8th International Congress on Drug Therapy in HIV Infection, Glasgow, November 2006.

The recent meeting in Glasgow saw new data on drug interactions presented, both on established and new antiretroviral agents. The following abstracts are summarised in this report. Links to the individual abstracts are provided.

**Established Drugs**

- Steady-state pharmacokinetics of tenofovir and fosamprenavir after once daily tenofovir with unboosted or ritonavir-boosted twice daily fosamprenavir in healthy volunteers.
- Plasma concentration of atazanavir in HIV patients treated with regimens including nevirapine.
- Pharmacokinetics of lopinavir and ritonavir after multiple dose administration of lopinavir/ritonavir tablet coadministered with efavirenz.
- Acetaminophen pharmacokinetics and hepatic transaminases are unaffected on atazanavir/ritonavir coadministration.
- Effect of boosted saquinavir on the pharmacokinetics and pharmacodynamics of racemic methadone in opiate-dependent patients on stable methadone maintenance therapy.
- A pilot comparative study of the antiviral activity of didanosine monotherapy administered with and without food.
- Clinical impact of antiretroviral therapy/antiepileptic drug interactions.

**New Drugs**

- No effect of TMC125 on the pharmacokinetics of oral contraceptives.
- Pharmacokinetics of TMC125 with atazanavir and atazanavir/ritonavir.
- Pharmacokinetic interaction between TMC114, a new protease inhibitor, and methadone.
- Pharmacokinetic interaction between TMC114, a new protease inhibitor, and the selective serotonin reuptake inhibitors, paroxetine and sertraline.
- Atazanavir and ritonavir increase plasma levels of MK-0518.
- Rifampin modestly reduces plasma levels of MK-0518.
- Lack of a pharmacokinetic interaction of MK-0518 on midazolam.
Established Drugs

Steady-state pharmacokinetics of tenofovir and fosamprenavir after once daily tenofovir with unboosted or ritonavir-boosted twice daily fosamprenavir in healthy volunteers. 
Coadministration of tenofovir (300 mg once daily) with fosamprenavir (1400 mg twice daily) or fosamprenavir/ritonavir (700/100 mg twice daily) was studied in healthy volunteers. When given with unboosted fosamprenavir, the AUC, Cmax and Cmin of tenofovir were reduced by 15%, 25% and 12% respectively; similar decreases were seen with boosted-fosamprenavir (decreases of 7%, 18% and 9% for AUC, Cmax and Cmin, respectively). Amprenavir exposure increased in the presence of tenofovir – increases in AUC, Cmax and Cmin were 7%, 3% and 31% for unboosted fosamprenavir and 16%, 4% and 31% for boosted fosamprenavir. The decreases in tenofovir are minor and the modest increases in amprenavir Cmin are unlikely to be clinically important.

Plasma concentration of atazanavir in HIV patients treated with regimens including nevirapine. 
Trough concentrations were obtained from 16 patients receiving nevirapine once daily (400 mg) with atazanavir/ritonavir (300/100 mg, n=7; 400/100 mg n=9). Median atazanavir trough concentrations were 340 ng/ml and 520 ng/ml for the 300 mg and 400 mg groups, respectively; values obtained from historical controls receiving 300/100 mg were 610 ng/ml. Nevirapine trough concentrations were 3900 ng/ml and 4000 ng/ml for the two groups and were comparable to literature values for patients treated with nevirapine alone (3700 ng/ml). Given the decrease in atazanavir trough concentrations, relative to historical controls, therapeutic drug monitoring of atazanavir may be appropriate for patients (especially if treatment experienced) receiving this combination.

Pharmacokinetics of lopinavir and ritonavir after multiple dose administration of lopinavir/ritonavir tablet coadministered with efavirenz. 
A dose increase to 533/133 mg was advised when lopinavir/ritonavir capsules were coadministered with efavirenz. As this dose increase is not possible with the new tablet formulation (200/100 mg lopinavir/ritonavir per tablet), the coadministration of 2 tablets of lopinavir/ritonavir (400/100 mg twice daily) with efavirenz (600 mg once daily) was studied in 21 HIV- subjects. Subjects received 3 lopinavir/ritonavir capsules (400/100 mg twice daily for 10 days) followed by 2 lopinavir/ritonavir tablets with efavirenz for 10 days. Lopinavir PK parameters were determined on days 10 (3 capsules alone) and 20 (2 tablets + EFV). Mean (± sd) lopinavir Cmax, AUC and Ctrough values on day 10 were 11.8±3.3 µg/ml, 95.7±33.7 µg.h/ml and 6.8±3.3 µg/ml, respectively. Cmax, AUC and Ctrough values obtained on day 20 were 10.5±4.0 µg/ml, 84.9±17.8 µg.h/ml and 5.0±2.7 µg/ml, respectively. Coadministration of efavirenz with the lopinavir/ritonavir tablet decreased lopinavir AUC and Ctrough by ~20% and 27%, respectively, compared to the capsule formulation administered alone. The concentrations obtained with the tablet + EFV were within the range of concentrations previously demonstrated to be efficacious in clinical trials.
Acetaminophen pharmacokinetics and hepatic transaminases are unaffected on atazanavir/ritonavir coadministration.


The pharmacokinetics of paracetamol (acetaminophen, 1 g twice daily) given alone (n=24) and in combination (n=10) with atazanavir/ritonavir (300/100 mg once daily) was studied in HIV- subjects. Coadministration had no effect on the pharmacokinetics, glucuronidation or sulfation of paracetamol. Point estimates (90% CI) for paracetamol Cmax and AUC were 0.87 (0.77, 0.99) and 0.97 (0.91, 1.03), respectively (combination vs alone). Atazanavir and ritonavir concentrations were similar to previous reports. Coadministration of atazanavir/ritonavir caused no significant increases in hepatic transaminases (AST or ALT) relative to paracetamol alone.

Effect of boosted saquinavir on the pharmacokinetics and pharmacodynamics of racemic methadone in opiate-dependent patients on stable methadone maintenance therapy.


The pharmacokinetics of total, R- and S-methadone were determined in 12 HIV- subjects stable on methadone maintenance therapy (60-120 mg per day) when given alone or in combination with saquinavir/ritonavir (1000/100 mg twice daily). Coadministration with saquinavir/ritonavir decreased systemic exposure of R-methadone by 18.6%; however, there were no signs or symptoms of methadone withdrawal. The decrease in R-methadone exposure is not clinically relevant and the triple combination was well tolerated.

A pilot comparative study of the antiviral activity of didanosine monotherapy administered with and without food.


The pharmacokinetics of enteric coated didanosine were determined in HIV+ subjects when administered with a fat meal (n=10) or on an empty stomach (n=11). Mean trough didanosine concentrations were 0.037 mg/L when administered with food and 0.041 mg/L when administered fasting. There was no difference in antiviral response between the two groups.

Clinical impact of antiretroviral therapy/antiepileptic drug interactions.


A case was reported describing the complex interactions that occurred between antiretroviral medications and antiepileptic medications in an alcoholic HIV subject. The subject was stable on efavirenz (600 mg once daily), nelfinavir (1250 mg twice daily) and abacavir (300 mg twice daily), but this was stopped when phenytoin was prescribed for the control of myclonic jerks. A high phenytoin maintenance dose (900 mg daily) was initially required, but carbamazepine (400 mg three times daily) was added and the phenytoin was reduced (350 mg twice daily). NRTI-based antiretroviral therapy was started (zidovudine, lamivudine, abacavir and tenofovir), but, due to resistance, this had to be changed to saquinavir (1000 mg twice daily), ritonavir (200 mg twice daily), lopinavir/ritonavir (400/100 mg twice daily) and efavirenz (600 mg once daily). Low plasma concentrations resulted in saquinavir being increased to 1200 mg twice daily and efavirenz being discontinued. Carbamazepine was reduced to 600 mg daily due to high plasma concentrations. After a few months the subject refused to take his antiretroviral medications, resulting in high phenytoin and carbamazepine concentrations which required dose reduction (phenytoin 300 mg twice daily). Further adjustment of the antiepileptic medications will potentially be required when antiretroviral medications are resumed.
New Drugs

No effect of TMC125 on the pharmacokinetics of oral contraceptives.
The effect of steady state TMC125 (200 mg twice daily) on pharmacokinetics of ethinylestradiol (35 µg once daily) and norethindrone (1 mg once daily) was studied in 30 HIV- females. Coadministration of TMC125 increased ethinylestradiol AUC, Cmax and Cmin by 22%, 33% and 9%, respectively. Norethindrone AUC decreased by 5%, Cmax increased by 5% and Cmin decreased by 22%. These changes are not considered clinically relevant and no loss in contraceptive efficacy is expected when TMC125 is coadministered.

Pharmacokinetics of TMC125 with atazanavir and atazanavir/ritonavir.
The pharmacokinetics of TMC125 were determined in 2 groups of HIV- subjects (n=16) after administration of TMC125 (800 mg twice daily) with atazanavir (400 mg once daily) or atazanavir/ritonavir (300/100 mg once daily). Exposure to TMC125 increased when given with atazanavir (Cmin increased by 58%, Cmax by 47%, AUC by 50%) and to a lesser extent with atazanavir/ritonavir (Cmin increased by 26%, Cmax by 30%, AUC by 30%). When atazanavir was coadministered with TMC125, atazanavir Cmin decreased by 47%, Cmax by 3% and AUC by 17%. Coadministration of TMC125 to atazanavir/ritonavir decreased atazanavir Cmin by 38%, Cmax by 3% and AUC by 14%. The increase in TMC exposure is not considered to be clinically relevant; however, due to the decrease in atazanavir Cmin, atazanavir should only be used with TMC125 in the presence of low dose ritonavir.

Pharmacokinetic interaction between TMC114, a new protease inhibitor, and methadone.
The effect of TMC114/ritonavir (600/100 mg twice daily) on the pharmacokinetics of R- and S-methadone was studied in 16 HIV- subjects stable on methadone maintenance therapy (60-200 mg per day). Coadministration decreased Cmin, Cmax and AUC of both active R-methadone (15%, 24%, 16%) and inactive S-methadone (40%, 44%, 36%). Moderate (grade 2) withdrawal symptoms were reported in one subject during the maintenance period and in another subject during the combination period. No a-priori adjustment of methadone dosage is required as the effect on R-methadone exposure was small and withdrawal symptoms were rare.

Pharmacokinetic interaction between TMC114, a new protease inhibitor, and the selective serotonin reuptake inhibitors, paroxetine and sertraline.
Coadministration of TMC114/ritonavir (400/100 mg twice daily) with paroxetine (20 mg once daily) or sertraline (50 mg once daily) was studied in 2 groups of HIV- subjects (16 per group). The pharmacokinetics of TMC114 were not significantly affected by paroxetine or sertraline, but decreases in AUC were observed for paroxetine (40%) and sertraline (50%). Similar results are expected with TMC114/ritonavir 600/100 mg twice daily (the dose recommended for treatment experienced patients). Although no correlation between plasma concentrations of SSRIs and antidepressant response, clinical monitoring is recommended and dose titration of the SSRI may be indicated when sertraline or paroxetine is coadministered with TMC114/ritonavir.
Atazanavir and ritonavir increase plasma levels of MK-0518.  
The effects of atazanavir/ritonavir (300/100 mg once daily) on the pharmacokinetics of the integrase inhibitor MK-0518 (400 mg twice daily) were studied in 10 HIV-subjects. Coadministration resulted in increases in MK-0518 Cmin (77%), AUC (41%) and Cmax (24%) values. However, the combination was generally well tolerated.

Rifampin modestly reduces plasma levels of MK-0518.  
The effect of rifampicin (600 mg once daily for 14 days) on the pharmacokinetics of a single dose of the integrase inhibitor MK-0518 (400 mg) was studied in 10 HIV-subjects. Rifampicin reduced the Cmin, AUC and Cmax of MK-0518 by 61%, 40% and 38%, respectively.

Lack of a pharmacokinetic interaction of MK-0518 on midazolam.  
The effect of multiple doses of MK-0518 (400 mg twice daily for 14 days) on a single dose of midazolam (2 mg) was studied in 10 HIV-subjects. Coadministration of MK-0518 had no significant effect on midazolam AUC (8% decrease) or Cmax (3% increase).