is approved for treatment of HCV GT1 infection including those with HIV-1 co-infection. TURQUOISE-I (NCT01939197) was designed to assess the safety and efficacy of the 3-DAA regimen with and without RBV in HIV/HCV co-infected adults. Preliminary results of a pharmacokinetic substudy of the 3-DAA regimen and darunavir are presented.

Materials & Methods: TURQUOISE I is an ongoing Phase 2/3, open-label, multicenter study. Subjects enrolled into the substudy and stable on an antiretroviral regimen containing darunavir once daily (QD) were randomized to maintain darunavir 800 mg QD or switch to darunavir 600 mg twice daily (BID) for a minimum of 14 days prior to starting the 3-DAA regimen. Darunavir pharmacokinetic parameters without the 3-DAA regimen were determined on Study Day -1.
On Study Day 1, subjects received ombitasvir/ paritaprevir/ritonavir 25/150/100 mg QD, dasabuvir 250 mg BID and weight based ribavirin with the darunavir based antiretroviral regimen. Low-dose ritonavir from the 3-DAA regimen boosted darunavir during HCV treatment. Subjects switched to darunavir BID also received ritonavir 100 mg with the evening dose of darunavir. Pharmacokinetic parameters for darunavir and the 3-DAA regimen when co-administered were determined at Week 4. Serial blood samples were collected over the dosing interval and pharmacokinetic parameters were assessed using non-compartmental analysis. Darunavir pharmacokinetic parameters were compared at Week 4 versus Study Day -1. Pharmacokinetic parameters of the 3-DAA regimen were compared to historical data from Phase 1 studies.

Results: The pharmacokinetic substudy enrolled 22 subjects; 10 subjects received darunavir QD and 12 subjects received darunavir BID. For darunavir QD with the 3-DAA regimen vs. alone, the central value ratios (90% confidence interval [CI]) for darunavir Cmax, AUC24 and C24 were 0.92 (0.72, 1.18), 0.83 (0.71, 0.98) and 0.64 (0.44, 0.93), respectively. For darunavir BID, the ratios (90% CI) for darunavir Cmax, AUC12 and C12 were 0.92 (0.76, 1.12), 0.88 (0.73, 1.05) and 0.73 (0.58, 0.92), respectively. Ombitasvir and paritaprevir AUC and Cmax in subjects receiving DRV QD were within the range (± 15%) of historical data; ritonavir and dasabuvir AUC were within range of historical data but Cmax was 32% and 34% lower. Ombitasvir and paritaprevir AUC and Cmax in subjects receiving DRV BID were similar to historical data; dasabuvir AUC was within range of historical data but Cmax was 43% lower. These differences are not considered clinically significant. Episodes of intermittent HIV-1 viremia (plasma HIV-1 RNA Ž40 and <200 copies/mL) during treatment occurred in 5 subjects (2 DRV QD, 3 DRV BID). The highest HIV-1 RNA observed during treatment was 79 copies/mL.

Conclusions: Co-administration of the 3-DAA regimen with darunavir QD or BID did not affect darunavir Cmax and AUC, whereas darunavir Ctrough decreased 36% with QD dosing and 27% with BID dosing. Changes in pharmacokinetic parameters of the 3-DAA regimen were not considered clinically significant. Episodes of intermittent HIV-1 viremia were infrequent and no relationship between reductions in DRV Ctrough levels and intermittent HIV viremia was observed.

Conflict of interest
All authors are employees of Abbvie.

Abstract: O_21

Drug Drug Interactions

Physiologically-based simulation of daclatasvir pharmacokinetics with antiretroviral inducers and inhibitors of cytochrome P450 and drug transporters

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Introduction: Many HIV-infected patients receive combination antiretroviral (ARV) regimens containing components that are inducers or inhibitors of cytochrome P450 (CYP) and/or drug transporters (DT). Coadministration of daclatasvir (DCV; pangenotypic NS5A inhibitor) with some individual ARVs in HIV–HCV coinfected patients requires adjustment of the standard 60 mg daily DCV dose (30 mg with ritonavir [r]- or cobicistat [c]-boosted atazanavir [ATV/r; ATV/c]; 90 mg with efavirenz [EFV] or nevirapine); however, recommending a DCV dose with complex combination regimens containing several CYP and/or DT perpetrators is a challenge. We used a verified physiologically based pharmacokinetic (PBPK) model of DCV to simulate the effects of combination ARV regimens on DCV systemic exposure to recommend an appropriate DCV dose.

Materials & Methods: PBPK models for DCV and several common ARVs and boosters were constructed in Simcyp Simulator (v14) using physicochemical parameters, combinations of *in vitro* data or *in silico* prediction, and clinical PK data. Prospective simulations of healthy-subject DCV PK studies were undertaken, and geometric mean ratios (GMRs) and 95% confidence intervals (95% CI) for DCV AUC and C_{max} were derived for DCV administration with vs without ARVs (6 simulation trials per regimen; 14 subjects per trial). A maximum of 3 CYP/DT perpetrators relevant to DCV PK were included per regimen. The optimal DCV dose with these combination regimens was assessed by comparing simulated GMRs with observed drug interaction data and corresponding dose recommendations.

Results: DCV GMRs and 95% CI were modelled for several regimens combining inducers (EFV) and inhibitors (ritonavir-boosted darunavir [DRV/r], ATV/r or ATV/c) of CYP3A4, with and without additional non-perpetrator ARVs (raltegravir [RAL], elvitegravir [EVG], maraviroc [MVC]). Nucleoside/nucleotide analogs were not included in the simulations. For EFV + DRV/r (with or without RAL and/or MVC), the DCV GMR (95% CI) was 1.57 (1.44–1.72) for AUC and 1.31 (1.25–1.39) for C_{max} for administration with vs without ARVs. For EFV + ATV/r (400/100 mg), the GMR (95% CI) was 2.36 (2.18–2.56) for AUC and 1.75 (1.66–1.85) for C_{max}, while for EVG + ATV/c (300/150 mg) these values were 2.92 (2.77–3.02) and 1.97 (1.90–2.05), respectively. Thus, with the exception of boosted ATV, combinations of boosted protease inhibitors with moderate CYP3A4 inducers such as EFV are predicted to result in no substantial change to DCV PK from the standard 60 mg daily DCV dose. ATV/r or ATV/c in combination with EFV is predicted to increase DCV exposure more than 2-fold; thus, a DCV dose reduction to 30 mg daily is recommended. Substitution of etravirine for EFV is expected to yield similar results due to similar CYP3A4 induction by both agents.

Conclusions: Based on PBPK modeling, the standard DCV dose of 60 mg daily is appropriate for ARV regimens containing both DRV/r and EFV. Regimens containing boosted ATV, with or without EFV, require a DCV dose reduction to 30mg.

Conflict of interest
financial relationship(s): I am an employee of Bristol-Myers Squibb.

Abstract: O_22

Drug Drug Interactions

A Clinically Meaningful Drug-Drug Interaction Observed Between ZepatierTM (Grazoprevir/Elbasvir) and Stribild® HIV Fixed-Dose Combination in Healthy Subjects

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Background: Zepatier™ is an approved once-daily treatment for chronic hepatitis C infection (HCV), and is a fixed-dose combination of 100 mg of grazoprevir (GZR), an HCV NS3/4A protease inhibitor, and 50 mg of elbasvir (EBR), an HCV NS5A inhibitor.
To inform dosing recommendations for ZepatierTM in HCV patients with HIV co-infection, this study was conducted to evaluate the potential for a drug-drug interaction between Zepatier™ and Stribild® (150 mg elvitegravir [EVG], 150 mg cobicistat [COBI], 200 mg emtricitabine [FTC], and 300 mg tenofovir disoproxil fumarate [TDF]).

Methods: This study was conducted with 22 healthy adults, 6 females and 16 males. This was a fixed-sequence, 3-period study. In Period 1, multiple oral doses of Stribild® were administered once-daily (QD) for 7 days followed by a washout period of 5 days. In Period 2, Zepatier™ was administered QD for 10 days. In Period 3, Stribild® was co-administered with Zepatier™ QD for 10 days. There was no washout between Periods 2 and 3. All study drugs were administered under fed conditions. Pharmacokinetics (PK) were determined over 24-hour intervals for GZR, EBR, EVG, COBI, FTC, and tenofovir (TFV). Plasma pharmacokinetic (PK) samples for EVG, FTC, TFV, COBI, GZR, and EBR were collected up to 24 hours following administration of the last dose in each treatment period to determine plasma concentrations.

Results: The EVG AUC_{0-24} and C_{max} geometric mean ratios (GMRs) (90% confidence intervals [CIs]) for Zepatier™ + Stribild® / Stribild® alone were 1.10 [1.00, 1.21] and 1.02 [0.93, 1.11], respectively. The FTC AUC_{0-24} and C_{max} [90% CI] was 1.07 [1.03, 1.10] and 0.96 [0.90, 1.02), respectively. For the same treatment comparison, the TFV AUC_{0-24} and Cmax GMRs [90% CIs] were 1.18 [1.13, 1.24] and 1.25 [1.14, 1.37], respectively. The COBI AUC_{0-24} and C_{max} GMRs [90% CIs] were 1.49 [1.42, 1.57] and 1.39 [1.29, 1.50], respectively. The GZR AUC_{0-24} and C_{max} GMRs [90% CIs] for the Zepatier™ + Stribild® / Zepatier™ alone comparison were 5.36 [4.48, 6.43] and 4.59 [3.70, 5.69], respectively. The EBR AUC_{0-24} and C_{max} GMRs [90% CIs] for the Zepatier™ + Stribild® / Zepatier™ alone comparison were 2.18 [2.02, 2.35] and 1.91 [1.77, 2.05], respectively.

Conclusions: Following coadministration of Zepatier™ and Stribild®, the pharmacokinetics of EVG, FTC, and TFV were not meaningfully altered as compared to administration of Stribild® alone. Cobicistat AUC_{0-24} and C_{max} increased 49% and 39%, respectively, when Stribild® was coadministered with Zepatier™ compared to when Stribild® was administered alone. A clinically relevant increase in AUC_{0-24} of GZR of ~5-fold was observed following concomitant administration of Stribild® and Zepatier™ as compared to that administration of Zepatier™ alone. The AUC_{0-24} of EBR was ~2-fold higher following concomitant administration of Stribild® and Zepatier™ as compared to administration of Zepatier™ alone.

Conflict of interest
financial relationship(s): I am an employee of Merck & Co. Inc.

Abstract: O_23

Drug Drug Interactions

Pharmacokinetics of Dolutegravir after Switching to Abacavir/Dolutegravir/Lamivudine from an Efavirenz Based Regimen: A PK Substudy from Striiving

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Introduction: Dolutegravir (DTG) is metabolized primarily by uridine diphosphate glucuronosyltransferase-1A1 (UGT1A1) and is a minor substrate for cytochrome P450-3A4 (CYP3A4). Co-administration of repeated once daily doses of DTG 50mg and EFV 600mg resulted in 57% and 75% reductions in plasma DTG area under the curve (AUC) and minimum concentration (C_{min}), respectively, as a consequence of CYP3A4 and UGT1A1 induction by EFV. To overcome this interaction, it is recommended DTG dose be increased to 50 mg twice daily when EFV is part of the antiretroviral treatment regimen for integrase-naive patients. The current study sought to evaluate the duration of EFV induction effect on the pharmacokinetic properties of DTG 50mg QD when virologically suppressed patients were switched from an EFV based regimen to a DTG based regimen.

Materials & Methods: STRIIVING evaluated the efficacy, safety, and satisfaction of switching from a current ART regimen (CAR) to ABC/DTG/3TC in virologically-suppressed, HIV-1 infected adults. Subjects were enrolled into this open label, North American study and randomized 1:1 to ABC/DTG/3TC or continue current ART for 24 weeks. A PK substudy was conducted to evaluate DTG trough concentrations, as well as residual drug concentrations of EFV, in a subgroup of subjects who switched from EFV. Early switchers were subjects randomized to switch to ABC/DTG/3TC and start treatment on Day 1. Late switchers were subjects randomized to continue their current regimen until Week 24 when they switched to ABC/DTG/3TC. Blood samples for evaluation of DTG and EFV plasma PK were collected predose at Day 1 (predose) and Weeks 1, 2, 4, 8, and 24 (early switchers); and at Week 24 (predose), and Weeks 25, 26, 28, 32 and 48 (late switchers).

Results: The primary virologic endpoint of non-inferiority at Week 24 was met (HIV-1 RNA <50 c/mL; ABC/DTG/3TC 85% vs. CAR 88%) and virologic suppression was maintained through Week 48. There were no protocol-defined virologic failures or treatment emergent resistance in either arm. 24 patients on an EFV based regimen were enrolled in the PK substudy and evaluated. On Day of Switch (Day 1/Week 24) geometric mean EFV concentrations were 1.70 ug/mL (Standard Deviation; 0.66) and decreased steadily to 0.255 ug/mL (0.23) by Week 1/Week 25 and 0.118 ug/mL (0.09) by Week 2/Week 26. By Week 4/Week 28 concentrations of EFV were 0.090 ug/mL . Geometric mean pre-dose DTG concentrations at Week 1/Week 24 were 643 ng/mL (955), increasing to 697 ng/mL (627) at Week 2/Week 26 and then 1049 ng/mL (710) by Week 4/Week 28. DTG concentrations remained steady at Week 8/Week 32 and Week 24/ Week 48.

Conclusions: After switching to ABC/DTG/3TC treatment, residual EFV plasma concentrations steadily decreased and DTG Cmin steadily increased, reaching steady-state by Week 4/Week 28. DTG mean concentrations were maintained above PA IC90 (64 ng/mL) at all sample times. Additionally, there was no time in the immediate post-switch period where both EFV or DTG measured concentrations fell below their respective effective concentrations. Collectively these PK data support switch to ABC/DTG/3TC from an EFV containing regimen without need for DTG dosage adjustment.

No conflict of interest

Abstract: O_24

Drug Drug Interactions

Evaluation of Pan Genotypic HCV NS3/4A Protease Inhibitor GS-9857 as the Object of Transporter and Cytochrome P450-Mediated Drug-Drug Interactions

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Background: GS-9857, a pan-genotypic HCV NS3/4A protease inhibitor (PI) with potent antiviral activity against HCV genotypes 1-6, is currently being evaluated in Phase 3 studies as part of a fixed dose combination with sofosbuvir (SOF: 400mg) and velpatasvir (VEL, GS-5816: 100mg). In vitro studies demonstrate that GS-9857 is a substrate of drug transporters (P-glycoprotein: P-gp, breast cancer resistance protein: BCRP and organic anion transporting polypeptides: OATPs) and possibly cytochrome P450 (CYP) enzymes, including CYP3A and CYP2C8. This Phase 1 study was designed to identify the contribution of these transporters and enzymes to the pharmacokinetics of GS-9857 in healthy volunteers.

Methods: This was an open-label, single-and multiple-dose, four cohort study in healthy volunteers. Subjects were administered a single dose of GS-9857 100mg alone or in combination with inhibitors or inducers of drug transporters or CYP enzymes: single doses of cyclosporine A (CsA: 600 mg fasted: OATP/MRP2/P-gp inhibitor), rifampin (RIF: 600 mg fasted: OATP inhibition), or grapefruit juice (GFJ: 300 ml fed: intestinal OATP inhibitor), or multiple doses of RIF (600 mg QD fed for 7 days: CYP/P-gp inducer), voriconazole (VORI: 200 mg BID fed 4 days: CYP3A inhibitor), or gemfibrozil (GFZ: 600 mg BID fed 4 days: CYP2C8 inhibitor). Safety was assessed by routine clinical and laboratory monitoring throughout the study. Geometric mean ratios and 90% confidence intervals were estimated for GS-9857 AUC_{inf} and C_{max} and compared against pre-specified lack of PK alteration boundaries of 70-143%.

Results: Ninety-eight subjects were enrolled across 4 cohorts. Five subjects discontinued study drug (1 Grade 1 AE [headache], 1 pregnancy, 2 due to investigator discretion, and 1 withdrew consent). Study treatments were safe and well tolerated; All AEs were Grade 1 in severity. Across treatments, 56% of individuals experienced at least one AE and the most common AEs were chromaturia (30%), nausea (19%) and headache (14%). The majority of laboratory abnormalities were Grade 1 or 2 in severity, and no Grade 4 laboratory abnormalities were reported.
GS-9857 exposure was significantly increased by potent hepatic OATP inhibition by single doses of RIF (AUC_{inf} 7.9-fold, C_{max} 11-fold) or CsA (AUC_{inf} 9.4-fold, C_{max} 19-fold) and to a lesser extent (< 2-fold) by intestinal P-gp inhibition (determined by assessing differential effects of single doses of CsA and RIF). Intestinal OATP inhibition by GFJ had no effect on GS-9857 exposure when administered with food. Potent inhibition of CYP3A (VORI) resulted in a modest increase in GS-9857 (AUC_{inf} 1.8-fold, C_{max} unchanged). Potent inhibition of CYP2C8 (GFZ) had no effect on GS-9857 exposure. Potent induction of CYPs and P-pg (multiple dose RIF) significantly reduced GS-9857 exposure (AUC_{inf} by 73%, C_{max} unchanged).

Conclusions: Hepatic OATP plays a significant role in the pharmacokinetics of GS-9857 with P-gp, and CYP3A contributing to a lesser extent. Based on these data, coadministration of GS-9857 with potent hepatic OATP inhibitors, or potent or moderate inducers of CYPs and P-gp is not recommended, future studies will inform dosing recommendations with moderate hepatic OATP inhibitors. GS-9857 may be coadministered with potent P-gp inhibitors with caution, or inhibitors of CYP3A or CYP2C8 without dose modification.

Conflict of interest
financial relationship(s): All authors are employees of Gilead Sciences Inc.

Abstract: O_25

Drug Drug Interactions

Evaluation of Transporter-Mediated Drug-Drug Interactions with the HCV Combination Regimen Sofosbuvir/Velpatasvir/GS-9857 and Phenotypic Probe Drugs

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Background: GS-9857, a pan-genotypic HCV NS3/4A protease inhibitor (PI) with potent antiviral activity against HCV genotypes 1-6, is currently being evaluated in Phase 3 studies as part of a fixed dose combination with sofosbuvir (SOF: 400 mg) and velpatasvir (VEL, GS-5816: 100 mg). Sofosbuvir is not an inhibitor of cytochrome P450 enzymes or drug transporters, VEL is an inhibitor of the drug transporters P-gp, OATP, and BCRP, and nonclinical data suggest that GS-9857 is a substrate of, and may inhibit BCRP and/or OATPs. This phase 1 study in healthy subjects was designed to characterize the effect of the combination of SOF/VEL/GS-9857 on P-gp, BCRP, and OATP activity to guide concomitant medication use in HCV infected patients.

Methods: This was an open-label, single-and multiple-dose, two cohort study in healthy subjects. Subjects were administered a single dose of dabigatran etexilate (75 mg N=36: P-gp probe), rosuvastatin (ROS 10 mg N=19: BCRP/OATP probe), or pravastatin (PRA 40 mg N=19: OATP probe), alone or in combination with steady-state administration (at least 7 days) of SOF/VEL/GS-9857 (1 x 400/100/100 mg + 1 x 100 mg GS-9857) with food. Safety was assessed by routine clinical and laboratory monitoring throughout the study. Serial blood samples were collected for 96 hours after administration of probe drugs for PK analyses of dabigatran (DAB; total and free), PRA, and ROS. Geometric mean ratios and 90% confidence intervals were estimated for AUC_{inf} and C_{max} of probe drugs and compared against pre-specified lack of PK alteration boundaries of 70-143%.

Results: Fifty six subjects were enrolled in these 2 cohorts. All 56 subjects received at least one dose of study drug. Study treatments were safe and well tolerated. There was no clinically significant Grade 3 or 4 laboratory abnormality. Nine subjects experienced AEs, all of which were Grade 1 or Grade 2 in severity; the most common AE was headache (n=3). The combination of SOF/VEL/GS-9857 inhibits P-gp (total DAB: AUC_{inf} 2.6-fold increase, C_{max} 2.9-fold increase, free DAB: AUC_{inf} 2.2-fold increase, C_{max} 2.3-fold increase), significantly inhibits BCRP (ROS AUC_{inf} 7.3-fold increase, C_{max} 18.9-fold increase), and to a lesser extent inhibits OATP (PRA AUC_{inf} 2.1-fold increase, C_{max} 1.8-fold increase).

Conclusions: The combination of SOF/VEL/GS-9857 is an inhibitor of intestinal BCRP and to a lesser extent, OATP and P-gp. The results from this study will support dosing recommendations in HCV infected subjects for use of concomitant medications that are sensitive substrates of these transporters.

Conflict of interest
financial relationship(s): All authors are employees of Gilead Sciences Inc.

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Abstracts

Poster Presentations

Abstract: P_26

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Is pregnancy a barrier to the proposed lower dose of efavirenz?

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Introduction: Globally, efavirenz (EFV) is a cornerstone for the treatment of HIV-1. A lower EFV dose was assessed in order to reduce drug-toxicities and costs. The ENCORE1 trial demonstrated that EFV 400mg once-daily (QD) is non-inferior to the standard dose of 600mg QD in adults. During pregnancy, the pharmacokinetics (PK) of antiretrovirals may be altered, potentially leading to sub-therapeutic exposure with an increased risk of perinatal HIV-1 transmission. Thus far, it remains unknown whether the 400mg dose is also appropriate during pregnancy. Moreover, CYP2B6 polymorphisms influencing EFV clearance can make inference challenging.

Our objective was to develop a physiologically-based population PK model to describe the PK of EFV in HIV-1-infected pregnant and non-pregnant women using the largest dataset yet available. This model was used to simulate EFV exposure following 400mg EFV QD during third trimester of pregnancy.

Material & Methods: PK data from pregnant and non-pregnant women using EFV were pooled from eight studies. A semi-physiological model with 3 transit absorption compartments, 2-compartment disposition, and elimination described using the well-stirred liver model was developed in NONMEM (v7.3). Flow parameters and volumes were allometrically scaled to body weight (70 kg). Pregnancy-induced decrease in protein-binding and increase in plasma liver flow were included, *a priori*, based on literature. We simulated (1000x/condition/phenotype) total and $EFV_{unbound}$ C_{12} for 400mg QD in pregnant (38 weeks) and non-pregnant women. We assessed the percentage with C12 below the suggested targets for virologic response (1.0 and 0.7 mg/L). Additionally, we used thresholds adjusted for protein-binding in non-pregnant state to evaluate simulated $EFV_{unbound}$.

Results: Data from 253 HIV-infected women (1699 samples) were included. Paired observations during pregnancy (642) and postpartum (466) were available from 79 women. Median (IQR) non-pregnant weight was 59 (52-68) kg. Median (range) GA was 35 (25-39) weeks. A mixture model was implemented to account for the multi-modal distribution of CL_{int} as a result of CYP2B6 polymorphisms by imputing missing (82%) CYP2B6-related phenotypes; slow (SM), intermediate (IM) and fast (FM) metabolizers. After controlling for pregnancy-induced changes in protein-binding and plasma liver flow, pregnancy had no effect on CL_{int}. For 400mg, the simulated median (IQR) C_{12} in pregnancy were 3.22 (2.23-4.57), 1.26 (0.92-1.75), and 0.82 (0.58-1.20) mg/L for SM, IM and FM, respectively, as compared to 4.37 (3.17-6.07), 1.74 (1.24-2.32), and 1.17 (0.84-1.64) mg/L for non-pregnant women. In SM, IM and FM pregnant women 1%, 30% and 61% had C_{12} below 1.0 mg/L, respectively, compared to 1%, 14%, and 38% in SM, IM and FM non-pregnant women. The frequencies of C_{12} below 0.7 mg/L were 38% in pregnancy and 15% for non-pregnant FM women. Despite this increase in concentrations below target in FM pregnant women, the predicted unbound concentrations were not altered by pregnancy. Simulated $EFV_{unbound}$ showed 18% of

C12 in FM pregnant women below the protein-binding-adjusted threshold of 0.7 mg/L, compared to 15% on non-pregnant women.

Conclusions: Pregnancy decreases total EFV C_{12}, but $EFV_{unbound}$ is predicted to be unchanged. Although this finding warrants *in-vivo* confirmation, it indicates that a dose reduction to 400mg may be feasible.

Conflict of interest
financial relationship(s): The PANNA network is funded by: NEAT/PENTA BMS, Merck, ViiV Healthcare, Janssen Pharmaceutica. P1026s is a protocol of the IMPAACT network, which is funded by NICHD, NIAID and NIMH. The 2NN study was sponsored by Boehringer Ingelheim

Abstract: P_27

Pharmacokinetics for Pediatrics, Pregnancy and other Special Populations

Population Pharmacokinetic Analysis of Velpatasvir, a Pangenotypic HCV NS5A Inhibitor in Healthy and Hepatitis C Virus-Infected Subjects

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Background: Velpatasvir (VEL, GS-5816), a potent pangenotypic HCV NS5A inhibitor is under regulatory review as part of a fixed-dose combination with sofosbuvir (SOF), a nucleotide analog HCV NS5B inhibitor for the treatment of chronic HCV infection. A population based pharmacokinetic (PopPK) model was developed to understand the clinical covariates of the PK of VEL in subjects with chronic HCV infection when administered VEL 100 mg in combination with SOF 400 mg.

Methods: The PopPK model for VEL was developed using VEL plasma concentration data from pooled intensive and sparse samples from 4 studies in healthy subjects (n=331) and 7 phase II/III studies in patients with chronic HCV infection (n=1691). 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, race, body weight, creatinine clearance (CLCR), hepatic impairment and cirrhosis status, disease status (healthy vs. HCV infected subjects), ribavirin usage, food, and concomitant medications including anti-coagulants, selective serotonin reuptake inhibitors, statins, calcium blockers, H2 receptor antagonists and diuretics were evaluated using a stepwise forward addition followed by backward elimination methodology for their effect on VEL PK. Clinical significance of statistically significant covariates was determined by a sensitivity analysis of their impact on the steady-state VEL exposure parameters AUC_{tau}, C_{max} and C_{tau}.

Results: Velpatasvir 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 (V_c), distribution clearance (Q), peripheral volume (Vp), relative bioavailability (F1), absorption rate constant (k_a), and lag time (T_{lag}).
Statistically significant parameter-covariate relationships were identified for sex, disease status, and decompensated cirrhosis [CPT-B or CPT-C]) on CL and V_c, and food on k_a, T_{lag} and F1. For a typical male HCV-infected subject without decompensated cirrhosis (CPT-A) administered VEL fasted, CL was 46.5 L/hr, V_c was 392 L, Q was 10.8 L/hr, V_p was 219 L, k_a was 0.78 1/hr, and T_{lag} was 0.295 hr. Interindividual variability was 50.8% for CL, 68.9% for V_c, 50.8% for V_p, and 54.2% for k_a. The sensitivity analysis showed the magnitude of effect of sex, or decompensated cirrhosis on VEL steady-state exposure in HCV-infected subjects was modest (AUC_{tau} <43%, C_{max} <44%, and C_{tau} <65%), the effect of food was minor (AUC_{tau} 9%, C_{max} 1.4%, and C_{tau} 15%), none of these relationships were considered to have a clinically meaningful impact on VEL PK in HCV-infected subjects.

Conclusions: Demographic variables such as age, sex, race, body weight, creatinine clearance (CLCR), hepatic impairment and cirrhosis status, ribavirin usage, food, or concomitant medications do not have a clinically relevant impact on VEL exposures in HCV-infected subjects.

Conflict of interest
financial relationship(s): Kirby, B., Mogalian, E., Bhasi, K., and Mathias A. are employees of Gilead Sciences Inc.

Abstract: P_28

PK-PD of Drug Efficacy and Toxicity

Quantitative Proteomic Analysis of Drug Transporter Expression in the GI Tract of Multiple Animal Models of HIV Infection

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Introduction: The persistence of HIV in tissue reservoirs such as the GI tract may be reduced or eliminated with optimized exposure of antiretrovirals (ARVs) at thesite of action. Drug transporters affect ARV tissue disposition and can be exploited to maximize ARV exposure, but quantitative measures of drug transporter protein expression across preclinical species are not available. In this study, we use proteomics to obtain absolute transporter concentrations and assess agreement with corresponding gene and immunometric protein data. We also examine the effect of HIV infection on transporter expression in the GI tract.

Material and Methods: Animals from two humanized mouse (hu-HSC-Rag (n=18); BLT (n=7)) and one primate (rhesus macaque, (NHP, n=3)) models were infected with HIV or SHIV for4-6 weeks before being dosed to steady-state with combination ARV treatment.Ileum and rectum were collected at necropsy and analyzed for protein expression of ARV efflux (MDR1,BCRP, MRP1, MRP2, and MRP4) and uptake (ENT1, OATP2A1, OCT3) transporters using quantitative targeted absolute proteomics (QTAP) and Western blot (WB).Transporter mRNA was measured by qPCR. Gene and protein expression were compared against historical data from uninfected animals, and comparisons between anatomic sites and animal models were made using ANOVA on ranks.Agreement between analytical techniques was assessed by linear regression. Data are presented as median concentration.

Results: QTAP analysis showed a 1.7 log increase in MDR1 expression in the ileum of infected mice versus infected macaques (49.9 vs 1.6 pmol/mg protein;$p<0.001$), and significantly higher OATP2A1 concentrations in macaque vs mouse rectum (10.4 vs undetectable pmol/mg protein;$p=0.002$). Transporter concentrations were similar between ileal and rectal tissues with the exception of ENT1, which was significantly higher in mice ileum versus rectum (1.1 vs undetectable pmol/mg protein;$p=0.002$). Gene expression was generally consistent between infected and uninfected animals ($p>0.05$), however ABCC4 gene expression was significantly higher in infected versus uninfected mice (97.4 vs 0.02 x 10^4 fold change vs GAPDH; $p<0.001$). There was little agreement between QTAP and qPCRor WB, with R^2 values ranging from 0.001 (MDR1 QTAP vs qPCR) to 0.34 (MRP1 QTAP vs WB).

Conclusions: This evaluation is the first to determine absolute protein concentrations of drug transporters across pre-clinical species. We observed significant differences in MDR1 and OATP2A1 concentrations between species, suggesting that the tissue exposure of their substrates, including many ARVs, may not be equal between these models. Further, the lack of differences in transporter expression between infected and uninfected animals suggests that HIV infection does not confound ARV distribution studies.

Finally, the lack of agreement between analytical techniques indicates that resources may need to be focused on generating high-throughput, downstream measures of protein expression.

Taken together, these data inform the use of pre-clinical models for studying ARV distribution and the design of targeted therapies for HIV eradication.

No conflict of interest

Abstract: P_29

PK-PD of Drug Efficacy and Toxicity

Effect of HCV & gene polymorphisms on chemotherapy toxicities in ALL children

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Introduction: The aim of the present study was to determine the correlation of hepatitis C virus (HCV) infection and polymorphisms in different genes with toxicity of either methotrexate (MTX) or 6-mercaptopurine (6-MP) administered to children with ALL.

Material & Methods: A hundred children with low risk ALL who were treated according to the adopted St. Jude Total therapy XV were recruited. The recruited children were receiving MTX and 6-MP during maintenance phase. Patients were excluded from the study if they had other types of leukemia. Genotyping analyses for the thiopurine Methyltransferase (TPMT), Methylenetetrahydro-folate Reductase (MTHFR), and Glutathione transferase (GST) genes were performed using a combination of polymerase chain reaction (PCR) and PCR- resriction fragment lenght polymorphism (PCR-RFLP) protocols. Relevant clinical data on adverse drug reactions were collected objectively (blinded to genotypes) from the patient medical profiles.

Results: There was a significant correlation between the combined presence of HCV and TPMT*3B G460A gene polymorphisms and grade 2-4 AST hepatotoxicity ($p < 0.04$). The same observation was seen when comparing either the presence of HCV alone or the presence of the gene polymorphism alone. A significant association between the combined presence of HCV and MTHFR C677T polymorphism and grades 2-4 ALT, AST, and ALP hepatotoxicity was observed (p values < 0.001, 0.02 and 0.001 respectively). The presence of HCV infection had a significant negative effect on hepatic transaminases.

Conclusions: The present data support a role for combining analysis of genetic variation in drug-metabolizing enzymes and the presence of HCV in the assessment of specific drugs toxicities in multi-agent chemotherapeutic treatment regimens.

No conflict of interest

Abstract: P_30

PK-PD of Drug Efficacy and Toxicity

Sofosbuvir/ledipasvir for eight weeks is associated with a high sustained virologic response rate in HIV/HCV co-infected patients

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Background: Eight weeks treatment duration with sofosbuvir/ledipasvir (SOF/LDV) in treatment-naïve, non cirrhotic hepatitis C (HCV) mono-infected individuals with a low viral load is

associated with a high rate of sustained virologic responses (SVR). The ION-4 study only assessed the efficacy of SOF/LDV for 12 weeks in patients co-infected with HIV/HCV. Recently, the GECCO investigators presented a 100% SVR rate in seven co-infected patients treated for eight weeks with SOF/LDV. The objective of our study is to describe the SVR rate in co-infected patients treated with SOF/LDV for eight weeks in a real world clinical practice setting.

Materials and Methods: This is a retrospective chart-review study at the Centre hospitalier de l'Université de Montréal, Québec, Canada. All co-infected patients treated with eight weeks of SOF/LDV were included. Demographics, HIV and HCV related characteristics were collected. Hepatic fibrosis was evaluated by transient elastography (Fibroscan, Echosens) or with FIB-4 score calculation. HIV and HCV viral loads were measured with RealTime HIV-1 and HCV (Abbott) tests.

Results: Since SOF\LDV approval, 10 patients (Metavir score F0-F1) were treated for eight weeks. Nine (90%) patients were men, the median age was 52 years old (Q1-Q3: 47-56). The median platelets (202 x 109/L ; 180- 305) and albumin (40 g/L; 39-42) were within normal values. Four patients were infected with HCV genotype 1a and six with genotype 1b. The median HCV viral load prior treatment was 968 277 UI/mL (387 214 – 2 194 026). None of the patients previously completed a treatment course for the same HCV genotype. All patients were on antiretrovirals at baseline and all had an undetectable HIV viral load except one. Combination antiretroviral therapy (cART) was evaluated prior to HCV treatment and patients received different antiretrovirals based on their treatment history including tenofovir/emtricitabine, abacavir/lamivudine, ritonavir-boosted and unboosted atazanavir, darunavir/ritonavir, dolutegrevir, raltegravir and rilpivirine. Two patients who completed treatment were lost to follow-up before SVR results were available. The proportion of SVR in the cohort reached 80% in intention to treat analysis and 100% per protocol analysis. SOF/LDV was well tolerated with no treatment discontinuation. No renal adverse events were seen in the four patients on tenofovir-based cART with HIV protease inhibitors despite the expected increase in tenofovir exposure. Of interest, one patient developed severe on-treatment hyperbilirubinemia which was suspected to be the consequence of a pharmacokinetic drug-drug interaction between ledipasvir and ritonavir-boosted atazanavir.

Conclusions: Eight weeks of SOF/LDV is associated with a high rate of SVR in carefully selected HIV/HCV co-infected patients. Most studies now suggest that co-infected patients respond as well as mono-infected HCV individuals to direct acting antivirals. Despite a small sample size, our study adds more evidence that HIV is no longer considered a negative predictive factor to HCV pharmacotherapy with the exception of a thorough evaluation of drug-drug interactions prior to HCV treatment.

Conflict of interest
financial relationship(s): D. Martel received honoraria for providing continuing education, serving as a consultant on advisory boards and/or travel grants from Abbvie, Gilead Sciences, Janssen, Lupin Pharmaceuticals, Merck and Seattle Genetics. M.E. Goyer received honoraria for providing continuing education, serving as a consultant on advisory boards and/or travel grants from Abbvie, Bristol-Myers Squibb, Indivior, Merck, Reckitt Benckiser and ViiV Healthcare. P. Côté received honoraria for providing continuing education, serving as a consultant on advisory boards and/or travel grants from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and ViiV Healthcare. S. Dufresne received honoraria for providing continuing education, serving as a consultant on advisory boards and/or travel grants from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and ViiV Healthcare. C. Blais has no financial relationship(s) to disclose. B. Trottier has no financial relationship(s) to disclose relevant to this work. V. Martel-Laferrière has financial relationships to disclose with Gilead Sciences and Merck.

Abstract: P_31

PK-PD of Drug Efficacy and Toxicity

Pharmacokinetics, safety and efficacy of atazanavir, dolutegravir, and lamivudine as maintenance regimen in HIV-infected patients: a pilot study

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Introduction: Today, HIV-infection can be considered a chronic disease requiring life-long medication intake. Given the ageing HIV-infected population, the ideal triple combination regimen should not only have a high genetic barrier for resistance, but also limited (long-term) side effects and low potential for causing drug-drug interactions. In this pilot study we evaluated the pharmacokinetics of a once daily, antiretroviral maintenance regimen consisting of unboosted atazanavir, dolutegravir and lamivudine. We think this will be a robust regimen with higher dolutegravir plasma concentrations due to inhibition of uridine diphosphate glucuronosyltransferase (UGT)1A1 by atazanavir. Since these agents are all known to cause limited toxicities we expect this regimen to be safe and well tolerated.

Materials & Methods: HIV-infected patients with undetectable viral loads during the previous six months and in need for a change in antiretroviral regimen were eligible for inclusion in this single-arm, open label pilot study. Patients were switched to QD atazanavir 400mg (unboosted), dolutegravir 50mg and lamivudine 300mg for 12 weeks. After 2 weeks of treatment, blood samples were taken to obtain a pharmacokinetic curve. Laboratory safety and efficacy were evaluated after 2, 6, and 12 weeks of treatment.

Results: Patients included in this pilot study (n=7) were all male and the median (range) age was 56 years (24-79). The geometric mean (GM) and coefficient of variation (%CV) for $AUC_{0\text{-}tau}$, C_{max}, C_{trough} and $t_{1/2}$ of dolutegravir were: 115.4 h*mg/L (55), 7.2 mg/L (43), 3.0 mg/L (79) and 18.2 hours (35), respectively. The $AUC_{0\text{-}tau}$, C_{max} and C_{trough} were approximately 2 to 3 times higher than was observed for dolutegravir 50 mg QD at steady-state in a 10-day monotherapy study in HIV-infected adults. Our results were more similar to the $AUC_{0\text{-}24h}$, C_{max}, C_{trough} and $t_{1/2}$ of dolutegravir 50mg BID seen in another study; 92.7 µg*h/mL, 5.55 µg/mL, 2.41 µg/mL and 9.5 hours. For atazanavir, $AUC_{0\text{-}tau}$, C_{max} and C_{trough} were 31.2 h*mg/L (49), 4.7 mg/L (42) and 0.22 mg/L (112), respectively. In two patients the atazanavir dose was increased to 600mg QD after 2 weeks because of low trough plasma concentrations (< 0.15 mg/L). So far, all patients that completed 12 weeks of treatment (n=4) have plasma HIV-1 RNA levels < 40 copies/ml. The combination of dolutegravir, atazanavir and lamivudine was generally well tolerated. Headache was the most reported adverse event (AE) (3 times reported; grade 2-4). Other grade 2 reported AEs were abdominal pain, creatinine and creatinine kinase increase, sleep disturbance and hoarseness (all reported once). Hyperbilirubinemia (grade 2) was reported in three patients. One patient discontinued the regimen due to AEs (not related to study medication).

Conclusions: This once-daily maintenance regimen consisting of unboosted atazanavir, dolutegravir and lamivudine showed a robust pharmacokinetic profile for dolutegravir in a small number of patients. Dolutegravir plasma concentrations were approximately 2-fold higher compared to normal plasma concentrations with dolutegravir 50mg QD, probably due to UGT1A1 inhibition by atazanavir. For unboosted atazanavir, therapeutic drug monitoring is recommended when using this regimen. Short term safety and efficacy was demonstrated with this regimen in a small number of patients.

No conflict of interest

Abstract: P_32

PK-PD of Drug Efficacy and Toxicity

Evaluation of the Effect of GS-9857, a Pan-Genotypic HCV NS3/4A Protease Inhibitor, on the QT/QTc Interval in Healthy Subjects

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Background: GS-9857, a pan-genotypic HCV NS3/4A protease inhibitor (PI) with potent antiviral activity against HCV genotypes 1-6, is currently being evaluated in Phase 3 studies as part of a fixed dose combination with sofosbuvir (SOF: 400 mg) and velpatasvir (VEL, GS-5816: 100 mg). *In vitro*, GS-9857 did not significantly inhibit hERG channel activity (IC50 > 30μM), however, in accordance with the ICH E14 requirement for clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential of non-antiarrhythmic drugs, a Phase 1 study was conducted to evaluate the effect of therapeutic and supra-therapeutic doses of GS-9857 on QTc interval.

Methods: Healthy volunteers (N=48) were enrolled into one of 8 treatment sequences and received a single dose of GS-9857 300mg (to match therapeutic exposure in patients), GS-9857 900mg (to match supratherapeutic exposure in patients), and GS-9857 placebo in a randomized, blinded fashion, and a single dose of open-label moxifloxacin (MOXI: positive control). All treatments were administered after a moderate-fat meal followed by a 10-day washout period. Triplicate time-matched ECGs were collected at baseline and following each treatment. Change from baseline QTc interval for GS-9857 or MOXI vs placebo was determined using the Fridericia correction (QTcF, primary) and population correction (QTcN, secondary) formulae. Pharmacokinetics (PK) and exposure-QT relationships (PK/PD) were evaluated. Safety was monitored throughout the study.

Results: Forty-eight subjects received study drug; Forty-seven subjects completed the study and were included in the PK, PD, and PK/PD analyses. One subject discontinued the study due to an adverse event (asymptomatic, elevation in amylase [grade 3] and potassium [grade 1]) following MOXI. Study treatments were safe and well tolerated; all AEs were Grade 1 or Grade 2 in severity, except the one leading to discontinuation noted above. The percentage of subjects with treatment-emergent AEs following administration of placebo, GS-9857 300mg, GS-9857 900mg, and MOXI were 9%, 17%, 53%, and 8%, respectively. Most AEs reported during administration of GS-9857 were Grade 1 and none were Grade 3 or 4. The most common AEs in subjects taking GS-9857 900mg were diarrhea (34%), vomiting (19%), and nausea (17%).
The lower bound of the 2-sided 96.67% CI for the mean difference in QTcF and QTcN for MOXI vs placebo was >5 msec at 3, 4, and 5 hours post-dose, establishing assay sensitivity. Mean GS-9857 AUC and C_{max} in the supratherapeutic dose were ~17.6-fold and 15.5-fold higher, respectively, relative to GS-9857 exposure in Phase 2 clinical studies in HCV infected patients with cirrhosis. Following therapeutic and supratherapeutic GS-9857 dosing, the upper bound of the 2-sided 90% CIs for the mean difference in time-matched baseline-corrected QTc between GS-9857 vs placebo was <10 msec at all timepoints using QTcF or QTcN. Categorical analyses did not demonstrate effects of GS-9857 on QTc intervals. The relationships between GS-9857 plasma concentrations and QTc intervals did not reveal an association using QTcF or QTcN.

Conclusion: The results from this study met the ICH E14 definition of a negative 'thorough QT/QTc study' and demonstrate that GS-9857 is not expected to prolong QTc interval in HCV infected patients.

Conflict of interest
financial relationship(s): All authors are employees of Gilead Sciences Inc.

Abstract: P_33

PK-PD of Drug Efficacy and Toxicity

Evaluation of ribavirin plasma concentrations in HIV/HCV co-infected patients from Thailand

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Background and aim: The World Health Organization estimated that 450,000 HIV infected patients were living in Thailand. It was estimated that 7.2% of these patients were co-infected with HCV, due to shared routes of transmission (2004). HCV treatment response is worse in HIV/HCV co-infected patients when treated with peg-interferon and ribavirin. A potential explanation is suboptimal ribavirin plasma concentrations compared with mono-infected patients. This abstract describes the efficacy of HCV treatment and the pharmacokinetic (PK) analysis of ribavirin plasma concentration in HIV/HCV infected Thai patients.

Methods: Patients were at least 18 years old and treated with peg-interferon alfa-2a (180mcg/week) or peg-interferon alfa-2b (1.5 mcg/kg body weight). Ribavirin was weight-based dosed: <64kg received 800mg/day, 65-80kg 1000mg/day, 81-105kg 1200mg/day, and >105 kg 1400mg/day. At week 8, 12, and 24 ribavirin plasma concentrations were determined with the aid of a validated HPLC-method with UV detection. Intra- and inter subject variation were calculated. Mann-Whitney U Test was used to check if anemia and sustained virological response (SVR) were related with ribavirin exposure at week 12. Additionally, ribavirin concentrations were compared between responders and non-responders. Receiver Operating Characteristic (ROC) analysis were conducted to find optimal cut-off values at week 12 (genotype 3 patients).

Results: In this analysis 56 patients were enrolled. Of these patients 91% was male and 79% was infected with genotype 3. The median week 12 ribavirin dose was 14.36mg/kg/day (range: 8.08-19.46mg/kg/day) and the ribavirin plasma concentrations (range) on week 8, 12, and 24 were 1.80 (0.50-3.46), 1.89 (0.45-9.98), and 1.93 (0.58-3.12) mg/L, respectively. The median intra subject variation was 12% and the inter subject variation (week 12) was 57%. SVR24 was achieved in 16/23 (70%) of the patients. Ribavirin levels were comparable for all patients achieving and not achieving SVR24 (median 1.91 vs 1.66mg/L, p=0.376).
During treatment, 16 patients developed anemia (hemoglobin <10g/dL), which was correlated with increased week 12 ribavirin concentrations (median 2.53 vs 1.83mg/L, p =0.006). ROC analysis showed a cut-off value for anemia of 2.28mg/L (sens: 0.714; 1-spec: 0.100; p=0.000).
An explorative sub analysis showed that 22 of the genotype 3 patients had an HCV RNA available at week 24 post dose (SVR24). Of which 15 were responders and 7 were non-responders. The ROC cut-off value at week 12 was 1.73mg/L (sens:0.800; 1-spec: 0.429; p=0.418).
These two cut-off values can be used to define a preliminary therapeutic range of 1.73-2.28mg/L for genotype 3 Thai patients. 8/9 patients in the therapeutic range achieved SVR and 2/9 developed anaemia. Below this range 3/7 achieved SVR and none had anaemia. At last, above the range 4/6 had SVR and 4/6 developed anaemia.

Conclusion: Median ribavirin plasma concentration was 1.89mg/L and 70% of the patients achieved SVR24. For Thai HIV/HCV co-infected patients with genotype 3,1.73-2.28mg/L could be the potential therapeutic range. However, this is an explorative analysis and these cut-off values should be validated in a larger data set. There might be an opportunity to increase RBV exposure and increase SVR-rates, since 32% (7/22) of the patients had ribavirin levels <1.73mg/L.

No conflict of interest

Abstract: P_34

PK-PD of Drug Efficacy and Toxicity

Effect of Cobicistat and Ritonavir on Cellular Concentrations and Elimination of Atazanavir and Darunavir in CD4+ Cell

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Background: Cobicistat (COBI) is a pharmacoenhancer that has been paired with protease inhibitors (PIs) like darunavir (DRV) and atazanavir (ATV). Plasma pharmacokinetics (PK) of both DRV and ATV support once daily administration, correlating with viral suppression. However, little is known pertaining to cellular disposition of ATV or DRV alone and in combination with ritonavir (RTV) and COBI. This is of particular importance since PI exert their antiviral activity through inhibiting viral protease which is found inside $CD4^+$ cells. We hypothesize that COBI and RTV can alter cellular disposition of PIs and their elimination.

Materials & Methods: $CD4^+$ CEM and U937 ($1X10^6$ cells) were treated with either ATV or DRV alone, or in combination with either 1000 ng/mL COBI or RTV. After incubation over various time points (i.e. 24 or 48 hrs), cellular concentrations (CC) of ATV and DRV were determined using LC-MS. Cellular elimination of the PIs alone or in combination with COBI or RTV were evaluated after washout for 24 and 48 hours. The impact of PI alone and in combination with COBI or RTV on expression of ABCB1, ABCC2, and ABCG2 was also evaluated using RT-PCR and Western analysis and correlated with CC of PI.

Results: After 3 to 24 hours of PI treatment, ATV or DRV CCs reached maximal levels, where the difference was not statistically significant. After 24 hours of incubation, COBI or RTV in combination with DRV did not significantly alter CCs. In this study, ATV combined with RTV significantly increased ATV when compared to ATV alone. ATV CCs after 24 hrs washout were approximately 10- and 1.5-fold higher when combined with COBI and RTV, respectively, when compared to ATV alone ($P<0.05$). There was no difference in the disposition of DRV with pharmacoenhancers when compared to DRV alone. In CEM, the calculated Ke for DRV alone, and in combination with COBI or RTV was 0.080,0.083, 0.71 hr^{-1}, respectively, while the Ke for ATV alone and in combination with COBI or RTV was 0.033, 0.033, and 0.063, respectively ($p<0.05$)

Conclusions: After incubation for 3 and 24 hours, DRV elimination was significantly faster ($p<0.05$) than ATV in U937, monocytic leukemia cells. In CEM lymphoblastic leukemia, maximal cellular DRV was higher than ATV, DRV elimination was still significantly faster than ATV. Both COBI and RTV at the concentrations tested did not alter cellular DRV CC levels or elimination. In contrast, ATV CCs were significantly different when combined with COBI or RTV in CEM. This difference will be verified using primary PBMCs, and its mechanism(s) is currently interrogated using flow cytometric studies.

Conflict of interest
financial relationship(s): Received an independent grant from BMS

Abstract: P_35

PK-PD of Drug Efficacy and Toxicity

Relative Bioavailability of Four Prototype Cabotegravir (CAB) Oral Tablets Compared to the Current Phase 2 Oral Tablet in Healthy Adults

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Introduction: CAB is an integrase inhibitor (II) in development for the treatment and prevention of HIV. Currently, oral CAB is formulated as a 30 mg tablet with micronized drug substance and a core weight (CW) of 800mg. This study evaluated the pharmacokinetics (PK) of four prototype, smaller sized, 30 mg tablet formulations of CAB with and without the micronization of drug substance as an alternative for use in adult phase 3 clinical studies and to serve as the planned commercial product.

Material and Methods: This randomized, open-label, two-cohort, balanced, three-way crossover study was conducted to evaluate PK following single dose administration of CAB 30 mg tablets in healthy adult subjects. All subjects would receive an 800 mg CW tablet with micronized drug substance as the reference treatment. Test treatments included micronized and unmicronized 500 mg CW tablets in cohort 1 and micronized and unmicronized 650 mg CW tablets in cohort 2. Study treatments were separated by 14 days. Serial PK sampling and safety assessments were conducted during each treatment period. CAB PK parameters were determined by non-compartmental analysis; geometric least squares (GLS) mean ratios with associated 90% CIs were generated for parameters to compare treatments. Bioequivalence would be declared if the 90% confidence interval for the GLS ratio was within (0.8-1.25).

Results: 37 subjects enrolled and 36 subjects completed the study. CAB was well tolerated. All adverse events reported were mild and none were drug-related. No subjects were withdrawn due to adverse events. The CAB 500 mg CW tablet formulated with micronized drug substance was bioequivalent to the reference formulation. Exposures following the 650 mg CW tablet with micronized drug substance were reduced 9% relative to the reference formulation. Exposures following the 500 mg and 650 mg CW tablets with unmicronized drug substance were reduced 18 - 21% and 25 - 32%, respectively, relative to the reference formulation. The apparent terminal phase t1/2 was similar between treatments.

Conclusions: The prototype CAB 30mg tablet formulated with micronized drug substance and a CW of 500 mg was bioequivalent to the Phase 2 reference formulation and was selected for progression into Phase 3 studies.

Conflict of interest
financial relationship(s): Employee of ViiV Healthcare

Abstract: P_36

PK-PD of Drug Efficacy and Toxicity

Evaluation of relationships between UGT1A1 and UGT1A9 genotypes and oral cabotegravir pharmacokinetics and tolerability

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Introduction: Cabotegravir (CAB) is an integrase strand transfer inhibitor in clinical development for the treatment and prevention of HIV-1 infection. CAB is primarily metabolized by UGT1A1 with a minor contribution from UGT1A9. Functional genetic variants in these genes may impact enzyme activity, drug exposure and treatment response. UGT1A1 functional variants significantly increase irinotecan exposure and risk of adverse events. In contrast, UGT1A1 functional variants modestly increase dolutegravir exposure and have no measureable impact on safety. Therefore, pharmacogenetic (PGx) analysis was undertaken to evaluate genetic effects of *UGT1A1* and *UGT1A9* genotypes on oral CAB pharmacokinetic (PK) parameters and selected tolerability endpoints.

Materials & Methods: 347 subjects across 4 phase I and 2 phase II clinical studies who received repeat doses of CAB 30mg once daily (tablet formulation), provided PGx consent and had blood samples genotyped for known functional variants in *UGT1A1* and *UGT1A9* were included. Genotypes for *UGT1A1* polymorphisms rs4148323 (*6 allele) and rs8175347 (*28, *36 and *37 alleles) and the *UGT1A9* polymorphism rs3832043 (*1B allele) were generated and used to classify subjects with genetically predicted UGT1A1 and UGT1A9 low, reduced, or normal enzyme activity. Genetically predicted enzyme activity was assessed for association with 30mg oral steady-state CAB PK parameters of Ct, AUCt, and Cmax. The relationship between carriage of known functional *UGT1A1* and/or *UGT1A9* variants and maximum on-treatment change from baseline in total bilirubin (TBL) and alanine aminotransferase (ALT) were also evaluated using data available from one phase II study. Linear regression models were used and significant clinical covariates were adjusted for within each model.

Results: Genetically predicted UGT1A1 activity was significantly associated with 30mg oral steady-state CAB Ct ($p=4.89x10^{-11}$), AUCt ($p=0.0013$), and Cmax ($p=0.0213$). There was a 1.5, 1.4 and 1.3-fold increase in mean Ct, AUCt, and Cmax, respectively, comparing subjects who had genetically predicted low vs. normal UGT1A1 activity. Genetically predicted UGT1A1 activity was also significantly associated with the maximum on-treatment change from baseline in TBL ($p=7.97x10^{-6}$), but not ALT ($p=0.6674$). Among the subset of subjects with genetic and laboratory data available, 5/163 subjects had a maximum observed on-treatment TBL ≥1.5x the upper limit of normal; four had low and one had reduced UGT1A1 enzyme activity. Genetically predicted UGT1A9 activity was analyzed for association with all endpoints and was only associated with TBL ($p=0.0412$). However, the association was no longer significant after adjusting for genetically predicted UGT1A1 activity within the model ($p=0.4481$). This suggests that the UGT1A9 association may be due to correlation between the two genes.

Conclusions: Increased CAB exposure in carriers of UGT1A1 reduced function polymorphisms is not clinically significant based on the cumulative CAB safety data collected to date; therefore no dose adjustment in these individuals is required. The observed association between genetically predicted UGT1A1 activity and change from baseline in TBL may represent benign manifestations of Gilbert's syndrome and may not be attributable to drug treatment.

Conflict of interest
financial relationship(s): Employee of PARAXEL International

Abstract: P_37

PK-PD of Drug Efficacy and Toxicity

Pharmacokinetics of Simeprevir and Risk of Skin Reactions in Patients with Co-infection HIV/HCV with or without a Protease Inhibitor Containing HAART

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Background: Increased incidence of hypersensitivity skin reactions has been associated with higher exposures of simeprevir (SMV). Moreover, higher exposures have been reported in uninfected volunteers with mild to moderate hepatic impairment (Child-Pugh class A or B). Co-administration of DRV/RTV increased SMV (50 mg once daily) AUC, Cmax and Cmin by 2.59-, 1.79- and 4.58-fold, respectively. Given these evidences, it is not recommended to coadminister SMV with the former, but due to complex HIV resistance profile, some patients with co-infection HIV/HCV may not avoid the use of protease inhibitors (PIs). Aim of our study was to evaluate the pharmacokinetics (PK) of SMV in coinfected patients treated with boosted PI-containing regimens in order to evaluate the association between skin reactions and SMV exposure in presence of mild to moderate hepatic impairment.

Methods: HIV/HCV-coinfected patients treated with SMV plus SOF for 12 weeks in ARV with or without PIs were enrolled. Steady-state SMV trough concentrations (SMV_{trough}) (22±2 hours after last intake) were measured by UPLC-MS/MS validated method. Values were expressed as ng/mL.

Results: 17 patients, 14 (82.4% male, all Caucasian) were considered. At baseline age and BMI were 52 years (49-55), 23 kg/m^2 (21-26). Sixteen patients had a Metavir score of 4, 1 had a score of 3. Child-Pugh score (CP) was mild in all but 1 with CP B. HCV genotype was 1a, 1b and 4 in 8 (47,1%), 4 (23,5%) and 5 (29,4%) patients respectively. Four patients (23,6) were receiving a PI-based regimen, 3 with DRV/r (800/100 QD in 1, 600/100 BID in 2), 1 with ATV/r 300/100. Thirteen received a combination of drugs not known to interact with SMV. Four patients had a skin reaction (mild to moderate): 2 (out of 4 PI-treated patients, 50%) with moderate rash, pruritus and photosensitivity were treated with DRV and required local steroids and systemic oral antihistamines; 2 were on a non-PI-based regimen (out of 13, 15.38%). No HCV treatment suspension was necessary. Forty-five SMV determinations were obtained. SMV_{trough} was 801 ng/mL (377-7039) in general population, 677 ng/mL (346-1756) and 10066 ng/mL (8947-10066) in non-PI and PI receiving respectively (p=0,09). In patients without or with skin reactions SMV_{trough} was 752 ng/mL (335-1798) and 8553 ng/mL (2136-18702) respectively (p=0,068). SMV_{trough} was higher in patients showing a skin reaction and on DRV [15823 ng/mL (10066-15823), p=0,027] compared to all other patients.

Conclusions: These are the first data showing an association between SMV exposures and skin reactions in patients treated with DRV with mild hepatic impairment and advanced fibrosis. Caution is suggested in subjects treated with SMV when a DRV-containing ARV is unavoidable because of the adjunctive uprising effect on SMV concentrations. Given the small number of patients considered, further studies are warranted in order to confirm these findings.

No conflict of interest

Abstract: P_38

PK-PD of Drug Efficacy and Toxicity

Comparison of lopinavir and ritonavir drug concentrations in plasma and dried blood spots (DBS) in HIV-infected adults and children in Thailand

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Background: Lopinavir/ritonavir (LPV/RTV) remains a commonly administered HIV protease inhibitor in HIV-infected patients in Thailand. Measurement of antiretroviral (ARV) concentrations in plasma is useful for the clinical management of drug toxicities and drug-drug interactions. Plasma samples must be stored and shipped under frozen conditions, which is often challenging. Conversely, dried blood spots (DBS) can be stored and shipped under ambient conditions. However, it is important to determine the relationship between DBS and plasma drug concentrations to facilitate interpretation in relation to plasma derived efficacy cut-offs. Our objectives were to (i) validate a method to quantify LPV/RTV concentrations in DBS using LC-MS/MS; and (ii) compare LPV/RTV concentrations in paired plasma and DBS samples from HIV-infected patients.

Materials & Methods: The method to quantify LPV/RTV concentrations in DBS was evaluated following the FDA Guidelines for Bioanalytical Method Validation. Paired plasma and DBS samples were collected from patients receiving LPV/RTV-containing antiretroviral therapy enrolled in the PHPT Cohort Study [NCT00433030]. LPV/RTV plasma concentrations were determined using a previously validated assay. Linear regression between LPV (and RTV) concentrations in plasma and DBS samples was assessed in a training set of patients. The linear equation describing this relationship was used to predict the plasma concentrations in a validation set of separate randomly selected patient samples. The predictive value of DBS measurements was validated using Bland-Altman plots.

Results: (i) DBS Assay Validation: sample preparation involved a liquid-liquid extraction and separation using a C18 column with stepwise gradient. Calibration curves for LPV and RTV were linear between 0.05-20 µg/mL (LLOQ 0.05 µg/mL). Average accuracy was 102-112% for LPV and 90-112% for RTV. Inter/intra assay precision was <5% (%CV) for LPV and <8.0% for RTV. Recoveries of LPV and RTV were 82.1% and 102.6%, respectively. Drugs were stable in DBS at room temperature for 3 months. Sample haematocrit (30-60%) had no effect. (ii) LPV and RTV plasma/DBS concentrations in patients: 172 HIV-infected patients had a paired plasma and DBS sample available, median (range) age of 35 (3 to 79) years, haematocrit (16.3 to 48.2) and samples were between 0.1-17 hours post-dose. Forty patients were randomly selected for the validation set. For the training set, plasma and DBS concentrations for LPV and RTV were highly correlated (r = 0.974 and r =0.988, respectively). The mean DBS/plasma ratio was 0.71 (95%CI 0.70 to 0.74) for LPV and 0.78 (0.76 to 0.80) for RTV. For the validation set, the mean difference was 2.1% (95%CI -2.8 to 7.1%) and for RTV was 2.0% (-3.2 to 7.1%). For RTV, 97% of the predicated plasma concentrations were within +/- 2SD of the mean difference; while this was 92.5% for LPV.

Conclusion: The validated LC-MS/MS assay for the quantification of LPV/RTV in DBS samples was robust, accurate and precise. Both LPV and RTV concentrations in DBS samples were lower than in plasma. A linear algorithm can correct LPV and RTV DBS concentrations to predict plasma concentrations but the model may be improved by taking into account drug and/or other factors to reduce the observed variability.

No conflict of interest

Abstract: P_39

Clin Pharmacology related to treatment of other viruses

Pharmacogenetics of Antiretrovirals' Penetration into the Cerebrospinal Fluid

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Background: Antiretrovirals' (ARVs) concentrations in the cerebrospinal fluid (CSF) show significant inter-patient variability. Plasma concentrations, time post-dose and blood brain barrier (BBB) permeability have been associated with ARVs CSF levels. Despite the presence of several transporters at the BBB and blood-CSF barrier, data on the effect of single nucleotide polymorphisms (SNPs) are scarce.

Materials and Methods: Patients enrolled in a prospective study with available plasma and CSF concentrations and whole blood for genetic analysis were included. ARVs' concentrations were measured through validated HPLC-MS/MS methods and SNPs through real-time PCR. SNPs in the following genes were investigated ABCB1, ABCC2, ABCG2, HNF-alpha4, SLCO1A2, SLC22A6. Two data sets were generated for patients on protease inhibitors (PIs) and nucleos(t)ide reverse transcriptase inhibitors (NRTIs). Data are presented as median values (interquartile ranges) and analyzed trough non-parametric tests. Multivariate linear regression analysis were generated correcting for plasma concentrations, CSF-to-serum-albumin ratios (CSAR), hours after drug intake and to once or twice daily administration (PI_dataset) and for PI-coadministration (NRTI-dataset).

Results: 85 patients were included in the PIs dataset (darunavir/r 56.5%, lopinavir/r 20%, atazanavir/r 15.3%, atazanavir 8.2%); median age and BMI were 46 years (37-56) and 23.2 Kg/m2 (20.1-25.5) and they were mostly male (61, 71.8%). Samples were withdrawn 13.5 hours (12-17) after drug intake (47.6% Ctrough). At multivariate linear regression analysis plasma concentrations (p=0.005), CSAR (p=0.038), ABCB1 (p=0.008) and ABCG2 SNPs (p=0.006) were independent predictors of CSF concentrations; CSAR (p=0.008), ABCB1 (p=0.004) and ABCG2 SNPs (p=0.047) were independent predictors of CPRs. 91 patients providing 162 samples were included in the NRTIs dataset (emtricitabine 37.7%, tenofovir 33.3%, lamivudine 18.5%, abacavir 10.5%); median age and BMI were 47 years (40-54) and 23.1 Kg/m2 (20.7-25.1) and they were mostly male (62, 68.1%). Samples were withdrawn 14 hours (12-21) after drug intake (23.3% Ctrough). At multivariate linear regression analysis plasma concentrations (p=0.002), ABCB1 (p=0.018) and ABCG2 SNPs (p=0.007) were independent predictors of CSF concentrations; no independent predictor of CPRs was identified. 20 CSF concentrations (12.3%) were undetectable (mostly tenofovir, 15 out of 54, 27.8%): patients with CC genotype at position 421 in ABCG2 had a 20% higher chance of having NRTIs CSF concentrations below the limit of detection (p=0.041).

Conclusions: Beside plasma concentrations and BBB permeability SNPs in the genes encoding P-glycoprotein (ABCB1) and Breast Resistance Cancer-2 (ABCG2) protein may influence ARV CSF concentrations.

No conflict of interest

Abstract: P_40a

Novel Drugs and Formulations

No Clinically Meaningful QTc Prolongation With the HCV Protease Inhibitor Elbasvir in Healthy Subjects

D. Wolford[1], X. Huang[2], H.P. Feng[3], F. Liu[2], M. Iwamoto[1], J. Butterton[4], W. Marshall[1], W. Yeh[4], W. Heber[5], G. Baheti[5], T.J. Faihst[5]

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Background: Elbasvir (MK-8742) is a once-daily (QD) inhibitor of HCV non-structural protein 5A (NS5A). Elbasvir is one component of a fixed-dose combination therapy with grazoprevir (HCV NS3/4A protease inhibitor), Zepatier™ (50-mg/100-mg elbasvir/grazoprevir), that is indicated for the treatment of chronic HCV infection. Elbasvir was evaluated for evidence of prolonged repolarization in pre-clinical studies and no evidence of QTc prolongation or potential for QTc prolongation was detected. The potential effect of a drug on cardiac repolarization can be measured in a clinical setting as prolongation of the QT interval on electrocardiographic recordings. This study assessed clinically the potential of elbasvir to affect cardiac repolarization/QTc interval at a supratherapeutic dose.

Materials & Methods: This was a randomized, placebo- and active-controlled, single-dose, double-blind (with respect to elbasvir only), three-period, crossover, thorough QTc study in healthy subjects (N=42). In each treatment period, subjects were randomized to receive a single oral supratherapeutic dose of 700 mg elbasvir, 400 mg moxifloxacin, or placebo; all doses were administered in the morning following an overnight fast. There was a washout between each period. Using Fridericia's method of correcting the QT interval for heart rate (QTcF), the mean differences and corresponding 90% CIs of QTc change from baseline between treatments and placebo were calculated.

Results: Following a single oral dose of 700 mg elbasvir, the upper limit of the 90% CI for placebo-corrected QTcF change from baseline did not exceed 3 msec at any time point postdose. There was no discernible relationship between elbasvir concentration and changes in QTcF. All subjects had QTcF readings of ≤450 msec and all subjects had a QTcF change from baseline of ≤30 msec. No specific trend between treatments was observed for the T-wave morphology and no U-waves were present. Moxifloxacin treatment demonstrated assay sensitivity with a maximum mean placebo-corrected QTcF change from baseline of 8.60 msec, with a 90% CI lower limit of 6.67 msec, recorded at 3 hours postdose. The dose of 700 mg of elbasvir resulted in a geometric mean AUC0-24 of 6.20 μM•hr and Cmax of 0.567 nM, providing ~3- and 4-fold margins to the corresponding steady-state AUC0-24 (2.18 μM•hr) and Cmax (~0.151 μM), respectively, of elbasvir following administration of 50 mg QD to HCV-infected patients. A single supratherapeutic dose of 700 mg elbasvir was generally well-tolerated.

Conclusions: A supratherapeutic dose of 700 mg elbasvir does not cause QTc prolongation. Therefore, at the clinical dose of 50 mg QD, elbasvir is not expected to cause a clinically relevant prolongation of the QTc interval.

Conflict of interest
financial relationship(s): I am an employee of Merck & Co. Inc.

Abstract: P_40b

Novel Drugs and Formulations

No Clinically Meaningful QTc Prolongation With the HCV Protease Inhibitor Grazoprevir in Healthy Subjects

D. Wolford[1], Z. Guo[2], L. Caro[3], M. Iwamoto[4], J. Butterton[5], W. Yeh[5], K. Dunnington[6], J. Brejda[6], A. Hohnstein[6], D. Stypinski[6]

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Background: Grazoprevir (MK-5172) is a once-daily (QD) inhibitor of hepatitis C virus (HCV) NS3/4A protease. Grazoprevir is one component of a fixed-dose combination therapy with elbasvir (HCV NS5A inhibitor), Zepatier™ (50-mg/100-mg elbasvir/grazoprevir), that is indicated for the treatment of chronic HCV infection. Grazoprevir was evaluated for evidence of prolonged repolarization in pre-clinical studies and no evidence of QTc prolongation or potential for QTc prolongation was detected. The potential effect of a drug on cardiac repolarization can be measured in a clinical setting as prolongation of the QT interval on electrocardiographic recordings. This study assessed clinically the potential of grazoprevir to affect cardiac repolarization/QTc interval at a supratherapeutic dose.

Materials & Methods: This was a randomized, placebo- and active-controlled, single-dose, double-blind (with respect to grazoprevir only), three-period, crossover thorough QTc study in healthy subjects (N=41). In each treatment period, subjects were randomized to receive either a single oral supratherapeutic dose of 1600 mg grazoprevir, 400 mg moxifloxacin, or placebo. All doses were administered in the morning following an overnight fast. There was a washout between each period. Using Fridericia's and population correction methods of correcting the QT interval for heart rate (QTcF and QTcP), the mean differences and corresponding 90% confidence intervals (CIs) of QTc change from baseline between each treatment and placebo at each pre-specified time point were calculated.

Results: Following a single oral dose of 1600 mg grazoprevir, the upper limit of the 90% CI for placebo corrected QTcF change from baseline did not exceed 2 msec at any time point post-dose. There was no discernible relationship between grazoprevir plasma concentration and changes in QTcF. All subjects had QTcF readings of ≤480 msec and all subjects had QTcF change from baseline of ≤30 msec. Analysis of QTcP yielded similar results. No specific differences between grazoprevir and placebo was observed for the T-wave morphology and no U-waves were present. Moxifloxacin treatment demonstrated assay sensitivity with a maximum mean placebo-corrected QTcF change from baseline of 14.53 msec, with a lower limit of the 90% CI of 12.47 msec, recorded at 3 hour postdose. The dose of 1600 mg of grazoprevir resulted in a geometric mean AUC0-24 of 77.0 μM•hr and Cmax of 14.1 μM, providing ~42- and 44-fold margins to the corresponding steady-state AUC0-24 (1.84 μM•hr) and Cmax (0.32 μM), respectively, of grazoprevir following administration of 100 mg QD to HCV-infected patients. A single supratherapeutic1600 mg dose of grazoprevir was generally well-tolerated.

Conclusions: A supratherapeutic dose of 1600 mg grazoprevir does not cause QTc prolongation. Therefore, at the clinical dose of 100 mg QD, grazoprevir is not expected to cause a clinically relevant prolongation of the QTc interval.

Conflict of interest
financial relationship(s): I am an employee of Merck & Co. Inc.

Abstract: P_41a

PK-PD of Drug Efficacy and Toxicity

No clinically meaningful QTc prolongation with the HCV NS5B inhibitor MK-3682 in healthy subjects

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Background: MK-3682 is a potent, selective pan-genotypic uridine nucleoside monophosphate prodrug inhibitor of the HCV NS5B RNA polymerase being developed for the therapy of chronic hepatitis C virus (HCV) infection in combination with other compounds. As the intracellular active MK-3682-NTP does not circulate in plasma, clinical studies are evaluating the pharmacokinetics (PK) of MK-3682 and a major circulating metabolite M6. The *in vitro* and preclinical *in vivo* evaluations indicated that the risk of QT prolongation caused by MK-3682 in humans would be low. However, in accordance with the ICH E14 requirement for clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential of non-antiarrhythmic drugs, a phase 1 study was conducted to evaluate the effect of supratherapeutic MK-3682 on QTc interval.

Material & Methods: Forty-two healthy volunteers enrolled into a double-blind (with respect to MK-3682 only), randomized, placebo- and active-controlled, 3-period, crossover thorough QTc study. In each period, subjects were randomized to receive MK-3682, moxifloxacin, or placebo. A total supratherapeutic dose of 1350 mg MK-3682 was administered as three 450 mg doses over 2-hr intervals. Each period included cardiodynamic and PK sampling for 48 hours postdose for MK-3682 or matching placebo or 24 hours for moxifloxacin. Placebo corrected change from baseline in QTc for MK-3682 or moxifloxacin was determined using several correction formulas including QTcF, QTcB and QTcP (population derived correction). Since QTcP was found to be the most appropriate correction, a linear mixed-effects model was used to estimate the mean between-treatment difference in QTcP change-from-baseline at each time point. Safety was monitored throughout the study.

Results: Thirty-six (36) out of 42 subjects completed the study. Six (6) subjects did not complete the study due to reasons other than an AE. A supratherapeutic dose of MK-3682 was generally well tolerated. Both QTcF and QTcB were inadequate correction methods with none-zero slopes. The QTcP was adequate with a slope (95% CI) of -0.0004 (-0.0043, 0.0034). Therefore, the primary analysis was performed on QTcP. The lower limit of the 2-sided 90% CI for the placebo corrected QTcP change from baseline for moxifloxacin was > 10 msec at 1, 2, 3 and 4 hours post-dose, establishing assay sensitivity. 1350 mg MK-3682 provided a ~2.9 and 1.5-fold margin to Cmax and ~3.6 and 1.4-fold margin to AUC0-24 for MK-3682 and M6, respectively, when compared with the steady-state exposures at the proposed clinical dose of 450 mg QD in HCV-infected patients. The upper limit of the 90% CIs for placebo corrected QTcP change from baseline for MK-3682 did not exceed 10 msec at any time point post-dose, with the maximum mean value [3.44 msec, 90% CI (1.26, 5.62)] at 2 hours post the first dose of MK-3682. There was no discernible relationship between MK-3682 or M6 concentration and changes in QTcP.

Conclusion: This study demonstrated that a supratherapeutic dose of 1350 mg MK-3682 did not cause QTc prolongation. Therefore, at the clinical dose of 450 mg QD, MK-3682 is not expected to cause a clinically relevant prolongation of the QTc interval.

Conflict of interest
financial relationship(s): I am an employee of Merck & Co., and I own stock of Merck & Co.

Abstract: P_41b

PK-PD of Drug Efficacy and Toxicity

No clinically meaningful QTc prolongation with the HCV NS5A inhibitor MK-8408 in healthy subjects

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Background: MK-8408 is a potent inhibitor of the HCV NS5A RNA replication complex being developed for the therapy of chronic hepatitis C virus (HCV) infection in combination with other compounds. The *in vitro* and preclinical *in vivo* evaluations indicated that the risk of QT prolongation caused by MK-8408 in humans would be low. However, in accordance with the ICH E14 requirement for clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential of non-antiarrhythmic drugs, a phase 1 study was conducted to evaluate the effect of supratherapeutic MK-8408 on QTc interval.

Materials & Methods: Thirty-six healthy volunteers enrolled into a double-blind (with respect to MK-8408 only), randomized, placebo- and active-controlled, 3-period, crossover thorough QTc study. In each treatment period, subjects were randomized to receive a single oral supratherapeutic dose of 600 mg MK-8408, 400 mg moxifloxacin, or placebo. Each dose was followed by cardiodynamic and pharmacokinetics (PK) sampling for up to 24 hours postdose. The washout period between doses was 7 days. Placebo corrected change from baseline in QTc for MK-8408 or moxifloxacin was determined using several correction formulas including QTcF, QTcB, and QTcP (population derived correction). Since QTcP was found to be the most appropriate correction, a linear mixed-effects model was used to estimate the mean between-treatment difference in QTcP change-from-baseline at each time point. Safety was monitored throughout the study.

Results: Thirty-five (35) out of 36 subjects completed the study. One subject discontinued prior to dosing of Period 2 due to mild adverse events (AEs) of alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) increases following administration of placebo in Period 1. Study treatments were generally well tolerated. Both QTcF and QTcB were inadequate correction methods with none-zero slopes. The population derived correction (QTcP) was adequate with a slope (95% CI) of -0.000608 (-0.00886, 0.00765). Therefore, the primary analysis was performed on QTcP. The lower limit of the 2-sided 90% CI for the placebo-corrected QTcP change from baseline for moxifloxacin was > 5 msec at 1, 2, 3 and 4 hours post-dose, establishing assay sensitivity. A 600 mg single dose of MK-8408 yielded a margin for C_{max} of approximately 2.9-fold and AUC_{0-24} of approximately 2.3-fold relative to MK-8408 steady state exposure at the 60 mg expected clinical dose. Following a single oral dose of 600 mg MK-8408, the upper limit of the 90% CIs for placebo corrected QTcP change from baseline did not exceed 10 msec at any time point post-dose, with the maximum mean value [-0.18 msec, 90% CI (-1.84, 1.49)] at 1 hours post the first dose of MK-8408. There was 1 incidence of QTcP > 450 msec at 3 hours after MK-8408 administration, but no incidences > 480 msec. There were no incidences of QTcP change-from-baseline > 30 msec following MK-8408 dosing.

Conclusion: This study demonstrated that a supratherapeutic dose of 600 mg MK-8408 did not cause QTc prolongation. Therefore, the clinical dose of 60 mg QD MK-8408 is not expected to cause a clinically relevant prolongation of the QTc interval.

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

Abstract: P_42

Drug Drug Interactions

Identification and management of drug-drug interactions by a clinical pharmacist in patients prescribed HCV treatment

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Background and Aims: Identification and management of potential drug-drug interactions (DDI) is a critical aspect of current hepatitis C virus (HCV) treatment. The aims of this retrospective analysis were to quantify (1) the type of DDIs commonly encountered in patients prescribed HCV treatment in an academic outpatient hepatology clinic, (2) the interventions made, and (3) the time spent in identification and management of DDIs.

Methods: Patients prescribed HCV treatment between November 2013 and July 2015 at the University of Colorado Hepatology Clinic wereidentified. The clinic is a regional transplant referral center, often treating more complex, cirrhotic patients. The number and type of DDIs identified were summarized with descriptive statistics.

Results: 664 patients (81% Caucasian, 57% male, mean age 57 years) were identified, 133 for sofosbuvir and ribavirin (SOF/RBV), 114 for simeprevir and sofosbuvir (SIM/SOF), 369 for ledipasvir/sofosbuvir (LDV/SOF) and 48 for paritaprevir/ritonavir/ombitasvir and dasabuvir (PrOD). 50% of patients were cirrhotic. Overall, 5,217 medications were reviewed (average of 7.86 medications per patient) and 781 interactions identified (1.18 interactions per patient). The number of interactions was fewest for SOF/RBV (0.16 interactions per patient) and highest for PrOD (2.48 interactions per patient). LDV/SOF and SIM/SOF had similar number of interactions (1.28 and 1.48 interactions per patient, respectively). Antihypertensive, psychiatric, and analgesic medications commonly caused interactions with PrOD and SIM/SOF, while gastric acid modifiers commonly caused interactions with LDV/SOF. To manage these interactions, the pharmacists most often recommended to discontinue the medication or use an alternative agent (30.9%), to increase monitoring for toxicities (24%), or to separate administration times (16%). The pharmacist chart review usually took between 20 to 30 minutes, with additional time for more complex patients. Most patients met with the pharmacist for a 'Teach Visit' prior to starting treatment. In conjunction with the care team, the pharmacist assisted with monitoring the patients throughout treatment.

Conclusions: DDIs are common in patients prescribed HCV medications. Identification and management of DDIs is resource intensive and requires medication adjustments and increased monitoring. An interdisciplinary care team including a clinical pharmacist is critical to optimize patient care for new HCV therapies.

Conflict of interest
financial relationship(s): J.A. Langness: None DeclaredA. Wieland: Grant Jannsen PharmaceuticaM. Nguyen: None DeclaredS. Lin: None Declared, J.J. Kiser: Grant Jannsen Pharmaceutica, ViiV Healthcare

Abstract: P_43

Drug Drug Interactions

Daclatasvir 30mg/day is the correct dose for patients taking atazanavir/cobicistat

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Background: Combined treatment with HIV and HCV drugs is common in daily practice, because globally 20-25% of HIV patients is co-infected with HCV. Ritonavir boosted atazanavir (ATV/r) is used for the treatment of HIV in combination with an NRTI backbone. For HCV/HIV co-infection, daclatasvir plus sofosbuvir can be administered with ATV/r. According to the label, the dose of daclatasvir should be reduced from 60mg/day to 30mg/day in case of concomitant administration, due to CYP3A4 inhibition by ritonavir. Recently, another CYP3A4 inhibitor, cobicistat, became licensed as booster for ATV (ATV/c). Cobicistat lacks some of the side effects and toxicity of ritonavir. However, the impact of cobicistat on daclatasvir pharmacokinetics (PK) is unknown. Therefore, we studied whether ATV/c has the same impact on daclatasvir PK as ATV/r.

Methods: This was a prospective, open-label, 2-period, randomized, cross-over trial in 16 healthy subjects. Treatment consisted of ATV/r 300/100mg plus daclatasvir 30mg QD for 10 days, followed by a wash-out period of 10 days, and a second period of ATV/c 300/150mg plus daclatasvir 30mg QD for 10 days, or vice versa. At steady-state, an intensive 24h PK curve was recorded for daclatasvir (12 samples). Daclatasvir plasma concentrations were determined using a validated UPLC method with ultra violet detector. Geometric mean ratios (GMR) of daclatasvir PK parameters (AUC_{tau}, C_{max}, C_{trough}) with 90% confidence intervals (CI) were calculated comparing the effect of ATV/c with the effect of ATV/r. Laboratory safety and adverse events were evaluated throughout the trial.

Results: All 16 healthy subjects (8 males) completed the study. Median age (range) was 48.5 (21-55) years and all subjects were Caucasian. Median BMI (range) was 24.5 (19.0-29.2) kg/m^2. GMR (90% CI) of AUC_{tau}, C_{max}, and C_{trough} of daclatasvir with ATV/c compared with ATV/r were 101% (92%-111%), 97% (89%-106%), and 101% (89-115%), respectively. No serious adverse events were reported. All subjects had at least grade I hyperbilirubinemia (>1.0 mg/dL), caused by ATV-induced inhibition of UGT 1A1. A total of 10 subjects developed jaundice. Bilirubin concentrations normalized after cessation of ATV.

Conclusions: **A**TV/c and ATV/r had a similar influence on the PK of daclatasvir in healthy volunteers. Daclatasvir 30mg QD can be combined with ATV/c. Since no unexpected side effects were reported in the trial, this combination can be safely used.

Conflict of interest
financial relationship(s): This study is funded by Bristol-Myers Squibb

Abstract: P_44

Drug Drug Interactions

Ledipasvir/Sofosbuvir and Tenofovir in HIV-HCV co-infected patients: Impact on Tenofovir Ctrough and Renal Safety.

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Background: Ledipasvir (LDV) is a hepatitis C virus (HCV) NS5A inhibitor, given once-daily with sofosbuvir (SOF), an HCV NS5B nucleotide polymerase inhibitor, in an oral fixed-dose (90/400 mg) combination tablet. LDV/SOF is indicated, with or without ribavirin, for the treatment of chronic HCV infection. LDV and SOF are not metabolized through cytochrome P450 (CYP) isoforms but are both substrates for P-gp and BCRP transporters and LDV is a weak inhibitor of both P-gp and BCRP. In healthy volunteers, LDV increases tenofovir (TFV) exposure (from 40 % to 98% for AUC and from 59% to 163% for Cmin) in combination with efavirenz, rilpivirine, dolutegravir or darunavir/ritonavir. Therefore, higher TFV exposures in patients receiving LDV/SOF combined to tenofovir(TDF)-based regimen may increase the risk of renal toxicity. We evaluate the impact of LDV/SOF treatment on both TFV concentration and renal safety in HIV/HCV co-infected patients receiving TDF-based regimen.

Material and Methods: Patients who started 12 or 24 weeks of LDV/SOF regimen between 09/01/2015 and 02/01/2016 were included in this observational study. TFV trough concentration (TFV-C_{trough}), measured by a liquid-chromatography coupled with tandem mass spectrometry method, was collected when available before and after initiation (M1) of LDV/SOF. Renal safety was assessed through estimated glomerular filtration rate (eGFR) using both Cockroft-Gault (CG) and MDRD formulas at baseline (D0), M1, end of treatment (EOT) and 12-weeks post-treatment (PT12). Results are presented by median (IQR; n). Statistical analysis was performed using non-parametric tests (Wilcoxon- test).

Results: We included 20 HIV-HCV co-infected patients [80% male, median age: 51.3 years; HCV genotype: 1a(55%), 1b(30%) and 4(15%)] receiving LDV/SOF for 12 weeks (n=18) or 24-weeks (n=2), including ribavirin in 3 patients. HAART included TDF/FTC combined to integrase inhibitor (40%), NNRTI (30%), or boosted-PI (30%) regimens, with a median TDF exposure of 7.1 years (IQR: 4.0-10.2). Currently, 13 patients completed HCV treatment and 8 reached PT12 (6 SVR, 2 relapsers). TFV-Ctrough significantly increased from 74 ng/ml (48-102; 13) at D0 to 147 ng/ml (87-175; 8) one month after LDV/SOF initiation (p=0.043). No significant difference on eGFR was observed between D0 [CG: 98.1 ml/min (86.1-115.1; 20); MDRD: 99.7 ml/min (89.4-114.2; 20)] and M1 [CG: 102 ml/min (79.6-105.3; 17), p=0.95; MDRD: 91.3 ml/min (87-115.1; 17), p=0.95], EOT [CG: 96.5 ml/min (86.6-112.3; 13), p=0.65; MDRD: 99.4 ml/min (92.1-116.1; 13), p=0.63] and PT12 [CG: 100.5 ml/min (79.0-112.7; 7), p=0.86; MDRD: 93.7 ml/min (86.8-116.2; 8), p=0.0.88]. Of the 13 patients who completed LDV/SOF treatment, only 3 progressed from CKD stage 1 to stage 2 at M1 but returned to stage 1 at EOT.

Conclusion: In our HIV-HCV coinfected population receiving TDF-based regimen, LDV/SOF did not significantly impact renal function although TFV exposure was significantly increased by 98%, confirming the drug-drug interaction between LDV and TDV through P-gp inhibition. This suggests that the short duration of LDV/SOF treatment for HCV chronic infection may be considered as safe for patients without renal dysfunction. However, monitoring TFV exposure and renal safety remains of interest in patients with renal impairment and/or at higher risk of nephrotoxicity.

No conflict of interest

Abstract: P_45

Drug Drug Interactions

High risk of drug-drug interactions with hepatitis C: a nationwide cohort

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Background: Treatment of chronic hepatitis C virus infection (HCV) has drastically improved with the introduction of direct-acting antivirals (DAAs). DAAs are extensively metabolized by the liver and influence various enzymes and transporters. As a result, there is a substantial risk for drug-drug interactions (DDIs). The aim of this study is to identify frequently used concomitant medication in a nationwide real life HCV cohort to predict clinically relevant DDIs.

Materials & Methods: We studied a cohort of HCV genotype 1 patients in the Netherlands. Patients started treatment in 2011-2014 with first generation protease inhibitors. We extracted data from the medical chart on the use of concomitant medication prior to commencement of HCV therapy. Concomitant medication was grouped according to Anatomical Therapeutic Chemical code. DDIs with DAA regimes approved for HCV genotype 1 patients (sofosbuvir-daclatasvir, sofosbuvir-simeprevir, sofosbuvir-ledipasvir, paritaprevir/ritonavir-ombitasvir-dasabuvir) were identified through www.hepdruginteractions.org (Oct 2015). We distinguished 4 DDI categories: 1) no interaction, 2) possible interaction, 3) contraindicated, and 4) unknown interaction. Category 2 and 3 are defined as clinically relevant DDIs.

Results: This cohort includes 461 patients of which 356 (77%) used concomitant medication (median: 2, range: 1-17 drugs per patient). We identified 1329 prescriptions (260 generics), most frequently used are antidepressants (7.4%), proton pump inhibitors (7.1%), benzodiazepine derivatives (7.1%), and drugs for opioid dependence (5.6%). Sofosbuvir combined with an NS5A inhibitor had lowest number of clinically relevant DDIs (sofosbuvir-ledipasvir: 38, sofosbuvir-daclatasvir: 40). In contrast, the combination of paritaprevir/ritonavir, ombitasvir, and dasabuvir had most DDIs (n=96). Majority of patients (59%) were at risk for a clinically relevant DDI with at least one of the DAAs: 52 (11%) patients had a contraindication for at least one of the DAAs and 223 (48%) patients had a possible interaction (Figure: risk on DDI per DAA regime per patient).

Conclusions: Concomitant medication use is high and rich in diversity in chronic HCV patients. Majority of patients are at risk for clinically relevant drug-drug interactions, this can increase the likelihood of treatment failure of both HCV and concomitant therapy. DDIs can be managed using a multidisciplinary approach involving a pharmacist.

No conflict of interest

Abstract: P_46

Drug Drug Interactions

Lack of Clinically Relevant Effect of Food on the Pharmacokinetics of Tenofovir Alafenamide

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Background: Tenofovir alafenamide (TAF) is a phosphonamidate prodrug of tenofovir (TFV) currently under regulatory review as a single agent for treatment of chronic hepatitis B (CHB).

TAF has also been recently approved within the fixed dose combination tablets elvitegravir/ cobicistat/emtricitabine/TAF (GENVOYA®) and rilpivirine/emtricitabine/TAF (ODEFSEY®) for treatment of HIV-1 infection.
TAF exhibits a favorable pharmacokinetic (PK) profile versus the currently approved prodrug tenofovir disoproxil fumarate (TDF), resulting in markedly lower circulating TFV in plasma, which provides safety benefits by reducing off-target effects associated with TFV, in particular renal and bone toxicity. This Phase 1 study evaluated the effect of food on the PK of TAF following administration of TAF 25 mg.

Materials and Methods: This was a randomized, open label, two treatment, two period, single center study. Treatments were administered to healthy subjects (n=40) following a 10 hour fast. Each subject received a single dose of TAF 25 mg in a crossover manner either fasted or following a standardized high-calorie/high-fat meal (~800 kcal; 50% fat), separated by a 7 day washout. Intensive PK sampling was performed and statistical comparisons of TAF exposures were conducted by geometric mean ratios (GMR) and associated 90% confidence intervals (CI) with fed conditions serving as the test and fasted conditions serving as the reference.
Safety was monitored throughout the study and follow-up (12-16 days after last treatment).

Results: Both treatments were well tolerated and all subjects completed the study except one subject that withdrew consent. The majority of subjects were male (65%), white (53%), and of Hispanic or Latino ethnicity (60%). Subjects had a mean (range) age and body mass index of 34 (21-45) years and 26.4 (20.9-31.9) kg/m^2, respectively. All adverse events (AE) observed were mild in severity (Grade 1) and there were no clinically relevant laboratory abnormalities. Following administration under fed conditions, TAF exposure was increased 65-68% (AUC_{last} and AUC_{inf} GMR (90% CI): 165 (151, 181) and 168 (154, 182), respectively), versus fasted administration. A 0.5 hour delay in T_{max} was also observed (median (Q1, Q3) of 0.50 (0.25, 0.50) hours under fasted conditions versus 1.00 (0.50, 1.50) hours under fed conditions). Importantly, the overall TAF exposures in the present study under both fasted and fed conditions were in the range of exposures in the TAF CHB Proof-of-Concept (TAF evaluated at 8, 25, 40, and 120 mg) and Phase 3 (TAF evaluated at 25 mg) studies, where no trends in exposure-response/safety were observed, indicating a wide therapeutic index of TAF for treatment of subjects with CHB.

Conclusions: The overall exposure of TAF was increased when administered under fed conditions, versus fasted. However, the observed changes in TAF PK are not considered clinically meaningful based on the wide range of TAF exposures associated with efficacy and safety established in the clinical development program for TAF for treatment of chronic hepatitis B.

Conflict of interest
financial relationship(s): Coauthors of this work are employees and shareholders of Gilead Sciences.

Abstract: P_47

Drug Drug Interactions

Lack of an effect of ledipasvir on CYP3A activity in healthy volunteers

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Introduction: Ledipasvir (LDV), a potent HCV NS5A inhibitor, is approved for the treatment of chronic HCV infection as a fixed-dose combination tablet with sofosbuvir. LDV is an inhibitor of P-gp and BCRP and may increase plasma concentrations of substrates for these transporters. Based on in vitro data, LDV is not expected to act as a perpetrator of cytochrome 450-mediated drug interactions. In Phase 1 studies, increases in plasma exposures of various CYP3A substrates (e.g. cobicistat, ritonavir, atazanavir or simeprevir) were observed in the presence of LDV (single agent or in combination with sofosbuvir). Accordingly, this study was conducted to evaluate the effect of LDV on in vivo CYP3A activity using midazolam (MDZ), a sensitive CYP3A substrate.

Materials & Methods: This was a fixed-sequence, open-label study in healthy subjects. All treatments were administered with a moderate-fat meal. A single dose of MDZ 2.5 mg was administered alone on Day 1, on Day 3 coadministered with a single dose of LDV 90 mg, and on Day 13 coadministered with LDV 90 mg following dosing of LDV 90 mg QD on Days 4-12. The PK of MDZ was assessed on Days 1, 3, and 13 and the PK of LDV was assessed on Days 3 and 13. Statistical comparisons of MDZ exposures (AUC_{inf} and C_{max}), administered with LDV on Days 3 and 13 versus alone on Day 1, were made using percent geometric mean ratios (%GMRs) and associated 90% confidence intervals (CI) with a PK no-interaction boundary of 70-143%. Safety was assessed throughout the study.

Results: All 30 enrolled subjects completed the study. Ledipasvir did not alter MDZ PK. Relative to MDZ administered alone on Day 1, the %GMR of MDZ AUC_{inf} was 99.3 (90% CI: 95.3, 103) and C_{max} was 107 (90% CI: 100, 114) on Day 3 after MDZ was coadministered with a single dose of LDV. The %GMR of MDZ AUC_{inf} was 89.5 (84.0, 95.4) and C_{max} was 95.0 (90% CI: 86.7, 104) on Day 13 after MDZ was coadministered with LDV following administration of LDV on Days 4-12. LDV single- and multiple-dose exposures were comparable to historical data. All treatments were safe and generally well tolerated.

Conclusions: These results offer direct clinical evidence that LDV does not inhibit or induce CYP3A in vivo suggesting that the drug interaction liability is limited to transporter-mediated interactions.

Conflict of interest
financial relationship(s): Nicholas T. Au, Polina German, Yizhao Li, Gong Shen, Chohee Yun, K.H. John Ling, and Anita Mathias are all employees of and own stock in Gilead.

Abstract: P_48

Drug Drug Interactions

Clinical, biological and Pharmacological relevance of Ledipasvir/Sofosbuvir drug interaction with TDF containing Regimen in HCV/HIV co-infected patients.

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Introduction: Sofosbuvir(SOF)/Ledipasvir(LDV) has been shown to increase tenofovir exposure, especially when used together with an HIV regimen containing TDF and a PK enhancer. The safety of TDF in the setting of SOF/LDV and a PK enhancer has not been established, particularly in patients at increased risk of renal dysfunction. The objective was to compare safety, antiretrovirals (TFV C24h) and Direct Antiviral Agents (DAA, SOF007, LDV) plasma concentrations and estimate glomerular filtration rate (eGFR) before, during and after treatment by SOF/LDV (400/90mg) QD in HCV/HIV co-infected patients.

Materials and Methods: HCV/HIV co-infected patients receiving SOF/LDV and TDF containing regimen were enrolled from a multicenter cohort. Plasma C24h were determined using UPLC-MS/MS (LOQ: LDV=10ng/mL, TFV=5ng/mL and SOF007=10 ng/mL). The kidney function was assessed by eGFR using CKD-epi formula, before and during the treatment. Median (IQR25-75%; CV%) are presented. Non-parametric analysis was used.

Results: Overall, 44 patients were recruited (68% men, age 51yo (43-55)). HCV genotypes: 1 (61%); 3 (2.5%); 4 (34%); unknown (2.5%). DAA duration was: 8 weeks (3 patients); 12 weeks (37 patients); 24 weeks (4 patients). Thirty four patients without cirrhosis (77%), 8 with cirrhosis (18%), 2 unknown (5%). Antiretroviral associated with TDF were: emtricitabine (42 patients) and abacavir (1 patient); etravirine (3 patients), rilpivirine (10 patients) and efavirenz (8 patients); darunavir/r (7 patients), atazanavir/r (3 patients); raltegravir (11 patients), dolutegravir (1 patient) and elvitegravir/cobi (4 patients). Median time between the 2 set points during and after LDV was 23 weeks (22-26). TFV C24h before LDV was 85ng/mL (52-136; n=15 samples; n=15 patients, CV 56%); during LDV was 85ng/mL (63-127; n=75 samples; n=44 patients, CV 60%); after LDV was 86 ng/mL (76-90; n=10 samples; n=9 patients, CV 67%) (p value=0.65). LDV C24h was 171ng/mL (95-290; n=75 samples; n=44 patients, CV 107%). SOF007 C24h was 390 ng/mL (255-622, n=75 samples; n=44 patients, CV 82%). eGFR before LDV was 85 mL/min (76-90; n=15 samples; n=15 patients, CV 15%); during LDV was 90 mL/min (78-90; n=75 samples; n=44 patients, CV 18%) and after LDV was 90 mL/min (84-90; n=9 samples; 9 patients, CV 14%) (p value=0.40). No adverse events were reported during treatment.

Conclusion: In a population of HCV/HIV co-infected patients chronically receiving TDF containing regimen, TDF C24h before DAA initiation were as expected in hepatic impairment, slightly higher compared to mono-HIV-infected patients with normal liver function (22-66 ng/mL). In these conditions, the drug-drug interaction between SOF/LDV and TFV appeared limited. Consequently, no impact on kidney function or safety considerations was observed during the short 8 to 24 weeks DAA treatment duration. Nevertheless, therapeutic drug monitoring should still be recommended in patients with pre-existent renal dysfunction.

No conflict of interest

Abstract: P_49

Drug Drug Interactions

Effects of Cobicistat and Ritonavir on Gene Expression in Human Hepatocytes In Vitro

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Introduction: Modulation of metabolic enzyme expression by antiretroviral compounds (ARVs) can lead to clinically-significant drug-drug interactions (DDIs), which can complicate treatment regimens in patients concomitantly receiving other medications. Ritonavir (RTV), and its derivative cobicistat (COBI), are both administered as pharmacoenhancers to improve the pharmacokinetics of selected ARVs; however, the effects of RTV and COBI upon metabolic enzyme expression have not yet been fully elucidated. The aim of this study was to use an *in vitro* human hepatocyte model to characterise the effects of RTV or COBI on the expression of a selection of genes encoding proteins involved in drug metabolism.

Materials & Methods: Cryopreserved human hepatocytes were plated on collagen-coated 96-well culture plates, overlaid with Geltrex™ and incubated for one day. Cells were subsequently treated with RTV (1 μM); COBI (1.28 μM); rifampicin (RIF; 10 μM; positive control); or methanol (0.3% v/v; vehicle control) in Williams' Medium E incubation medium, once a day for a total of three days. Total RNA was extracted, and qPCR gene expression analysis was carried out using Human Drug Metabolism RT² Profiler™ PCR Arrays (Qiagen). Validation studies were completed using TaqMan® Gene Expression Assay probes (Life Technologies). Changes in gene expression relative to the vehicle control were determined, and gene expression relative to

that induced by the positive control was also quantified. Each condition within the validation studies was assessed in triplicate, using hepatocytes obtained from three individual donors.

Results: From a total of 84 genes analysed, COBI (1.28 μM), and RTV (1 μM), induced expression (by ≥2-fold above vehicle control) of three, and five genes, respectively. RIF (10 μM) - a well-established inducer of several enzymes involved in drug metabolism - induced expression of ten genes (by ≥2-fold above vehicle control). Validation studies showed that RIF (10 μM) induced *CYP2B6*, *CYP2C8* and *CYP3A4* expression by 4.3 ± 1.5-fold, 4.4 ± 2.8-fold and 11.3 ±6.1-fold, respectively (*n*=6). COBI, and RTV, induced *CYP3A4* expression by 2.9 ± 0.8-fold, and 9.2 ± 1.2-fold, respectively (*n*=3). Expression of *CYP2B6* was induced 1.4 ± 0.3-fold, and 2.4 ± 0.2-fold, by COBI, and RTV; whereas expression of *CYP2C8* was induced 1.6 ± 0.3-fold, and 3.3 ± 0.5-fold, by COBI, and RTV, respectively (*n*=3). *CYP3A4* expression induced by COBI, or RTV, relative to that induced by RIF, was 49.0 ± 10.8% and 56.7 ± 7.2%, in turn (*n*=3). Induction of *CYP2B6* expression by COBI or RTV as a percentage of RIF-induced expression was 37.5 ± 10.4%, and 57.9 ± 12.0%, respectively (*n*=3); whilst the corresponding induction of *CYP2C8* expression by COBI, or RTV, compared to that of RIF, was 54.9 ± 11.2% and 53.7 ± 14.8% (*n*=3). **Conclusions:** Whilst COBI and RTV both serve as net inhibitors of CYP3A4 activity *in vivo*, it was found that in a hepatocyte-based *in vitro* model of drug metabolism, both COBI and RTV moderately induced the expression of *CYP2B6*, *CYP2C8* and *CYP3A4*. This model provides a valuable description of the mechanisms underpinning DDIs, and these results represent useful data to inform future clinical investigations of potential DDIs in HIV patients.

No conflict of interest

Abstract: P_50

Drug Drug Interactions

Open-Label, Drug–Drug Interaction Study between Second-generation HIV-1 Maturation Inhibitor BMS-955176 and Tenofovir in Healthy Subjects

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Introduction: BMS-955176 is a second-generation HIV-1 maturation inhibitor that targets Gag, inhibiting the final protease cleavage event between capsid protein p24 and spacer peptide-1, resulting in the production of immature, non-infectious virions. BMS-955176 could potentially be coadministered with the nucleoside reverse transcriptase inhibitor, tenofovir disoproxil fumarate (TDF; a prodrug of tenofovir), in HIV-1-infected patients. To evaluate potential drug–drug interactions (DDI) and guide dosing when coadministered in Phase 2 trials, the pharmacokinetic (PK) interaction between BMS-955176 and tenofovir was assessed in healthy subjects.

Materials & Methods: AI468005 was an open-label, multiple-dose, single-sequence, three-period, two-way interaction study in healthy adult subjects, aged 18–50 years, with a body mass index of 18.0–32.0 kg/m^2. Eligible subjects received TDF 300 mg QD between Days 1 and 5 (Treatment A). Following a 4-day washout period, subjects received BMS-955176 40 mg QD (spray-dried dispersion [SDD] formulation) between Days 10 and 17 (Treatment B), then BMS-955176 40 mg QD + TDF 300 mg QD between Days 18 and 25 (Treatment C). Serial blood samples were collected up to 24 hours after the final study drug administration in each treatment period. Additional pre-dose trough blood samples were

collected on Days 3 and 4 for tenofovir and Days 15 and 16 for BMS-955176. PK parameters were derived by non-compartmental methods. Geometric mean ratios and 90% confidence intervals (CIs) were derived using linear mixed-effects models. No clinically relevant effect of BMS-955176 on tenofovir C_{max}, AUC_{TAU} and C_{24} would be concluded if 90% CIs fell within the lower and upper bounds of 0.7 and 1.5, respectively. There were no predefined boundaries for BMS-955176 PK. Subjects were monitored for adverse events (AEs) throughout the study.

Results: In total, 18 subjects received treatment and all completed the study. Systemic exposures of BMS-955176 were comparable following BMS-955176 monotherapy versus BMS-955176 + TDF coadministration; geometric means (comparison; 90% CI) were: $C_{max,}$ 1385 ng/mL versus 1411 ng/mL (1.019; 0.971, 1.068); $AUC_{TAU,}$ 25348 h*ng/mL versus 26064 h*ng/mL (1.028; 0.997, 1.061) and C_{24}, 906 ng/mL versus 888 ng/mL (0.980; 0.948, 1.013). Systemic exposures of tenofovir were comparable following TDF monotherapy versus BMS-955176 + TDF treatment; geometric means (comparison; 90% CI) were: $C_{max,}$ 324 ng/mL versus 310 ng/mL (0.957; 0.897, 1.020); AUC_{TAU}, 2853 h*ng/mL versus 2774 h*ng/mL (0.972; 0.928, 1.019); $C_{24,}$ 55.0 ng/mL versus 56.2 ng/mL (1.022; 0.961, 1.088). 90% CIs for tenofovir were within pre-specified limits. All treatments were generally well tolerated; AEs were mild and there were no deaths, serious AEs or AEs leading to discontinuation.

Conclusions: No clinically relevant DDIs were observed between BMS-955176 and tenofovir at the doses studied and no dose adjustments are required. The BMS-955176 40 mg SDD dose used in this study produces exposures comparable to a 60 mg micronized crystalline tablet dose, which is the lowest dose being tested in Phase 2b studies. A sub-study in Phase 2b will assess DDIs between higher doses of BMS-955176 and tenofovir. BMS-955176 was generally well tolerated when administered alone or with TDF in healthy subjects.

Conflict of interest
financial relationship(s): I am an employee and shareholder of Bristol-Myers Squibb.

Abstract: P_51

Drug Drug Interactions

Open-Label, Drug–Drug Interaction Study between HIV-1 Attachment Inhibitor BMS-663068 and Maraviroc in Healthy Subjects

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Introduction: BMS-663068 is a prodrug of BMS-626529, a first-in-class attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into host CD4+ T cells. BMS-663068 could potentially be coadministered with the CCR5-receptor antagonist, maraviroc, in heavily treatment-experienced HIV-1-infected patients (the focus population of the BMS-663068 Phase 3 program). To evaluate potential drug–drug interactions, the pharmacokinetics (PK) between BMS-626529 and maraviroc were assessed in healthy subjects. BMS-663068 was administered using the formulation and dose being evaluated in the ongoing Phase 3 trial.

Material & Methods: AI438052 (NCT02480894) was a Phase 1, open-label, single-sequence, two-way interaction study. Eligible subjects received BMS-663068 600 mg BID (as an extended-release tablet) between Days 1 and 3, with a single dose of BMS-663068 administered on the morning of Day 4 (Treatment A). Following a 3-day washout period, subjects received maraviroc 300 mg BID between Days 7 and 11 (Treatment B). Subjects then received BMS-663068 600 mg BID + maraviroc 300 mg BID between Days 12 and 17 with single doses of BMS-6630668 and maraviroc administered on the morning of Day 18 (Treatment C). Serial blood samples for the PK analysis of BMS-626529 were collected on Days

4 and 18, and for maraviroc on Days 11 and 18. PK parameters were derived by non-compartmental methods. Geometric mean ratios and 90% confidence intervals (CI) were derived using linear mixed-effects models. No clinically relevant effect of BMS-663068 on maraviroc C_{max} and AUC_{TAU} was to be concluded if the 90% CI fell within 0.67–1.50. There were no predefined boundaries for BMS-626529 PK. Subjects were monitored for adverse events (AEs) throughout the study.

Results: In total, 14 subjects received treatment and 12 completed the study. Multiple-dose coadministration of BMS-663068 with maraviroc resulted in a 13% increase in the geometric means of BMS-626529 C_{max} (90% CI: 0.962–1.323), a 10% increase in AUC_{TAU} (90% CI: 0.993–1.226), and a 10% decrease in C_{12} (90% CI: 0.691–1.174) compared with BMS-663068 monotherapy. Coadministration of maraviroc with BMS-663068 resulted in a 0.6% increase in the steady-state C_{max} of maraviroc (90% CI: 0.844–1.199), a 25% increase in AUC_{TAU} (90% CI: 1.076–-1.440), and a 37% increase in C_{12} (90% CI: 1.257–1.483) compared with maraviroc monotherapy; 90% CIs for maraviroc C_{max} and AUC_{TAU} were within pre-specified bounds. All treatments were generally well tolerated. Two subjects discontinued due to AEs, neither were considered related to study medication.

Conclusions: There was no clinically relevant effect of BMS-663068 600 mg BID on maraviroc 300 mg and as the 90% CIs included 1.0, the modest effects of maraviroc on BMS-626529 PK are unlikely to be clinically relevant. BMS-663068 administered alone or in combination with maraviroc was generally well tolerated. Coadministration of BMS-663068 with maraviroc at the evaluated doses requires no dose modification.

Conflict of interest
financial relationship(s): I am employee and shareholder of Bristol-Myers Squibb.

Abstract: P_52

Drug Drug Interactions

No clinically significant interaction of MK-3682 with the HIV medications: dolutegravir, raltegravir, rilpivirine, and tenofovir disoproxil fumarate

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Background: MK-3682 is a potent and selective pan-genotypic uridine nucleoside mono-phosphate prodrug inhibitor of the HCV NS5B RNA polymerase being developed for therapy of chronic hepatitis C virus (HCV) infection in combination with other compounds. MK-3682 is anticipated to be frequently used with antiretroviral compounds in the HIV/HCV co-infected patient population. This study evaluated the safety and pharmacokinetics (PK) of coadministration of MK-3682 with four first-line antiretroviral (ARV) medications: dolutegravir, raltegravir, rilpivirine, and tenofovir disoproxil fumarate (TDF).

Material & Methods: This was a 4-part, open-label drug-interaction study. Parts 1-3 of this study assessed the one-way interaction of multiple doses of MK-3682 on single doses of dolutegravir, raltegravir and rilpivirine, respectively. In period 1, single doses of ARV were administered, followed by a wash-out period of 3 days for dolutegravir and raltegravir and 10 days for rilpivirine. In period 2, subjects received 300 mg MK-3682 once daily for 7 days to achieve steady state, and single doses of ARV on day 7. Part 4 assessed the two-way interaction of multiple doses of MK-3682 and TDF. In period 1, subjects received 300 mg TDF once daily for 7 days, followed by a washout period of 7 days, and received MK-3682 300 mg once daily for 7 days in period 2. In period 3, subjects received MK-3682 300 mg once daily and TDF 300 mg once

daily for 7 days. Blood samples were collected for ARV in parts 1-4 and MK-3682 and its circulating metabolite M6 in part 4. 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 $AUC_{0-\infty}$/AUC_{0-24} and C_{max} using mixed effect modelling. Safety assessments included ECGs, vital signs, clinical laboratory tests, physical examination, and adverse event monitoring.

Results: 54 healthy male and female subjects were enrolled (N=12 each for Parts 1, 2 and 4 and N=18 for Part 3). Coadministration with MK-3682 did not meaningfully affect the pharmacokinetics of dolutegravir, raltegravir, and rilpivirine, with GMRs for $AUC_{0-\infty}$ and C_{max} close to 1. Multiple doses of MK-3682 increased TDF C_{max} by 41% with no meaningful effect on AUC_{0-24} and C_{24}. Coadministration of TDF increased MK-3682 $AUC_{0-\infty}$ and C_{max} by 24% and 55%, and M6 C_{max} by 21% with minimal effect on M6 AUC_{0-24}. The increases on TDF C_{max} and MK-3682 and M6 exposures were modest and not considered to be clinically meaningful. Coadministration of MK-3682 with ARVs in this study was generally well tolerated.

Conclusions: Multiple doses of MK-3682 did not meaningfully affect the pharmacokinetics of single doses of dolutegravir, raltegravir, rilpivirine, and coadministration of MK-3682 with TDF did not result in clinically significant drug interactions. These results support co-administration of MK-3682 with dolutegravir, raltegravir, rilpivirine, and TDF.

Conflict of interest
financial relationship(s): I am Merck&Co. employee and I own stock of Merck&Co.

Abstract: P_53

Drug Drug Interactions

No clincally significant interaction of MK-8408 with the HIV medications dolutegravir, raltegravir, rilpivirine, and tenofovir disoproxil fumarate

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Background: MK-8408 is a potent inhibitor of the HCV NS5A replication complex being developed for therapy of chronic hepatitis C virus (HCV) infection in combination with other compounds. MK-8408 is anticipated to be frequently used with antiretroviral compounds in the HIV/HCV co-infected patient population. This study evaluated the safety and pharmacokinetics (PK) of coadministration of MK-8408 with four first-line antiretroviral (ARV) medications: dolutegravir, raltegravir, rilpivirine, and tenofovir disoproxil fumarate (TDF).

Methods: This was a four-part, open-label, drug-interaction study in healthy subjects. Parts 1-3 consisted of 2-period fixed sequences assessing the one-way interaction of multiple doses of MK-8408 on single doses of dolutegravir, raltegravir, and rilpivirine, respectively. A single dose of ARV was administered in period 1 followed by a wash-out period of 3 days for dolutegravir and raltegravir and 10 days for rilpivirine. In period 2, subjects received 60 mg MK-8408 for 5 days prior to coadministration with a single dose of ARV on Day 6. Part 4 was a 3-period fixed sequence study assessing the two-way interaction of multiple doses of MK-8408 and TDF. Subjects received 300 mg TDF once daily for 7 days followed by a washout period of 7 days in period 1, 60 mg MK-8408 once daily for 6 days in period 2, and 60 mg MK-8408 and 300 mg TDF once daily for 7 days in period 3. Blood samples were collected for ARV in parts 1-4 and MK-8408 in part 4. 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 $AUC_{0-\infty}$, AUC_{0-24} and C_{max} using a linear mixed effect model. Safety assessments included ECGs, vital signs, clinical laboratory tests, physical examination, and adverse event monitoring.

Results: Forty-four (44) healthy male and female subjects were enrolled (N=10 each for Parts 1 and 2 and N=12 for Parts 3 and 4). Coadministration with MK-8408 did not meaningfully affect the pharmacokinetics of raltegravir and rilpivirine with GMRs for $AUC_{0-\infty}$ and C_{max} close to 1. Multiple doses of MK-8408 increased dolutegravir $AUC_{0-\infty}$ by 29% and C_{max} by 15%. Multiple doses of MK-8408 increased TDF AUC_{0-24} and C_{24} by 17% and C_{max} by 29%. Coadministration of TDF had no meaningful effect on MK-8408 PK. The increases of dolutegravir and TDF exposures were modest and not considered to be clinically meaningful. Coadministration of MK-8408 with ARVs in this study was generally well tolerated.

Conclusions: Multiple doses of MK-8408 did not meaningfully affect the pharmacokinetics of single doses of dolutegravir, raltegravir, and rilpivirine, and coadministration of MK-8408 with TDF did not result in clinically significant drug interactions. These results support coadministration of MK-8408 with dolutegravir, raltegravir, rilpivirine, and TDF.

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

Abstract: P_54

Drug Drug Interactions

Should Drug-Drug Interaction Studies between HIV Medications and Acid Reducing Agents be Conducted in HIV Patients?

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Introduction: Drug-Drug interaction (DDI) studies between HIV medications and acid-reducing agents (ARAs) are typically conducted in healthy subjects. Subjects with HIV infection have a higher rate of hypochlorhydria and thus, higher baseline gastric pH. Drugs with pH-dependent absorption will have different bioavailability in subjects with HIV infection relative to healthy subjects and absolute changes in pH caused by ARAs may have a differential effect on absorption of such drugs in these two populations. Therefore; results of DDI studies between HIV medications and ARAs in healthy volunteers may not apply to subjects with HIV infection (the target population).

Methods: A database of HIV medications and ARA DDI studies was compiled using drug labels and clinical pharmacology reviews available on the Drugs@fda website. The database contains information regarding trial design (population, type of ARA used, dose, number of subjects) and results (exposure parameters and resulting clinical recommendations).

Results: A total of 59 DDI evaluations between HIV medications and ARAs have been reviewed and included in US prescribing information. All of these studies except one were conducted in healthy subjects. Raltegravir is the only antiretroviral drug where a DDI study with antacids in HIV-infected subjects was conducted. A literature search identified one DDI study between raltegravir and omeprazole in HIV patients and one DDI study with antacids in

healthy subjects that was not presented in the raltegravir prescribing information.
Results of these studies are shown in the Table below.

Acid Reducing Agent	Healthy Subjects			Subjects with HIV		
	N	AUC Ratio (ARA/no ARA)	Cmax Ratio (ARA/no ARA)	N	AUC Ratio (ARA/no ARA)	Cmax Ratio (ARA/no ARA)
Omeprazole	14	3.12 (2.13, 4.56)	4.15 (2.82, 6.10)	18	1.39**	1.51**
Aluminum and magnesium hydroxide antacid (simul-taneous)	16	0.26* (0.22, 0.32)	0.28* (0.23, 0.33)	25	0.51 (0.40, 0.65)	0.56 (0.42, 0.73)
Aluminum and magnesium hydroxide antacid (2 h before)	16	0.74* (0.61, 0.89)	0.82* (0.69, 0.98)	23	0.49 (0.5, 0.67)	0.49 (0.33, 0.71)
*J Antimicrob Chemother. 2011 Jul;66(7):1567-72 **Abstract, 12th European AIDS Conference/EACS, Cologne, Germany, November 11-14, 2009.						

Conclusions: Given the widespread availability and use of ARAs in HIV patients, consideration should be given to conduct DDI studies between HIV drugs and ARAs in subjects with HIV infection rather than healthy subjects when a drug's bioavailability is known to be altered by changes in pH. As the raltegravir-ARA cross-study comparison shows, the effect of ARAs on raltegravir exposure can be significantly different between healthy subjects and subjects with HIV infection, depending on temporal separation. Further complicating the translatability of ARA effects in healthy subjects to HIV-infected subjects is the different drug exposures between the two populations that often occurs with antiretrovirals. Thus, conducting studies in healthy subjects may mask the true extent of an ARA's effect on HIV medications.

No conflict of interest

Abstract: P_55

Drug Drug Interactions

Review of the Use of PBPK Modeling for Antiviral Drugs in Regulatory Decision-Making

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Introduction: Physiologically based Pharmaco-kinetic (PBPK) modeling is becoming more frequently used to aid in the prediction of pharmacokinetics to support almost every phase of drug development. Some previous reports from FDA regarding PBPK modeling were cases involving broad categories such as CYP inducers and inhibitors, or classes of drugs such as hematological products. Here we describe how PBPK modeling has contributed to regulatory decision-making for antiviral drugs.

Methods: A database of all drugs for which PBPK modeling has been submitted to FDA was searched and antiviral drugs were identified. Of those antiviral drugs, the list was further refined to include only those for which the analysis was either described in a publicly available review on the Drugs@FDA website or has otherwise been presented in a public forum (and permission granted to use the data in this review).

Results: A total of six antiviral drug programs have submitted PBPK modeling for review to support various types of decisions. At this time, three of these submissions were identified that satisfy the abovementioned criteria. However, since the case for simeprevir has been previously presented in detail, it is not described here.
Case 1: PBPK modeling was used to evaluate the effect of clopidogrel on the exposure of dasabuvir following a literature article that raised concerns for a potential and serious interaction between clopidogrel and dasabuvir. PBPK simulations showed that under a worst-case scenario, the predicted increase in Cmax of dasabuvir is anticipated to be lower than the mean dasabuvir

Cmax that may be associated with the potential for QT prolongation. As a result, the review team concluded that the Viekira Pak label does not need to be updated with this interaction information.
Case 2: A PBPK model for rilpivirine was developed to further characterize the potential for a drug interaction with ketoconazole since the clinical dose of rilpivirine was not used in the original drug interaction study. After verifying the model with the results of the higher dose of rilpivirine used in the ketoconazole study, the review team concluded that a minimal effect of rilpivirine on ketoconazole exposure would be expected at the clinical dose. A PBPK model to predict the effect of mild and moderate hepatic impairment on rilpivirine exposure was also submitted but did not result in a specific labeling recommendation.

Conclusions: PBPK models that are submitted to the FDA to support labeling recommendations are fully evaluated for their validity and predictive value. PBPK modeling can and has been used successfully in antiviral drug development to support labeling recommendations or to confirm that an additional clinical study is not needed.

No conflict of interest

Abstract: P_56

Drug Drug Interactions

Coadministration of ZepatierTM (Grazoprevir/Elbasvir) with Tenofovir Disoproxil Fumarate Resulted in No Clinically Meaningful Drug-Drug Interaction in Healthy Subjects

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Background: Zepatier™ is an approved once-daily treatment for chronic hepatitis C infection (HCV), and is a fixed-dose combination of 100 mg of grazoprevir (GZR), an HCV NS3/4A protease inhibitor, and 50 mg of elbasvir (EBR), an HCV NS5A inhibitor. To inform dosing recommendations for Zepatier™ in HCV patients with HIV co-infection, this study was conducted to evaluate the potential for a drug-drug interaction between Zepatier™ and the antiretroviral drug tenofovir disoproxil fumarate (TDF). Previous clinical drug-interaction studies showed no effect of TDF on GZR or EBR when GZR and EBR were administered separately.

Methods: This study was conducted with 14 healthy adults, 6 females and 8 males. This was a fixed-sequence study with 2 treatment periods. In Period 1, multiple oral doses of 300 mg TDF were administered once-daily (QD) for 7 consecutive days. In Period 2, 300 mg QD doses of TDF were co-administered with Zepatier™ QD for 12 consecutive days. There was no washout between Periods 1 and 2. All study drugs were administered under fasting conditions. Plasma pharmacokinetic (PK) samples were collected up to 24 hours after the last dose in each period to determine tenofovir (TFV) concentrations.

Results: Tenofovir pharmacokinetics are not meaningfully altered by concomitant administration of multiple doses of TDF and Zepatier™ as compared to administration of multiple doses of TDF alone. The TFV AUC_{0-24}, C_{max}, and C_{24} GMRs [90% CI] for Zepatier™ + TDF / TDF alone were 1.27 [1.20, 1.35], 1.14 [0.95, 1.36], and 1.20 [1.09, 1.40], respectively. The 1.35 upper limit for the GMR 90% CI of TFV AUC_{0-24} is below the 1.43 clinical relevance bound for TFV. The observed median TFV T_{max} of ~ 1 hour was similar when administered alone or in combination with Zepatier™.

Conclusions: This drug interaction study demonstrated that coadministration of Zepatier™ and TDF did not result in a clinically relevant change in TFV exposure. Previous studies demonstrated that coadministration with TDF did

not affect GZR or EBR exposure. Together, the drug interaction study results support the coadministration of Zepatier™ and TDF in HIV co-infected HCV patients. The concomitant use of TDF with Zepatier™ was well-tolerated in Phase 2 and 3 clinical trials for treatment of HCV infection.

Conflict of interest
financial relationship(s): I am an employee of Merck & Co. Inc.

Abstract: P_57

Drug Drug Interactions

Metabolism and Excretion of GS-9857, a Pan-Genotypic HCV NS3/4A Protease Inhibitor in Humans

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Background: GS-9857, a pan-genotypic HCV NS3/4A protease inhibitor (PI) with potent antiviral activity against HCV genotypes 1-6, is currently being evaluated in Phase 3 studies as part of a fixed dose combination with sofosbuvir (SOF: 400 mg) and velpatasvir (VEL, GS-5816: 100 mg). Nonclinical data indicate that GS-9857 is metabolically stable, primarily eliminated unchanged in the bile, and minimally excreted in the urine. The present study was conducted to understand the metabolic and excretory pathways of GS-9857 in humans.

Methods: Healthy male volunteers (n=8) were given a single oral dose of an ethanolic solution of 100 mg GS-9857 containing 100µCi [^{14}C]-labeled in a capsule after a standardized meal. Blood, urine and feces samples were collected until prespecified standard criteria for collection of administered radiolabeled material were met. Total radioactivity was assessed in all samples by liquid scintillation counting (LSC), and plasma and whole blood by accelerator mass spectrometry (AMS). Pooled plasma and excreta samples were subject to HPLC radioprofiling (AMS and LSC, respectively), and plasma samples were subject to HPLC-MS/MS analyses. Quantification of GS-9857 was performed using a synthetic standard, and previously identified metabolites were quantified based on HPLC profiles of radioactivity. Safety was assessed by routine clinical and laboratory monitoring throughout the study.

Results: Eight subjects enrolled, received study drug and completed the study. Total recovery of radioactivity in excreta was 93.9 ± 6.1% (mean ± SD of dose); all radioactivity was recovered in the feces, and none was recovered in urine. The predominant circulating species in plasma was GS-9857 (> 90% of total radioactivity AUC). The whole blood to plasma ratio of total radioactivity was 0.50- 0.80 indicating exclusion of total radioactivity from erythrocytes. GS-9857 was the major species detected in the feces (40% of dose) with Des-[methylcyclopropylsulphonamide]-GS-9857 (M19) accounting for 22.1% of the dose, with dehydro-GS-9857-2 (M9) and des-[methylcyclopropylsulphonamide]-oxy-GS-9857-1 (M21) accounting for 7.5% and 5.4% of the dose, respectively. The remaining components in the feces each accounted for a mean of less than 4% of the dose with 86% of the dose being quantified in the feces overall. Three adverse events (AEs) were reported, none were serious or drug related. The reported AEs were all mild in severity, including change of diarrhea, eye irritation and scratch. No Grade 3 or higher laboratory abnormalities occurred.

Conclusions: [14C]-GS-9857 is moderately metabolized in humans, with GS-9857 accounting for >90% of systemic plasma exposure, and is exclusively eliminated in the feces (94% of the dose) predominantly as GS-9857 (40% of the dose), with M19, M9, and M21 accounting for 22.1%, 7.5% and 5.4% of the dose respectively. These data indicate the potential for a favorable drug-drug interaction profile and ability for use in the setting of renal dysfunction.

Conflict of interest
financial relationship(s): All authors are employees of Gilead Sciences Inc.

Abstract: P_58

Drug Drug Interactions

Prevalence of self-medications, clinical relevance and drug-drug interaction in HIV-infected virologically controlled patients

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Introduction: Information on self-medications potentially interacting with antiretrovirals (ARV) are poorly documented in hospital patient's database. Consequently, all intervention to anticipate the eventual drug-drug interaction (DDI) is null and void.

Objectives: To evaluate the prevalence of Non-steroidal anti-inflammatory drugs (NSAIDs) and gastro-intestinal agents (GIAs) self-medications in HIV-infected virologically controlled patients receiving TDF containing regimen and their clinical relevance on eGFR and consecutive potential DDI.

Materials & Methods: a questionnaire (10min duration) was given prospectively by a pharmacist to HIV-infected patients during their hospital visit, relative to the NSAIDs and GIAs use (drugs, frequency, intake, adherence, tolerance etc.) and regarding their ARV treatment. The hospital database was checked to retro-collect the patient's clinical, biological and therapeutic characteristics. All of them, enrolled in this study, gave their written informed consent to have their medical chart recorded in the electronic medical record system. Median (IQR25-75%) are presented.

Results: Among the 223 screened patients in this single center, prospective study, 182 were eligible based on the information available in database: 104 males; 50yrs (42-57); BMI 24kg/m^2 (22-27); African (64%), Caucasian (22%) and other geographic origins (14%); HIV-infection duration 14yrs (6-20); plasma HIV-1 RNA (pVL) zenith 69,746 copies/mL (17,917-244,800); CD4 nadir 200/mm^3 (77-320); contamination modes: heterosexual (60%), MSM (17%), others (10%) and unknown (13%); Co-infections: HCV (7%), HBV (10%), HCV/HBV (1%); ARV experienced 84% with 5 previous lines of ARV (3-8). At baseline, ARV triple therapy: QD (85%); STR (36%); TDF containing regimen (67%); EFV (11%); RPV (14%); E/c/F/TDF (6%); DTG/3TC/ABC (7%); DRV/r (31%) and ATV+r (8%); pVL<50 copies/mL (92%); eGFR calculated with MDRD formula was 84 mL/min/1.73m^2 (71-100). Among the 182 patients, 74 (41%) declared using NSAIDs rarely (11%), occasionally (52%), usually (30%) and frequently (7%). Among them, NSAIDs were: ibuprofen (74%); ketoprofen (22%); diclofenac (22%); naproxen (5%); tiaprofenic acid (3%); flurbiprofen (3%); piroxicam (1%). Among the 182 patients, 32 (18%) and 37 (20%) declared using Proton Pump inhibitors (PPIs) or anti-H2 and other GIAs, respectively, rarely (10%), occasionally (31%), usually (19%) and frequently (40%). Among them, PPIs/anti-H2 were: omeprazole (64%), rabeprazole (12%), pantoprazole (3%), ranitidine (3%) and GIAs were: aluminium alginate (68%), diosmectite (46%), magnesium/aluminium hydroxyde (8%) and colloidal aluminium phosphate (5%). Finally, 52%, 18% and 57% of patients declared using self-medications of NSAIDs, PPIs/anti-H2 and GIAs, respectively. Only 34 (46%) on the 74 patients using NSAIDs reported an associated PPIs/anti-H2 or GIAs. For PPIs/anti-H2 and GIAs, 26% were taken concomitantly, 40% separately and 33% regardless the ARV intake. Retrospectively, detection of theoretical DDI between TDF and NSAIDs (n=53) demonstrated no impact on eGFR, even with diclofenac. RPV or ATV+r and associated PPIs/anti-H2 or GIAs was 20% and 7%, respectively. Only 1 pVL (105 copies/mL) was detected with RPV associated with ranitidine.

Conclusions: In that population well-knowing their HIV infection (85% knew their last pVL), the majority of self-medication information was not previously recorded in the patient's hospital database: 73% and 62% unknown for NSAIDs and PPIs/anti-H2 and GIAs, respectively. Fortunately, possible DDI occurred rarely and with minimal impact on pVL or eGFR.

No conflict of interest

Abstract: P_59

Drug Drug Interactions

Pharmacokinetic Interaction Between Emtricitabine/Tenofovir Alafenamide and Boosted-Atazanavir

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Introduction: Tenofovir alafenamide (TAF) is a prodrug of tenofovir (TFV) designed to improve safety compared with tenofovir disoproxil fumarate. TAF has been coformulated into a fixed dose combination with emtricitabine (F, FTC) as a NtRTI backbone to be combined with a variety of different third agents. Several clinical studies have demonstrated that TAF exposure is increased when coadministered with cobicistat (COBI), due to increased bioavailability via inhibition of (P-glycoprotein) P-gp-mediated intestinal efflux of TAF by COBI. In addition, TAF is a substrate of the hepatic uptake transporters OATP1B1/3 and the protease inhibitor atazanavir (ATV) is an inhibitor OATP1B1/3. The objectives of this study were to (1) evaluate the effect of ATV boosted by COBI on the pharmacokinetics (PK) of TAF and FTC, and (2) evaluate the effect of TAF on the PK of ATV and COBI.

Material & Methods: Healthy subjects 18 to 45 years of age (n=20) were enrolled in the open-label, fixed sequence, 3-period, crossover study. Subjects received the following treatments: (A) F/TAF (200/10 mg) once daily with food on Days 1 to 7; (B) ATV 300 mg + COBI 150 mg + F/TAF (200/10 mg) once daily with food on Days 8 to 14; and (C) ATV 300 mg + COBI 150 mg once daily with food on Days 15 to 21. Intensive PK assessments were performed on Days 7, 14, and 21, and PK parameters area-under-the-curve over the dosing period (AUCtau), AUC from time zero to the time of the last quantifiable concentration (AUClast), maximum concentration (Cmax) and concentration at the end of dosing period (Ctau) were determined. Statistical comparisons for FTC, TAF, TFV, ATV, and COBI were made using geometric least-squares mean ratios and associated 90% confidence interval (CI) no-effect boundary of 70 to 143%, with F/TAF + ATV + COBI as the test treatment and F/TAF as reference for objective (1), and ATV+COBI as the reference for objective (2). Safety was assessed throughout the study

Results: Compared to administration of F/TAF alone, F/TAF+ATV+COBI led to increases in TAF exposure (AUClast) of 75% and TAF Cmax of 80%; increases in TFV AUCtau of 248%, TFV Cmax of 216% and TFV Ctau of 273% were also observed. These increases are expected and consistent with the effect of a P-gp inhibitor on TAF exposure and its metabolite TFV, as demonstrated in previous studies with ritonavir. Coadministration of ATV+COBI with F/TAF did not affect the PK of FTC, ATV, or COBI. ATV+COBI and F/TAF+ATV+COBI were well-tolerated. No subject had any adverse events (AEs) leading to discontinuation, Grade 3 or 4 AEs, or serious AEs.

Conclusions: Coadministration of F/TAF and ATV+COBI led to an expected increase in TAF and TFV exposures, consistent with the effect of a P-gp inhibitor on TAF exposures and, subsequently, its metabolite TFV.
Coadministration of F/TAF and ATV+COBI did not affect the PK of FTC, ATV, or COBI. The increase in TAF and TFV exposures do not pose safety concerns.

Conflict of interest
financial relationship(s): Employees of Gilead Sciences Inc.

Abstract: P_60

Drug Drug Interactions

Lack of Pharmacokinetic Interaction Between Emtricitabine/Tenofovir Alafenamide and Oral Contraceptive Ethinyl Estradiol/Norgestimate

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Introduction: HIV-1 infection in women is most prevalent among those of childbearing potential. Hormonal contraceptives, especially combinations of an estrogen and a progesterone component, are one of the most commonly used methods of family planning/pregnancy prevention. Tenofovir alafenamide (TAF) is a prodrug of tenofovir (TFV) designed to improve safety compared with tenofovir disoproxil fumarate. TAF has been coformulated into a fixed dose combination with emtricitabine (F, FTC) as a NtRTI backbone to be combined with a variety of different antiretroviral agents for treatment of HIV. The objective of this study is to evaluate the pharmacokinetics (PK) of a commonly used oral contraceptive (OC) ethinyl estradiol and norgestimate (EE/NGM) when coadministered with F/TAF 200/25 mg.

Material & Methods: Healthy, nonpregnant, nonlactating, nonsmoking, premenopausal female subjects 18 to 45 years of age (n=13) completed the study. Subjects received the following treatments sequentially: (1) Lead-in phase: 28 day-cycle of EE/NGM (2) Cycle 1 (Days 1 – 28): 28-day cycle of EE/NGM, and (3) Cycle 2 (Days 29 – 56): 28-day cycle of EE/NGM and F/TAF (200/25 mg) concurrently on Days 29 – 42. Intensive PK assessments were performed on Days 14 and 42 and PK parameters area-under-the-curve-over-the-dosing-period (AUCtau), maximum concentration (Cmax) and concentration at the end of dosing interval (Ctau) were determined. Pharmacodynamic assessment for luteinizing hormone (LH) and follicle stimulating hormone (FSH) were also collected on Days 14 and 42, and progesterone was collected on Days 21 and 49. Statistical comparisons for norelgestromin (NGMN), norgestrel (NG) and EE were made using geometric mean ratios (GMR) and associated 90% confidence interval (CI) no-effect boundary of 70-143%, with F/TAF+OC as the test treatment and OC alone as reference. Pharmacodynamic parameters were summarized, and safety was assessed throughout the study.

Results: Systemic exposures of NGMN, NG and EE were not altered when OC was coadministered with F/TAF. The GMR and the associated 90% CI of all primary PK parameters of NGMN, NG and EE were within the prespecified no effect bounds of 70 to 143%.
LH, FSH, and progesterone median concentrations were comparable across all treatment cycles. LH and progesterone median values were lower than those expected for ovulatory or luteal phases, respectively. Follicle stimulating hormone was in the lower range for the ovulatory phase and was consistent with a possible decrease in serum LH and FSH by oral hormonal contraceptives and absence of ovulation, as indicated by very low progesterone values on Day 21. Coadministration of OC with F/TAF was well-tolerated in this study. No subject had any adverse events (AEs) leading to discontinuation; there were no Grade 3/4 AEs or serious AEs observed in the study. Three subjects had grade 3/4 laboratory abnormalities; one subject had a Grade 4 transient low lymphocytes, and 2 subjects had Grade 3 urine occult blood but none was considered to be clinically significant (linked to menses).

Conclusions: Coadministration of OC with F/TAF was generally safe and well-tolerated. No loss of contraceptive efficacy is expected with coadministration of OC with F/TAF as no pharmacokinetic and pharmacodynamics interactions were observed.

Conflict of interest
financial relationship(s): Employees of Gilead Sciences Inc.

Abstract: P_61

Novel Drugs and Formulations

Phosphoramidate prodrugs of uridine analogs, including sofosbuvir, are metabolized to both uridine and cytidine triphosphates in Huh-7 cells and primary human hepatocytes

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Introduction: Sofosbuvir is a phosporamidate prodrug of a uridine nucleoside analog, and similar prodrugs of novel uridine nucleoside analogs are in development to treat HCV infection. It is known that cytidine analogs are metabolized intracellularly into pharmacologically active cytidine and uridine triphosphates, but phosphoramidate prodrugs of uridine analogs are believed to generate only the pharmacologically active uridine triphosphate. During the profiling of MDV-845, a phosphoramidate prodrug of a novel uridine anlog that inhibits HCV replication *in vitro*, the intracellular metabolites of MDV-845 and sofosbuvir were determined.

Methods: Antiviral activity was evaluated using a HCV GT1b replicon in Huh-7 cells. Uridine and cytidine triphosphates were tested against recombinant HCV GT1b NS5B polymerase, and levels were determined in Huh-7 cells, primary human hepatocytes and in dog liver after oral dosing.

Results: MDV-845 and sofosbuvir exhibited EC_{90} values of 0.9μM and 2.2μM in replicon cells respectively. For both protides, CC_{50} values were >100μM in Huh-7 cells. At EC_{90} levels of MDV-845 or sofosbuvir, the intracellular concentrations of MDV-845-UTP and Sof-UTP in Huh-7 cells were 11μM and 91μM respectively. MDV-845-UTP and sof-UTP were potent inhibitors of HCV NS5B polymerase with K_i values of of 1.7μM and 0.5μM respectively. Since MDV-845 was more potent than sofosbuvir in replicon cells, but less yielded lower intracellular concentrations of its less active UTP metabolite when compared with sofosbuvir, we explored whether additional active metabolites were formed in Huh-7 cells.

We discovered that MDV-845-CTP and sof-CTP (mericitabine-TP) were formed in MDV-845- and sofosbuvir-treated Huh-7 cells respectively, and were formed in a concentration dependent manner. At EC_{90} levels of MDV-845 or sofosbuvir, the intracellular concentration of MDV-845-TP was 100μM (909% that of the corresponding UTP metabolite) and the intracellular concentration of mericitabine-TP was 6μM (7% of the corresponding UTP metabolite). MDV-845-CTP and mericitabine-TP were potent inhibitors of the HCV NS5B polymerase with K_i values of 0.20μM and 0.12μM respectively. MDV-845-CTP and mericitabine-TP were also generated in primary human hepatocytes from MDV-845 and sofosbuvir respectively, but to a lesser extent than in Huh-7 cells. Both MDV-845-UTP and MDV-845-CTP were found in dog liver after oral dosing of MDV-845.

Conclusions: The phosphoramidate prodrugs of uridine analogs, sofosbuvir and MDV-845, are metabolized to the corresponding cytidine triphosphates within human liver cells. Cytidine metabolites need to be included in the antiviral and safety profiling of prodrugs of novel uridine analogs with anti-HCV activity.

Conflict of interest, financial relationship(s): Employee and shareholder of Medivir AB

Abstract: P_62

Novel Drugs and Formulations

Relative Bioavailability and Food Effect of Fixed Dose Combination Tablets of Dolutegravir and Rilpivirine in Healthy Subjects

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Background: The efficacy and safety of a 2-drug regimen of the integrase inhibitor dolutegravir (DTG, Tivicay®) with the non-nucleoside reverse transcriptase inhibitor rilpivirine (RPV, Edurant®) is being evaluated in two ongoing Phase 3 trials. The objective of the present 2-part study **(**NCT02373930) was to evaluate the relative oral bioavailability of 5 prototype fixed dose combination (FDC) DTG/RPV tablets in healthy subjects, under fed and fasted conditions.

Materials & Methods: Part 1 was a randomized, 3-way crossover, incomplete block Youden square design in a single cohort (N=24). Each subject was randomized to receive the reference treatment (Tivicay 50mg + Edurant 25mg single entity tablets) and 2 of 4 FDC tablets (A, B, C, D; n=12/FDC) within 30 minutes of a high-fat meal. Two FDC formulations from Part 1 (B, D) and a previously untested FDC (E) were evaluated in Part 2 in a 3-way crossover in three parallel cohorts of n=12 subjects each. Subjects were randomized to: 1) reference fasted; 2) test FDC fasted; 3) test FDC fed (moderate fat meal). In both parts, serial PK samples were collected over 168h. The test/reference geometric least squares (GLS) means ratio and associated 90% confidence intervals (CI) of non-compartmental PK parameters (ln-transformed) were determined using a mixed effects model.

Results: In Part 1 (high-fat fed), DTG and RPV AUC and Cmax were similar to the reference for all FDC tablets. GLS means ratios (90%CI) were 1.011 (0.949, 1.077), 1.057 (0.992, 1.126), 1.016 (0.954, 1.082), and 1.083 (1.016, 1.154) for DTG AUC(0-∞) and 0.997 (0.911, 1.091), 1.055 (0.960, 1.160), 1.054 (0.963, 1.153), 1.096 (0.997, 1.205) for RPV AUC(0-∞); for A, B, C, D, vs. reference, respectively. In Part 2 (fasted), GLS means ratios (90%CI) for DTG AUC(0-∞) were 0.871 (0.720, 1.054), 0.944 (0.761, 1.170), and 0.880 (0.752, 1.031) for B, D, E, vs reference, respectively, with corresponding ratios (90%CI) for RPV AUC(0-∞) of 1.040 (0.818, 1.323), 1.065 (0.929, 1.222), and 0.985 (0.784, 1.238). Administration of the FDC tablets after a moderate fat meal increased the AUC(0-∞) of DTG by 74-87% and RPV by 38-57% across FDCs. A high-fat meal increased (cross-cohort comparison) the AUC(0-∞) of DTG by 71-87% and RPV by 68-72% across FDCs. Food also increased the Cmax for both drugs. No deaths, serious AEs, clinically significant changes in clinical laboratory values, vital signs, or ECGs were observed. Four subjects were withdrawn early (2 positive drugs of abuse; 1 tooth abscess, 1 elevated ALT).

Conclusions: All FDCs yielded comparable DTG and RPV exposures to the reference single entity formulations in both the fed and fasted states. Food increased the exposure to RPV and DTG, consistent with previous observations for the single entity products. All treatments were generally safe and well-tolerated. Selection of a FDC for further development will be based primarily on pharmaceutical and manufacturing considerations.

Conflict of interest
financial relationship(s): Employee of ViiV Healthcare

Abstract: P_63

Novel Drugs and Formulations

Pharmacokinetics and Exploratory Interactions of HIV Maturation Inhibitor BMS-955176 in Healthy Subjects: Single- and Multiple-Ascending Dose Studies

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Introduction: BMS-955176 is a second-generation HIV-1 maturation inhibitor that targets Gag, inhibiting the final protease cleavage event between capsid protein p24 and spacer peptide-1, resulting in the production of immature, non-infectious virions. Single-ascending and multiple-ascending dose studies were conducted to assess BMS-955176 pharmacokinetics (PK) in healthy subjects. BMS-955176 may be coadministered with HIV protease inhibitors in clinical studies, and because BMS-955176 is a substrate of CYP3A4 and P-glycoprotein, there is potential for drug–drug interactions (DDIs). Thus, preliminary assessments of DDIs between BMS-955176 and ritonavir (RTV) and atazanavir (ATV) were evaluated as well.

Material & Methods: AI468001 was a Phase 1, randomized, double-blind, placebo-controlled, sequential, single-ascending (Part A) and multiple-ascending (Part B) dose study. In each arm, eight subjects were randomized 3:1 to receive BMS-955176 or placebo. In Part A, subjects received a single dose of spray-dried dispersion (SDD) BMS-955176 (10 mg, 20 mg, 40 mg, or 120 mg) on Day 1. On Day 8, one group received 40 mg SDD + RTV 100 mg. In Part B, subjects received BMS-955176 (10 mg, 20 mg, or 80 mg) once daily (QD) for 14 days, BMS-955176 40 mg QD for 28 days, or BMS-955176 40 mg QD + ATV 400 mg QD for 14 days. Serial blood samples were collected and PK parameters were derived by non-compartmental methods. Geometric mean ratios were calculated from log-transformed data by mixed-effect modeling.

Results: In total, 79/80 subjects completed the study. In Part A, BMS-955176 exposures increased in a less-than-dose-proportional manner; slopes (90% confidence intervals [CIs]) were 0.845 (0.730, 0.961) and 0.900 (0.790, 1.009) for C_{max} and AUC_{inf}, respectively. Following single-dose administration of BMS-955176, the mean terminal half-life ranged from 34.0 to 38.9 hours. BMS-955176 total clearance (CLT/F) after single SDD doses and CLT/F at steady state were similar (ranges: 17.9–21.4 mL/min and 20.3–25.5 mL/min, respectively). In Part B, steady state was achieved ~7 days after multiple-dose administration of BMS-955176. The accumulation indices for C_{max}, AUC_{TAU} and C_{24} were similar across the 10–80 mg range (~2-fold). Coadministration of single-dose BMS-955176 40 mg with two RTV 100 mg doses (12 hours apart) increased the geometric means of C_{max} and AUC_{inf} of BMS-955176 by 11% and 48%, respectively. After 14 days of BMS-955176 40 mg QD + ATV 400 mg QD, AUC_{TAU} increased 26% versus BMS-955176 administered alone. BMS-955176 was generally well-tolerated.

Conclusions: BMS-955176 is rapidly absorbed, with time-independent PK and a half-life supportive of QD dosing. The modest effects of RTV and ATV suggest a minor role of CYP3A4 and/or P-glycoprotein in the disposition of BMS-955176. These data informed dose selection (5–120 mg QD) for the BMS-955176 Phase 2a proof-of-concept study (AI468002; NCT01803074).

Conflict of interest
financial relationship(s): I am an employee and shareholder of Bristol-Myers Squibb.

Abstract: P_64

PK/PD modeling

Population Pharmacokinetics of Raltegravir and Raltegravir Glucuronide in Healthy Adults Receiving UGT1A1 Modulators Ritonavir, Ketoconazole or Rifampicin

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Introduction: Raltegravir (RAL) is a first-in-class HIV-1 integrase inhibitor for the treatment of HIV infection. The objective of this study was to quantify the effects of pre-treatment with UGT1A1 modulators ritonavir, ketoconazole or rifampicin on RAL and raltegravir glucuronide (RALG) pharmacokinetics in healthy adult volunteers using the population pharmacokinetic modelling approach.

Materials & Methods: A total of 52 healthy adults underwent four periods of treatment – baseline (reference) period; period 1: either ketoconazole 200 mg or ritonavir 100 mg twice daily given for 3 days; period 2: either ritonavir or ketoconazole given for 3 days (periods 1 and 2 in a randomised crossover design); and Period 3: rifampicin 600 mg given nightly for 2 weeks. At the end of each period, each subject was orally administered with 400mg RAL. Venous blood samples were collected over 12 hours after the RAL dose, and plasma was analysed for RAL and RALG using a validated liquid chromatography/mass spectrometry method. Nonlinear mixed-effects modelling was conducted using NONMEM.

Results: The time course of plasma RAL concentration was best described by a one compartment linear model with three parallel absorption processes, each of which consisted of mixed zero-and first order absorption. Additions of inter-occasional variability to the absorption parameters significantly improved the model's fit. Disposition of the metabolite in plasma was best described by a one-compartment model linked to the RAL model. Covariate evaluation demonstrated that ritonavir and ketoconazole decreased apparent RAL clearance (CL_{RAL}/F) by 38 and 52%, respectively, while rifampicin increased CL_{RAL}/F by 27%. In addition, the apparent volume of distribution of RAL fell by 10L from the typical value of 37L after ketoconazole pre-treatment. A visual predictive check indicted that the final model provided a robust and unbiased fit to the data.

Conclusions: A population pharmacokinetic model describing the complex, multiple peak absorption kinetics of RAL was formulated using three parallel, mixed zero and first-order absorption pathways. The extents by which ketoconazole, ritonavir and rifampicin modulated apparent RAL clearance were quantified.

No conflict of interest

Abstract: P_65

PK/PD modeling

A Semimechanistic Enzyme-Turnover Model for Simulating Darunavir/Cobicistat Pharmacokinetics over 72h Following Drug Cessation in Healthy Volunteers

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Background: Plasma pharmacokinetic (PK) data describing time-courses of antiretrovirals beyond the dosing interval are important for management of late or missed doses. Cobicistat, a mechanism-based CYP3A4 inhibitor, has been co-formulated with darunavir (DRV/COBI; 800/150 mg once

daily; *qd*) for treatment of HIV, and demonstrated comparable DRV exposure to DRV/ritonavir (RTV; 800/100 mg *qd*) in healthy volunteers. Modelling and simulation was used to simulate DRV/COBI PK up to 72 hours following drug cessation using DRV/RTV as a paradigm.

Materials & Methods: In two separate PK studies healthy volunteers received DRV/RTV (800/100 mg *qd*) or elvitegravir/COBI (150/150 mg *qd*) for 10 days and serial sampling performed for 72 or 216 hours following the final dose, respectively. DRV/RTV data over 72 hours were modelled simultaneously and a COBI PK model to 72 hours developed (NONMEM v. 7.2). Assuming the same model structure as DRV/RTV for the interaction between DRV/COBI, estimates for the inhibition of DRV by COBI were obtained using published data of DRV/COBI (800/150 mg *qd*; mean PK profile to 24 hours) and DRV alone (800 mg twice daily; mean PK profile to 24 hours). DRV/COBI and DRV/RTV PK profiles to 72 hours were simulated using final model parameters (n=1000).

Results: DRV and RTV PK were described by a 2 and 1-compartment model, respectively (n=17; 7 female). An E_{max} function linked RTV concentrations to an enzyme turnover model inhibiting the zero-order production rate of a theoretical enzyme pool [k_{enz} (95% CI): 0.056 h^{-1} (0.041-0.072)]; the amount of enzyme directly influenced DRV apparent oral clearance (CL/F). DRV CL/F in the absence of RTV was 57 L/h (31-86) and a RTV concentration of 0.047 mg/L (0.016-0.077) was associated with 50% maximum inhibition (IC_{50}). A 2-compartment model described COBI PK over 72 hours (n=17; 12 female). Corresponding values for k_{enz}, IC_{50} and DRV CL/F without COBI were 0.050 h^{-1} (RSE% 10%), 0.022 mg/L (5.0%) and 66 L/h (2.0%). Predicted DRV exposure and half-life in the absence of RTV and COBI were comparable: 13.7 *vs.* 12.1 mg.h/L and 1.2 *vs.* 1.1 h, respectively. Median simulated DRV half-life 24 and 72 hours after stopping drug decreased from 10.4 to 6.5 h, respectively with RTV and from 16.0 to 6.2 h with COBI.

Conclusions: A semimechanistic PK-enzyme turnover model adequately described the elimination of boosted DRV beyond the dosing interval. Given the shared mechanism of inhibition by RTV and COBI, the modelling approach allowed exploration of the potential PK forgiveness of coformulated DRV/COBI in the absence of clinical data. Model validation and refinement with real-life DRV/COBI concentrations to 72 hours is necessary.

No conflict of interest

Abstract: P_66

PK/PD modeling

Population Pharmacokinetics and Pharmacodynamics Model Linking TDF/FTC with the dNTP Pool

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Introduction: Previous work showed that TDF/FTC lowered endogenous deoxynucleoside triphosphate (dNTP) pools. The active phosphorylated anabolites of tenofovir (TFV-DP) and emtricitabine (FTC-TP) compete with endogenous dATP and dCTP at the active site of HIV reverse transcriptase. In this study, we used PK/PD link models to investigate the interaction between TDF/FTC and the dNTP pool.

Materials & Methods: HIV-negative adults (n=21) were enrolled in a pharmacokinetic study of daily TDF/FTC for 30 days, followed by a 30 days of washout; treatment-naïve HIV-positive adults (n=19) received TDF/FTC/EFV (efavirenz) treatment for 60 days. PBMC samples were assayed from before the initiation of treatment (baseline), as well as at 1, 2, 4, 8, and 24 hours post-dose on days 1 (first dose) and 30 (steady-state); at 8-hour post dose on days 3, 7, and 20; at 5, 15, and 30 days of washout (HIV-negative); and day 60 (HIV-positive). TFV and FTC in plasma and TFV-DP, FTC-TP, dATP, dCTP, dGTP, and TTP in PBMC were quantified using

validated LC/MS/MS. Data were fitted sequentially using NONMEM 7.3 (ADVAN13, FOCEI). Plasma concentrations were used to stimulate the corresponding intracellular active metabolite levels. Intracellular TFV-DP was then linked to changes in dATP and dGTP (purines), and FTC-TP linked to dCTP and TTP (pyrimidines). Models were evaluated using goodness of fit plots, bootstrapping, and visual predictive checks.

Results: A tolerance model best described the stimulation of intracellular concentration by plasma level, and an indirect PD response model best fit the dNTP data. TFV-DP and FTC-TP inhibited dNTP formation (K_{in}) via an E_{max} model. To avoid overparameterization, E_{max} and elimination rate constant (K_{out}) were fixed to 1. The EC_{50} (Interindividual variability, (%CV)) of TFV-DP on the inhibition of dATP formation were 1022 fmol/10^6 cells (130%). A transient effect that reduced overtime ($E_{max}/(1+time^{0.9})$) was observed on dGTP, with an EC_{50} of 54 fmol/10^6 cells (interindividual variability not estimated). In addition, the EC_{50} of FTC-TP on the inhibition of dCTP and TTP formation were 44 pmol/10^6 cells (82.5%) and 19 pmol/10^6 cells (101%). Simulation (median (5% and 95% percentile)) showed dATP decreased by 11% (0.45%, 53%); dCTP and TTP decreased by 14% (2.6%, 35%) and 24% (4.5%, 62%); dGTP reached nadir around day 2.5 with a reduction of 13% (6.9%, 21%), then returned to the baseline value; other components in the dNTP pool returned to baseline in the washout period. No covariate was significant in PK/PD link models.

Conclusions: PK/PD modeling and simulation described the interaction between TDF/FTC and the dNTP pool in both HIV-negative and HIV-positive adults. The reductions in dNTP pool were small but would increase the drug:dNTP ratio, potentially enhancing treatment effects. In this study, the small sample size limited the ability to estimate some parameters and the influence of covariates. Further research is needed to better understand the clinical significance and mechanism of these effects.

No conflict of interest

Abstract: P_67

PK/PD modeling

Population pharmacokinetics of rilpivirine in HIV-1-infected patients treated with the single-tablet regimen rilpivirine/ tenofovir/emtricitabine

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Background: Rilpivirine (RPV) is a second generation non-nucleoside reverse transcriptase inhibitor, widely prescribed with tenofovir (TDF) and emtricitabine (FTC) as a single-tablet regimen (STR) for the treatment of HIV infection. An important pharmacokinetic variability on the RPV trough concentration is observed in clinical practice that could affect RPV efficiency and/or safety profile. However, pharmacokinetics of RPV has been poorly studied and a pharmacokinetic-pharmacodynamic relationship has been reported in the ECHO/THRIVE phase 3 trials. We aim to determine the population pharmacokinetics (POP PK) parameters of RPV in adult HIV-infected patients, and to quantify the interindividual variability in pharmacokinetic parameters.

Materials and methods: We conducted a multicenter, retrospective and observational study in patients treated with the once-daily regimen RPV/TDF/FTC for which TDM plasma samples were collected, at steady state, at various times ranging from 1 to 30 hours post-dose. RPV plasma concentrations were measured by liquid chromatography coupled with tandem mass spectrometry. POP PK analysis was performed using NONMEM software, version VI. The first-order conditional estimation with INTERACTION (FOCEI) method was employed. To build the structural model, one- and two-compartment models with first order absorption were tested, with or without a lag time. Available pathophysiological covariates were tested for their ability to explain the interindividual variability (IIV) in pharmacokinetic parameters: age, body weight, body mass index (BMI), creatinine clearance, gender, hepatitis B/C coinfection, background HIV treatment. Information tools were used to screen influential covariates, before including them in the population pharmacokinetics model. Model qualification was performed by both statistical and graphical methods.

Results: Overall, 260 patients were included in the study (74% male, mean age= 45 years, 14% were naïve and 86% pretreated) and 695 plasma RPV concentrations were analyzed. The RPV POP PK was best described using a two-compartment model with first-order absorption with a lag time and a proportional residual error model. Due to the sparseness of the data (maximum 3 samples per patient), absorption constant rate (Ka), absorption lag time (ALAG), apparent volume of the central compartment (V2/F) and apparent intercompartmental clearance (Q/F) needed to be fixed to values obtained in the only POP-PK analysis available (Ka= 1.5h-1, ALAG= 1.3 h, V2/F=152 L and Q/F=87.9 L/h). Estimated typical values for PK parameters (95% confidence interval) were as follows: oral clearance (Cl/F) = 9 L/h (8.5-9.6), apparent volume of the second compartment (V3/F) = 140 L (64.3-215.7). IIV of Cl/F, V2/F and V3/F were 36%, 65% and 74%, respectively. The estimated terminal half-life was 11 hours. The covariates BMI, body weight and gender added on V2/F, V3/F and Cl decreased significantly the objective function value.

Conclusion: RPV PK was best described by a two-compartment model as previously reported. Our results show a wide interindividual variability for the PK parameters particularly on V2/F and V3/F. In this 'real-life' population, a lower half-life was found compared with the reported value of 45h from phase 3 trials. BMI, body weight and gender were the only covariates which influence significantly the RPV PK. A better understanding of RPV PK may improve RPV-based regimen individualization.

No conflict of interest

Abstract: P_68

PK/PD modeling

Pharmacokinetic and pharmacogenetic analysis of Unbound Atazanavir (ATV), Ritonavir (RTV) and Efavirenz (EFV) in HIV-infected Patients

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Introduction: Unbound concentrations drive efficacy; for highly bound antiretrovirals (ARVs), characterizing influences on unbound fraction (f_u) and intrinsic clearance (CL_{int}) can guide dosing. With increasing age, changes in f_u and CL_{int} may alter unbound PK, while total PK remains constant. Polymorphisms in drug metabolic enzymes and transporter (DMET) genes may also contribute to inter-subject variability. Here, we applied population pharmacokinetic-pharmacogenetics (PK-PGx) modeling to describe total and unbound ATV, RTV and EFV PK in HIV-infected subjects.

Material & Methods: Plasma samples were collected from 91 HIV-infected adults receiving ATV/RTV (n=31) or EFV (n=60) at steady-state, with tenofovir/emtricitabine (TFV/FTC) backbones. Subjects underwent frailty phenotyping; genotyping of DMET (Affymetrix DMET chip), $p16^{INKA4a}$ expression, a marker of senescence, and cytokine concentrations were measured. Drug concentrations were determined by LC-MS/MS, with rapid equilibrium dialysis for unbound concentrations. Population analysis was performed in NONMEM 7.3. The likelihood ratio test was used for model discrimination (α= 0.05). Forward addition/backward elimination (α= 0.05/0.01) was used for covariate analysis. Pharmacogenetic analysis was conducted on post-hoc PK estimates and selected gene polymorphisms using one-way ANOVA, with adjustment for multiple comparisons (α= 0.05). Genes with minor allele frequency >5% were included in the analysis.

Results: The median (range) age of the enrolled subjects was 49 (22-73) years, with 30 females; 58 were African Americans; 3 displayed the frailty phenotype; 1 had a viral load >50 copies/mL. Total and unbound PK were simultaneously described, and the protein bound drug was related to unbound drug with f_u. ATV and EFV were fit with 2-compartment models, and RTV with 1-compartment model, following 1st-order absorption. An absorption lag time was used in the ATV and RTV models. RTV apparent intrinsic clearance and apparent volume of distribution were scaled to body mass index (BMI). Proportional residual error models were used. Covariate analysis included age, sex, HIV and regimen duration, BMI, frailty score, $p16^{INK4a}$ expression, cytokine concentrations, focusing on CL_{int} and f_u. In the RTV final model, BMI was a significant covariate on f_u. Subjects with BMI <30 kg/m^2 had a 52% increased f_u compared to those with higher BMI (0.95% vs. 0.63%). Age, frailty and $p16^{INK4a}$ expression were not significant covariates. Pharmacogenetic analysis found that RTV apparent intrinsic clearance was 58% lower in subjects with the *ABCB1 3435C>T* allele which encodes P-glycoprotein (*P* = 0.039). For EFV, the *CYP2B6 516G>T* genotype predicted 27% lower apparent intrinsic clearance in heterozygotes and 63% lower in homozygotes (*P* = 0.024). No significant genetic predictors were found for ATV PK.

Conclusions: This population PK-PGx model investigated protein binding of ATV, RTV and EFV in HIV-infected subjects. When given with ATV/TFV/FTC, RTV protein binding is higher with lower BMI. Aging, frailty, nor senescence reveal significant effects on the f_u or CL_{int} of these drugs. Therefore, current dosing strategies for ATV/RTV and EFV are expected to provide efficacious unbound concentrations regardless of age. This analysis identifies the potential of *ABCB1 3435C>T* to decrease RTV apparent intrinsic clearance, and further confirms that the *CYP2B6 516G>T* genotype is a significant predictor of EFV elimination.

No conflict of interest

Abstract: P_69

Therapeutic Drug Monitoring

Measuring plasma concentrations of ribavirin: first report from a quality control program

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Background: Cirrhotic patients with a chronic hepatitis C virus (HCV) infection are treated with the novel direct-acting antivirals. Cirrhotics are harder to treat and ribavirin is added to improve treatment response. Ribavirin has a concentration-effect relationship and Therapeutic Drug Monitoring (TDM) can be used to optimize the dose. No commercial assays are available, thus laboratories have developed analytical methods themselves. According to international guidelines, clinical laboratories have to participate

in proficiency testing. This abstract describes the first year of an international proficiency testing program (KKGT) for ribavirin.

Method: The program consisted of two rounds each year. Each round included two samples that were spiked with a high and low concentration of ribavirin. We used freeze dried bovine serum for these samples. The spiked concentrations resembling ribavirin plasma concentrations as found in patients. Participating laboratories measured ribavirin concentrations, which were reported back to KKGT. Required accuracy was defined as 80%-120% of the spiked 'expert' concentration, and was calculated dividing the reported concentration by the expert value.

Results: Eight laboratories participated in the first two rounds of this program and a total of 24 samples were measured. A total of six samples fell outside the 80%-120% range: three high and three low-spiked samples. The high expert concentrations for round 1 and 2 were 3.64 mg/L and 2.18 mg/L, respectively. The measured concentration relative to the expert value for round 1 (n=8) varied from 55% to 160%. For round 2 (n=6) the range was 87% to 303%. The low expert concentrations for round 1 and 2 were 0.80mg/L and 0.55mg/L, respectively. The measured concentration relative to the expert value for round 1 (n=8) ranged from 86% to 336% and for round 2 (n=6) the range was 97%-148%.

Conclusion: This analysis showed that 6/24 samples were not accurately reported. Low-spiked samples had the highest variation in reported ribavirin concentrations. Inaccurate measurement of ribavirin could result in unnecessary dose reductions (possibly risking virologic failure) or increased dosages (leading to severe anemia). Thus, measuring the correct ribavirin concentration is important for HCV treatment. Our external quality control program can contribute to the quality of ribavirin assays. Laboratories are encouraged to participate in our proficiency testing program (www.kkgt.nl).

No conflict of interest

Abstract: P_70

Therapeutic Drug Monitoring

Fingerstick vs. Venipuncture Sampling for Dried Blood Spots to Measure Cumulative Adherence to Tenofovir Therapy

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Background: Sustained drug exposure and adherence to antiretroviral therapy are critical to achieving viral suppression and preventing HIV transmission. Tenofovir-diphosphate (TFV-DP) in dried blood spots (DBS) is a useful biomarker for cumulative adherence due to its 17-day half-life and approximately 25-fold accumulation to steady state with daily dosing. Currently, TFV-DP has been mostly measured in DBS collected from venipuncture. However, capillary blood obtained from fingerstick is a potential sampling strategy for this matrix that is easy to obtain at a low cost and requires minimal processing. In this study, we investigated the linear relationship between DBS TFV-DP levels obtained by fingerstick versus venipuncture.

Material & Methods: HIV infected adults ≥18 years old who were taking any TFV based regimen for any duration of time were enrolled in an observational cohort that involved up to 3 visits over 48 weeks. During one of the three visits, a sample of whole blood was collected by venipuncture into an EDTA tube and later spotted on a 903 protein saver card in 25µl aliquots. A second sample was obtained at the same time where five drops of blood were spotted on a protein saver card from a capillary puncture on the distal tip of the index, ring, or middle finger using a lancet. DBS fingerstick and DBS venipuncture samples were extracted from the protein saver cards in 3mm punches for analysis. TFV-DP was measured in DBS using a previously validated

LC-MS/MS method. Fingerstick and venipuncture TFV-DP levels were compared using linear regression and Bland-Altman plots (MS Excel). The alpha level was set at 0.05. Data are mean (95% CI), unless noted otherwise.

Results: 30 participants with a median age of 49 years (range 26 to 63) contributed one fingerstick sample and one venipuncture sample, for a total of 30 paired samples. The mean fingerstick TFV-DP was 1531 fmol/punch (1264 to 1797), whereas the mean venipuncture TFV-DP was 1612 fmol/punch (1329 to 1896). The correlation of TFV-DP between the two sampling methods was defined by a linear relationship where venipuncture = 1.03*fingerstick + 30.4 fmol/punch with an $r^2 = 0.94$ ($p < 0.001$). The mean difference between venipuncture and fingerstick was -3.73% (-8.32 to 0.86). Ninety-percent (27/30) of fingerstick samples were within ± 15% of the venipuncture TFV-DP result. In the Bland Altman plots, the mean difference between fingerstick and venipuncture was 81.8 fmol/punch (-443 to 279) with no significant level-dependent bias ($p = 0.18$).

Conclusions: mDBS TFV-DP concentrations obtained via fingerstick show excellent agreement with venipuncture levels in this matrix. These results support DBS fingerstick sampling as a potential alternative for monitoring cumulative adherence to TFV based therapy. This method of collection offers the possibility for self-collection, field implementation, and use in resource-limited settings.

No conflict of interest

Abstract: P_71

Therapeutic Drug Monitoring

What minimal concentration of darunavir in maintenance darunavir/ritonavir 800/100 mg once-daily with 2 NRTIs (DAMAR study)?

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Introduction: Darunavir/ritonavir (DRV/r) is one of the most prescribed ritonavir boosted protease inhibitor in both antiretroviral naïve and experienced patients. A lack of knowledge of an efficacy threshold of DRV plasma concentration for HIV-infected patients in maintenance regimen impede treatment optimization is reported. The use of the 10-fold *in vitro* protein adjusted 50% inhibitory concentration on wild-type (WT) HIV viruses (550 ng/mL) had to be proved in routine practice. The objectives was to assess the DRV trough concentration (C24h) efficacy threshold in patients receiving DRV/r (800/100mg QD) with 2 NRTIs in maintenance with plasma HIV-1-RNA (pVL)<50 copies/mL for at least two years.

Materials & Methods: Observational, multicentre study. HIV-1-infected patients receiving DRV/r 800/100mg QD in maintenance and good adherence profile were recruited. Maintenance phase was defined as plasma HIV-1-RNA (pVL) <50 copies/mL for at least 2 years on unchanged treatment. Simultaneous antiretroviral (darunavir, ritonavir, abacavir, emtricitabine, lamivudine and tenofovir) plasma concentrations were determined using UPLC-MS/MS (Waters Acquity®). pVL quantification was performed using COBAS®AmpliPrep/COBAS®TaqManv2.0®. Residual viremia was defined by: (i) the presence of signal with quantification test (<20copies/mL); (ii) pVL between 20 and 50 copies/mL. Median (IQR25-75%) are presented. Statistical analysis was performed using Mann-Whitney test.

Results: 230 patients with pVL and available antiretroviral plasma concentrations were enrolled. Patients' characteristics are: 48 yo (41-54); HIV transmission modes: heterosexual 56%, homosexual 28%, IV drug 6%; African 62%, Caucasian 34%, South American 3%; Body Mass Index: 24.9 kg/m^2 (22.2-27.6); duration since HIV diagnosis 13.0 years (7.6-20.2); duration of ART 10.0 years (5.4-16.2); duration of pVL<50 copies/mL 3.8 years (2.8-5.3); duration of treatment with DRV/r 3.7 years (2.6-4.7), number of experienced patients 83%; Zenith of pVL 5.0

log_{10} copies/mL (4.4-5.5); HBV 7%; HCV 12%; HBV/HCV 1%; nadir of CD4 195 cells/mm^3 (89-294), gain of CD4 since ART: 386 cells/mm^3 (286-527). Overall, median antiretroviral C24h were: darunavir 1,754 ng/mL (1,206-2,423; n=230), ritonavir 57 ng/mL (30-102; n=230), emtricitabine 157 ng/mL (89-276; n=168), tenofovir 61 ng/mL (49-82; n=173), lamivudine 123 ng/mL (83-190; n=36) and abacavir 5 ng/mL (5-5; n=40). 76% patients had no detection of pVL signal, 20% had a detected pVL signal and 4% had a pVL between 20 and 50 copies/mL. No statistical relationship was observed between DRV C24h and pVL (signal or not) in the whole population: 1,756 ng/mL (1,203-2,381, n=174) *versus* 1,658 ng/mL (1,204-2,696, n=56) for not detected pVL and pVL with signal, respectively (p=0.58). Over 95% of patients presented DRV C24h>550 ng/mL.

Conclusions: In our settings of HIV-1-infected patients presenting a pVL<50 copies/mL for at least 2 years, DRV C24h were found to be high and consistent with those reported in MONOI study (patients receiving DRV/r monotherapy as maintenance treatment). However, among treatment-experienced patients, the trend of higher DRV C24h in patients with no residual viremia than in patients with, suggests a possible relationship between C24h and residual viremia. These results support the assessment of a decreased DRV daily-dose to reach the 550 ng/mL DRV efficacy threshold. Further studies are needed to assess if high DRV C24h would allow dual- or monotherapy maintenance.

No conflict of interest

Abstract: P_72

Therapeutic Drug Monitoring

Efavirenz Therapeutic Range in HIV-1 Treatment Naïve Participants

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Introduction: Efavirenz is currently suggested as an alternative to recommended ARV regimens by the Department of Health and Human Services for the treatment of HIV-1 in antiretroviral naïve patients. A mid-dosing interval therapeutic range for efavirenz between 1,000-4,000 ng/mL has been proposed in the literature, with patients more likely to experience virologic failure below this range, and adverse effects above. We investigated the therapeutic range in AIDS Clinical Trials Group Study (ACTG) protocol 5202 and compared efavirenz concentrations between subjects experiencing virologic failure and those obtaining virologic suppression in a clinical trial setting.

Materials & Methods: This analysis examined efavirenz plasma concentrations obtained from participants enrolled in ACTG 5202 and compared subjects who achieved virologic suppression and those that experienced virologic failure following treatment initiation with efavirenz plus abacavir/lamivudine or tenofovir/emtricitabine. The plasma concentrations were separated into those that had 'high' (at least 1 sample >4,000 ng/mL), 'within' (all samples within 1,000-4,000 ng/mL), or 'low' (at least 1 sample <1,000 ng/mL) plasma concentrations, based on the therapeutic range cited the literature. The virologic outcome groups were further compared on number of samples collected, proportion of males and females, race/ethnicity, assigned NRTI backbone, age, and the outcome associated with baseline HIV RNA level. The Pearson's Chi Square test was used to evaluate the relationship between the virologic failure and virologic suppression groups for categorical variables, and a two-sample t-test was used to compare the mean age in years at the beginning of the study.

Results: A total of 2,000 efavirenz samples from 796 study participants were included in the

analysis**.** Approximately 18% of the population was female, with approximately 39% white, non-Hispanic, 34% black, non-Hispanic, and 23% Hispanic. With 98 subjects comprising the virologic failure group and 698 the virologic suppression group. Efavirenz concentration groups ('high', 'within', 'low') were comparable for those with virologic failure and suppression (failure (%)/suppression (%) 'high '(11 (11%)/113 (16%); 'within' 65 (66%) / 493 (71%); 'low' 19 (19%) / 87 (13%)) (p = 0.095). When examining the distribution of race and ethnicity between those achieving viral suppression and those experiencing viral failure, a difference was noted (p = *0.023*), with the greatest percentage of subjects in the virologic failure group having black, non-Hispanic race and ethnicity. A significant difference was found in the mean age in years at the beginning of the study, the average (range) was 36 (18-58) and 39 (18-69), (p = 0.005).

Conclusions: The often cited therapeutic range for efavirenz to guide dosing strategies was not evident in ACTG 5202.

No conflict of interest

Abstract: P_73

Therapeutic Drug Monitoring

A UHPLC-MS/MS method for the quantification of currently used direct antiviral agents in human plasma and evaluation of "normalized matrix effect".

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Introduction: To date, the new standard for treatment of chronic hepatitis C is based on the administration of novel direct acting antivirals. Among these, sofosbuvir, simeprevir, daclatasvir, ledipasvir, dasabuvir, ombitasvir and paritaprevir already entered the clinical use. Anyway, since few pharmacokinetic studies have been conducted on these drugs in a 'real life' context, poor knowledge is available about their optimal therapeutic range. Without this background, therapeutic drug monitoring is not applicable for treatment optimization. Up to now, a few methods are reported to quantify these drugs in human plasma, and none of them in a simultaneous way. The aim of this work was to develop and validate a simple, fast and cheap, but still reliable UHPLC-MS/MS method for the quantification of these drugs, feasible for a clinical routine use.

Material & Methods: Sample preparation was performed through solid phase extraction using HLB C18 96-well plates. Chromatographic separation was performed on a BEH C18 1.7 µm, 2.1 mm×50 mm column, settled at 50°C, with a gradient run of two mobile phases: ammonium acetate 5mM (pH 9,5) and acetonitrile, with a flow rate of 0.4 mL/min for 5 minutes. Tandem-mass detection was carried out in positive electrospray ionization mode. This method underwent the full validation following FDA and EMA guidelines. Moreover, in addition and in accordance with international guidelines for the evaluation of matrix effect, we proposed a further investigation of internal standards (quinoxaline and deuterated daclatasvir) normalized matrix effect.

Results: Both inter and intraday imprecision and inaccuracy were below 15%, as required by FDA and EMA guidelines, while both recoveries and matrix effects, including the 'normalized matrix effect', resulted within the acceptance criteria (<15%). The method resulted specific and selective without interfering peaks; no significant carryover was observed in blank plasma. The method was tested on 80 patients samples with good performance.

Conclusions: The developed and validated method (for sofosbuvir and its metabolite, simeprevir, daclatasvir, ledipasvir, dasabuvir, ombitasvir, paritaprevir and ritonavir) fills the need for high throughput analysis and a low volume of samples, other than the simultaneous quantification of all the currently used drugs in a single run. Moreover, according to guidelines, it resulted to be enough robust, simple and fast to be used in the future clinical therapeutic drug monitoring routine.

No conflict of interest