

# THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

## Report From Boston (*continued*): The 13<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI)

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### Clinical Pharmacology Update

By *Adriana Andrade, M.D., M.P.H.*

Clinical pharmacology received substantial attention during the 13<sup>th</sup> CROI, and several studies presented at this conference increased our understanding of drug interactions, therapeutic drug monitoring, and the pharmacokinetics of antiretrovirals in pregnancy. Discussed below are selected presentations from the conference.

#### Drug Interactions

##### Tipranavir, Etravirine, and Darunavir

Protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) undergo metabolism through the cytochrome P450 (CYP450) pathway and can also inhibit and/or induce these enzymes, making them susceptible to clinically significant pharmacokinetic interactions. Because PIs and NNRTIs are often combined in salvage regimens, it is important to understand drug interactions among these agents. Tipranavir (TPV), the PI most recently approved by the FDA, is a substrate, inhibitor, and potent inducer of the CYP3A4 enzyme and also induces the drug efflux pump P-glycoprotein (P-gp). TPV markedly lowers the plasma concentrations of several PIs; therefore, its co-administration with other PIs is contraindicated [Walmsley S, et al. XV International AIDS Conference, Bangkok 2004, Abstract WeOrB1236]. Etravirine (TMC125), a second-generation investigational NNRTI, is a substrate of both CYP3A4 and P-gp. Although TPV does not seem to affect the metabolism of any currently approved NNRTIs, the drug interaction between etravirine and TPV has not been characterized.

Schöller and colleagues evaluated the safety and pharmacokinetics of etravirine when co-administered with ritonavir (RTV)-boosted TPV (TPV/r) [Abstract 583]. In their study, 24 healthy subjects (19 males, 5 females) first received etravirine 800 mg bid for 8 days, followed by a 14-day washout period. They were then subdivided in two groups of 12 each. In group I, subjects received TPV/r 500/200 mg bid from day 1 to 16,

then etravirine 800 mg bid from day 9-16. In group II, participants were given TPV/r 500/200 mg bid from day 1 to 16, then etravirine 800 mg bid from day 1 to 8. The etravirine steady-state mean AUC<sub>12h</sub> decreased by 76% and C<sub>min</sub> by 82% when co-administered with TPV/r compared to when given alone. TPV and RTV AUC<sub>12h</sub> increased by 18% and 23%, respectively. Thirty-eight percent of the subjects discontinued study treatment because of drug toxicity, and 25% of the discontinuations occurred during the TPV treatment period.

These results probably reflect the induction of P-gp and hepatic CYP3A4 activity by TPV, with consequent effects on etravirine metabolism. Given the significant reduction in etravirine plasma concentration that was produced by co-administration of TPV, this NNRTI joins the list of antiretroviral agents that cannot be given with TPV. This is unfortunate, given the need to identify additional drugs for PI/NNRTI combinations that could be used for the treatment of treatment-experienced patients.

A second poster described the pharmacokinetic interactions between etravirine and darunavir (TMC114/r), a second-generation investigational PI. Like etravirine, darunavir is a substrate of CYP3A4 and P-gp, and it can also induce the CYP3A4 pathway; consequently, there is considerable potential for drug interaction when these two agents are combined. Boffito and coworkers conducted an open label steady-state study to evaluate the pharmacokinetic parameters and safety profile of combined etravirine and darunavir given with at least 2 NRTIs, with or without enfuvirtide (ENF, T20) in 10 multi-class experienced HIV-infected patients [Abstract 575c].

Etravirine did not significantly alter the pharmacokinetic parameters of darunavir, and there was a modest reduction in etravirine exposure when compared to historical control data. Etravirine pharmacokinetic parameters were also comparable to historical data from patients taking etravirine with boosted PIs. All patients achieved a decrease in plasma HIV RNA of at least a 2 log<sub>10</sub> at week 6, and co-administration of etravirine and darunavir was safe and well tolerated.

Although limited by their small sample size, these results suggest that etravirine and darunavir in combination do not cause harmful pharmacokinetic interactions, making these two drugs good candidates for salvage therapy, a strategy that is now being studied in the Tibotec-sponsored DUET studies.

##### Lopinavir/Ritonavir and Tipranavir

Harris and colleagues explored dose adjustment strategies to overcome the drug interaction between lopinavir/ritonavir (LPV/r) and TPV [Abstract 584]. In their study, 13 HIV-infected subjects on a stable regimen of LPV/r 400/100 mg bid (no other PIs or NNRTIs) added TPV and RTV with or without additional LPV/r to their regimens, as shown in Table 1; drug concentrations were measured on day 1, pre-dosing and again on day 14. LPV trough concentrations in both groups on day 14 were not statistically different from those on day 1, although substantial interpatient variability was observed on day 14. TPV concentrations on day 14 were higher in both groups compared to historical controls with standard doses of TPV/r. Adverse events (primarily GI toxicity) were more common in Group B.

*continued on page 2*

### Inside This Issue

Treatment Interruption in Children . . . . . 6  
OIs and Other Comorbidities . . . . . 7

HIV-1 Infection of  
CD4+ T Cells in the Gut . . . . . 8



## Clinical Pharmacology Update

continued from page 1

**Table 1. LPV and RTV Plasma Concentrations**

	Day 1	Day 14
	LPV Concentrations (µg/mL)	
Group A: Added TPV 500 mg + RTV 200 mg (total LPV/r 400/300 mg, n=7)	4.17 (1.74-6.67)	7.05 (0.84-12.27)
Group B: Added TPV 500 mg + LPV/r 133/33 mg + RTV 100 mg (total LPV/r 533/233mg, n=6)	4.77 (3.60-7.73)	5.20 (1.44-7.62)
	RTV Concentrations (µg/mL)	
Group A: Added TPV 500 mg + RTV 200 mg (total LPV/r 400/300 mg, n=7)	0.107 (<0.25-0.294)	0.674 (<0.25-2.528)
Group B: Added TPV 500 mg + LPV/r 133/33 mg + RTV 100 mg (total LPV/r 533/233mg, n=6)	0.153 (<0.25-0.250)	0.456 (0.155-1.106)

Although the increase in the RTV and LPV levels seemed to compensate for the inducing effects of TPV on LPV metabolism, the substantial interpatient variability is of concern. These investigators suggested that TDM could be used to avoid under- or overdosing in patients taking this dual PI combination. However, before the combination of LPV/r plus TPV can be recommended, further prospective studies are needed, especially in light of the current limitations of the therapeutic drug monitoring of antiretroviral agents [Andrade A and Flexner C, *HHR* 2005;17(3):6]. For now, it may be best to avoid co-administration of these agents and instead employ other better-studied PI combinations.

### Atazanavir and Other Protease Inhibitors

The possibility of pharmacokinetic interactions between ATV and LPV surfaces frequently in clinical practice. Paul Pham and colleagues from Johns Hopkins conducted an open-label, steady-state study to evaluate the pharmacokinetics of the combination of ATV and LPV/r [Abstract 585]. Fifteen HIV-negative subjects received ATV/r 300/100 mg qd from day 1-10 (Period I), ATV 300 mg qd + LPV/r 400/100 mg bid from day 11-24 (Period II), and ATV/r 300/100 mg qd + LPV/r 400/100 mg bid from day 25-34 (Period III). The addition of LPV/r to ATV 300 mg during period II resulted in a slight increase in ATV  $C_{min}$ . Boosting ATV with RTV 100 mg in period III did not further increase ATV plasma concentrations. LPV pharmacokinetic parameters in period II were comparable to historical controls on LPV/r 400/100 mg bid, suggesting that ATV 300 mg did not significantly affect LPV plasma concentrations. LPV  $C_{min}$  during period III was 28% higher, but LPV AUC and  $C_{max}$  were not significantly different. LPV and ATV were well tolerated; the only reported adverse event was hyperbilirubinemia. This study indicates that when combining these PIs, the dose regimen used in period II seems to be adequate, and there is little additional benefit and probably a higher risk of toxicity by adding the

extra dose of RTV 100 mg used in period III. Further clinical studies in HIV-infected patients will be required before this combination can be recommended. Additionally, the LPV/r capsule formulation was used in this study; further investigation is needed using the new LPV/r tablet formulation.

There is considerable interest in combining ATV with SQV because of the minimal effects of these two PI agents on lipids, their divergent resistance profiles, and data suggesting that the two agents act synergistically in vitro. Investigators from the ASPIRE II study evaluated the pharmacokinetics, tolerability, and safety of ATV/SQV bid as a potentially useful dual-PI, RTV-sparing combination [Abstract 586]. In this open-label, sequential, 3-way crossover study, 16 healthy volunteers underwent three 10-day treatment phases separated by a 10-day washout period using the new SQV tablet formulation (doses are shown in Table 1). The pharmacokinetic parameters for ATV were similar for Periods 2 and 3; the ATV  $C_{max}$  and  $C_{12h}$  were 55% lower and 99% higher, respectively, than for historical controls receiving ATV 400 mg qd. SQV pharmacokinetic parameters were significantly higher in Period 1 than in Periods 2 or 3. Women had significantly higher  $C_{max}$  and AUC<sub>12h</sub> values than men for all 3 PIs, even after adjusting for weight (median weight, 84.8 kg for men and 62.3 kg for women).

In this pharmacokinetic study evaluating ATV/SQV dosed twice daily, SQV/ATV

1500/200 mg bid did not generate plasma SQV concentrations comparable to those obtained with SQV/r. However, it is important to note that 75% of the participants on the SQV/ATV 1500/200 mg combination had SQV plasma concentrations above the estimated protein binding-corrected IC95 for SQV (approximately 100 ng/mL). The authors concluded that prospective studies using SQV/ATV 1500/200 mg bid are needed for characterization of the safety, tolerability, and pharmacokinetics of this combination of PIs in antiretroviral naïve patients.

The question of whether gender differences in pharmacokinetics really exist continues to be investigated. While the mechanisms underlying pharmacokinetic sex-based differences did not fall within the scope of this study, these findings are consistent with prior reports suggesting that drug metabolism may differ between sexes [Flexner C. *HHR*, 2005;17(4):1; Andrade A, Flexner C. *HHR*, 2004;16(3):1]. However, to date there are no compelling data to justify antiretroviral dose modifications based on sex-related pharmacokinetic differences.

Finally, Clay and colleagues presented the results of a prospective, randomized, 3-way crossover study evaluating the pharmacokinetic interactions between ATV and fosamprenavir (FPV) [Abstract 587]. Twenty-one HIV-negative subjects (11 men, 48% non-white) received in random order: FPV 1400 mg qd, ATV 400 mg qd, or ATV 400 mg + FPV 1400 mg qd for 14 days. Treatment arms were separated by 14-day washout periods. ATV significantly enhanced the APV AUC by 78%, while the ATV AUC was reduced by 33% when co-administered with FPV. The FPV/ATV combination is another example of a potentially useful dual-PI therapy with favorable toxicity and resistance profiles. Although this combination resulted in a favorable pharmacokinetic profile for FPV, further prospective studies are needed to evaluate this therapy more thoroughly.

### Carbamazepine Plus Efavirenz

Epilepsy is prevalent in HIV-infected patients, and management of this condition involves the use of anticonvulsant agents. Carbamazepine (CBZ),

**Table 2. Pharmacokinetic Parameters for SQV, RTV, and ATV**

	Period 1		Period 2		Period 3	
	SQV 1000 bid	RTV 100 bid	SQV 1000 bid	ATV 200 bid	SQV 1500 bid	ATV 200 bid
$C_{max}$ (ng/mL)	4065	1893	1322	2272	1888	2557
$C_{min}$ (ng/mL)	599	255	75	265	129	262
AUC <sub>12</sub> (mg•h/L)	24.66	10.20	4.03	12.59	7.55	11.38



## Clinical Pharmacology Update

phenobarbital, and phenytoin, are potent CYP3A4 inducers and can lower the plasma concentrations of PIs and NNRTIs that are substrates, inducers, and/or inhibitors of this enzyme. Previous studies have shown that co-administration of phenytoin with nelfinavir (NFV) and LPV/r results in a two-way drug interaction, with reductions in phenytoin, LPV, and NFV plasma concentrations [Shelton, 40<sup>th</sup> ICAAC, 2003 Abstract 426; Lim ML, et al. 10<sup>th</sup> CROI, 2003 Abstract 535]. Kaul and colleagues reported the results of a study in healthy volunteers that was designed to determine whether a pharmacokinetic drug interaction occurs between efavirenz (EFV) and CBZ (Abstract 575c).

The investigators found a two-way drug interaction in which EFV decreased the CBZ AUC<sub>24h</sub>, C<sub>max</sub>, and C<sub>min</sub> by 27%, 20%, and 35%, respectively, and CBZ decreased the EFV

AUC<sub>24h</sub>, C<sub>max</sub>, and C<sub>min</sub> by 36%, 21%, and 47%, respectively. These results illustrate the complexity of drug interactions involving CYP450 inducers and substrates. In this case, EFV and CBZ are inducers and substrates of CYP3A4 and accelerated each other's clearance, probably by inducing hepatic CYP3A4. The authors did not make any recommendations about dose adjustments to counteract this interaction but suggested use of alternative anticonvulsants not dependent on CYP3A4 metabolism (such as gabapentine and levetiracetam) when concomitant treatment with EFV is needed.

### Lopinavir/Ritonavir and Acid-Reducing Agents

Recent data on the profound reduction in ATV concentration associated with co-administration of the proton pump inhibitor, omeprazole, have raised concerns that suppression of gastric acid secretion could also affect the

bioavailability of other PIs. Researchers from Abbott Laboratories presented results of a multiple-dose, open-label, pharmacokinetic interaction study in 71 healthy volunteers that compared the new melt-extrusion LPV/r tablet formulation, ATV/r, omeprazole, and the H<sub>2</sub> antagonist, ranitidine [Abstract 578].

LPV bioavailability was not affected by either omeprazole or ranitidine, which is not surprising, given that the solubility of LPV is not pH-dependent. Plasma concentrations of omeprazole and ranitidine were comparable to historical control values. ATV C<sub>max</sub> and AUC<sub>12h</sub> decreased by 48% and 65%, respectively, reinforcing the notion that ATV absorption is affected by acid-lowering agents.

*continued on page 4*

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## Clinical Pharmacology Update

continued from page 3

### Lopinavir/Ritonavir and Rosuvastatin

Hyperlipidemia is a common adverse event in PI therapy. A number of HMG Co-A reductase inhibitors ("statins") undergo hepatic CYP3A4 metabolism, resulting in pharmacokinetic drug interactions when these agents are combined with PIs and NNRTIs. Inhibition of CYP3A4 by SQV/r significantly increases simvastatin and atorvastatin concentrations, while induction by EFV reduces simvastatin and atorvastatin levels. CYP3A4 induction can produce subtherapeutic levels, potentially reducing the effectiveness of these drugs, while inhibition can result in higher plasma concentrations and cause serious drug toxicity. [Fichtenbaum CJ, et al. *AIDS* 2002;16:569-77; Gerber et al. *J Acquir Immune Defic Syndr*. 2005;39:307-12].

Investigators from the Netherlands evaluated the effects of rosuvastatin on LPV plasma

concentrations (and vice versa) in 22 HIV-infected patients [Abstract 588]. Subjects were treated with rosuvastatin 10 mg qd for 12 weeks, and rosuvastatin dose escalation was undertaken to 20 or 40 mg if predetermined fasting target lipid values were not met. Treatment with rosuvastatin did not alter LPV plasma concentrations. However, the median rosuvastatin trough concentrations for 10, 20, and 40 mg were 1.5, 1.6, and 1.9 times higher, respectively, than for historical controls. This finding was surprising, given that rosuvastatin does not undergo CYP3A4 metabolism. Unfortunately, the design of this study made it impossible to identify the mechanism for the observed drug interaction. Nevertheless, it is reassuring that the magnitude of the change in the rosuvastatin trough concentrations was significantly lower than the 25-fold and 74% increases in simvastatin and atorvastatin concentrations, respectively, when used in combination with PI therapy. The minimal increase in rosuvastatin concentrations suggests that this statin is probably a safe choice for co-administration with PIs.

### Enfuvirtide and Tipranavir/Ritonavir

TPV and enfuvirtide (ENF) are common components of salvage regimens. Investigators from Italy examined whether co-administration of ENF 90 mg SQ bid with TPV/r would affect the steady-state pharmacokinetics of TPV and RTV [Abstract 579]. Thirty-nine HIV-infected patients were studied: 20 on TPV/r- and ENF-containing regimens and 19 on TPV/r without ENF. TPV and RTV trough concentrations were higher in the presence of enfuvirtide, which is surprising, since ENF is not a known CYP450 inducer, inhibitor, or substrate. Although at present there is no biological explanation to support these findings, the investigators hypothesized that a higher volume of distribution and elimination half-life for both PIs in the presence of enfuvirtide could explain their results. It is important to point out that limitations in the study design could also have affected the results, which will need to be confirmed in future studies.

### Lopinavir/Ritonavir, Efavirenz, and Hemodialysis

Gupta and coworkers conducted a prospective, observational study to evaluate the steady-state pharmacokinetics of EFV and LPV in HIV-infected patients undergoing hemodialysis [Abstract 573]. Twenty-six subjects (13 per arm) on stable LPV/r or EFV-containing regimens underwent a full pharmacokinetic sampling on a non-dialysis day. EFV and LPV/r AUC values were equivalent to those in historical controls with normal renal function who had received the same formulations of EFV and LPV/r. There was substantial variability in EFV pharmacokinetics, and pharmacogenomic

evaluation is ongoing to determine whether genetic polymorphism could explain these results. LPV pharmacokinetic parameters were modestly lower in HD patients compared to historical controls, and protein binding evaluations are pending. It is important to note that the LPV/r capsule formulation was used in this study, and further investigation is warranted with the new tablet formulation. Overall, these findings suggest that dose adjustments for these two antiretroviral agents are not necessary in patients on hemodialysis.

### Lopinavir/Ritonavir and Tenofovir

Co-administration of LPV/r and tenofovir disoproxil fumarate (TDF) results in a 30% increase on tenofovir plasma concentrations. Although this raises concerns about drug-induced toxicity, to date, there is no clinical evidence of increased TDF toxicity in patients taking PIs. The mechanism underlying this interaction is unclear. Investigators from the University of Colorado presented data regarding the effects of LPV/r on the clearance of tenofovir, in an attempt to shed some light on the mechanism of this drug interaction [Kiser J, et al. Abstract 570]. Thirty HIV-infected adults (73% males, 20% black) with a mean age of 42 (GFR > 60 mL/min, no hypertension, diabetes, or hepatitis C) and on a stable TDF-containing regimen were enrolled into one of two groups: Group 1 received TDF 300 mg qd + LPV/r 400/100 mg bid + other NRTI; Group 2 received TDF 300 mg qd + other NRTI or NNRTIs but no PIs. After adjusting for estimated GFR, the tenofovir clearance was 1.16 times greater in subjects not taking a PI than in those taking LPV/r. Weight, CD4, serum creatinine, and estimated GFR were comparable between the two groups, suggesting that interactions between these two drugs occur at the renal level.

### Therapeutic Drug Monitoring

The use of therapeutic drug monitoring (TDM) for antiretrovirals continues to be debated by the pharmacology community and has been reviewed in several issues of the *Hopkins HIV Report* [Flexner C, *HHR* 2002;2:1, Flexner, C, *HHR* 2000;12(2):5]. Several presentations at CROI attempted to shed more light on this controversial topic.

TDM studies for antiretroviral-experienced subjects have employed a variety of ratios that combine the patients' drug concentrations and resistance mutations to correct drug doses above or below a desired therapeutic level [Flexner C. *HHR* 2002;(14)3:6]. Bonora presented the results of a prospective study investigating whether the virological response to TPV was associated with TPV genotypic inhibitory quotient (gIQ), defined as the ratio between the mean of all available TPV

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## Clinical Pharmacology Update

$C_{\text{trough}}$  concentrations and the number of TPV-associated mutations [Abstract 577]. Twenty-seven heavily antiretroviral-experienced patients treated with TPV/r 500/200 mg bid + 2 NRTIs with or without ENF had  $C_{\text{trough}}$  concentrations measured at baseline and weeks 4, 8, and 12, and a *VircoTYPE* analysis was performed at baseline. Optimized background score (OBS), defined as the number of active drugs in the regimen based on resistance test results, was also used to assess virologic response to ENF. By logistic regression analysis, TPV gIQ was the only predictor of viral suppression at 12 weeks; OBS, TPV  $C_{\text{trough}}$ , and the number of TPV mutations were not predictive. At 12 weeks, the viral load had fallen by 2.15 log, and 40.7% of the patients had an undetectable viral load. The TPV gIQ  $EC_{50}$  at week 12 was 13,000 (50% probability of reaching an undetectable viral load at week 12); 7/9 subjects with a TPV gIQ >13,000 and 4/18 with a TPV gIQ <13,000 had an undetectable viral loads at that time point.

This study reinforces the notion that drug concentrations alone are poor predictors of virological outcomes in patients with complex treatment histories. Integration of viral susceptibility into the interpretation of drug levels is crucial when using TDM in this population.

Podsadecki and colleagues described the effects of “white coat compliance” (improved adherence immediately preceding a clinic visit) on TDM estimates [Abstract 590]. These investigators studied 178 antiretroviral-naïve subjects enrolled in a randomized, open-label trial comparing the efficacy, tolerability, and safety of LPV/r qd or bid plus emtricitabine (FTC) plus TDF. They monitored adherence to LPV/r using MEMS caps and measured LPV plasma concentrations during weeks 3, 8, 16, 24, and 48. In a majority of the patients (66%), adherence was >95% (defined as “perfect adherence”) in 31% of the clinic visits for pharmacokinetic sampling, but only in the 1-3 days immediately prior to that visit; outside that window, adherence was <95%. These findings suggest that patients could have had therapeutic drug concentrations on days of pharmacokinetic sampling, even though their adherence during most of the study duration was below the 95% cutoff level. These results might explain detectable viremia in patients who are reportedly adherent to HAART and have therapeutic drug concentrations. They underscore the limitations of TDM, challenging the potential utility of this approach in predicting long-term exposure to drug concentrations.

In an attempt to identify factors that could influence antiretroviral pharmacokinetic parameters used in the TDM of antiretrovirals, Ghandi and collaborators performed full

pharmacokinetic samplings of PIs and NNRTIs in HIV-infected women enrolled in the Women’s Interagency HIV Study [Abstract 592]. In this study, 99, 76, and 115 patients, respectively, were on NVP-, EFV-, and LPV/r-containing regimens. Doubling the AST and ALT increased the EFV AUC by 37% and 28%, respectively while doubling the AST and ALT increased the NVP AUC by 23% and 24%, respectively. Women co-infected with hepatitis C who had impaired renal function had 1.23- and 1.38-fold higher NVP AUCs, respectively, compared to their HCV-negative counterparts with normal renal function. An increase in fat-free mass was associated with an increased NVP AUC, while an increase in body weight was associated with a reduction in EFV and LPV AUCs. Fluconazole therapy was associated with a 3.5-fold increase in the EFV AUC, while use of St. John’s wort, anticonvulsants, or rifamycin decreased the LPV AUC by 47%.

As we learn more about the TDM of antiretrovirals, it is becoming clear that this analysis is considerably more complex than simply measuring drug plasma concentrations. Interpretation of TDM results is also challenging, as it can be influenced by a number of factors prevalent in HIV-infected patients (e.g., those identified by Gandhi and colleagues). We recently learned that there is a significant degree of intra-individual variability in antiretroviral concentrations that could produce misleading TDM results [Nettles R, et al. 12<sup>th</sup> CROI Abstract 642]. The factors identified in this study certainly underscore the complexity of TDM use in this population and reinforce the need for large prospective trials to advance our understanding of the usefulness of this practice.

### Pharmacokinetics of Antiretroviral Agents in Pregnancy

Physiologic changes during pregnancy may affect the pharmacokinetics of antiretroviral agents as a result of changes in protein binding, plasma volume, excretion, and metabolism. These changes are important to assess, as achieving therapeutic plasma concentrations of antiretroviral drugs is critical for prevention of HIV mother-to-child transmission and for maintaining appropriate

control of maternal infection. Several presentations addressed this important issue.

Khuong-Josses reported on the results of a pharmacokinetic study in a cohort of French HIV-infected pregnant women (35 black, 3 white, 2 Asian) receiving nelfinavir (NFV)-containing regimens [Abstract 707]. NFV trough concentrations were measured 2 weeks after treatment initiation and during the second and third trimester of pregnancy. NFV was administered at 1250 mg bid or 750 mg tid in 36 and 4 women, respectively; dietary counseling was provided throughout the study. Eighteen of the 40 women (42%) did not achieve NFV target trough concentrations ( $1.27 \pm 0.86$  vs 1 ng/mL). Women with NFV concentrations below the target trough appeared to experience a lower decline in viral load than did their counterparts, although this was not statistically significant. Although the dose was increased to 1500 mg bid in 8 of these 18 women, the NFV trough remained below 1 ng/mL in 2 of them. Viral load decreased from 4.12 log<sub>10</sub> to 2.02 log<sub>10</sub> c/mL after a median of 15 days of treatment and was undetectable in 25 of 37 women at the time of delivery; no vertical transmission occurred during the study.

Two studies presented at the 13<sup>th</sup> CROI examined LPV plasma concentrations in pregnant, HIV-infected women. Mirochnick [Abstract 710] reported on the follow-up to the PACTG 1026 study first presented at the XV International AIDS Conference in Bangkok, showing that standard LPV/r dosing during the third trimester of pregnancy resulted in reduction of approximately 50% in LPV plasma concentrations compared to the postpartum period [Stek A, et al. XV International AIDS Conference 2004, Abstract LbOrB08]. The recent, prospective, non-blinded study included a cohort of pregnant women receiving standard dosing of the gel capsule formulation of LPV/r 400/100 mg bid (n=8) during the second trimester and 533/100 mg bid (n=26) during the third trimester and first 2 weeks postpartum (n=22). Intense steady-state pharmacokinetic sampling was performed during

*continued on page 6*

**Table 3. LPV Pharmacokinetic Data By Pregnancy Trimester**

	2 <sup>nd</sup> Trimester	3 <sup>rd</sup> Trimester	2 Weeks Postpartum
LPV/r dose (mg)	400/100 bid	533/133 bid	533/133 bid
Mean AUC ±SD (µg*h/mL)	57.9 ± 21.6	85 ± 28.2	145.8 ± 50.0
Met AUC target/Total	5/8	20/23	17/18
Mean $C_{\text{min}}$ ± SD (µg/mL)	2.4 ± 1.6	4.5 ± 2.4	8.7 ± 4.5



## Clinical Pharmacology Update

continued from page 5

the third trimester and postpartum period and was optional in the second trimester. As shown in Table 3, LPV AUC<sub>12hr</sub> and C<sub>min</sub> were lower during the second trimester of pregnancy than in the third trimester and postpartum period. It is also important to note that LPV concentrations were significantly higher during the postpartum period, probably reflecting a return to antenatal physiology. The higher dose of LPV/r was well tolerated, and viral load was <400 c/mL in 23/24 women at delivery. A study to evaluate the new LPV/r tablet formulation is planned.

Lyons and colleagues measured steady-state LPV trough concentrations in 16 women in their third trimester receiving standard doses of LPV/r capsules combined with an NRTI backbone (zidovudine/lamivudine or tenofovir/lamivudine) [Abstract 709]. Adherence was monitored throughout the study, and the use of medications known to interfere with LPV metabolism was prohibited. The median trough concentrations of LPV were 3660 ng/mL; 15 women (94%) met the minimum LPV trough concentration for inhibiting wild-type virus (1000 ng/mL). Viral load was undetectable in 14 of 16 women; the two with detectable virus were felt to have inadequate adherence. There were no cases of vertical transmission.

While the sample sizes were small in all three studies presented, the results of two of these studies suggest that physiological changes during pregnancy can significantly affect drug pharmacokinetics. Limitations with the NFV study design could have affected the findings. For example, inclusion of a small number of patients on NFV three times daily, which has been shown to produce variable and generally lower plasma concentrations of NFV in pregnancy compared to twice daily dosing, might have affected viral load decline. It is also important to point out that both LPV/r studies were performed using the capsule formulation, so their currently applicability is unknown. A follow up study with the new tablet formulation is in development by Mirochnick and colleagues. Overall it remains unclear whether these differences in plasma concentration significantly affect the efficacy of antiretroviral agents in preventing HIV mother-to-child transmission or in controlling maternal viral load. Currently there are insufficient data to support a recommendation to use increased doses of NFV or LPV/r in pregnant women as an attempt to compensate for the physiological pharmacokinetic changes that occur during pregnancy. Further prospective studies are needed to guide clinical practice. ▲

## Treatment Interruption in Children

By Deborah Persaud, M.D.

Data from four large clinical trials in adults, most notably the SMART trial, on CD4 guided treatment interruption were prominently featured at the 13<sup>th</sup> CROI and were cogently summarized by Joel Gallant [*HHR* 2006; 18(2):1]. That the largest randomized study to date on treatment interruption in adults living in resource-rich settings (n=5472 patients in 33 countries) was stopped prematurely because of an increased risk of clinical disease progression or death will have a dramatic impact on the future of this treatment strategy in patients of all ages, including children and adolescents. Similarly, in the Trivicam study (n=940), conducted in West Africa, the CD4-guided arm, in which therapy was resumed when the CD4 count fell below 250 cells/mm<sup>3</sup>, was discontinued because of the increased incidence of tuberculosis and serious bacterial infections with organisms resistant to the prophylaxis regimen (cotrimoxazole). This is likely to discourage the study of treatment interruption in resource-poor settings, where the cost-benefit ratio is likely to be greatest.

Two studies on treatment interruption in children were reported at CROI this year. The first was PACTG 1015, a proof of concept trial in which 14 children who had maintained suppression of viral replication for more than one year underwent incremental increases in time off therapy, starting with a 3-day cycle that was increased by 2 days for each subsequent cycle [Borkowsky W, et al. Abstract 19]. The overall goal of the study was to evaluate whether this “gentle” approach of cycling on and off therapy induced HIV-specific immunity in children who had achieved prior control of virus replication with HAART. Levels of rebound viremia during successive cycles off therapy and the total duration of each STI cycle before treatment re-initiation were recorded. Peak levels of rebound viremia (4.4 log<sub>10</sub> c/mL at cycle 7) were reported to decline to lower levels (3.9, 4, and 3.7 log<sub>10</sub> at cycles 9, 12, 15 respectively) with successive increases in time off therapy; however, these differences were not statistically significant. Drug resistance mutations resulted in study discontinuation in 3 of the 14 subjects, and the median CD4 percentage dropped slightly for the group (40.5% vs 36.5%).

The occurrence of drug resistance mutations and a trend towards CD4 decline observed in this small study highlight the risk of this treatment strategy. However, these risks need to be balanced with the requirement for life-long therapy in children, many of whom are now surviving to their twenties. Importantly, a sequential increase in HIV-specific, interferon-g producing cells was

observed with this “gentle” cycling approach. Whether this increase in HIV-specific immunity provides clinical benefit is unclear, but demonstrates that HIV-infected children treated with effective HAART can mount HIV-specific immune responses to autologous virus, a finding that has relevance to the development of therapeutic vaccine strategies. Similar studies in HIV-1 infected adult patients have also shown no long term clinical benefit of cyclic treatment interruption strategies [Fisher M; *AIDS* 2003; 17:195-9].

Data from a CD4-guided interruption study in children, the Botswana/Baylor Antiretroviral Assessment Trial (BANA 2), were also reported [Lowenthal E. et al. Abstract 700]. BANA 2 is a prospective, randomized, comparative trial (n=600) of continuous versus intermittent lopinavir/ritonavir (LPV/r)-based HAART for HIV-infected infants and children in Botswana. In this trial, children who remain in CDC immunologic category 1 (CD4% ≥25%) for greater than 6 months while on HAART are allowed to discontinue their therapy until they experience progression to immunologic category 2 (15-24%) or 3 (<15%). A repeat interruption was allowed for children who experience immune reconstitution and remained in immunologic category 1 for at least 3 months. The majority of the children enrolled in the trial were immune category 2 (114/263 or 43%) or 3 (133/263 or 50%), and were symptomatic. Only 31% of the children (44 of 142 subjects) enrolled in the interruption arm reached criteria for treatment discontinuation possibly due to the low baseline CD4 counts at the initiation of therapy. Nearly half required resumption of therapy, but the longest duration off therapy was 14 months. Importantly, the majority (95%) of subjects achieved suppression of viral loads to <400 c/mL with treatment re-initiation.

In this larger study of treatment interruption in children residing in a resource-limited setting, no increases in toxicity or disease progression were observed. Such studies are important for guiding policies on the time to start therapy in children. Given the high rates of disease progression in the first year of life for HIV-infected infants, a planned CD4-guided treatment interruption strategy for older children who start HAART from infancy may make early therapy feasible for infants living in resource-poor settings where early infant diagnosis is possible. ▲



## Opportunistic Illnesses and Other Comorbidities

By Kelly Gebo, M.D., M.P.H. and  
Lucy Wilson M.D., Sc.M.

The 13<sup>th</sup> CROI clearly reinforced the shift in HIV clinical practice from the management of opportunistic infections (OI) to the management of chronic HIV infection and its comorbidities. There were relatively few abstracts addressing OIs, although several were worth noting.

In an oral session using data from the Moore clinic database in Baltimore, Lau and colleagues demonstrated a decrease in HIV-related mortality in the current era of HAART [Abstract 29]. HIV-associated mortality decreased from 41 to 20 per 1000 person-years (PY) between 1997 and 2004, while non-AIDS mortality increased from 11 to 23 per 1000 PY in the same interval. Although all-cause mortality was the same in injection drug users (IDUs) and non-IDUs during this interval, IDUs had much greater mortality due to non-AIDS related conditions than non-IDUs. Current analyses are ongoing to evaluate the primary causes of non-AIDS related deaths in this cohort.

Evaluation of 2,149 AIDS Clinical Trials Group (ACTG) patients by Smurzynski and colleagues revealed an increased risk of OIs in the first 24 weeks of HAART among individuals followed in the ACTG Longitudinal Linked Randomized Trials (AALRT) [Abstract 783]. At baseline, all patients were HAART naïve; however, 332 (15%) patients developed an OI during the study period. Interestingly, 52% of first OIs occurred within 24 weeks of starting HAART. Not surprisingly, the most common OIs were *Pneumocystis jiroveci* pneumonia (20%), disseminated *Mycobacterium avium* complex (MAC) (17%), esophageal candidiasis (17%), cytomegalovirus disease (7%), and tuberculosis (7%). They found that high viral loads, lower CD4 counts, increasing age and female gender (OR 1.6) were associated with increased risk of development of an OI within 6 months of starting HAART.

A study from the EuroSIDA cohort evaluated the incidence of OIs in patient groups having CD4 counts higher than would be expected (i.e. group 1, CD4 count >100 cells/mm<sup>3</sup>, risk for CMV disease, disseminated MAC or toxoplasmosis; group 2, CD4 count >200 cells/mm<sup>3</sup>, risk for *Pneumocystis jiroveci* pneumonia or esophageal candidiasis and group 3, CD4 >300 cells/mm<sup>3</sup>, risk for pulmonary TB) [Podlekareva D, et al. Abstract 783]. The incidence of OIs in these groups were low: 1.7, 3.8, and 1.3 per 1000 PY, respectively. IDU was the only risk factor for pulmonary TB. Being started on HAART and having an increase in CD4 count of 50% from baseline were associated with a lower risk of development of CMV disease, disseminated MAC, toxoplasmosis, and PCP.

### Malignancies

Engels and associates linked AIDS and cancer registries in 11 US regions to assess AIDS-associated cancer risk from 1980-2002, comparing the pre-HAART, early HAART and current-HAART eras [Abstract 810]. The risk of both Kaposi's sarcoma (KS) and Non-Hodgkins lymphoma (NHL) dropped in the early HAART era (RR 0.41 and 0.64, respectively), but then reached a plateau in the current HAART era. In contrast, cervical cancer risk remained low and was unchanged over the 3 times periods analyzed. This study suggests that HAART may have substantially contributed to the declines in KS and NHL but not cervical cancer. The residual incidence may be due to antiretroviral drug resistance or access to care issues affecting those with HIV/AIDS. Ginges and colleagues observed similar trends in the pre- and current HAART eras in a Canadian cohort [Abstract 830]. They noted that KS and NHL cases predominated in those with declining CD4 cell counts or failing HAART. Consistent with Engel's study, they noted a decline in mortality from KS and NHL.

Kirk and coworkers examined lung cancer mortality among the ALIVE IDU cohort in Baltimore [Abstract 811]. They found that a history of smoking and age greater than 50 years were strongly associated with lung cancer death. Adjusting for other risk factors, including smoking, HIV seropositivity was a risk factor for lung cancer deaths (RR 3.04). Additionally, among those with HIV infection, recurrent pneumonia, defined as 2 or more hospitalizations, was also associated with lung cancer death (RR 1.99; 1.10-9.20), and explained a proportion of the HIV effect. CD4 cell count, viral load, and HAART usage were not associated with lung cancer mortality.

Patel and collaborators evaluated incidence rates of AIDS-defining and non-AIDS defining malignancies in HIV-infected and -uninfected persons using data from the HIV Outpatient Study (HOPS) and the Adults/Adolescent Spectrum of Disease Project (ASD) [Abstract 813]. They demonstrated significantly increased adjusted rates of the following cancers among HIV-infected patients: KS, NHL, Hodgkin's lymphoma, melanoma, cervical cancer, anal cancer, liver cancer, testicular cancer, oropharyngeal cancer, and lung cancer. Among HIV-infected and -uninfected patients, similar rates of colorectal and renal cancer were reported. HIV-infected patients had significantly decreased rates of breast (RR 0.7) and prostate cancer (RR 0.3), which could be due to decreased rates of screening for these diseases.

The prevalence of anal dysplasia was high in several studies, suggesting the need for better

screening and evaluation. Using data from an outpatient Spanish clinic, Sirera and associates demonstrated a high prevalence of abnormal anal cytology (43%); however, there was no difference in the rates among MSM (48%) and heterosexual men (32%) [Abstract 806]. Multivariate logistic regression analysis revealed that those with a viral load >400 c/mL (AOR 3.5) or at least 5 episodes of receptive anal intercourse per lifetime (AOR 4.6) had a higher risk of abnormal anal cytology. Of note, CD4 cell count nadir, current CD4 cell count, use of HAART, previous STIs, tobacco, and alcohol were not associated with abnormal cytology. The prevalence of HPV infection was 78%, with all those with abnormal anal cytology having high-risk HPV types present.

Using data from men followed in an outpatient clinic in San Diego, Caperna and colleagues showed no change in the incidence rates of invasive anal cancer between pre-screening time period (1995-2001) and current screening period (2002-2005) [Abstract 808]. This suggests the need to identify more effective screening for anal dysplasia as well as more standardized monitoring and treatment protocols. Of note, they did find the incidental presence of asymptomatic gonorrhea or *Chlamydia* (4.2%) to be higher than expected.

### Other Infections

Burkey presented the results of a study that evaluated the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the Johns Hopkins Moore clinic in the period 2000-2003 [Abstract 789]. The incidence of *S. aureus* bacteremia among this cohort was 19.1 events/1000 PY between 2000-03 and increased significantly during this interval. The proportion of all *S. aureus* cases that were due to MRSA increased from 24% in 2000 to 47% in 2003. Not surprisingly, IDU, end stage renal disease, greater viral load, and CD4 count <200 cells/mm<sup>3</sup> were associated with increased odds of MRSA bacteremia in an adjusted multivariate analysis. This analysis suggests that use of vancomycin should be considered in HIV-infected patients who present with sepsis.

Overall, the 13<sup>th</sup> CROI revealed that OIs still occur, although less frequently than before. In addition, while overall mortality has decreased, non-AIDS related mortality remains a significant issue, particularly among IDUs. AIDS-related and non-AIDS-related malignancies remain a significant comorbidity in HIV infected patients. Managing concomitant drug and tobacco abuse, along with vigilant cancer screening are important in helping our HIV-infected patients reduce cancer risk. ▲



## HIV-1 Infection of CD4+ T Cells in the Gut

By Megan Wind-Rotolo Ph.D. and  
Joel N. Blankson M.D., Ph.D.

Clinicians and researchers have used peripheral blood as a convenient way of obtaining information on CD4 cell counts and the extent of viral replication in HIV-infected individuals. However, it should be noted that only 2% of the total body store of lymphocytes circulate in the peripheral blood; the other 98% reside in lymphatic tissue scattered throughout the body. Gut-associated lymphatic tissue (GALT) represents the single largest pool of lymphocytes, and as such, it is not surprising that it is a major target for HIV infection. In the past few years several major observations have been made regarding GALT. First, there is a massive depletion of GALT CD4 cells during primary infection. These cells are affected to a much higher degree than CD4 cells in the peripheral blood [Veazey R, et al. *Science* 1998;280:427-431, Brenchley JM, et al. *J Exp Med* 2004;200:749-759]. Furthermore, there is little or no reconstitution of these cells after the initiation of HAART in chronically infected patients [Guadalupe M, et al. *J Virol* 2003;77:11708, Mehandru S, et al. *J Exp Med* 2004;200:761-770]. Finally, HIV-1 DNA and RNA can be detected in rectal biopsies from patients on HAART with undetectable plasma viral loads, suggesting that GALT CD4 cells can serve as a reservoir for HIV infection [Anton PA, et al. *AIDS* 2003;17:53-63]. At this year's CROI there were numerous oral presentations regarding this interesting topic.

Brenchley and colleagues determined the frequency of HIV-infected CD4 cells in the gut of HIV-infected patients who had been on HAART for up to 3 years [Abstract 38]. They found that on average the frequency of infection of GALT CD4 cells was 10 times higher than that of CD4 cells from blood. Memory CD4 cells from the gut were also shown to be capable of producing virus, and while there was no direct evidence of active replication, it was concluded that gut depletion is likely caused by ongoing infection of local CD4 cells. In addition, few HIV-specific CD8 cells were found in the gut compared to the blood, indicating that the

proposed ongoing viral replication in GALT is associated with a lack of local HIV-specific immunity.

Baker and colleagues also measured the frequency of CD4 cells in GALT and showed that the percentage of CD4 cells in this region is 50% lower in HIV-infected patients compared to non-infected controls [Abstract 41]. Interestingly, while there was a significant increase in peripheral CD4 cell counts after 6 months of HAART, there was no increase in the percentage of GALT CD4 cells. This is more evidence that CD4 cell depletion in the gut may not be reversible in chronically infected patients. The effect of depletion of gut CD4 cells is unknown, but there was an incidental finding of intestinal polyps in 6/31 relatively young HIV-infected patients, including 1 precancerous lesion and 1 case of cancer.

HIV-infected patients who started HAART within 3 weeks of infection were shown to be able to repopulate memory CD4 cells in the gut [Dandekar, et al. Abstract 39]. The initiation of HAART was also associated with a lower frequency of infection of GALT CD4 cells. The expression of genes in the gut of patients who started HAART early was compared with that of patients who started HAART at later time points. Those who were started HAART early showed lower expression of inflammation and cellular activation genes and increased expression of mucosal repair and regeneration genes. These results led to the conclusion that the disruption of the gut microenvironment causes the depletion of CD4 cells.

Having shown a high frequency of infection of GALT CD4 cells, Douek and colleagues looked at other mucosal sites as well [Abstract 166]. Massive depletion of CD4 cells in the lung has previously been described in pathogenic SIV infection of Rhesus macaques [Picker LJ, et al. *J Ex Med* 2004;200:1299-1314.] The investigators have begun to study the effect of HIV on CD4 cells of the lung by analyzing cells from bronchoalveolar lavage of HIV-uninfected and HIV-infected patients. Preliminary data indicate

that the pattern seen at this site differs markedly from that observed in the GALT. There is no depletion of CD4 cells associated with HIV infection; instead, an increase in the number of both CD4 and CD8 cells is seen. In contrast to the high frequency of infected cells in the GALT, the frequency of infection of lung CD4 cells is relatively low (comparable to the frequency of infection of peripheral blood CD4 cells). In addition, HIV-specific CD8 and CD4 cell responses are preserved at this site, and it was proposed that this local immunity may explain the low cellular viral loads and the preservation of normal CD4 cell counts.

What are the clinical consequences of CD4 cell infection in GALT? While it appears that the poor reconstitution of CD4 cells at this site is not associated with major GI symptoms in most patients on HAART, the relatively high frequency of pathology seen by Baker and colleagues is concerning [Abstract 41]. Confirmatory studies in larger cohorts of patients are needed. If reconstitution of GALT CD4 cells is important, then the work of Dandekar and colleagues [Abstract 39] would suggest that there is a major advantage to early treatment with HAART. The GI tract appears to be the major target in primary infection; therefore, it follows that preventative vaccines will need to induce strong mucosal immunity in order to be effective. The high frequency of infected cells in the GALT has been interpreted by some investigators to be evidence of ongoing replication in patients on HAART. If this is correct, it could potentially explain treatment failure in some patients. This issue clearly needs to be definitively addressed, and tissue drug levels at this site should be measured. Finally, investigators working on eradication of HIV infection have based their models on the rate of decay of latently infected cells in the peripheral blood. Nothing is known about the half-life of infected cells in GALT. As these cells and infected cells from other anatomical reservoirs are studied, major revisions in these models will likely be needed. ▲

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