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The LipoWatch program from Visionary Health Concepts is designed to support providers and patients with education that integrates a "real world" focus with scientific data. This month we provide an update on the clinical management of lipodystrophy. NOTE: Lipo-Watch faxes are archived on the web at [http://www.vhconcepts.com/edu\\_prog.cfm](http://www.vhconcepts.com/edu_prog.cfm).

Several presentations at this year's 10th Conference on Retroviruses and Opportunistic Infections (CROI) dealt with the metabolic complications of HIV antiretroviral therapy. A major concern is whether antiviral therapy increases the risk of cardiovascular events. For the next two months, LipoWatch will focus on this question. This current issue, an overview of clinical management of metabolic complications, is based on a presentation by Peter Reiss at CROI, which can be viewed as a webcast<sup>(1)</sup>.

**Elevated Lipids:** Reiss noted that statins and fibrates are the drugs of choice for lowering lipids in the general population, but that they may be less effective in people with HIV. Combined statin/fibrate therapy, although often used in the general population, raises concerns in the HIV population due to the increased risk of rhabdomyolysis. As for switching from protease inhibitor-containing regimens to nevirapine, efavirenz or abacavir in hopes of reducing serum lipids, the Spanish NEFA study<sup>(2)</sup> showed a less atherogenic profile by switching to PI-sparing regimens, partly due to increases in HDL cholesterol. Reiss cautioned that the likelihood of nucleoside analogue resistance mutations in both circulating and archived virus should be assessed before switching to abacavir to minimize the risk of virologic failure. Switching to atazanavir also appears promising based on lipid results to date. For example, 24 weeks of atazanavir therapy resulted in lower LDL cholesterol, total

cholesterol and triglycerides as well as higher HDL cholesterol, compared with an efavirenz-containing regimen<sup>(3)</sup>.

**Fat Maldistribution:** Fat redistribution can reinforce or sustain other metabolic abnormalities, possibly reducing the impact of interventions to improve insulin sensitivity or reduce serum lipids. For example, in the NEFA study, lipid-lowering medications were more effective in patients without lipodystrophy. Another group<sup>(4)</sup> found little impact on insulin resistance by switching from PIs to abacavir in patients with "established lipodystrophy." Fat maldistribution can be very difficult to treat but is potentially reversible with changes in antiviral regimens. Studies, however, have shown only modest improvements noted on DEXA scans but rarely noticeable to physicians or patients<sup>(5)</sup>.

**"Two-Edged Swords:"** Interventions to benefit one metabolic complication may worsen another. For example, human growth hormone can effectively reduce visceral adiposity, but may increase glucose intolerance, at least temporarily<sup>(6)</sup>. Metformin may be useful in treating visceral adiposity but also decreases peripheral fat<sup>(7)</sup>. Switching from all-nucleoside regimens to nucleoside-sparing regimens in one study increased peripheral fat but also visceral fat (undoubtedly because of switching to PIs)<sup>(8)</sup>. Also, some interventions may work better in the context of changes in antiviral therapy. For example, Reiss speculated that the glitazones, which have been shown to lower insulin resistance with mixed results on visceral and peripheral fat, may work better after discontinuing protease inhibitors or nucleoside analogs. Reiss noted that we have no proven way to reverse facial lipodystrophy apart from cosmetic surgery, and he noted problems with its availability and

reimbursement, as well as the lack of practitioners adequately trained in this particular application.

**Focus on Prevention?** Given the difficulties in treating metabolic complications, Reiss suggested we might focus on preventing them, at least where that option may be available in treatment-naïve patients. For example, AZT when compared to d4T is associated with a slower rate of fat wasting<sup>(9)</sup>, and if mitochondrial toxicity proves to contribute to fat atrophy, then nucleoside-sparing regimens, or drugs less toxic to the mitochondria (such as abacavir), might be helpful. Finally, in a theoretical discussion of cardiovascular risk factors and antiviral regimens, Reiss concluded that although absolute risk levels are quite low, it may make sense to choose PI-sparing regimens for patients with pre-existing significant CV risk factors.

He concluded that improved management of metabolic complications depends on better understanding of their pathogenesis and physiology, which should permit improved treatment strategies to postpone or prevent them.

<sup>1</sup>New Insights in the Clinical Management of HIV-1 Associated Metabolic Complications - Putting Guidelines in Perspective." 10th CROI, February 10-14, 2003, Boston, MA, Abstract 163. Webcast available at [www.confconferences.org/2003/webcast.htm](http://www.confconferences.org/2003/webcast.htm) (under Thursday.)

<sup>2</sup>Martinez E, Podzamczak D, Ribera E, et al. Switching Protease Inhibitors to Nevirapine (NEV), Efavirenz (EFA) or Abacavir (ABA): A randomized, multicenter, open-label, simplification trial. Program and abstracts of the 9th CROI, February 24-28, 2002; Seattle, Washington, Abstract LB15.

<sup>3</sup>Sension M. Absence of insulin resistance through week 24 with atazanavir once-daily and efavirenz once-daily each with fixed dose zidovudine plus lamivudine. Antiviral Therapy 2002;7:L26.

<sup>4</sup>Van Walk et al. in press

<sup>5</sup>See for example Carr A, Hudson J, Chuah J, Mallal S et al for the PILLR study group, HIV Protease Inhibitor Substitution in Patients with Lipodystrophy: a randomized, controlled, open-label, multicenter study. AIDS 2001;15:1811-1822

<sup>6</sup>Kotler D, Thompason M, Grunfeld C, Gertner J, Muurahaianen N. Transient Insulin Resistance During Recombinant Human Growth Hormone (rhGH) Therapy for HIV-Associated Adipose Redistribution Syndrome (HARS). Abstracts, 42nd ICAAC, September 27-30, 2002, San Diego, CA

<sup>7</sup>Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, Grinspoon S. Metformin in the Treatment of HIV Lipodystrophy Syndrome: a randomized controlled trial. JAMA. 2000;284:472-477.

<sup>8</sup>Boyd M, Bien D, van Warmerdam P, Hassink E et al. Lipodystrophy in Patients Switched to Indinavir/Ritonavir 800/100 mg BID and Efavirenz 600 mg QD after Failing Nucleoside Combination Therapy: A Prospective, 48-week Observational Sub-study of HIV-NAT 009. Abstracts, 10th CROI, February 10-14, 2003, Boston MA, Abstract 738.

<sup>9</sup>Dubé MP, Zaackin R, Tebas P, Roubenoff R et al. Prospective study of regional body composition in antiretroviral-naïve subjects randomized to receive zidovudine-lamivudine or didanosine-stavudine combined with nelfinavir, efavirenz, or both: A5005s, a substudy of ACTG 384. Antiviral Therapy 2002; 7:L18

Next month's LipoWatch will discuss HIV Treatment and Cardiovascular Disease.

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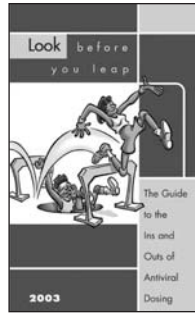
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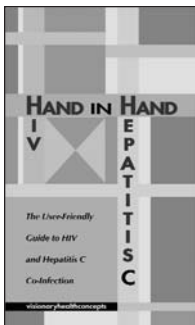
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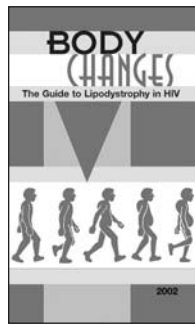


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