

# Topics in HIV Medicine®

A publication of the International AIDS Society–USA

## Perspectives

Drug-Drug Interactions and the Pharmacotherapy of  
HIV Infection 64

*Angela D. M. Kashuba, PharmD*

*Atazanavir/Ritonavir and Saquinavir/Ritonavir • Efavirenz and Buprenorphine •  
Antiretrovirals and Depomedroxyprogesterone • PI Cytochrome P450 Inhibition and  
Induction: Lopinavir/Ritonavir and Phenytoin • Double-Boosted PIs • Tenofovir and  
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The International AIDS Society–USA

## About This Issue

This issue features 3 *Perspectives* articles based on presentations from the International AIDS Society–USA continuing medical education courses held in New York, Atlanta, and Los Angeles in March and April of this year. Angela D. M. Kashuba, PharmD, described recent findings in drug-drug interactions and the pharmacotherapy of HIV infection. Donna E. Sweet, MD, outlined the metabolic complications associated with antiretroviral therapy and discussed issues such as risk factors and drug selection. Molly E. Eaton, MD, described the characteristics, diagnosis, treatment, and prognosis of several uncommon noninfectious syndromes associated with HIV infection.

This issue also features a *Review* article by Ighovwerha Ofotokun, MD, MSc, examining sex-related differences in the pharmacologic effects of antiretroviral drugs and the role that drug transporter genes, proteins, and enzymes might play in these observed differences.

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## Topics in HIV Medicine®

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## Perspective

# Drug-Drug Interactions and the Pharmacotherapy of HIV Infection

Angela D. M. Kashuba, PharmD

*Knowledge of drug-drug interactions is crucial to HIV therapeutics. Recent reports in this area include reduced atazanavir exposure with coadministration of omeprazole or rifampin; increased hepatic toxicity with coadministration of saquinavir and rifampin; reduced buprenorphine exposure with concurrent efavirenz administration; absence of clinically significant interactions of depomedroxyprogesterone with nevirapine, efavirenz, or nelfinavir; increased atazanavir and saquinavir exposure with the double-boosted regimen of atazanavir/saquinavir/ritonavir; reduced amprenavir, lopinavir, and saquinavir exposure with the addition of tipranavir/ritonavir therapy; and reduced lopinavir and amprenavir exposure with the addition of fosamprenavir or fosamprenavir/ritonavir to lopinavir/ritonavir. This article summarizes a presentation on drug-drug interactions in HIV therapeutics by Angela D. M. Kashuba, PharmD, at the International AIDS Society–USA course in Los Angeles in April 2005.*

Identical doses of a given drug do not necessarily produce the same plasma concentrations in patients because of genetic and environmental differences in absorption, distribution, metabolism, and excretion. Differences in drug pharmacokinetics may result in differences in pharmacodynamics, augmenting or diminishing the therapeutic or adverse effects of a drug. Drug-drug interactions are one of the factors that can exacerbate pharmacokinetic variability, along with drug-food interactions, drug-disease interactions (eg, due to alterations in gastrointestinal, renal, and hepatic function), and sex differences in drug pharmacokinetics, including those associated with pregnancy. Understanding drug interactions is crucial to the management of patients with HIV disease, given the multiple antiretroviral agents that must be taken and the use of other medications for HIV-related and non-HIV-related conditions. Recent findings on drug-drug interactions in HIV therapy are summarized herein.

## Atazanavir/Ritonavir and Saquinavir/Ritonavir

### Omeprazole

A recent study of 48 HIV-uninfected subjects indicated that coadministration of omeprazole 40 mg with atazanavir 300

mg/ritonavir 100 mg markedly reduced atazanavir trough plasma concentrations ( $C_{trough}$ ) (Figure 1; Agarwala et al, 12th CROI, 2005). The effect of omeprazole was not countered by increasing the atazanavir dose to 400 mg or ingestion of 8 oz of cola to produce an acidic gastric/duodenal environment. Omeprazole concentrations were not significantly altered. It is currently recommended that the 2 drugs not be coadministered. One

alternative acid-suppressing agent that could be used with atazanavir is famotidine. Recently presented data (Agarwala et al, 6th Int Workshop on Clin Pharmacol of HIV Ther, 2005) suggest that the atazanavir-famotidine interaction can be overcome by increasing doses or temporal dose separation. To achieve atazanavir systemic concentrations similar to those seen with a dose of 400 mg once daily, famotidine administration should be separated by at least 10 hours, or atazanavir should be given with ritonavir at a dose of 300 mg/100 mg once daily. To achieve exposures equivalent to those seen with an atazanavir/ritonavir regimen of 300 mg/100 mg once daily, the atazanavir dose could be increased to 400 mg.

### Rifampin

In a study of 71 HIV-uninfected subjects, coadministration of rifampin and

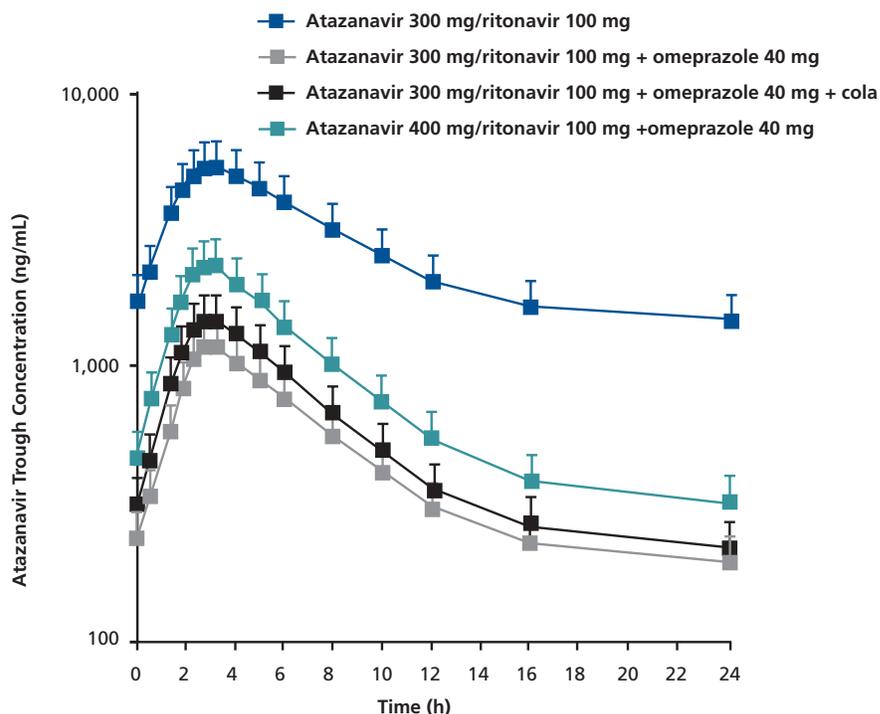


Figure 1. Effect of omeprazole on atazanavir trough concentrations in HIV-uninfected subjects. Adapted with permission from Agarwala et al, 12th CROI, 2005.

Dr Kashuba is an Associate Professor of Pharmacy at the University of North Carolina at Chapel Hill.

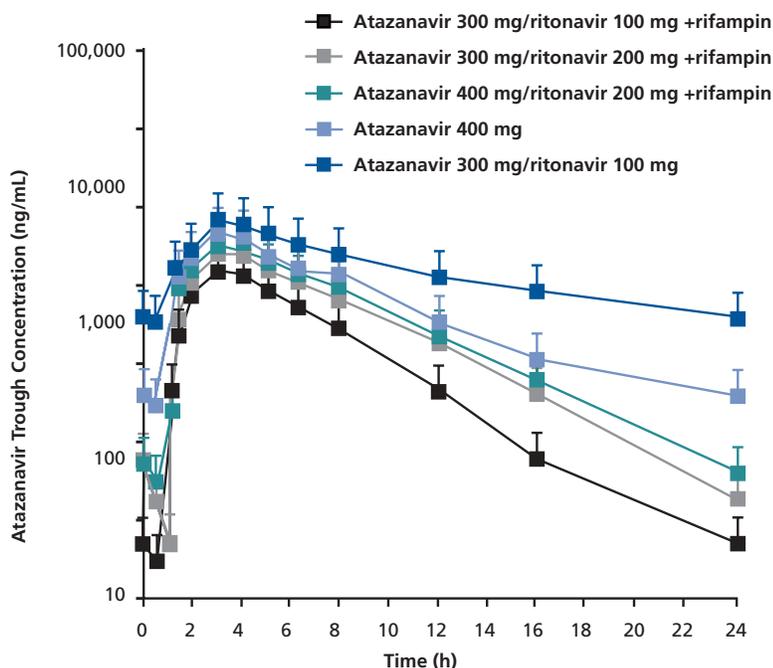


Figure 2. Effect of rifampin on atazanavir trough concentrations in HIV-uninfected subjects. Adapted with permission from Burger et al, 12th CROI, 2005.

atazanavir 300 mg/ritonavir 100 mg reduced atazanavir exposure, with the reduction again not being countered by an increase in the atazanavir and ritonavir doses to 400 mg and 200 mg, respectively (Figure 2; Burger et al, 12th CROI, 2005). Coadministration of atazanavir/ritonavir and rifampin should be avoided.

With regard to rifampin and other boosted protease inhibitors (PIs), a recent Dear Doctor letter described increased hepatotoxicity with coadministration of rifampin 600 mg once daily and saquinavir 1000 mg/ritonavir 100 mg twice daily. Elevated liver enzymes (up to 5-fold changes) were detected in 40% of the HIV-seronegative subjects evaluated. The mechanism of the liver toxicity is currently being investigated. It is recommended that saquinavir/ritonavir and rifampin not be used together.

### Efavirenz and Buprenorphine

Buprenorphine is a partial opioid agonist recently approved for treatment of opioid tolerance. In a study of HIV-uninfected patients receiving buprenorphine, treatment with efavirenz for 15 days resulted in an approximate 50% decrease in buprenorphine exposure (McCance-Katz et al, 12th CROI, 2005). As a percent of pre-efavirenz values,

post-efavirenz values for buprenorphine were 51% for area under the concentration-time curve (AUC) over 24 hours, 55% for maximum concentration ( $C_{max}$ ), 49% for minimum concentration ( $C_{min}$ ), and 72% for half-life. Efavirenz concentrations were within the therapeutic range. There was no change on the opiate withdrawal scale after 15 days; however, the long half-life of buprenorphine may have precluded seeing pharmacodynamic changes over this short time frame. This pharmacokinetic interaction is similar to that seen in studies of efavirenz and methadone. In these studies, symptoms of withdrawal were observed only after 3 to 4 weeks. Based on the currently available data, patients receiving efavirenz and buprenorphine should be closely monitored for symptoms of withdrawal.

### Antiretrovirals and Depomedroxyprogesterone

Evaluation of changes in antiretroviral drug exposure in women receiving depomedroxyprogesterone showed little effect over 4 weeks.  $AUC_{0-12h}$  values over 24 hours before and after depomedroxyprogesterone administration were 10.98 and 11.14 ng•h/mL for nevirapine ( $P=0.048$ ), 3.56 and 3.50 ng•h/mL for efavirenz ( $P=$  not significant [NS]), 10.49

and 10.29 ng•h/mL for nelfinavir ( $P=$  NS), and 8.78 and 8.84 ng•h/mL for the active M-8 nelfinavir metabolite ( $P=$  NS; Cohn et al, 12th CROI, 2005). The small change in nevirapine exposure, although statistically significant, is likely not clinically significant. There was no evidence of ovulation over the short duration of the study, and none of the women became pregnant. However, the study was not powered to test the effects of antiretroviral agents on depomedroxyprogesterone efficacy. The potential for interactions of depomedroxyprogesterone with other PIs and with tenofovir needs to be evaluated.

### PI Cytochrome P450 Inhibition and Induction: Lopinavir/Ritonavir and Phenytoin

All PIs are metabolized by (ie, are substrates for) the cytochrome P450 (CYP450) enzymes; some PIs and some nonnucleoside reverse transcriptase inhibitors (NNRTIs) inhibit particular CYP450 enzymes, some induce CYP450 enzymes, and some both inhibit and induce these enzymes. Pharmacokinetic interactions may be difficult to predict based on the relative magnitudes of inhibition and induction reported from in vitro studies. Further, in vitro studies may be particularly inaccurate in characterizing enzyme induction, since they may measure responses of enzymes removed from intact cell systems. Lopinavir and ritonavir are metabolized by the CYP3A4 enzyme, and the anticonvulsant phenytoin is an inducer of CYP3A4; coadministration would thus be predicted to result in decreased lopinavir and ritonavir levels. Phenytoin is metabolized via the CYP2C9 and CYP2C19 enzymes, and lopinavir/ritonavir is reported to be an inhibitor of both enzymes; coadministration would thus be expected to result in increased phenytoin levels. In a study in which lopinavir/ritonavir and phenytoin were coadministered, lopinavir AUC and  $C_{trough}$  were reduced by 33% and 46%, respectively; ritonavir AUC and  $C_{trough}$  were reduced by 28% and 47%, respectively; and phenytoin AUC and  $C_{trough}$  were reduced by 31% and 34%, respectively. The reduction in phenytoin levels was an unexpected finding (Lim et al, *J Acquir Immune Defic Syndr*, 2004). Subsequent

investigation of the effects of lopinavir/ritonavir in non-HIV-infected volunteers showed that in vivo lopinavir is an inducer of CYP2C9 (approximate 25% increase) and CYP2C19 (approximate 75% increase; Yeh et al, 5th Int Workshop on Clin Pharmacol of HIV Ther, 2004).

## Double-Boosted PIs

### Atazanavir/Ritonavir Plus Saquinavir

There is considerable interest in using 2 PIs with pharmacokinetic boosting from ritonavir—for example, to increase PI levels in patients with prior extensive treatment so that each PI might retain activity against virus resistant to the other PI. Such a strategy entails investigation of the pharmacokinetic interactions of the drugs considered for use. In one study, 40 patients received atazanavir 300 mg/ritonavir 100 mg daily plus saquinavir 1000 mg twice daily, 50 received atazanavir 300 mg/ritonavir 100 mg daily plus an nRTI

twice daily, and 100 received saquinavir 1000 mg/ritonavir 100 mg twice daily plus an nRTI twice daily (Von Hentig et al, XV Int AIDS Conf, 2004). It was found that the addition of saquinavir significantly increased the  $C_{min}$  of atazanavir, compared with that of atazanavir/ritonavir, and that the AUCs of both atazanavir and saquinavir significantly increased with the double-boosted regimen, compared with the single-boosted regimens. Sex and coadministration of tenofovir did not appear to have any effect on atazanavir AUC at steady state. The double-boosted regimen of atazanavir/ritonavir plus saquinavir at full therapeutic doses thus does not appear to have detrimental pharmacokinetic interactions.

### Tipranavir/Ritonavir

In contrast, it was found in one study that adding PIs to a tipranavir 500 mg/ritonavir 200 mg regimen results in a detrimental interaction among the PIs. As shown in Figure 3, the AUC,  $C_{max}$ , and  $C_{min}$  of ritonavir-boosted amprenavir,

lopinavir and saquinavir decreased markedly with the addition of tipranavir (Walmsley et al, XV Int AIDS Conf, 2004). This effect was not expected on the basis of the effects of tipranavir/ritonavir on hepatic CYP3A enzyme activity. The mechanism of the interaction is unclear, although it may relate to the effects of tipranavir on drug transporter activity, or a physical incompatibility of drugs in the gut.

### Lopinavir/Ritonavir Plus Fosamprenavir

The A5143 study of lopinavir/ritonavir and fosamprenavir was the first evaluation intended to prospectively assess the efficacy of a double-boosted PI regimen compared with 2 single-boosted PI regimens. However, in a pharmacokinetic substudy, a significant interaction among the drugs was found, resulting in discontinuation of the study (Kashuba et al, *AIDS*, 2005; Wire et al, 11th CROI, 2004). As shown in Table 1, marked reductions in lopinavir and amprenavir AUC values

**Table 1.** Effect of Fosamprenavir or Fosamprenavir/Ritonavir and Lopinavir/Ritonavir Coadministration on Lopinavir and Amprenavir Exposure

Regimen/ parameter	Lopinavir			Amprenavir		
	Lopinavir/ ritonavir dose (mg)	AUC <sub>0-12h</sub>	C <sub>12h</sub>	Fosamprenavir or fosamprenavir/ ritonavir dose (mg)	AUC <sub>0-12h</sub>	C <sub>12h</sub>
Control <sup>1</sup>	400/100 bid	93 (μg•h/mL)	5.8 (μg/mL)	700/100 bid	41.8 (μg•h/mL)	2.3 (μg/mL)
Lopinavir/ ritonavir +fosamprenavir	400/100 bid	48 (μg•h/mL)	2.3 (μg/mL)	700 bid	15.2 (μg•h/mL)	0.7 (μg/mL)
Geometric mean ratio <sup>1</sup>		0.52	0.39		0.36	0.31
Geometric mean ratio <sup>2</sup>	400/100 bid	1.37	1.52	700/100 bid	0.37	0.35
Geometric mean ratio <sup>2</sup>	533/133 bid	0.95	1.01	1400 bid	0.75	0.58

<sup>1</sup>Kashuba et al, *AIDS*, 2005

<sup>2</sup>Wire et al, 11th CROI, 2004

AUC<sub>0-12h</sub> indicates area under the concentration-time curve from 0 to 12 hours; C<sub>12h</sub>, 12-hour concentration; bid, twice daily.

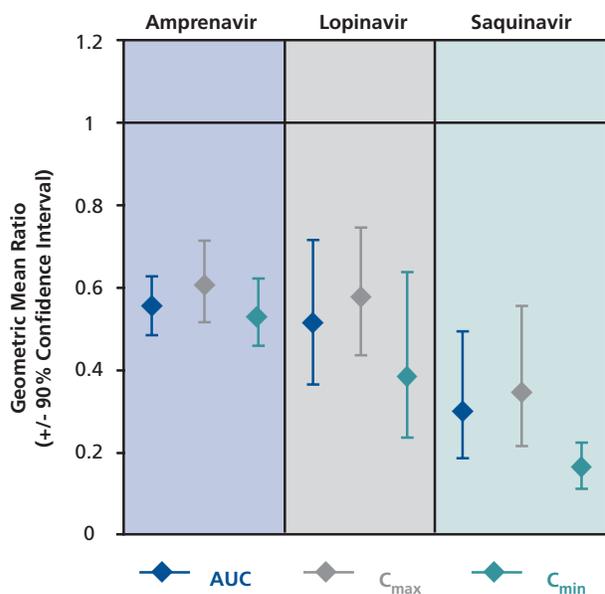


Figure 3. With-tipranavir to without-tipranavir ratio of amprenavir, lopinavir, and saquinavir area under the concentration-time curve (AUC), maximum concentration ( $C_{max}$ ), and minimum concentration ( $C_{min}$ ) for amprenavir/ritonavir, lopinavir/ritonavir, and saquinavir/ritonavir. Adapted with permission from Walmsley et al, XV Int AIDS Conf, 2004.

were observed with concomitant administration of lopinavir 400 mg/ritonavir 100 mg twice daily and fosamprenavir 700 mg twice daily. Boosting fosamprenavir 700 mg with ritonavir 100 mg twice daily resulted in increased lopinavir concentrations but not increased amprenavir concentrations. Increasing the lopinavir/ritonavir dose to 533 mg/133 mg twice daily and the fosamprenavir dose to 1400 mg twice daily brought lopinavir concentrations to control values, but amprenavir concentrations remained reduced. Additionally, this regimen was associated with significant toxicity. In another strategy to overcome what might be physical incompatibility of the 2 agents in the gut, lopinavir 800 mg/ritonavir 200 mg and fosamprenavir 1400 mg/ritonavir 200 mg were given once daily, 12 hours apart. Lopinavir exposure was similar to control values, but amprenavir exposure was still dramatically reduced (Corbett et al, 11th CROI, 2004). Data from the 56 patients enrolled in A5143 before the study was stopped indicated no significant differences between lopinavir/ritonavir plus fosamprenavir and lopinavir/ritonavir or fosamprenavir/ritonavir in virologic response rate (75% and 61%, respectively), CD4+ cell count response (increases of 81/ $\mu$ L and 41/ $\mu$ L, respec-

tively), or reduction of plasma HIV RNA level to 50 copies/mL (54% and 46%, respectively; Collier et al, 12th CROI, 2005). Although the authors have concluded that the reduced drug exposure did not adversely affect response, since the hypothesis of the trial was that double boosting would improve virologic response, an adverse virologic effect of the interaction cannot be excluded.

### Tenofovir and Didanosine

Among nRTIs, there are interactions between tenofovir and didanosine despite the fact that they are not metabolized to active form via the same intracellular pathways. Tenofovir also has pharmacokinetic interactions with lopinavir/ritonavir, atazanavir, atazanavir/ritonavir, and tipranavir/ritonavir, indicating that nRTIs may sometimes affect metabolism of agents that are hepatically metabolized. Some of these may be occurring through transporter-mediated interactions. In the case of tenofovir and didanosine, coadministration has been found to increase didanosine AUC by 44% to 60%. The mechanism of interaction appears to involve the catabolic pathway for didanosine, in which the drug is metabolized to other compounds

by purine nucleoside phosphorylase (PNP) and then eliminated in the urine. PNP is ubiquitous in the body, and is known to be present in erythrocytes, which are believed to be one of the main routes for didanosine elimination. Didanosine is the only antiretroviral agent known to be cleared by PNP. Tenofovir monophosphate and diphosphate have significant affinity for PNP and inhibit PNP degradation of didanosine (Ray et al, *Antimicrob Agents Chemother*, 2004).

A number of adverse pharmacodynamic effects have been observed with the combination of tenofovir and didanosine, and it is possible that some of these are related to the same pharmacokinetic mechanism. A retrospective analysis comparing CD4+ cell count change over 48 weeks in patients on standard-dose tenofovir plus didanosine with those on either tenofovir or didanosine for reasons other than virologic failure showed that only patients receiving the combination exhibited a significant decline in CD4+ cell count (50% > 100 cells/ $\mu$ L, 30% > 200/ $\mu$ L), despite viral load remaining below limits of assay detection (Negeredo et al, *AIDS*, 2004). A subset of patients who had the didanosine dose reduced to 250 mg exhibited CD4+ cell count increases that did not, however, reach baseline levels. In another cohort of 295 patients receiving tenofovir, the probability of developing K65R (particularly in the setting of a triple-nucleoside regimen) substantially increased with concomitant didanosine or abacavir therapy. The frequency of the mutation was negligible in boosted PI regimens and low in tenofovir regimens that did not include abacavir or didanosine, and the addition of zidovudine to treatment substantially reduced risk of the mutation (Staszewski et al, 44th ICAAC, 2004). An increased risk of hyperglycemia was observed in patients receiving tenofovir plus didanosine compared with those receiving only tenofovir or didanosine, with 60% of these patients receiving a reduced dose of didanosine (Garcia-Benayas et al, 12th CROI, 2005). However, a poor immunologic response was not seen in a retrospective analysis of 219 patients treated with tenofovir plus didanosine, 89% of whom were receiving the 250 mg dose of didanosine (Karrer et al, 12th CROI, 2005).

**Table 2. Pharmacology Information Resources**

- <http://aidsinfo.nih.gov>  
(formerly [www.hivatis.org](http://www.hivatis.org))
- [www.thebody.com](http://www.thebody.com)  
(general information and news)
- [www.iasusa.org](http://www.iasusa.org)  
(International AIDS Society–USA)
- [www.hivinsite.org](http://www.hivinsite.org)  
(University of California San Francisco)
- [www.aidsmeds.com](http://www.aidsmeds.com)
- [www.hivpharmacology.com](http://www.hivpharmacology.com)

It has been hypothesized that the CD4+ cell decline with the tenofovir/didanosine combination and the failure of triple-nRTI regimens including either tenofovir/didanosine or tenofovir/abacavir may be related to the effects on PNP (Kakuda et al, *AIDS*, 2004). PNP is involved in both the adenine and guanine metabolic pathways, in which it catalyzes the degradation of the purines to hypoxanthine and guanine. It is known that a hereditary deficiency in PNP is associated with increased deoxyguanosine triphosphate (dGTP) and deoxyadenosine triphosphate (dATP) levels, severe lymphopenia, and reduced T-cell number and function. Given the effect of tenofovir in inhibiting PNP and increasing didanosine concentrations, the questions have been posed whether (1) the lymphocyte toxicity observed with the full-dose combination is caused by PNP inhibition resulting in excess nucleotides; and (2) the failure of triple-nRTI therapy with tenofovir/abacavir/lamivudine and tenofovir/didanosine/lamivudine is related to imbalance in the deoxynucleotide triphosphate (dNTP) to dideoxynucleotide triphosphate (ddNTP) pools as a result of PNP inhibition. These potential effects of PNP inhibition are currently being investigated.

## Conclusion

The potential for drug interactions in the treatment of HIV infection and its complications is unprecedented. The virtually limitless number of drug combinations that may be taken by patients undergo-

ing treatment of HIV infection makes pharmacokinetic and pharmacodynamic drug-drug interactions almost inevitable. This presentation reviewed some of the more important recent pharmacology findings. Up-to-date information can also be found on the Web sites listed in Table 2, which also contain links to a large number of other resources.

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## Suggested Reading

Agarwala S, Gray K, Wang Y. Pharmacokinetic effect of omeprazole on atazanavir co-administered with ritonavir in healthy subjects. [Abstract 658.] 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005; Boston, MA.

Agarwala S, Eley T, Villegas C, et al. Pharmacokinetic effect of famotidine on atazanavir with and without ritonavir in healthy subjects. [Abstract 11.] 6th International Workshop on Clinical Pharmacology of HIV Therapy. April 28-30, 2005; Quebec City, Quebec.

Burger D, Agarwala S, Child M, Wang Y, Grasela D. Effect of rifampin on steady-state pharmacokinetics of atazanavir and ritonavir in healthy subjects. [Abstract 657.] 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005; Boston, MA.

Cohn SE, Watts D, Lertora J, Park JG, Yu S, the A5093 Team. An open-label, non-randomized study of the effect of depot-medroxyprogesterone acetate on the pharmacokinetics (PK) of selected protease inhibitors and non-nucleoside reverse transcriptase inhibitors therapies among HIV-infected women. [Abstract 82.] 12th Conference on Retroviruses and

Opportunistic Infections. February 22-25, 2005; Boston, MA.

Collier A, Tierney C, Downey G, et al. Randomized study of twice-daily lopinavir/ritonavir or fosamprenavir + ritonavir vs lopinavir/ritonavir + fosamprenavir (with tenofovir DF and nucleosides) as rescue therapy. [Abstract 577.] 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005; Boston, MA.

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## Perspective

# Metabolic Complications of Antiretroviral Therapy

Donna E. Sweet, MD

*HIV-infected patients receiving long-term antiretroviral treatment experience a number of metabolic abnormalities, including lipid abnormalities, dysregulation of glucose metabolism, body-fat redistribution, mitochondrial abnormalities, and bone abnormalities, as well as the sequelae of these disorders. These complications can be severe and life threatening, disrupt adherence to antiretroviral therapy, limit options in therapy, and profoundly affect quality of life. Risk for such complications should be considered in selection of antiretroviral therapy, and patients should be monitored for the occurrence of abnormalities and changes in risk factors. This article summarizes a presentation by Donna E. Sweet, MD, on the metabolic complications of long-term antiretroviral therapy at the IAS–USA course in New York in March 2005.*

Many advances have been made in understanding the pathogenesis and progression of HIV disease, developing effective antiretroviral agents and regimens, learning how best to use these regimens for prolonged maximal viral suppression, lowering the pill burden of regimens, and managing many acute adverse effects of treatment. The problems for many patients on long-term effective antiretroviral therapy are the long-term metabolic complications of treatment. Much work remains to be done in identifying how best to avoid these complications and how to effectively treat them when they cannot be avoided.

## Clinical Implications of Metabolic Abnormalities

HIV-infected patients receiving long-term antiretroviral therapy exhibit a number of metabolic complications, including lipid abnormalities, dysregulation of glucose metabolism, body-fat redistribution, mitochondrial abnormalities, and bone abnormalities, as well as the sequelae of these disorders. The etiology of these abnormalities remains largely undefined, and it is unclear whether they represent individual or multiple syndromes. The prospect of patients ultimately experiencing these abnormalities influences the timing of initiation of antiretroviral therapy, since the risk of long-term toxicity must be considered against the virologic and immunologic benefits of early treatment. The risk of these abnormali-

ties should also influence the choice of initial therapy, and the selection should be individualized as much as possible based on risk factors for the abnormalities. The metabolic derangements have an impact on adherence to therapy, which threatens efficacy, and their presence may limit options in salvage therapy. Specific strategies to minimize the occurrence of these abnormalities, such as simplification of regimens, need to be developed to preserve the efficacy of antiretroviral treatment.

## Lipodystrophy

Lipodystrophy, including lipoatrophy (wasting) and lipohypertrophy (accumulation), has occurred in an estimated 40% to 50% of patients on long-term treatment, and the morphologic changes have a substantial impact on patient quality of life. The lack of a standardized case definition for lipodystrophy complicates characterization, diagnosis, and tracking of the disorder. The etiology of the abnormalities remains unknown, although it appears to be multifactorial and influenced by specific antiretroviral drugs, host factors such as age and genetics, and HIV disease stage. Because there are probably multiple causes of fat redistribution, it is unlikely that a single uniform treatment approach will be successful. Management strategies for lipodystrophy include exercise and diet, switching of antiretroviral drugs, anabolic steroids, testosterone, recombinant human growth hormone, metformin and glitazone treatment, lipid-lowering therapy, and plastic surgery. The benefits of most of these strategies remain largely unproven.

With regard to risk associated with particular nucleoside reverse transcriptase inhibitors (NRTIs), a number of studies have shown that the use of an NRTI backbone of didanosine/stavudine is associated with greater fat loss than is zidovudine/lamivudine (eg, the AIDS Clinical Trials Group [ACTG] 384 study) or abacavir/lamivudine (eg, Strategies for Management of Antiretroviral Therapy–Terry Bein Community Programs for Clinical Research on AIDS [SMART-CPCRA] study 065C). A recent report from the metabolic substudy in the FIRST study showed reductions in total and regional fat in patients receiving didanosine/stavudine but not in those receiving abacavir/lamivudine over 32 months (Shlay et al, XV Int AIDS Conf, 2004). Increases in body cell mass and fat were observed in both treatment groups through month 12. However, overall changes from month 0 to 32 for the didanosine/stavudine and abacavir/lamivudine treatment arms, respectively were  $-0.08$  kg/month and  $+0.08$  kg/month in total body fat,  $-0.18$  cm/month and  $+0.10$  cm/month in hip circumference,  $-0.21$  cm<sup>2</sup>/month and  $+0.05$  cm<sup>2</sup>/month in mid-arm skinfold fat area, and  $-0.62$  cm<sup>2</sup>/month and  $+0.62$  cm<sup>2</sup>/month in waist skinfold fat area ( $P < .05$ ).

A number of studies on drug switching were reported at the recent Conference on Retroviruses and Opportunistic Infections. In brief, findings in these studies indicate that substituting a protease inhibitor (PI) with a nonnucleoside reverse transcriptase inhibitor (NNRTI) appears safe, decreases insulin resistance, usually reduces triglyceride levels, has inconsistent effects on total cholesterol and high-density lipoprotein (HDL) cholesterol levels, and has no consistent effects on fat gain or loss. Other findings indicated that abacavir substitution for stavudine results in increased subcutaneous adipose tissue (SAT) but no change in visceral adipose tissue (VAT).

Findings to date on studies of the effects of rosiglitazone in lipodystrophy indicate that it may not be effective in

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increasing subcutaneous fat in patients with lipoatrophy alone but may increase fat mass in those with both insulin resistance and lipoatrophy. Treatment with this agent improves insulin sensitivity, hyperinsulinemia, and adiponectin levels, but may result in increased total and low-density lipoprotein (LDL) cholesterol levels. Further studies with newer glitazones are needed to define subpopulations of patients most likely to benefit from such treatment.

### Dyslipidemia and Coronary Heart Disease

Traditional cardiovascular risk factors contribute to cardiovascular disease in HIV-infected patients and these risk factors need to be managed aggressively. HIV-infected patients appear to be at increased risk of coronary heart disease (CHD), as well as for diabetes and hypertension, both major risk factors for CHD. Antiretroviral therapy appears to accelerate the progression of insulin resistance and dyslipidemia. A recent study has indicated that HIV infection alone, prior to initiation of therapy, is associated with increased cholesterol levels and an adverse effect on insulin sensitivity (El-Sadr et al, *HIV Med*, 2005). HIV-mediated inflammation may also play a role in accelerated CHD. Treatment of risk factors for CHD is complicated by drug-drug and drug-disease interactions in HIV-infected patients. Further studies are needed to understand the pathogenesis of dyslipidemia and cardiovascular disease in HIV-infected patients.

Some of the data indicating an increased risk of cardiovascular disease in the HIV-infected population include a Veterans Administration study showing cardiovascular disease rates of 11.8 per 1000 person-years in HIV-infected patients, compared with 8.1 per 1000 person-years in HIV-uninfected individuals matched for age and sex. In the Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) study, conducted in 11 cohorts in Europe, Australia, and the United States, 126 cases of myocardial infarction (MI), 28% of which were fatal, were found in 36,479 person-years of observation. The relative risk for MI in HIV-infected patients on long-term therapy was 1.26 per year of therapy; a recent update after an additional year of follow-up indicates a relative risk of 1.17 per year of antiretroviral therapy (Sabin et al, 12th CROI, 2005). Another study has reported that patients with AIDS have a relative risk of 10.4 for stroke. Another has suggested that carotid artery intima media thickness, a surrogate marker for coronary disease, is greater and increases more rapidly in HIV-infected patients than in age-matched controls.

Recommendations for treating dyslipidemia in HIV-infected patients to reduce cardiovascular risk include following the National Cholesterol Education Panel (NCEP) recommendations for the general population, including institution of diet and exercise and smoking cessation. Drug-drug interactions and liver toxicity in association with HIV-hepatitis B or C virus coinfection need to be taken into careful consideration when selecting

lipid-lowering drug therapy. For drug therapy, statin treatment may consist of pravastatin 40 mg or atorvastatin 5 or 10 mg; higher doses of atorvastatin may be needed if patients are taking efavirenz. Low-dose fluvastatin may also be considered, with careful dose titration; fluvastatin should not be used if the patient is taking saquinavir/ritonavir or nelfinavir. Simvastatin and lovastatin should be avoided until further pharmacokinetics studies are performed to identify drug interactions. Fenofibrate 160 mg may also be used to treat dyslipidemia. Other agents under study in the HIV-infected population include niacin, fish oil, and ezetimibe. A recent study indicated that fish oil taken 3 times daily produced a large decrease in triglycerides in hypertriglyceridemic patients, although levels remained elevated above normal (Wagh, *Expert Rev Cardiovasc Ther*, 2004). For patients in whom hyperlipidemia is present before beginning antiretroviral therapy, regimens containing atazanavir, tenofovir, or efavirenz may be appropriate to have less effect on lipid profiles. As shown in Figure 1, both atazanavir-based and efavirenz-based therapies resulted in stability or an increase in appendicular and truncal fat on dual energy x-ray absorptiometry scan and increased SAT and VAT on computed tomography in the BMS-034 study (Noor et al, XV Int AIDS Conf, 2004).

With regard to the effects of anabolic steroid treatment on lipid profiles and fat distribution, a recent 12-week study in 32 patients indicated that oxandrolone with exercise caused worsening in lipid

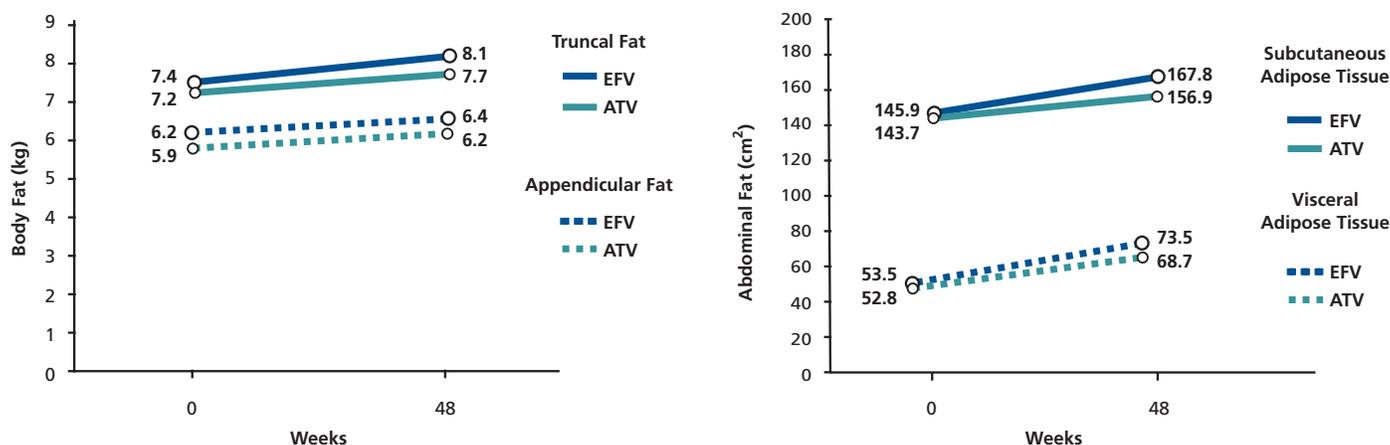


Figure 1. Changes in body fat (left) on dual energy x-ray absorptiometry (DEXA) and in abdominal fat (right) on computed tomography (CT) over 48 weeks of efavirenz-based (EFV) or atazanavir-based (ATV) treatment in the BMS-034 study. Adapted with permission from Noor et al, XV Int AIDS Conf, 2004.

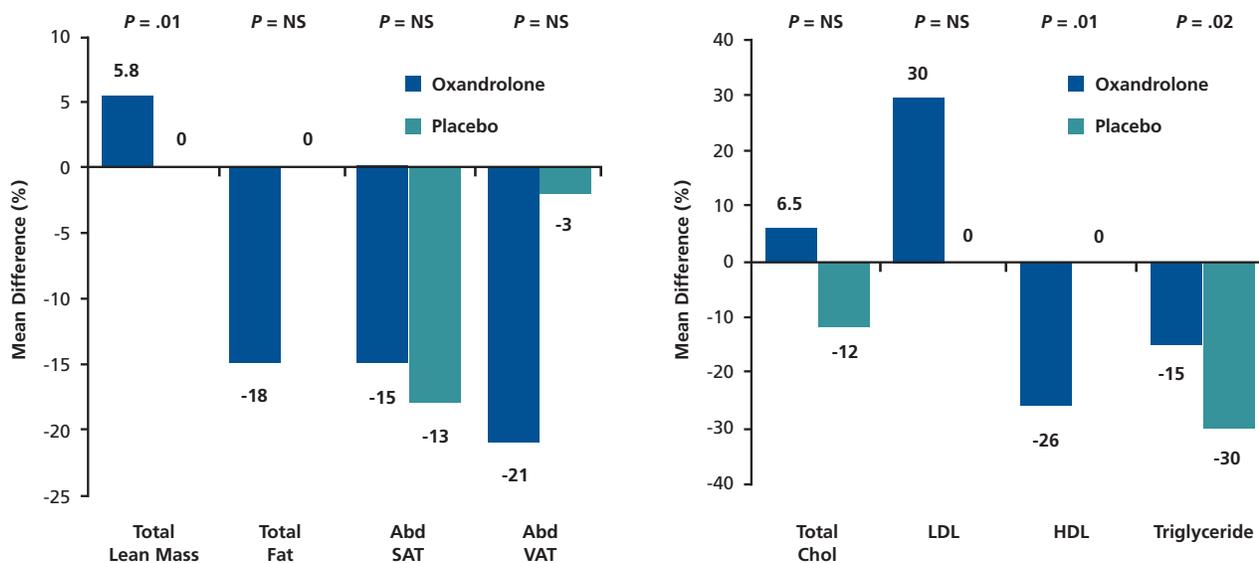


Figure 2. Changes in body fat and lipid measures over 12 weeks with oxandrolone treatment plus exercise (oxandrolone) or exercise alone (placebo). Abd SAT indicates abdominal subcutaneous adipose tissue; Abd VAT, abdominal visceral adipose tissues; Chol, cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; NS, not significant. Adapted with permission from Smith et al, XV Int AIDS Conf, 2004.

measures (increased LDL cholesterol and reduced HDL cholesterol levels) compared with exercise alone (Figure 2); however, the study groups were not well matched for lipid variables at baseline (Smith et al, XV Int AIDS Conf, 2004).

### Glucose Metabolism

Abnormalities of glucose homeostasis, primarily insulin resistance, are common in patients on antiretroviral therapy, with a greater frequency of abnormalities observed in patients receiving PIs. The mechanisms of these abnormalities remain largely undefined. Management includes encouraging weight loss for overweight individuals. Treatment with insulin-sensitizing agents may be beneficial; diabetes treatment guidelines should be followed in HIV-infected individuals.

Recent findings in this area include an association of hyperinsulinemia with the dorsocervical fat deposit termed “buffalo hump” in HIV-infected patients (Mallon et al, *J Acquir Immune Defic Syndr*, 2005). This finding indicates that patients with buffalo hump should be closely followed for insulin resistance and diabetes. It also suggests that caution should be exercised when using human growth hormone for treating buffalo hump, since growth hormone is associated with hyperinsulinemia.

Another recent study indicates that abnormal glucose metabolism may fuel cognitive dysfunction in HIV-infected patients (Valcour et al, *J Acquir Immune Defic Syndr*, 2005). The study indicated that diabetes is an independent risk factor for HIV-associated dementia, with the data hinting that subtle, prediabetic abnormalities in glucose regulation may also pose a risk for cognitive impairment. Among 203 adult patients aged 20 to 76 years (approximately 50% aged >50 years), older patients with diabetes were more likely to meet the research classification of HIV dementia. After adjustment for age, education, ethnicity, CD4+ cell count, duration of HIV infection, and PI-based therapy, diabetes was significantly associated with risk for HIV-associated dementia, with an odds ratio of 5.43, and the significant association remained after adjustment for coexisting vascular risk factors for dementia.

### Bone Disorders

Osteopenia, osteoporosis, and avascular necrosis have been reported in patients with HIV infection. An association of these disorders with PI-containing regimens with tenofovir has been reported in the past, but some recent small studies call this into question. Various risk factors may contribute to these abnor-

malities, including prior steroid treatment for avascular necrosis, cigarette smoking, and hormone therapy for osteoporosis. Clinicians need to be aware of the potential for bone disorders and should treat them early; however, routine screening is not recommended. Further study is needed to identify the etiology of decreased bone mineral density, risk factors, and appropriate prevention and treatment strategies. One recently reported study followed bone changes over 144 weeks in initially antiretroviral-naïve patients. Approximately 40% of patients had osteopenia at baseline, but, with treatment, there was no progression to osteoporosis over the course of follow-up. However, approximately 40% of patients were lost to follow-up, making it difficult to interpret the study findings.

### Mitochondrial Disorders

Mitochondrial toxicity of nRTIs may underlie or contribute to many of the metabolic abnormalities associated with these agents. Older nRTIs (eg, stavudine, didanosine, zidovudine, zalcitabine) are associated with a greater risk of toxicity than newer agents (eg, lamivudine, emtricitabine, abacavir, tenofovir). Mitochondrial toxicity has been implicated in neuromuscular toxicities such as polyneuropathy (zalcitabine, didanosine,

stavudine), myopathy (zidovudine, didanosine), and cardiomyopathy (zidovudine, zalcitabine, didanosine); pancreatitis (didanosine, stavudine); pancytopenias (zidovudine); hepatic microvesicular and macrovesicular steatosis (zidovudine, didanosine, stavudine, zalcitabine); peripheral fat wasting (stavudine); and hyperlactatemia and lactic acidosis. The role of HIV per se in mitochondrial toxicity is not clear.

There are data that indicate recovery in mitochondrial DNA following a switch to an nRTI-sparing regimen. In one study, mitochondrial DNA in both fat biopsies and peripheral blood mononuclear cells (PBMCs) increased in patients switched from nRTI therapy to an nRTI-sparing regimen (Boyd et al, XV Int AIDS Conf, 2004). The gain in fat mitochondrial DNA was significant only when the switch was from stavudine, not zidovudine, and the increase in DNA in PBMCs was significant only after switching from zidovudine, not stavudine (Figure 3; Boyd et al, XV Int AIDS Conf, 2004).

### Hyperlactatemia and Lactic Acidosis

As noted, hyperlactatemia and lactic acidosis appear to be due to nRTI mitochondrial toxicity, and greater risk is associated with older nRTIs, such as zalcitabine, didanosine, stavudine, zidovudine, lamivudine, and abacavir. The lactic acidosis observed is a "type B" lactic acidosis (dysfunction not due to lack of oxygen supply to tissue), for which mitochondrial dysfunction is a common pathophysiologic mechanism. Diagnosis

is difficult because symptoms are vague and nonspecific. Symptoms include nausea and vomiting, abdominal pain or gastric discomfort, unexplained fatigue, malaise, weight loss, and dyspnea. Symptoms may progress to severe, life-threatening metabolic acidosis. Although severe lactic acidosis is relatively rare, a high index of suspicion must be maintained for the disorder in any patient receiving nRTIs. Prompt discontinuation of the offending nRTI is associated with better prognosis. Onset of symptoms cannot be predicted by routine monitoring of lactate levels. Risk factors include older age, obesity, and female sex. Hepatic steatosis usually is present and may be a key part of the syndrome. A milder variant of the syndrome may exist in the form of hyperlactatemia without acidosis. Asymptomatic hyperlactatemia is, however, very rare.

The clinical significance of low-level hyperlactatemia is unclear. Of concern is the role of the liver in the syndrome, with the findings being similar to what is observed in nonalcoholic steatohepatitis. Questions that remain to be answered include whether the condition poses potential for progression to cirrhosis and whether it is a confounding risk factor for liver failure in patients coinfecting with hepatitis B or C virus.

### Peripheral Neuropathy

nRTI-associated peripheral neuropathy is characterized by bilateral, symmetric, painful tingling sensations (dysesthesias) in the feet and toes, loss of tendon

reflexes (areflexia), and distal sensory loss. The disorder is primarily seen with didanosine and stavudine. It is variably reversible after stopping nRTI therapy. Nerve biopsies show damaged mitochondria. The condition is sometimes difficult to distinguish from neuropathy associated with HIV infection per se. Risk factors during nRTI treatment include low CD4+ cell count (<100/ $\mu$ L), prior history of an AIDS-defining illness or neoplasm, prior history of peripheral neuropathy, and use of other neurotoxic agents, including high alcohol consumption. Combination therapy with didanosine and stavudine increases risk of the disorder.

### Pancreatitis

Treatment with didanosine and stavudine is associated with a dose-dependent risk of pancreatitis, with the incidence probably ranging from 4% to 7% at currently recommended doses. Mitochondrial toxicity of nRTIs has been demonstrated in human pancreatic cell lines.

### Myopathy and Cardiomyopathy

Myopathy has been seen most commonly with zidovudine, although it is less frequent at current dosing levels. Mitochondrial DNA depletion and abnormal mitochondria have been described in skeletal and endomyocardial muscle from affected patients. Zidovudine-associated myopathy is difficult to distinguish from that caused by HIV infection per se. In the case of confirmed zidovudine-

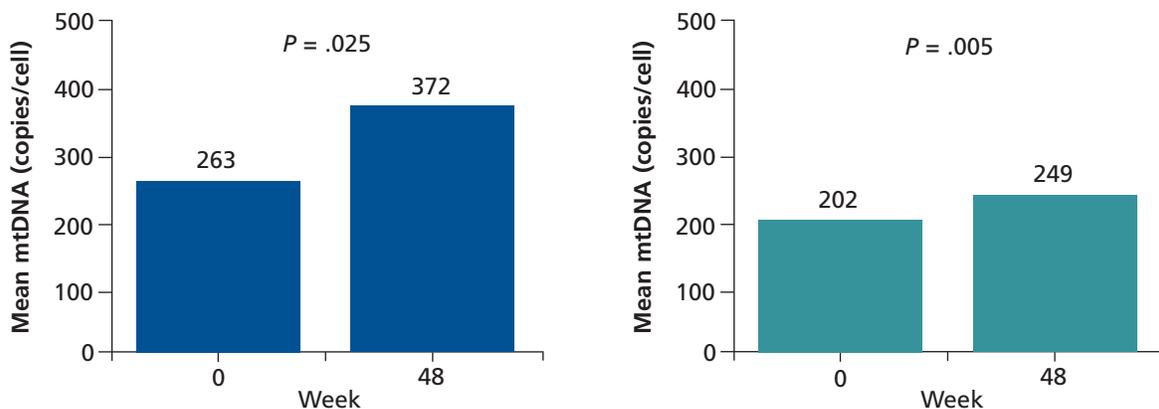


Figure 3. Changes in mitochondrial DNA (mtDNA) level in fat (left) and in peripheral blood mononuclear cells (PBMCs; right) over 48 weeks after switch to nRTI-sparing regimen. After stratification for prior nRTI, increase in fat mtDNA was significant only with switch from stavudine (not zidovudine) and increase in PBMC mtDNA was significant only with switch from zidovudine (not stavudine). Adapted with permission from Boyd et al, XV Int AIDS Conf, 2004.

**Table 1. Guidelines for Reducing Risk of Metabolic Complications**

- Think about the metabolic consequences of starting or switching antiretroviral therapy
- Assess the patient's risk factors and modify them when possible
- Lipodystrophy is easier to prevent than to reverse—avoid didanosine/stavudine
- Treat dyslipidemia, insulin resistance, and hypertension aggressively
- Think about lactate levels in patients with suggestive symptoms
- Be vigilant for bone disease—investigate symptoms, and treat such disease appropriately

associated myopathy and cardiomyopathy, clinical and histologic changes are reported to be reversible.

## Summary

Patients should be assessed for risk factors for metabolic complications of antiretroviral therapy prior to initiation of therapy and should be monitored for such complications every 3 to 6 months after starting treatment, at the time of switching therapy, and at least annually thereafter. Routine measurement of fasting glucose or glucose tolerance testing and routine monitoring of fasting lipids are recommended. Routine monitoring of anthropometric measurements, serum lactate levels, and bone density currently is not recommended.

Success of antiretroviral therapy does not depend solely on reducing plasma HIV-1 RNA levels to below 50 copies/mL. Metabolic complications of long-term therapy threaten the clinical benefits of such effective treatment. Table 1 provides basic guidelines for reducing the risk of metabolic complications.

*Presented in March 2005. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Sweet in June 2005.*

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## Suggested Reading

Boyd MA, Bien D, Ruxrungtham A, et al. Reversal of mitochondrial DNA and RNA depletion in patients switched to indinavir/ritonavir 800/100mg bid and efavirenz 600mg qd after failing NRTI combination therapy: a prospective, 48 week substudy of HIV-NAT 009. [Abstract WePpB2064.] XV International AIDS Conference. July 11-16, 2004; Bangkok, Thailand.

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## Perspective

# Selected Rare, Noninfectious Syndromes Associated With HIV Infection

Molly E. Eaton, MD

*Infrequent and sometimes treatable noninfectious syndromes associated with HIV disease include tenofovir-associated Fanconi syndrome, a proximal renal tubular disorder; pulmonary hypertension that appears to be due to HIV-driven inflammation resulting in endothelial proliferation; thrombotic thrombocytopenic purpura, characterized by intravascular coagulopathy; diffuse infiltrative lymphocytosis syndrome, which can affect multiple organs; and Castleman's disease, a lymphoproliferative disorder that usually occurs in a multicentric form with poor prognosis in HIV-infected patients. This article summarizes a presentation on the characteristics, diagnosis, treatment, and prognosis of these disorders by Molly E. Eaton, MD, at the International AIDS Society–USA course in Atlanta in March 2005.*

Infrequent and treatable noninfectious syndromes associated with HIV infection include nucleotide reverse transcriptase inhibitor (nRTI)-associated Fanconi syndrome, pulmonary hypertension, thrombotic thrombocytopenic purpura, diffuse infiltrative lymphocytosis syndrome, and Castleman's disease. This review will summarize the characteristics, diagnosis, treatment, and prognosis of these selected disorders.

## Nucleotide Reverse Transcriptase-Associated Fanconi Syndrome

Fanconi syndrome is a generalized dysfunction of the proximal tubule with no primary glomerular involvement. It has been observed several weeks after initiation of treatment with the nRTI tenofovir. Tenofovir undergoes renal excretion by active secretion and glomerular filtration; animal studies raised some concerns regarding potential bone and renal toxicity, but clinical trials did not indicate any substantial risk of renal toxicity.

Fanconi syndrome is characterized by variable increase in creatinine levels; proteinuria; normoglycemic glycosuria; phosphaturia and hypophosphatemia; potassium wasting and hypokalemia; HCO<sub>3</sub> wasting and non-anion gap acidosis; and polydipsia, polyuria, and dehydration. Patients with tenofovir-associated

ed Fanconi syndrome often present with fatigue, weight loss, and dry mouth. The workup for proximal renal tubular dysfunction includes serum chemistries to identify abnormal phosphate, potassium, and bicarbonate values; urinalysis to identify proteinuria and glycosuria; and measurement of urine electrolytes (sodium, potassium, chloride) to permit calculation of the urine anion gap. Renal biopsy may be indicated in cases in which symptoms and biochemical abnormalities do not resolve after stopping tenofovir treatment.

The mechanism of this toxic effect is not completely clear. Tenofovir in usual concentrations does not appear to be toxic to renal cells, and the toxic effect may require accumulation of elevated drug levels. Tenofovir is imported into the renal tubule cell via the organic anion transporter 1 (OAT-1) and efflux occurs via the MRP2 gene-encoded conjugate export pump. It is thought that these transporters may be relatively inefficient in some individuals, allowing accumulation of tenofovir within the proximal tubule. Some protease inhibitors (PIs), such as ritonavir and lopinavir, have been found to inhibit the pump, and this may contribute to tenofovir accumulation, although this interaction has not been proven. Fanconi syndrome is more likely to occur in patients with unrecognized decreased creatinine clearance prior to the start of tenofovir treatment.

Patients on tenofovir should undergo urinalysis and serum phosphate measurement every 6 months. Patients with normal serum creatinine may still have

abnormal creatinine clearance, and the latter should be calculated prior to beginning treatment. The drug should be stopped in patients with evidence of acidosis, glycosuria, proteinuria, or hypophosphatemia. Phosphorus supplementation is recommended in cases of isolated low serum phosphate level, although the benefit of such supplementation remains unclear. The toxicity has been found to be mostly reversible. Currently, there are no recommendations regarding reintroduction of tenofovir in a new regimen once the syndrome has resolved.

## Pulmonary Hypertension

Pulmonary hypertension is more common in the HIV-infected population than in the general population, with prevalence estimates of 5 per 1000 versus 2 per million (Recusani et al, *AIDS*, 2003). In the general population, pulmonary hypertension is more common in women. Data from cases reported in HIV-infected individuals from 1987 to 1999 indicate that 54% of cases were in men; however, men accounted for the majority of the HIV-infected population during this period as well. No predisposing factor other than HIV infection is recognized in 82% of cases, and there is no correlation of onset with stage of HIV infection (Mehta et al, *Chest*, 2000). Presenting signs and symptoms include fatigue, syncope, and chest pain; progressive shortness of breath has been reported in 85% of cases, pedal edema in 30%, and nonproductive cough in 19%. There usually are signs of right-sided heart failure, including right-sided gallop, loud P2 heart sound, tricuspid regurgitation murmur, increased jugular venous distention, and edema.

Workup for the condition is fairly straightforward after chest x-ray has shown dilated pulmonary vessels and right-sided cardiomegaly. Electrocardiogram may show right ventricular and atrial hypertrophy and right axis deviation. The echocardiogram may show dilated

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right heart chambers, and can exclude valvular lesions that may cause secondary pulmonary hypertension. It can also identify the high mean pulmonary arterial pressure. The elevated pressure should always be confirmed with right-sided catheterization, which also permits assessment of response to vasodilators.

The causes of HIV-associated pulmonary hypertension remain unclear. Histopathology is the same for HIV-related pulmonary hypertension and primary pulmonary hypertension in HIV-uninfected persons, showing overgrowth of the endothelium that leads to obstruction. A mutation in the *BMPT2* gene that results in reduced inhibition of endothelial proliferation in cases of familial primary pulmonary hypertension has not been identified in HIV-associated pulmonary hypertension. In patients with HIV-associated pulmonary hypertension, pulmonary status continues to deteriorate even when viral load is well controlled, suggesting that HIV may be a trigger, but not the sole culprit, in pathogenesis. Further, no HIV is found in lung tissue in affected individuals. It is thus believed that the condition may be caused by increased inflammatory mediators in susceptible individuals, resulting in increased production of endothelin-1 and increased endothelial proliferation. A recent study suggested a role for Kaposi's sarcoma-associated human herpesvirus 8 (HHV-8) in pulmonary hypertension in HIV-uninfected individuals, although the virus could not be identified in 3 patients with HIV-associated pulmonary hypertension included as controls in the study. The findings from this study need to be confirmed.

Therapeutic options in patients with HIV-associated pulmonary hypertension are the same as in HIV-uninfected patients, including vasodilator treatment with calcium channel blockers, phosphodiesterase blockers (eg, sildenafil), or prostacyclins (eg, epoprostenol infusion). Symptomatic relief is crucial and may involve home oxygen use, diuretics, and digoxin. Anticoagulant therapy makes sense in this context, although there are few data on its use. Use of antiretroviral therapy in affected patients is recommended, although there are no data to indicate that it is of benefit in reversing the underlying endothelial proliferation.

Prognosis is very poor for patients with this disorder, with a median time span of 6 months from diagnosis to death. Suppression of viral replication does not improve prognosis. Better New York Heart Association functional classification at the time of diagnosis has been found to be the only predictor of better outcome (Recusani et al, *AIDS*, 2003).

### Thrombotic Thrombocytopenic Purpura

The incidence of all cases of thrombotic thrombocytopenic purpura (TTP) increased by 16-fold between 1973 and 1991. The incidence of TTP in the HIV-infected population likely has contributed to this overall increase, but the precise magnitude of this contribution remains unclear. It is imperative to recognize TTP early because response to treatment is generally excellent if intervention is initiated early, and the condition can be fatal if it is not treated promptly (Torok et al, *Am J Hematol*, 1995).

The 5 main symptoms of full-blown TTP are thrombocytopenia, anemia, central nervous system abnormalities, renal dysfunction, and fever. The primary dysfunction is intravascular clotting, which consumes platelets and causes an often very marked thrombocytopenia; hemorrhage is nevertheless uncommon. Shearing forces within the clots result in intravascular hemolysis, manifested as high lactate dehydrogenase levels, low haptoglobin, high reticulocyte count, and often a high indirect bilirubin level. Clotting in intracerebral vessels results in ischemia that can present as headache, focal deficits, seizure, and coma. Central nervous system imaging is almost always negative. Clotting in vessels in the kidney can be manifested as hematuria and increased creatinine. Fever is usually but not invariably present; infection must be ruled out in febrile patients. Figure 1 shows the classic finding of schistocytes, fragments of red blood cells that have been torn apart as they move through a clot; platelets are notably absent in the smear.

TTP is associated with large multimers of von Willebrand factor, resulting from a severe deficiency in ADAMTS13, a protease that cleaves von Willebrand factor into smaller multimers. The most common cause of sporadic TTP is an inhibitory antibody that binds ADAMTS13. Because of immune dysregulation, HIV-infected patients make inhibitory antibodies to many blood components, and it is believed that the high incidence of TTP in HIV-infected individuals is associated with high levels of inhibitory antibodies to ADAMTS13 (Tsai, *J Am Soc Nephrol*, 2003).

Treatment is plasmapheresis. After obtaining a hematology consultation and contacting the American Red Cross, plasmapheresis should be performed as soon as possible to reduce risk to the brain and kidney. Plasmapheresis removes the ADAMTS13 inhibitor, infuses large volumes of plasma that dilute inhibitor concentrations, and replenishes ADAMTS13. In cases in which plasmapheresis is not available, plasma infusions may be helpful, although the presence of significant renal failure may prohibit infusion of sufficient volume. The initial response to plasmapheresis usually is excellent. Relapse occurs in approximately 30% of HIV-uninfected patients and probably in a higher per-

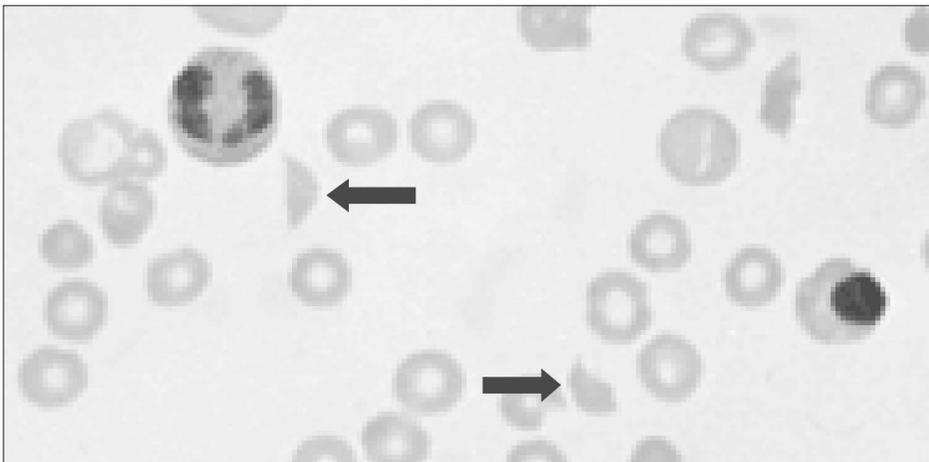


Figure 1. Schistocytes in blood from patient with thrombotic thrombocytopenic purpura.

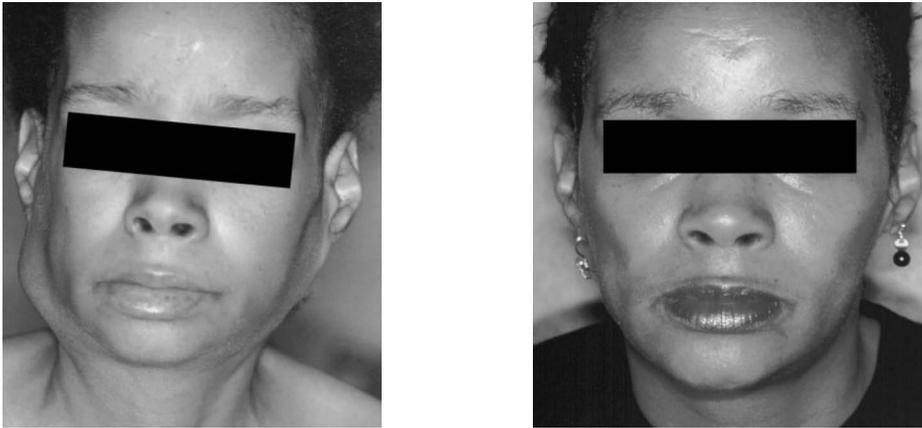


Figure 2. Patient with diffuse infiltrative lymphocytosis syndrome with characteristic bilateral parotid gland enlargement (left) and after antiretroviral treatment (right).

centage of HIV-infected patients. Antiretroviral therapy, which is believed to remove the antigen drive for antibody production, has been reported to reduce the rate of relapse in case studies. Steroids may also be helpful in this regard. In refractory cases, other options include rituximab, anti-CD20 monoclonal antibody, vincristine, azathioprine, and splenectomy. Despite the severe thrombocytopenia, platelet infusions are contraindicated because they can fuel the intravascular clotting. Overall, survival is greater than 90% if treatment is initiated early in patients receiving plasmapheresis, antiretroviral therapy, and adequate supportive care.

### Diffuse Infiltrative Lymphocytosis Syndrome

Diffuse infiltrative lymphocytosis syndrome (DILS) is an autoimmune syndrome characterized by the oligoclonal expansion of CD8+ T lymphocytes in

Table 1. Visceral Involvement in Diffuse Infiltrative Lymphocytosis Syndrome

- **Parotid involvement**
- **Lung**
  - Lymphocytic interstitial pneumonitis
- **Gastrointestinal tract**
  - Lymphocytic hepatitis
  - Plastica gastric lymphocytic infiltration—linitis
- **Nerve**
  - Cranial nerve palsies
  - Peripheral neuropathies
- **Muscle**
  - Inflammatory myositis

response to HIV antigens. It is often accompanied by lymphocytic infiltration of the salivary glands, as well as of the visceral organs. DILS may be seen in all stages of HIV infection; in one study of 35 patients, 37% of whom had AIDS, diagnosis occurred at a mean CD4+ cell count of 342/ $\mu$ L (range, 44-876/ $\mu$ L; Kazi et al, *AIDS*, 1996). The disorder appears to be more common in populations with major histocompatibility complex (MHC) class 1 and 2 alleles consisting of human leukocyte antigen (HLA)-DR5 and HLA-DRw6. HLA-DR5 and DILS are both more common in African Americans. It is estimated that patients with DILS are more than twice as likely to be African American and 2.8 times more likely to have acquired HIV via homosexual sexual contact than those without DILS.

Bilateral parotid gland enlargement, which occurs in approximately 90% to 100% of cases, is the most common presentation of DILS (Figure 2). Patients often have the associated symptoms of dry mouth and dry eyes, similar to that observed in Sjogren syndrome but without anti-Rho or anti-La antibodies. Patients may have extremely high CD8+ cell counts. In one study, the mean CD8+ cell count was 1639/ $\mu$ L, with a range of 560/ $\mu$ L to nearly 5000/ $\mu$ L. Lymphocyte infiltration of extraglandular organs is common (Table 1). Visceral involvement can include the lungs; 31% of patients presented with lymphocytic interstitial pneumonitis in one study (Kazi et al, *AIDS*, 1996).

Patients may be asymptomatic or present with mild to moderate dyspnea on exertion. The pneumonitis is similar to other forms of pneumonitis observed

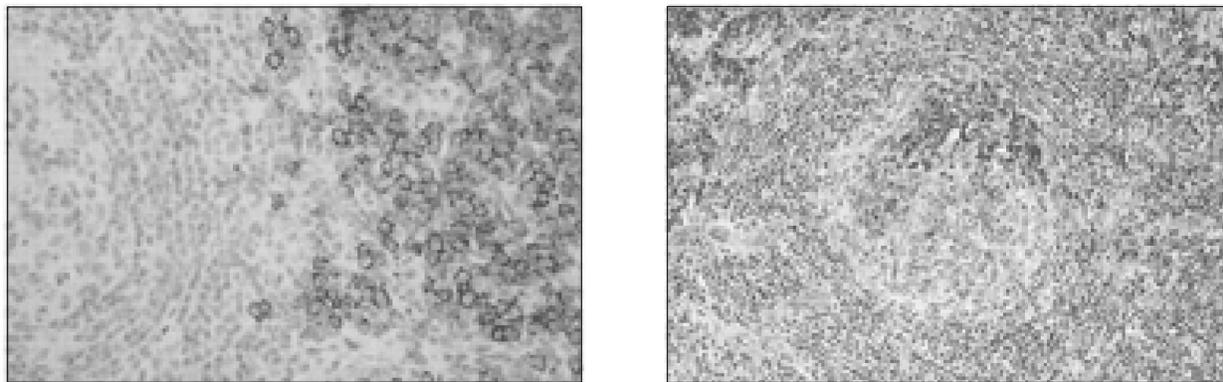
in HIV disease, making it important to perform a diagnostic bronchoscopy with biopsy. Lymphocytic hepatitis may be manifested as elevated liver enzymes but may also progress to frank liver failure. Gastric involvement may need to be differentiated from gastric cancer or syphilis. Peripheral neuropathy is common and resembles HIV-associated neuropathy, although the neuropathy may occur at higher CD4+ cell counts in DILS. Next to effects in the lung, muscle involvement is most common, occurring in 26% of patients. Patients have elevated serum creatine phosphokinase and can have marked symptoms of myalgia and muscle weakness, with the presentation closely resembling polymyositis. In addition to a positive HIV test, diagnosis of DILS involves tissue diagnosis via labial salivary gland biopsy and other tissue biopsies, including bronchoscopy with biopsy and liver biopsy, as well as gallium and computed tomography (CT) scans.

Patients with DILS usually do very well from an HIV disease standpoint. Some data indicate a slower progression of HIV disease in patients with DILS, presumably as a result of the heightened CD8+ cell response to the virus. The goal of treatment is to minimize damage due to the exuberant lymphocyte response. High-dose prednisone can be used to decrease inflammation. The best treatment is antiretroviral therapy, to remove the antigenic drive underlying the inflammatory response. An example of response of the condition to initiation of antiretroviral therapy is shown in Figure 2.

### Castleman's Disease

The following case illustrates some of the findings in HIV-associated Castleman's disease.

A 33-year-old African American man with AIDS, CD4+ cell count of 20/ $\mu$ L, was admitted to the hospital with fever and increasing abdominal fullness. He had been diagnosed with disseminated *Mycobacterium avium* complex infection several weeks prior to admission and was taking sulfamethoxazole/trimethoprim, ethambutol, and clarithromycin. He had been unable to tolerate his antiretroviral regimen of efavirenz, lamivudine, and zidovudine. He was toxic and febrile and had massive hep-



**Figure 3.** Histologic variants of Castleman's disease. Left shows plasma cell form, characterized by interfollicular predominance of plasma cells positive for CD138. Right shows hyaline vascular form, characterized by germinal centers with vascularization and an "onion skin" arrangement of mantle-cell lymphocytes. Reproduced with permission from Zietz et al, *N Engl J Med*, 1999.

atomegaly and splenomegaly. Laboratory results showed platelet count of 83,000/ $\mu$ L, hemoglobin 7.5 gm/dL, and lactate dehydrogenase 497 U/L. CT scans showed shotty hilar adenopathy in the lungs, massive hepatosplenomegaly in the abdomen, and scattered small mesenteric lymph nodes. Liver biopsy was normal, and bone marrow biopsy showed no granulomas, fungal elements, or lymphoma. The patient underwent laparotomy with splenectomy. At laparotomy, 3 celiac nodes were removed, with histology being consistent with hyaline vascular Castleman's disease. The patient defervesced and was started on efavirenz, stavudine, and lamivudine. He continues to do well 2 years later. This, however, is not the typical outcome of the disease.

Castleman's disease is a lymphoproliferative disorder seen in HIV-infected and HIV-uninfected patients. It presents with adenopathy, hectic fevers, splenomegaly, hepatomegaly, and polyclonal gammopathy. It can occur as 2 clinical syndromes. Localized Castleman's disease is more common in HIV-uninfected individuals. It may be asymptomatic or it may be associated with symptoms caused by compression of organs by the large lymph node mass. Multicentric disease is more common in HIV-infected patients. It is characterized by numerous enlarged, usually peripheral, lymph nodes; organomegaly; and systemic symptoms such as hectic fever. Lab abnormalities include thrombocytopenia and anemia. The 2 histologic variants of Castleman's disease are the plasma cell form and the hyaline vascular form (Figure 3). The hyaline vascular form is more common

in localized Castleman's disease than the plasma cell form; the 2 variants may coexist.

Castleman's disease is highly associated with HHV-8, which is found in 100% of HIV-infected Castleman's disease patients and in 40% of HIV-uninfected Castleman's disease patients. Exacerbation of Castleman's disease is associated with increased HHV-8 viral load and appears to correlate with serum levels of viral interleukin (IL)-6 levels (analogous and homologous with human IL-6). Treatment for localized Castleman's disease is excision of the affected nodes, which is associated with good prognosis. Treatment for multicentric Castleman's disease is not well established, and prognosis remains poor in patients with this form. Steroids, rituximab, and chemotherapy have been used in multicentric disease, but no consistent responses have been observed. Antiretroviral therapy does not consistently alter the course of the disease. Treatments under investigation include a humanized antibody to IL-6 receptor.

The noninfectious syndromes discussed above are not common, but they can mimic more common HIV-associated diseases. Recognizing these syndromes can not only limit unnecessary workup and treatment, but in some cases, such as TTP, can be lifesaving.

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## Review

# Sex Differences in the Pharmacologic Effects of Antiretroviral Drugs: Potential Roles of Drug Transporters and Phase 1 and 2 Metabolizing Enzymes

Ighowwerha Ofotokun, MD, MSc

*Sex differences in the pharmacologic effects of antiretroviral drugs are increasingly being reported. Emerging evidence suggests that women may be at increased risk of developing adverse effects of antiretroviral drugs. Several mechanisms have been proposed to explain sex differences in drug effects, including physiologic differences between men and women and the influence of sex hormones on drug metabolism. This article reviews sex-related variations in the levels of expression and activities of drug transporters and metabolizing enzymes involved in the disposition of the antiretroviral drugs, and postulates that these variations may partly explain sex differences in the responses to these drugs. Studies that explore relationships between levels of expression and activities of relevant enzymes and drug transporters and observed sex-related differences in treatment responses to antiretroviral drugs will help clarify the extent to which molecules involved in drug disposition affect sex differences in treatment response.*

## Introduction

The relationship between a patient's sex and that individual's ability to tolerate antiretroviral drugs is increasingly being examined. Several lines of evidence suggest that women are more likely than men to experience adverse effects of antiretroviral drugs.<sup>1</sup> Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is associated with rash and hepatitis more frequently in women than men.<sup>2-6</sup> Protease inhibitor (PI)-associated gastrointestinal intolerance and metabolic disorders are also reported more frequently among women.<sup>7-10</sup> Boxwell and colleagues<sup>11</sup> reported that 83% of 60 cases of lactic acidosis in HIV-infected patients treated with nucleoside reverse transcriptase inhibitors (nRTIs) involved women, and 85% of the 20 fatal cases were in women. Another study<sup>12</sup> examined the relationship between sex

and lipodystrophy in 2258 HIV-infected persons on antiretroviral therapy and found that morphologic alterations were twice as likely in women. These observations suggest that adverse effects may be more frequent in women than in men receiving antiretroviral therapy.

It has been generally presumed that the efficacy of an antiretroviral drug is comparable in men and women. However, 3 recent studies suggest that this may not always be the case. One study from the United Kingdom<sup>13</sup> evaluated the effectiveness of potent antiretroviral therapy in 91 women and 366 men. Virologic suppression was achieved more rapidly in women, and the response was more durable. A second study<sup>14</sup> evaluated sex differences in the clinical response to antiretroviral therapy in 497 men and 146 women who were observed for more than 13 months. Disease progression occurred in 11% of men and in 8% of women. Hospital admission for an AIDS-defining illness was required for 17% of the men and 12% of the women. A third study,<sup>9</sup> involving 78 women and 616 men, found that the efficacy of antiretroviral therapy in reducing the plasma HIV-1 RNA concentration was similar for men and women; however, the mean increase in the CD4+ cell count was greater in women (116/ $\mu$ L)

than in men (84/ $\mu$ L). Although these studies need to be corroborated, the findings suggest that sex may influence the pharmacologic effects of the antiretroviral drugs. Data that indicate increased adverse effects and possibly greater efficacy suggest that women may have better virologic responses to comparable drug doses than do men, or that women may experience higher serum or tissue drug concentrations.

Mechanisms proposed to explain sex differences in drug effects have included physiologic differences in factors such as total body weight, fat distribution, protein binding, gastric motility and acid secretions, glomerular filtration rates, and the influence of sex hormones on drug metabolism. More recently, however, there is growing evidence to suggest that the mechanism of sex-related differences in drug effects may occur at the molecular level. Sex-related variations in the expression and activities of drug transporter genes, proteins, and enzymes involved in phase 1 and 2 biotransformation that form the xenobiotic cascade may underlie some of the observed differences between men and women in responding to certain drugs. This report examines how differences in the expression and activities of these important drug-disposing molecules may explain some of the sex-related differences reported in association with the effects of the antiretroviral drugs.

## Antiretroviral Drug Transporters

The drug transporter P-glycoprotein (Pgp) is an important component of the xenobiotic cascade that influences the bioavailability of drugs. Pgp is encoded by the human multidrug resistance (*MDR1*) gene and is constitutively expressed in epithelial cells, especially in tissues important for drug disposition, such as the apical surfaces of intestinal enterocytes, hepato-

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cytes, and proximal renal tubular cells.<sup>15</sup> Expression of Pgp by these tissues reduces drug absorption from the gastrointestinal tract and enhances drug elimination into bile and urine.<sup>16</sup> Because of the key role played by Pgp in drug disposition, sex-mediated differences in its expression and activities could result in differences between men and women in the pharmacologic activities of drugs transported by this molecule.

Recent observations indicate that Pgp influences the disposition of antiretroviral drugs, particularly HIV PIs. Using L-MDR1 and Caco 2 cell lines that overexpress Pgp, Kim and colleagues<sup>17</sup> demonstrated that indinavir, nelfinavir, and saquinavir are transported by Pgp. They also showed that the plasma concentrations of these drugs after oral administration were 2- to 5-fold higher in *mdr1a* knockout mice than in wild-type mice. Another study<sup>18</sup> showed that the transport of saquinavir and ritonavir was 3 times lower across a monolayer of Pgp-enriched Calu-3 cells derived from human airway epithelium than across a similar layer of cells with little Pgp. Several other studies using in vitro models, such as Caco-2 or MDR1-transfected LLC-PK1 cells, have shown that HIV PIs exhibit directional transport.<sup>19,20</sup> In addition, Pgp inhibitors such as LY-335979, cyclosporin, and verapamil, block cellular transport of HIV PIs, confirming that the PIs are substrates for Pgp.<sup>21</sup> The regulatory role of drug transporters in the disposition of the HIV nRTIs has not been extensively studied. However, data from 2 studies indicate that the multidrug resistance proteins MRP4 and MRP5 may efflux monophosphate metabolites of nucleoside analogues such as nRTIs from cells.<sup>22,23</sup>

Given the role of drug transporters in the bioavailability of antiretroviral drugs, in particular the PIs, factors that regulate the expression of these transporters might influence responses to these drugs. Data from animal models and human studies suggest that sex may play a role in the expression of Pgp and other drug transporters. One example of such evidence was provided by Schuetz and colleagues,<sup>24</sup> who evaluated the expression of Pgp by hepatic cells in 41 subjects and found that Pgp activity among women was only one third to one half that of men. In another study, involving 36 men and 25 women with

B-cell chronic lymphocytic leukemia, Steiner and colleagues<sup>25</sup> showed that women were almost 2 times less likely than men to be positive for the *MDR1* genotype that encodes for Pgp expression. Sex differences in Pgp expression have also been demonstrated in rats<sup>26</sup> and Chinese hamsters.<sup>27</sup> Sex-dependent expression has been described for other transporters, including sodium taurocholate cotransporting polypeptide (NTCP)<sup>28</sup> and the organic cation transporter 2 (OCT2).<sup>29</sup> These observed lower expressions of Pgp in women suggest that women might be more likely than men to achieve higher cellular and tissue concentrations of antiretroviral drugs that are Pgp substrates. This may partially explain the increased frequency and severity of adverse reactions and perhaps the enhanced efficacy of some of these drugs in women compared with men.

### Antiretroviral Metabolizing Enzymes

Other important components of the xenobiotic disposition pathway that limit the bioavailability of drugs are the drug-metabolizing enzymes. The cytochrome P450 (CYP450) superfamily of enzymes accounts for more than 95% of the phase 1 metabolism of all drugs.<sup>30</sup> The CYP450 system consists of at least 11 families of enzymes, of which 3 (CYP1, CYP2, and CYP3) are important in humans. The liver is the primary site of CYP450 activity, but CYP3A is also present in the gastrointestinal enterocytes. CYP3A is the most abundant CYP450 enzyme in the human liver and is responsible for the metabolism of approximately one half of all drugs that undergo phase 1 hepatic metabolism. Phase 2 pathways in drug metabolism include conjugation reactions, such as glucuronidation, sulfation, acetylation, methylation, and glutathione conjugation.

All currently approved HIV PIs are metabolized by CYP450 isoforms. Fitzsimmons and Collins<sup>31</sup> demonstrated the in vitro biotransformation of saquinavir by intestinal and hepatic microsomes to multiple hydroxylated derivatives and also showed that CYP3A4 was the main enzyme involved in the biotransformation. CYP3A4 is also responsible for the metabolism of indinavir,<sup>32</sup> amprenavir,<sup>33</sup> nelfinavir,<sup>34</sup> and

lopinavir.<sup>35</sup> Ritonavir is metabolized primarily by CYP3A4 and, to a lesser extent, by CYP2D6 and CYP2C9.<sup>36</sup>

The CYP450 enzyme system is also responsible for the biotransformation of the NNRTIs. In vitro studies of nevirapine biotransformation have demonstrated that the isoenzymes CYP2B6 and CYP3A4 metabolize nevirapine, with CYP2D6 playing a minor role.<sup>37</sup> The isoenzyme primarily responsible for the biotransformation of efavirenz is CYP2B6, with some involvement by CYP3A4.<sup>38</sup> Delavirdine is metabolized primarily by CYP3A4 and, to a lesser extent, by CYP2D6.<sup>39</sup> Many PI and NNRTI metabolites generated by CYP450 biotransformation subsequently undergo phase 2 reactions before being eliminated in urine or bile.

The nRTIs, on the other hand, are eliminated unchanged in the urine, or undergo hepatic glucuronidation prior to excretion in urine or bile.<sup>40-44</sup> Changes in plasma concentrations of the nRTIs, however, may be of less clinical relevance than for PIs and NNRTIs, because their antiviral effects mainly depend on the rate and extent of intracellular phosphorylation by cellular kinases into triphosphate derivatives.<sup>45</sup> The intracellular accumulation of nRTI mono- or diphosphates resulting from rate-limiting steps in this phosphorylation pathway could be responsible for some of the toxic effects of the drugs, particularly within mitochondria.<sup>46</sup>

Knowledge is growing about sex differences in regulating the expression and activity of phase 1 and phase 2 drug-metabolizing enzymes, which are probably related to endogenous sex hormones.<sup>47</sup> Activities of CYP1A2 and CYP2E1 may be higher in men than in women,<sup>48-51</sup> whereas CYP2D6 activity may be higher in women than in men.<sup>52</sup> Sex differences in CYP2C19 activity appear to show ethnic variations: CYP2C19 activity is higher in Chinese, Jewish-Israeli, and African American women than in men of these ethnic backgrounds.<sup>53-55</sup> No sex difference in the activity of CYP3A seems to exist.<sup>56</sup> Although hepatic clearance of drugs that are substrates for both CYP3A and Pgp (such as erythromycin and verapamil) appears to be higher in women than in men, this may be explained largely by lower hepatic Pgp activity in women.<sup>57-59</sup>

The activities of some phase 2 isoen-

zymes also exhibit sex differences. Thiopurine methyltransferase (TPMT) activities are 14% lower in liver tissues from women than from men.<sup>60</sup> Similarly, levels of catechol-O-methyltransferase activity are lower in women.<sup>61</sup> The activity of several isoenzymes of the uridine 5-diphosphate glucuronosyltransferase (UGT) superfamily, including UGT1A1, UGT1A6, UGT1A8, UGT1A9, and UGT1A10, is also lower in women.<sup>62-65</sup> A study from Finland shows that phenol sulfotransferase activity is more than 60% lower in women than men.<sup>65</sup> Sex differences in regulation of the activities of the cellular kinases that activate nRTIs remain undefined.

Based on available studies, enzymes involved in phase 1 reactions may have only a limited role, if any, in the sex-related differences in pharmacologic effects of the antiretroviral drugs. The activity of CYP3A, the principal isoform of the CYP450 system, in the biotransformation of PIs and NNRTIs does not appear to be influenced by sex. Although CYP2D6 activity is reported to be higher in women than in men, the role of this isoform in the metabolism of ritonavir and delavirdine is limited. In contrast, activities of many isoenzymes involved in phase 2 reactions are lower in women than in men, suggesting that antiretroviral agents (or their metabolites) that undergo biotransformation by these pathways may reach higher concentrations in the cells and tissues of female HIV patients than in male patients.

Sex differences in the activities of cellular kinases that activate nRTIs remain unclear. Studies to explore sex differences in the expression and activities of these key enzymes in the metabolism of the nRTIs will be of interest for 2 reasons. First, there are documented sex differences between men and women in the development of adverse effects associated with the nRTIs, in particular, lactic acidosis. Second, both the efficacy and the toxic effects of the nRTIs are related to the phosphorylated products of the cellular kinases.

## Conclusion

HIV infection has become a chronic, treatable illness, especially in the developed countries, as many HIV-infected patients are on antiretroviral therapy and

are living longer. The adverse effects of these drugs, particularly in women, are a growing source of concern, because many observational studies have shown that women experience greater toxic effects with all classes of antiretroviral drugs. Although sex differences in the effects of these drugs may be due in part to physiologic and hormonal differences between men and women, variations in the activities of drug transporters and metabolizing enzymes involved in phase 1 and 2 reactions may also be involved. Further studies are needed to relate activities of these enzymes and drug transporters and observed sex differences to the effects of the antiretroviral drugs. Such studies will enhance our ability to develop new agents that are better tolerated by both sexes, and to identify drug dosages that are most effective for women.

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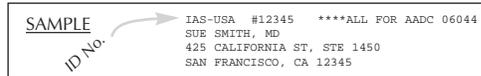
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