

**Drug Interaction Studies presented at the
18th Conference on Retroviruses and Opportunistic Infections,
Boston, Feb/Mar 2011.**

This report summarises interaction studies presented at the recent meeting in Boston.

A direct link to the abstract on the conference website is provided in this document. In some cases, posters are available – this will show as a pdf icon in the results listing when the search option is used. Webcasts of the oral presentations are also available on the conference website.

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HIV

TMC278 + EFV (abstract 630)

Pharmacokinetic parameters of once-daily TMC278 following administration of efavirenz in healthy volunteers.

Crauwels H, Vingerhoets J, Ryan R, et al.

TMC278 and EFV share overlapping metabolic pathways, which could lead to drug-drug interactions when switching from EFV to TMC278. 17 HIV-negative subjects received a fixed sequence of treatments: period A, TMC278 25 mg once daily for 14 days, followed by a 14- to 21-day washout; period B, EFV 600 mg once daily for 14 days, immediately followed by period C, TMC278 25 mg once daily for 28 days. Pharmacokinetic profiles for TMC278 were determined on days 1 and 14 during period A and on days 1, 14, 21, and 28 during period C. EFV plasma concentrations were determined at regular time points during periods B and C. At days 1, 14, and 21 of period C, TMC278 pharmacokinetics were lower than in period A: AUC and C_{max} decreased by 46% and 36% on day 1; AUC, C_{max} and C_{min} decreased by 18%, 19% and 28% on day 14; AUC, C_{max} and C_{min} decreased by 16%, 13% and 28% on day 21. By day 28 of period C, TMC278 AUC and C_{min} were similar to Day 14 of period A (9% decrease in AUC, 8% decrease in C_{max}), but C_{min} was decreased by 25%. Plasma concentrations of EFV were <100 ng/mL (quantification limit) by 7 days after period B ended. Ex vivo antiviral activity in serum was ≥50% of the reference range in >80% of subjects, and TMC278 was generally safe and well-tolerated throughout the study. These data support the evaluation of a treatment switch from EFV to TMC278 in HIV+ subjects when clinically appropriate.

RAL + GSK2248761 (abstract 631)

Lack of drug-drug interaction between the NNRTI GSK2248761 and raltegravir.

Kim J, Gould E, Lou Y, et al.

GSK2248761 is a once daily, next-generation NNRTI with activity against efavirenz-resistant strains of HIV. Coadministration of GSK2248761 (200 mg once daily) and RAL (400 mg twice daily) was studied in 15 HIV-negative subjects. Coadministration was well tolerated and all subjects completed the study. The AUC, C_{max} and C_{trough} of GSK2248761 increased by 15%, 16% and 13% respectively in the presence of raltegravir. RAL AUC and C_{max} both decreased by 18% in the presence of GSK2248761, but there was no change in C_{trough}. The small changes in GSK2248761 and RAL exposure were not considered clinically meaningful and no dose modification is required when coadministered.

Note: In February 2011, ViiV Healthcare announced that the FDA had placed a hold on the development of GSK2248761.

Once daily RAL/ATV (abstract 634)

Pharmacokinetics of once daily RAL/ATV in HIV-1-infected patients.

Jansen A, Colbers A, van der Ven A, et al.

This study compared the pharmacokinetics of RAL (400 mg twice daily or 800 mg once daily) in 17 HIV+ subjects on unboosted ATV (600 mg once daily). The geometric mean (90% CI) of once daily RAL AUC₀₋₂₄ was 79% (24 to 157%) higher than the AUC₀₋₁₂ of twice daily RAL. When the AUC of once daily RAL was halved, it was not significantly different from the AUC of twice daily RAL. C_{max} of once daily RAL was 33% higher than twice daily RAL, whereas C_{min} of once daily RAL was 81% lower than twice daily RAL. ATV pharmacokinetics were similar during both RAL regimens. All patients maintained an undetectable viral load and the regimens were well tolerated.

Once daily MVC + DRV/r (abstract 636)

MVC 300 mg once daily + DRV/RTV 800/100 mg once daily provides MVC trough concentrations comparable to trough concentrations in HIV-1 patients taking MVC 300 mg twice daily + Truvada: implications for phase 3 studies.

Taylor S, Dufty N, Watson J, et al.

Peak (2 h post dose) and trough (12 or 24 h post dose) plasma concentrations were determined in HIV+ subjects (n=20) following coadministration of MVC (300 mg once daily) and DRV/r (800/100 mg once daily) and compared to those obtained from another group of HIV+ subjects (n=13) coadministered MVC (300 mg twice daily) and TDF/FTC. MVC concentrations were comparable between the groups and all trough concentrations exceeded 25 ng/ml. Median MVC concentrations (range) in the once daily group were 384 (291-1408) ng/ml at peak and 49 (32-88) ng/ml at trough. In the twice daily group, peak concentrations were 429 (167-960) ng/ml and trough concentrations were 57 (44-149) ng/ml. All DRV concentrations were in the therapeutic range. MVC concentrations were lower than expected compared with PK modelling data, which may have implications for phase 3 studies using DRV/r 800/100 mg once daily with MVC dosed at 150 mg once daily. Formal drug interaction studies with once-daily DRV/r at doses of 150 mg and 300 mg once daily are urgently required before proceeding with phase 3 studies.

NVP + oral contraceptives (abstract 637)

Pharmacokinetic and pharmacodynamics activity of the combined oral contraceptive in HIV+ women in Lilongwe, Malawi.

Stuart G, Moses A, Corbett A, et al.

The pharmacokinetics and pharmacodynamics of a combined oral contraceptive containing norgestrel (300 mg once daily) and ethinylestradiol (30 µg once daily) were studied in three groups of women – (1) HIV-positive receiving NVP + 3TC/d4T, (2) HIV-positive not receiving antiretrovirals, and (3) HIV-negative. Each group contained 3 women and all women had been on norgestrel/ethinylestradiol for at least 6 weeks. Median levonorgestrel AUC values for groups 1, 2, and 3 were 78.3, 46.0, and 24.0 ng/ml.h, respectively. Ethinylestradiol AUCs in groups 1, 2, and 3 were 816.5, 816.3, and 669.9 pg/ml.h, respectively. Women in group 1 demonstrated ovulation suppression despite previous predictions of combined oral contraceptive method failure. Levonorgestrel concentrations were highest in group 1, also conflicting with previously published data. Antiretroviral concentrations were similar to those previously reported in Malawians. The unexpected levonorgestrel concentrations, in addition to the maintenance of ovulation suppression in this population further support the need for broader pharmacokinetic/pharmacodynamic investigations in multiple, clinically relevant, settings.

RAL + DRV/r (abstract 638)

Intracellular pharmacokinetics and drug interaction between DRV/r once daily and RAL once and twice daily in HIV-infected individuals.

Jackson A, Back D, Khoo S, et al.

The plasma and intracellular pharmacokinetics of DRV/r (800/100 mg once daily) and RAL (400 mg twice daily or 800 mg once daily) were determined in 24 HIV+ subjects. There was no evidence of an interaction between RAL (once or twice daily) and once daily darunavir/ritonavir. The GMR ratio (90% CI) for plasma AUCs for RAL (without/with DRV) were 0.86 (0.7 to 1.4) for twice daily RAL and 1.04 (0.9 to 1.4) for once daily RAL. DRV plasma GMR (90% CI) with and without RAL were 1.13 (1.0 to 1.14) for the twice daily group and 1.14 (1.1 to 1.2) for the once daily group. Intracellular/plasma AUC ratios were 5.11 for RAL 400 mg twice daily alone and 5.10 for DRV (when given as DRV/r 800/100 mg twice daily alone).

Immunosuppressants + RAL/NRTIs (abstract 644)

Combination of RAL + 3TC or FTC + ABC or TDF is safe, effective and prevents pharmacokinetic interactions with immunosuppressive drugs in HIV-1-infected solid organ transplant recipients.

Miro J, Manzardo C, Brunet M, et al.

This single centre, prospective study investigated the efficacy and safety of ciclosporin, tacrolimus and mycophenolic acid in 15 transplant recipients receiving RAL with 3TC/ABC or TDF/FTC. In a sub-study, the pharmacokinetics of RAL and mycophenolic acid were determined in 6 transplant recipients. The combinations were effective and safe and allowed standardization of the dosage of ciclosporin and tacrolimus. RAL did not significantly interfere in the metabolism of mycophenolic acid and its pharmacokinetics were not changed in the presence of mycophenolic acid.

Anti-epileptics + HAART (abstract 646)

Co-administered HAART and CYP450 enzyme inducing anti-epileptics: implications for HIV/epilepsy treatment in resource limited settings.

Okulicz J, Grandits G, French J, et al.

The virological response to HAART in patients on concurrent anti-epileptic therapy was evaluated in the US Military HIV Natural History Study. Patients taking enzyme-inducing anti-epileptics (phenytoin, carbamazepine, or phenobarbital; n=21) and patients using other anti-epileptics that are not enzyme-inducing (lamotrigine, levetiracetam, pregabalin, or gabapentin; n=85) for indications of seizures or neuropathy were studied. Patients were required to have received HAART for ≥ 6 months including a HAART/anti-epileptic overlap period of ≥ 28 days. Virological failure was defined as 2 consecutive viral loads ≥ 400 copies/mL after 6 months of HAART or having all viral loads in the first 6 months of HAART ≥ 400 copies/mL (at least 2 values). Patients on enzyme-inducing anti-epileptics had significantly greater virological failure (10/17, 59%) compared to patients on non-enzyme-inducing anti-epileptics (20/75, 27%) (OR 3.9 [1.3 to 11.7]; $p = 0.01$). Average viral load was also greater during HAART in the enzyme-inducing group (3.2 ± 1.3) than non-enzyme-inducing group (2.4 ± 1.2 ; $p < 0.01$). Concurrent use of enzyme-inducing anti-epileptics and HAART should be avoided when possible.

Rifabutin + LPV/r (abstract 650)

Pharmacokinetic evaluation of different rifabutin dosing strategies in African TB patients on lopinavir/ritonavir-base ART.

Naiker S, Conolly C, Weisner L, et al.

The pharmacokinetics of rifabutin were evaluated in 16 HIV/TB co-infected patients before and after the introduction of LPV/r tablets (400/100 mg twice daily). Prior to ART, all subjects were receiving rifabutin 300 mg once daily. At the introduction of ART, the patients were randomized to receive rifabutin 150 mg daily for 1 month followed by 150 mg 3 times weekly, or to receive the 3 times weekly doses followed by daily doses. Rifabutin was well tolerated at all doses. One case of uveitis occurred prior to starting LPV/r, and 1 grade 2 transaminitis and 1 grade 2 neutropenia were reported. Median rifabutin AUC and C_{max} were 3026 ng/ml.h and 297 ng/ml (300 mg once daily alone), 2307 ng/ml.h and 168 ng/ml (150 mg three times weekly with LPV/r) and 5010 ng/ml.h and 311 ng/ml (150 mg once daily with LPV/r). In the presence of LPV/r, rifabutin 150 mg once daily produced C_{max} concentrations within the recommended target range of 300-900 ng/ml.

Hepatitis

Interactions with boceprevir (abstract 118)

Clinical pharmacology of boceprevir: metabolism, excretion, and drug-drug interactions.

Kasserra C, Hughes E, Treitel M, et al.

Interaction studies of boceprevir were conducted in HIV-negative subjects using probe drugs and medications likely to be co-administered in patients with hepatitis C.

Comedication	Effect on Boceprevir			Effect on Comedication	
	AUC	Cmax	Cmin	AUC	Cmax
Midazolam				↑ 430%	↑ 177%
Ketoconazole	↑ 131%	↑ 41%			
Diflunisal	↓ 4%	↓ 14%	↑ 31%		
Clarithromycin (+ diflunisal)	↑ 21%	↑ 36%			
Ritonavir 100 mg once daily (BOC thrice daily)	↓ 19%	↓ 27%			
Ritonavir 100 mg twice daily (BOC twice daily)	↓ 18%	↓ 34%			
Pegylated interferon 2b (PEG2b)	↔	↓ 12%		↔	
Tenofovir	↑ 8%	↑ 5%		↑ 5%	↑ 32%
Efavirenz	↓ 19%	↓ 8%	↓ 44%	↑ 20%	↑ 11%
Drospirenone + Ethinylestradiol	↔			↑ 99%	↑ 57%
				↓ 24%	↔

Exposure data suggest CYP3A4 and P-gp do not contribute substantially to boceprevir metabolism and/or elimination; increased exposure to boceprevir with ketoconazole suggests involvement of another non-CYP3A4-mediated pathway. The increase in midazolam supports boceprevir as a strong, reversible inhibitor of CYP3A4. No dosage adjustment for boceprevir is needed with co-administration of PEG2b or TDF. The clinical implications of a reduced boceprevir trough concentration when co-administered with efavirenz are unclear. Boceprevir did not affect the exposure to drospirenone or ethinylestradiol in a manner likely to reduce contraceptive efficacy.

Interactions with telaprevir (abstract 119)

Pharmacokinetic interactions between ARV agents and the investigational HCV protease inhibitor telaprevir in healthy volunteers.

Van Heeswijk R, Vandevorde A, Boogaerts G, et al.

Coadministration of telaprevir (750 mg every 8 h) and boosted HIV protease inhibitors was studied in groups (n=20) of HIV- and HCV-negative subjects. Results are summarised in the table below:

Comedication	Effect on Telaprevir		Effect on Comedication	
	AUC	Cmin	AUC	Cmin
Atazanavir/ritonavir (300/100 mg once daily)	↓ 20%	↓ 15%	↑ 17%	↑ 85%
Darunavir/ritonavir (600/100 mg twice daily)	↓ 35%	↓ 32%	↓ 40%	↓ 42%
Fosamprenavir/ritonavir (700/100 mg twice daily)	↓ 32%	↓ 30%	↓ 47%	↓ 56%
Lopinavir/ritonavir (400/100 mg twice daily)	↓ 54%	↓ 52%	↑ 6%	↑ 14%

Appropriate doses have not been established for telaprevir with ritonavir boosted protease inhibitors.

Produced by www.hiv-druginteractions.org

In another study, 20 subjects started telaprevir (750 mg every 8 hours for 7 days) followed by EFV/TDF (600/300 mg once daily for 7 days) after a washout. Subsequently, they received telaprevir 1125 mg every 8 hours and EFV/TDF 600/300 mg once daily for 7 days or telaprevir 1500 mg every 12 hours and EFV/TDF 600/300 mg once daily for 7 days in a randomized order without a washout. Results are summarised in the table below:

Telaprevir Dose	Effect on Telaprevir		Effect on EFV		Effect on TDF	
	AUC	Cmin	AUC	Cmin	AUC	Cmin
1125 mg every 8 h	↓ 18%	↓ 25%	↓ 18%	↓ 10%	↑ 10%	↑ 17%
1500 mg every 8 h	↓ 20%	↓ 48%	↓ 15%	↓ 11%	↑ 10%	↑ 6%

A higher dose (1125 mg every 8 h) could partly offset the interaction with EFV.

Telaprevir + ritonavir (abstract 629)

Low dose ritonavir and the pharmacokinetics of the investigational HCV protease inhibitor telaprevir in healthy volunteers.

Garg V, Luo X, McNair L, et al.

The effects of low dose ritonavir on the pharmacokinetics of telaprevir were determined in three groups of HIV-negative subjects (n=6 per group). Subjects received telaprevir alone (750 mg every 8 h) or telaprevir (250 mg or 750 mg twice daily) with ritonavir (100 mg twice daily). Following multiple doses of telaprevir and ritonavir, no significant boosting of telaprevir exposure by ritonavir was observed. When given with ritonavir, the C_{max} and C_{min} of the lower telaprevir dose decreased by 59% and 74%, respectively compared to telaprevir alone: C_{max} and C_{min} of the higher telaprevir dose decreased by 15% and 32%.