

Drug Interaction and Pharmacology Presentations at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 2009.

*This report summarises drug interaction and pharmacology studies presented at the recent meeting.
Abstracts are available for a limited time at www.icaac.org.*

Contents

Interactions with Existing HIV Drugs	2
EFV and substance abuse. (Abstract H-228).	2
Interactions with vicriviroc. (Abstract H-230).	2
ATV and tobacco or marijuana. (Abstract H-231).	2
DRV/r and buprenorphine/naloxone. (Abstract H-232).	3
DRV and food. (Abstract H-233).	3
RAL and methadone. (Abstract A1-1295).	3
RAL and rifabutin. (Abstract A1-1296).	3
RAL and FPV or FPV/r. (Abstract A1-1297).	4
ETV and LPV/r. (Abstract A1-1298).	4
ETV and fluconazole or voriconazole. (Abstract A1-1299).	5
NRTIs and buprenorphine. (Abstract A1-1306).	5
LPV/r and echinacea. (Abstract A1-1307).	5
New Drugs, Combinations or Formulations	5
“Quad” FDC and food. (Abstract A1-1300).	5
ATV and GS-9350 or RTV. (Abstract A1-1301).	6
S/GSK1349572 and TDF. (Abstract A1-1303).	6
S/GSK1349572 and boosted PIs. (Abstract A1-1304).	6
S/GSK1349572 and antacid or multivitamins. (Abstract A1-1305).	6
NVP extended release formulation. (Abstract A1-1310).	7
Other Pharmacology	7
RAL concentrations in CSF. (Abstract A1-1311).	7
DRV concentrations in CSF. (Abstract A1-1312).	7

Interactions with Existing HIV Drugs

EFV and substance abuse. (Abstract H-228).

Effects of CYP2B6 single nucleotide polymorphisms (SNPs) and substance abuse on efavirenz (EFV) pharmacokinetics

Ma Q, Venuto C, Brazeau D, et al.

This study evaluated efavirenz trough concentrations in 17 HIV+ subjects with substance-related disorders (SRDs) and 20 HIV+ subjects without SRDs. The median efavirenz trough concentrations in the SRD groups were lower with tobacco (1.76 vs 2.295 µg/ml), alcohol (1.41 vs 2.25 µg/ml), marijuana (1.73 vs 2.24 µg/ml) and cocaine (1.92 vs 2.05 µg/ml), but higher with opioids (2.41 vs 1.85 µg/ml). Only the differences with tobacco and alcohol were statistically significant. There was no significant relationship between SRD and antiviral response.

Interactions with vicriviroc. (Abstract H-230).

Assessment of pharmacokinetic and safety interactions between vicriviroc and CYP3A4 substrates, inhibitors, and inducers

Kasserra C, O'Mara E, Lisbon E.

Drug interactions with vicriviroc (30 mg alone or with RTV) were studied in healthy volunteers. There was no effect on midazolam when administered with vicriviroc alone, but there was a marked increase when administered with RTV. Ketoconazole increased vicriviroc AUC by 136% when administered alone and by 503% when administered with ritonavir. There was no effect on vicriviroc exposure with rifabutin when administered with RTV (200 mg once daily). Rifampicin markedly decreased vicriviroc exposure when coadministered with RTV (100 mg twice daily) – the relative oral bioavailability was 11.6% based on AUC. Carbamazepine had no effect on vicriviroc when administered with RTV (100 mg twice daily). In the presence of RTV, addition of another CYP3A4 inhibitor or modestly potent CYP3A4 inducer will not require dose adjustment of vicriviroc. If carbamazepine or rifabutin are coadministered with vicriviroc in a RTV-boosted PI-containing regimen, no vicriviroc dose adjustment is required, but RTV should be increased to 100 mg twice daily or 200 mg once daily. Coadministration of rifampicin with vicriviroc is not recommended.

ATV and tobacco or marijuana. (Abstract H-231).

Tobacco and marijuana uses significantly decrease atazanavir (ATV) Trough concentrations in HIV-infected individuals

Ma Q, Fehintola F, Zingman B, et al.

Atazanavir trough concentrations were evaluated in 32 HIV+ subjects with substance-related disorders (SRDs) and 35 HIV+ subjects without SRDs. The median atazanavir trough concentrations in the SRD groups were lower with tobacco (0.314 vs 0.957 µg/ml), marijuana (0.238 vs 0.593 µg/ml), alcohol (0.534 vs 0.558 µg/ml), and opioids (0.325 vs 0.712 µg/ml), but higher with cocaine (0.768 vs 0.544 µg/ml). Trough concentrations in the SRD group were below the therapeutic range in 36% of tobacco users and 50% of marijuana users. Only the differences with tobacco and marijuana were statistically significant. There was no significant direct effect of SRD on viral load or CD4 count.

DRV/r and buprenorphine/naloxone. (Abstract H-232).**Pharmacokinetic (PK) Interaction between darunavir in combination with low-dose ritonavir (DRV/r) and buprenorphine/naloxone (bup/nlx)**

Sekar VJ, Tomaka F, Meyvisch P, et al.

The effect of DRV/r (600/100 mg twice daily for 7 days) on the pharmacokinetics of buprenorphine was assessed in 17 HIV- subjects stable on buprenorphine/naloxone maintenance therapy (daily doses up to 24/6 mg). There was no effect on buprenorphine AUC, C_{max} or trough concentrations; however, norbuprenorphine C_{max} increased by 36% and AUC increased by 46%. No subject required dose adjustment of buprenorphine/naloxone. Given the increase in norbuprenorphine concentrations, close clinical monitoring of patients is recommended.

DRV and food. (Abstract H-233).**Bioavailability and food effect of darunavir (DRV) following administration of an oral suspension**

Sekar VJ, Lavreys L, de Paepe E, et al.

The oral bioavailability and steady state pharmacokinetics of an paediatric oral suspension of DRV were assessed in two studies in 23 HIV- adult subjects. Firstly RTV (100 mg twice daily) was administered on days 1-5 and a single 600 mg dose of DRV on day 3 as a) tablet with food, b) suspension fasted, and c) suspension with food. In the second part, DRV pharmacokinetics were assessed following administration of the suspension (600 mg twice daily) with ritonavir (100 mg twice daily) for 7 days. In the first study the criteria for bioequivalence (90% CI of LSM ratios within limits of 80-125%) were met for C_{max} and AUC when comparing tablet (with food) and suspension (with or without food). Pharmacokinetic data obtained with the suspension in the second study were comparable to historical data obtained with the same dose in the tablet formulation. The oral suspension will be further evaluated in paediatric HIV+ subjects.

RAL and methadone. (Abstract A1-1295).**Effect of raltegravir (RAL) on the pharmacokinetics (PK) of methadone**

Anderson MS, Luk JM, Hanley WD, et al.

The effect of raltegravir (400 mg twice daily) on the pharmacokinetics of methadone were investigated in 12 HIV- subjects stable on methadone. There was no change in either methadone AUC or C_{max} in the presence of raltegravir and no dose adjustment is required.

RAL and rifabutin. (Abstract A1-1296).**Lack of a Clinically important effect of rifabutin (RFB) on raltegravir (RAL) pharmacokinetics**

Brainard DM, Petry AS, Fang L, et al.

Coadministration of raltegravir (400 mg twice daily) and rifabutin (300 mg once daily) was investigated in 16 HIV- subjects. Raltegravir AUC increased by 19%, C_{max} increased by 39% and C_{trough} decreased by 20%. These changes were not deemed to be clinically significant and no dose adjustment is required.

RAL and FPV or FPV/r. (Abstract A1-1297).**Steady-state pharmacokinetics (PK) of fosamprenavir (FPV) and raltegravir (RAL) alone and combined with unboosted and ritonavir-boosted FPV**

Luber A, Slowinski D, Acosta E, et al.

The interaction between raltegravir and atazanavir or atazanavir/ritonavir and the effect of food was studied in HIV- subjects. Raltegravir (400 mg twice daily) and fosamprenavir (1400 mg twice daily) or fosamprenavir/ritonavir (700/100 mg twice daily or 1400/100 mg once daily) were administered alone and in combination with and without a light meal. The effects are summarised below:

FPV 1400 mg twice daily + light meal:

Raltegravir AUC, C_{max} and C_{min} decreased by 29%, 5% and 68%.

Amprenavir AUC, C_{max} and C_{min} decreased by 19%, 17% and 33%.

FPV 1400 mg twice daily, fasted:

Raltegravir AUC, C_{max} and C_{min} decreased by 37%, 28% and 38%.

Amprenavir AUC, C_{max} and C_{min} decreased by 36%, 27% and 43%.

FPV/r 700/100 mg twice daily + light meal:

Raltegravir AUC, C_{max} and C_{min} decreased by 30%, 15% and 41%.

Amprenavir AUC and C_{max} increased by 13% and 27%; C_{min} decreased by 27%.

FPV /r 700/100 mg twice daily, fasted:

Raltegravir AUC decreased by 15%, C_{max} increased by 6%, C_{min} decreased by 25%.

Amprenavir AUC, C_{max} and C_{min} decreased by 24%, 18% and 50%.

FPV/r 1400/100 mg once daily + light meal:

Raltegravir AUC, C_{max} and C_{min} decreased by 254%, 56% and 54%.

Amprenavir AUC, C_{max} and C_{min} decreased by 25%, 25% and 33%.

FPV /r 1400/100 mg once daily, fasted:

Raltegravir AUC, C_{max} and C_{min} decreased by 55%, 51% and 36%.

Amprenavir AUC, C_{max} and C_{min} decreased by 16%, 14% and 19%.

Although raltegravir exposure decreased with fosamprenavir, especially at higher doses of ritonavir, raltegravir C_{min} were 3- to 9-.4-fold higher than the IC₉₅ for WT HIV (14.6 ng/ml). Amprenavir concentrations were decreased, however, C_{mins} for the boosted regimens were 2.1- to 7.8-fold higher than the EC₉₀ for PI-naïve HIV+ patients (228 ng/ml). The clinical implications of these results have yet to be determined.

ETV and LPV/r. (Abstract A1-1298).**Pharmacokinetic (PK) Interaction between etravirine (ETR) and lopinavir/ritonavir (LPV/r)**

Scholler-Gyure M, Kakuda TN, Akuma SH, et al.

This study looked at the interaction between etravirine (200 mg twice daily) and the tablet formulation of lopinavir/ritonavir (400/100 mg twice daily) in 16 HIV- subjects. Coadministration decreased etravirine AUC, C_{max} and C_{min} by 35%, 30% and 45%, respectively; lopinavir AUC, C_{max} and C_{min} decreased by 13%, 11% and 20%, respectively. There was no change in the pharmacokinetics of ritonavir. These etravirine results are in contrast to previous data obtained with capsule formulation of lopinavir/ritonavir which showed increased etravirine exposure. No dose adjustment of etravirine is required as the effect of lopinavir/ritonavir tablets is similar to the effect of darunavir/ritonavir seen in clinical trials which demonstrated favourable etravirine efficacy and safety. The decrease in lopinavir concentrations was similar to earlier data and is not considered clinically relevant.

ETV and fluconazole or voriconazole. (Abstract A1-1299).**Pharmacokinetic (PK) interaction between etravirine (ETR) and fluconazole (FLU) or voriconazole (VOR) in HIV-negative volunteers**

Scholler-Gyure M, Kakuda TN, van Solingen-Ristea R, et al.

The pharmacokinetic interaction between etravirine (200 mg twice daily) and fluconazole (200 mg once daily) or voriconazole (200 mg twice daily) was studied in HIV- subjects. Fluconazole increased etravirine AUC, C_{max} and C_{min} by 86%, 75% and 2.09-fold, respectively (n=16); fluconazole AUC, C_{max} and C_{min} decreased by 6%, 8% and 9%, respectively (n=15). Voriconazole increased etravirine AUC, C_{max} and C_{min} by 36%, 26% and 52%, respectively (n=16); voriconazole AUC and C_{min} increased by 14% and 23%, but C_{max} decreased by 5% (n=14). Combinations were generally safe and well tolerated.

NRTIs and buprenorphine. (Abstract A1-1306).**Interactions between buprenorphine and antiretrovirals: nucleos(t)ide reverse transcriptase inhibitors (NRTI) didanosine, lamivudine and tenofovir**

Baker K, Gruber VA, Moody DE, et al.

The interaction between buprenorphine and didanosine, lamivudine and tenofovir was investigated in 27 HIV-, buprenorphine/naloxone maintained subjects. Data for didanosine and tenofovir were compared to values obtained from 20 control subjects not receiving buprenorphine; lamivudine was compared to control data. No significant changes in buprenorphine pharmacokinetics were observed when coadministered with didanosine, lamivudine and tenofovir. When compared to controls, buprenorphine had no statistically significant effect on NRTI concentrations.

LPV/r and echinacea. (Abstract A1-1307).**Echinacea purpurea does not alter the steady state pharmacokinetics of lopinavir or ritonavir in healthy human volunteers**

Malati CY, Robertson SM, Hunt JD, et al.

The effect of echinacea (500 mg three times daily for two weeks) on the pharmacokinetics of lopinavir/ritonavir (400/100 mg twice daily) was studied in 16 HIV- subjects. Neither lopinavir nor ritonavir pharmacokinetics were altered by coadministration of echinacea (lopinavir AUC decrease by 4% and there was no change in C_{max}). Although echinacea has been shown modulate P450 3A4 in vitro, these data suggest a clinically significant interaction is unlikely.

New Drugs, Combinations or Formulations

“Quad” FDC and food. (Abstract A1-1300).**Effect of food on pharmacokinetics (PK) of elvitegravir (EVG), emtricitabine (FTC), tenofovir DF (TDF) and the pharmacoenhancer GS-9350 as a fixed dose combination tablet**

German P, Warren D, Wei L, et al.

A “quad” fixed dose combination tablet containing emtricitabine (200 mg), tenofovir (300 mg), elvitegravir (150 mg) and the boosting agent GS-9350 (150 mg) is currently in development. This evaluated the effects no food, or light (373 kcal, 20% fat) or high (800 kcal, 50% fat) meals on single doses of the “quad” tablet in 24 HIV- subjects. The pharmacokinetics of emtricitabine were equivalent when given fasted or with either meal. Compared to the fasting state, tenofovir AUC increased by 24% with a light meal and by 23% with a high fat meal; C_{max} increase by 20% with a light meal, but was similar to fasting with a high fat meal. Elvitegravir AUC and C_{max} increased by 34% and 22% with a light meal and increased by 87% and 56% with a high fat meal (all compared to

fasting). The AUC of GS-9350 was similar with a light meal, but decreased by 17% with a high fat meal (all compared to fasting).

ATV and GS-9350 or RTV. (Abstract A1-1301).

Pharmacokinetic boosting of atazanavir with the pharmacoenhancer GS-9350 versus ritonavir

Ramanathan S, Warren D, Wei L, Kearney B.

GS-9350 is CYP3A4 inhibitor currently in development as an alternative boosting agent to ritonavir. The study compared the effects of GS-9350 (100 or 150 mg once daily) and ritonavir (100 mg once daily) on the pharmacokinetics of atazanavir (300 mg once daily) in 33 HIV- subjects. The higher dose of GS-9350 was found to be bioequivalent (80-125%) to 100 mg ritonavir (atazanavir GMRs of 1.01 for AUC, 0.92 for C_{max} and 0.98 for C_{min}). Atazanavir exposure was lower with the lower dose of GS-9350.

S/GSK1349572 and TDF. (Abstract A1-1303).

Lack of interaction between the HIV integrase inhibitor, S/GSK1349572, and tenofovir disoproxil fumarate (TDF) in healthy subjects

Song I, Min S, Borland J, et al.

S/GSK1349572 is a once daily, unboosted integrase inhibitor currently in development. The interaction between S/GSK1349572 (50 mg once daily) and tenofovir (300 mg once daily) was evaluated in 15 HIV- subjects. There were no significant changes in pharmacokinetics parameters for either drug when coadministered. S/GSK1349572 AUC increased by 1%, C_{max} decreased by 3% and C_{min} decreased by 8%; tenofovir AUC, C_{max} and C_{min} increased by 12%, 9% and 19%, respectively. The combination was well tolerated and can be taken without dose adjustment.

S/GSK1349572 and boosted PIs. (Abstract A1-1304).

The effect of ritonavir-boosted protease inhibitors (PIs) on the HIV integrase inhibitor, S/GSK1349572, in healthy subjects

Song I, Min S, Borland J, et al.

This study (in two groups of HIV- subjects, n=15 per group) investigated the effect on boosted-PIs on the pharmacokinetics of S/GSK1349572, a once daily, unboosted integrase inhibitor currently in development. Coadministration of S/GSK1349572 (30 mg once daily) and lopinavir/ritonavir (400/100 mg twice daily) decrease S/GSK1349572 AUC by 3%, had no effect on C_{max} and increased C_{min} by 2%. In contrast, coadministration of the same dose of S/GSK1349572 with darunavir/ritonavir (600/100 mg twice daily) decreased S/GSK1349572 AUC, C_{max} and C_{min} by 22%, 11% and 38%, respectively, though these decreases are not deemed to be clinically significant. No dosage adjustment of S/GSK1349572 is required with lopinavir/ritonavir or darunavir/ritonavir.

S/GSK1349572 and antacid or multivitamins. (Abstract A1-1305).

Evaluation of antacid and multivitamin (MVI) effects on S/GSK1349572 pharmacokinetics (PK) in healthy subjects

Song I, Patel A, Min S, et al.

Previous studies of have shown that S/GSK1349572 exposure is reduced by binding to metal cations, which may be present in products such as antacids and multivitamins. This study investigated the effect of antacid (Maalox maximum strength, 20 ml) or multivitamins on a single dose of S/GSK1349572 (50 mg) in 16 HIV- subjects. Coadministration with multivitamins decreased S/GSK1349572 AUC, C_{max} and C_{trough} by 33%, 35% and 32%, respectively. When administered simultaneously with antacid, the AUC, C_{max} and C_{trough} of S/GSK1349572 decreased by 74%, 72% and 74%, respectively. In contrast, administering antacid 2 h before S/GSK1349572 resulted in

decreases of S/GSK1349572 AUC, C_{max} and C_{min} of 26%, 18% and 30%. The reduction seen with multivitamins is not considered clinically significant. However, S/GSK1349572 should be taken 2 h before or 6 h after antacids.

NVP extended release formulation. (Abstract A1-1310).

Steady state evaluation of two extended release (XR) nevirapine (NVP) tablets 400 mg QD compared with immediate release (IR) NVP tablets 200 mg BID in HIV-1 infected patients

Quinson A, Arasteh K, Plettenberg A, et al.

Nevirapine is licensed for twice daily administration, but is frequently given once daily. Two extended release formulations of nevirapine are currently in development. Patients who were stable on twice daily nevirapine were switched to one of two extended release formulations (XR25% and XR20%). In the 92 patients treated with XR, absorption was decreased – T_{max} increased from ≤2h with the twice daily dosing to 6.7-8.6 h with the XR formulations. C_{min} of XR formulations were comparable to the twice daily formulation, whereas C_{max} of the XR formulations were lower. Relative bioavailability (based on AUC₀₋₂₄) was 80% for the XR25% formulation and 71% for the XR20% formulation. No virological failures were observed. The XR25% formulation has been selected for further development due to its increased bioavailability and decreased variability compared to XR20%.

Other Pharmacology

RAL concentrations in CSF. (Abstract A1-1311).

Raltegravir concentrations in CSF exceed the median inhibitory concentration

Letendre SL, Best B, Breidinger S, et al.

Raltegravir concentrations were determined in 22 matched CSF and plasma samples from 18 HIV+ subjects. Lower limits of quantification were 2 ng/ml for plasma and 0.25 ng/ml for CSF. The median raltegravir concentration was 13.9 ng/ml (IQR 8.9-24.6), with no subject having undetectable concentrations. The median CSF to plasma ratio was 7.3% (IQR 2.2-17). CSF concentrations correlated with plasma concentrations, but not with post-dose sampling time. Raltegravir CSF concentrations exceeded the IC₅₀ of wild-type HIV in 17/18 subjects by a median of 4.1-fold (IQR 2.6-7.2).

DRV concentrations in CSF. (Abstract A1-1312).

Darunavir concentrations in CSF exceed the median inhibitory concentration

Letendre S, Rossi S, Best B, et al.

Darunavir concentrations were measured in 29 paired CSF and plasma samples from 16 HIV+ subjects. Darunavir was detectable (LLQ 5 ng/ml) in all CSF samples, with a median concentration of 56.9 ng/ml (IQR 39.6-81.4). Median CSF to plasma ratio was 1.4% (IQR 0.9-1.8) for total darunavir and 9.4% (IQR 6.8-14.2%) for unbound darunavir. Darunavir concentrations in CSF exceeded the IC₅₀ of wild-type HIV in all samples by a median of 20.7-fold.