

**Drug Interaction Studies presented at the  
12<sup>th</sup> International Workshop on Clinical Pharmacology of HIV Therapy,  
Miami, April 2011.**

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

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## New ARVs

### **Cobicistat and desipramine, EFV or digoxin**

#### **The effect of cobicistat on cytochrome P450 2D6, 2B6 and P-glycoprotein using phenotypic probes.**

*German P, Mathias A, Wei L, et al.*

Abstract: O\_01

Cobicistat is a CYP3A inhibitor that is being developed as a pharmaco-enhancer. This open-label, three cohort crossover study investigated the non-CYP3A interactions of steady-state cobicistat and single doses of probe drugs for CYP2D6 (desipramine, n=9), CYP2B6 (EFV, n=22) and P-gp (digoxin, n=17). Coadministration increased desipramine AUC by ~58-65% and increased C<sub>max</sub> by ~13%. There was no change in EFV AUC, but a small reduction in C<sub>max</sub> (~13%). Digoxin AUC was unchanged, but C<sub>max</sub> increased by ~41%. Pharmacokinetics of cobicistat were similar to historical controls. All study drugs were safe and well tolerated. Based on a <2-fold increase in desipramine exposure, cobicistat may be classified as a weak CYP2D6 inhibitor. Additional studies with substrates of CYP2D6, CYP2B6 and P-gp are not required and no dose modifications are needed.

### **EVG/cobicistat/FTC/TDF and oral contraceptives**

#### **Pharmacokinetic interaction between norgestimate/ethinyl estradiol and EVG/COBI/FTC/TDF single tablet regimen.**

*German P, Wang M, Warren D, Kearney BP.*

Abstract: O\_17

This open-label fixed-sequence study investigated the pharmacokinetics of a combined oral contraceptive containing 25 µg ethinylestradiol and norgestimate with a fixed dose combination tablet containing EVG, cobicistat, FTC and TDF ("quad"). Steady-concentrations of ethinylestradiol, norelgestromin (the active metabolite of norgestimate), EVG and cobicistat were determined in 15 HIV-negative women receiving the oral contraceptive alone or with the "quad" tablet. Coadministration decreased the AUC of ethinylestradiol by ~25% and increased the AUC of norelgestromin by ~2-fold. Concentrations of EVG and cobicistat were within the range of values observed in previous studies. Changes in progesterone and FSH were similar in both treatment phases, but changes in LH were greater in the combination phase. In light of the decrease in ethinylestradiol, it is recommended that when coadministered with the "quad" tablet, oral contraceptives should contain at least 30 µg ethinylestradiol.

### **EVG/cobicistat and acid reducing agents**

#### **Effect of acid reducing agents on the relative bioavailability and pharmacokinetics of cobicistat-boosted elvitegravir.**

*Mathias A, Koziara J, Wei L, et al.*

Abstract: P\_13

The effects of omeprazole (20 mg once daily) or famotidine (40 mg once daily) on the pharmacokinetics of EVG and cobicistat were studied in HIV-negative subjects (n=11 per group). When omeprazole was administered 2 h prior to EVG and cobicistat the AUC and C<sub>max</sub> of EVG increased by 10% and 16%, but those of cobicistat decreased by 8% and 10%. Separating omeprazole and EVG and cobicistat by 12 h had no effect (<10% change) on the AUC or C<sub>max</sub> of EVG or cobicistat. Administration of famotidine 12 h apart from EVG and cobicistat had no effect (<10% change) on the AUC or C<sub>max</sub> of EVG or cobicistat. Similar results were observed in a separate study (n=16) of the simultaneous coadministration of famotidine with EVG and cobicistat. No dosing restrictions are necessary on the administration of EVG and cobicistat with proton pump inhibitors. Based on the available data, EVG and cobicistat should be administered simultaneously with, and/or 12 hours after, dosing of H<sub>2</sub>-receptor antagonists.

*Abbreviations: ATV, atazanavir; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; FPV, fosamprenavir; FTC, emtricitabine; LPV, lopinavir; MVC, maraviroc; NVP, nevirapine; RAL, raltegravir; RTV/r, ritonavir; TDF, tenofovir; TPV, tipranavir; 3TC, lamivudine.*

### **Dolutegravir and TPV or EFV**

#### **Effects of enzyme inducers, tipranavir and efavirenz, on the pharmacokinetics of the integrase inhibitor, dolutegravir (S/GSK1349572).**

*Song I, Borland J, Lou Y, et al.*

Abstract: O\_02

Dolutegravir (DTG, S/GSK1349572) is an unboosted, once daily integrase inhibitor currently in late stage development. The effect of TPV/r (500/200 mg twice daily, n=14) or EFV (600 mg once daily, n=12) on the pharmacokinetics of DTG (50 mg once daily) was studied in HIV- subjects. The combinations were generally well tolerated, but 4 of the 18 subjects discontinued the TPV/r study due to increases in ALT related to TPV/r. Coadministration with TPV/r decreased DTG AUC, C<sub>max</sub> and C<sub>trough</sub> by 59%, 46% and 76%, respectively. Similarly, coadministration with EFV decreased DTG AUC, C<sub>max</sub> and C<sub>trough</sub> by 57%, 39% and 75% respectively. The decrease in DTG exposure is likely due to induction of UGT1A1 and CYP3A4. Since DTG concentrations remained above the protein adjusted-IC<sub>90</sub> for wild type HIV, the authors concluded that DTG can be administered with EFV or TPV/r in integrase-naïve subjects without dosage adjustments.

*Editorial Comment: There was discussion around the recommendation given the magnitude of effect.*

### **Dolutegravir and food**

#### **Effect of food on the pharmacokinetics of the integrase inhibitor, dolutegravir (S/GSK1349572).**

*Song I, Borland J, Chen S, et al.*

Abstract: P\_12

This randomised, open label, crossover study investigated the effect of low fat (300 kcal, 7% fat) moderate fat (600 kcal, 30% fat) or high fat (870 kcal, 53% fat) meals on the pharmacokinetics of single dose DTG in 18 HIV-negative subjects. When compared to DTG given under fasting conditions, coadministration with low, moderate or high fat meals increased DTG AUC by 33%, 41% and 66%, respectively; C<sub>max</sub> increased by 46%, 52% and 67%, respectively. T<sub>max</sub> increased from 2.1 h (fasting) to 3.0 h (low fat), 4.0 h (moderate fat) and 5.0 h (high fat). The effect of food was not considered clinically significant and DTG can be given with or without food and without regard to fat content.

### **Lersivirine and rifabutin**

#### **Effect of rifabutin on the pharmacokinetics (PK) of lersivirine, and lersivirine on the PK of rifabutin/25-O-desacetyl-rifabutin, in healthy subjects.**

*Vourvahis M, Wang R, Choo HW, Tawadrous M.*

Abstract: P\_08

This open label, randomised, three way crossover study investigated the interaction between lersivirine (1000 mg once daily) and rifabutin (300 mg once daily) in 18 HIV-negative subjects. Coadministration decreased lersivirine AUC, C<sub>max</sub> and C<sub>min</sub> by 34%, 25% and 58%, respectively. The rifabutin concentration profile or overall exposure did not change in the presence of lersivirine; however, lersivirine lowered exposure of 25-O-desacetyl rifabutin (AUC, C<sub>max</sub> and C<sub>min</sub> decreased by 27%, 27% and 15%, respectively). Lersivirine dose modification may be required, but the decreased exposure to the rifabutin metabolite is unlikely to be of clinical significance as it contributes only up to 10% of total antimicrobial activity.

Note: In February 2011, the FDA placed a hold on the development of GSK2248761

### **Formulation and food effects for GSK2248761**

#### **GSK2248761 development; formulation and food effect.**

*Johnson M, Kim J, Lou Y, et al.*

Abstract: P\_06

Two crossover studies were performed in HIV-negative subjects to evaluate the bioavailability and effect of food on capsule or tablet formulations of GSK2248761, a next generation NNRTI. Compared to the gel capsule (given with food), the tablet forms given fasted had similar, or better, AUC and Cmax. A moderate food effect was observed with the tablet formulations when administered with a moderate (30%) fat meal (57% increase in Cmax, 33% increase in AUC, no change in C24). All three tablet formulations achieved higher Cmax and AUC compared to the gel capsule with negligible impact on C24. As all of the tablet formulations performed reasonably well, the final choice for further development (roller compaction tablet formulation) was made based on ease of future manufacturing. The modest food effect is not thought likely to be clinically significant or to require food restrictions for dosing.

### **GSK2248761 and statins**

#### **Inhibition potential for GSK2248761, a next generation NNRTI, on HMGCoA reductase inhibitors simvastatin, atorvastatin and rosuvastatin.**

*Kim J, Ford SL, Lou Y, et al.*

Abstract: P\_09

This study investigated the possible enzyme inhibition by GSK2248761 (a novel next generation NNRTI) on simvastatin and atorvastatin (both CYP3A4 and OATP1B1 substrates) and on rosuvastatin (an OATP1B1 substrate). Subjects (n=12) received single doses of simvastatin (20 mg), atorvastatin (20 mg) and rosuvastatin (10 mg) alone and after multiple doses of GSK2248761 (200 mg once daily). Coadministration increased simvastatin AUC and Cmax by 3.7- and 4.3-fold: the AUC and Cmax of simvastatin acid increased by 3.0- and 3.9-fold. Atorvastatin AUC and Cmax increased by 47% and 25%, with the AUC and Cmax of ortho-hydroxy-atorvastatin decreasing by 24% and 59%. Rosuvastatin AUC and Cmax increased by 26% and 32%. Based on these results, atorvastatin or rosuvastatin would be preferable to simvastatin when coadministered with GSK2248761.

## Existing ARVs

### MVC and ETR

#### Pharmacokinetic interaction between maraviroc and etravirine: a multicentre study in HIV-patients receiving an antiretroviral regimen without PI.

Solas C, Garraffo R, Gagnieu MC, et al.

Abstract: O\_13

ETR and MVC steady-state concentrations were determined in 64 HIV+ patients receiving ETR and MVC in the absence of protease inhibitors. Subjects were receiving MVC 300 mg twice daily (n=28) or 600 mg twice daily (n=36) and ETR 200 mg twice daily. In total 100 concentrations were determined, of which 77 were classed as trough (12-14 h post dose). MVC C<sub>avg</sub> and C<sub>trough</sub> for the 300 mg group were 59 ng/ml (29-112, n=37) and 53 ng/ml (27-75, n=28). For the 600 mg group, MVC C<sub>avg</sub> and C<sub>trough</sub> were 64 ng/ml (36-92, n=63) and 60 ng/ml (36-85, n=49). C<sub>avg</sub> was below 75 ng/ml in 62% of the whole population, with no difference between the two dosing groups. C<sub>trough</sub> was below <75 ng/ml in 67% of the whole population, (75% in 300 mg group, 63% in 600 mg group). ETR trough concentrations were 723 ng/ml (478-1055, n=76) and ~180-fold higher than the protein adjusted EC<sub>50</sub> for wild type virus. MVC trough concentrations were similar between both doses with a high proportion (65-70%) below the proposed target of 75 ng/ml.

*Editorial Comment: The method of determining C<sub>avg</sub> here is different from that used previously by Pfizer. There was considerable discussion about MVC target concentrations.*

### MVC, ETV and RAL

#### Clinical pharmacology of complex regiment of antiretroviral therapy including etravirine, maraviroc and raltegravir.

Corcione S, Calcagno A, Bonora S, et al.

Abstract: P\_29

Trough concentrations (10-14 h post dose) were determined in groups of HIV+ patients receiving RAL, ETR and MVC (n=29) or RAL plus other drugs (n=30). MVC concentrations were significantly lower in the ETR containing group (57 vs 173.5 ng/ml) despite a dose increase to 600 mg twice daily for this group.

### MVC and digoxin

#### Lack of a clinically relevant effect of maraviroc on the pharmacokinetics of digoxin in healthy volunteers.

Vourvahis M, Fang J, Choo HW, Heera J.

Abstract: P\_14

The effect of MVC (300 mg twice daily for 6 days) on single doses of digoxin (0.25 mg) was studied in an open label, fixed sequence, cross over study in 12 HIV-negative subjects. No effect on digoxin AUC was observed and C<sub>max</sub> increased by 4%. The lack of a clinically relevant effect on digoxin exposure suggests that MVC is not a clinically significant inhibitor of P-gp and no dose adjustments are warranted with P-gp substrates when coadministered with maraviroc.

### **MVC and ATV/r**

#### **Modeling of maraviroc pharmacokinetics in the presence of atazanavir/ritonavir in healthy volunteers and HIV-1-infected patients.**

*Weatherley B, Vourvahis M, McFadyen L.*

Abstract: P\_05

This analysis used a semi-physiological MVC PK model to explore the interaction of MVC with ATV/r using data from two studies in which ATV/r (300/100 mg once daily) was given with MVC to HIV-negative subjects (300 mg twice daily) or treatment naïve HIV+ subjects (150 mg once daily). Data from both sets of subjects were consistent in the effect of ATV/r on MVC exposure. In HIV+ subjects, MVC 150 mg once daily with ATV/r produced less peak-trough fluctuation with lower C<sub>max</sub> and C<sub>avg</sub>, but similar C<sub>min</sub> and effective constant concentrations to HIV-negative subjects given MVC 300 mg twice daily in the absence of ATV/r.

### **MVC and DRV/r**

#### **Once daily maraviroc (OD) MVC in combination with ritonavir-boosted darunavir (800/100mg): What is the optimal MVC dose? 300mg OD or 150mg OD?**

*Okoli C, Marco S, William S, et al.*

Abstract: P\_37

A retrospective review of MVC plasma concentrations (C<sub>trough</sub> and C<sub>max</sub>) from patients receiving MVC (300 mg twice daily; group 1) with TDF/FTC, or MVC (300 mg once daily; group 2) with DRV/r (800/100 mg once daily), or MVC (150 mg once daily; group 3) with DRV/r (800/100 mg once daily) was performed. Median C<sub>max</sub> values for groups 1, 2 and 3 were 384 (n=8), 773 (n=37) and 364 (n=2) ng/ml, respectively. Median trough concentrations for groups 1, 2 and 3 were 48 (n=10), 70 (n=36) and 50 (n=16) ng/ml, respectively. MVC trough concentrations were significantly higher in group 2 (300 mg once daily + DRV/r), but no differences in C<sub>max</sub> were noted between the groups. MVC C<sub>max</sub> and C<sub>trough</sub> values were higher in Black patients than in White patients (C<sub>max</sub> 801 vs 383 ng/ml; C<sub>trough</sub> 92 vs 49 ng/ml). Ethnicity was the only factor independently associated with C<sub>max</sub>, while dose and ethnicity were independently associated with C<sub>trough</sub>. All regimens were well tolerated.

### **FPV/r and olanzapine**

#### **Effect of fosamprenavir/ritonavir on the pharmacokinetics of single-dose olanzapine in healthy volunteers.**

*Burger D, Jacobs BS, Colbers EPH, et al.*

Abstract: P\_10

Olanzapine is primarily metabolised by CYP1A2 and UGT and high doses of RTV had been shown to increase elimination of olanzapine. The effect of low dose RTV is unknown, but it has been hypothesised that olanzapine exposure would be similar following 10 mg alone or 15 mg with FPV/r. This open label, randomised, two period, cross over study investigated the effect of FPV/r (700/100 mg twice daily) on single doses of olanzapine (10 mg alone or 15 mg with FPV/r) in 20 HIV-negative subjects. Increasing the dose of olanzapine with FPV/r produced an equivalent AUC and a 32% increase in C<sub>max</sub>: geometric mean ratios (FPV/r vs alone) for olanzapine AUC, C<sub>max</sub> and half life were 1.00, 1.32 and 0.67 respectively. AUC, C<sub>max</sub> and C<sub>min</sub> of amprenavir were consistent with data from the literature. The dose of olanzapine should be increased by 50% when combined with FPV/r.

### LPV/r and rifabutin

#### Pharmacokinetic evaluation of rifabutin and its active metabolite LM565 coadministered with lopinavir/r in HIV-infected patients.

Cusato M, Matteeli A, Villani P, et al.

Abstract: O\_14

This preliminary study investigated rifabutin and LM565 (25-O-desacetyl rifabutin) exposures in 14 HIV/TB coinfecting patients starting LPV/r (400/100 mg twice daily) and rifabutin (150 mg 3 times weekly). Control values for rifabutin alone (300 mg once daily) were obtained prior to starting LPV/r. Control values for LPV/r alone were obtained 10 weeks after stopping rifabutin. Pharmacokinetic parameters (median, range) are shown in the table. Rifabutin AUC was below the target of 4.5 µg.h/ml in 42% of patients at week 2 of therapy and in 28% of patients at week 6 of therapy. The change in LM565 AUC was significantly greater than the change in rifabutin AUC. When given with LPV/r, rifabutin 150 mg three times weekly may result in low rifabutin concentrations.

	Rifabutin alone	Rifabutin + LPV/r		LPV/r alone
		Week 2	Week 6	
<b>Median (range) Rifabutin</b>				
AUC0-24h (µg.h/mL)	3.01 (1.4-10.5)	4.2 (1.9-5.5)	2.4 (1.3-6.4)	
Ctrough (ng/mL)	91 (11-152)	87 (20-104)	42 (8-114)	
Cmax (ng/mL)	330 (106-1950)	309 (106-564)	239 (151-526)	
<b>Median (range) LM565</b>				
AUC0-24h (µg.h/mL)	0.7 (0.18-2.4)	1.6 (0.35-2.6)	1.6 (0.79-2.4)	
Ctrough (ng/mL)	4 (3-10)	33 (10-71)	30 (13-75)	
Cmax (ng/mL)	52 (32-72)	115 (90-190)	122 (40-221)	
<b>Median (range) LPV</b>				
AUC0-12h (µg.h/mL)		143 (86.3-278)	137 (46.8-303)	124 (74.7-139.4)
Ctrough (µg/mL)		10 (5.6-20)	8.8 (1-17.6)	7.8 (5.1-9)
Cmax (µg/mL)		14.4 (9.2-34)	16.3 (15.4-33)	13.7 (7.8-20.9)

*Editorial Comment: This study highlights the importance of the active metabolite when rifabutin is given with LPV/r.*

### ETV and ritonavir and/or food

#### No effect of ritonavir or timing of food intake on etravirine pharmacokinetics in HIV-negative volunteers.

Kakuda TN, De Smedt G, Peeters M, Woodfall BJ.

Abstract: P\_11

In an open label, randomised, four way, crossover study HIV-negative subjects (n=20 per group) received single doses of ETR (200 mg) under fed or fasting conditions, alone or 4 h before or after single doses of RTV (100 or 400 mg). When ETR was given with food, simultaneous coadministration of RTV 100 mg had no effect on ETR AUC or Cmax. Simultaneous coadministration of RTV 400 mg had no effect on ETR AUC (8% decrease) or Cmax (9% decrease) relative to RTV 100 mg. Similarly, administering RTV 100 mg 4 h after or before ETR had no effect ETR AUC and Cmax relative simultaneous administration. Giving ETR in the fasted state decreased ETR AUC and Cmax by 17% and 23%. There was no effect on ETR AUC or Cmax when ETR was administered fasted, but RTV was administered with food (relative to ETR and RTV both with food). Separation of ETR and RTV by time or food intake is not expected to result in clinically relevant changes to ETR pharmacokinetics in multiple dose trials.

### **TDF/FTC/EFV and food**

#### **Effect of food on the steady state pharmacokinetics of a fixed-dose combination tablet containing tenofovir, emtricitabine and efavirenz in HIV-positive Ugandan patients.**

*Lamorde M, Byakika-Kibwika P, Kiweewa F, et al.*

Abstract: P\_39

An open label, two phase, cross over study was conducted in 15 HIV+ Ugandan patients to determine the effect of food (650 kcal, 19 g fat) on the pharmacokinetics of TDF, FTC and EFV administered as a fixed dose combination tablet (Atripla<sup>®</sup>, once daily). TDF C<sub>max</sub> and AUC increased by 4% and 19% in the presence of food; C<sub>24h</sub> decreased by 1%. The C<sub>max</sub>, AUC and C<sub>24h</sub> of FTC decreased by 17%, 13% and 9% in the presence of food. When given with food, EFV C<sub>max</sub>, AUC and C<sub>24h</sub> increased by 47%, 13% and 1%, respectively. The significant increase in EFV C<sub>max</sub> with food may suggest that patients experiencing EFV-related toxicity could take this fixed dose combination without food.

### **RAL and DRV/r**

#### **Pilot pharmacokinetic study of dual therapy with raltegravir 400 mg BID and darunavir/r 800/100 mg QD in HIV-1 infected patients.**

*Martinez-Rebollar M, Munoz A, Perez I, et al.*

Abstract: P\_30

The pharmacokinetics of RAL (400 mg twice daily) and DRV/r (800/100 mg once daily) were studied in 15 HIV+ subjects. Geometric mean values for DRV AUC, C<sub>max</sub> and C<sub>trough</sub> were 69280 ng.h/ml, 7630 ng/ml and 1330 ng/ml, respectively. DRV C<sub>trough</sub> was above the IC<sub>90</sub> for both wild type (55 ng/ml) and resistant (550 ng/ml) HIV-1 strains. Geometric mean values for RAL AUC, C<sub>max</sub> and C<sub>trough</sub> were 4050 ng.h/ml, 970 ng/ml, 80 ng/ml, respectively. No side effects were described and at week 24 all patients had viral loads below 37 copies/ml.

*Editorial Comment: The abstract stated a value of 500 ng/ml for the IC<sub>90</sub> for resistant HIV-1 strains – this should have been 550 ng/ml.*

### **RAL and ribavirin**

#### **Lack of relevant pharmacokinetic interaction between raltegravir and ribavirin in HIV/HCV coinfecting patients.**

*Piedoux S, Piroth L, Solas C, et al.*

Abstract: P\_38

A retrospective analysis was performed on data from 11 HIV/HCV coinfecting patients who received RAL (400 mg twice daily, initiated prior to HCV therapy) and ribavirin (initiated at 400-1600 mg daily). HIV viral load remained undetectable in all patients during anti-HCV therapy. HCV early virological response was achieved in 8 patients and no patient experienced major hepatic toxicity. Median ribavirin trough concentration at steady state was 1.98 mg/L (ribavirin dose 100-2000 mg/day). Median RAL trough concentration in the presence of ribavirin was 0.051 mg/L compared to 0.071 mg/L prior to ribavirin. The combination of raltegravir and ribavirin/peg-interferon appears to be safe, with RAL and ribavirin plasma concentrations similar to those previously described.

### **ATV and 50 or 100 mg RTV**

**No changes in atazanavir exposure when boosted with 100mg or 50mg of ritonavir in healthy volunteers.**

*Estevez J, Molto J, Tuneu L, et al.*

Abstract: P\_31

The pharmacokinetics of ATV (300 mg once daily) and RTV (50 or 100 mg once daily, oral solution) were evaluated in 12 HIV-negative subjects in a cross over, single blind, two period study. No differences were observed in ATV total systemic exposure between the two RTV doses (AUC 47.09 vs 50.62 mg.h/L; Cmax 5.07 vs 5.19 mg/L; 50 vs 100 mg RTV). ATV Ctrough were above 0.15 mg/L in all subjects. RTV exposures were lower after the 50 mg dose than after the 100 mg dose (AUC 4.5 vs 12.54 mg.h/L; Cmax 0.75 vs 1.82 mg/L). RTV Ctrough could not be calculated since all of 50 mg group and the majority of 100 mg group values were below the limit of quantification. The lower RTV dose was associated with a lower impact on lipid profile.

### **ATV and smoking**

**The influence of tobacco smoking on atazanavir pharmacokinetics.**

*Blonk MI, Colbers EPH, Child M, et al.*

Abstract: P\_34

A retrospective analysis was performed on data from two ATV studies to determine the effect of moderate tobacco use (up to 10 cigarettes per day) on the pharmacokinetics of ATV (400 mg once daily) or ATV/r (300/100 mg once daily). Data were available from 68 subjects (18 smokers) taking ATV alone and from 64 subjects (15 smokers) taking ATV/r. No statistically significant differences in ARV AUC, Cmax or Cmin were observed between smokers and non-smokers in either the ATV alone group or the ATV/r group. ATV Cmin was above the target of 0.12 mg/L in all subjects receiving ATV/r. For subjects receiving ATV alone, 7/50 non-smokers and 6/18 smokers had subtherapeutic Cmin values.

### **Doxycycline and PIs or NNRTIs**

**Lack of pharmacokinetic interaction between doxycycline and protease inhibitors or non-nucleoside reverse transcriptase inhibitors in HIV patients.**

*Le Bel J, Abgrall S, Laouenan C, et al.*

Abstract: P\_15

The effect on doxycycline on antiretroviral concentrations was investigated in HIV+ subjects starting malaria prophylaxis. Trough concentrations of ATV alone (n=1) ATV with RTV (n=14), LPV/r (n=23), EFV (n=17) and NVP (n=10) were determined in subjects stable on regimens containing each drug prior to starting doxycycline and after at least 15 days of doxycycline therapy. No patient was infected with malaria and no statistically significant effect on antiretrovirals was observed when tested by class (i.e. PIs or NNRTIs).