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ABSTRACTS

11th International Workshop on Clinical Pharmacology of HIV Therapy

7 - 9 April 2010, Sorrento, Italy
Abstract: 1

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Placental transfer of antiretroviral drugs in HIV-infected women: a retrospective study from 2002 to 2009.

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Background: The rate of mother-to-child transmission (MTCT) of HIV-1 is as low as 0.5% in non–breast-feeding mothers who delivered at term while receiving HAART with a plasma RNA < 500 c/mL in the French ANRS perinatal cohort. The degree of fetal exposure depends largely on the amount of placental transfer of drugs. The TDM of antiretroviral drugs (ARV) in HIV-infected pregnant women was used to detect adherence difficulties or intolerance.

Objectives: to evaluate the in vivo maternofetal transfer of ARV used to prevent MTCT based on the determination of concentrations in different compartments of the maternofetal unit.

Materials & Methods: paired maternal and cord blood and amniotic fluid samples were collected at delivery from HIV-1 infected women to determine steady-state plasma concentrations of ARV using HPLC coupled with UV-PDA or fluorimetric detection. Results from gemellary pregnancy were excluded from the study. The in vivo placental transfer of ARV was calculated as the ratio of cord (CP) to maternal plasma (MP) concentrations. Median ratio are presented and compared to the results of the ex vivo double perfusion of placental cotyledon reported in the literature. Other in vivo transfer ratio including amniotic fluid (AF) concentrations were calculated as AF/MP and AF/CP in a subgroup of patients.

Results: A total of 354 paired CP and MP were obtained from HIV-1 infected women (31.4 yrs) between 2002 and 2009. Among them, 65 had an AF sample collected. The main triple ARV combination found was LPV/r + ZDV/3TC (43%). CP/MP ratio were: ZDV (with pre-labour infusion 1.1, n=195 and without 167, n=78); 3TC (1.2, n=267); ABC (0.8, n=37); ddI (1.0, n=21); TFV (0.7, n=20); IDV (0.65, n=19); RTV (0.15, n=294); LPV (0.13, n=204); NFV (0.13, n=14); M8 (0.23, n=14); SQV (0.03, n=30); APV (0.21, n=12); NVP (0.81, n=21) and T20 (0.01, n=5). These in vivo results were statistically associated to the ex vivo results using the double perfusion of placental cotyledon (R\(^2\)=0.42; p=0.04) and related to the respective plasma protein binding percentage (R\(^2\)=0.79; p<0.0001). Other determinant factors for a poor placental transfer were the high liposolubility (logP>2.8) and high Molecular Weight (T20~4565 Da). AF/MP, CP/MP and AF/CP ratio were: ZDV (with pre-labour infusion: 2.8, 0.8, 2.0, n=31 and without: 349, 123, 3.0, n=7), 3TC (10.7, 1.4, 6.1, n=37), ABC (7.4, 0.6, 8.8, n=2), TFV (6.6, 0.1, 85, n=2), IDV (1.0, 0.2, 8.6, n=19), LPV (0.14, 0.12, 1.0, n=31), RTV (0.18, 0.15, 1.0, n=52), NFV (0.47, 0.12, 3.9, n=3), M8 (1.0, 1.0, 1.0, n=3) APV (0.2, 0.14, 1.4, n=2), T20 (0.2, 0.02, 8.9, n=2).

Conclusions: Triple drug regimens reported in this study were in accordance with the successive French Guidelines to prevent MTCT. High transfer of NRTI, NVP and IDV in cord blood (Ratio > 0.7) was found regarding to their low protein binding, low liposolubility and low Molecular Weight. The ex vivo model of double perfusion of placental cotyledon might be a good predictor of the in vivo placental transfer. Because of high placental transfer, NRTI accumulation in amniotic compartment was found.

No conflict of interest
Abstract: 2

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Tenoforv population pharmacokinetics in HIV-infected children and adolescents

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Background: Tenofovir (TDF), at a fixed dose of 300 mg once daily, is commonly used in combination with other antiretrovirals to treat human immunodeficiency virus (HIV) in adults, adolescents and children. Yet, factors affecting pharmacokinetic variability of TDF in HIV-infected children and adolescents have not been evaluated.

Materials & Methods: Data for this analysis were collected from a multicenter study conducted through the International Maternal, Pediatric and Adolescent AIDS Clinical Trials Group (IMPAACT) Protocol P1058 which evaluated the pharmacokinetics of TDF 300 mg once daily in combination with efavirenz (EFV), darunavir/ritonavir (DRV/rtv) or atazanavir/ritonavir (ATV/rtv) in 47 HIV-infected patients 8 to 18 years of age. Fifty-two intensive pharmacokinetic data sets for TDF were available. Nonlinear mixed effects modeling (NONMEM VI) was used to develop the population pharmacokinetic model and explore the influence of demographic covariates (age, sex, weight, height, body surface area, Tanner stage) and concomitant medication (EFV, DRV/rtv or ATV/rtv) on TDF pharmacokinetics.

Results: Median (range) age, weight and creatinine clearance of patients were 14 (8-17) years, 48.1 (32.6-102.6) kg and 154 (74.8-267.6) ml/min/1.73m2, respectively. A two-compartment model with first-order absorption described TDF pharmacokinetics. Allometric scaling of subject size improved the model over a linear weight model and this approach limited the impact of age on TDF CL/F. Typical population estimates of apparent central distribution volume (Vc/F), peripheral distribution volume (Vp/F) and intercompartmental clearance (Q/F) for a 50 kg individual with a CRCL of 156.44 ml/min/1.73m2 were 923 L, 1400 L, and 253 L/hr, respectively. The model for the typical value of clearance (L/hr) was (65.3 + 0.377*CRCL)*(wt/70)**0.75. The model was further improved by allowing subjects to be classified as slow absorbers (final estimate of 0.43 hr)-1 or rapid absorbers (final estimate of 18 hr)-1. The estimated inter-subject variabilities for CL/F and Vc/F were 28.4% and 78.3%, respectively. The correlation between CL/F and Vc/F was 0.612. The residual variability included a proportional component with a CV of 25.9% and an additive component with a standard deviation of 0.0298 ng/mL. A predictive check assessment indicated satisfactory model performance without any systematic bias.

Conclusions: A population pharmacokinetic model satisfactorily described TDF pharmacokinetics, including effects of known covariates. Apparent plasma TDF clearance (96.2 L/hr) was slightly higher in our subjects compared with adults (90.9 L/hr) and affected by CrCL. Differences in rate of absorption were likely a result of food intake with medication administration. Age, sex, Tanner stage and concomitant medications did not affect tenofovir clearance or volume of distribution.

No conflict of interest
Abstract: 3

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Tenofovir disoproxil fumarate (TDF) pharmacokinetics (PK) with increased doses in HIV-1 infected pregnant women and their newborns (HPTN 057)

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Background: Tenofovir (TFV) has proven animal model efficacy in prevention of mother to child HIV transmission but there are few data describing its PK when administered to pregnant women during labor or to newborns. In previous dosing cohorts of this study, administration of a maternal 600 mg dose during labor and administration of three infant 4 mg/kg doses during the 1st week of life did not maintain target infant plasma TFV concentrations (>50 ng/mL) throughout the first week of life.

Materials & Methods: HPTN 057 is a phase I trial of tenofovir disoproxil fumarate (TDF) administered to HIV infected pregnant women and their neonates in Malawi and Brazil. In the current study cohort, women received a single 900 mg TDF dose at the onset of labor or 4 hours prior to C section (C/S) and newborns received 6 mg/kg TDF x 3 doses given as soon as possible after birth and 72 hours and 120 hours after birth. TFV concentration (conc) was determined by HPLC/MS/MS; lower limit of quantitation was 5 ng/mL. The pharmacokinetic target was to keep infant TFV conc >50 ng/mL (mean trough conc in nonpregnant adults) for the first week of life. Amniotic fluid samples were collected from C/S mothers. Data are presented as median (range).

Results: 36 mother-infant pairs were studied (23 vaginal deliveries, 13 C/S). Delivery occurred at a median of 3.33 (0.4 - 39.25) hours after dosing. Median maternal TFV conc at delivery was 200 (blq – 556) ng/mL. Median cord blood TFV conc was 123 (blq – 538) ng/mL. Cord blood TFV conc was > 50 ng/mL in 26/31 (84%) and median ratio of cord blood to maternal delivery TFV conc was 0.59 (0 - 3.06). Infant predose TFV conc was >50 ng/mL in 7/32 (22%) of infants before the initial TDF dose, 2/34 (6%) before the 72 hr dose and 2/32 (6%) before the 120 hr dose. Median TFV conc in amniotic fluid (n=11) was 319 (84-574) ng/mL and the median ratio of amniotic fluid to maternal delivery TFV conc was 1.05 (0.37 – 3.32). Median maternal PK parameters: AUC=5283 (3513 – 10670) ng*hr/mL, Cmax=458 (134 – 1149) ng/mL, t½=16.4 (11.6 – 28.5) hrs. Median infant PK parameters following the initial dose were: predose conc=33 (blq – 86) ng/mL, Cmax=292 (43 – 700) ng/mL, AUC=5801 (1471 – 9664) ng*hr/mL, t½=22.2 (17.5 - 36.7) hrs; following the 72 hrs after birth dose: predose conc= 22 (9 – 69) ng/mL, Cmax=326 (21 – 577) ng/mL, AUC=3821 (653 – 7256) ng*hr/mL, t½=16.2 (9.3 – 28.7) hrs; following the 120 hrs after birth dose: predose conc=24 (6 – 71) ng/mL, Cmax=188 (21 – 518) ng/mL, AUC=3139 (349 – 5345) ng/mL, t½=17.0 (12.2 - 31.2) hrs. All mothers and infants tolerated TDF well.

Conclusions: Although this dosing regimen resulted in cord blood TFV above the 50 ng/mL target in most infants, TFV elimination was as rapid in the infants as in the mothers and the current dosing regimen failed to keep infant TFV conc above 50 ng/mL during the first week of life. A fourth cohort with daily infant dosing is underway.

No conflict of interest
Abstract: 4
Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Pharmacokinetics of Lopinavir in HIV-1 infected children

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Introduction: Lopinavir (LPV) is a protease inhibitor (PI) that can be administered in different pharmaceutical forms liquid or tablets co-administered with another PI, ritonavir used like a booster (LPV/r), leading to less fluctuation LPV levels in blood. Therapeutic drug monitoring of antiretrovirals (ARV) may be useful in HIV infected children because of differences in pharmacokinetics of several ARV drugs between children and adults. Moreover maturation of difference organs involved in absorption and metabolism could be related to changes in pharmacokinetics of ARV drugs during growth in children.

Objectives: Previous works have shown a great interindividual variability in LPV levels in children treated with LPV/r. The aim of this work was to study the LPV levels in HIV-1 infected children treated with different oral formulations of LPV/r and to study different co-variables that could be involved in pharmacokinetics variability of LPV in this population.

Material & Methods: 60 patients treated with LPV/r (Kaletra, Abbott-capsules, tablets or solution) were included. Dose regimen was 12 mg/kg/12 hours for children < 15 kg and 10 mg/kg/12 hours for children ≥ 15 kg. Therapeutic drug monitoring of LPV in blood was performed. Samples were drawn between 1 and 4 hours after the corresponding dose (C1) or previous to the corresponding dose (Cmin). The samples were measured by means of HPLC-UV. Demographic data, dose regimen, sampling times and co-medication were also registered.

Results: 104 LPV plasma levels (57 Cmin and 47 C1) were obtained. The median age was 7.0 years old (range: 4 months-19 years old). A significant interindividual variability in LPV levels was observed (CV Cmin: 160.9%, C1: 127.4%). No statistical significant difference in LPV plasma levels were observed after the administration of liquid or solid formulations. 12 patients showed LPV levels < 1 µg/ml. No relationship was observed between LPV level normalized by dose and age. In children ≤ 2 years old, 6 patients showed LPV levels higher than 1 µg/ml, LPV levels were subtherapeutic (< 1 µg/ml) in 5 patients, although 4 patients showed no compliance or intolerance to the liquid formulation.

Conclusions: The great variability observed in LPV levels, including patients with subtherapeutic levels; suggest that therapeutic drug monitoring of LPV could be advisable in HIV-1 infected children treated with LPV/r in order to optimize ARV treatment.

No conflict of interest

Abstract: 5
Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Sub-optimal nevirapine concentrations during intrapartum compared with postpartum in HIV-1 infected Ugandan women.

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Introduction: Nevirapine (NVP)-based antiretroviral therapy (ART) is recommended for prevention of mother-to-
child transmission of HIV-1 in developing countries. There are conflicting data on the effect of pregnancy on steady-state NVP plasma concentrations and steady-state NVP concentrations during pregnancy have not been characterized in East African women.

**Material & Methods:** This was a prospective, non-blinded study of antiretroviral pharmacokinetics (PK) in Ugandan women receiving NVP-based ART during pregnancy. Subjects underwent intensive 12-hour PK sampling between weeks 20-24 (T2; n=4) and weeks 32-36 (T3; n=15) of gestation, followed by six weeks postpartum (PP; n=15). Patients were excluded if they did not complete the PP visit. All patients received NVP 200mg twice daily for at least two weeks before PK sampling. HIV-1 RNA was performed within two weeks of each study visit. Estimation of NVP concentration was performed by reverse-phase high-performance liquid chromatography with a quantification limit of 0.5 mcg/mL. NVP concentration 12-hours post-dose (C12) below 3 mcg/mL was considered sub-therapeutic based on the suggested target trough concentration for therapeutic drug monitoring (minimum effective concentration, MEC). Area under the concentration time curve (AUC0-12) was calculated by non-compartmental analysis.

**Results:** For T2, T3 and PP, C12 and AUC0-12 (GM, 90% confidence intervals) were 3.03 (2.80 - 3.35), 3.12 (2.68 - 4.14) and 3.93 (3.48 - 4.86) mcg/mL and 42.99 (41.27 - 45.05), 47.33 (41.57 - 58.89) and 59.40 (53.60 - 69.58) mcg.h/mL, respectively. For T2 versus PP and T3 versus PP, GM ratios for C12 and AUC0-12 were 0.87 (0.74 - 1.02), p=0.27 and 0.79 (0.70 - 0.90), p=0.01; and 0.76 (0.70 - 0.83), p=0.07 and 0.80 (0.72 - 0.88), p<0.01. The C12 for 3, 10 and 4 subjects measured below 3 mcg/mL in T2, T3 and PP, respectively. Only 3 out of the 10 subjects with a NVP C12 below the MEC at T3 measured below the MEC at the PP visit. In all patients, HIV-1 RNA was <1000 copies/mL at T3 and <400 copies/mL at PP.

**Conclusions:** NVP exposure was reduced approximately 20% in Ugandan women during their 3rd trimester compared to the same women postpartum. Although adequate virologic suppression was observed despite sub-therapeutic concentrations in pregnancy, investigation of the long term implications of these sub-optimal concentrations on NVP efficacy should be considered.

No conflict of interest

**Abstract: 6**

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

**Plasma protease inhibitor concentrations and fasting lipid profiles in HIV-infected children**

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**Background:** Protease inhibitors (PI) are widely used in HIV-infected children. In adults and children PI use has been associated with elevated total cholesterol (TCH) and triglycerides (TG). The aim of this study was to evaluate the associations between plasma concentrations of nelfinavir (NFV), lopinavir (LPV), atazanavir (ATV), and ritonavir (RTV) and the fasting plasma lipid concentrations of pediatric treatment-experienced patients.

**Materials & Methods:** HIV-infected children receiving PI-based HAART with NFV, LPV/RTV or ATV/RTV for a minimum of 4 weeks were enrolled prospectively. Area under the concentration-time curves (AUCs) were estimated for NFV, LPV, ATV and RTV by the trapezoidal algorithm from 7 plasma
concentrations measured by a published mass-spectrometry assay over a single 12-hr interval following an observed PI dose. Fasting TCH, low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL), and triglycerides (TG) were measured during the PK study visit. Multivariate linear regression models were used to estimate primary associations of plasma lipids with AUCs and demographic factors.

Results: From 2004-2008, 67 children had 72 visits that included 4 repeats following a change of the PI or PI dose. Participants had a mean ± SD age of 11.6 ± 3.6 yrs; 47% were male; and 88% were African American. LPV/RTV was used in 49 (68%), NFV in 17 (24%), and ATV/RTV in 6 (8%) patient episodes; the mean duration of PI treatment was 3.4 ± 2.0 yrs. The NRTI backbone contained AZT or d4T in 47% of the regimens. The majority had a healthy weight (80.6%), with 10.4% overweight and 9% obese children. Mean BMI was 19.4 ± 4.7. Mean fasting TCH was 167.7 ± 37.8 mg/dL, with mean LDL of 103.5 ± 34.3 mg/dL, VLDL of 26 ± 20.6 mg/dL and HDL of 41.1 ± 12.2 mg/dL; mean TG was 119.5 ± 73.5 mg/dL. RTV AUC was significantly and positively associated with increased HDL (p=0.0006), while having a near-significant effect on TCH (p=0.069). NFV AUC was associated with a significant increase in VLDL (p=0.038), and near-significant increase in TG (p=0.077). ATV had the strongest negative effects on TCH, LDL, VLDL and TG, although none were statistically significant, probably due to the low number of patients on ATV. When all PIs excluding RTV were grouped, increased AUC trended towards mildly increased TCH (p=0.055), but was not significantly associated with other lipid concentrations. Age, gender, duration of PI therapy, thymidine analogue backbone, and BMI were not significantly associated with plasma lipids concentrations.

Conclusions: Even at lower plasma concentrations with smaller boosting doses, an increased RTV AUC, regardless of co-administered PI, was associated with elevated fasting HDL in pediatric patients. NFV AUC was associated with increased VLDL. ATV had the trend to decrease all lipids in an exposure-dependent manner except for HDL. Further studies are warranted on the long-term consequences of PI-associated lipid profile changes in HIV-infected children.

No conflict of interest

Abstract: 7
Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Effect of hemodialysis on raltegravir clearance in HIV-infected patients with end stage renal disease

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Background: Little is known about raltegravir removal by hemodialysis in HIV-infected patients with end-stage renal disease (ESRD). Our objective, therefore, was to evaluate the effect of hemodialysis on raltegravir clearance in two anuric ESRD HIV-infected patients undergoing routine hemodialysis who were receiving antiretroviral therapy with raltegravir.

Material & Methods: Predialyzer and postdialyzer blood samples were collected at the beginning and end of a single dialysis session. Raltegravir concentrations were determined by using high-performance liquid chromatography with a fluorescence detector, according to a validated method. The hemodialysis extraction ratio (ER) for raltegravir was calculated as ER = (Cin-Cout)/Cin; where Cin is predialyzer raltegravir concentration, and C_out is postdialyzer raltegravir concentration. Raltegravir dialysis clearance (CL_D) in terms of plasma was
calculated as $\text{CL}_D = \text{ER} \times Q_p$; where $Q_p$ is plasma flow through the dialyzer.

**Results:** Patient 1 was a 53-year-old man who was receiving antiretroviral therapy with nevirapine (200 mg twice daily) and raltegravir (400 mg twice daily). Patient 2 was a 50-year-old man receiving antiretroviral therapy with efavirenz (600 mg once daily) plus tipranavir/ritonavir (500/200 mg twice daily) and raltegravir (400 mg twice daily). Both patients were undergoing 4-hour hemodialysis sessions three times a week (Fresenius F8HPS in patient 1, Polyflux 17C in patient 2). Dialysate and blood flows were 500 mL/min and 300 mL/min, respectively. At the end of the session, raltegravir concentrations had decreased by 68% in patient 1 and by 45% in patient 2. However, the raltegravir hemodialysis ER and $\text{CL}_D$ were only 5.5% and 9.1 mL/min in patient 1, and 9.5% and 19.1 mL/min in patient 2, respectively. Both patients maintained raltegravir concentrations higher than 15 ng/mL at the end of the dialysis session.

**Conclusions:** Our results show minimal removal of raltegravir by hemodialysis. Raltegravir dosage adjustments seem, therefore, to be unnecessary in HIV-infected patients with ESRD undergoing hemodialysis.

**No conflict of interest**

**Abstract:** 8

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

**Antiretroviral pharmacokinetics in HIV-positive women with full virologic suppression on current regimens**


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**Introduction:** Higher antiretroviral concentrations may contribute to increased adverse event rates. Although some studies have shown higher antiretroviral concentrations in women as compared to men, data are limited. We conducted a cross-sectional study of HIV-positive women to determine if PI and NNRTI Cmin and Cmax values are significantly higher in women as compared to the historical general (predominantly male) population and to evaluate variables associated with higher concentrations.

**Methods:** HIV-positive women with virologic suppression (VL<50copies/mL) on their first antiretroviral regimen were enrolled from 14 sites across Canada. Timed blood samples for Cmin and Cmax were drawn weekly for 3 weeks. Demographic and clinical data were collected. The ratio of each individual’s median Cmin and Cmax to the published population Cmin and Cmax mean for the antiretroviral was calculated and assessed using a Wilcoxon sign-rank. Linear regression models were used to identify predictors of log-transformed Cmin ratio.

**Results:** Data from 83 women enrolled between 2/2007 and 11/2008 were analyzed. Median age was 42 years (IQR=36-48), CD4 count was 490/?L (IQR=380-640) and all participants had VL<50copies/mL. The median duration of antiretrovirals was 3.8 years (IQR=1.8-
Median antiretroviral Cmin and Cmax ratios were 1.17 (IQR=0.73-2.0), p<0.001 and 0.86 (IQR=0.59-1.25), p=0.16, respectively. Median (IQR) Cmin and Cmax by drug were: Atazanavir (n=28): 1.14 (0.74, 1.75) and 0.68 (0.51, 0.84); Lopinavir (n=20): 1.15 (0.79-1.8) and 1.21(0.87-1.52); Nevirapine (n=19): 1.66(1.06-2.14) and 1.01(0.81-1.47); Efavirenz (N=16): 0.98 (0.7-2.05) and 0.79(0.62-1.25). IDUs had significantly lower Cmin ratio and participants with higher CD4>200/mL had a higher Cmin ratio. No other variables predicted Cmin including race, body weight or age.

**Conclusions:** Cmin ratios were highly variable within and between antiretrovirals. Median ratios were significantly greater than 1 indicating that the Cmin in the women enrolled in this study were higher than historical control data. No relevant predictors of high Cmin were found.

**Speaker for or received grants from** BMS, Tibotec, Abbott, Pfizer and Merck

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**Abstract: 9**

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

**Standard dose generic lopinavir/ritonavir provides adequate lopinavir plasma levels during the 3rd trimester of pregnancy in Thai HIV-1 infected women**

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**Background:** For the prevention of mother-to-child transmission of HIV during pregnancy and delivery, HIV-infected pregnant women are preferably treated with HAART, usually an NRTI backbone combined with a protease inhibitor (PI). As a consequence of pregnancy-induced changes in the gastro-intestinal tract, volume of distribution and drug elimination, the standard dose of lopinavir/ritonavir (LPV/r) may lead to reduced or even inadequate plasma concentrations during gestation, particularly during the third trimester. Therefore, some guidelines recommend an increased dose of LPV/r during pregnancy. Thai HIV-infected patients often have higher plasma concentrations after intake of standard doses of ARVs, including LPV/r, compared to Caucasian patients. Therefore, we hypothesized that Thai HIV-infected pregnant women will have sufficient LPV/r concentrations in the third trimester with the standard dose (400/100 mg BID) and do not require a dose increase.

**Material & Methods:** This was a prospective single-centre study. HIV-infected pregnant women were started on generic LPV/r 400/100 mg BID with 2 NRTIs. 12h pharmacokinetic curves were recorded at gestational age 20 weeks (GA20, optionally), 33 weeks (GA33) and 12 weeks post-partum (12PP, optionally). Blood samples were obtained pre-dosing (with a standardized breakfast) and at t=1, 2, 3, 4, 6, 8, 10 and 12h post-dosing. Pharmacokinetic parameter calculation and statistical analysis was performed with Stata 11.0. Regression models comparing the effect of pregnancy included 12 women with curves at both GA33 and PP12

**Results:** Twenty women were included in this study: all completed the GA33 curve, 4 completed the GA20 curve and 12 completed the 12PP curve. The median age (IQR) was 28 (25-33) years. Mean (standard deviation (SD)) body weight at GA33 was 59.9 kg (4.18). Mean (SD) values for lopinavir AUC0-12h, Cmax, Cmin and Thalf were 65.74 (21.07) mg/L.h, 8.61 (2.56) mg/L, 2.40 (0.87) mg/L and 3.7 (0.2) h on GA20, 72.91 (19.15) mg/L.h, 9.28 (2.23) mg/L, 3.20 (1.31) mg/L and 4.8 (2.4) h on GA33 and 98.04 (24.14) mg/L.h, 11.68 (2.24) mg/L, 4.71 (2.17) mg/L and 5.9 (2.7) h on 12PP. In the twelve women who recorded both the GA33 and 12PP curves, the mean lopinavir AUC was significantly lower at
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GA33 (coefficient -24.05 (95%CI -44.38-3.73). At GA33, 19/20 women had a sufficient lopinavir level (defined as >1.0 mg/L) and at 12PP all women had lopinavir plasma concentrations above 1.0 mg/L. None of the women stopped LPV/r prior to the planned discontinuation (either after delivery or at 12PP) due to side effects. At delivery, 19/20 women had a viral load below 50 copies/ml.

Conclusion: The use of standard dose LPV/r (400/100 mg BID) in Thai HIV-1 infected pregnant women leads to significantly reduced, but still adequate plasma concentrations during the third trimester. The generic LPV/r tablet is well-tolerated and effective for use during pregnancy.

No conflict of interest

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Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Raltegravir and Darunavir plasma pharmacokinetic in HIV-1 infected patients with advanced liver disease

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Background: During HAART, the risk for liver toxicity increases in HCV or HBV co-infected patients. The liver diseases, such as cirrhosis, can lead alterations in absorption, metabolism, pharmacological effect or clearance of drugs. Darunavir (DRV) and raltegravir (RAL) share a relatively safe liver toxicity profile, but special caution is necessary, since both drugs were primarily metabolized by liver. We analysed the PK profile of DRV and RAL in HIV-1 infected patients with moderate to severe liver disease.

Materials and Methods: Five HIV-HCV co-infected patients with moderate to severe hepatic impairment who started a RAL and DRV-based Highly Active AntiRetroviral Treatment were consecutively enrolled. Blood samples for RAL and DRV Ctrough evaluation were collected at day 14 and 30 after new regimen was started. Viro-immunological and safety parameters were also evaluated. Antiretroviral’s plasma concentrations were measured using a validated high-performance liquid chromatography method. Twenty-four matched HIV-1 mono-infected patients with normal liver function treated with RAL and DRV were used as a control group.

Results: Five HIV-HCV co-infected subjects were consecutively enrolled. All patients were Caucasian male, with a mean age of 48 years (SD, ±5 years) and a mean history of HIV-infection of 16 years (±6 years). Mean nadir CD4 cell count was 58/mmc (±63). At baseline, the mean BMI was 23 (±1.3) kg/m2 and all but two patients were in virological failure with their current HAART regimen. Based on the ultrasonographic and histological evaluation, 2 patients presented chronic active hepatitis HCV-related, 3 patients had a diagnosis of cirrhosis (Child Pug stage B). Concomitant antiretroviral therapies included dual NRTI in 2 of 5 patients; NNRTI in 1/5 patients and boosted PI in 2/5 patients. The mean RAL and DRV Ctrough in patients with hepatic impairment was 637 (mean Ctrough in control group: 221± 217 ng/ml) and 8519 ng/mL (mean Ctrough in control group: 3236± 2183 ng/ml), respectively. In a sub-group analysis, patient with cirrhosis had higher mean RAL Ctrough than patients with active non cirrhotic hepatitis (665 vs. 581 ng/mL). The mean DRV Ctrough was consistently higher in cirrhotic than non cirrhotic patients (9820 vs. 2016 ng/mL). No differences in viro-immunological outcome and safety parameters’ changes were found between cirrhotic and non cirrhotic patients. A cirrhotic patient dead one month after RAL-DRV based HAART because of acute hepato-renal syndrome.

Conclusions: Raltegravir and darunavir were both primarily metabolized by liver. A single report in non-HIV patients with moderate hepatic impairment demonstrated no clinically significant increase in RAL concentration compared with healthy controls. In our report, both RAL and DRV Ctrough resulted higher in the study population compared with
controls. Cirrhotics had similar RAL plasma concentrations than non cirrhotics. Conversely, DRV Ctrough were highest in cirrhotics. This evidence suggests special caution in the use of RAL, and especially of DRV, in patients with moderate to severe liver impairment because of the risk of additive toxicity.

No conflict of interest

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Evaluating the effect of gender on darunavir and ritonavir exposure in HIV infected subjects (a post-hoc analysis of the GRACE PK sub-study)

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Background: Gender-related differences in the pharmacokinetics (PK) of some protease inhibitors (PI) have been reported. The Week 4 analysis from the GRACE PK sub-study found darunavir (DRV) and low-dose ritonavir (RTV) exposure was ~20% and a ~70% higher in females, with no differences in PK attributed to ethnicity (Black vs. Hispanic), age or weight. Since estrone sulphate (E3S) is the highest circulating estrogen and a substrate for the hepatic uptake transporter SLCO1B1, we hypothesised that fluctuations in plasma E3S may impact the PK of DRV and/or RTV since some PI have been demonstrated to be weak substrates of this transporter. Our initial approach was to confirm the affinity of E3S and DRV for SLCO1B1 in vitro and then determine E3S concentrations in plasma samples from the GRACE PK sub-study.

Material & Methods: SLCO1B1 was cloned, verified and used to generate cRNA for use in the Xenopus laevis oocyte transport system. E3S and DRV were tested for their substrate affinity and transport. Pharmacokinetic data from 29 treatment experienced patients (19 female, 10 male) who participated in the GRACE PK sub-study (Week 4) were included in this post-hoc analysis. Patients received DRV/r (600/100 mg bid) plus an OBR. Subjects were predominately black (n=19) with a median age of 43 years. Two (11%) women were postmenopausal. E3S was determined by a radioimmunoassay (Diagnostic Systems Laboratories; LLQ 0.01 ng/ml) for each patient at 0, 2, 6 and 12h post-dose. Statistical analyses (SPSS, version 17) were performed to evaluate differences between males and females. Subjects were stratified according to gender and Spearman correlations used to identify associations between DRV/RTV PK parameters (AUC, Cpredose, Cmax) and average E3S concentrations (Cav). Intraclass correlation coefficients (ICC, 95% CI) were calculated to assess the reliability of using Cav E3S over 12h.

Results: The accumulation of E3S in oocyte injected with SLCO1B1 RNA versus water injection was greater (ratio ≥20) than for DRV (ratio 1.75), indicating that E3S is likely a better substrate. Median (range) Cav E3S were within the physiological range reported in females and males, and did not differ significantly by gender [females: 0.45 ng/ml (0.16-1.86), males: 0.69 ng/ml (0.45-1.63) P=0.1]. E3S AUC0-12 were 5.5 ng.h/ml (2.8-23.7) in females and 8.2 ng.h/ml (5.3-19.9) in males (P=0.19). Inter-subject variation (%CV) in Cav E3S was higher in females (77%) than in males (42%). Intra-subject variation in E3S over 12h was low: ICC for Cav=0.97 (0.94-0.98). E3S Cav in all subjects also did not significantly correlate with DRV [Rho -0.211 (AUC) -0.293 (Cpredose) -0.355 (Cmax) P >0.14] or RTV (Rho <0.005; P >0.76 ) PK parameters.

Conclusions: Despite E3S and DRV being substrates for SLCO1B1 in vitro we failed to demonstrate any relationship between plasma concentrations of DRV/RTV and this circulating hormone. Further studies are in progress to...
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determine plasma concentrations of key cytokines (IL-2, IL-10, IL-17) since it is known that cytokines can have a significant impact on mRNA and protein expression of both transport proteins and CYP450 enzymes.

No conflict of interest

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Population pharmacokinetics of Nevirapine and Rifampicin in TB-HIV co-infected patients

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Introduction: To study the population pharmacokinetics (PK) of Nevirapine (NVP) and rifampicin (RFM) in African HIV- and TB-infected patients who were taking NVP-based antiretroviral therapy and RFM-based anti-TB therapy.

Material and Methods: We evaluated 24 patients with documented HIV-1 infection, CD4+ T lymphocyte < 100 cells /cm³, no previous history of HAART and TB diagnosis according to national guidelines. Standard anti-TB therapy (2 RHZE/4 RH) based on patient body weight and standard HAART (fixed dose combination of stavudine, lamivudine and nevirapine) was used in all cases. HAART was started within 30 days of the start of anti-TB therapy; NVP was given as 200 mg OD for 2 weeks, then 200 mg BID. Blood samples for determination of NVP and RFM plasma concentrations were obtained at time 0 (Ctough) and 1, 2, 4, 6, 8, 12 hours after drugs intake. Four NVP pharmacokinetic curves were analyzed: a) after 1 month and b) after 2 months of RFM+NVP; c) 1 month and d) 6 months after termination of anti-TB therapy. RFM pharmacokinetic curves were obtained: a) at steady-state, before NVP therapy; b) after 1 month of RFM+NVP; c) after 2 months of RFM+NVP. NVP and RFM plasma concentrations were measured by validated HLPC assays. A population pharmacokinetic analysis was performed by P-PHARM using a dataset including 24 patients (434 plasma concentrations).

Results: A one-compartment model with first-order absorption, an absorption lag-time and first-order elimination adequately described NVP and RFM disposition. Final mean (CV%) NVP population PK parameters (oral clearance, volume of distribution, absorption rate constant, lag-time) after 1 month of combined therapy: CL/F=4.05L/h(27%), Vd=105.7L(6%), ka=3.9h⁻¹(30%), lag-time=0.88h(15%). After 2 months of combined therapy: CL/F=3.77L/h(36%), Vd=102.9L(3%), ka=4.2h⁻¹(24%), lag-time=0.85h(11%). NVP PK parameters 1 month after RFM termination were: CL/F=3.51L/h(27%), Vd=101.8L(10%), ka=3.8h⁻¹(28%), lag-time=0.7h(46%). Six months after RFM termination: CL/F=3.35L/h(30%), Vd=113.9L(7L), ka=4.6h⁻¹(24%), lag-time=0.79h(18%). Final RFM population PK parameters (CV%), at steady-state, before starting NVP therapy: CL/F=0.77L/h/kg(47%), Vd=2.0L/kg(36%), ka=0.83h⁻¹(62%) lag-time=0.54h (75%). After 1 month of combined therapy: CL/F=0.56L/h(58%), Vd=2.4L(44%), ka=1.3h⁻¹(58%) lag-time=0.61h(46%). After 2 months of combined therapy: CL/F=0.46L/h/kg(43%), Vd=1.82L/kg(37%), ka= 0.01 h⁻¹(60%), lag-time=0.6h(47%).

The cofactors we considered for population PK modeling (age, weight, height, gender) were poorly predictive of drug exposure. A mean reduction of 21% in NVP CL/F was found in HIV-infected patients 1 month after termination of RFM therapy. 70% of patients showed a variable reduction in CL/F values ranging from 15 to 44%. In 30% of patients, NVP CL/F was not influenced by RFM co-administration. The CL/F of RFM decreased by 40% during 2 months of combined therapy.

Conclusions: A population PK model for NVP and RFM in African TB/HIV co-
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infected patients has been developed. The inductive effect of RFM on NVP PK was apparent in the majority of (70%) but not in the whole population. Cytochrome P450 polymorphisms may influence the magnitude of RFM inducing effect. Changes in hepatic cytochrome P450 behavior may account for the gradual decrease in RFM CL/F during prolonged co-administration with NVP.

No conflict of interest

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Dose adjustments of efavirenz based on therapeutic drug monitoring maintains virologic suppression in HIV-infected children and adolescents

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Introduction: Therapeutic drug monitoring (TDM) is a useful tool in pediatrics due to important interpatient and intrapatient pharmacokinetic variability attributed in part to growth and metabolic changes with age. Efavirenz (EFV) is commonly prescribed in pediatrics. Target EFV concentrations are between 1-4 mg/L. EFV TDM is done every three months in pediatric patients at CHU Sainte-Justine. We describe TDM results for these patients and the virologic and immunologic impact of EFV dose adjustments.

Material & Methods: A retrospective study was conducted. HIV-infected patients less than 18 years of age followed at CHU Sainte-Justine on whom TDM was performed were included in the study. Samples were taken during the 24-hour dosing interval. Virologic and immunologic data were available at the time of TDM. EFV concentrations were measured by a validated LC/MS/MS assay. Medians with interquartile ranges are presented unless otherwise specified.

Results: 31 patients provided 283 samples. Patients at first TDM were 64.5% male, 12 (10-14) years old, 83.8% black, and weighed 38.6 (32.9-49.1) kg. The time on EFV before the first TDM was 2.6 (0.2-4.3) years. At first TDM, 84% of patients had undetectable viral loads and the CD4+ count was 630 (480-851) cell/mm³. The EFV dose and concentration were 10.7 (9.5-12.4) mg/kg and 2.58 (1.69-4.08) mg/L. EFV concentrations ranged from 0.05 to 30.7 mg/L. Indications for TDM were: 89.4% control, 3.2% non-adherence, 1.4% toxicity and 6% other. 37.1% of concentrations were suboptimal (11% subtherapeutic and 26.1% supratherapeutic). 29 dose adjustments were prescribed in 12 patients (13 decreases and 16 increases). 62.5% of dose increases and 92.3% of dose decreases were following therapeutic and supratherapeutic concentrations, respectively. Only 15% of dose decreases associated with supratherapeutic concentrations resulted in therapeutic concentrations at the next TDM. Most patients with supratherapeutic concentrations required numerous dose decreases before reaching the target range. Two patients required substantial dose decreases (38% and 58%). All patients with dose decreases maintained an undetectable viral load and were stable immunologically. Dose increases were mostly prescribed with increasing body weight. Three dose increases were secondary to subtherapeutic concentrations and two of these dose increases subsequently resulted in therapeutic concentrations. Overall only 9.7% of subtherapeutic EFV concentrations were followed by a dose increase. This may be so as the first recommendation was to verify and encourage adherence. Four patients with subtherapeutic concentrations developed virologic failure. Three of these four...
patients never had dose increases despite subtherapeutic concentrations. Non-adherence was suspected in two of these patients. Even with a total dose increase of 400 mg, the fourth patient continued to have virologic failure.

Conclusions: Suboptimal EFV concentrations are frequent in pediatrics. Over a quarter of EFV levels were supratherapeutic increasing the risk of CNS toxicity. Dose reductions were safe as virologic response was maintained. Our results show that it may be warranted to be more aggressive with dose adjustments following subtherapeutic and supratherapeutic concentrations to prevent virologic failure and CNS adverse effects. In the presence of virologic failure, resistance testing should rapidly be performed. We recommend routine EFV TDM in pediatrics.

No conflict of interest

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TDM of antiretroviral drugs in HIV-infected pregnant women: transplacental diffusion, newborn clinical status and maternal immuno-virological outcome

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Background: To evaluate antiretroviral (ARV) drugs compartment levels, transplacental diffusion, clinical assessment of the newborn and maternal immuno-virological outcome at month 18 after delivery.

Methods: Antiretroviral concentrations were determined in mother and cord blood and in amniotic fluid by high-performance liquid chromatography. Cord-to-mother ratio (C:M) was calculated to estimate the ARVs placental passage. Newborn gestational age, weight, Apgar score and complications were recorded at birth. HIV-RNA load and CD4 cell count were recorded at month 3, 6,12 and 18 after delivery.

Results: Fifty-nine HIV-infected pregnant women were enrolled. Maternal nevirapine mean C_{trough} was 3832 (SD± 900) ng/mL with a mean C:M ratio of 0.64 (SD ± 0.15), maternal nelfinavir C_{trough} was 760 (SD± 608) ng/mL with a mean C:M ratio of 0.42 (SD± 0.27), maternal atazanavir C_{trough} was 1007 (SD ± 799) ng/mL with a mean C:M ratio of 0.18 (SD± 0.11), maternal saquinavir C_{trough} was 903 (SD± 137) ng/mL with a mean C:M ratio of 0.13 (SD± 0.03), maternal fosamprenavir C_{trough} was 395 (SD ± 134) ng/mL with a mean C:M ratio of 0.21 (SD± 0.01), and maternal lopinavir C_{trough} was 4316 (SD± 2468) ng/mL with a mean lopinavir level in the cord blood samples of 369.3 (SD±153.5) ng/mL. Darunavir samples obtained at delivery from only one patient evidenced maternal blood, cord blood, amniotic and cervicovaginal fluid darunavir concentrations, of 4086, 430, 980 and 380 ng/ml, respectively. Respective darunavir C:M, amniotic fluid-to mother plasma and cervicovaginal-to mother plasma ratios were 0.11, 0.24 and 0.09. Lopinavir, atazanavir and darunavir amniotic fluid levels were 204 (SD±13.8) ng/mL, 492 (SD±300.5) ng/mL e 980 ng/mL respectively. Atazanavir and darunavir were twice more concentrated in amniotic fluid than in cord blood. The observed prevalence rate of neonatal low birth weight (LBW) and preterm delivery was 22% (n=11/50) and 16% (n=8/50), respectively. The preterm delivery was caused by the premature rupture of membranes in 4 cases (8.8%). All 6 patients (10.2%) treated during pregnancy only for prevention of HIV vertical transmission maintained the immunological set-point at 18 month follow-up above the nadir CD4 cell count. Among 9 (15.2%) women experiencing a C_{trough} below recommended drug C_{min}
during the III trimester or at delivery, 3 (33.3%) women reported a virologic failure within the month 18 after delivery. In group of women with adequate drug exposure (n=50, 84.7%) the virologic failure occurred in 5 women (10%). C\textsubscript{trough} below recommended drug C\textsubscript{min} during pregnancy or at delivery was not associated to virological failure during follow-up (p=NS).

Conclusions: Measurement of antiretroviral exposure in different compartments during pregnancy may be needed to identify sub- or supra-therapeutic drug exposure. Further longitudinal data on the maternal viro-immunological outcome after delivery are warranted to assist in selecting optimal drug regimens and to justify implementation of antiretroviral dose adjustment during pregnancy.

No conflict of interest

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Pharmacokinetics (PK), safety, and tolerability of Maraviroc in subjects with various degrees of renal impairment and normal renal function

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Introduction: Maraviroc (MVC) is primarily cleared by metabolism via CYP3A4. Renal clearance accounts for < 30% of MVC’s total clearance. Many HIV-infected patients receive background therapy with agents that are potent CYP3A4 inhibitors, such as protease inhibitors. The combination of impaired renal function with inhibited metabolic clearance has not been studied with MVC. This study evaluated the PK, safety, and tolerability of MVC alone, and also in the presence of a potent CYP3A4 inhibitor, in subjects with varying degrees of renal function.

Material & Methods: This was an open-label, nonrandomized study of HIV-negative subjects. Thirty subjects (6/group) were assigned to one of the following 5 treatment groups based on degree of renal impairment as measured by CL\textsubscript{CR}: Group 1: normal (> 80 mL/min), Group 2: mild (> 50 - ≤ 80 mL/min), Group 3: moderate (≥ 30 - ≤ 50 mL/min), Group 4: severe (< 30 mL/min), Group 5: end-stage renal disease (ESRD) receiving dialysis. Subjects in Groups 1 (Period 1), 4, and 5 received a single 300 mg dose of MVC alone. Subjects in Groups 1 (Period 2), 2, and 3 received MVC 150 mg BID, QD, or QOD, respectively, all in combination with saquinavir/ritonavir (SQV/r) 1000/100 mg BID for 7 days. Blood samples were collected over 72 hours following a single dose of MVC and following the last steady-state MVC (+SQV/r) dose. Dialysate samples were collected throughout hemodialysis. Safety was also assessed.

Results: Following a single dose of MVC, the geometric mean (CV\%) AUC\textsubscript{inf} (ng·h/mL) was as follows: normal, 1348 (61%); severe impairment, 4368 (52%); ESRD before dialysis, 2806 (45%); ESRD after dialysis 2677 (40%); corresponding values for C\textsubscript{max} (ng/mL) were 336 (87%), 801 (56%), 479 (38%), and 577 (51%), respectively.

In combination with SQV/r, the geometric mean (CV\%) for MVC AUC\textsubscript{tau} (ng·h/mL) was 5341 (27%), 9502 (36%), and 6496 (27%) and C\textsubscript{max} (ng/mL) was 951 (23%), 1151 (32%), and 674 (38%) for subjects with normal renal function, mild, and moderate renal impairment, respectively. Transient increases in mean serum creatinine were observed in all treatment groups receiving MVC + SQV/r. One subject who had moderate renal impairment withdrew from the study due to elevated serum creatinine.

Conclusions: Exposures observed after a single 300 mg dose of MVC in subjects with severe impairment or ESRD were higher than exposures observed in healthy subjects in this study, but appeared to be comparable to historical AUC values in healthy subjects (mean 2908 ng·h/mL; Reviews in Antiviral Therapy & Infectious Diseases – Volume 2; 2010
MVC US prescribing information). Hemodialysis had a minimal effect on MVC exposures in subjects with ESRD. Less frequent dosing of MVC in subjects with renal impairment, when co-administered with SQV/r, achieves exposures comparable to MVC BID in subjects without renal impairment. The PK data from this study, along with historical data, will be modeled in order to refine dosing recommendations for this population. MVC was well tolerated in subjects with renal impairment, both alone or when co-administered with a potent CYP3A4 inhibitor.

Conflict of interest
financial relationship(s): All authors are employees of Pfizer

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Intrinsic/extrinsic covariates and darunavir pharmacokinetics in treatment-experienced patients in GRACE (Gender, Race And Clinical Experience)

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Introduction: GRACE, a Phase IIIb study, enrolled a high proportion of treatment-experienced women and people of color to receive a darunavir (DRV)/ritonavir 600mg/100mg twice daily-based regimen, which could include etravirine (ETR; 200mg twice daily) in the background regimen. Here we present the effect of extrinsic and intrinsic covariates (use of ETR, use of tenofovir [TDF], age, sex, race, body weight and hepatitis B co-infection) on DRV pharmacokinetics (PK) parameters over 48 weeks of therapy.

Materials and Methods: Sparse PK sampling was performed at Weeks 4, 8, 24 and 48 for DRV in all patients. Intensive PK sampling was conducted for DRV over 12 hours post-dose after 4, 24 and 48 weeks of treatment, as a substudy. A previously developed population PK model was applied to the sparse PK data to derive empirical Bayesian estimates of DRV area under the curve (AUC12h) and trough concentration (C0h). The impact of covariates on DRV PK was explored graphically, using descriptive statistics and with an analysis of covariance (ANCOVA). PK parameters from the intensive PK sampling were derived using standard non-compartmental analysis.

Results: Of 429 patients in GRACE, 67% were women and 84% were black or Hispanic. Evaluable PK data from sparse sampling were available for 376 patients (women, n=248; men, n=128; black, n=226; Hispanic, n=84; Caucasian, n=62; Asian or Other, n=4). Overall, the median (range) AUC12h and C0h were 60,642 (26,117–128,790) ng.h/mL and 3624 (931–9570) ng/mL, respectively. For all patients, DRV C0h was above the protein binding corrected EC50 for multidrug-resistant virus (550ng/mL). Median (range) AUC12h and C0h were similar between women (AUC12h: 61,190 [33,050–128,790] ng.h/mL; C0h: 3663 [1258–9570] ng/mL) and men (AUC12h: 59,702 [26,117–100,710] ng.h/mL; C0h: 3566 [931–6943] ng/mL), and between black (AUC12h: 60,451 [26,117–128,790] ng.h/mL; C0h: 3566 [931–9570] ng/mL) and Hispanic (AUC12h: 58,215 [34,981–100,710] ng.h/mL; C0h: 3576 [1169–6943] ng/mL) and Caucasian (AUC12h: 63,705 [42,491–120,880] ng.h/mL; C0h: 3721 [2360–8906] ng/mL) patients. Use of ETR or TDF, hepatitis B co-infection status, age or body weight did not affect DRV AUC12h or C0h. Intensive PK sampling from 32 patients showed no time-dependent relationship for DRV exposure over 48 weeks and showed results similar to the population PK results.

Conclusions: Exposure to DRV was not influenced by age, body weight, hepatitis B co-infection status, or use of ETR or TDF. There were no clinically relevant differences in exposure to DRV according to race or sex. These results from this study are in agreement with previous
findings in treatment-experienced HIV-infected patients.

Conflict of interest financial relationship(s): Tibotec, Inc. Employee and stockholder

Abstract: 17

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

Intracellular pharmacokinetics of boosted and unboosted Atazanavir in HIV infected patients


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Introduction: Atazanavir (ATV) is a protease inhibitor that can be administered at 400 mg once daily (unboosted) or 300 mg with a 100-mg dose of ritonavir once daily (boosted). Plasma concentrations are commonly considered as an indicator of drug exposure but the antiretroviral activity of protease inhibitors may correlate better with intracellular concentrations. The aim of this study was to evaluate ATV accumulation in PBMCs and to compare unboosted and boosted ATV treatments.

Materials and Methods: Patients were recruited in Torino (Italy). Sampling was performed after written informed consent was obtained in accordance with local ethics committee indications. Patients receiving ATV as part of their antiretroviral therapy were included in the study. Main inclusion criteria were, no concomitant interacting drugs (except TDF), no hepatic or renal impairment and self-reported adherence > 95%. Ctrough was measured in samples collected 22-26 h after dosing. Plasma sample were analysed by a validated HPLC-PDA method and intracellular samples were analysed using a validated HPLC-MS method plus a Coulter Counter for cells count and mean cellular volume (MCV) quantification. The ratio of the intracellular Ctrough/plasma Ctrough was calculated to determine cellular drug accumulation.

Results: 29 patients were included in the study, 14 treated with unboosted and 15 treated with boosted ATV. Median (IQR) ATV intracellular Ctrough was higher than median plasma Ctrough, 328 ng/ml (168-440) vs 132 ng/ml (111-184), p = 0.001, for unboosted ATV and 1032 ng/ml (819-3091) vs 543 ng/ml (393-1081), p = 0.005, for boosted ATV. However, plasma and intracellular concentrations were not correlated in either treatment group (rho = 0.44, p = 0.11 for unboosted ATV and rho = 0.23, p = 0.41 for boosted ATV). Median (IQR) ATV intracellular Ctrough was higher for boosted ATV compared to unboosted ATV, 1032 ng/ml (819-3091) vs 328 ng/ml (168-440), p = 0.001. Cellular drug accumulation was comparable between the two treatment groups, 1.9 (1.2-2.3) for unboosted ATV vs 2 (1.5-4.9) for boosted ATV, p = 0.5.

Conclusions: Intracellular ATV concentrations were higher than plasma concentrations, indicating an accumulation of ATV in PBMCs. Patients treated with boosted ATV had a higher intracellular exposure but cellular drug accumulation was similar in the two treatment groups. The lack of a clear correlation between plasma and intracellular concentrations suggest a potential role for uptake and/or efflux transporters in regulating intracellular accumulation of ATV.

No conflict of interest
Abstract: 18

Drug Development Science

Metabolism and excretion in humans of the pharmacoenhancer GS-9350

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Introduction: GS-9350 is a potent, mechanism-based inhibitor of human CYP3A enzymes under development to increase the systemic exposure of co-administered agents metabolized by these enzymes. Preclinical data suggest that CYP3A-mediated oxidative metabolism is the major biotransformation pathway for GS-9350. The present study was conducted to understand the metabolic and excretory pathways of GS-9350 in humans.

Methods: GS-9350 has been shown to display time-dependent pharmacokinetics, accordingly, healthy male volunteers (n=8) received unlabeled GS-9350 (150 mg once-daily) for seven days to achieve steady state conditions prior to administration of radiolabel. Study drug administered on Day 7 contained a trace dose (100 mCi) of radiolabeled [14C]GS-9350. Blood, urine, and feces samples were collected until specified standard criteria for collection of administered radiolabeled material were met. Samples were analyzed for total radioactivity and subject to HPLC-radioprofiling and HPLC-MS/MS analyses. Quantification of GS-9350 and previously identified metabolites was performed using synthetic standards. Safety was assessed by routine clinical and laboratory monitoring throughout the study.

Results: Eight subjects enrolled and completed study. Total recovery of radioactivity in excreta was 94.4 ± 3.75% (mean ± SD) of dose, primarily in feces (86.2 ± 3.95%). Renal excretion was a minor pathway for elimination (<10% of dose). The predominant species circulating in plasma was GS-9350 (86.4% of the total radioactivity over 24 hours); the total metabolite to parent ratio was <10%. In most subjects, plasma radioactivity was undetectable beyond 28 to 32 hours post dose. GS-9350 (analysed by HPLC-radiometry and LC-MS/MS) was the major species in the feces (27%) followed by oxidative metabolites E3 (14%) and E1 (5.5%). All other metabolites detected in the feces were in trace amounts, with no values exceeding 3% of the dose. Whole blood to plasma concentration ratio of GS-9350 was approximately 0.5 indicating that GS-9350 was predominantly in the plasma. There were no study drug discontinuations or Grade 2 or higher laboratory abnormalities, or drug-related adverse events.

Conclusion: GS-9350 is extensively metabolized and primarily eliminated in the feces. Following administration of GS-9350, systemic exposure is almost exclusively parent drug. The human data are consistent with the established preclinical profile of GS-9350.

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

Abstract: 19

Pharmacogenetics

Single-nucleotide polymorphisms ABCB1 3435C>T, 1236C>T and CYP2B6 516G>T predict higher plasma concentrations of nevirapine (NVP)

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Background: Nevirapine (NVP) is widely used in naïve patients worldwide. Minimum effective concentration (MEC) of NVP is known to be 3400 ng/ml. However, our group previously described an higher Ctrough cut off (4300 ng/ml) associated
with lower probability of selection of NVP-associated primary resistance mutations (NVP-PRMs) in case of virological failure. Since activity of both transporters (P-Glycoprotein) and metabolic enzymes (CYP450 isoform 2B6 and 3A4) may influence NVP plasma concentrations, we evaluated whether single-nucleotide polymorphisms (SNPs) in these genes may work as predictors of NVP exposure above 4300 ng/ml.

Materials and Methods: Patients were recruited in Torino. Patients administered with NVP plus 2 N(t)RTIs since at least 3 months were considered in the study. Sampling was performed after written informed consent was obtained in accordance with local ethics committee indications. Main inclusion criteria were, no concomitant interacting drugs, no hepatic or renal function impairment, self-reported adherence > 95%. NVP Ctrough was measured in samples collected 10-14 h after dosing by a validated HPLC-PDA method. Genotyping was conducted by real time PCR based allelic discrimination using standard methodology. Statistical analysis was conducted by Mann Whitney or Spearman Rank to assess the effects of weight, age, gender, and genotype on NVP Ctrough. Median value of individual measurements was considered. Values were expressed as ng/ml

Results: 108 patients met the inclusion criteria. Median number of Ctrough measurement for patients was (±SD) 1.59 (±0.85). No associations between weight, age, gender and NVP Ctrough were observed. The mean of median NVP Ctrough in individuals with mutant allele (GT or TT, n=54) for CYP2B6 516 was higher as compared to patients wild-type genotype (GG, n=54) [5624 (±1812) vs 4468 (±1568), respectively, p=0.001]. These two genetic groups were then subdivided based on the presence of at least one of ABCB1 3435 and 1236 homozygote mutate genotype (3435CC/CT+1236CC/CT vs 3435TT/1236TT) and finally four groups were identified: GG/3435CC/CT + 1236CC/CT (group 1), GG/3435TT/1236TT (group 2), GT-TT/3435CC/CT + 1236CC/CT (group 3), and GT-TT/3435TT/1236TT (group 4). A significant positive correlation between level of NVP Ctrough and genetic group was observed, (p=.373 p<0.001). Forty-three percent of the patients in group 1, 86% in group 2, 73% in group 3, and 97% in group 4 showed NVP Ctrough above the suggested cut-off value of 4300 ng/ml. In multivariate logistic regression analyses, being in group 2 or higher was shown to be the only independent predictor of NVP Ctrough above 4300 ng/ml (OR = 3.53, 95% CI 1.48 to 8.43; p = 0.004).

Conclusions: These findings suggest that the combined effect of CYP2B6 516G>T and ABCB1 3435C>T plus 1236 C>T may actually determine an important influence on NVP plasma exposure and therefore on the likelihood of achieving a Ctrough above 4300 ng/ml, a previously suggested cut off of lower probability of selection of NVP-PRMs. Further clinico-pharmacologic studies are now required to confirm this association and to see whether the best candidates to NVP therapy may be identified by relying upon such pharmacogenomic approach.

No conflict of interest

Abstract: 20

Pharmacogenetics

A novel application of population pharmacokinetic analysis: simulating nevirapine dose adjustment according to CYP2B6 516G>T polymorphism

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Background: Nevirapine (NVP) is metabolized by CYP2B6 and a previously presented analysis showed that single nucleotide polymorphisms (SNPs) within the CYP2B6 gene can partly explain inter-individual variability in NVP
pharmacokinetics (PK). We have now expanded this analysis to model the complex relationship between drug exposure, weight and genetics (based on combined analysis of CYP2B6 516G>T and 983T>C SNPs). Simulation of drug exposure was performed for different groups across a range body weights for twice and once daily NVP regimens.

Methods: A population analysis was performed with 406 plasma drug concentrations from 276 patients receiving a NVP containing regimen for at least 4 weeks. DNA was available from all patients and was used to genotype CYP2B6 variants by real-time PCR allelic discrimination. Combining genetic and demographic covariates, non-linear mixed effects modelling (NONMEM v. VI 2.0), was used to estimate pharmacokinetic parameters, inter-individual variability, residual error, and the influence of different patient characteristics. The model was validated by means of simulation and visual predictive check. Simulations of the NVP concentration profile were performed with a dosing regimen at 200 mg bd and 400 mg od for individuals with body weight of 50, 70 and 90kg in combination with the CYP2B6 genetics variations.

Results: The gene frequencies of 516G>T and 983T>C were 60% and 3.3%, respectively. Both were in Hardy-Weinberg equilibrium. A one-compartment model with first-order absorption best described the data. Population clearance (CL) was 3.46 l/h with inter-patient variability of 34%. 516T homozygosity and 983C heterozygosity were associated with 37% and 28% lower CL, respectively. Body weight was the only significant demographic factor influencing CL, which increased by 5% for every 10 kg increase. For 400 mg od simulations, the proportion of patients with the sub-therapeutic trough concentrations (C_{\text{trough}}) were 516TT vs 516GG: 50kg (1.4% vs 22%), 70kg (4.3% vs 32%) and 90kg (9% vs 42%). For 200mg bd simulations these proportions were: 50kg (1% vs 14%), 70kg (1.5% vs 20%) and 90kg (3.8% vs 27.6%).

Conclusions: For individuals with higher body weight, once daily NVP was associated with greater risk of sub-therapeutic drug exposure than twice daily regimen. This risk was offset in individuals who were 516T homozygous in which drug exposure was optimal for >95% of patients with body weight of 70kg and below. For those with body weight of 90kg (especially for 516GG), twice daily dosing is likely to be more robust. This approach of integrating population PK analysis, simulated dosing regimens and pharmacogenetics may have wider applications.

No conflict of interest

Abstract: 21

Pharmacogenetics

Investigation of the association of CYP2B6 haplotypes with Efavirenz plasma concentrations in a Chilean HIV cohort

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Background: Efavirenz (EFV) is extensively metabolized by cytochrome P450 2B6 (CYP2B6). Associations between polymorphisms of the CYP2B6 gene and increased plasma EFV exposure have been reported in a diverse range of ethnicities. To date, little is known of the effect of CYP2B6 polymorphisms on the pharmacokinetics of EFV in Latin American populations.

Methods & Materials: Two hundred and nineteen HIV+ patients were recruited at Fundación Arriarán, Chile between September and December 2008. EFV plasma concentrations were determined using a validated LC-MS/MS assay. All individuals were genotyped for 30 SNPs with a minor allele frequency (MAF)>0.05 in the HapMap CEU population at intervals of ~1kB across the CYP2B6 locus using the Sequenom iPLEX MALDI-TOF-based genotyping platform. SNPs with a MAF<0.01 and Hardy Weinberg
disequilibrium p-value<0.01 were omitted from subsequent analysis. All SNPs had call-rate >90%.

**Results:** Thirteen SNPs passed QC and were carried forward for further analysis (Table 1). One-way analysis of variance (ANOVA) of EFV plasma concentration with genotype for individual SNPs indicated statistical significance (p<0.001) for 11/13 SNPs within the CYP2B6 gene. The exceptions were rs4802100 (5’ upstream) (p=0.08) and rs34083050 (Intron 4) (p=0.91). The statistical significance of the genotype associations with EFV plasma concentrations ranged from p=4.4x10^-8 (rs227344) to p=3.6x10^-22 (rs8192719) (Figure 1). Linkage disequilibrium analysis of the 13 CYP2B6 polymorphisms showed a significant degree of LD (Figure 1). Pair-wise tagging SNP analysis (R^2>0.8) identified 3 SNPs (rs10403955, rs2279345 and rs8192719) which were representative of the 11 plasma EFV concentration-associated SNPs.

A composite genetic model of these 3 high EFV concentration associated alleles was constructed. An association between carriers of 4-6 copies of these alleles and risk of EFV plasma concentration > an upper limit for C_rough of 4µg/ml was identified. 22/38 individuals with EFV > 4µg/ml possessed 4-6 associated alleles compared to 4/140 of those with EFV plasma concentration< 4µg/ml. This represents an odds ratio of 48.1 (95%CI: 13.5-207.7). The positive predictive value was 84.6% and negative predictive value was 89.8% with a sensitivity of 57.9% and specificity of 97.2%.

**Conclusions:** Our data suggest that in a Chilean HIV+ population, a number of polymorphisms in the CYP2B6 gene are associated with an increased plasma EFV concentration. A representative composite model of these associations consisting of 3 SNPs has a high predictive value. Further investigation of the functional basis of this association is needed.

No conflict of interest
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2 (2.4%) genotypes, respectively. Ethnic variation in allele frequencies is Serbian population in comparison with other Caucasian subjects (Haas DW, Journal of Infectious Diseases 2005, 192:1931-42) was observed for CYP3A5. In fact, the frequency of the CYP3A5 wild type allele is 6.2 times higher in SCP than in Caucasians (p<0.0001).

Conclusions: Our results shown that the CYP3A5 mutation is very rare in the Serbian Caucasian population. Therefore, our results contribute to a better understanding of the molecular basis of ethnic differences in drug response, which may help to improve individualization of drug therapy and offer a preliminary basis for more rational use of drugs that are substrates for CYP3A5 in the Serbian population.

No conflict of interest

Abstract: 23

Pharmacogenetics

Single-nucleotide polymorphisms ABCB1 3435C>T, 1236C>T and CYP2B6 516G>T influence plasma concentrations of Efavirenz (EFV).

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Background: Efavirenz (EFV) is mainly metabolised by cytochrome P450 2B6 (CYP2B6) and diminished-function alleles in the CYP2B6 gene significantly affect EFV pharmacokinetics. Previous study showed a potential influence of ABCB1 3435C>T on plasma concentrations of EFV, despite EFV disposition in-vitro seems not to be affected by P-glycoprotein (P-gp). Moreover, recent data suggest a role of CAR on EFV plasma pharmacokinetics. The objective of our study was to clarify if SNPs in ABCB1 and CAR genes can influence EFV plasma concentrations in HIV infected patients.

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

Results: 118 patients met the inclusion criteria. Median number of plasma measurement for patients was (±SD) 1.50 (±0.91). No associations between patient demographics (weight, age, gender) or NRTIs co-administration with EFV concentrations were observed. All the patients were CYP2B6 983 wild-type. EFV concentrations were significantly influenced by CYP2B6 516 SNP (GG, n=64; GT=45, TT=9) [2199 (1553-2789) vs 3144 (2371-3883) vs 6004 (4035-9222), p <0.001]. In P-gp analysis, SNP 3435TT carriers had significantly lower concentrations compared to 3435CC/CT group (CC/CT=77 vs TT=41) [2788 (2071-3674) vs 2334 (1762-3005), p=0.023]. Furthermore 1236TT carriers showed lower plasmatic concentrations but the difference was no statistically significant (CC/CT=91 vs TT=27) [2618 (2017-3640) vs 2732 (1826-3022), p=0.358]. However, in presence of at least one ABCB1 SNP homozygote mutate (3435TT and/or 1236TT) EFV plasma exposure was significantly lower than all wild-type/heterozygote ABCB1 genotypes (wt/het=71 vs mut=47) [2788 (2036-3676) vs 2352 (1765-3022), p=0.044]. Finally, a trend toward significance was observed between CAR rs2307424CC, CT and TT. (CC, n=52; CT=52, TT=14) [2730 (2048-3909) vs 2336 (1632-3091) vs 2696 (2186-4006), p=0.097].
Conclusions: Our finding confirm the effect of CYP2B6 516G>T and suggest an influence of ABCB1 3435C>T plus 1236 C>T on EFV plasma concentrations; ABCB1 3435TT particularly shows a statistically lower concentration leaving 2B6 516 genotype out of consideration. Moreover our data show a no statistically significative trend of CAR rs2307424 SNP on EFV plasmatic concentrations. Although further studies are now required to confirm these associations, we can hypothesize that P-gp may be involved in EFV disposition, despite EVF has not been demonstrated as P-gp substrate in in-vitro study.

No conflict of interest

Abstract: 24

Pharmacogenetics

Application of population pharmacokinetic modelling to quantify the impact of SLCO1B1 521T>C polymorphism on lopinavir clearance

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Background: The OATP/SLCO family represents an important class of hepatic drug uptake transporters that mediate the sodium independent transport of a diverse range of amphipathic organic compounds, including the HIV protease inhibitors. The SLCO1B1 521T>C single nucleotide polymorphism (SNP) has been consistently associated with reduced transport activity in vivo, and we previously showed an association of this polymorphism with lopinavir (LPV) plasma concentrations (Hartkoorn, R.C. et al 2010, Pharmacogenet Genomics). The aim of this study was to develop a population pharmacokinetic (PK) analysis to quantify the impact of 521T>C on LPV clearance.

Materials & Methods: A population PK analysis was performed with 616 plasma samples from 390 randomly selected patients receiving LPV/ritonavir (82% male). The median (range) age and weight were 40 (20 - 67) years and 72 (45-160) kg. All the patients were from the Liverpool Therapeutic Drug Monitoring Registry. Concentrations of LPV were quantified using liquid chromatography-tandem mass spectrometry. Genotyping was performed by allelic discrimination using real-time polymerase chain reaction. Non-linear mixed effects modelling was applied (NONMEM v. VI 2.0) to explore the effects of SLCO1B1 521T>C and patient demographics. The model was validated by means of simulation and visual predictive check.

Results: A one-compartment model with first-order absorption best described the data. Population clearance was 5.5 L/h with inter-patient variability of 44%. Homozygosity for the C allele was associated with a 17% lower clearance that was statistically significant. Body weight was the only demographic factor influencing clearance, which increased 0.7 L/h for every 10 kg increase.

Conclusion: These data show an association between SLCO1B1 521T>C and LPV clearance. The association is likely to be mediated by reduced uptake of LPV by hepatocytes with a resultant decrease in clearance. Further studies are now required to confirm the association and to assess the influence of other polymorphism in the SLCO family.

No conflict of interest

Abstract: 25

Pharmacogenetics

Preliminary results of a case-control study of genetic polymorphisms as risk factors for cutaneous hypersensitivity in patients on Nevirapine

Reviews in Antiviral Therapy & Infectious Diseases – Volume 2; 2010
Background: Although antiretroviral therapy (ARV) has changed the natural history of HIV infection, at present, their toxicity in the short and long term of these drugs is a major concern. Drug toxicity has an interpatient variability related to immunogenetics and pharmacogenetics factors. Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor, commonly use in the treatment of HIV-1 infected patients with confirmed efficacy and has been associated with hypersensitivity (HSR) and hepatotoxicity. CD4 count at the beginning of the treatment, gender and some polymorphism and HLA antigens variability have been related either to HSR and/or hepatotoxicity. The aim of our study is to estimate whether there is an association between nevirapine-related HSR and the genetic polymorphism HLA, taking gender and CD4 level into account.

Methods: Unicenter, retrospective case-control study. We analyzed Caucasian adult patients from the HIV-cohort of the Hospital Clinic (Barcelona) that started NVP for the first time between January 1997 and May 2008. DNA isolation was performed from blood frozen at -20°C using QiAmp DNA blood minikit. DNA was quantified using Nanodrop. HLA class I genes were typed using reverse SSO (RELI™ Dynal, Madrid, Spain). Allele definition was automatically assigned by the RELITM SSO Pattern matching program (Dynal, Madrid, Spain) software and was manually supervised. Genomic typing for class II genes was performed by amplification of exon 2 from DRB1 gene followed by sequencing (SBT) using commercial kits. Typing was performed using the Pharmacia Typing Software (Alfwin 1.10/ HLA sequityper 2.0 software) comparing sequences with the manufacturer's data base. Qualitative characteristics were described using median values and interquartile ranges (IQRs) and compared between groups using the Mann-Whitney test.

Results: A total number of 113 patients were included; 53 HSR cases and 60 controls. Sixty eight (60%) were males, the median CD4 count was 296 cells per mm3 (IQR: 207-465). HIV plasma viral load was 3.7 log10 (4.2 in cases vs. 2.9 in controls) and the median age was 37. Twenty seven patients (24%) (13 cases vs. 14 controls) were naive and 36 (17 cases vs. 19 controls) were confected by HCV or HBV. The genetic polymorphism HLA analysis showed: HLA-DRB*0101 positive in 13 patients (9 cases vs 4 controls), HLA-B*27 in 5 (2 cases vs 3 controls), HLA-B*35 in 17 (9 cases vs 8 controls), HLA-B*57 in 4 (1 case vs 3 controls), HLA-C*08 in 10 (6 cases vs 4 controls) and HLA-A*02 in 46 (19 cases vs 27 controls). No statistically significant differences were found between cases and controls in terms of genetic polymorphism HLA analyzed.

Conclusion: Our preliminary results show no evidence of genetic polymorphism HLA associated with NVP HSR. However, further studies with larger number of patients are needed to identify, if they exist, pharmacogenetic markers of NVP HSR.

No conflict of interest

Abstract: 26

Drug Interactions

The effect of Etravirine alone and with boosted protease inhibitors on the pharmacokinetics of the integrase inhibitor, S/GSK1349572

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Background. S/GSK1349572 is an unboosted, once daily integrase inhibitor with a markedly different resistance profile that is currently in Phase 2b trials. Two studies evaluated the effects of etravirine (ETV) alone (Study 1) and in combination with ritonavir (RTV)-boosted protease inhibitors (PIs) (Study 2) on S/GSK1349572 pharmacokinetics (PK).

Materials & Methods. Study 1 was an open-label, two-period, crossover study in 16 healthy adult subjects. S/GSK1349572 50mg q24h was administered alone for 5 days in Period 1 followed by S/GSK1349572 50mg q24h and ETV 200mg q12h for 14 days in Period 2. All doses were given with a moderate fat meal and there was no washout between periods. Study 2 was a randomized, open-label, crossover study in 17 healthy adult subjects. Subjects received S/GSK1349572 50mg q24h alone for 5 days in Period 1, and S/GSK1349572 50mg q24h + ETV/lopinavir (LPV)/ritonavir (RTV) 200/400/100mg q12h or S/GSK1349572 50mg q24h + ETV/darunavir (DRV)/RTV 200/600/100mg q12h for 14 days in Period 2. Safety assessments were performed throughout the studies and PK samples for S/GSK1349572 were collected during each period. Non-compartmental PK analysis was performed and geometric least squares mean ratios (GLS-MR) and 90% confidence intervals (CI) were generated by the mixed effect model for within-subject treatment comparison.

Results. No deaths, serious adverse events, or withdrawals due to adverse events were reported in either study. No clinically significant changes in clinical laboratory values, vital signs, or ECGs were observed. In study 1, ETV significantly decreased exposures of S/GSK1349572. S/GSK1349572 GLS-MR and 90% CI for S/GSK1349572 administered with ETV relative to S/GSK1349572 alone were 0.294 (0.257, 0.337) for AUC(0-τ), 0.484 (0.433, 0.542) for Cmax, and 0.121 (0.093, 0.157) for Cτ. In study 2 when combined with a RTV-boosted PI, the effect of ETV on S/GSK1349572 was markedly reduced. S/GSK1349572 co-administration with ETV/LPV/RTV had no effect on S/GSK1349572 steady state plasma AUC(0-1) and Cmax, while Cτ increased by 28%. S/GSK1349572 co-administration with ETV/DRV/RTV modestly decreased plasma S/GSK1349572 AUC(0-1), Cmax, and Cτ by 25%, 12%, and 37%, respectively. Such effects of ETV/LPV/RTV and ETV/DRV/RTV are not considered clinically relevant.

Conclusion. The co-administration of S/GSK1349572 with ETV alone or with LPV/RTV and DRV/RTV was generally well-tolerated in healthy adult subjects. While co-administration of S/GSK1349572 and ETV resulted in a significant decrease in plasma S/GSK1349572 exposures, the addition of LPV/RTV or DRV/RTV attenuated the effect of ETV. S/GSK1349572 may be co-administered with ETV without a dosage adjustment if LPV/RTV or DRV/RTV is concurrently administered.

Conflict of interest
financial relationship(s): All authors are employees of GlaxoSmithKline or Shionogi & Co.

Abstract: 27

Drug Interactions

Effect of Efavirenz and Darunavir/Ritonavir on bilirubin levels in healthy adult volunteers: Role of induction of UGT1A1 and bile efflux transporters

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Background: Efavirenz is an inducer of various drug metabolism enzymes while ritonavir is a mixed inducer/inhibitor of cytochromes. We studied the effect of efavirenz and ritonavir-boosted darunavir...
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on UDP-glucuronosyl transferase (UGT) 1A1 using serum unconjugated bilirubin as a probe. Increased activity of UGT1A1 should increase the clearance of unconjugated bilirubin, reducing unconjugated bilirubin and elevating conjugated bilirubin concentrations.

**Materials & Methods:** Healthy male and female volunteers were enrolled in a clinical trial that was primarily designed to study the drug interactions between once-daily darunavir/ritonavir and efavirenz. The study had 3 phases: Phase I, 10 day administration of darunavir 900 mg QD with ritonavir 100 mg QD; Phase II, 14 day co-administration of efavirenz 600 mg QD with darunavir/ritonavir; and Phase III, 14 day administration efavirenz 600 mg QD alone. Serum bilirubin (conjugated and total) concentrations were obtained at baseline, at the end of each phase and at exit. Unconjugated bilirubin was calculated by subtracting conjugated bilirubin from total bilirubin.

**Results:** We recruited 7 males and 5 females, ages 24 to 49 years, weighing 50 to 83 kg. One subject developed grade 3 hepatitis while on efavirenz and was excluded from the analyses (final N=11). Mean serum unconjugated bilirubin concentrations were 6.09 µmol/L (95% CI, 4.99-7.19) at baseline, 5.82 (4.88-6.76) after darunavir/ritonavir, 4.00 (2.92-5.08) after darunavir/ritonavir with efavirenz, 3.55 (2.58-4.51) after efavirenz alone and 5.27 (3.10-7.44) at exit. Unconjugated bilirubin concentrations were significantly lower after both the efavirenz phases (P<0.01) compared to baseline. Mean serum conjugated bilirubin concentrations were 3.55 µmol/L (95% CI, 2.73-4.36) at baseline, 3.73 (2.77-4.68) after darunavir/ritonavir, 2.91 (2.04-3.78) after darunavir/ritonavir with efavirenz, 2.64 (1.95-3.33) after efavirenz alone and 3.55 (2.19-4.90) at exit. Conjugated bilirubin concentrations were also significantly lower after both the efavirenz phases (P<0.05) compared to baseline.

**Conclusions:** Efavirenz significantly decreased unconjugated bilirubin by 42% and conjugated bilirubin by 26%. Ritonavir-boosted darunavir had no significant effect on bilirubin concentrations. This suggests that efavirenz induces UGT1A1, a finding which is consistent with a 36% reduction of raltegravir AUC when co-administered with efavirenz. Efavirenz might also increase conjugated bilirubin excretion by inducing bile efflux transporters. Darunavir/ritonavir had no apparent net induction or inhibition effect on UGT1A1 or these transporters. These results indicate that efavirenz may reduce concentrations of drugs or endogenous substances metabolized by UGT1A1 or excreted by bile efflux transporters.

**Conflict of interest financial relationship(s):** C.Flexner has served on scientific advisory boards for Bristol-Myers-Squibb and Tibotec, and has received honoraria for lectures sponsored in part by Abbott Laboratories. P.Pham has served on scientific advisory board for Tibotec.

**Abstract:** 28

**Drug Interactions**

**Relative bioavailability and pharmacokinetics of Darunavir when boosted with the pharmacoenhancer GS-9350 versus ritonavir**

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**Introduction:** GS-9350 is a specific, potent, mechanism-based inhibitor of human cytochrome P450 3A (CYP3A) and has demonstrated to effectively boost exposure of orally administered CYP3A substrates, including midazolam, elvitegravir and atazanavir *in vivo*. Ritonavir-boosted darunavir [DRV; 800 with 100 mg of ritonavir (r)] is a DHHS-preferred HIV protease inhibitor for use in treatment-naïve HIV patients. This study evaluated the pharmacokinetics (PK) of DRV/GS-9350 compared to DRV/r.

**Methods:** This was a randomized, 24-day, two-period (each of 10 days), multiple dose, two-sequence, crossover study in healthy volunteers (n=17/sequence). Subjects received Treatment A, DRV/GS-9350 (800/150 mg QD) or Treatment B,
DRV/r (800/100 mg QD) under fed conditions, with a 4-day washout between treatments. DRV, GS-9350, and ritonavir PK were assessed on Day 10 of each period. Predefined lack of PK alteration bounds for 90% confidence intervals (CI) about the geometric mean ratio (GMR) were 80-125% for DRV Cmax, Ctau, and AUCtau.

Results: Thirty-three subjects enrolled and thirty-one completed the study; one subject discontinued due to a treatment–related adverse event (maculopapular rash, Treatment A); the other was discontinued at the investigator’s discretion. For the PK analyses set (n=31), the GMR(%) (90% CI) for AUCtau, [102 (97.4, 106)] and Cmax [103 (100, 106)] were within limits of bioequivalence following once-daily dosing of DRV/GS-9350 versus DRV/r. Ctau values were lower [GMR (90% CI): 69.4 (59.0, 81.7)], secondary to unexpected increasing DRV concentrations at the 24-hr time point for the DRV/r treatment. DRV predose concentrations (C0h) following observed, multiple doses of study drug at steady-state were also equivalent [GMR (90% CI): 89.4 (80.4, 99.4)] between both treatments and > 37-fold above the protein-adjusted EC50 for wild-type virus (55 ng/mL).

Conclusion: GS-9350 adequately boosts DRV, resulting in equivalent Cmax and AUCtau and with trough concentrations established to have effective and durable antiviral response in treatment-naive patients.

Conflict of interest
financial relationship(s): All authors are employees of the respective pharmaceutical companies

Abstract: 29

Drug Interactions

Drug–drug interactions between raltegravir and pravastatin in healthy volunteers

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Introduction: Dyslipidemia is a common complication during chronic HIV-infection. Because of its low propensity for Cytochrome P450 mediated drug interactions, pravastatin is considered a preferred lipid-lowering drug for HIV-infected patients. We studied the effect of the HIV-integrase inhibitor raltegravir on pravastatin pharmacokinetics and vice-versa, because both drugs share a common metabolic pathway (i.e., glucuronidation).

Methods: This was an open-label, randomized, 3-period, cross-over, single-centre trial in 24 healthy volunteers. Participants were divided into 6 groups of 4 subjects. In group 1, participants received 40mg of pravastatin once-daily (QD) during 4 days. After a wash-out period of 10 days, participants received raltegravir 400mg twice-daily (BD) for 4 days. After a second wash-out period of 10 days, participants received both pravastatin (40mg QD) and raltegravir (400mg BD) for 4 days. The other 5 groups were exposed to the same drug regimens, but each in a different order. On the 4th day of each treatment period, blood was collected throughout a 24-hour period (12 samples). Plasma concentrations of raltegravir and pravastatin were determined with a validated HPLC and LC-MS/MS method, respectively. Pharmacokinetic parameters were calculated using WinNonlin software version 5.2.1. Serum lipid levels were obtained under fasting conditions on day 1 and day 5 of each treatment period in order to calculate low-density lipoprotein (LDL) concentrations with the Friedewald equation.

Results: All 24 subjects completed the trial. No serious adverse events were reported. Geometric mean ratios (GMRs) (+90% CI) of pravastatin AUC0->24 and Cmax when taken with raltegravir versus pravastatin alone were 0.96 (0.83-1.11) and 1.04 (0.85-1.26), respectively. The mean LDL decrease after 4 days of pravastatin was 0.42 mmol/l, both in the presence and the absence of raltegravir (p=0.98, paired samples t-test). The GMR
Abstracts

Conclusions: Raltegravir did not influence the pharmacokinetics or the short-term lipid-lowering effects of pravastatin, whereas pravastatin increased the C\text{max} but decreased the C\text{12} of raltegravir. Clinical experience from phase II and phase III trials suggests that a 60% lower C\text{12} is not associated with reduced raltegravir efficacy. Given this, and the lack of an effect of pravastatin on the raltegravir AUC, which is probably better correlated to raltegravir efficacy, the effects of pravastatin on raltegravir pharmacokinetics are not likely to be clinically relevant. The data from our study support co-administration of raltegravir and pravastatin without dose-adjustments.

Conflict of interest

financial relationship(s): D.M. Burger has received honoraria for serving on advisory boards, speaker’s fees, and educational grants for clinical research from Merck, the manufacturer of raltegravir. M. van Luin has received honoraria for serving on advisory boards of Merck Sharp & Dohme. H.G da Silva is an employee of Merck. All other authors have no conflict of interest to declare. This study was funded by a research grant from Merck.

Abstract: 30

Drug Interactions

The effect of food on the pharmacokinetics of atazanavir/ritonavir 300/100 mg daily in HIV-infected patients

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Background: Atazanavir/ritonavir (ATVr) is a widely used component of HAART. It is known that food increases the absorption of ATVr in healthy volunteer single dose study. We assessed the impact of food on ATVr in a clinical setting, involving HIV patients taking ATVr with or without food for several days.

Materials & Methods: This was a randomized multiple dose crossover food effect study in virologically suppressed HIV-infected patients receiving ATVr 300/100mg QD as part of their HIV treatment. In this 15 day study, each participant took ATVr with a standardized meal for 3 days followed by pharmacokinetic study day, and without food (10 hours prior and 2 hours post dose) for 3 days followed by pharmacokinetic study day. Intensive blood sampling was performed on both pharmacokinetic study days and all samples were analyzed for atazanavir (ATV) and ritonavir (RTV) concentrations using a validated HPLC tandem mass spectrometry method. The pharmacokinetic parameters of ATV and RTV were calculated using a non compartmental pharmacokinetic analysis. Following calculation of the geometric mean ratios (GMR) and 90% confidence intervals, the classical bioequivalence approach with boundaries of 0.80 to 1.25 was used to evaluate the results for AUC, Cmax and C24. Paired t-tests or Wilcoxon signed ranks tests were used for the other pharmacokinetic parameters.

Results: The study included 12 adult male HIV-infected patients, of whom 11 were Caucasian and one was black. Their median (interquartile range) age was 50 (42-55) yrs, height was 1.73 (1.70-1.76) m, weight was 73.7 (70.2-87.4) kg and BMI was 26.4 (24.2-28.6) kg/m2. All participants had an undetectable viral load (<50 copies/mL) and the mean (±SD) CD4 cell count was 498 (266-725) at start of study. Six patients were being treated with tenofovir which was continued during the study. Two patients were hepatitis B surface antigen positive and one patient was hepatitis C antibody positive. GMR (90% CI) of fasted over fed ATV were: 0.59 (0.42-0.84) for AUC, 0.68 (0.45-1.02) for Cmax and 0.47 (0.31-0.71) for C24. For RTV these numbers were: 0.74 (0.58-0.94) for AUC, 1.04 (0.78-1.40) for Cmax and 0.47 (0.31-0.70) for C24. In one patient, ATV C24 was below the recommended cutoff level of 0.15 mg/L. No patients showed evidence of viral
replication in subsequent viral load measurements.

Conclusions: When ATVr 300/100mg QD is given without food, the exposure (AUC) of ATV dropped by 41% along with decreases in Cmax and C24 by 32% and 53% respectively. Although in the majority of patients the occasional intake of ATVr without food will not lead to subtherapeutic atazanavir levels, it should be kept in mind that food maximizes the absorption of ATV, which supports the current recommendation to take ATVr with food.

No conflict of interest

Abstract: 31

Drug Interactions

Patterns and correlates of the use of complementary and alternative medicine among HIV-infected patients

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Background: The use of complementary and alternative medicine (CAM), including herbal remedies, seems to be common in HIV-infected patients, with wide variations among studies. The aims of this study were i) to evaluate the prevalence of use of CAM, and particularly of herbal remedies, in a cohort of HIV-infected outpatients; ii) to investigate correlates of the use of herbal remedies; and, iii) to assess the risk of potentially relevant drug interactions and adverse events associated with the use of such therapies.

Material & Methods: Cross-sectional survey study including 1,000 HIV-infected out-patients attending the Pharmacy Department or the HIV Clinic at the Hospital Universitari Germans Trias i Pujol, in Barcelona (Spain). Participants completed a self-administered questionnaire that gathered information on sociodemographic characteristics, the use of CAM within the previous year, perceived benefits and risks of these therapies, attitudes and views towards antiretroviral therapy, and presence of symptoms including fatigue, sadness or nervousness. Clinical data including time since diagnosis of HIV infection, route of transmission, clinical stage (CDC), HIV-1 RNA load, CD4+ T lymphocyte count, time receiving antiretroviral therapy, prior number of antiretroviral regimens, and antiretroviral drugs in current use were collected from medical records. The completed questionnaires were scrutinized for potential drug interactions and adverse effects.

Results: Participants were mostly Caucasian males with medium to high education level who had acquired HIV infection through sexual exposure, and who were receiving antiretroviral therapy at the time of the study. Overall, 584 (58.4%) patients reported having used some CAM within the previous year, with a median [interquartile interval] of 3 [2-7] remedies per patient. The two most frequent types of CAM among CAM users were dietary supplements (n=429, 73.5%) and herbal remedies (n=355, 60.8%). Only 324 (55.5%) CAM users had ever consulted on the possibility of using these remedies with their HIV physicians or pharmacists, and only 124 (21.2%) of them had been monitored by their primary HIV care givers while they were using CAM. Variables significantly associated with higher prevalence of herbal remedy use in the final multivariate logistic regression model were (odds ratio, 95% confidence interval [OR, 95%CI]) non-Caucasian race (OR 1.65, 95%CI 1.07-2.56, p=0.024), a secondary school education or higher (OR 2.63, 95% CI 1.78-3.88, p<0.001), feelings of fatigue, sadness or nervousness (OR 1.68, 95%CI 1.24-2.28, p=0.001), perception of CAM therapies as totally or partially effective (OR 2.28, 95%CI 1.18-4.41, p=0.015), and consultation on the possibility of using CAM with their HIV physician (OR 3.12, 95%CI 2.30-4.23, p<0.001). Concerns about potentially relevant drug interactions or added adverse effects with antiretroviral

No conflict of interest
agents were identified in 211 (36.1%) of all CAM users.

Conclusions: While not without health risks, the use of CAM and herbal remedies is common among HIV-infected patients in the clinical practice. Both HIV care givers and patients should be sensitized to the potential risks derived from the use of CAM and especially herbal remedies, and encouraged to discuss such therapies openly during the clinical visits.

No conflict of interest

Abstract: 32

Drug Interactions

Prevalence of co-medication use and adverse effects in HIV patients treated with HAART in Chile

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Background: The current successful outcomes of HIV treatments lead patients to have a longer survival and face a variety of different pathologies. The use of ART and co-medications for such other pathologies can result in drug-drug interactions and/or additional adverse events (AEs). This may affect treatment adherence and immune or virological success.

Objectives: To study the prevalence study of co-medication use, AEs and laboratory abnormalities in a cohort of HIV patients using HAART.

Methods: Cross sectional analysis of co-medication used for laboratory abnormalities AEs and comorbidities. After approval by the local ethics committee a voluntary survey was answered by each participant. Information regarding use of concomitant drugs, AEs, and medication prescribers was obtained. General and HIV related laboratory results were obtained from clinical charts and were grouped according to the number of co-medications used (0-2 or 3 or more).

Results: A total of 150 patients, 12.7% women with a median age of 42.1 (IQR 36.1-47.8) years were included in this study. This sample represented 10% of the patients on ART of Fundación Arriarán, Santiago, Chile, were evaluated between September and December 2009. The median time after HIV diagnosis was 5.5 (3.8-10.6) years and 4.4 (2.0-6.8) years after ART initiation. Alcohol and tobacco were used by 54.7% and 58.0% respectively, whereas recreational drug use was reported by 12% (88.9% marijuana). More prevalent concomitant conditions were: mental health issues (29.3%), dyslipidemia (28.7%), drug allergy (16.0%) and hypertension (10.0%). The median number of concomitant drugs per patient was 2, and the percentages of patients using at least 1, 2, 3, 4, 5 or 6-11 concomitant drugs besides ART were 89.3%, 61.3%, 40.1%, 20.0%, 7.3% and 3.3%. The most frequently used drugs were: analgesics (31.0%), antibiotics (11.2%), gastrointestinal medications (7.7%) and others (8.6%). 33% of the co-medications were obtained without prescription, 30% were prescribed by physicians at the HIV clinic, 27.8% by other specialists and 8.6% by general practitioners. There was no difference in the median number of co-medications according the use of NNRTI versus PI. The most frequently reported AEs in the 10 days preceding the survey were: headache (52.7%), sleeping problems (49.3%), nausea (32.7%) and abdominal pain (20.0%). There was a significant higher rate in diarrhea (p = 0.0025) and a trend in sleeping issues (p = 0.06) in the group using 3 or more co-medications versus 0-2, after adjusted for use of lopinavir and efavirenz respectively. There was no difference regarding hematological or biochemical laboratory results between groups. CD4 cell count was significantly higher in the group with less co-medications 488 versus 325 cells/mm3 (p=0.0008). No difference was noted in the viral suppression rates between groups.

Conclusions: Co-medications are frequently used in this Chilean population and about one third of the co-medications were obtained without prescription. This signal should warn the different health
care teams to pay adequate attention to medication review to prevent and manage drug interactions, and improve adherence and adverse event profiles. The wide variety of prescribers also indicates that communication between the different health care providers is needed.

No conflict of interest

Abstract: 33

Drug Interactions

Pharmacokinetic interaction study between TMC278, a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), and methadone.

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Introduction: TMC278 is a next-generation NNRTI with sustained efficacy and good tolerability through 96 weeks in ARV-naive HIV-infected patients (Pozniak et al. AIDS 2010). TMC278 is currently being investigated in Phase III trials at a dose of 25 mg once daily (qd), in combination with a background regimen of two NRTIs. The current trial evaluated the effect of TMC278 on the pharmacokinetics and pharmacodynamics of methadone.

Methods: This was an open-label, single-sequence, add-on drug-drug interaction trial in 13 HIV-negative volunteers who were on stable methadone maintenance therapy. Volunteers received methadone (individualised stable methadone maintenance dose, between 60 and 150 mg qd) from Day −14 through 11, and TMC278 25 mg qd was added from Day 1 through 11. All intakes were witnessed, and all treatments were taken following breakfast. Pharmacokinetic profiles up to 24 hours after intake were determined on Day −1 (methadone alone) and on Day 11 (methadone + TMC278) for R- and S-methadone, and on Day 11 for TMC278. Plasma samples were analysed using validated LC-MS/MS methods. Pharmacokinetic parameters were calculated using non-compartmental analysis. The least square (LS) means ratios (test/reference) and associated 90% CI were calculated based on log-transformed pharmacokinetic parameters. Pharmacodynamic assessments of symptoms of methadone withdrawal (Short Opiate Withdrawal Scale [SOWS], Desires for Drugs Questionnaire [DDQ], pupillometry) were performed on Day −7 and daily from Day −3 until Day 11, within 2 hours before the intake of methadone.

Results: When TMC278 25 mg qd was added onto a stable methadone maintenance therapy, the mean Cₘᵋᵣₐᵛₜ, Cₘₐₓ and AUC₂₄₉ₗ of the biologically active R-isomer of methadone decreased by 22% (LSmean ratio 0.78; 90%CI 0.67–0.91), 14% (0.86; 0.78–0.95) and 16% (0.84; 0.74–0.95), respectively, as compared with administration of methadone alone. The mean Cₘᵋᵣᵣᵠ, Cₘₐₓ and AUC₂₄₉ₗ of the inactive S-methadone decreased by 21% (0.79; 0.67–0.92), 13% (0.87; 0.78–0.97) and 16% (0.84; 0.74–0.96), respectively. The AUC ratio for S-/R-methadone was similar during co-administration with TMC278 or when methadone was administered alone (1.01; 0.96–1.05). The exposure to TMC278 in the presence of methadone was within the expected range. During co-administration with TMC278, no clinically relevant changes in the pharmacodynamic assessments of methadone withdrawal symptoms (SOWS, DDQ scores, pupil dilation) were observed. Co-administration of methadone and TMC278 was generally safe and well tolerated. No grade 3 or 4 adverse events (AEs) and no serious AEs were reported. There were no discontinuations due to AEs.

Conclusions: No a-priori adjustment of the methadone dosage is required when initiating co-administration with TMC278. Clinical monitoring for withdrawal symptoms is, however, recommended, as methadone maintenance therapy may need to be adjusted in some patients.

Conflict of interest

financial relationship(s): All authors are employees of J&J/Tibotec
Abstract: 34

Drug Interactions

Factors associated with atazanavir plasma levels in subjects receiving different doses of atazanavir/ritonavir with efavirenz or nevirapine

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Introduction: Efavirenz and nevirapine have been shown to decrease atazanavir plasma levels. The optimal atazanavir/ritonavir dose when coadministered with NNRTIs is unclear. We examined factors associated with higher atazanavir plasma levels in patients receiving these regimens.

Materials & Methods: HIV+ patients aged ≥19 years who had therapeutic drug monitoring (TDM) between 1-January-2003 and 30-June-2009 while taking atazanavir/ritonavir and efavirenz or nevirapine were identified from the BC Centre for Excellence in HIV/AIDS Laboratory Database. After >2 weeks on a stable regimen, blood was drawn within 2 hours prior to and 1 hour following atazanavir/ritonavir dosing. Plasma was separated within 1 hour and stored at –70°C until analysis. Plasma drug concentrations were determined by a validated high performance liquid chromatography method with tandem mass spectroscopy (HPLC-MS/MS) with limits of quantification of 50-10,000 ng/mL for both atazanavir and ritonavir. The lowest observed level (Cmin) was used in the analysis. Samples were excluded for major drug interactions (e.g. PPIs, clarithromycin, phenytoin, coadministered H2 antagonists), multiple protease inhibitor regimens, or lack of clinical information. Univariate and multivariate Poisson regression using generalized estimating equations (GEE) were used to estimate associations between atazanavir Cmin, key demographic variables, antiretroviral regimens, and laboratory results. GEE were used to account for repeated measures using an exchangeable correlation matrix and an adjustment was made for over-dispersion. Model selection was achieved through the minimization of Akaike's Information Criterion where every parameter estimate had a p-value <0.20.

Results: 170 samples from 119 subjects were included in the analysis. 96% of samples came from subjects who were male. Median age was 49 years (interquartile range [IQR] 43, 55), median CD4 was 445 cells/mm3 (IQR 350, 580), 86% had plasma viral load <50 copies/mL, 14% had known hepatitis B and/or C coinfection, and median bilirubin level was 22 µmol/L (IQR 14, 32) at the time of TDM. Efavirenz was included in the regimen for 30% of samples (n=51), nevirapine for 70% (n=119), and tenofovir for 65% (n=111). Atazanavir/ritonavir doses (in mg) at the time of TDM were 300/100 for 38 samples (22%), 300/200 for 11 (7%), 400/100 for 70 (41%), and 400/200 for 51(30%). Median time on the current regimen before TDM was 36.5 days (IQR 28, 57). In univariate analysis, higher atazanavir Cmin was associated with atazanavir dose (400mg vs. 300mg), ritonavir dose (200mg vs. 100mg), higher ritonavir Cmin, and higher bilirubin (unadjusted relative risk [RR] 1.03 per 1 µmol/L increase, 95% confidence interval [CI] 1.02, 1.03, p<0.0001), but not with age, CD4, viral suppression, hepatitis coinfection, efavirenz vs. nevirapine, or tenofovir vs. tenofovir-sparing regimen. In multivariate analysis, only atazanavir dose (adjusted RR 1.61 for 400mg vs. 300mg, 95% CI 1.34, 1.93, p<0.0001) and ritonavir Cmin (adjusted RR 1.07 per 10ng/mL increase, 95% CI 1.05, 1.09, P=0.0001) were associated with higher atazanavir Cmin levels.

Conclusions: Among HIV+ adults taking various doses of atazanavir/ritonavir plus efavirenz or nevirapine, higher atazanavir Cmin was associated with atazanavir dose of 400mg and higher ritonavir Cmin, but not with specific NNRTI nor with tenofovir-sparing regimens.

No conflict of interest
Abstract: 35
Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Generic lopinavir/ritonavir is bioequivalent to Aluvia, but neither result in adequate lopinavir exposure at 50% dose reduction: HIVNAT 085

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Background: The tablet formulation of lopinavir combined with ritonavir (LPV/r), which is widely available as Aluvia or Kaletra, has many advantages over the original soft gel capsule formulation; the tablets are heat stable and there is no food effect on the bioavailability. However, Aluvia is expensive and only the pediatric formulation is available in Thailand. In Thailand, a generic tablet formulation of LPV/r is also available from GPO, which has proven to result in adequate lopinavir levels at the standard dose of 400/100mg BID in Thai HIV-1 infected adults. It has been demonstrated that dose reductions of several PIs in Thai HIV-1 infected patients result in adequate plasma concentrations and, if effective, dose reduction of LPV/r could diminish the cost of HIV-treatment and improve access to second line therapy. This study describes and compares the pharmacokinetic profiles of reduced dose generic LPV/r and pediatric Aluvia (200/50 mg BID).

Material & Methods: This was a prospective, two arm, randomized PK study with cross-over design. HIV-infected patients were randomized to receive either generic LPV/r 200/50 mg BID (arm 1) or Pediatric Aluvia 200/50 mg BID (arm 2) with an appropriate NRTI backbone. At week 2, blood samples for pharmacokinetic analysis were collected pre-dosing and at t=1, 2, 3, 4, 6, 8, 10 and 12h post-dosing with a standardized breakfast, after which patients crossed-over to the other study arm. At week 4 the second 12h sampling was performed. Patients continued their study regimen until week 12, when the final safety assessment was performed. Pharmacokinetic parameter calculation and statistical analysis were conducted using Stata version 10. ANOVA was used to compare the PK parameters of both groups.

Results: Twenty patients were included in this study, ten in each arm. There were no differences in term of demographics between the arms. The median (IQR) age was 38.6 (34.4-42.5) years and the median weight was 59.8 (52.9-62.0) kg. The generic LPV/r and Aluvia showed no difference in lopinavir PK parameters. For generic LPV/r and Aluvia, respectively, the mean AUC 0-12 (SD) was 46.6 (10.7) and 45.1 (16.9) (p=0.98) h*mg/l, C max was 6.2 (1.4) and 6.1 (2.2) mg/l (p=0.91), and C min was 1.5 (0.6) and 1.6 (0.9) mg/l (p=0.92). For ritonavir, the mean AUC 0-12 (SD) was 1.98 (0.5) and 1.93 (0.7) (p=0.77) h*mg/l, C max was 0.28 (0.08) and 0.26 (0.1) mg/l (p=0.46), and C min was 0.07 (0.02) and 0.07 (0.03) mg/l (p=0.34), respectively. Ten patients (50%) had subtherapeutic C min concentrations of lopinavir (defined as <1.0 mg/l); four patients were on the generic LPV/r and six patients were on Aluvia. At week twelve, all 20 patients had plasma HIV-RNA below 50 copies/ml.

Conclusions: Our results show that the generic LPV/r is bioequivalent to Aluvia. However, dose reduction to 200/50 mg twice daily does not result in adequate PK parameters in a large number of Thai HIV-1 infected patients. This is most likely because lopinavir levels are ritonavir-dose dependent and a 50% reduction of ritonavir dose leads to insufficient boosting of lopinavir.

No conflict of interest
Abstract: 36

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Lack of adherence to treatment drives Maraviroc exposure-response in the MERIT study in treatment-naïve HIV-1 infected subjects

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Background: Exposure-response analyses of the maraviroc (MVC) 300mg BID arm in the MERIT study has been reported. Logistic regression with generalised additive modelling (GAM) was used to assess the influence of MVC exposure on success (<50 copies/mL viral RNA (discontinuation=failure) at 48 weeks), in the presence of other predictive factors. MVC exposure was derived from population pharmacokinetic modelling of sparse PK samples and patient-reported dosing. MVC concentrations below quantification limit (BLQ) were retained and set to 0.25 ng/mL (=1/2 BLQ). Two major variables predictive of outcome were identified: a tropism switch from CCR5-tropic (R5) at screening to dual/mixed (DM) at baseline and MVC exposure. Probability of failure was greatly increased below MVC average (Cavg) or minimum concentration (Cmin) of approximately 75 and 25ng/mL, respectively. Eighteen of 20 subjects with BLQ values were in Q1. Cmin values in Q1 were lower than expectations for phase 1/2a. Cavg was no longer statistically significant in GAM analyses with BLQ as a separate variable (in addition to Cavg) and in a subset excluding subjects with BLQ values. Subjects who failed in the MVC arm with sensitive R5 virus were more likely to have MVC BLQ values (and/or low Cavg/Cmin) than those failing with DM or MVC-resistant virus.

Results: Distributions were similar for MERIT and phase 1/2a except at very low exposures. Following 300mg doses in phase 1/2a, MVC was detectable up to 72 hours after the last dose, suggesting BLQ values result from at least 3 missed BID doses in MERIT. Quartile (Q) analysis of Cmin showed that success with maraviroc was reduced from 72.2 % in quartile 2, to 57.3% in Q1 (lowest exposure), with median Cmin of 39 and 23ng/mL, respectively. Subjects who failed in the MVC arm with sensitive R5 virus were more likely to have MVC BLQ values (and/or low Cavg/Cmin) than those failing with DM or MVC-resistant virus.

Conclusions: Subjects with MVC BLQ values were responsible for driving the previously reported exposure-response relationship for maraviroc in the MERIT study. Consistent with poor adherence, such patients are likely to fail with MVC-sensitive virus.

No conflict of interest
Abstract: 37

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Pharmacokinetics of QD Maraviroc co-administered as part of a novel NRTI-sparing regimen with Atazanavir/ritonavir in HIV treatment-naive patients

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Introduction: Maraviroc (MVC) is a potent CCR5 antagonist approved for the treatment of CCR5-tropic HIV-1. This pharmacokinetic (PK) substudy is a component of a pilot study designed to assess the safety and efficacy of MVC 150 mg once daily (QD) + atazanavir/ritonavir (ATV/r). MVC is primarily cleared by metabolism via CYP3A4. In a drug-drug interaction study, ATV/r was shown to increase MVC exposures 4.9-fold in healthy volunteers. PK modeling studies suggest that ATV/r, a potent CYP3A4 inhibitor, may make it possible to dose MVC once daily. In the pivotal Phase 3 MOTIVATE studies, where maraviroc was given once- or twice-daily with an optimized background regimen to treatment-experienced patients, the inter-subject variability in the average concentrations (Cavg) of MVC was thought to be largely influenced by background therapy. This PK substudy will examine the PK of MVC 150 mg once daily in combination with ATV/r, without confounding effects of other background therapy. Based on exposure-response analysis from the MERIT study, the pharmacokinetics of this novel, once-daily, nucleoside (NRTI)-sparing regimen in treatment-naive patients appear promising. The efficacy and safety data are awaited.

Material & Methods: Treatment-naive patients (N = 121) were randomized 1:1 to either receive MVC 150 mg QD or tenofovir/emtricitabine 300/200 mg (Truvada®) QD both in combination with ATV/r 300/100 mg QD for 48 weeks. A subset of 15 patients in the MVC treatment arm at participating US sites was included in this PK substudy. Blood plasma samples were collected at predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours postdose at Week 2. Based on the individual plasma concentration-time data, using actual sampling times, the AUC24h, Cavg (AUC/τ), Cmax, and Cmin at Week 2 were determined by non-compartmental analyses and summary statistics were determined.

Results: 15 subjects, all men, were enrolled into the PK substudy; 11 were White, 3 were Black and 1 subject was of mixed race. The PK data [median (range)] for MVC when dosed once daily in combination with ATV/r at Week 2 were as follows: AUC24 = 4330 ng·h/mL (1920-7310); Cavg = 180 ng/mL (80-305); Cmax = 650 ng/mL (178-1490); Cmin = 37.0 ng/mL (8.4-92.7).

Conclusions: All 15 subjects achieved the targeted MVC Cavg (≥75 ng/mL) for near maximal virologic efficacy based on the exposure-response analysis from the MERIT study. The pharmacokinetics of this novel, once-daily, nucleoside (NRTI)-sparing regimen in treatment-naive patients appear promising. The efficacy and safety data are awaited.

Conflict of interest financial relationship(s): All authors are employees of Pfizer

Abstract: 38

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Impact of age on renal function in patients receiving tenofovir

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Reviews in Antiviral Therapy & Infectious Diseases – Volume 2; 2010
**Background:** Tenofovir is an acyclic phosphonate nucleotide analogue eliminated by glomerular filtration and active tubular secretion. A small fraction of patients experience acute renal toxicity and a Fanconi-like syndrome. In most studies, chronic use of tenofovir is safe and produces a small, clinically insignificant reduction in renal function. Tenofovir use is also associated with mild tubular toxicity resulting in sub-clinical loss of phosphate, protein, and glucose. There is a well-recognized age-related decline in renal function, and HIV-infected individuals are living significantly longer as a result of HAART utilization. Older individuals may display differences in pharmacokinetic parameters which could affect drug toxicity. We explored the impact of age on tenofovir-mediated effects on estimated glomerular filtration rate (eGFR).

**Methods:** The analysis used all patients included in a single clinic database between 2002 and 2009 who received tenofovir as part of their HAART regimen. Serum creatinine values collected at clinic visits from the start of tenofovir to discontinuation or end of study period were used to compute eGFR by the MDRD method. A repeated measures analysis was performed using mixed-effects regression modeling. Statistical analysis performed with STATA IC.

**Results:** 1031 patients were included in the analysis with a total of 17383 observations. The composition of the cohort was as follows: 67.24% male, 32.1% Caucasian, 67.9% African-American. The median number of clinic visits was 10 (IQR= 4-16) and the mean time on tenofovir was 700 days. The average eGFR at baseline was 112.7 ml/min. The median age was 43 years. In a univariate analysis, there was a decrease in eGFR \( [\text{MA1}] \) of 0.016 ml/min \((\text{days on tenofovir}) \) -0.017 (age 30-45) -11.9 (age>45) + 0.645 (baseline MDRD) \(-0.014\) (concurrent protease inhibitor use) \((R^2 =0.32)\).

**Conclusion:** We observed an effect of tenofovir on eGFR related to the duration of exposure, consistent with previous studies. Age independently affected eGFR in patients on tenofovir, both as a continuous variable and when stratified by age category. Other important covariates included baseline eGFR, co-morbidities that affect renal function, and concomitant exposure to protease inhibitors. Tenofovir may require closer monitoring in older individuals.

**No conflict of interest**

**Abstract: 39**

**Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity**

**An evaluation of cutaneous adverse drug reactions and antiretroviral therapy use in HIV infected patients in a resource limited setting.**

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**Background:** The severity of cutaneous adverse drug reactions (CADRs) caused by antiretroviral therapy (ART) varies greatly, and may be difficult to manage. Various patient and drug-related factors...
contribute to the risk of adverse drug reactions. Hypersensitivity typically manifests as erythematous maculopapular, pruritic and confluent rash with or without fever. Rash is most prominent on the trunk of the body and arms usually appearing after 1-2 weeks post initiation of therapy. This study was aimed at ascertaining causality and measuring incidence of cADRs in HIV infected patients receiving ART from a public rollout programme.

Materials & Methods: A Retrospective record review, in an adult population of HIV-infected patients on ART was carried out at the Family Care Centre (HIV clinic at the largest referral hospital in Zimbabwe). 221 medical records of patients initiated on a new drug regimen within 2008 were reviewed. Instances of cADRs were recorded on the Medicines Control Authority of Zimbabwe (MCAZ) adverse drug reaction case report forms which were subsequently sent to the MCAZ for assessment and causality classification. Data recorded included, patient demographics, description of the skin reaction, type of treatment given, outcome of treatment, suspected offending drug information and other co-administered drugs.

Results: A total of 221 medical records were reviewed for those initiated on a new ARV regimen between January 2008 and December 2008, of which 125 (56.6%) were females. The mean age of patients who developed cutaneous drug eruptions was 40.6 years, (SD 11.16, range 19-76 years). Cutaneous drug eruptions were noted in 39 patients (17.6%). The majority (72%) of the eruptions were seen in the age group between 26 to 35 years. There were more women on ART compared to men, however the likelihood of women developing a cutaneous eruption was not significantly greater than that for men (p = 0.8 at 95% confidence interval). The causality assessment and classification revealed five cases to be probable, twenty four to be possible, three to be unlikely and seven cases were unclassified due to unavailability of patient’s clinical data relating to the assumed adverse drug reaction. Of the twenty nine cases classified as probable and possible, nevirapine was implicated in 14 (48%) cases, efavirenz in 7 (24%) cases, zidovudine in 3 (13%) cases, lopinavir/ritonavir in 3 (13%) cases and abacavir in 1 (3%) case. Pharmacotherapy interventions included, oral antihistamines (61.8%) which were the most commonly used drugs, followed by topical corticosteroids (14.7%) and topical antifungals (14.7%).

Conclusion: The incidence of cADRs in this setting was 13.1%. Most offending ARV drugs were withdrawn as the reaction progressed, moreover some offending drugs were withdrawn at a later stage when the patient had already gone through extreme morbidity and disfiguring. The study revealed that there was a need to identify specific populations at risk of developing adverse drug reactions and increase monitoring in this group. Specific factors that predispose patients to cADRs need to be identified to improve patient monitoring.

Conflict of interest financial relationship(s): Tinashe Mudzviti received an award through the AIDS International Training and Research Program (AITRP)that gave funding for the student to carryout this research. Tinashe Mudzviti received the International Clinical, Operational and Health Services Research and Training Award (ICOHRTA)that assisted in funding the student to carryout the research project.

Abstract: 40

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Population pharmacokinetic analysis of low dose indinavir boosted with ritonavir in HIV-infected Thai adults


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Reviews in Antiviral Therapy & Infectious Diseases – Volume 2; 2010
Background: Protease inhibitor (PI)-based highly active antiretroviral therapy (HAART) regimens are mainly used for second-line regimens in resource limited settings. Until recently, indinavir boosted with ritonavir (IDV/r) based HAART was the cheapest PI regimen in Thailand. Price reductions have now made lopinavir boosted with ritonavir (LPV/r) the preferred PI for second line. Despite indinavir use being slowly phased out it still remains one of the few alternatives to LPV/r. A reduced dose of IDV/r 400/100 mg, twice daily, has been shown to provide adequate indinavir plasma concentrations and an improved tolerability profile in Thai adults. Our aim was to develop and validate a population pharmacokinetic model to describe IDV/r concentrations in HIV-infected Thai patients receiving such low doses and identify individual patient characteristics which contribute towards its pharmacokinetic variability.

Methods & Methods: Intensive and sparse pharmacokinetic sampling from patients initiating 600/100 mg and 400/100 mg IDV/r, twice daily, were included. IDV/r concentration data from 513 plasma samples were used in a population PK analysis: full pharmacokinetic curves were available from 11 patients and 19 patients had sparse pharmacokinetics evaluations. IDV/r plasma concentrations were determined by high performance liquid chromatography. Population means and variances of indinavir and ritonavir pharmacokinetic parameters were estimated using non-linear mixed effects regression models (NONMEM Version VI). The validity of the final model was evaluated using a visual predictive check (VPC) and bootstrap re-sampling techniques. Using the final model, Monte Carlo simulations were performed to estimate the probability of achieving indinavir target trough concentrations across the weight range of the Thai population.

Results: Thirty HIV-infected patients were included in this analysis: 12 men and 18 women, median (range) weight was 58 kg (51-73) for men and 53 kg (46-59) for women. IDV/r pharmacokinetics was best described by a one compartment model coupled with a single transit compartment absorption model. Body weight influenced indinavir apparent oral clearance (CL/F) and volume of distribution (Vd/F) and allometric scaling significantly reduced the interindividual variability. Final population estimates (percentage interindividual variability) of indinavir CL/F and Vd/F were 21.3 L/h/70kg (30%) and 90.7 L/70kg (22%), respectively. The probability to achieve an IDV trough concentration > 0.1 mg/L was >98% for 600/100 mg and >92% for 400/100 mg, twice daily, in patients 40-70 kg; however, the probability of achieving IDV concentrations associated with an increased risk of drug toxicity (>10.0 mg/L), increased from 1% to 18% with 600/100 mg compared to <1% to 4% with 400/100 mg when body weight decreased from 70 to 40 kg. Final population estimates (percentage interindividual variability) of ritonavir CL/F and Vd/F were 10.1 L/h/70kg (48%) and 49.6 L/70kg (45%), respectively.

Conclusions: The validated model developed predicts that low doses of IDV/r provide efficacious plasma concentrations in the majority of patients; however, as body weight influences indinavir CL/F and V/F the risk of achieving toxic plasma indinavir concentrations significantly increases at 600/100 mg compared to 400/100 mg between 40 to 70 kg.

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Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

AUC0-3h of raltegravir is correlated to AUC0-12h: a novel approach for therapeutic drug monitoring of raltegravir

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Introduction: A pharmacokinetic-pharmacodynamic study of raltegravir in patients from phase II/III studies showed that (1): the $C_{\text{min}}$ of raltegravir could not be related to antiviral response, and (2): the geometric mean value of raltegravir concentrations determined in all available samples during 48 weeks of follow-up ("GMall") was weakly but statistically significantly related to antiviral response (Wenning et al. 48th ICAAC, Washington, 2008, abstract # H-4054). This GMall could be a better indication of the AUC over the 12h dose interval than the $C_{\text{min}}$. In agreement with this, McSharry et al. have found that the AUC/EC$_{50}$ of raltegravir was the pharmacodynamically linked parameter in a hollow fiber infection model system (McSharry et al. 10th International Workshop on Clinical Pharmacology of HIV Therapy, Amsterdam, abstract # O_09). Because GMall or AUC$_{0-12h}$ are not easily determined in daily clinical practice and monitoring of $C_{12h}$ appears irrational, we hypothesized that an abbreviated AUC may be sufficient to predict AUC$_{0-12h}$ for raltegravir. Also, we wanted to verify whether GMall is indeed reflecting AUC$_{0-12h}$.

Materials & Methods: We used steady state pharmacokinetic data from 2 healthy volunteer studies: one study investigated the interaction between combined use of raltegravir and pravastatin (Van Luin et al. submitted); the other one studied the interaction between raltegravir and lamotrigine (Van Luin et al. J Clin Pharmacol 2009). In the first study, a 12h curve was recorded after intake of 400mg of raltegravir alone (without pravastatin) on an empty stomach; in the second study 400mg of raltegravir was concomitantly given with 100mg of lamotrigine on an empty stomach (NB lamotrigine did not influence raltegravir plasma concentrations in that study). Raltegravir plasma concentrations were determined with a validated HPLC method with fluorescence detection. AUC$_{0-12h}$ and abbreviated AUCs were calculated with WinNonlin 5.2. Linear regression analyses were performed with SPSS version 16.0.

Results: Raltegravir plasma concentrations and AUC were available from 47 healthy subjects. The mean ($\pm$ SD) of GMall, $C_{12h}$, and AUC$_{0-12h}$ were 0.43 ($\pm$ 0.28) mg/L, 0.12 ($\pm$ 0.43) mg/L, and 6.89 ($\pm$ 4.56) h.mg/L, respectively. As expected, $C_{12h}$ was not significantly related to AUC$_{0-12h}$ or GMall: R-Squared: 0.000, F=0.010, p=0.92, and R-Squared 0.016, F=0.753, p=0.39, respectively. When analyzing other single time points, several of these had a strong correlation (R-Squared > 0.70) with AUC$_{0-12h}$: $C_{1.5h}$, $C_{2h}$, $C_{2h}$, C$_{3h}$, and C$_{4h}$. The best correlation was with $C_{2h}$: R-Squared 0.815, F=199; p < 0.001. A stronger correlation was found between AUC$_{0-3h}$ and AUC$_{0-12h}$: R-Squared 0.929, F = 568; p < 0.001.

Conclusions: We found that GMall reflects AUC$_{0-12h}$ for raltegravir. Also, the large intersubject variability in $C_{12h}$ and the lack of correlation between $C_{12h}$ and GMall is in line with the observations of Wenning et al. Finally, if we assume that AUC is the important PK parameter for raltegravir, then therapeutic drug monitoring should preferably use $C_{2h}$ or an abbreviated AUC$_{0-3h}$ to estimate reliably AUC$_{0-12h}$. These observations should be tested prospectively in another (patient) data set.

Conflict of interest financial relationship(s): DM Burger has received research grants from and has served as an advisor to Merck, and has been speaker on Merck sponsored scientific symposia

Abstract: 42

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Bilirubin levels in HIV+ patients switching from atazanavir (ATV) 400 mg QD to ATV 200 mg BID

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Background. Switching from ATV 400 mg QD to ATV 200 mg BID has been recently proposed by our group as a possible intervention to optimize ATV exposure in subjects not tolerating RTV boosted regimens.. However, no complete data of bilirubin levels throughout dosing interval has been yet obtained, being
unconjugated hyperbilirubinemia then most frequent ATV-related effect. Therefore, our aim was to study the changes of total, conjugated and unconjugated bilirubin levels associated with this switch.

Methods. Ten HIV+ patients administered with an ATV 400 mg QD-containing HAART gave informed consent to switch ATV to 200 mg BID for 10 days. On day 0 and 10 they underwent to repeated sampling over the dosing interval and plasma ATV concentrations were measured by an HPLC-UV validated method. Total, conjugated and unconjugated bilirubin levels were also measured at the same time points. Time concentration curve was performed for both ATV and bilirubin levels, and parameters were calculated by Non Compartmental Analysis. Wilcoxon test and geometric means ratio (95% confidence interval, CI) were used as appropriate.

Results. Switching to 200 mg BID had previously shown to led to a significant increase of ATV Ctrough value (ratio bid/qd 2.20, p=0.005), a significant decrease of Cmax value (ratio bid/qd 0.47, p=0.022) in plasma, while no difference in AUC (ratio bid/qd 0.81, p=0.445), nor in alpha elimination half life (ratio bid/qd 1.09, p=0.169) or other PK parameters was observed. Total bilirubin at Ctrough and AUC24 were slightly increased after switch (median 1.1 vs 1.92 mg/dl, ratio bid/qd 1.31, p=0.05; and 41,225 vs 54,30 , ratio 1.15, p=0.069, respectively), while maximum total bilirubin was unchanged (median 2.13 vs 2.67 mg/dl, ratio bid/qd 0.99, p=0.42). Unconjugated bilirubin at Ctrough and AUC24 were also increased after switch (median 1.2 vs 1.55 mg/dl, ratio bid/qd 1.31, p=0.058; and 35,065 vs 44,63 , ratio 1.15, p=0.093, respectively), while maximum unconjugated bilirubin was unchanged (median 1.9 vs 2.33 mg/dl, ratio bid/qd 1.24, p=0.32) Tmax of ATV concentrations and bilirubin levels (total and unconjugated) was 4 and 8 hours, respectively.

Conclusions. Concomitant increase of bilirubin levels related to switch to ATV 200 mg BID was not clinically significant, despite a significant increase of ATV Ctrough. Bilirubin time-concentration curve throughout dosing interval showed to be similar to pattern of ATV plasma concentrations, excepting a time-delay, as showed by longer Tmax. In this way, when ATV concentrations reach the maximum levels, maximum occupancy of UGT1A1 binding sites is likely to occurs, but bilirubine continues to accumulate until ATV unbound from UGT1A1, allowing bilirubin binding to UGT1A1 and subsequent elimination. This is coherent with higher affinity of occupancy of UGT1A1 binding sites by ATV. These data suggest that unconjugated bilirubin increase associated with ATV administration is rapidly reversible.

No conflict of interest

Abstract: 43

Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations

Population modelling of Maraviroc pharmacokinetic data when administered with and without Saquinavir/ritonavir in subjects with renal dysfunction

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Background: Maraviroc (MVC), approved for combination treatment of HIV-1 in subjects with CCR5-tropic virus, is a substrate for both CYP3A4 and Pgp and hence its pharmacokinetics are affected by many other antiretroviral agents which are inducers and/or inhibitors of these enzymes/transporters. In subjects with normal renal function MVC doses are adjusted accordingly, from 300 mg BID to 600 mg BID for inducers and to 150 mg BID for inhibitors. In the absence of CYP3A4/Pgp inhibitors renal elimination accounted for approximately 23% of total MVC clearance after a 30 mg IV dose. The presence of

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CYP3A4/Pgp inhibitors are expected to increase MVC exposure by both increasing absorption via Pgp effects and reducing non-renal clearance (CL_H) and first pass effects via pre-systemic CYP3A4, the latter making the relative contribution of the renal route to total clearance greater. Thus no dose adjustment of MVC would be expected in subjects with renal dysfunction in the absence of potent CYP3A4/Pgp inhibitors. However further dose interval adjustments were predicted to be necessary in subjects with renal dysfunction taking potent CYP3A4/Pgp inhibitors.

A study in a limited number of subjects with normal renal function and varying degrees of renal dysfunction was performed with MVC administered alone and/or with saquinavir/ritonavir (SQV/r), a potent inhibitor of MVC CL. These data were jointly modelled to quantify the effect of renal impairment on the pharmacokinetics of MVC in the presence and absence of SQV/r. The model was used for simulations to make dosage recommendation in scenarios not studied.

**Materials & Methods**: Forty one concentration time profiles (484 concentration measurements) were available from 29 subjects with varying degrees of renal dysfunction (normal, mild moderate, severe and end stage renal disease) for nonlinear mixed effects modelling with NONMEM (version VI). A semi-mechanistic model used in earlier analyses was updated for this analysis to better account for Cmax. The new model comprised a 4 compartment disposition model (based on IV data) with 2 absorption compartments with different lag times. Absorption was assumed to input into a liver compartment with metabolic clearance that may be inhibited by concomitant agents. Renal clearance from the central compartment was scaled using an individual’s baseline creatinine clearance (CLCR).

The model was used to simulate MVC concentration profiles and average viral inhibition for CLCR from 5-160 mL/min with varying doses/dose intervals for:

- Absence of inducers/inhibitors
- With weak/moderate inhibition e.g. with fosamprenavir/ritonavir
- With very potent inhibitors (SQV/r)

**Results**: The model predictions are in agreement with data from other studies and with noncompartmental analysis for this study. SQV/r increased absorption from 83% to 92% and decreased CL_H from 36 to 10 L/h

**Conclusions**: The use of the model for simulations allowed investigation of dosing and concomitant medication scenarios not studied. These simulations support the following MVC dose recommendations in renal dysfunction:

- If administered without potent CYP3A4 inducers, no dose interval adjustment required: 300 mg BID
- If coadministered with fosamprenavir/ritonavir: 150 mg BID
- If coadministered with potent CYP3A4 inhibitors (SQV/r, lopinavir/ritonavir, darunavir/ritonavir, atazanavir/ritonavir, ketoconazole): 150 mg QD

No conflict of interest

**Abstract: 44**

**Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity**

**Circulating levels of alpha-1-acid glycoprotein do not affect free Lopinavir pharmacokinetic profile**

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**Background**: Human immunodeficiency virus (HIV) induced chronic immune activation up-regulates circulating α-1-acid glycoprotein (AAG), an acute phase reactant, to which protease inhibitors (PI) bind with strong affinity. Circulating AAG level has been shown to correlate with plasma total PI concentrations, and differences in AAG levels likely contribute to inter- and intra-individual total drug pharmacokinetic (PK) variability. We speculated that changes in circulating AAG levels as HIV infection is treated may...
alter plasma free PI concentrations and impact the intracellular drug exposure. The objective of this study was to examine the relationship between plasma AAG levels and free lopinavir (LPV) PK profile.

**Materials & Methods:** In a prospective 2-stage PK study design, steady state plasma samples were obtained for LPV drug concentrations and AAG levels following initiation of lopinavir/ritonavir 400/100 mg BID- based antiretroviral therapy in treatment-naïve, adult patients. Levels of AAG in the serum were quantified using enzyme-linked immunosorbent (ELISA) method. The limit of quantification for this assay was 80 ng/mL, with intra-assay and inter-assay coefficient of variation (CV) of 4.3% and 7.0% respectively. Intensive PK samples were collected at weeks 2 and 16. Blood was drawn at 0 hr, and 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. Plasma free LPV concentrations were quantitated by ultrafiltration methods and PK analyses were performed using WinNonLin v5.2.1.

**Results:** Data was evaluable for 15 volunteers, with a mean entry age of 42.4±14.6 years, log10 HIV-RNA-PCR=5.24±0.4 c/mL, CD4+ counts=40±32 cells/L and AAG level=159.75±95.8 mg/dL (3-fold>historic control). Free LPV concentration was accurately determined and the percent CVs were ≤15% for all quality control levels. The detection limit was 0.025 ng/mL.

LPV protein binding was extremely high; 99.75±0.15%, and the area-under-the-concentration-curve (AUC12) for protein-free LPV was 0.24% of the AUC12 for total LPV. Large inter-patient variability was observed for total (AUC12 CV=46.94%) and the free (AUC12 CV=58.84%) drug concentrations. The Spearman coefficient of rank correlation between total and free LPV PK profile (AUC12 (R²=0.048; and Cmax (R²=0.194)) was weaker than previously observed. There were no significant correlations between plasma AAG levels and free LPV AUC12 (R²=0.004); or free LPV Cmax (R²=0.0002), (Figure 1). There was a 40% decline in plasma AAG level observed between week 2 and week 16 that was not associated with changes in free LPV AUC12, geometric mean ratios (90% confidence interval)=0.90 (0.71, 1.14); free LPV Cmax=0.94 (0.77, 1.16), and Free LPV Cmin=0.69 (0.37, 1.30) (Table 1).

**Conclusion:** Although percent protein binding was markedly elevated in this cohort of HIV-infected subjects with high circulating AAG levels, changes in AAG did not influence free LPV PK profile. The weaker relationship observed between total and free drug concentration probably reflects the selective impact of circulating AAG on the total but not the free drug concentration.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Relative Plasma Exposure (Total Concentration)</th>
<th>Relative Plasma Exposure (Free Concentration)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*Point Estimate</td>
<td>90% CI</td>
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<tr>
<td>AUC12 (ng*h/L)</td>
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<td>Cmax (ng/mL)</td>
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<td>C12 (ng/mL)</td>
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<td>CL/F (L/h)</td>
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<td>0.91 – 1.61</td>
</tr>
</tbody>
</table>

*a Antilogarithm of the difference (Period 2 – Period 1) of the least squares means for logarithms.

*Statistically significant

Relative Plasma Exposure and 90% Confidence Intervals for Total and Free Lopinavir Pharmacokinetic Profile, Comparing Period 2 (week 16) and Period 1 (week 2), n = 15.

No conflict of interest
Abstract: 45

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Plasma darunavir (DRV) and ritonavir (RTV) concentrations versus adherence in the MONET trial

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Background: The MONET trial evaluated DRV/r monotherapy versus DRV/r + 2NRTIs in patients with HIV RNA <50 copies/mL at screening. PK analysis was performed to determine whether low DRV plasma levels correlated with a higher risk of HIV RNA viraemia.

Methods: 256 patients with HIV RNA <50 copies/mL on current HAART for over 24 weeks (NNRTI based (43%), or PI based (57%)), switched to DRV/r 800/100 mg once daily, either as monotherapy (n=127) or with 2NRTIs (n=129). Three separate groups of patients were evaluated for DRV and RTV plasma PK levels by validated LS/MS-MS: Group 1 - patients with elevations in HIV RNA >50 copies/mL at two consecutive visits; Group 2 - patients with at least one HIV RNA >50 copies/mL; Group 3 - patients with HIV RNA consistently below 50 copies/mL during the trial. Adherence was evaluated at each visit, using the M-MASRI questionnaire. Multiple linear regression was used to correlate DRV and RTV plasma levels with time since last dose, treatment group, mean adherence and HIV RNA <50 copies/mL at each patient visit.

Results: In the primary efficacy analysis, HIV RNA <50 copies/mL by Week 48 (Per Protocol) was 86.2% versus 87.8% in the DRV/r and control arms, proving non-inferiority for DRV/r monotherapy versus triple therapy. There were 454 PK levels available at patient visits during the trial, from the 257 patients. DRV PK levels were highly correlated with the time since last dose (p<0.001) and adherence (p<0.001). Mean DRV PK levels were 1528 ng/mL for patients with up to 80% adherence, versus 3199 ng/mL for those with 100% adherence. RTV PK levels were also correlated with time since last dose (p<0.001) and adherence (p<0.001). Mean RTV PK levels were 66ng/mL for patients with 80% adherence, versus 111ng/mL for those with 100% adherence. Ritonavir levels fell significantly during the trial (p<0.001), from a peak of 135ng/mL at Week 12 to mean 65ng/mL at Week 48. RTV levels were slightly higher in the DRV/r monotherapy arm (mean 128ng/mL) versus the DRV/r + 2NRTI arm (mean 107ng/mL). In multivariate analyses, there was no significant correlation between DRV or RTV levels and the risk of HIV RNA levels above 50 copies/mL at each patient visit.

Conclusions: In the MONET trial, plasma PK levels of DRV and RTV correlated most strongly with time since last dose and mean adherence levels, but not with episodes of HIV RNA viraemia. This result confirms PK/PD analysis from other trials of DRV/r, which also showed no correlation between DRV plasma PK levels and the risk of HIV RNA viraemia.

Conflict of interest financial relationship(s): AH and MK have received consultancy payments from Tibotec. YD and CM are employees of Tibotec/Janssen

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Drug Interactions

Altered plasma levels of nevirapine after commencing rifampicin containing TB regimens in Malawi


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Introduction: The reduction in nevirapine exposure by rifampicin is well characterised in patients commencing antiretroviral therapy (ART). Conversely there are limited data on the impact of rifampicin on patients stable on nevirapine containing ART who develop TB. In such patients, the national treatment protocol for Malawi stipulates continuation of ART (without dose-modification) in addition to rifampicin-containing TB treatment for 6 months. A major concern is that rifampicin induces CYP450 enzymes leading to a reduction in nevirapine plasma levels.

Materials & Methods: We conducted a prospective cohort study in HIV positive patients stable on NVP containing ART (200mg twice daily, for at least 2 weeks) and who started rifampicin-based TB treatment. To determine the effect of rifampicin on plasma nevirapine levels, a truncated nevirapine PK profile (2ml of blood taken at 0, 1, 2, 4, 8 hours post dose) was performed in 10 male and 10 female patients on day 0 and day 14 after commencing TB treatment. In addition, a single trough level was measured on day 3 and 7 to determine how rapidly nevirapine levels declined. Nevirapine levels were measured by LC-MS at the University of Liverpool.

Results: Of the 20 patients, 2 had sub-therapeutic levels on day 0. Overall By day 14, there was a 22% reduction in the geometric mean AUC of nevirapine. Six (30%) patients had sub therapeutic nevirapine levels at day 14. This reduction occurred as early as day 3 with a progressive drop in geometric mean concentration.

Conclusions: Our data show that there is a moderate decrease in plasma nevirapine levels when rifampicin is commenced in a patient stable on ART. More research is required to determine the consequences on ART outcome and the value of changing nevirapine to efavirenz during TB treatment or increasing the nevirapine dosage temporarily.

No conflict of interest

Abstract: 47

Drug Interactions

The pharmacokinetics of Lopinavir in South African HIV-infected volunteers receiving rifampicin with adjusted doses of Lopinavir/ritonavir.

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Background: Rifampicin co-administration dramatically reduces plasma lopinavir concentrations. Doubling the dose of the capsule formulation of lopinavir/ritonavir (LPV/r) overcame this interaction in a healthy volunteer study. However, a subsequent study in healthy volunteers receiving the tablet formulation of LPV/r was stopped early due to high rates of hepatoxicity, possibly due to the sequence of administration (rifampicin was started first) or not escalating the LPV/r dose gradually. We evaluated the steady state pharmacokinetics of LPV in HIV-infected adults virologically suppressed on a LPV/r regimen who were given rifampicin and the dose of LPV/r gradually increased.

Materials & Methods: Steady state pharmacokinetics of LPV was evaluated at baseline in a cohort of HIV-infected adults virologically suppressed on a LPV/r regimen (400 mg/100 mg 12 hourly of the tablet formulation). Rifampicin 600mg daily was commenced and after a week the LPV/r dose was increased 1.5 times (600 mg/150 mg 12 hourly); after another week the dose of LPV/r was doubled (800 mg/200 mg 12 hourly). Intense pharmacokinetic sampling was done after each dose adjustment. Safety assessments were conducted throughout the study: liver enzymes were measured and symptoms assessed at least twice weekly.
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Results: 21 participants, of which 18 were female, were enrolled. The median (IQR) age was 36 (31-38) yrs and the mean (SD) CD4-count was 543±216 cells/mm³. The median (IQR) 12 hour LPV concentration (C₁₂) was 4.3 (3.5-6.5) mg/L at baseline; 0.2 (0.1-0.5) mg/L after 7 days of rifampicin; 1.7 (0.14-4.4) mg/L with 1.5 times the dose of LPV/r; and 3.7 (1.2-7.7) mg/L with double dose LPV/r. There were no significant differences in LPV AUC₁₂, C₀, C₁₂ and Cmax between the baseline and double dose LPV/r time points. Treatment was generally well tolerated with two participants developing asymptomatic grade 3/4 alanine aminotransferase elevation.

Conclusion: Doubling the dose of the tablet formulation of LPV/r overcomes the induction of rifampicin. Less hepatotoxicity occurred in our cohort of HIV-infected participants compared with those reported in healthy normal volunteer studies.

Conflict of interest
financial relationship(s): Funded by the European and Developing Countries Clinical Trials Partnership (EDCTP)

Abstract: 48

Drug Interactions

Evaluation of ritonavir-boosted Elvitegravir PK upon coadministration with a second potent CYP3A inhibitor, ketoconazole

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Introduction: Elvitegravir (EVG; GS-9137) is a potent HIV-1 integrase inhibitor in development for treatment of HIV infection. EVG is primarily biotransformed by CYP3A metabolism with glucuronidation as a secondary pathway. Clinically, EVG can be boosted with either low dose ritonavir (RTV or r; 100 mg) or the investigational pharmacoenhancer GS-9350 (150 mg) to increase its systemic exposure. This study was conducted to evaluate the impact of another potent CYP3A inhibitor such as ketoconazole (KTZ) on boosted-EVG exposures.

Methods: In a 15-day, fixed sequence, multiple dose study, healthy volunteers (n=18) received EVG/r (150/100 mg once-daily) for 10 days followed by EVG/r (150/100 mg once-daily) plus KTZ (200 mg BID) for an additional 4 days. Pharmacokinetic (PK) assessments were conducted under steady state conditions (day 11 and day 15) for EVG and KTZ. Based on the historical data, lack of PK interaction boundaries of 70–143 % were defined for EVG. KTZ PK was explored relative to historical controls. In addition, midazolam (MDZ, 5 mg po) a CYP3A probe substrate was administered on day 1, 11 and 15 to delineate between CYP3A versus UGT mediated change in EVG apparent clearance as KTZ has been shown to also affect UGT metabolism. Safety was assessed by routine clinical and laboratory monitoring throughout the study.

Results: Eighteen subjects enrolled and completed the study. Study treatments were generally well tolerated in these healthy volunteers. Within the PK analyses set (n=18), concurrent administration of EVG/r and KTZ resulted in modest increases in exposure of EVG; the geometric least-squares means ratio (GMR) and associated 90% confidence interval (CI) for Cmax, AUCτau and Cτau was 117 (104, 133), 148 (136, 162) and 167 (148, 188) respectively. KTZ increased the mean exposure of EVG in the setting of minimal additional inhibition of CYP3A metabolism as measured by the probe MDZ as well as CYP3A-mediated metabolite of EVG (M1). The GMR (90%CI) of MDZ on administration with EVG/r plus KTZ versus EVG/r for Cmax, AUCinf and AUClast was 100 (90.3, 111), 117 (104, 132), 107 (93.5, 122) respectively. No differences in the plasma concentrations (values below the limit of quantitation at all time points; LLOQ 20 ng/mL) of M1 were noted in treatment of MDZ with EVG/r or EVG/r plus KTZ. KTZ PK was similar to published historical controls.

Conclusion: Addition of supra-therapeutic, twice-daily KTZ, a strong CYP3A and UGT inhibitor resulted in only incremental inhibition of the CYP3A and
modest increases in EVG exposure; thus, clinically relevant drug interactions with boosted EVG and additional CYP3A metabolic inhibitors are not expected. For KTZ, consistent with its dosing recommendation with other RTV-boosted agents, a maximum dose of 200 mg once-daily is recommended when used with boosted-EVG.

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

Abstract: 49

Drug Interactions

Exposure-related effects of unboosted atazanavir on the pharmacokinetics of raltegravir in HIV-1 infected patients

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Introduction: Raltegravir (RAL) is the first of a new class of antiretroviral drugs (integrase inhibitors), recently approved for first-line treatment in HIV-1 infected patients. This drug is primarily metabolized by glucuronidation mediated by the uridine diphosphate glucuronosyl transferase 1A1 isoenzyme (UGT1A1). Atazanavir (ATV), a strong inhibitor of UGT1A1, has shown to increase plasma levels of RAL approximately by 50% in healthy volunteers. The extent of such interaction has not been extensively studied in HIV infected patients.

Materials & Methods: A steady-state 12h intensive pharmacokinetic study was carried out in HIV-infected adults (≥18 years) treated with a dual regimen of RAL 400 mg BID plus ATV 300 mg BID. RAL and ATV concentrations in plasma samples were determined by a validated LC-MS/MS method. In order to assess the RAL plasma increase via ATV inhibition of UGT1A1, PK parameters in our patients were compared with the ones from HIV-infected historical controls on 10-day RAL monotherapy. The AUCs for both drugs were estimated by the trapezoidal rule, correlations were performed by linear regression plot and comparison-between groups by unpaired T-test or Mann-Whitney, as deemed appropriate.

Results: A total of 22 HIV-1 infected patients completed the study. Mean (±SD) age was 45 (±7) years, 19 were Caucasians and 17 male. Mean Body Mass Index (±SD) was 24 (±5) kg/m2. Two patients had RAL AUC0-12 >35000 ng•h/mL and they were excluded from the analysis. RAL geometric mean (GM) AUC0-12 (90% CI) was 6166 (2772-15615) ng•h/mL and was comparable to historical HIV controls, whose GM AUC was 6851 (3667-12835) ng•h/mL. However, ATV exposure showed a high variability [GM AUC0-12 (90% CI) = 14622 (4052-45707) ng•h/mL with CV = 68.3%]. Linear regression analysis showed a highly significant correlation between RAL and ATV AUC0-12 (r=0.600, p=0.005) and patients with ATV AUC0-12 >14622 ng•h/mL had a 2-fold higher exposure to RAL compared with patients with lower values [RAL GM AUC0-12 (90% CI): 8738 (3921-16060) vs 4027 (1823-12172) ng•h/mL, p=0.021]. A similar trend (despite a larger distribution) was observed using RAL and ATV trough concentrations [r=0.452, p=0.039 for linear regression; RAL GM Ctrough (90% CI): 235 (47-876) vs 440 (113-1290) ng/mL, p=0.112].

Conclusions: Overall, concomitant administration of unboosted ATV did not significantly increase RAL exposure. However, a wide inter-patient variability was observed for both drugs and the patients with higher ATV exposure had higher RAL plasma levels, confirming the expected booster effect.

No conflict of interest
Abstract: 50

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Meta-analysis of pharmacokinetic-pharmacodynamic relationship of integrase inhibitors following short-term monotherapy

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Introduction: Integrase inhibitors (INIs) are a potent new class of antiretrovirals. S/GSK1349572 (572) and S/GSK1265744 (744) are two once daily, unboosted INIs currently in clinical development which have demonstrated unprecedented antiviral activity during 10-day monotherapy studies. Exposure-response relationships have been characterized for 572, S/GSK364735 (735), and elvitegravir (ELV), but not raltegravir (RAL) in short-term monotherapy studies. In order to understand the similarity or disparity of the PK/PD relationship across INIs, a meta-analysis was performed based on pooled published and GSK PK/PD data on these INIs.

Methods: PK parameters (AUC0-τ, Cmax, and Cτ) and reduction in plasma HIV RNA (log10) from baseline to Day11 for RAL, ELV, 572, 735, and 744 were extracted (treatment means) from publications or GSK clinical trials. Inhibitory quotients (IQs) were calculated using these PK parameters divided by the in vitro protein-binding adjusted IC90 for each compound. Relationship between IQs (IQ_AUC0-τ, IQ_Cmax, and IQ_Cτ) and PD measures (reduction in plasma HIV-1 RNA) was assessed using various Emax models. Model selection was based on Akaike Information Criteria value.

Results: When PK measures are presented as IQs, all INIs showed similar PK-PD relationships, and data from RAL coincide with those from all other INIs. The relationship between exposure (IQ) and reduction in plasma HIV-1 RNA (log scale) from baseline for pooled INIs data is best described by an Emax model with IQ on linear scale, Emax=2.25log10 with 95% confidence interval of [2.06log10, 2.44log10], and Hill Coefficient (γ)=1. IQ_Cτ (IQ calculated as Cτ divided by IC90) was the PK parameter that best predicted reduction in plasma HIV RNA (log scale) from baseline, compared to IQ_AUC0-τ and IQ_Cmax. EC50 for IQ_Cτ was estimated at 0.28 [0.16, 0.40]. RAL failed to show a PK/PD relationship due to the narrow dose/exposure range studied and highly variable PK.

Conclusion: The antiviral activity of INI class appears to be primarily driven by Cτ. IQ_Cτ was the best predictor of antiviral activity in short-term monotherapy for all INIs. 572 and 744 demonstrated the largest declines in viral load compared to other INIs at the highest doses studied in short-term monotherapy and the superior potency is attributable to the high IQs achieved. The PK/PD relationship of INIs identified in this meta-analysis has been successfully utilized in cost-effective Proof of Concept study design with optimal dose selection.

Conflict of interest financial relationship(s): The authors of this abstract are current employees at GlaxoSmithKline

Abstract: 51

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity

Population pharmacokinetic and viral dynamic modeling of S/GSK1349572 in patients with HIV infection

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Background: S/GSK1349572 (572) is an unboosted, once daily integrase inhibitor (INI) currently in PhIIb clinical trials for the
treatment of HIV infection. The aim of this analysis was to develop a population pharmacokinetic-viral dynamic model to characterize the relationship between plasma 572 concentrations and HIV viral load in HIV infected patients.

Materials & Methods: Plasma concentration (947 samples) and viral load (404 observations) data were obtained from a PhIIa study in HIV-infected INI naïve patients (n=35). The analysis was performed using a mixed-effects modeling approach with the first-order conditional method with interaction (FOCEI) of NONMEM. A two-stage modeling approach was applied to characterize the population pharmacokinetics (PK) of 572 and its effect on viral dynamics. A viral dynamic model involving uninfected, actively infected, and latently infected CD4+ cells was used to characterize the dynamics of HIV-1 virus and the antiviral effect of S/GSK1349572. The model utilized the observed baseline viral load with added variability to account for measurement errors. Given the large number of the parameters in the viral dynamic model, the majority of parameter were fixed to the literature values (Funk et al 2001; Phillips 1996) with viral reproductive ratio (R0) and death rate of actively infected CD4+ cells (dA) being estimated, birth rate of CD4+ cells (λ) and viral infectivity constant (β) derived. A visual predictive check was implemented for final model evaluation.

Results: 572 PK was best described by a 2-compartment disposition model with a first-order absorption and the estimated typical values of clearance (CL/F) and volume of distribution (V/F) are 1.19 L/hr (RSE=7.6%) and 17.9 L (RSE=7.4%), respectively. CL/F was shown to increase with age. The estimated typical values of R0 and dA were 10.3 (RSE=12.3%) and 0.65 1/day (RSE=6.7%), respectively. Geometric means of the derived λ and β were 0.64 cells/µL/day and 0.0018 day/(copies/µL), respectively. The inhibitory effect of 572 on β was best described by an Emax model with IC50 of 72.7 ng/mL (RSE=38.7%). In addition to the reduction of β , modeling suggested that 572 further suppressed viral production by inhibiting activation of latent infected cells with unintegrated proviral DNA (96% inhibition, RSE=2.5%). The final model predicted that daily doses of 50mg S/GSK1349572 would reduce viral load by an average of 2.5 log drop (95%CI=2.0-3.0) in HIV-infected antiretroviral naïve patients on Day 10, in agreement with the observed 2.5 mean log drop (95%CI=1.9-3.2) from the PhIIa study at the same dose.

Conclusions: The developed pharmacokinetic and viral dynamic model adequately described the relationships between plasma 572 concentrations and viral load in HIV-infected INI naïve patients. The model revealed that INIs exhibit rapid and potent effect to suppress viral growth through inhibition of multiple mechanisms in the life cycle of HIV. The integrated population PK-viral dynamic model will be further validated using data from PhaseIb studies.

Conflict of interest financial relationship(s): I’m an employee of GlaxoSmithKline

Abstract: 52
Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity
Modeling and clinical trial simulation to support dose selection of S/GSK1349572 in phase IIB studies

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Introduction: Mathematical models have been widely used for understanding HIV virus and CD4 cell life cycles and to aid development decisions, e.g. dose selection. S/GSK1349572 (572) is an unboosted, once daily integrase inhibitor (INI) and demonstrated unprecedented antiviral activity in a 10-day monotherapy study. PhaseIb studies are currently ongoing to evaluate the long-term efficacy and safety of 572 at doses ranging at 10-50mg once daily. A PK-viral dynamic model was developed to characterize the relationship between plasma 572 concentrations and HIV viral load based on data from the monotherapy study and clinical trial simulations were performed to
support dose selection in Phase2b clinical trials.

**Material & Methods:** 572 plasma concentration and plasma HIV-1 RNA data from the 10-day monotherapy study were used to fit a modified viral dynamic model [FUNK 2001] using a mixed-effects modeling approach. The equivalent constant concentration (ECC) based on observed drug concentration was used in the modeling to obviate the need for compartmental PK modeling [Poland 2008]. Visual predictive check was implemented for final model evaluation. Clinical trial simulations using Trial Simulator© were performed to predict short- and long-term response rate (e.g. reduction in HIV-1 RNA, % subject with <50 c/mL of HIV-1 RNA) of 572-containing combination therapy in different patient populations including treatment-naïve, treatment-experienced/INI-naïve, and INI-resistant. Simulations were conducted for various dosing regimens of 572 as well as scenarios for various baseline HIV-1 RNA, baseline resistance, and background therapies.

**Results:** A PK-viral dynamic model was developed and adequately described the relationship between ECC and changes in plasma HIV-1 RNA over time observed in the Phasella study. Trial simulations suggested that 572 (1) is likely to show equivalent long-term (48 weeks and beyond) antiviral response rates at once daily doses of ≥10mg; (2) is likely to show similar response rate at once daily doses of ≥10mg compared to RAL 400mg BID in treatment-naïve and treatment-experienced/INI-naïve, and INI-resistant patients. In INI-resistant patients with no active agent in the background regimens, response rate is primarily driven by baseline resistance to INI as well as 572 exposure; 572 50mg once daily dose is predicted to produce good short-term response rate in majority of the patients and higher doses may be required for INI baseline resistance greater than 10 folds above wild-type virus.

**Conclusion:** Integrated PK-viral dynamic modeling and trial simulation is a useful and powerful tool for clinical trial design and decision-making. The analysis predicted that 572 will exhibit desirable long-term clinical efficacy in a broad range of HIV-infected patient populations and supported the selection of 572 doses ranging from 10mg to 50mg once daily for further evaluation in PhaseIIb studies.

**Conflict of interest**
financial relationship(s): The author of this abstract is an employee at GlaxoSmithKline

**Abstract:** 53

**Therapeutic Drug Monitoring**

**Adherence to TDM guidelines in The Netherlands: combined use of lopinavir/ritonavir plus an NNRTI as an example**


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**Background:** In 2005, the Dutch Association of Physicians in AIDS issued guidelines for the treatment of HIV-infected patients, including recommendations for Therapeutic Drug Monitoring (TDM). The guideline recommended TDM in all patients who started combination antiretroviral therapy (cART), but also for specific indications, such as drug-drug interactions. A well-known example of a drug interaction is the use of lopinavir/ritonavir with a non-nucleoside reverse transcriptase inhibitor (NNRTI). We evaluated the use of TDM in patients who started the combination of lopinavir/ritonavir + an NNRTI before (2004), during (2005-2006) and after (2007-2008) introduction of the guideline.

**Methods:** From the ATHENA observational cohort study, we selected all patients who started lopinavir/ritonavir + an NNRTI between 2004 and 2008.
Adherence to the guideline was defined as the presence of at least one lopinavir plasma concentration in ATHENA between week 1 and 12. Patients who discontinued use of lopinavir/ritonavir + an NNRTI within three weeks were excluded. We used multivariable logistic regression modeling to identify factors associated with adherence to the TDM guideline. Furthermore, we assessed the effect of TDM on virologic response, which was defined as a viral load below 50 copies/mL at week 48. We used an observed-failure approach in which patients who discontinued the combination due to virologic failure were considered failures at subsequent time points, whereas patients who discontinued due to other reasons were censored from that moment onwards. All data were analyzed with SPSS, version 16.0.1.

Results: A total of 257 patients started lopinavir/ritonavir plus an NNRTI between 2004 and 2008. TDM of lopinavir was performed in 120 patients (46.7%). The use of TDM increased significantly from 32.4% in 2004 (pre-guideline) to 55.3% during introduction of the guideline in 2005-2006. In 2007-2008, the use of TDM remained stable (49.0%). Multivariable logistic regression analysis demonstrated that patients in large non-academic outpatient clinics (defined as > 220 patients under care) were less likely to receive TDM compared to patients in academic clinics (adjusted odds ratio (OR) (95% CI) 0.24 (0.10-0.57), p=0.001). Furthermore, treatment-experienced patients with a detectable viral load at baseline were more likely to receive TDM compared to patients with a detectable viral load at baseline (adjusted OR (95% CI) 2.62 (1.08-6.40, p=0.034). At week 48, 79.6% of the patients who received TDM achieved virologic response, compared to 73.9% of the patients who did not receive TDM (p=0.50). At week 48, a total of 18 patients had discontinued lopinavir because of toxicity or patient’s choice: 2.5% of the TDM group and 10.9% of the non-TDM group (p=0.008). In agreement with this, patients who received TDM had a significantly lower hazard ratio (HR) for toxicity-induced lopinavir discontinuations in a multivariable Cox-proportional hazard analysis (adjusted HR (95%CI)=0.16 (0.036-0.71), p=0.016).

Conclusions: The introduction of TDM guidelines resulted in moderately increased use of TDM in patients who started lopinavir/ritonavir plus an NNRTI. The hospital-type and the patient’s pre-treated status appeared to be important predictors for the use of TDM. Our data suggest that TDM in this scenario may help to prevent toxicity-induced lopinavir discontinuations.

No conflict of interest

Abstract: 54

The international interlaboratory quality control program for measurement of antiretroviral drugs in plasma: a global proficiency testing program

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Introduction: The International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma was initiated in 1999 by Radboud University Nijmegen Medical Center, The Netherlands. After two pilot years, the Program was continued in collaboration with the Dutch Association for Quality Assessment in Therapeutic Drug Monitoring and Clinical Toxicology (www.kkgt.nl). The aim of this analysis was to evaluate the first 10 years of the Program and to determine variables associated with reporting of less accurate results.

Methods: For each year of the Program, two rounds were organized in which blind samples were shipped to participants containing either a low, medium, or high concentration of each antiretroviral drug. The Program started with ritonavir, saquinavir, indinavir and nelfinavir in 1999; amprenavir, lopinavir, nevirapine and...
efavirenz were added in 2001. Most recent additions to the Program were atazanavir (2005), tipranavir and darunavir (both in 2009). Any result that deviated more than 20% from the spiked concentration was defined as inaccurate. For this analysis, data on darunavir, tipranavir and ritonavir were excluded due to insufficient numbers.

Results: By the end of 2009, the number of laboratories participating in the Program had increased to 56; 44 (79%) laboratories are located in Europe. The remaining 12 laboratories are spread over four continents: North America (n=8), Asia (2), Africa (1), Australia (1). Within Europe, the Program is dominated by laboratories from The Netherlands (n=11) and Spain (10). In 2008, a small majority of the labs (52%) was using HPLC as the analytical method, with the remaining 48% using LC-MS. A total of 12,798 test results was available for analysis, of which 2,104 (16.4%) were reported as inaccurate. Performance was best for samples containing nevirapine (mean (± SD) of inadequate scores per round: 11.1% ± 5.5%) and lopinavir (11.9% ± 6.5%), and worst for indinavir (18.7% ± 12.5%), atazanavir (18.9% ± 9.9%), saquinavir (19.6% ± 8.8%) and nelfinavir (21.3% ± 11.7%). Amprenavir and efavirenz scored in between. High and medium concentrations were less frequently reported as inaccurate than low concentrations: 13.5%, 13.0%, and 22.4%, respectively. Although the overall performance of the laboratories varied per year, a trend was visible for improvement over time, with 19.9% of the results being inaccurate in 2002 (n=20 laboratories) to 15.7% in 2009 (n=56 laboratories). As an example of this “learning curve”, laboratories that already participated in 2002 tended to have a better performance in analyzing nelfinavir in 2009 (on average 27.8% of the results were inaccurate) than laboratories who joined the program after 2002: (32.9% inaccurate results).

Conclusions: The Program provides a proficiency testing program in which laboratories are alerted to potential analytical errors while performing Therapeutic Drug Monitoring. Laboratories should put more effort in adequately analyzing concentrations of antiretroviral drugs with low minimum effective concentrations.

No conflict of interest

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**Abstract: 55**

**Therapeutic Drug Monitoring**

**Simultaneous determination of 13 antiretrovirals in cerebrospinal fluid by LC-MS/MS: a case report of meningoencephalitis in HIV-1 infected patient**

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**Introduction:** Highly active antiretroviral therapy is effective for the treatment of central nervous system neurological disorders including acute HIV meningoencephalitis. Diffusion through the blood-brain barrier differs among antiretroviral drugs and as a consequence, cerebrospinal fluid (CSF) concentrations are highly variable. Therefore, a sensitive and specific method for the quantification of antiretroviral concentrations in CSF would be required. A liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was developed for the quantification of amprenavir, atazanavir, darunavir, etravirine, efavirenz, indinavir, lopinavir, maraviroc, nevirapine, raltegravir, ritonavir, saquinavir and tipranavir in CSF. We report the case of a patient who developed HIV-1 meningoencephalitis and the improvement in virologic response by using CSF drug monitoring.

**Material and Methods:** A liquid-liquid extraction using sodium hydroxide (0.1N) and a solution of hexan/ethyl acetate (25:75, v/v) was applied on 100µL of CSF sample containing internal standards (ritonavir analog, methyl indinavir, lopinavir-d8 and maraviroc-d6). Chromatographic separation was achieved on a C18 HPLC column (Waters Sunfire 100x2.1mm, 3.5µm). A mobile phase gradient containing water/ammonium acetate 2mM/formic acid 0.1% and methanol/formic acid 0.1% was performed at a flow rate of 0.3mL/min. A LC-MS/MS
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system (Waters Quattro Premier XE) was used for the determination of antiretroviral concentrations.

Results: This method showed an excellent linearity for all calibration curves ($r^2>0.998$). The lower limit of quantification was established at 1 ng/mL except for maraviroc at 0.6 ng/mL with precision and accuracy within ±20% and 80-120% for all analytes. Intra- and inter-assay precision and inaccuracy ranged from -12.6% to 14.8% and -7.8% to 14.3%, respectively. No matrix effect was observed for any of the antiretrovirals studied. We report a case of a 47-year-old woman with HIV/HCV coinfection diagnosed in 1987. She had not been under treatment since 1995. In March 2009, the patient was admitted for clinically acute meningoencephalitis secondary to HIV infection. Plasma and CSF viral load were 5.64 and 5.65 log 10 copies/mL respectively, with a CD4 cell count of 410 cell/µL. No mutation associated with drug resistance in plasma and CSF was found. Treatment was initiated with tenofovir, emtricitabine and raltegravir. After 8 days, a 1 log 10 decrease in viral load was observed in plasma but not in CSF and no clinical improvement was noted. Raltegravir plasma and CSF concentrations were 178 ng/mL and 21 ng/mL, respectively. Therapy was switched to zidovudine, lamivudine and lopinavir/ritonavir. In November 2009, plasma viral load was <1.4 log 10 copies/mL and CSF viral load was still detectable at 1.58 log 10 copies/mL. The lopinavir plasma and CSF concentrations were 5055 ng/mL and 8 ng/mL, respectively. Lopinavir/ritonavir treatment was switched to darunavir/ritonavir because of persistence of a low viral replication in CSF associated with low lopinavir CSF concentration below the IC50 value for wild-type virus.

Conclusions: A rapid, specific and sensitive LC-MS/MS method was successfully developed in human CSF to determine 13 antiretrovirals. Quantification of antiretroviral CSF concentrations may contribute to a better management of neurological complications in HIV-infected patients.

No conflict of interest

Abstract: 56

Therapeutic Drug Monitoring

Pharmacological evaluation of new antiretroviral drugs in the elderly HIV-1 infected people

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Background: The pharmacokinetics of antiretroviral agents may be altered due to age-related decrements in hepatic and renal function. The elderly may be more sensitive than younger people to antiretroviral drug toxicity. A better understanding of the pharmacokinetics of antiretroviral agents in the elderly is of importance for the successful management of complex antiretroviral regimens in this population. In the present study, we compared the PK profile of atazanavir (ATV), darunavir (DRV), raltegravir (RAL) and efavirenz (EFV) in younger and older HIV-1 infected patients.

Materials and Methods: From INMI TDM database, we examined HIV-1 infected patients treated with EFV (19 patients), ATV/r (28 patients), RAL (47 patients) or DRV/r (40 patients) for whom, because of toxicity or viro-immunological failure, a therapeutic drug monitoring was performed. Blood samples were collected for the evaluation of antiretrovirals’ trough plasma concentrations. Viro-immunological and safety parameters were also evaluated. Drug plasma concentrations were measured using a validated high-performance liquid chromatography method. For analysis, patients treated were divided in 3 groups according to the age (group A: ≤39 years; group B: 40-49 years; group C: ≥50 years).

Results: One hundred thirty-four HIV-1 infected patients, for a total of 249 samples, were analyzed. All patients were Caucasian, 65% were male. At the time of PK sampling, the median age of patients was 46 years (range: 20-76 years),
median body mass index (BMI) 23 kg/m\(^2\) (range 17-38), median CD4 cell count 334/mm\(^3\) (range 9-1416). Therapeutic drug monitoring was requested in the 70% of cases because of viro-immunological failure and in the 11% for drug-related toxicity. CD4 cell count and BMI were similar among the 3 groups for each single drug. Mean ATV C\(_{\text{trough}}\) resulted lower in elderly patients than young (1013 ±808 vs. 1968 ±1143 vs. 1483 ±11143 ng/mL, in group C, B and A, respectively), but this difference was not statistically significant. Patients treated with RAL presented similar mean C\(_{\text{trough}}\) irrespective to the age (210 ±232 ng/mL in group A, 263 ±307 ng/mL in group B and 177 ±243 ng/mL in group C). Similarly, patients treated with DRV presented comparable C\(_{\text{trough}}\) among the 3 groups (2633 ±1819 ng/mL in group A, 3077 ±2180 ng/mL in group B and 2581 ±1402 ng/mL in group C). Otherwise, patients group C (≥50 years) treated with EFV presented significantly higher mean C\(_{\text{trough}}\) than those in group A or B (2950 ±14644 ng/mL vs. 2148 ±186 ng/mL and 2097 ±1069 ng/mL, in group C, B and A, respectively; p=0.05). No linear correlation between age and drug concentration was found for any drug.

**Conclusions:** Atazanavir/r, raltegravir and darunavir pharmacokinetics appeared to be unaffected by age in HIV-1 infected patients. Different studies demonstrated a correlation between EFV plasma concentration and neurological adverse event during EFV-containing HAART. In the present study, we observed that efavirenz C\(_{\text{trough}}\) is significantly higher in elderly than young people, with a possible increased risk for neurological toxicity. Special caution, particularly in presence of co-medications, is necessary to avoid risk of additive toxicity.

No conflict of interest

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**Abstract: 57**

**Therapeutic Drug Monitoring**

**Hepatitis/HIV co-infection without hepatic impairment does not alter lopinavir plasma concentrations in HIV-1 infected adults**

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**Introduction:** As hepatitis co-infection may influence the cytochrome P450 mediated metabolism of HIV protease inhibitors, our objective was to investigate lopinavir/ritonavir (LPV/RTV) plasma concentrations in HIV-1 infected adults with chronic hepatitis co-infection (CHILD-PUGH status A).

**Material & Methods:** Steady-state 12-hour LPV/RTV pharmacokinetic profiles were assessed (LC-MS/MS analysis) in chronically HBV/HCV and HIV co-infected patients (group1, n=15), taking LPV/RTV 400/100mg BID plus reverse transcriptase inhibitors, and were compared to that of patients without hepatitis (group2, n=57). Individual (gender, age, weight, BMI), pharmacological (formulation, co-medication), clinical (Hepatitis co-infection, Child-Pugh-Status) and virologic/immunological parameters (baseline HIV-viral load/CD4 cell count) were included in the multivariate analyses.

**Results:** The mean (95%CI) LPV minimum/maximum concentrations, C\(_{\text{min}}\)/C\(_{\text{max}}\), area under the concentration-time curve, AUC, and total oral clearance, CL\(_{\text{tot}}\), of group 1 vs. group 2 were 3388 (2352-4452) vs. 3746 (3176-4316) ng/mL (p=.529), 6716 (4956-8476) vs. 7497 (6718-8276) ng/mL (p=.399), 60483 (46413-74552) vs. 69138 (61774-76502) ng/12h/mL (p=.261) and 128 (101-154) vs. 114 (99-130) mL/min (p=.370). Cofactors for high LPV plasma concentrations (>2-fold SD of the mean) were a higher age (>50 years, p=.010) and the use of the film coated tablet (FCT, p=.028) vs. the former soft-gel capsule. Chronic HBV/HCV-co-
infection, gender, Caucasian or black African ethnicity, baseline HIV-RNA PCR or CD4 cell count were not related to altered LPV plasma concentrations in this retrospective cohort analysis.

**Conclusion:** HBV/HCV co-infection without signs of hepatic impairment does not alter LPV pharmacokinetics in HIV-1 infected adults. A significant increase of LPV plasma concentrations in elderly patients taking lopinavir/ritonavir FCT deserves further clinical attention.

**No conflict of interest**

**Abstract:**

**Therapeutic Drug Monitoring**

**Undetectable Ritonavir plasma concentrations in different boosted PI-based regimens as a marker of non-adherence: analysis of a large TDM registry**

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**Background:** Suboptimal adherence to antiretroviral drugs is frequent and it can dramatically affect HAART durability. Patients' intolerance to boosted protease inhibitors could lower their compliance to medication and lead to missing doses and selective avoidance of ritonavir (due to its capsule size, side effects, and storage requirements). The different patterns of non-adherence and the frequency of such behaviors are seldom detected in the clinical practice: TDM can be a useful tool in this setting. Therefore aim of our study was to evaluate the prevalence of undetectable ritonavir (RTV) levels in a cohort of PI-treated patients.

**Materials & Methods:** Our TDM registry was searched out for patients administered with boosted PIs (ATV/r 300/100 qd, DRV/r 600/100 bid and LPV/r 400/100 bid). After excluding potential confounding factors (interacting drugs, pregnancy, delayed sampling later than 14 hours for twice daily regimens and 26 for once daily ones, according to reported time of last intake) the prevalence of undetectable ritonavir levels were analyzed. Patients were stratified as "non-adherent" (missed more than one dose: both RTV and PI undetectable), "partially adherent" (missed last dose or selectively non-adherent to RTV: RTV undetectable but detectable PI concentrations) and "adherent" (both RTV and PI detectable). Limits of detection of our validated HPLC assay were 9.8, 58.6, 11.7, and 19.5 ng/ml for RTV, LPV, ATV and DRV, respectively.

**Results:** 2486 samples from 723 patients were analyzed (median 2 sample for patient). 359 (68.3%) were male, of mean age (±SD) 43.7 (±9.3) years and weight 68.4 (±13.1) Kg. 53.8% of them were on LPV/r, 30.6% on ATV/r and 15.6% on DRV/r. Undetectable RTV was found in 55 (4.8%), 73 (9.8%) and 21 (3.6%) of LPV, ATV and DRV samples, respectively. Of those 69.1%, 19.2% and 42.9% showed concomitant undetectable PI concentrations. Therefore, 14 (1.9%) and 59 (7.9%) of samples of ATV/r, 9 (1.5%) and 12 (2.0%) of DRV/r and 38 (3.3%) and 17 (1.5%) of LPV/r were categorized as non-adherent and partially adherent, respectively. 115 patients (15.9%) had RTV below the limit of detection at least one time: 1.2 episodes/patients (range 1-5). ATV intakers had a higher prevalence of non-adherence episodes: 24.4% vs. 11.6% of LPV/r and 14.2% of DRV/r recipients [ORs 1.48 (95% CI 1.18-1.85) and 1.60, (95% CI 1.01-2.54) resp.].

**Conclusions:** In our TDM registry, measurement of RTV concentrations showed to be a possible marker of recent non-adherence, allowing to detect a not negligible discordance with reported intake of boosted PI. In fact, RTV resulted undetectable in 15.9% of patients, with higher prevalence in patients on ATV compared to LPV and DRV. Moreover, combined analysis with detectability of boosted PI could allow to discriminate between different patterns of recent non-adherence.

**No conflict of interest**
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Therapeutic Drug Monitoring

Pharmacokinetics of Raltegravir, Etravirine and Maraviroc regimen in the clinical setting.

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Background: Treatment of multiexperienced patients with the association of Raltegravir (RGV), Etravirine (ETV) and Maraviroc (MVC) has showed high efficacy both as virological suppression rates and immunological recovery. This NRTIs and PIs-sparing regimen has also a potential promising applicability in selected groups of patients. Interactions between ETV and RGV and between RGV and MVC emerged in studies performed in healthy volunteers. Aim of current analysis is to investigate in the clinical setting the PK features of this novel antiretroviral combination.

Materials & Methods: Multiexperienced patients placed on RGV (400 mg bid) plus ETV (200 mg bid) plus MVC (600 mg bid) and not taking interacting comedications were included in the analysis. Samples were withdrawn 12 hours after drug intake at 4, 12, 24, 36 and 48 weeks from baseline. After being stocked a -20°C they were processed through a validated HPLC-PDA assay with limit of detection of 11.7 ng/ml (etravirine and raltegravir) or through a validated HPLC-UV assay with limit of detection of 5 ng/ml (maraviroc). Average concentration of all available samples was calculated for every single patient. Data are expressed as mean (± standard deviation).

Results: Thirty-seven patients were enrolled. 35 (94.6%) were male, aged 49 (±8.2) years and with a mean BMI of 23.3 (±3.2) Kg/m². 126 samples (mean 3.4 per patient) were withdrawn after 12.5 (±1.6) hours from drug intake. Mean ETV, RGV and MVC trough concentrations were 515.2 (±276.8), 442.7 (±439.3) and 91.4 (±76.8) ng/ml. Intra-patient and inter-patient variability were 46% and 90% for ETV, 77% and 100% for RGV, 63% and 80% for MVC, respectively. Maraviroc trough levels were below the suggested target concentration (50 ng/ml) in 80 (37.2%) of samples and, at least once, in 25 (67.5%) patients.

Conclusions: In this regimen adequate ETV trough concentrations are achieved and similar to the ones previously reported in literature (446-545 ng/ml). RGV plasma levels seem to be higher than the previously reported in other drug associations (142 ng/ml) and a lower intra-patient variability emerged. MVC exposure seems higher than the one achieved through the standard dose of 300 bid (37.2-60 ng/ml) but a significant proportion of patients had trough concentrations below the suggested target. The analysis of the clinical impact on the long-term efficacy of this novel regimen are currently ongoing.

No conflict of interest

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Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is of benefit in routine clinical practice

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Background: Therapeutic drug monitoring (TDM) is a valuable tool used to optimise antiretroviral (ARV) therapy and assist in the management of selected patients. The BHIVA guidelines recommend that TDM may be considered in certain situations e.g. drug-drug or drug-food interactions; pregnancy; children; suspected non-adherence; lack of virological response; to confirm unlicensed doses. TDM can
Abstracts currently be used to determine levels of non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and integrase inhibitors. The aims of this study were to identify: Reasons for and appropriateness of TDM; which drugs were monitored; whether TDM prompted a change in therapy.

Methods: Retrospective observational study of all TDM samples from October 2008 to September 2009 inclusive. Analysis of drug levels was carried out by Delphic Laboratories (Liverpool); these results were obtained and additional data were collected from pharmacy records and patient notes, including reason(s) for test, recommendations and outcome.

Results: 206 samples from 94 patients were collected during this time period. Of these, 36 patients were taking 2 or 3 drugs requiring TDM simultaneously. Drugs analysed were: Darunavir - 57 samples (28%), efavirenz - 46 samples (22%), raltegravir - 33 samples (16%), etravirine - 31 samples (15%), atazanavir – 22 samples (11%), lopinavir - 10 samples (5%), nevirapine - 5 samples (2%), saquinavir – 2 samples (1%). Reasons for TDM were: low level viraemia- 38 patients, risk of interactions (non-TB meds)- 33 patients; adherence-12 patients; potential interaction with anti-TB drugs in 6 patients, dose confirmation- 4 patients, toxicity- 2 patients, drug confirmation- 1 patient (>1 reason allowed). Results were discussed at multidisciplinary meeting and drug or dose changes were recommended in 38 samples (18%); 8 of these recommendations were not followed. Of the 206 samples, 35 were repeats, taken for the following reasons: 22 following dose changes, 8- VL remained>40, 2- interacting drugs, 2 following regimen change, 1- confirm low drug levels.

Conclusion: TDM was carried out appropriately in most cases and results were acted upon. The majority of samples revealed adequate drug levels and therefore dose did not require alteration. Where TDM prompted a drug or dose change, repeat TDM should be carried out to confirm appropriate levels were obtained; this did not always happen. Although it is possible to obtain integrase inhibitor levels there is currently no consensus on the significance of these. Of note, raltegravir and etravirine levels were measured due to concerns regarding a potential interaction; otherwise the drugs sampled reflect current prescribing habits.

No conflict of interest

Abstract: 61

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

Population pharmacokinetic model for the interaction between darunavir and ritonavir in HIV-infected adults

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Background: Darunavir is a protease inhibitor of HIV which is co-administered with low doses of ritonavir in order to enhance its pharmacokinetic profile. After oral administration, darunavir plasma concentrations can vary widely among different HIV-infected patients. Thus, the objective of the present study was to develop a simultaneous population pharmacokinetic model for darunavir and ritonavir in a population of HIV-infected adults. The model sought was to incorporate patient characteristics influencing variability in drug concentration and the interaction between the two compounds.

Material & Methods: A population analysis was performed using non-linear mixed effects modelling (NONMEN, version VI) with 41 full concentration-time profiles and 141 randomly collected plasma samples (total 480 plasma samples) from a cohort of HIV-infected
adults on stable therapy with darunavir/ritonavir for at least 2 weeks. Darunavir and ritonavir concentrations in plasma were determined by high performance liquid chromatography. First, a population pharmacokinetic model was developed for darunavir and for ritonavir separately. Pharmacokinetic parameters, interindividual variability and residual error were estimated, and the influence of different patient characteristics on the pharmacokinetics of darunavir and ritonavir was explored. Subsequently, a simultaneous model estimating the pharmacokinetics of both drugs together and incorporating the influence of ritonavir on darunavir oral clearance (CL/F) was developed. The visual predictive check was used to validate the final model.

Results: A total of 47 Caucasian patients were included (79% males, mean age 45.9±8.4 years, mean body weight 70.4±10.9 kg). Patients were receiving darunavir/ritonavir at a dosage of 600/100 mg twice daily but 12 of them were switched to 900/100 mg once daily, with plasma samples available for the two dosage regimens. Darunavir concentrations were best described by a two-compartment model while ritonavir concentrations were described by a one-compartment model, both with first order absorption and elimination. Darunavir central volume of distribution was increased 1.98 fold in females. On the other hand, there was an inverse relationship between a1-acid glycoprotein (AAG) concentrations and darunavir central and peripheral volume of distribution. Darunavir CL/F was inhibited by ritonavir concentrations. The interaction between the two drugs was best described following a maximum effect model (Imax=1, IC50=0.37 mg/L). The final model appropriately predicted ritonavir and darunavir concentrations, with no systematic bias and with adequate precision.

Conclusions: A population pharmacokinetic model to simultaneously describe the pharmacokinetics of darunavir and ritonavir and their interaction was developed in HIV-infected patients. Bayesian estimates of the individual parameters of ritonavir and darunavir based on gender and AAG concentrations could be useful to predict darunavir exposure under different darunavir/ritonavir dosage regimens in an individual manner.

No conflict of interest

Abstract: 62

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

Are intracellular drug concentrations underestimated? The role of medium corpuscular volume (MCV) for a correct determination.

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Background: HAART can rely on more than 20 drugs to inhibit viral replication and most of them have an intracellular target. In many studies, correlations between NNRTIs and PIs plasma concentrations and efficacy have been found, however PBMCs concentrations could be a more reliable measure of drug exposure. Intracellular quantification of anti-HIV drugs requires sensitive instrumentations (e.g. HPLC-MS), an accurate PBMCs count, and the need of a standardized methodology. Medium corpuscular volume (MCV) is commonly estimated to be 400 femtolitres (fL) and cell count is often manually performed by microscope observation at Burker/Malassez counting chamber. In this way, intracellular concentrations measurement could be potentially biased by error in the PBMCs count and by inter-individual variability of corpuscular volume evaluation. Aim of this study was to compare intracellular concentrations obtained by two methods to evaluate PBMCs volume: adoption of fixed value of 400 fL, as currently suggested, or individualisation of MCV calculation by means of a Coulter Counter.
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Advanced Investigations in Pharmacology: Protein Binding, Intracellular Drug Concentrations, and Compartmental Pharmacokinetics

Sequential population pharmacokinetic modelling of lopinavir and ritonavir: Investigation of different dosing strategies

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Background: There is increasing interest in considering lower doses of certain antiretroviral drugs as an option for some HIV-infected patients to help lower costs and reduce adverse events. The approved twice daily dose of lopinavir/ritonavir (LPV/RTV) is 400/100mg but Hill and colleagues (Hill et al., 2009 AIDS) have suggested that a dose of 200/150mg twice daily may produce similar exposures to the standard dose. We have explored different dosage strategies by means of population pharmacokinetic modelling and simulation. Due to the dependence of LPV on RTV concentrations a model that incorporates this relationship has clear advantages. We have therefore developed a model incorporating the inhibition of LPV by RTV and investigated different LPV/RTV combinations.

Materials & Methods: Sixteen healthy volunteers were administered LPV/RTV tablets (400/100mg twice daily) to steady-state under fed conditions and on the day of pharmacokinetic sampling the evening dose was omitted. Serial blood samples were drawn pre-dose (0h) up until 72 hours post-dose (18 time-points) and LPV and RTV concentrations determined by HPLC-MS/MS. Initially, non-linear mixed effects

Materials & Methods: PBMCs were isolated from blood samples of HIV-1 infected patients administered with PIs, NNRTIs or Raltegravir (RGV), after written informed consent given. Separation of PBMCs from whole blood was accomplished through density gradient centrifugation using Ficoll. In a polypropylene tube (50 ml) about 15 ml of whole blood, collected in two lithium heparin tubes (7ml), was stratified on 15 ml Ficoll gradient and centrifuged at 700×g for 25 min at +4°C. The PBMCs layer was transferred into a polypropylene tube (50 ml) and was washed three times with a ice-cold PBS solution (40 ml) to avoid drug efflux and inhibit enzymatic activity. After second wash step, PBMCs count and volume (MCV) were calculated by a Coulter Counter instrument (Beckman Coulter Z2) and data used to calculate total PBMCs volume. PBMCs pellet was finally resuspended in 1 ml solution Methanol:Water solution (70:30), aliquoted into two criovials (500 µl/each) and stored at -80°C until use. Analyses were performed by a HPLC-MS validated method for PIs, NNRTIs and RGV. Intracellular concentrations were evaluated as ratio of drugs quantified by HPLC-MS and total PBMCs volume or 400 fl, and expressed as ng/ml.

Results: 200 PBMCs samples were collected from 86 patients. Mean MVC (±SD) was 282.5 fl (±22.4 min 232.5 - max 341.2) with a SD% of 7.9. Intra-patients MVC SD% (6 samples from 17 patients collected for AUC studies) was 3.3. Mean difference between intracellular concentrations calculated using total PBMCs volume and standard MCV value of 400 femtolitres was 42% (17% – 70%).

Conclusions: In our study, observed mean MVC (282.5 fl; min 232.5 - max 341.2) was lower than 400 fl. Use of the latter as a presumptive standard value could significantly bias the methods of quantification, and consequently previous reports could have potentially underestimated intracellular drugs exposure. Therefore, we suggest calculation of individual MCV as a more accurate and reliable tool way to quantify intracellular antiretroviral drugs concentrations.

No conflict of interest
modelling (NONMEM v. VI 2.0) was applied to LPV and RTV data separately. Interindividual variability and residual error were estimated and covariates that could potentially influence pharmacokinetic parameters explored. A sequential model incorporating the interaction between RTV concentrations and LPV apparent oral clearance (CL/F) was then developed. The models were validated by visual predictive checks and an external HIV-infected cohort of 12 patients receiving LPV/RTV tablets 400/100mg twice daily. Using the final model 10 simulations of the dataset were performed at LPV/RTV doses of 200/50mg, 200/150mg and 400/200mg twice daily and a comparison of LPV area under the curve (AUC₀₋₁₂) to the standard dose made via geometric mean ratios (GMR) and 95%CI.

**Results:** A one-compartment model with first order or sequential first-zero order absorption with absorption lag-time best described LPV and RTV, respectively. RTV AUC₀₋₇₂ was the only covariate significantly associated with LPV CL/F and vice versa. An inhibitory I MAX model best described the relationship between RTV concentrations and LPV CL/F \[ I_{\text{MAX}} \] (RSE%):0.93 (0.21); IC₅₀=0.06mg/L (4.4). Overall 91 and 94% of observed concentrations were encompassed by the prediction intervals (P2.5-P97.5; LPV and RTV, respectively), indicative of an adequate model. The model provided precise and unbiased predictions of LPV AUC₀₋₁₂ from the external validation dataset. Calculated LPV AUC₀₋₁₂ at a dose of 400/200mg was 36% higher than the standard dose (GMR, 95%CI: 1.36, 1.28-1.46). LPV/RTV 200/150mg and 200/50mg produced significantly lower LPV AUC₀₋₁₂ compared to the standard dose (0.60, 0.57-0.64 and 0.35, 0.32-0.38, resp.).

**Conclusions:** A model has been developed in healthy volunteers and validated in HIV patients to describe the relationship between LPV and RTV pharmacokinetics over 72 hours following drug cessation. Based on simulated data, lowering the LPV dose to 200/150mg or 200/50mg decreased LPV exposure by 30 and 65%, respectively. LPV dose reductions may be viable in some patients; however clinical endpoint studies are necessary to determine how this would impact outcome.

*No conflict of interest*
dose intake by the patient before a PK visit is accurate, (ii) full dosing-histories as recorded by MEMS are exact, and (iii) “reliable” dosing-history data consists only of MEMS records concordant (within 3 hours) with last reported time of dose intake before a PK visit (gold standard). Dosing-history assumption impact on population PK analysis outcomes were compared to the gold standard reference.

Results: A one compartment model best described plasma atazanavir concentrations. With the gold standard dosing-history assumption, apparent clearance (CL) and volume of distribution (Vd) were 6.93 L/hr and 81.1 L, with associated inter-individual variabilities of 40% and 31%, respectively, translating to a half life of 8.11 hr. Based on hierarchical model comparisons, the transit compartment model substantially improved observed data description compared to zero or first order absorption models: absorption rate constant of 3.1 hr⁻¹, mean transit time of 1.35 hr and 11.5 transit compartments. Median model predicted maximal (Cmax) and trough concentrations (Ctrough) of atazanavir at W4 were 3770 ng/mL (range, 1950-11000), and 552 ng/mL (range, 40-695), respectively. Median tmax and AUC at W4 were 2.87 h (range, 1.34-6.17) and 42.9 h.mg.L⁻¹ (range, 16.2-169), respectively. Assuming SS in all patients gave rise to significant quantifiable inter-occasion variability in CL (26.5% CV), while using unmodified MEMS dosing-history led to biased Vd parameter estimates and numerical difficulties during estimation procedure thereby potentially adversely affecting individual patient drug exposures.

Conclusions: The proposed model described the pharmacokinetics of atazanavir well. Study results show that it is important to critically assess MEMS data in order to collect reliable records and suggest that erroneous dosing-history assumptions without taking into account adherence information may lead to biased parameter estimates and significant inter-occasion variability. In combination with exact dosing history as recorded by MEMS, the one-compartment with transit absorption model proposed in this study provides a useful tool for correct quantification of an individual patient’s drug exposure which is essential information for understanding individual virological response and potential success/failure of the therapy.

No conflict of interest

Abstract: LB-01

Pharmacokinetics of once-daily raltegravir (800 mg) in plasma and PBMCs in HIV-infected patients.

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Background: Recently there has emerged considerable interest in the possibility of once-daily dosing for raltegravir. PK/PD analyses for raltegravir have failed to identify any meaningful correlations between viral response and drug concentrations in plasma, suggesting that the efficacy of raltegravir may be dependent on intracellular rather than on serum levels. However, little is known about the intracellular pharmacokinetics of raltegravir in HIV-infected patients, especially when it is dosed once instead of twice daily. The objective of this study was, therefore, to evaluate plasma and intracellular pharmacokinetic parameters of raltegravir in HIV-infected patients receiving once-daily raltegravir.

Methods: Open-label, pilot study in 5 male HIV-infected patients on stable antiretroviral therapy with lopinavir/ritonavir in monotherapy whose HIV-1 RNA load was < 50 copies/mL. Raltegravir was added to the antiretroviral regimen at a dose of 800 mg once daily from days 0 to 10. Raltegravir was administered in the morning, without...
regard to food intake except on day 10, when it was administered in the fasted state. On day 10, serial blood samples were collected at 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 hours post-dose. Raltegravir concentrations in plasma and in PBMCs were determined by high performance liquid chromatography with fluorescence detector and by liquid chromatography-tandem mass spectrometry (LC-MS/MS), respectively. Raltegravir pharmacokinetic parameters in plasma and in PBMCs were calculated by noncompartmental analysis (WinNonlin).

**Results:** Baseline characteristics: median (range) age 40 (24-47) years, BMI 24.4 (18.2-25.5) kg/m². Raltegravir was well tolerated and all participants completed the study. No differences were observed in raltegravir Tmax or t1/2 in plasma vs. PBMCs. Geometric mean (range) raltegravir Cmax, Ctrough, and AUC in plasma vs. PBMCs were 2639.6 (887.0-10605.0) vs. 198.5 (81.7-856.9) ng/mL (GMR 13.30; 3.11-56.88, p=0.003), 89.3 (51.0-200.0) vs. 6.8 (1.6-15.2) ng/mL (GMR 13.21; 3.94-44.27, p=0.001), and 12199.7 (5151.5-30130.0) vs. 908.9 (499.1-2188.8) ng.h/mL (GMR 13.43; 5.12-35.17, p<0.001).

**Conclusion:** Raltegravir has poor penetration in PBMCs, with intracellular concentrations about one tenth of the concentrations in plasma. Despite this, all patients receiving 800 mg of raltegravir once daily maintained trough concentrations in PBMCs above the EC50 for wild-type viral strains (0.4 ng/mL).


**No conflict of interest**
visit and a mean of 16 and 8, respectively, samples per patient were collected. Mean of LPV Ctrough geometric means resulted of 9188 ng/ml (±SD, ±3539); no difference in plasma values was recorded between the two arms (9175 vs. 7912, p=0.49). All analyzed samples but one were over the proposed MEC (1000 ng/ml). Geometric mean of LPV available through concentrations (and LPV concentrations in the first 14 days) were related to the time to undetectability: higher levels were correlated to a longer time needed to reach a viral load below 50 copies/ml (rho=0.54 with p=0.016 and rho=0.71 with p=0.001 respectively).

Mean of enfuvirtide geometric means was 2686 (± 1183) ng/ml. Sixty-seven samples (75%) were above the proposed target trough concentration for experienced patients (2100 ng/ml). Enfuvirtide plasma levels were directly related to the CD4+ lymphocytes percentage recovery at 48 weeks (R2= 0.45, p=0.03).

Conclusion: In this small pilot study the addition of enfuvirtide to a PI-based 3-drug regimen was associated to a significantly greater immunological recovery as compared to the same conventional, 1st line, antiretroviral regimen. Higher lopinavir through levels were associated with a longer time needed to reach the complete viral suppression, with baseline inflammatory/immune-mediated changes (rise in acute-phase reactants, e.g. AAG) possibly responsible for these findings. Enfuvirtide exposure was directly associated with the CD4+ cell count increase at 48 weeks: the mechanism of this immunological benefit is not clear, but should this be confirmed in larger trials innovative strategies could be tested in this group of patients at high-risk of poorer therapeutic response.

No conflict of interest

Abstract: LB-03

Raltegravir therapeutic drug monitoring in pre-treated patients receiving raltegravir + 2 NRTIs

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Background: Raltegravir (RAL) is a potent HIV integrase inhibitor, first approved for treatment experienced HIV-patients. At present, the concentration-effects relationships for RAL are not well defined and it is not clear if the practice of TDM could be of interest to optimise antiretroviral therapy in patients treated with RAL. Therefore, we evaluated the RAL plasma concentration (Cmin) and virologic response in pre-treated patients under a RAL + 2 NRTIs regimen.

Material & Methods: HIV-infected pre-treated patients, receiving RAL associated with 2 NRTIs, were included in this observational, multicenter and prospective study. Plasma RAL Cmin (T12±2 hours) was determined at least one month after treatment initiation and RAL TDM was repeated for some patients over the follow-up period (12 months). Plasma RAL quantification was performed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Plasma HIV-RNA (VL) and CD4 cells count were collected at months 3 (M3) and 6 (M6). Median (IQR) are presented. Statistical analysis for inter-group comparison was performed using Mann-Whitney test (PASW Statistics 17).

Results: Thirty-six patients (53% male, 46 years (43-51), 39% HCV+, 36% CDC class C), were receiving RAL at 400mgx2, except for two patients under rifampicin who received 800mgx2, associated with TDF+FTC (n=26), 3TC+ABC (n=8) or 3TC+AZT (n=2). Reasons for switching to RAL were mainly for toxicity (67%) and drug-drug interaction (22%). At baseline (BL), 25/36 (69%) had an undetectable
plasma VL below 50 copies/mL while 11/36 (31%) had a mean±SD VL of 3±1.5 log10 copies/mL. BL CD4 cells count was 352 (233-564). Patients had previously received 9 (7-13) ARV regimens and 3 (1-5) PI resistance associated mutations and 1 (0-4) RT resistance associated mutations. RAL Cmin were 218 ng/ml (64-424, n=36, CV=171%) at M2 and 157 ng/ml (84-241, n=19, CV=90%) at M6. None patient had a RAL Cmin below the IC95 (15 ng/ml) and below the interval usually observed at the standard dose (29-118 ng/ml). At M3 and M6, 85% and 87% had a VL<50 and CD4 cells count were 332 (201-475) and 459 (272-613), respectively. RAL Cmin (range) in responders and non responders were 228 ng/ml (25-3957) and 243 ng/ml (33-1094) at M3 and 209 ng/ml (33-3957) and 400 ng/ml (25-1094) at M6.

Conclusions: We observed a high rate of virologic response under RAL+2 NRTIs regimen in pre-treated patients, in accordance with suitable plasma RAL Cmin. A wide interpatient variability in RAL Cmin was noted. Due to a small number of patients who failed the regimen, no significant difference was observed in RAL Cmin between responders and non responders. However, RAL Cmin was always above the IC95 and the expected interval at this dose, reflecting a good adherence. RAL TDM does not appear to be relevant in this study but most of the patients were already undetectable at BL and therefore it may be difficult to assess a PK-PD relationship. This study is still ongoing to precise the interest of RAL TDM over a longer follow-up period and on a larger number of patients.

No conflict of interest

Abstract: LB-04

Comparative plasma and intracellular pharmacokinetics of microdosing and standard dosing of zidovudine with accelerator mass spectrometry (AMS)

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Background: Using microdosing or phase 0 studies to obtain human pharmacokinetic data in the early stages of drug development may facilitate the identification of promising drug candidates and reduce the cost of drug development. Whether the PK of a microdose predicts the PK of eventual therapeutic drug doses is controversial. Accelerator Mass Spectrometry (AMS) is a sensitive technique that can be used to detect tiny amounts of radiolabeled investigational drugs and drug metabolites as a component of Phase 0 studies. We have shown that AMS has comparable accuracy to LC/MS/MS methods and a much higher sensitivity using a 100 μg microdose of 14C-zidovudine (ZDV) combined with a 300 mg therapeutic dose. Here we directly compare intracellular ZDV-triphosphate (ZDV-TP) measured in total peripheral blood mononuclear cells (PBMCs) and CD4+ T cells in vivo in subjects receiving a microdose or therapeutic dose of ZDV.

Material & Methods: Six healthy volunteers were given a single oral dose of 100 μg (20 μCi) of 14C-labeled ZDV, and after 30 days wash out a second dose of 100 μg (20 μCi) of 14C-labeled ZDV combined with 300 mg non-radioactive oral ZDV. Plasma, PBMCs and CD4+ T cells were collected at predose, 2h, 4h, 8h, 12h, and 24h after dosing. ZDV-TP was isolated from cells with a single column extraction and measured as total 14C using AMS. Total plasma 14C was measured simultaneously.
**Results:** Total $^{14}$C in plasma (including both $^{14}$C-ZDV and its major metabolite $^{14}$C-ZDV-glucuronide) was similar comparing the microdosing and standard dosing regimens, suggesting similar bioavailability. $T_{\text{max}}$ occurred at 2 hours for all subjects in both dosing regimens. For the microdose, median $C_{\text{max}}$ was 169.8 (range 106.4-312.5) dpm/mL. For standard dose, median $C_{\text{max}}$ was 207.5 (range 164.0-533.6) dpm/mL. $T_{\text{max}}$ for intracellular $^{14}$C-ZDV-TP was also 2 hours for all cell types. The median $C_{\text{max}}$ in total PBMCs for $^{14}$C-ZDV-TP was 97.3 (range 78.6-1059.9) amol/10$^6$ cells after microdosing versus 28.5 (range 10.6-48.8) amol/10$^6$ cells for the combined ZDV/$^{14}$C-ZDV dose. In CD4$^+$ cells, the median $C_{\text{max}}$ of intracellular $^{14}$C-ZDV-TP was 68.1 (range 38.5-126.5) amol/10$^6$ after microdosing versus 5.01 (range 3.5-13.3) amol/10$^6$ cells after receiving the combined 300 mg unlabelled dose. In a nonparametric paired analysis, intracellular $^{14}$C labeled ZDV-TP was 4.8 fold (range 1.8-25.2) and 17.0 fold (range 3.4-20.1) greater with the microdose when compared to the combined dose for PBMC and CD4$^+$ cells, respectively ($p=0.028$ for both). $^{14}$C-ZDV-TP was detectable by AMS in all subjects except one 24 hours post-dosing (range 0.167-27.7 amol/10$^6$ cells). Intracellular $^{14}$C-ZDV-TP concentrations per cell were generally higher with the microdosing regimen as compared to subjects given the same microdose plus an unlabelled 300 mg standard dose of ZDV, and $^{14}$C-ZDV-TP was generally lower in CD4$^+$ T cells when compared to PBMCs.

**Conclusions:** These results suggest that the kinetics of intracellular ZDV-TP formation change several fold over the dose range studied (100 μg to 300 mg). The similarity of our results to those using LC/MS/MS confirms the promise of AMS for assessing the PK of intracellular nucleotides.

*No conflict of interest*
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