

# Topics in HIV Medicine®

A publication of the International AIDS Society–USA

## Perspectives

Emerging Resistance Profiles of Newly Approved Antiretroviral Drugs 110

*Eric S. Daar, MD*

*Protease Inhibitors • CCR5 Antagonists • Integrase Strand-transfer Inhibitors • Nonnucleoside Analogue Reverse Transcriptase Inhibitors*

Non–AIDS-Defining Malignancies in HIV 117

*Ronald T. Mitsuyasu, MD*

*Contributing Factors in NADC • NADC Risk in HIV Infection • Issues in Management, Treatment, and Outcome*

Renal Dysfunction and Tenofovir Toxicity in HIV-infected Patients 122

*Lynda A. Szczech, MD, MSCE*

*Renal Dysfunction in HIV • Renal Effects of Antiretroviral Drugs*

Pathogenesis and Treatment of Lipodystrophy: What Clinicians Need to Know 127

*Fred R. Sattler, MD*

*Body Composition Changes • Insulin Resistance • Effects of Antiretroviral Therapy • Treatment*

## Reprint

Antiretroviral Treatment of Adult HIV Infection: 2008 Recommendations of the International AIDS Society–USA Panel Insert

*Hammer SM, Eron JJ Jr, Reiss P, et al. JAMA 2008; 300:555-570.*



## About This Issue

This issue contains 4 *Perspectives* articles and a reprint insert. The first *Perspective* article summarizes a presentation given by Eric S. Daar, MD, at an International AIDS Society–USA Continuing Medical Education course in Los Angeles in March 2008, at which he discussed emerging resistance profiles of newer antiretroviral drugs in established and new drug classes. A second *Perspective* article, based on a presentation by Ronald T. Mitsuyasu, MD, at an International AIDS Society–USA CME course in San Francisco in May 2008, discusses malignancies in HIV infection, particularly the increase in incidence of non–AIDS-defining cancers during the potent antiretroviral therapy era. The various causes of renal dysfunction in HIV, not limited to tenofovir toxicity, are described in a summary of a presentation made by Lynda A. Szczech, MD, MSCE, at an International AIDS Society–USA CME course in Washington, DC, in May 2008. The final *Perspective* article, based on a May 2008 CME presentation by Fred R. Sattler, MD, in Washington, DC, reviews factors contributing to lipodystrophy in HIV-infected patients and discusses strategies that have had success in the treatment of fat accumulation and fat loss. The insert is a reprint from the August 6, 2008, issue of *JAMA* of the newest guidelines from an International AIDS Society–USA panel on antiretroviral treatment of adult HIV infection. These guidelines update the panel's 2006 recommendations and were warranted by the availability of new antiretroviral drugs and formulations and recent data on treatment options for antiretroviral-naïve and -experienced patients.

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## Perspectives

- |   |     |
|---|-----|
| Emerging Resistance Profiles of Newly Approved Antiretroviral Drugs<br><i>Eric S. Daar, MD</i>          | 110 |
| <hr/>   |     |
| Non–AIDS-Defining Malignancies in HIV<br><i>Ronald T. Mitsuyasu, MD</i>                                 | 117 |
| <hr/>   |     |
| Renal Dysfunction and Tenofovir Toxicity in HIV-infected Patients<br><i>Lynda A. Szczech, MD, MSCE</i>  | 122 |
| <hr/>   |     |
| Pathogenesis and Treatment of Lipodystrophy: What Clinicians Need to Know<br><i>Fred R. Sattler, MD</i> | 127 |
| <hr/>   |     |

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- 

## Announcements

- |  |                   |
|--|-------------------|
| Update on the Chikumbuso Project                           | 116               |
| Correction   | 121               |
| Cases on the Web   | 134               |
| Educational Programs of the International AIDS Society–USA | 135               |
| Subscription Request/Address Change Form                   | 136               |
| Guidelines for Authors and Contributors                    | Inside Back Cover |

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## Perspective

# Emerging Resistance Profiles of Newly Approved Antiretroviral Drugs

*The antiretroviral treatment goal in highly treatment-experienced patients is now suppression of viral replication to undetectable levels, a goal that can be achieved by strategic use of combinations that include newer antiretroviral drugs. Newer drugs in established classes that improve virologic response when added to optimized background therapy include the protease inhibitors darunavir and tipranavir and the second-generation non-nucleoside analogue reverse transcriptase inhibitor etravirine. New drugs from new classes that have proved active in treatment-experienced patients include the chemokine coreceptor 5 (CCR5) antagonist maraviroc and the integrase strand-transfer inhibitor raltegravir. Knowledge of the resistance patterns and predictors of response with these new agents and careful selection of background therapy are crucial to maximizing virologic response and preventing emergence of resistance. This article summarizes a presentation on emerging resistance profiles of newer antiretroviral drugs made by Eric S. Daar, MD, at an International AIDS Society–USA Continuing Medical Education course in Los Angeles in March 2008. The original presentation is available as a Webcast at [www.iasusa.org](http://www.iasusa.org).*

The goal of antiretroviral therapy in treatment-experienced patients is to achieve maximal suppression of HIV replication. As stated in the 2006 International AIDS Society–USA treatment guidelines (Hammer et al, *JAMA*, 2006), “Trials with newer antiretroviral agents have shown that it is possible to achieve plasma HIV-1 RNA levels below 50 copies/mL even in highly treatment-experienced patients,” recommendations that are unchanged in the 2008 guidelines (Hammer et al, *JAMA*, 2008). Similarly, the latest US Department of Health and Human Services guidelines, issued in January 2008, state “In those with prior treatment and drug resistance, the goal is to resuppress HIV-1 RNA levels maximally and prevent further selection of resistance mutations, if possible” (Panel on Antiretroviral Guidelines for Adults and Adolescents, January 29,

2008). A major reason for redefining treatment goals in antiretroviral therapy–experienced patients is the availability of newer antiretroviral drugs from established and new drug classes. Effective use of these newer drugs depends on knowledge of predictors of response to given agents and the resistance consequences of failure that have been identified during the early experience with these drugs and included in recent IAS–USA guidelines and reviews on drug resistance testing (Hammer et al, *JAMA*, 2008; Hirsch et al, *Clin Infect Dis*, 2008).

### Protease Inhibitors

The availability and activity of the protease inhibitors (PIs) darunavir and tipranavir and the entry inhibitor enfuvirtide provided the first evidence that full virologic suppression could be achieved in highly treatment-experienced patients. In the Randomized Evaluation of Strategic Intervention in Multi-drug-resistant Patients with Tipranavir (RESIST) studies, which involved approximately 1500 heavily treatment-experienced patients, the addition of ritonavir-boosted tipranavir (tipranavir/ritonavir) to optimized background reg-

imens (OBRs; based on resistance data and including investigators’ choice of a ritonavir-boosted PI) significantly increased the rate of virologic response, including the rate of achieving plasma HIV RNA levels of less than 50 copies/mL at week 48, from 10% to 23% ( $P < .0001$ ) over OBR with comparator PI alone.

Enfuvirtide was added at physician discretion. Some patients were enfuvirtide-naïve, others were currently using the drug, and still others had prior experience, including those with no response during prior use. Among patients receiving enfuvirtide, response rates were 28% versus 14% for tipranavir/ritonavir versus OBR, respectively, and 21% versus 9%, respectively, among those not receiving enfuvirtide.

An analysis of virologic response at 24 weeks according to tipranavir resistance mutation score at pretreatment (based on 21 initially identified resistance mutations) was conducted in 718 patients receiving tipranavir/ritonavir. Among 144 patients with 0 or 1 mutation (median 0.7- to 0.9-fold change in susceptibility), the median decrease in HIV RNA level was 2.10  $\log_{10}$  copies/mL, compared with 0.89  $\log_{10}$  copies/mL in 242 patients with 2 or 3 mutations (median 1.1- to 1.4-fold change), 0.45  $\log_{10}$  copies/mL in 260 patients with 4 or 5 mutations (median 2.0- to 3.1-fold change), 0.49  $\log_{10}$  copies/mL in 68 patients with 6 or 7 mutations (median 3.3- to 3.9-fold change), and 0.08  $\log_{10}$  copies/mL in 4 patients with 8 or 9 mutations (median 14.7- to 52.5-fold change) (Baxter et al, *J Virol*, 2006).

In the Performance of Darunavir (TMC114)/ritonavir When Evaluated in Treatment-experienced Patients with Protease Inhibitor Resistance (POWER) studies, which involved more than 300 treatment-experienced patients, the addition of darunavir/ritonavir (600 mg/100 mg) twice daily to OBR increased virologic response ( $< 50$  cop-

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ies/mL at week 48) from 14% to 45% ( $P < .0001$ ) over OBR with comparator PI; response rates were 58% versus 11% among patients also receiving enfuvirtide, all of whom were enfuvirtide-naïve at pretreatment, and 44% versus 10% among those not receiving enfuvirtide (Clotet et al, *Lancet*, 2007). Eleven PI resistance mutations were associated with reduced response to darunavir/ritonavir. Virologic response occurred in 64% of 67 patients with no darunavir resistance mutations at pretreatment, 50% of 94 patients with 1 mutation, 42% of 113 patients with 2 mutations, 22% of 58 patients with 3 mutations, and 10% of 41 patients with at least 4 mutations (De Meyer et al, *Antivir Ther*, 2006).

Table 1 shows the current darunavir and tipranavir resistance mutations used in genotypic scoring. There are also evolving clinical cutoff values being generated for darunavir and tipranavir by each company performing phenotypic drug resistance testing. Some of the resistance mutations for the 2 agents are nonoverlapping, indicating that activity of 1 may be retained in the presence of resistance to the other. There are currently no data directly comparing darunavir and tipranavir. Consequently, for patients in whom both drugs are predicted to be active based on genotypic or phenotypic analysis, selection should consider convenience, tolerability, and experience of the physician.

The TMC114/r in Treatment-experienced Patients Naïve to Lopinavir (TITAN) trial compared darunavir/ritonavir with lopinavir/ritonavir, each plus OBR in treatment-experienced but lopinavir-naïve patients with plasma HIV RNA levels greater than 1000 cop-

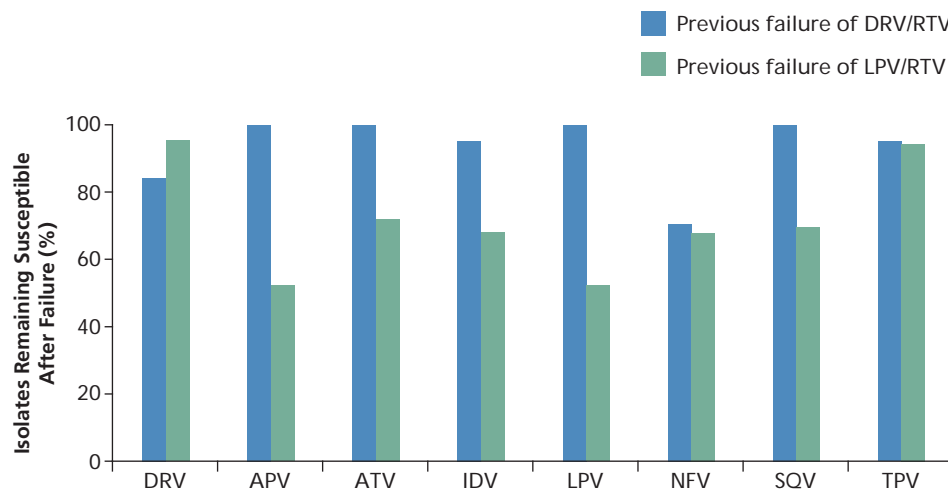


Figure 1. Percentage of patients in whom pretreatment isolates that were susceptible to protease inhibitors remained susceptible after virologic failure of darunavir/ritonavir or lopinavir/ritonavir in the TITAN trial. APV indicates amprenavir; ATV, atazanavir; DRV, darunavir; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; RTV, ritonavir; SQV, saquinavir; TPV, tipranavir. Adapted from De Meyer et al, CROI, 2008.

ies/mL who had been on a stable anti-retroviral therapy regimen for at least 12 weeks. Darunavir/ritonavir met the criterion for noninferiority to lopinavir/ritonavir in virologic response (the primary study endpoint), defined as HIV RNA level less than 400 copies/mL at week 48 on per-protocol analysis (Madruga et al, *Lancet*, 2007). Darunavir/ritonavir also met criteria for superiority for proportions of patients with reductions to less than 400 copies/mL and less than 50 copies/mL at week 48 on intent-to-treat analysis. However, the proportion of patients with pretreatment susceptibility to the study PI to which they were assigned (darunavir or lopinavir) was higher in the darunavir group, and the statistical significance of the superiority was lost when analysis excluded patients with

resistance to their assigned treatment.

An analysis of proportions of patients retaining pretreatment susceptibility to other PIs after virologic failure while receiving darunavir/ritonavir or lopinavir/ritonavir plus OBR is shown in Figure 1 (De Meyer et al, CROI, 2008). The data suggest that patients for whom darunavir/ritonavir is failing are less likely to lose susceptibility to other PIs. Although some of the difference may reflect a higher pretreatment frequency of resistance to the assigned PI for those given lopinavir/ritonavir, the findings still provide support for the notion that darunavir/ritonavir could be used earlier in treatment-experienced patients with some assurance that future use of other PIs will not be overly compromised in cases of virologic failure.

Table 1. Genotypic Scoring for Darunavir and Tipranavir

Darunavir	V11I	V32I	L33F	I47V			
Tipranavir	L10V	I13V	K20M/R/V	L33F E35G M36I K43T M46L I47V			
Darunavir	I50V	I54L/M	G73S	L76V	I84V	L89V	
Tipranavir	I54A/M/V	Q58E	H69K	T74P	V82L/T	N83D	I84V

From Baxter et al, *J Virol*, 2006, and Clotet et al, *Lancet*, 2007.

## CCR5 Antagonists

HIV variants use chemokine coreceptors CXCR4 (X4 variants) or CCR5 (R5 variants) or both (X4/R5, dual-tropic variants) for target cell entry, and individuals with HIV infection may have a mix of variants. The Efficacy and Safety of Maraviroc Plus Optimized Background Therapy in Viremic, ART-experienced patients Infected with

CCR5-tropic HIV-1 (MOTIVATE)-1 and -2 trials examined the addition to OBR of the CCR5 antagonist maraviroc, either once or twice daily (dosing depended upon other drugs in the regimen), in 1049 highly treatment-experienced patients with no detectable CXCR4-utilizing HIV variants on pretreatment assay (approximately 50%-60% of screened patients) (Hardy et al, CROI, 2008). Virologic response defined as plasma HIV RNA level less than 50 copies/mL at 48 weeks occurred in 45.5% of patients in the OBR plus twice-daily maraviroc group and 43.2% in the OBR plus once-daily maraviroc group versus 16.7% of those receiving OBR only (both  $P < .0001$ ).

In a phase IIb study, 167 screened patients with detectable CXCR4-utilizing virus (ie, with dual/mixed or X4 only) or nonphenotypable virus entered the trial. Treatment consisted of the same 3 regimens as in the MOTIVATE trials: OBR plus maraviroc once or twice daily or OBR only (Goodrich et al, IDSA, 2007). At 48 weeks, there were no statistically significant differences between the OBR plus maraviroc regimens versus OBR only with regard to change in HIV RNA level ( $-0.62$  and  $-1.11$  vs  $-0.84$   $\log_{10}$  copies/mL, respectively) or change in CD4 + count ( $+65$  and  $+78$  vs  $+51$  cells/ $\mu$ L, respectively), suggesting that maraviroc is likely of little virologic benefit in patients with detectable CXCR4-using variants.

Data from subjects screened for the MOTIVATE-1 and -2 studies ( $n = 2560$ ), the Study of the Consequences of the Protease Inhibitor Era (SCOPE) trial ( $n = 186$ ), and the AIDS Clinical Trials Group (ACTG) 5211 study ( $n = 391$ ) showed that in treatment-experienced patients, the proportion without detectable CXCR4-using variants ranged from 49% to 60%, whereas dual/mixed variants were detected in 39.5% to 47% and X4-only in 0.5% to 4% (Coakley et al, 2nd International Workshop on Targeting HIV Entry, 2006; Hunt et al, *J Infect Dis*, 2006; Wilkin et al, *Clin Infect Dis*, 2007). In contrast, the absence of detectable CXCR4-using virus is more common in patients with earlier, untreated HIV infection. In treatment-na-

ive study populations ranging in size from 299 to 1428 patients, this was seen in 81% to 88%, with dual/mixed variants in 12% to 19%, and X4-only variants in less than 1% (Brumme et al, *J Infect Dis*, 2005; Moyle et al, *J Infect Dis*, 2005; Demarest et al, ICAAC, 2004; Coakley et al, 2nd International Workshop on Targeting HIV Entry, 2006).

The original phenotypic coreceptor tropism assay that was validated in many of the studies listed above was reported to be virtually 100% sensitive for detecting variants that use CXCR4 (X4 and dual-tropic variants) when they constitute 10% or more of the viral population, with sensitivity declining for smaller minority populations.

Reflecting the issue of assay sensitivity, approximately 5% of patients without detectable CXCR4-using variants at screening for the MOTIVATE trials using the original tropism assay had evidence of dual/mixed variants at the trial entry assessment, a phenomenon that has been consistent across studies in this area. Among this subset of patients, an HIV RNA level of less than 50 copies/mL was observed at week 24 in only 27% of patients receiving OBR plus maraviroc once daily, 18% of those receiving OBR plus maraviroc twice daily, and 18% of those receiving OBR alone.

By comparison, response rates were 50% in both OBR plus maraviroc groups versus 26% in the OBR-only group in those patients without detectable CXCR4-using variants at screening and at pretreatment (van der Ryst et al, ICAAC, 2007; Lewis et al, CROI, 2008). An enhanced assay has replaced the earlier version, with data indicating that it has 100% and 81% sensitivity to detect CXCR4-using virus present at frequencies of 0.3% and 0.1%, respectively, detecting these variants in about half of the 5% of cases that were missed at the time of screening when using the earlier assay (Su et al, *Antivir Ther*, 2008; Trinh et al, *Antivir Ther*, 2008).

The selection for, or emergence of, CXCR4-using variants appears to be an important pathway to virologic failure in patients initially responding to maraviroc. At week 48 in the MOTIVATE-1 trial, approximately 50% of patients

in the maraviroc once-daily group and 63% in the twice-daily group with available data had evidence of CXCR4-using variants at the time of virologic failure (Hardy et al, CROI, 2008). Clonal analysis over time in individual patients with virologic failure indicates that this largely reflects the selection for preexisting but undetected CXCR4-using variants under CCR5 antagonist treatment. With cessation of CCR5 antagonist treatment, the CXCR4-using variants often become undetectable by the standard tropism assay (Lewis et al, *Antivir Ther*, 2007).

Although data are currently limited, a potential implication of these findings is that a response would be unlikely to a different CCR5 antagonist in those patients who experience virologic failure while receiving a CCR5 antagonist that is associated with the detection of CXCR4-using variants. True drug resistance of R5 variants—in which the virus utilizes the CCR5 receptor despite the presence of a CCR5 antagonist—also occurs and is responsible for some proportion of virologic failure (Coakley et al, *Curr Opin Infect Dis*, 2005; Westby et al, *J Virol*, 2006; Mori et al, *Antivir Ther*, 2007). Mutations in the V3 loop of HIV gp120 have been associated with maraviroc resistance, although patterns of amino acid changes differ among patients. The resistance is manifest as a plateau effect in percent inhibition of virus at increasing drug concentrations in vitro. No assays are yet clinically available to identify maraviroc resistance.

## Integrase Strand-transfer Inhibitors

In the Blocking Integrase in Treatment-experienced Patients with a Novel Compound Against HIV, Merck (BENCHMRK)-1 and -2 trials, approximately 700 treatment-experienced patients received the integrase strand-transfer inhibitor raltegravir 400 mg twice daily or placebo plus OBR. In BENCHMRK-1 ( $n = 350$ ), plasma HIV RNA level was reduced to less than 50 copies/mL in 65% of raltegravir patients versus 31% of placebo patients ( $P < .001$ ) at 48 weeks (Steigbigel et

al, *N Engl J Med*, 2008). Rates of virologic failure for raltegravir versus placebo were 15% and 51%, respectively, in BENCHMRK-1, and 15% and 48%, respectively, in BENCHMRK-2 (Steigbigel et al, *N Engl J Med*, 2008).

The primary genotypic pathways to raltegravir resistance have been identified as mutations at codons 155 and 148 and to a lesser extent at codon 143 (Cooper et al, *N Engl J Med*, 2008). These key mutations are associated with minor mutations that result in a marked increase in raltegravir 50% inhibitory concentration (Figure 2). The codon N155H and codon Q148 mutations infrequently occur together. A

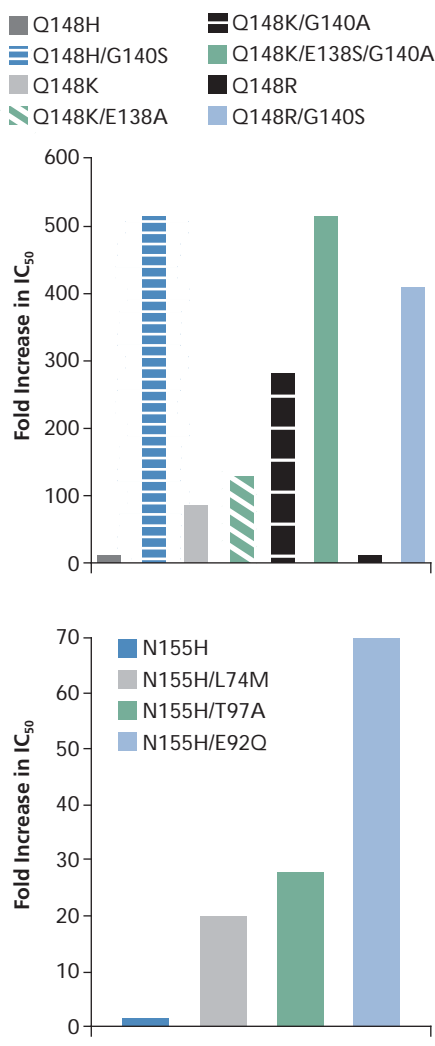


Figure 2. Fold increases in raltegravir 50% inhibitory concentration (IC<sub>50</sub>) with key Q148H/K/R (top) and N155H (bottom) mutations and associated minor mutations. Adapted from Hazuda et al, *Antivir Ther*, 2007.

high frequency of resistance is found in patients having virologic failure while using raltegravir and the investigational integrase inhibitor elvitegravir. Among 94 patients in BENCHMRK-1 and -2 with nonresponse of viral rebound that underwent genotypic testing, 64 (68%) had detectable mutations associated with raltegravir resistance. Of these, 27 (29%) had a mutation at codon 148 and 38 (40%) at codon 155 (Cooper et al, *N Engl J Med*, 2008). These findings emphasize the need to use such drugs selectively and to ensure that background therapy is truly optimized.

Failure also occurs rapidly during treatment with the investigational integrase inhibitor elvitegravir in the absence of adequate background therapy (Figure 3) (Zolopa et al, ICAAC, 2007). Further analyses of patients receiving elvitegravir/ritonavir 125 mg/100 mg in a phase IIb trial showed that E92Q, E138K, Q148H/K/R, and N155H were the most common mutations (38%), with other mutations including S147G (32%) and T66I/A/K (18%) (McColl et al, *Antivir Ther*, 2007). The mutations were associated with a mean greater-than-150-fold increase in the 50% inhibitory concentration (range, 1.2- to 301-fold increase). Also, replication of mutants was decreased by 50% compared with

that of wild-type virus. The effect of a single integrase mutation on susceptibility to raltegravir and elvitegravir and the effect of clinical mutation patterns with elvitegravir treatment on raltegravir susceptibility are shown in Table 2. The data indicate substantial cross-resistance between these drugs (McColl et al, *Antivir Ther*, 2007).

## Nonnucleoside Analogue Reverse Transcriptase Inhibitors

Etravirine was designed to retain activity against virus with the characteristic nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) K103N resistance mutation. The DUET-1 and -2 trials examined the addition of etravirine to OBR containing darunavir/ritonavir (with at least 2 nucleoside analogue reverse transcriptase inhibitors, with or without enfuvirtide) in approximately 1200 treatment-experienced patients (Lazzarin et al, *Lancet*, 2007; Madruga et al, *Lancet*, 2007). A statistically significantly higher proportion of patients receiving etravirine had HIV RNA level reduction to less than 50 copies/mL at week 48 than did the patients receiving placebo (61% vs 40%,  $P < .0001$ ).

As has been consistently shown in trials of newer drugs in highly treat-

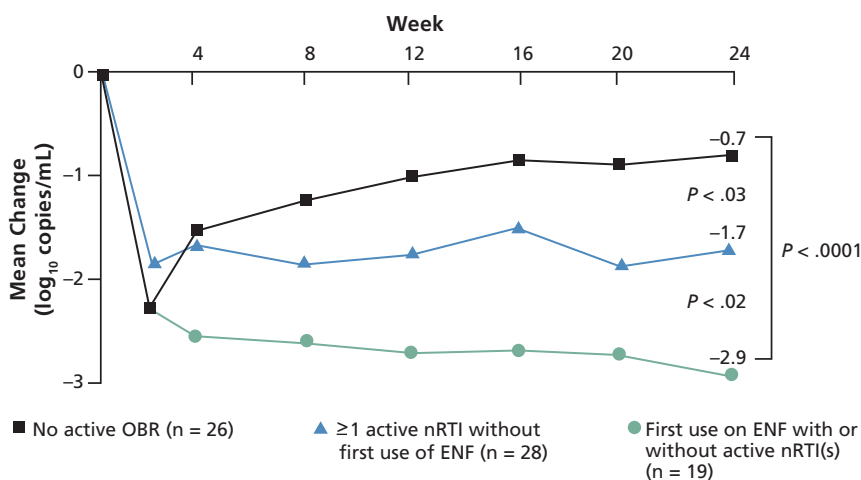


Figure 3. Mean change from pretreatment plasma HIV RNA level in patients receiving the investigational drug elvitegravir 125 mg with ritonavir 100 mg according to activity of optimized background regimen (OBR). Data from patients receiving elvitegravir/ritonavir after addition of a protease inhibitor were excluded. ENF indicates enfuvirtide; nRTI, nucleoside analogue reverse transcriptase inhibitor. Adapted from Zolopa et al, ICAAC, 2007.

**Table 2.** Cross-resistance Between Raltegravir and Elvitegravir<sup>a</sup> Based on Single Integrase Mutations and Clinical Mutation Patterns with Elvitegravir<sup>a</sup>

Fold Change in IC <sub>50</sub> of Mutant Viruses: Single Integrase Mutations									
	T66I	E92Q	E138K	G140S	S147G	Q148H	Q148H	Q148H	N155H
Raltegravir	1.4	6.0	0.9	2.0	1.0	20	34	30	23
Elvitegravir <sup>a</sup>	15	33	0.7	5.0	8.0	6.4	67	118	38

Fold Change in IC <sub>50</sub> of Mutant Viruses: Clinical Elvitegravir <sup>a</sup> Mutation Patterns					
	T66I/ S147G	T66I/ E92Q	E92Q/N155H	G140S/Q148H	E138K/S147G/ Q148R
Raltegravir	2.5	33	135	>1000	34
Elvitegravir <sup>a</sup>	46	145	166	>1000	175

<sup>a</sup>Investigational drug.Adapted From McColl et al, *Antivir Ther*, 2007.

ment-experienced patients, virologic response rates even in placebo-treated patients were increased according to the number of active drugs in the background regimen. Rates for etravirine versus placebo were 33% and 0%, respectively, in patients with no active drugs, 60% and 26%, respectively, in those with 1 active drug, and 76% and 61%, respectively, in those with at least 2 active drugs (Haubrich et al, CROI, 2008; Johnson et al, CROI, 2008). Such findings again stress the importance of ensuring that the background regimen is as active as possible to achieve and maintain suppression and prevent resistance to new agents.

Initially a total of 13 mutations were found to confer reduced etravirine susceptibility: V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, and G190A/S. Response rates according to the number of these mutations present at pretreatment were 75% in the 40% of patients with no mutations, 60% in the 30% of patients with 1 mutation, 58% in the 16% of patients with 2 mutations, 41% in the 8% of patients with 3 mutations, and 25% in the 6% of patients with at least 4 mutations (Cahn et al, ICAAC, 2007). Thus, the presence of at least 3 mutations was associated with a response rate comparable to that seen with the addition of placebo to OBR; this 3-mutation threshold for loss of activity for etravirine has also been observed in analyses using established non-etravirine-specific NNRTI

mutations (excluding K103N). More recently, further study has demonstrated that 17 mutations may be associated with reduced phenotypic susceptibility to etravirine. Furthermore, some mutations have a greater effect on susceptibility than others, allowing for the creation of a weighted mutation score to further enhance the ability to predict the likelihood of a given individual's virus being susceptible to this drug and how that might influence the patient's ultimate response to therapy (Vingerhoets et al, *Antivir Ther*, 2008).

Based upon the initial mutations reported to be associated with reduced etravirine response, it was found that 14% of patients receiving etravirine in the DUET trials had at least 3 resistance mutations at pretreatment. Moreover, the prevalence of virus with at least 3 etravirine mutations was reported to be relatively low in other cohorts, such as 30% in a study in Thailand (n = 158) (Sungkanuparph et al, CROI, 2008), 10% in a study in Nigeria (n = 214) (Taiwo et al, CROI, 2008), 9.3% in a study in Spain (Llibre et al, CROI, 2008), and 7.3% in a large commercial (Virco Lab, Inc) database (n = 226,491) (Picchio et al, CROI, 2008). Thus, although pretreatment resistance to etravirine and other second-generation NNRTIs in development may be relatively uncommon, it is clearly a real phenomenon, and careful genotypic analysis is warranted when use of these drugs is considered.

Phenotypic cutoff values for etravirine are also being developed (Vingerhoets et al, *Antivir Ther*, 2008).

## Conclusion

The goal of therapy in antiretroviral drug-experienced patients is to achieve a viral load below the limits of assay detection. The availability of new drugs in existing and new classes has increased the likelihood of achieving this goal. Defining resistance patterns for new drugs in existing classes allows for optimization of their use in antiretroviral drug-experienced patients. Defining how resistance develops to new drugs in new classes is key to understanding the risks of virologic failure. The strategic use of antiretroviral drugs to enhance successful suppression of virus is the best way to avoid resistance to new agents and new classes.

*Presented by Dr Daar in March 2008. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Daar in August 2008.*

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## Update on The Chikumbuso Project

As attendees to our Continuing Medical Education courses know, the International AIDS Society–USA has been selling colorful hand-crocheted tote bags made of recycled plastic bags by the women of Lusaka, Zambia, to support the Chikumbuso Project. This project is the 2008 International AIDS Society–USA Charitable Partner, and it supports medical care and social programs for widows, orphans, and grandmothers in the Ng’ombe township whose lives have been impacted by HIV and AIDS.

The IAS–USA is pleased to report that as of September, 2008, sales of the bags at our courses have raised more than \$25,000 directly for the Chikumbuso Project. We thank the many attendees of our courses who have purchased

these bags and/or made additional donations to the project. The final chance to purchase a bag will be at our CME course in New York on October 3, 2008. Additional donations can be made at any time by mailing a check made out to “Second Baptist Church” (with “Chikumbuso Project” in the memo field) to:

Second Baptist Church  
146 Pendleton Hill Road  
North Stonington, CT 06359

Further information is available by contacting Linda Wilkinson at [chikumbusoproject@yahoo.com](mailto:chikumbusoproject@yahoo.com).

The International AIDS Society–USA is actively seeking a new Charitable Partner for 2009.

## Perspective

# Non-AIDS-Defining Malignancies in HIV

*During the potent antiretroviral therapy era, the incidence of AIDS-defining cancers has decreased and the incidence of non-AIDS-defining cancers (NADCs) has increased, as has the proportion of mortality associated with NADC in HIV-infected patients. The increase in NADCs is partly associated with increased longevity of the HIV-infected population, but it may also reflect consequences of increased immune activation and decreased immune surveillance as well as direct effects of HIV. The NADCs appear to have earlier onset and worse prognosis in HIV-infected patients than in the general cancer population. Among cancers that have increased in incidence are lung cancer, with its strong association with tobacco use, and skin cancers. Much remains to be learned about risk, risk reduction, optimal treatment, and drug interactions in HIV-infected cancer patients. This article summarizes a presentation on malignancies in HIV infection made by Ronald T. Mitsuyasu, MD, at an International AIDS Society-USA Continuing Medical Education course in San Francisco in May 2008. The original presentation is available as a Webcast at [www.iasusa.org](http://www.iasusa.org).*

The incidence of non-AIDS-defining cancers (NADCs) has increased by greater than 3-fold over the past 10 years and has now surpassed that of AIDS-defining cancers (ADCs) in HIV-infected patients. Some of this increase is associated with the longer survival and aging of patients in the potent antiretroviral therapy era, but some also appears to be associated with direct effects of HIV that increase susceptibility to such cancers.

Early reports in the 1980s suggested that malignancies might constitute a second “epidemic” within the AIDS epidemic (Monfardini et al, *AIDS*, 1989). Kaposi sarcoma and non-Hodgkin lymphoma (NHL) initially accounted for the majority of malignancy-associated morbidity and mortality in HIV disease. With the advent of effective antiretroviral therapy, NADC as a cause of death in people with HIV has increased from less than 1% in the pre-potent antiretroviral therapy era to as high as 13% (Stein et al, *Am J Med*, 1992; Bonnet et al, *Cancer*, 2004).

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A report on cancer trends in HIV-infected patients between 1989 and 2002 showed that there has been an overall decline in cancer incidence from 77 cases to 12 cases per 1000 patient-years, reflecting a decline in incidence of ADC. During this period, however, the incidence of NADCs increased from 3.3 to 10.9 cases per 1000 patient-years (relative risk, 3.3; 95% confidence interval [CI], 1.7-6.6) (Bedimo et al, *Clin Infect Dis*, 2004). Among types of malignancies, incidences of Kaposi sarcoma and central nervous system lymphoma have decreased, those of prostate and breast cancer have remained relatively constant, and those of other lymphomas (eg, NHL and Hodgkin disease) and of cervical, anal, and lung cancers have increased (Table 1).

### Contributing Factors in NADC

In addition to increased life expectancy and reduction of other causes of death in HIV-infected persons, contributors to the increased prevalence of NADCs include (1) greater prevalence of coinfection with viruses that have etiologic roles in cancer, including human herpesvirus 8 (primary effusion lymphoma, Kaposi sarcoma, Castleman disease), human papilloma virus (HPV);

cervical, anal, penile, and possibly head and neck cancers), Epstein-Barr virus (Hodgkin disease, NHL, primary central nervous system lymphoma, pediatric leiomyosarcoma), and hepatitis B and C viruses (hepatomas); (2) behaviors and environmental toxins, including tobacco and alcohol use; and (3) effects of HIV infection, including potential direct effects of the virus and the consequences of long-term immunosuppression.

Potential direct effects of HIV include HIV Tat protein transactivation of cellular genes or proto-oncogenes. Various HIV genes have also been reported to inhibit tumor suppressor genes (eg, *TP53*). The incidence of lung cancers has rapidly increased in HIV-infected individuals, and cell culture studies have shown a 6-fold higher frequency of microsatellite alterations in cells from HIV-infected lung cancer patients than from non-HIV-infected cancer patients; it is suspected that the genetic instability may be a direct effect of HIV. Infection with HIV is believed to also increase the susceptibility of tissues to

**Table 1.** Changes in Incidence of Cancers Associated with HIV Since the Beginning of the Potent Antiretroviral Therapy Era in 1998

Kaposi sarcoma	↓
Central nervous system lymphoma	↓
Lymphoma (non-Hodgkin)	↑
Lymphoma (Hodgkin disease)	↑
Cervical cancer	↑
Anal cancer	↑
Lung cancer	↑
Prostate	↔
Breast	↔
Hepatoma	↔

Derived from data in Patel et al, *Ann Intern Med*, 2008.

the effects of carcinogens. Endothelial cell abnormalities have also been detected in HIV infection, including elaboration of angiogenic factors, which could serve to facilitate tumor growth.

A recent meta-analysis comparing the incidence of cancers in HIV-infected persons and immunosuppressed transplant recipients has strongly suggested a link between immunosuppression and cancer (Grulich et al, *Lancet*, 2007). Among 444,172 HIV-infected patients and 31,977 transplant patients, both groups had a significantly increased incidence of 20 of 28 cancers examined. For example, standardized incidence ratios for cancers in patients with HIV and AIDS and transplant recipients were 2.7 and 2.2 for lung cancer, 3.2 and 2.4 for leukemia, 1.5 and 6.8 for kidney cancer, 1.6 and 3.1 for esophageal cancer, and 1.9 and 2.0 for stomach cancer, respectively. There was some indication that hematologic malignancies may be more common in HIV-infected patients, with both populations having high frequencies of numerous solid tumors.

### NADC Risk in HIV Infection

Data from the HIV Outpatient Study (HOPS) indicate differences in cancer risk among HIV-infected patients and non-HIV-infected cancer patients. In this analysis, age-, race-, smoking-, and sex-adjusted rates of NADCs were compared between 7893 HIV-infected patients in Chicago and Illinois cancer registry patients during the period of 1992 to 2002 (Clifford et al, *J Natl Cancer Inst*, 2005; Long et al, *AIDS*, 2008; Phelps et al, *Int J Cancer*, 2001; Serraino et al, *AIDS*, 2000; Giordano and Kramer, *Clin Infect Dis*, 2005; Patel et al, *Ann Intern Med*, 2008). HIV-infected patients had increased relative risk for Hodgkin disease (77.4), head and neck cancer (10.0), anorectal cancer (5.0), melanoma (4.1), and lung cancer (3.6). No excess risk for breast, colon, or prostate cancer was detected. The excess lung cancer risk was primarily related to tobacco use. Cancers occurred at an earlier age in both men and women with HIV infection than in non-HIV-infected patients.

An HIV natural history study among US military beneficiaries found 133 cases of NADC among 4144 participants during the period of 1988 to 2003, yielding an incidence rate of 980 cases per 100,000 person-years (Burgi et al, *Cancer*, 2005). The most common primary cancer was basal cell skin cancer, accounting for 32.3% of cancer cases, followed by squamous cell skin cancer (12.0%), Hodgkin disease (9.8%), anal cancer (7.5%), melanoma (6.8%), colorectal cancer (6.0%), prostate cancer (4.5%), renal cancer (3.0%), and lung cancer (2.3%); other cancers accounted for 15.8%.

The low rate of lung cancer in this study underscores the notion that rates of particular cancers in HIV disease reflect different risks (eg, behavioral, environmental, and genetic risk factors and prevalence of coinfections) in different populations. Comparison of rates in the study cohort with rates reported in the general population in the US Surveillance Epidemiology and End Results (SEER) database showed that white patients with HIV infection had higher rates of basal and squamous cell skin cancer, melanoma, Hodgkin disease, and anal cancers, whereas black patients with HIV infection had higher rates of lung and colorectal cancers in addition to higher rates of Hodgkin disease and anal cancers. On multivariate analysis in this cohort, predictors of NADC (all  $P < .001$ ) were age greater than 40 years versus less than 24 years (odds ratio [OR], 12.2), white or non-Hispanic ethnicity versus black (OR, 2.1), longer duration of HIV infection (OR, 1.2 for each year), and history of opportunistic infection (OR, 2.5), with antiretroviral therapy being a negative predictor (OR, 0.21). Neither CD4+ cell count at time of diagnosis nor nadir CD4+ cell count was predictive of NADC.

At least 1 analysis also suggests that risk for NADC is not associated with viral load. The Strategies for Management of Antiretroviral (SMART) study, in which 5472 patients with CD4+ counts of 250 cells/ $\mu$ L to 350 cells/ $\mu$ L underwent randomization to either continuous viral suppression or drug-conserving, intermittent antiretroviral

therapy, was stopped early because of greater frequency of mortality or other endpoints in the drug-conserving group. The second highest proportion of endpoints was from NADC (36%, with 25% of the 60 events being fatal) after cardiovascular disease (42%; hepatic and renal endpoints accounted for 12% and 10%, respectively) (Silverberg et al, *AIDS*, 2007). Analysis of risk for NADC, according to latest measure of plasma HIV RNA level less than or equal to 400 copies/mL versus greater than 400 copies/mL, did not yield a significant hazard ratio after adjustment for other risk factors (age, sex, prior diagnosis of AIDS, hepatitis B and C virus coinfections, smoking, latest CD4+ count) (Silverberg, *AIDS*, 2007). In this analysis, significantly reduced risk with lower versus higher viral load was observed for all serious non-AIDS-defining events, renal events, cardiovascular events, and other non-AIDS mortality, but not for liver events.

A review of the literature on NADC published in 2003 (Chiao and Krown, *Curr Opin Oncol*, 2003) indicated increased incidence rates in the United States for anal cancer, Hodgkin disease (mixed cellularity and lymphocyte-depleted types), lung cancer (adenocarcinoma, tobacco-related), testicular cancer (mostly seminoma), skin cancers (basal and squamous cell and melanoma), multiple myeloma, leukemia (mostly M4, M5 subtypes), and pediatric leiomyosarcoma (affecting 1 in 5000 and accounting for 8%-14% of pediatric cancers), as well as for lip, head and neck, penile, and conjunctival cancers. As of the time of that review, there had been no obvious increase in breast, colon, or prostate cancers, although it is possible that increased risk will be observed for these malignancies with longer and closer follow-up.

It has been difficult, however, to accurately define risk for cancer overall and for individual malignancies in HIV-infected persons because of several factors. These include absence of relevant or good-quality data in registries and databases, competing risk factors for death, underreporting, variations in screening practices, and underdiagnosis, as well as population

factors including differences in behavior and coinfections. The National Cancer Institute (NCI) has initiated a concerted effort to improve access to information on the incidence of cancer in HIV disease in both HIV cohorts and cancer registries in the United States. This and other efforts will ultimately allow us to better define risks and risk factors.

### Issues in Management, Treatment, and Outcome

Available evidence suggests that HIV-infected cancer patients have a worse prognosis than similarly staged non-HIV-infected patients with the same cancer; they are also more likely to have more advanced disease at diagnosis. Data from a retrospective study comparing characteristics of HIV-infected patients and HIV-indeterminate subjects with lung cancer are shown in Table 2 (Brock et al, *JAIDS*, 2006). HIV-infected patients were much younger (median age 46 vs 64 years); were more likely to be black, past or current smokers, and injection drug users; had more advanced disease and a history of fewer pack-years of smoking; were less likely to undergo surgery with curative intent; and had significantly reduced median survival. An earlier study indicated that, as in the non-HIV-infected population, median survival was longer in HIV-infected lung cancer patients able to undergo resection (approximately 17 months) than in those receiving radiotherapy (approximately 7 months) or chemotherapy (approximately 3 months) without surgery, although few patients had resection as an option (4% vs 10% for radiotherapy and 86% for chemotherapy) (Powles et al, *Br J Cancer*, 2003).

Although available evidence also suggests that HIV-infected cancer patients should receive at least the same intensity of cancer therapy as non-HIV-infected patients, much remains to be learned in every facet of treatment and management of patients with NADCs. Unanswered questions and research needed can be categorized generally as follows:

**Table 2. Lung Cancer Characteristics in HIV-infected Patients and HIV-indeterminate Patients**

	HIV-infected (n = 92)	HIV-indeterminate (n = 4973)	P Value
<b>Sex, no. (%)</b>			
Male	62 (67.4)	2860 (57.5)	.06
Female	30 (32.6)	2113 (42.5)	
<b>Age in years, no. (%)</b>			
<40	12 (13.0)	99 (2.0)	
40-60	70 (76.1)	1594 (32.1)	<.001
>60	10 (10.9)	3280 (66.0)	
Age in years, median (IQR)	46 (42-59)	64 (57-71)	
<b>Race, no. (%)</b>			
White	19 (20.7)	3749 (75.4)	<.001
Black	73 (79.4)	1224 (24.6)	
<b>Histology, no. (%)</b>			
Adenocarcinoma	44 (47.8)	1754 (35.3)	
Squamous	16 (17.4)	1225 (24.6)	
NSCLC	14 (15.2)	814 (16.4)	.19
Small cell	8 (8.7)	379 (7.6)	
Large cell	5 (5.4)	432 (8.7)	
Other	5 (5.4)	371 (7.5)	
<b>Stage, no. (%)</b>			
I	6 (6.5)	1150 (23.1)	
II	6 (6.5)	447 (9.0)	<.01
III	17 (18.5)	1059 (21.3)	
IV	63 (68.5)	2317 (46.6)	
<b>Smoking status, no. (%)</b>			
Never	1 (1.1)	510 (11.2)	
Ever	91 (98.9)	4037 (88.8)	
Former	8 (8.7)	1815 (39.9)	<.001
Current	83 (90.2)	2222 (48.8)	
Pack-years, median (IQR)	30 (20-45)	50 (30-75)	
<b>Injection drug use, no. (%)</b>	53 (57.6)	47 (1.0)	<.001
<b>Surgery with curative intent, no. (%)</b>	13 (14.1)	1343 (27)	<.001
<b>Survival, months, median (IQR)</b>	6.3 (2.3-11.4)	9.4 (3.6-24.0)	<.001

IQR indicates interquartile range; NSCLC, non-small-cell lung cancer.  
Adapted from Brock et al, *JAIDS*, 2006.

### Efficacy

Are standard treatments for each stage of each cancer in non-HIV-infected patients similarly effective in HIV-infected patients? Does the presence of worse prognostic factors in HIV-infected patients require the use of more aggressive cancer therapy? Are molecular and virally targeted therapies more or less appropriate for use in HIV-infected patients?

### Adverse Effects and Complications

Do HIV-infected patients experience additional and more severe toxicities from cancer therapies? What are the pharmacokinetic and pharmacodynamic drug interactions of HIV medications with cancer therapies? How can HIV therapies and cancer therapies be adjusted to minimize toxicities? For example, it is already known that the dosage of iri-

notecan, which is metabolized by cytochrome P450 enzymes, needs to be reduced in patients receiving HIV protease inhibitor therapy, and holding antiretroviral therapy may be prudent in some cases in which short-term, high-dose cancer chemotherapy is required that contains agents known to interact with antiretroviral drugs. We still need to determine what degree of toxicities is acceptable and can be managed in patients treated for NADC as well as the overall effect of these toxicities on quality of life. Are standard palliative measures for adverse effects effective in HIV-infected patients? What are the costs and benefits of more aggressive therapy, if such is needed in this population?

### Additional Questions

Some evidence indicates that the rate of relapse is higher for anal cancer and Hodgkin disease in HIV-infected patients than in non-HIV-infected patients, and AIDS Malignancy Consortium (AMC) studies are examining the potential role of intensification of cancer therapy in these settings. Is a higher relapse rate characteristic of NADC in HIV-infected patients? Is intensification therapy needed for some or many of these diseases? To what extent is the rate of cancer progression dependent on the degree of HIV replication control or the level of immunodeficiency? Does HIV therapy or therapy for opportunistic conditions influence cancer progression? Which diseases and treatments need to be factored in when planning cancer therapy?

### Prevention

Among prevention measures, smoking cessation may be the highest priority. Smoking is associated with several cancers, and lung cancer is clearly increasing rapidly in the HIV-infected population. Use of hepatitis and HPV vaccines should be considered in seronegative individuals; immunogenicity studies currently are being conducted for HPV vaccine in HIV-infected persons. A high index of suspicion for cancer must be

maintained in HIV-infected patients. Yearly cervical and anal Papanicolaou testing should be performed, including gynecologic examinations and high-resolution anoscopy. Yearly breast examinations and prostate examinations (including measurement of prostate-specific antigen) should be performed. In patients who are hepatitis B virus- or hepatitis C virus-seropositive, liver function tests and alpha-fetoprotein measurements should be performed periodically. A complete family history of malignancies should be obtained because the results can increase index of suspicion and lead to early detection of disease that might otherwise be missed. Sunscreen use and avoidance of overexposure to sunlight should be stressed, given the observed increase in skin cancers and evidence indicating that endothelial and epithelial cells in HIV-infected individuals may be more susceptible to carcinogenesis.

### Resource-limited Settings

Cancers are distributed unevenly throughout the world. As examples, high incidences of head and neck cancers and plasmablastic lymphomas (aggressive Epstein-Barr virus-associated cancers) occur in India, and a high incidence of squamous cell tumors, including conjunctival cancers, occurs in Africa. Challenges include determining which treatments are available locally and which treatments are reasonable to use in locales where high-dose chemotherapy is beyond the reach of most patients and extensive palliative therapy and supportive treatment may not be available. Questions that must be confronted include the following: Can effective treatments that are easier to administer and locally feasible be designed? What are the medical and public health trade-offs that must be faced? What prevention and risk-reduction approaches can be instituted locally?

### Current Needs, Future Prospects

Prospective studies are needed both to more accurately assess risk and risk factors for NADC and to determine op-

timal treatment strategies for NADCs. Efforts aimed at defining optimal treatment and management should have increased focus on pathogenesis-directed treatment and prevention strategies and greater emphasis on use of antiretroviral drugs, prophylactic antibiotics, and other supportive measures. It is crucial that interactions among cancer chemotherapies, antiretroviral drugs, and other drugs routinely used in HIV-infected patients be identified. Ultimately, simpler but effective treatments for both ADCs and NADCs need to be designed, and screening guidelines need to be developed to facilitate earlier recognition of disease and improve treatment options and outcomes.

### Conclusion

As patients with HIV disease live longer, morbidity and mortality from NADCs are increasing. Cancers in HIV infection need to be quantified and characterized, particularly given that the types and frequencies of cancers are likely to vary in different populations and locales. Treatment of malignancies in HIV disease should be vigorous and appropriate to the disease and stage of disease. Optimal treatment strategies and strategies for treating and preventing adverse effects associated with antiretroviral therapy and cancer therapy need to be identified. Prevention strategies for viral-associated malignancies need to be investigated, and strategies for reducing or eliminating known risk factors need to be implemented.

For information on AIDS Malignancy Consortium clinical trials, see: <http://pub.emmes.com/study/amc/public/index.htm>. For information on NCI programs in HIV cancer, see: <http://www.cancer.gov/cancertopics/types/AIDS/>.

*Presented by Dr Mitsuyasu in May 2008. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Mitsuyasu in July 2008.*

*Dr Mitsuyasu received a research grant awarded to the University of California Los Angeles from Pfizer Inc.*

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*Top HIV Med*. 2008;16(4):117-121

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## Correction

An error was made in "Update of the Drug Resistance Mutations in HIV-1: Spring 2008" from the March/April 2008 issue, Volume 16, Issue 1. On page 66 in Footnote 12, the second sentence should have read, "The K103N or Y188L mutation alone prevents the clinical utility of *efavirenz and nevirapine* (Antinori et al, *AIDS Res Human Retroviruses*, 2002)." The correction was previously made in the PDF version of the article on our Web site, [www.iasusa.org](http://www.iasusa.org), where updates are posted as they become available.

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## Perspective

# Renal Dysfunction and Tenofovir Toxicity in HIV-infected Patients

*Potentially nephrotoxic drugs are only 1 of several causes of renal dysfunction in HIV. Data from the period before the wide use of tenofovir show a variety of prerenal, renal, and obstructive causes of acute renal failure (ARF) in HIV outpatients. Results of clinical trials of tenofovir indicate a rate of ARF of approximately 1%, with observational cohort data indicating a somewhat higher rate. Thus, in evaluating patients with rising serum creatinine levels, including those receiving tenofovir, diagnostic efforts should go beyond discontinuation of potentially offending drugs. This article summarizes a presentation on renal dysfunction in HIV and renal toxicity of antiretroviral drugs made by Lynda A. Szczech, MD, MSCE, at an International AIDS Society–USA Continuing Medical Education course in Washington, DC, in May 2008. The original presentation is available as a Webcast at [www.iasusa.org](http://www.iasusa.org)*

As HIV practitioners, we are often caught in the position of determining whether complications arising in our patients stem from the treatments we have used in an effort to help them. An enduring lesson from the Strategies for Management of Antiretroviral Therapy (SMART) trial is that although we have to expect toxicities from HIV medications and know how to manage them, delaying or suspending medication use can have worse consequences. In that study, patients underwent randomization to continuous antiretroviral therapy (viral-suppression group) or a drug-conservation strategy in which treatment was deferred or suspended when CD4+ count was higher than 350 cells/ $\mu$ L and started or resumed when the count fell below 250 cells/ $\mu$ L. Risk of death from any cause or opportunistic infection, risk of major cardiovascular, renal, or hepatic disease, and risks of cardiovascular and renal disease separately were statistically significantly lower in the viral-suppression group than in the drug-conservation group. For fatal or nonfatal renal disease, the hazard ratio in the drug-conservation group was 4.5 ( $P = .05$ ) (SMART Study Group et al, *N Engl J Med*, 2006).

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## Renal Dysfunction in HIV

Renal dysfunction has numerous causes in our patients. Acute renal failure (ARF) is signalled by a marked acute rise in serum creatinine level, but no specific magnitude of increase defines the condition. In the HIV outpatient population, Franceschini and colleagues (*Kidney Int*, 2005) reported a rate of ARF of 5.9 cases per 100 person-years in 754 patients observed from 2000 to 2002. Rates of ARF in HIV outpatients were reported at 2.9% in 1995 and 6.0% in 2003 in a study of 25,114 patients (Wyatt et al, *AIDS*, 2006).

In the study by Franceschini and colleagues, ARF had prerenal causes (mostly diarrhea and nausea/vomiting or infection) in 38% of cases, renal causes (mostly ischemic or medication-related) in 46%, and obstructive causes in 7% (Table 1) (Franceschini et al, *Kidney Int*, 2005). The study was conducted before the heavy penetration into clinical practice of the nucleotide analogue reverse transcriptase inhibitor (nRTI) tenofovir, the antiretroviral drug most associated with renal toxicity. The data should serve as a reminder that, even in the patient receiving tenofovir, numerous factors can cause renal dysfunction.

When evaluating a patient with a rising serum creatinine level indicative

of abnormal renal function, the practitioner should first determine whether the patient is in the “glomerular” group (ie, has a disease affecting the glomeruli) or the “tubular” group (ie, has a lesion affecting the tubules) (Figure 1). The urinalysis is essential in this determination. In broad terms, glomerular dysfunction in HIV patients may be indicative of HIV-related kidney disease or other secondary diseases such as diabetes mellitus, whereas drug toxicities more often manifest as tubular dysfunction. Glomerular involvement is indicated by the finding of protein-

**Table 1.** Causes of Acute Renal Failure in HIV Outpatients, 2000 to 2002, Before Widespread Use of Tenofovir

<b>Prerenal, n = 43, 38%</b>
Diarrhea, nausea/vomiting: 18
Heart failure: 2
Hepatorenal: 9
Pancreatitis: 2
Adrenal insufficiency: 1
Infection: 10
Erythroderma: 1
<b>Renal, n = 48, 46%</b>
Acute tubular necrosis
Ischemic: 22
Medications: 17
Contrast: 2
Allergic interstitial nephritis: 5
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome: 2
<b>Obstructive, n = 9, 7%</b>
Kidney stones: 2
Crystalluria: 6
Gross hematuria: 1

Adapted from Franceschini et al, *Kidney Int*, 2005.

uria alone or combined with hematuria; the presence of hematuria alone probably signifies a problem outside of the kidney parenchyma such as in the ureter, bladder, or prostate.

The role of the tubule is to separate substances for resorption from those for excretion, and tubular dysfunction is suggested by abnormalities in dilution or acidification of urine. Isosthenuria (indicated by urine specific gravity of 1.010) shows that the renal tubules are neither diluting or concentrating the urine. Although this is not necessarily a sign of pathology, it may indicate tubular damage. The presence of casts in urine may also be indicative of tubular dysfunction. Urine is often bland (ie, contains no protein or blood) if there is tubular dysfunction but the glomeruli are intact.

Among tubular disorders, acute tubular necrosis (ATN) consists of damage to tubular cells and results in accumulation of an aggregate of Tamm-Horsfall protein and degenerated cells that form into casts. Direct tubular cell toxicity can be caused by such agents as aminoglycosides, amphotericin B, radiocontrast, pentamidine, heroin or cocaine, nonsteroidal anti-inflammatory drugs, adefovir, and tenofovir. Volume depletion can also result in ATN when reduced perfusion limits blood flow to tubular cells.

Allergic interstitial nephritis (AIN) is a more insidious process in which allergic reaction within the interstitium results in infiltration of inflammatory and plasma cells that inhibit tubule function and damage the interstitium. Drugs that can cause AIN include beta-lactam antibiotics, quinolones, sulfonamides, rifampin, phenytoin, and atazanavir. Casts in the urine are less common in AIN than in ATN.

In Fanconi syndrome, tubular resorption of glucose, phosphate, amino acids, bicarbonate, sodium, or any combination of these is blocked, usually only partially, and urinary wasting occurs. These resorptive abnormalities can manifest as glycosuria in a patient with a normal serum glucose level, low serum phosphorus level (and a compensatory increase in serum parathyroid hormone level), proximal renal

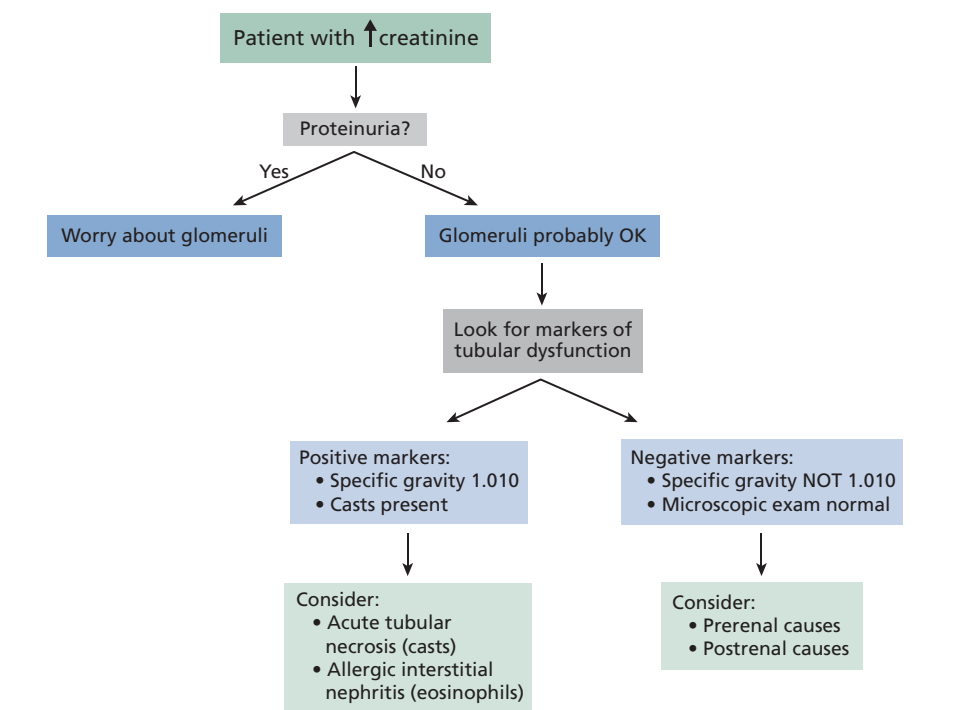


Figure 1. A simple flow diagram for evaluating HIV patients with increased serum creatinine levels.

tubular acidosis, or volume depletion. Renal loss of phosphate is indicated by increased levels of urine phosphate ( $>5$ - $10$  mg/dL or  $>100$  mg/day) and a value for the fractional excretion of phosphorus that is greater than 5% (as calculated using the following formula: [urine phosphate level  $\times$  serum creatinine level]  $\div$  [serum phosphate level  $\times$  urine creatinine level]). Nonrenal phosphate loss (eg, via gastrointestinal loss) or poor oral intake is indicated by a decreased urine phosphate level ( $<5$ - $10$  mg/dL or  $<100$  mg/day) and a value for the fractional excretion of phosphorus that is less than 5%.

### Renal Effects of Antiretroviral Drugs

Apart from a number of case reports of interstitial nephritis associated with atazanavir, concern over antiretroviral drug-associated renal toxicity largely has been focused on tenofovir. The literature on renal toxicity of tenofovir is nonstandardized, but studies assessing prior clinical trials and observational cohorts are all limited by lack of diagnostic specificity for the cause of the renal event, thereby producing confu-

sion about the true frequency of this complication.

In the selected populations enrolled in these clinical trials, which include rigorous monitoring of renal function, tenofovir appears to be associated with a low risk of adverse renal effects. The recently reported Head-to-Head Epzicom and Truvada (HEAT) trial compared 343 subjects treated with abacavir/lamivudine with 345 subjects given tenofovir/emtricitabine, both in combination with lopinavir/ritonavir for 48 weeks in treatment-naïve patients (Smith et al, CROI, 2008). Reduced glomerular filtration rate (GFR) was noted in 5% of each treatment group, and ARF occurred in less than 1% of patients in the tenofovir/emtricitabine group and none in the abacavir/lamivudine group. Assessment of renal function at 48 weeks showed median changes in the abacavir/lamivudine group similar to those in the tenofovir/emtricitabine group in creatinine clearance, using the Cockcroft-Gault formula (+9 vs +6 mL/min, respectively), in estimated GFR using the Modification of Diet in Renal Disease (MDRD) formula (+7 vs 0 mL/min/1.73 m<sup>2</sup>, respectively), in the protein:creatinine ratio (−0.01 vs

0, respectively), in serum phosphate level ( $-0.3$  vs  $-0.4$  mg/dL, respectively), and in urine glucose concentration (0 vs 0 mg/dL, respectively).

In the ALERT trial, 106 treatment-naïve patients received a tenofovir/emtricitabine backbone plus either fosamprenavir/ritonavir or atazanavir/ritonavir (Smith et al, IAC, 2007). Mean changes in GFR adjusted for body weight were approximately  $+4$  and  $-4$  mL/min/1.73 m<sup>2</sup> at 48 weeks in the fosamprenavir/ritonavir and atazanavir/ritonavir groups, respectively.

The single-arm Boosted Atazanavir and Truvada Given Once Daily (BATON) trial examined atazanavir plus tenofovir/emtricitabine in 102 treatment-naïve patients (Gilead Sciences, Foster City, CA, data on file). Over 48 weeks, creatinine clearance decreased from 109 mL/min to 104 mL/min using the Cockcroft-Gault equation, and the GFR using the MDRD formula decreased from 93 mL/min/1.73 m<sup>2</sup> to 80 mL/min/1.73 m<sup>2</sup>. One patient discontinued tenofovir/emtricitabine early because of a grade 1 increase in serum creatinine level; 2 additional patients had confirmed graded increases (grade 1 and grade 2).

It is unclear how to interpret the group change in MDRD measurement with regard to individual patient risk. Do we expect every patient to exhibit on average a 13 mL/min/1.73 m<sup>2</sup> decrease in GFR, or will a small number of subjects experience more substantial changes associated with ARF? In the Gilead 934 study, 517 treatment-naïve patients received efavirenz plus tenofovir/emtricitabine or zidovudine/lamivudine/efavirenz for 144 weeks, after which all patients received efavirenz/tenofovir/emtricitabine for an additional 96 weeks. At 144 weeks, there was no statistically significant difference in change from pretreatment levels in median creatinine clearance using the Cockcroft-Gault equation in either treatment group (118 vs 115 mL/min for zidovudine/lamivudine and tenofovir/emtricitabine, respectively, from a pretreatment value of 121 mL/min for both). However, the change from pretreatment using the MDRD equation was statistically significantly

greater in the tenofovir/emtricitabine group (from median 110 to 98 mL/min/1.73 m<sup>2</sup>) than in the zidovudine/lamivudine group (from median 105 to 106 mL/min/1.73 m<sup>2</sup>) ( $P < .001$ ).

The finding of no difference in change between the tenofovir comparator groups using the Cockcroft-Gault equation but some difference using the MDRD equation is similar to observations from the HEAT trial. While a discussion of the limitations of each formula is beyond the scope of this presentation, it should be noted that both use demographic and clinical variables to approximate muscle mass and “normalize creatinine.” The differences between formulae are based on the relative emphasis of age and sex as well as the presence of weight in the Cockcroft-Gault formula and race in the MDRD formula. The consideration of how a differential change in weight could have masked a “real” change in renal function using the Cockcroft-Gault formula or, conversely, how the addition of lean body mass could result in the “appearance” of a change in renal function using the MDRD formula should be further explored.

This trend did not continue in longer term observation, however. In the continuation group of the trial (study 903E), treatment with tenofovir for up to 6 years was associated with at least stability in renal function, with creatinine clearance level increasing from 116 mL/min to 128 mL/min ( $P = .015$ ) using the Cockcroft-Gault equation, and with the estimated GFR increasing from 112 mL/min/1.73 m<sup>2</sup> to 117 mL/min/1.73 m<sup>2</sup> ( $P = .058$ ) using the MDRD equation (Gilead Sciences, data on file).

The clinical trial data suggest that risk of tenofovir renal toxicity is low (approximately 1%) in selected populations with good dosing practices and vigilance in patient monitoring. However, some observational cohort studies suggest a higher risk—not surprising given that patient populations are more heterogeneous and treatment is more complex in real life. Rates of tenofovir nephrotoxicity in retrospective cohort studies have been reported in general at approximately 2% (1.90% [Karras et al, *Clin Infect Dis*, 2003],

1.60% [Padilla et al, *AIDS Patient Care STDS*, 2005], 0.80% [Jones, *JAIDS*, 2004], 0.78% [Franceschini, *Kidney Int*, 2005], and 0.00% [Gallant et al, *Clin Infect Dis*, 2005]).

Variation in incidence in these reports may be attributable to surveillance and recognition biases, lack of a standard definition of toxicity, and reporting of mean versus median renal function values. Whether the frequency of tenofovir-related ARF is approximately 1%, as suggested by clinical trials, or approximately 2%, as might be surmised from cohort studies, recall the background rate of ARF in the HIV population of approximately 6%, as observed in the study by Franceschini and colleagues conducted before the wide use of tenofovir. It is thus potentially dangerous to assume that all cases of impaired renal function in a patient receiving tenofovir are caused only by tenofovir and to respond to such a finding by simply stopping the drug without a thorough search for other causes. Failure to consider other causes may result in a missed opportunity for an early diagnosis of another condition that could be the real culprit and that may continue unchecked.

That said, it is still instructive to examine observational cohort data closely to derive an idea of risk in the clinical setting. Johns Hopkins cohort data showed significant reductions in creatinine clearance at 180 days, 270 days, and 360 days over a 360-day follow-up in 344 patients receiving tenofovir compared with 314 patients who received nRTIs other than tenofovir (Gallant et al, *Clin Infect Dis*, 2005). Pretreatment values and changes in renal function are shown in Table 2.

A study in the HIV Outpatient Study (HOPS) cohort examined the potential effects of concomitant protease inhibitor (PI) and tenofovir treatment. Over 12 months, median changes in creatinine clearance were  $-2.8$  mL/min versus  $-5.1$  mL/min, respectively, in patients without PI exposure ( $n = 210$ ) versus those receiving atazanavir/ritonavir or lopinavir/ritonavir ( $n = 99$ ) in addition to tenofovir ( $P = .51$ ); median changes in GFR were  $-5$  mL/min/1.73 m<sup>2</sup> versus  $-5$  mL/

**Table 2.** Changes in Renal Function in Patients Receiving Tenofovir Versus Nucleoside Analogue Reverse Transcriptase Inhibitors (nRTIs) in the Johns Hopkins Cohort

	Tenofovir Group (n = 344)	nRTI Group (n = 314)	P Value
Serum creatinine at pretreatment, mg/dL	0.8 <sup>a</sup>	0.8	.56
Creatine clearance at pretreatment, mL/min	117	118	.69
Treatment period, days	303	336	.19
Maximum serum creatinine, mg/dL	1.0	0.9	.17
Absolute change in serum creatinine, mg/dL	+0.15	+0.10	.17
Calculated minimum creatine clearance, mL/min	98	102	.43
Absolute change in creatine clearance, mL/min	-13.3	-7.5	.005
Percent change in creatine clearance	-10	-6	.007
Patients with decline in creatine clearance, no. (%)			.14
>50%	15 (4.4)	6 (1.9)	
25%-50%	46 (13.4)	34 (10.8)	
1%-50%	158 (45.9)	141 (44.9)	
No decline	125 (36.3)	133 (42.3)	

<sup>a</sup>Data are median unless otherwise indicated.

Adapted from Gallant et al, *Clin Infect Dis*, 2005.

min/1.73 m<sup>2</sup> in patients without (n = 208) or with (n = 97) PI exposure (P = .55) (Buchacz et al, *JAIDS*, 2006). However, a recent study indicated a statistically significant reduction (approximately 13 mL/min) in creatinine clearance at 48 weeks in 51 patients receiving tenofovir and lopinavir/ritonavir compared with 66 patients not receiving tenofovir and 29 receiving tenofovir plus nonnucleoside reverse transcriptase inhibitors (NNRTIs), with the change in the latter 2 groups (an approximate 5 mL/min reduction) being similar (Goicoechea et al, *J Infect Dis*, 2008)

## Summary

The risk of toxicities from drugs used in HIV clearly exists, but the risk of kidney dysfunction is even greater when

HIV goes untreated too long. Various causes of ARF in HIV patients can be major clinical problems. Stopping a drug with recognized renal adverse effects is the correct course of action for a patient with ARF, but we should not lose sight of the fact that other causes may lead to loss of function and that drug discontinuation alone can leave us with a clear but unsupported opinion on causality of the ARF in our increasingly complex patients.

Presented by Dr Szczech in May 2008. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Szczech in August 2008.

Dr Szczech received research support and honoraria from or served as a consultant to Gilead Sciences and GlaxoSmithKline.

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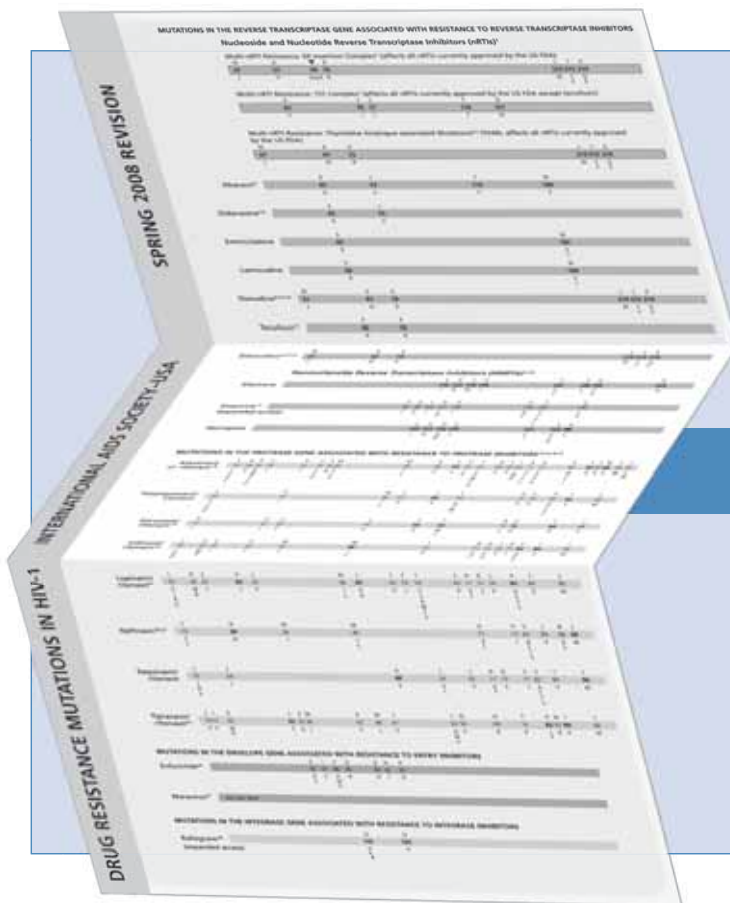
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## Spring 2008 Updated Drug Resistance Mutations Figures

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## Perspective

# Pathogenesis and Treatment of Lipodystrophy: What Clinicians Need to Know

The pathogenesis of lipodystrophy in HIV-infected patients is likely multifactorial, involving effects of antiretroviral medications, HIV itself, as well as genetic and other host factors. Protease inhibitors have been associated with fat accumulation, and the nucleoside analogue reverse transcriptase inhibitors (nRTIs) stavudine, didanosine, and zidovudine have been associated with fat loss (lipoatrophy). Strategies that have met with some success in reducing central fat accumulation include treatment with growth hormone or growth hormone-releasing hormone. Strategies that have met with some success for lipoatrophy include switching from nRTIs associated with lipoatrophy or starting treatment with regimens that include drugs associated with lower risk of lipoatrophy (tenofovir, abacavir, lamivudine, emtricitabine). This article summarizes a presentation on lipodystrophy made by Fred R. Sattler, MD, at an International AIDS Society–USA Continuing Medical Education course in Washington, DC, in May 2008. The original presentation is available as a Webcast at [www.iasusa.org](http://www.iasusa.org).

Lipodystrophy is a disorder of fat metabolism that may be clinically evident as adipose tissue accumulation (eg, in intraabdominal, dorsocervical, or breast tissues, and lipomas), lipoatrophy (loss of fat mass, eg, of the face, limbs, buttocks), and metabolic abnormalities (eg, insulin resistance, diabetes, dyslipidemia, hypertension, or lactic acidemia). The pathogenesis of lipodystrophy in HIV-infected patients is multifactorial (Mallon, *AIDS Rev*, 2007) and includes effects of antiretroviral therapy, HIV itself, and genetics and other host factors. Evidence suggests that the nucleoside analogue reverse transcriptase inhibitors (nRTIs) stavudine, didanosine, and zidovudine may cause mitochondrial toxicity by inhibiting mitochondrial DNA polymerase- $\gamma$  in fat and other tissues and thus interfering with respiratory chain complexes (Figure 1). The result is impaired fatty acid oxidation and intracellular accumulation of triglycerides and lactate, which can enter the systemic circulation.

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Protease inhibitors (PIs) inhibit maturation of sterol response element binding proteins (SREBPs, Figure 2A), which affect intracellular fatty acid and

glucose metabolism and adipocyte differentiation (Mallon et al, *J Infect Dis*, 2005). The PIs also down-regulate peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), an important nuclear transcription factor that is affected by SREBPs and is necessary for adipocyte differentiation and function and fatty acid metabolism (Figure 2B). The HIV viral protein R (vpr) accessory protein also inhibits PPAR $\gamma$ , and PPAR $\gamma$ -deleted mice exhibit lipoatrophy, hepatic steatosis, and increased triglyceride levels. In addition, the duration of HIV infection and its treatment as well as nadir CD4+ cell count have been implicated in lipodystrophy. Lipodystrophy is also observed in acute HIV infection, lending support to a direct viral role as well.

Potential host risk factors include age, sex, and race or ethnicity. Lipodys-

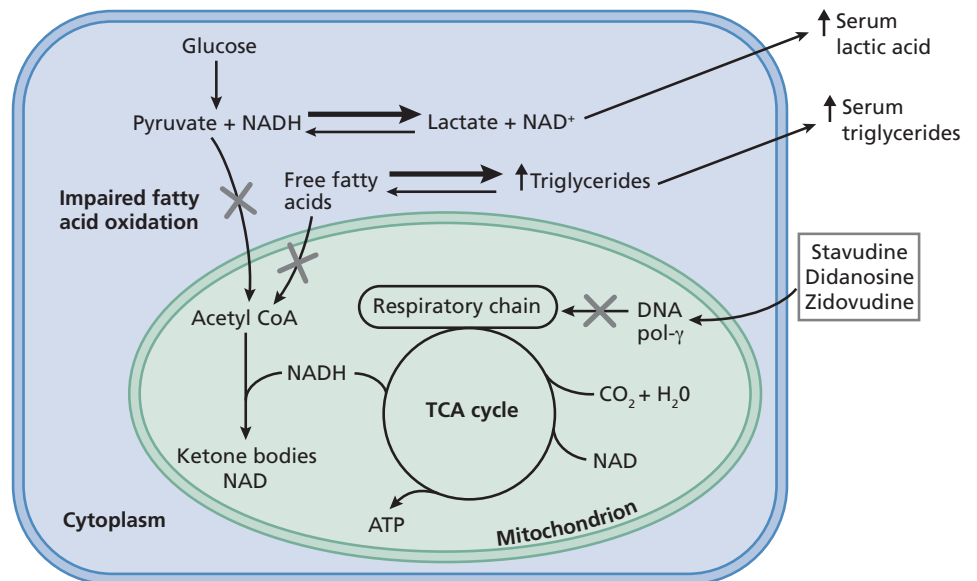
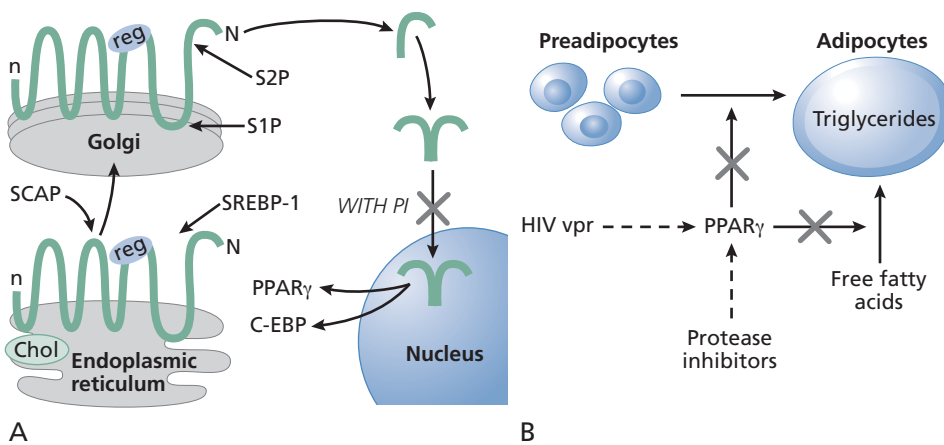


Figure 1. Major intracellular metabolic pathways associated with increased triglyceride and lactic acid production and impaired adenosine triphosphate (ATP) energy production that may contribute to cell death in adipocytes in subjects with lipodystrophy. The nucleoside analogue reverse transcriptase inhibitors stavudine, didanosine, and zidovudine inhibit DNA polymerase gamma (DNA pol- $\gamma$ ), which is necessary for replication of mitochondrial DNA and synthesis of respiratory chain enzyme complexes required in the tricarboxylic acid (TCA) cycle used to generate ATP. Acetyl CoA indicates acetyl coenzyme A; NAD, nicotinamide adenine dinucleotide; NADH, reduced NAD.



**Figure 2.** A: potential effects of HIV protease inhibitors (PIs) on sterol response element binding protein (SREBP) metabolism. These sterol-sensing transcription factors, which affect intracellular lipid metabolism and transcription of a number of gene products including peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) are complexed in an inactive form with SREBP cleavage-activating protein (SCAP). In response to intracellular sterol depletion, both are transported to the Golgi apparatus, where the amino terminus is released by site proteases (S1P, S2P). At the nucleus, the process of signal transduction (which may be inhibited by PIs) results in synthesis and translocation of PPAR $\gamma$  to the cytoplasm. Chol indicates cholesterol; EBP, enhancer-binding protein; reg, regulatory domain that interacts with SCAP. Adapted from Mallon, *AIDS Rev*, 2007. B: both HIV protease inhibitors and HIV viral protein (vpr) accessory protein may inhibit intracellular PPAR $\gamma$ , which is necessary for differentiation of preadipocytes to mature adipocytes and their accumulation of lipid.

trophy is more common in older patients; fat accumulation is more common in women and lipoatrophy in men; and non-Hispanic black patients appear to be at lower risk of lipoatrophy. A genetic component is indicated by a recent analysis in AIDS Clinical Trials Group (ACTG) study 5005s, suggesting either predisposition or protection associated with mitochondrial DNA polymorphisms. Patients homozygous for C/C at the HFE187 locus ( $n = 71$ ) had a 0.6-kg and 12.5% loss of limb fat at weeks 48 to 64, with 37 (52%) of the 71 patients diagnosed with clinical lipoatrophy. By comparison, heterozygous patients with HFE187C/G had a 0.2-kg and 6.1% increase in limb fat, with 6 (26%) of 23 patients having clinical lipoatrophy ( $P < .05$  for all comparisons) (Hulgan et al, *J Infect Dis*, 2008).

### Body Composition Changes

The Fat Redistribution and Metabolic Change in HIV (FRAM) study (Bacchetti et al, *JAIDS*, 2005) showed that HIV-infected men with lipoatrophy had less peripheral and central subcutaneous

adipose tissue (SAT) and less visceral adipose tissue (VAT), contrary to the early impression that peripheral lipoatrophy was frequently accompanied by central fat accumulation. The study included 425 HIV-infected patients and 152 HIV-seronegative subjects. All underwent total body magnetic resonance imaging (MRI), and diagnosis of lipoatrophy was based on the concordance of self-report and HIV Out-patient Study (HOPS) criteria. Relative to noninfected patients, HIV-infected patients with clinical lipoatrophy had markedly greater reductions in adipose tissue volume in the leg, lower trunk, upper trunk, and arm, and in VAT than did HIV patients without clinical abnormalities. Among HIV patients, there was no difference in frequency of peripheral lipoatrophy according to the presence or absence of central fat accumulation. Of patients with central lipoatrophy, however, 90% also had peripheral lipoatrophy, compared with less than 40% of those without central lipoatrophy (odds ratio, 18.9;  $P < .001$ ).

In a study in the Women's Interagency Health Study (WIHS) popula-

tion, dual-energy x-ray absorptiometry (DEXA) scans were performed in 359 mostly overweight or obese women, and differences in fat distribution were compared among 88 women who were HIV-seronegative, 70 who were HIV-infected but receiving no antiretroviral therapy, 48 receiving PI-containing antiretroviral therapy, and 53 receiving antiretroviral therapy with no PI (Mulligan et al, *JAIDS*, 2005). Overall, HIV patients receiving either type of antiretroviral therapy had greater decreases in leg fat than in trunk fat relative to non-HIV-infected women or those not receiving antiretroviral therapy. Trunk fat appeared to be retained in women receiving PI-containing antiretroviral therapy but significantly reduced in those not receiving a PI ( $P < .05$ ).

### Insulin Resistance

Numerous studies have shown that fat loss in the extremities is accompanied by insulin resistance. An early study comparing fasting insulin levels in 71 HIV patients with lipodystrophy versus those in 213 control subjects from the Framingham cohort that were matched for age, sex, and body mass index showed statistically significantly higher levels in HIV patients but no difference between HIV patients with lipodystrophy and those with fat accumulation (Hadigan et al, *J Clin Endocrinol Metab*, 2001).

In the FRAM study (Grunfeld et al, *JAIDS*, 2007), increased values of VAT and upper trunk SAT were independently associated with insulin resistance as assessed by the homeostasis model assessment of insulin resistance (HOMA-IR) in non-HIV-infected control subjects and in HIV patients (Table 1). The finding of a strong association of insulin resistance with upper trunk SAT as well as VAT was somewhat surprising because previous assumptions were that the predominant association is between insulin resistance and VAT accumulation.

Insulin resistance is part of the metabolic syndrome, which poses increased risk of cardiovascular disease complications (eg, heart attack, stroke, peripheral vascular disorders). It is noteworthy that other features of the metabolic syndrome, including cen-

**Table 1.** Association Between Increased Fat Volume and Insulin Resistance in Non-HIV-infected and HIV-infected Patients in the FRAM Study

	Non-HIV-infected Patients (n = 248)		HIV-infected Patients (n = 926)	
	HOMA-IR value > 4	Odds Ratio (P value)	HOMA-IR value > 4	Odds Ratio (P value)
<b>Visceral Adipose Tissue</b>				
3rd vs 1st tertile	63%	12.1 (<.001)	55%	3.1 (<.001)
2nd vs 1st tertile	18%	1.9 (.31)	38%	1.9 (.002)
1st tertile (reference)	6%	--	22%	--
<b>Upper Trunk Subcutaneous Adipose Tissue</b>				
3rd vs 1st tertile	61%	9 (.001)	57%	2.1 (.001)
2nd vs 1st tertile	20%	2.4 (.26)	36%	1.2 (.33)
1st tertile (reference)	5%	--	27%	--

FRAM indicates Fat Redistribution and Metabolic Changes in HIV; HOMA-IR, homeostatic model assessment of insulin resistance. Adapted from Grunfeld et al, *JAIDS*, 2007.

tral obesity, hypertension, and dyslipidemia (hypertriglyceridemia and low high-density lipoprotein [HDL] cholesterol level), frequently are present in HIV patients with lipodystrophy.

### Effects of Antiretroviral Therapy

Of commonly used drugs, stavudine (a thymidine analogue) is the nRTI most frequently associated clinically with lipoatrophy. The fact that some patients have received stavudine for years and do not develop lipoatrophy suggests that host and genetic factors may be contributing to the pathogenesis of (or protection from) the syndrome. Didanosine, which is now used infrequently, has been clearly associated with the occurrence of clinical lipoatrophy. Zidovudine (a thymidine nRTI) has also been implicated but to a lesser degree than the other 2 nRTIs. A good example of body composition changes associated with antiretroviral therapy is demonstrated in several substudies performed by Dube and colleagues in ACTG study 384 (Dube et al, *AIDS*, 2005; Mulligan et al, *JAIDS*, 2006; Dube et al, *JAIDS*, 2007), in which antiretroviral therapy-naïve patients received nelfinavir or efavirenz plus either didanosine/stavudine or zidovudine/lamivudine. Analysis of trunk fat

changes at 64 weeks showed statistically significantly greater increases with efavirenz versus nelfinavir (16.5% vs 8.1%;  $P = .01$ ) and with zidovudine/lamivudine versus didanosine/stavudine (13.5% vs 5.3%;  $P = .02$ ). However, nelfinavir (approximately  $-15\%$  vs  $+3\%$ ;  $P = .003$ ) and didanosine/stavudine (approximately  $-17\%$  vs  $+5\%$ ,  $P < .001$ ) were associated with a statistically significantly greater loss in limb fat. These losses plateaued at approximately 80 weeks and amounted to a loss of approximately 0.90 kg.

### Treatment

#### Strategies to Reduce Central Obesity

A number of strategies for reducing central obesity have been investigated. Stopping PI treatment has not been effective. Changes in diet and exercise have produced improvements, but adherence to a regimen of lifestyle change is difficult for most patients. Liposuction has produced acceptable results (particularly with dorsocervical fat accumulation, ie, "buffalo hump"). Results of 7 studies of thiazolidinediones (Walli et al, *Res Exp Med* (Berl), 2000; Sutinen et al, *Antivir Ther*, 2003; Hadigan et al, *Ann*

*Intern Med*, 2004; van Wijk et al, *Ann Intern Med*, 2005; Gavrila et al, *Clin Infect Dis*, 2005; Feldt et al, *Infection*, 2006; Mulligan et al, *AIDS*, 2007) have shown no change in VAT. Five studies of metformin (Hadigan et al, *JAMA*, 2000; Martinez et al, *Antivir Ther*, 2003; Driscoll et al, *J Clin Endocrinol Metab*, 2004; Hadigan et al, *Ann Intern Med*, 2004; Mulligan et al, *AIDS*, 2007) showed no change in VAT, and 1 (van Wijk, *Ann Intern Med*, 2005) showed a decrease of 25 cm<sup>2</sup> compared with no change with rosiglitazone ( $P < .05$ ).

Testosterone replacement to physiologic levels reduces VAT, total fat, and abdominal fat and improves insulin sensitivity and lipid profile in older, non-HIV-infected men with upper body obesity and low testosterone levels. In a recent study, 88 HIV-infected men with central obesity (waist circumference > 100 cm) and low testosterone levels (< 400 ng/dL) underwent randomization to testosterone as a transdermal gel at a dose of 10 g daily or placebo for 24 weeks (Bhasin et al, *J Clin Endocrinol Metab*, 2007). The testosterone group had statistically significant reductions in abdominal fat ( $-1.5\%$  vs  $+4.3\%$ ), abdominal SAT ( $-7.2\%$  vs  $+8.1\%$ ), trunk fat ( $-9.9\%$  vs  $+4.6\%$ ), and limb fat ( $-10.1\%$  vs  $+3.1\%$ ); the latter finding is of potential concern in a population predisposed to lipoatrophy. No statistically significant difference in change in VAT ( $+0.9\%$  vs  $+2.3\%$ ) was observed, and no statistically significant differences were observed in changes in lipid levels, fasting blood glucose levels, insulin levels, or insulin resistance.

Like testosterone, growth hormone (GH) has fat-oxidizing and lipolytic properties. A substantial proportion of HIV patients with central obesity (approximately 30%-40%) have impaired GH biology, including reduced GH mass secretion, reduced response to GH-releasing hormone (GHRH) and free fatty acids, and increased somatostatin tone, which suppresses GH. A number of recent studies have assessed GH treatment in HIV patients with fat accumulation. In 1 study, 325 HIV patients with increased waist:hip ratios and increased VAT measurements received

**Table 2.** Metabolic Changes in HIV Patients With Increased Waist:Hip Ratios and Visceral Adipose Tissue Measurements After Treatment With Recombinant Human Growth Hormone (rhGH)<sup>a</sup>

	Change at 12 Weeks (P value)	Change at 36 Weeks (P value)	Change at 36 Weeks (P value)
	rhGH 4 mg/day Weeks 0-12	rhGH 4 mg/day Weeks 0-12+	rhGH 4 mg/day Weeks 0-12+
		rhGH 2 mg/day Weeks 13-36	Placebo rhGH Weeks 13-36
Visceral adipose tissue, cm <sup>2</sup>	-32.6 (<.001)	-15.7 (.001)	-7.9 (.03)
Abdominal subcutaneous adipose tissue, cm <sup>2</sup>	-14.3 (<.001)	8.5 (.67)	5.1 (.82)
Limb fat, kg	-0.4 (<.001)	0.0 (.63)	0.1 (.19)
Non-HDL cholesterol, mmol/L	-13.0 (<.001)	-6.7 (.03)	-4.3 (.61)
Triglycerides, mmol/L	-11.3 (.63)	4.5 (.42)	-7.8 (.84)
Fasting blood glucose, mg/dL	6.0 (<.001)	-0.4 (.29)	-0.3 (.89)
Insulin AUC, $\mu$ IU/mL	1466 (<.001)	30.7 (.31)	-1070 (.008)

AUC indicates area under the concentration curve; HDL, high-density lipoprotein.

<sup>a</sup>Study subjects were treated with supraphysiologic doses (4 mg/day) of rhGH for 12 weeks, followed by alternate-day treatment with either rhGH (2 mg/day) or placebo for 24 weeks.

Adapted from Grunfeld et al, *JAIDS*, 2007.

supraphysiologic doses of recombinant human GH (rhGH) consisting of 4 mg daily for 12 weeks and then alternate-day treatment with either 2 mg rhGH or placebo for an additional 24 weeks (Grunfeld et al, *JAIDS*, 2007).

As shown in Table 2, after 12 weeks, there were statistically significant reductions in VAT and abdominal SAT, and a statistically significant decrease in limb fat. Non-HDL cholesterol level was modestly reduced. However, there was also a statistically significant decrease in limb fat and statistically significant increases in fasting blood glucose levels and the insulin area under the concentration curve (indicating increased insulin resistance).

After an additional 24 weeks of alternate-day treatment, the reduction in VAT was reduced by half and the reduction in abdominal SAT was lost, but the adverse effect on glucose metabolism resolved. In the group receiving placebo for 24 weeks, the overall reduction in VAT was modest (about one-fourth of that achieved after 12 weeks with 4 mg/

day) but remained statistically significant, and there was a statistically significant improvement in insulin sensitivity. Thus, there are early adverse effects associated with supraphysiologic doses of rhGH (namely loss of limb fat, decreases

in HDL-cholesterol, and impaired carbohydrate metabolism). Although these appear largely to abate with longer therapy at lower doses, the improvements in trunk fat have been modest.

A second study evaluated the effects physiologic doses of rhGH in 56 HIV patients with lipodystrophy and low GH levels after a GHRH/arginine stimulation test (Lo et al, *CROI*, 2008). Patients received either placebo or rhGH sufficient to increase levels of insulin-like growth factor 1 (IGF-1) into the upper quartile. The dose was 2.1  $\mu$ g/kg, approximately one-thirtieth the dose used in the study of supraphysiologic doses. As shown in Table 3, patients receiving rhGH had large and statistically significant reductions in VAT, smaller but statistically significant reductions in trunk fat, no loss of extremity fat, and statistically significant reductions in diastolic blood pressure. Unfortunately, there was no overall reduction in carotid intima-media thickness, and rhGH treatment was again associated with evidence of insulin resistance.

In a potentially more promising approach to GH modulation, another study evaluated treatment with 2 mg daily of an investigational GHRH agent, tesamorelin, versus placebo in 412 HIV patients with high waist circumferences (Falutz et al, *N Engl J Med*, 2007). Table 4 shows that GHRH treatment was associated with a large and statistically

**Table 3.** Metabolic Changes in HIV Patients with Lipodystrophy and Low Growth Hormone Levels Receiving Recombinant Human Growth Hormone (rhGH)<sup>a</sup>

	rhGH (2.1 $\mu$ g/kg)	Placebo	P Value
Visceral adipose tissue, cm <sup>2</sup>	-22	-4	<.001
Trunk fat, kg	-0.5	0.2	.04
Extremity fat, kg	0.3	0.3	.94
Diastolic blood pressure, mmHg	-3	4	.006
Intima-media thickness, mm	0.003	-0.003	.78
2-hour glucose (OGTT), mg/dL	16	-4	.009

OGTT indicates oral glucose tolerance test.

<sup>a</sup>Subjects (n = 56) were treated with rhGH or placebo for 18 months.

Adapted from Lo et al, *CROI*, 2008.

significant reduction in VAT with only a marginal reduction in abdominal SAT, and a statistically significant reduction in triglyceride levels and improvement in adiponectin; there was no apparent adverse effect on glucose metabolism. Although the change in limb fat was statistically different from that in the placebo group, the absolute change (0.02 kg) was quite small and unlikely to be of clinical importance. As with rhGH, 24 weeks after discontinuation of treatment, improvements in VAT dissipated, indicating that long-term suppressive therapy will be necessary to sustain these improvements (Falutz et al, CROI, 2008).

Although the GH and GHRH therapies show some promise, there are limitations to their use. They are parenteral therapies and either expensive (rhGH) or not FDA-approved (tesamorelin). Thus far, there is evidence of waning durability of the reduction in VAT after their discontinuation, short-term increases in insulin resistance with rhGH, and small short-term reductions

in SAT and limb fat, especially with high-dose rhGH. Short-term reductions in VAT have thus far not been associated with reductions in carotid intima-media thickness. The long-term safety of such treatments also has not been established, and it is uncertain whether there is increased risk of cancer if IGF-1 levels are excessively elevated. This latter issue is of theoretical concern, but in fact, when rhGH is used to treat other conditions and IGF-1 levels are increased, there has not been a demonstrable increase in risks of cancer, but those studies are relatively small. Further, the potential benefits in reducing cardiovascular risks through these strategies (eg, through beneficial effects on blood pressure and lipid levels) remain undefined.

#### Strategies to Increase Subcutaneous Fat

Strategies to increase SAT in patients with lipodystrophy include facial implants, uridine treatment to replenish

intracellular pyrimidines, switching from stavudine, didanosine, or zidovudine, treatment with a thiazolidinedione, and initial antiretroviral therapy with “lipoatrophy-friendly” drugs such as tenofovir, abacavir, lamivudine, or emtricitabine.

The benefits of switching antiretroviral therapy were shown in the Mitochondrial Toxicity (MITOX) study (Martin et al, *AIDS*, 2004). In that study, 111 patients who developed lipodystrophy while receiving stavudine or zidovudine underwent randomization to continue treatment or switch to abacavir. At week 24, control patients were permitted to switch to abacavir. At week 104, results of DEXA measurements showed that the abacavir group gained 1.26 kg of limb fat versus 0.49 kg in control subjects ( $P = .008$ ). No statistically significant differences were found in change in VAT, nor was there clinical evidence of lipoatrophy.

In the Randomized Abacavir Versus Viread Evaluation (RAVE) study (Moyle et al, *AIDS*, 2006), thymidine nRTIs were replaced with tenofovir or abacavir in 105 patients with lipodystrophy. After 48 weeks, there were statistically significant within-group reductions in lipoatrophy, with limb fat gains of 0.33 kg in patients taking tenofovir ( $P = .01$ ) and 0.48 kg in those taking abacavir ( $P = .0001$ ). There were no changes in trunk fat or VAT measures. Tenofovir treatment was associated with modest reductions in levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, whereas there were no lipid changes with abacavir treatment.

In a study of patients with advanced HIV disease, 62 patients (with plasma HIV RNA levels < 200 copies/mL) were switched to an nRTI-sparing regimen of lopinavir/ritonavir plus efavirenz versus a PI-sparing regimen of efavirenz plus 2 nRTIs for 48 to 104 weeks (Tebas et al, *JAIDS*, 2007). At 48 weeks, there was a statistically nonsignificant increase in limb fat of approximately 0.6 kg in patients taking the nRTI-sparing regimen, and a marginally statistically significant ( $P = .05$ ) decrease of more than 0.2 kg in patients taking the PI-sparing regimen. At week 104, there

**Table 4.** Metabolic Changes in HIV Patients with High Waist Circumferences Receiving Investigational Growth Hormone–Releasing Hormone (GHRH)<sup>a</sup>

	GHRH	Placebo	P Value
Visceral adipose tissue, cm <sup>2</sup>	-27.8	5.1	<.001
Abdominal subcutaneous adipose tissue, cm <sup>2</sup>	-3.3	2.3	.05
Limb fat, kg	-0.0	0.2	.006
IGF-1, ng/mL	109	-16	<.001
Triglycerides, mg/dL	-50	9	<.001
Total cholesterol, mg/dL	-10	-3	.2
Adiponectin, µg/mL	0.5	-0.1	.03
Fasting blood glucose, mg/dL	3	1	.28
Insulin, µU/mL	2	3	.93

IGF-1 indicates insulinlike growth factor 1.

<sup>a</sup>Subjects (n = 412) received the investigational GHRH tesamorelin 2 mg/day or placebo for 26 weeks.

Adapted from Falutz et al, *N Engl J Med*, 2007.

was an increase of 0.8 kg in the nRTI-sparing group ( $P = .07$ ), compared with a decrease of 0.85 kg ( $P = .07$ ) in the PI-sparing group ( $P = .002$  for between-group comparison). However, the gain in fat associated with the nRTI-sparing regimen was accompanied by greater increases in triglyceride levels and total cholesterol levels. No changes in trunk fat, insulin, glucose, or insulin resistance (as measured by HOMA-IR values) were observed.

The thiazolidinediones may be of benefit in lipoatrophy by stimulating adipogenesis through an agonist effect on PPAR $\gamma$ . A number of studies have shown no effect of rosiglitazone on lipoatrophy (Sutinen et al, *Antivir Ther*, 2003; Carr et al, *Lancet*, 2004; Cavalcanti et al, *J Infect Dis*, 2007). Others have shown partial effects, including increased abdominal SAT (Gelato et al, *J AIDS*, 2002), increased abdominal SAT and VAT (van Wijk et al, *Ann Intern Med*, 2005), and increased limb fat (Hadigan et al, *Ann Intern Med*, 2004; Mulligan et al, *AIDS*, 2007).

In a recent study (Mulligan et al, *AIDS*, 2007), 105 patients with increased waist:hip ratios and evidence of insulin resistance received metformin, rosiglitazone, a combination of the 2, or double placebo for 16 weeks. Among patients receiving only rosiglitazone 4 mg daily, there was a 4.8% increase in leg fat (approximately 0.22 kg) from pretreatment ( $P = .03$ ), no change in VAT, an increase in adiponectin levels (3.0  $\mu\text{g}/\text{mL}$ ;  $P < .001$ ), and a reduction in insulin area under the concentration curve (25.7  $\mu\text{U}/\text{mL}$ ;  $P = .01$ ), indicating improved insulin sensitivity. However, there was also a decrease in HDL cholesterol level (5 mg/dL;  $P = .005$ ) and an increase in LDL cholesterol level (7 mg/dL;  $P = .048$ ). In addition to the short duration of the study, another limitation is that the study was not controlled for use of thymidine nRTIs.

Promising results have been observed with pioglitazone. In a study comparing pioglitazone 30 mg daily ( $n = 64$ ) with placebo ( $n = 66$ ) in patients with lipodystrophy (Slama et al, *Antivir Ther*, 2008), pioglitazone

was associated with an increase in limb fat of 0.38 kg versus 0.05 kg ( $P = .051$ ), respectively, at 48 weeks. Among patients not receiving stavudine ( $n = 48$  vs 46), the increase was 0.45 kg versus 0.04 kg ( $P = .013$ ), respectively, whereas the increase was 0.17 kg versus 0.07 kg ( $P = .40$ ), respectively, among those receiving stavudine ( $n = 16$  vs 20). Pioglitazone was also associated with an increase in thigh circumference (1.4 cm vs 0.2 cm;  $P = .017$ ), with no statistically significant differences observed between groups in changes in VAT (5.3  $\text{cm}^2$  vs 7.7  $\text{cm}^2$ ) or abdominal SAT (16.3  $\text{cm}^2$  vs 7.8  $\text{cm}^2$ ). High-density lipoprotein cholesterol level increased in pioglitazone patients (3.3 mg/dL vs -3.2 mg/dL;  $P = .005$ ). There were no statistically significant differences in clinical manifestations of lipodystrophy or changes in other lipid levels or in glucose metabolism. Pioglitazone, unlike rosiglitazone, is metabolized by cytochrome P450 3A4 enzymes and thus has potential for pharmacokinetic interactions with PIs.

A successful strategy in antiretroviral therapy-naïve patients is selection of initial regimens less likely to be associated with lipoatrophy. For example, 2 studies have shown benefit in this regard with use of initial regimens including tenofovir/emtricitabine versus zidovudine/lamivudine; the results suggested that tenofovir causes less lipoatrophy than zidovudine. In 1 study (Gallant et al, *JAMA*, 2004) involving 753 patients, use of tenofovir/emtricitabine statistically significantly reduced the rate of clinical lipodystrophy at 3 years to 3% versus 19% with zidovudine/lamivudine ( $P < .001$ ). Limb fat measurements showed greater fat with tenofovir/emtricitabine at week 96 (7.9 kg vs 5.0 kg;  $P < .001$ ;  $n = 262$ ) and at week 144 (8.6 kg vs 4.5 kg;  $P < .001$ ;  $n = 232$ ). In another study (Gallant et al, *N Engl J Med*, 2006) involving 517 patients, weight gain was similar with tenofovir/emtricitabine and zidovudine/lamivudine (2.1 vs 1.1 kg, respectively;  $P = .14$ ), and limb fat was statistically significantly greater (8.9 kg vs 6.9 kg;  $P = .03$ ) among 100

patients with measurements taken at 48 weeks. These studies were limited by the absence of pretreatment DEXA measurements, although pretreatment body weights were comparable in the 2 groups in both studies.

## Summary

Fat accumulation and lipoatrophy syndromes in HIV patients most likely differ mechanistically. The pathogenesis of these syndromes is not established, but it is clear that thymidine nRTIs and PIs contribute to lipodystrophy. For treatment of fat accumulation, (1) stopping PIs is not effective; (2) diet and exercise adjustments are effective, but long-term maintenance is difficult; (3) liposuction works for dorsocervical fat; (4) metformin and testosterone administration do not appear to be effective in reducing VAT; and (5) rhGH and GHRH treatments decrease VAT and improve lipid levels—although rhGH is associated with musculoskeletal adverse effects, insulin resistance, and reduced limb fat, maintenance treatment is required, and benefits in terms of cardiovascular risk reduction have not been defined.

For treatment of lipoatrophy, (1) facial implants are successful (although poly-L-lactic acid implants may be lumpy, and the radiopacity of synthetic calcium hydroxylapatite needs to be noted); (2) the effectiveness of uridine treatment remains to be established; (3) switching from thymidine nRTIs is partially effective; (4) thiazolidinedione treatment is minimally effective; and (5) initial therapy with tenofovir, abacavir, lamivudine, or emtricitabine should minimize risk. A primary goal of current and future study is improved understanding of the mechanisms of and genetic predilections for lipodystrophy.

*Presented by Dr Sattler in May 2008. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Sattler in September 2008.*

*Dr Sattler has no relevant financial affiliations to disclose.*

## Suggested Reading

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### CASE-BASED FORMAT

Our *COW* activities feature a dynamic case-based format. Each activity introduces a case and a series of clinical decision points. At each decision point, learners choose the decision option that they believe is most sound and read the presenter's explanation of their choice. Selecting the best option links learners to a supporting discussion of related medical findings, research-based evidence, and additional case management considerations.



### NEW

#### HIV-associated Cognitive Impairment

by Miguel G. Madariaga, MD, and Susan Swindells, MBBS

HIV-associated cognitive impairment remains a difficult diagnosis that requires the exclusion of several other conditions including psychiatric illness, substance use, opportunistic infection, neoplasia, and other causes of dementia. This case will help learners distinguish between the clinical manifestations of HIV-associated cognitive impairment and those of conditions with a similar presentation. Learners will also consider the selection of appropriate diagnostic tests and the clinical management of an HIV-infected patient with this condition.

#### Special Cases in Antiretroviral Therapy Initiation: Focus on Acute HIV and HIV/Hepatitis B Virus Coinfection

by Charles Hicks, MD, and Elizabeth Reddy, MD

HIV health care practitioners should be aware of special situations such as acute HIV infection or HIV and hepatitis B virus (HBV) coinfection that may affect the timing of antiretroviral therapy. In this comprehensive activity, learners will compare the benefits and risks of initiating therapy for acute HIV infection and consider the use of resistance testing in such situations. This activity also demonstrates appropriate choices of therapy in patients with acute HIV or HIV/HBV coinfection and alerts learners to the risks of discontinuing antiretroviral therapy, particularly in patients with HIV and HBV coinfection.

#### Sexual Addiction in an HIV-infected Patient

by Edward R. Hammond, MD, MPH, and Glenn J. Treisman, MD, PhD

Patients who engage in a variety of specific sexual practices are at increased risk of acquiring and transmitting HIV, and some of these sexual practices have been associated with sexual addiction, also called paraphilia. Unfortunately, paraphilia in HIV-infected patients often goes undiagnosed and untreated. This fascinating activity describes features of paraphilic behavior and explains its management. Learners will also identify comorbid conditions that could complicate the treatment of paraphilic behavior in HIV-infected patients.

#### Treatment of Hepatitis C Virus and HIV Coinfection: Selecting Candidates for HCV Therapy and Managing Side Effects of Treatment

by Melissa K. Osborn, MD

Treatment of hepatitis C virus (HCV) is crucial in HIV-coinfected patients to slow progression to cirrhosis and end-stage liver disease. This state-of-the-art activity describes differences in the response to HCV therapy in HIV-coinfected patients compared with HCV-monoinfected patients. Learners will identify candidates for HCV therapy, understand management of the adverse effects of therapy, and explore treatment options for those who do not respond to peginterferon alfa and ribavirin therapy or who experience recurrence of active infection.

#### Managing Initiation of Antiretroviral Therapy in a Patient with Chronic Methamphetamine Use and Depression

by Sara Vazquez, MD, and J. Kevin Carmichael, MD

Drug toxicities, changes in HIV resistance mutation profiles, and drug interactions complicate the selection of antiretroviral regimens. This activity examines strategies for initiating antiretroviral therapy in a newly diagnosed, treatment-naïve patient with relapsing substance use and depression. Learners will review current guidelines for starting therapy, compare the advantages and disadvantages of initial drug regimens, and consider the laboratory tests needed to support the selection of an initial regimen.

### COMING IN FALL 2008!

Look for these new *Cases on the Web* in coming months.

- **Drug Interactions and Liver Transplantation in Hepatitis C Virus/HIV Coinfection**
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These activities have been approved for **AMA PRA Category 1 Credit™**.

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