Convenience and long-term tolerability have become increasingly important aspects of antiretroviral therapy in patients with human immunodeficiency virus. To date, the most worrisome long-term complications of therapy have been subcutaneous fat wasting; visceral obesity; and metabolic abnormalities, such as dyslipidemia and insulin resistance, that may increase the risk of cardiovascular disease in some patients.

Toxicities associated with nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) appear to be overlapping but not identical. The NRTIs, particularly stavudine, are most strongly associated with hyperlactatemia, subcutaneous fat wasting, and elevated triglyceride levels, whereas the PIs are more strongly associated with insulin resistance, dyslipidemia, and visceral obesity.

Recent studies have shown that lipoatrophy can be reversed by switching from stavudine to abacavir or zidovudine, although the rate of subcutaneous fat restoration is very slow. This underscores the importance of preventing lipoatrophy by optimal selection of initial therapy regimens.

Studies in which a PI is switched to a non-NRTI while maintaining 2 NRTIs have shown that the lipid profile and insulin sensitivity may improve. Similarly, switching a PI-containing regimen to a triple NRTI combination of abacavir, lamivudine, and zidovudine given as a single tablet leads to an improvement in the lipid profile, adherence to therapy, and quality of life.

Managing long-term tolerability includes assessment and modification of vascular risk factors, consideration of individual host factors, initiating therapy with the most benign regimens, early recognition of toxicity, switching therapy as appropriate, and avoiding drug combinations with overlapping toxicities.

(Advanced Studies in Medicine. 2002;2(23):832-836)
is therefore necessary to evaluate these host risk factors and modify them when possible, and to try to tailor antiretroviral therapy according to these factors to minimize the risk of long-term complications.

Prior to the advent of highly active antiretroviral therapy (HAART), metabolic problems in HIV-infected individuals included HIV/acquired immune deficiency syndrome wasting, abnormalities of triglyceride and cholesterol, and lactic acidosis. However, since 1996, several other clinical and subclinical toxicities have emerged. These include lipoatrophy, visceral obesity, dyslipidemia, insulin resistance, chronic hyperlactatemia, endothelial dysfunction, and tissue-specific mitochondrial deoxyribonucleic acid (DNA) depletion in vivo. Because visceral obesity, dyslipidemia, insulin resistance, and endothelial dysfunction are recognized risk factors for cardiovascular disease, vascular events may also be among the long-term toxicities associated with HAART.

Toxicities associated with nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) are overlapping but not identical (Figure 1). In the long term, the NRTIs, particularly stavudine, are most strongly associated with hyperlactatemia, subcutaneous fat wasting, and hypertriglyceridemia, whereas the PIs are more strongly associated with insulin resistance, dyslipidemia, and visceral obesity. There is some evidence to support a possible interaction between NRTIs and PIs to accelerate subcutaneous fat wasting.

Evidence is also accumulating that both drug classes may have early and direct effects on adipocytes with immediate metabolic consequences, with NRTIs causing mitochondrial toxicity and PIs causing insulin resistance and impaired adipocyte maturation. However, the morphological changes resulting from these 2 mechanisms do not become clinically apparent for some time.

**Lipodystrophy**

The changes in body fat distribution and metabolic complications associated with HAART in HIV-infected patients have been referred to collectively as lipodystrophy syndrome(s). Changes in body fat most commonly include subcutaneous fat wasting and accumulation of fat within the abdomen or the breasts. A characteristic localized accumulation just below the back of the neck known as a buffalo hump and localized fat accumulations known as lipomata have also been observed and are argued to be part of the syndrome. Metabolic complications commonly include elevated levels of triglyceride-rich lipoproteins, such as low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol, with low levels of high-density lipoprotein cholesterol, insulin resistance, and in rare cases, type 2 diabetes.

An analysis of more than 17 observational cohort studies in different study populations involving more than 8500 patients found that stavudine was associated with a higher risk of “lipodystrophy” (variably defined but most commonly including subcutaneous fat wasting) compared with zidovudine. Three independent randomized clinical trials evaluating NRTI combinations found that the incidence of lipodystrophy and fat wasting was significantly higher in patients receiving combinations that included stavudine compared with patients receiving combinations of NRTIs.

A study comparing changes in the percentage of leg fat over 40 months in 11 patients receiving stavudine plus an NRTI vs changes in 14 patients receiving zidovudine plus an NRTI, as well as in 25 patients receiving stavudine plus a PI vs 24 patients receiving zidovudine plus a PI found that patients receiving stavudine in either combination lost a higher percentage of leg fat than patients receiving zidovudine in either combination. All patients were naïve to HAART prior to this study.

**Figure 1. Overlapping But Not Identical Toxicities Associated With NRTIs and PIs**

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>PIs</th>
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<tr>
<td>d4T &gt; ZDV/ABC</td>
<td></td>
</tr>
</tbody>
</table>

ABC = abacavir; d4T = stavudine; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine.

Adapted with permission from John et al.
to the study. The results of dual-energy X-ray absorptiometer (DEXA) scanning over time in such studies have revealed the importance of assessing fat changes from baseline by objective measures. Fat wasting is a chronic cumulative process that is not immediately clinically obvious. Some patients who are losing fat on HAART may not have lost enough to reach clinically obvious change, but progressive lipodystrophy or lipoatrophy is evident on DEXA scan.

**Hyperlactatemia**

Hyperlactatemia is a spectrum of clinical disorders, ranging from chronic compensated hyperlactatemia with blood lactate levels only mildly elevated at 2.5 mmol/L to 5.0 mmol/L to decompensated lactic acidosis and hepatic steatosis with blood lactate levels above 5.0 mmol/L. Compensated chronic or intermittent hyperlactatemia appears to be common and stable over time in the vast majority of patients. There is no systemic acidosis and often no discernible symptoms. Stavudine and didanosine increase the risk of this entity, and abacavir lowers the risk. By comparison, decompensated lactic acidosis is rare and characterized by rapidly progressive acidosis. Obesity and pre-existing liver disease, such as hepatitis B or C coinfection, increase the risk but because decompensated lactic acidosis is rare, the differences in risk associated with different NRTIs cannot be easily measured.

A subgroup of patients present with moderate hyperlactatemia without overt decomposition but with some symptoms. A recently reported study involving 2144 patients with HIV who were being treated with NRTIs found that 498 had at least 1 symptom compatible with hyperlactatemia and 81 had symptoms plus blood lactate levels above 2.1 mmol/L on 2 consecutive occasions. The incidence of symptomatic hyperlactatemia was lowest among patients receiving zidovudine plus lamivudine, and rose gradually but consistently among patients receiving stavudine plus lamivudine, stavudine plus abacavir, and stavudine plus didanosine, with the incidence highest in the last-mentioned group.

**Dyslipidemia**

In a recently reported study examining the effect of 3 different HAART regimens on mean levels of total cholesterol, LDL-C, and triglycerides, the investigators found that 48 weeks of therapy with (lamivudine + zidovudine)/abacavir, (lamivudine + zidovudine)/nelfinavir, or stavudine/lamivudine/nelfinavir raised mean levels of total cholesterol and triglycerides from baseline, with the smallest increases seen with the first combination and the greatest increase seen with the third combination. The increases in triglyceride levels with each of the 3 regimens were more pronounced in men compared with women.

After 48 weeks of therapy, 13% of patients receiving (lamivudine + zidovudine)/abacavir had LDL-C levels above 130 mg/dL and 25% had total cholesterol levels above 200 mg/dL; no patients had LDL-C levels above 160 mg/dL. Of those receiving (lamivudine + zidovudine)/nelfinavir, 43% had LDL-C levels above 130 mg/dL, 25% had LDL-C levels above 160 mg/dL, and 51% had total cholesterol levels above 200 mg/dL. Of those receiving stavudine/lamivudine/nelfinavir, 41% had LDL-C levels above 130 mg/dL, 22% had LDL-C levels above 160 mg/dL, and 57% had total cholesterol levels above 200 mg/dL. These results are consistent.
with several others, illustrating the predominant role of PIs in increasing the risk of lipid abnormalities. NRTIs are independently associated with triglyceride elevation, and it is possible that mitochondrial DNA depletion in subcutaneous fat and associated mitochondrial dysfunction may synergize with PI-induced insulin resistance and impaired maturation of adipocytes to contribute to loss of lipogenic and triglyceride-storing capacity of adipose tissue (Figure 2).^{10}

**Switch Studies**

Recent studies have shown that lipoatrophy can be reversed by switching from stavudine to abacavir or zidovudine. However, the rate of subcutaneous fat restoration is very slow, and it is uncertain at this time whether complete fat restoration will ever be possible. This underscores the importance of preventing lipoatrophy by optimal selection of HAART regimens rather than trying to reverse it once it occurs.

Studies in which a PI was switched to a non-NRTI (while maintaining 2 NRTIs as the backbone of the HAART regimen) in patients with sustained undetectable viral loads have shown that the switch reduced triglycerides, total cholesterol, and LDL-C and increased insulin sensitivity.^{11,12} Similarly, a study in patients with sustained undetectable viral loads in which a PI was switched to a triple NRTI combination of abacavir, lamivudine, and zidovudine given as a single tablet found that the switch resulted in decreases in triglycerides, total cholesterol, and LDL-C, improved adherence to therapy, better quality of life, and easier dosing.^{13} Clinical outcomes of PI-based antiretroviral therapy switches are summarized in the Table. [It should be noted that many clinicians find that stavudine is better tolerated than zidovudine and is often substituted when patients cannot tolerate zidovudine.]

**Conclusions**

Learning to live with antiretroviral therapy depends in large measure on how well long-term tolerability is managed. Increased understanding of the risk factors and possible pathogenesis of the metabolic and morphologic complications of antiretroviral therapy has shifted the focus of clinical management toward individualized risk assessment and prevention. Specifically, physicians should consider individual factors, assess and modify vascular risk factors, and treat risk factors in therapy-naïve patients according to standard guidelines. When initiating therapy, physicians should start with the most benign regimen and, if possible, use objective assessment measures at baseline and at regular intervals to recognize toxicity early. With regard to lipoatrophy, it is easier to spare peripheral fat than to restore fat that has been lost.

Physicians may switch therapy in appropriate settings, keeping in mind that switches have been shown as long as patients have sustained strong viral suppression before the switch, avoid combinations with overlapping toxicities, and explore other management options if HAART-induced metabolic abnormalities arise.

**REFERENCES**


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Table. Outcomes With Switching PI-Based Antiretroviral Therapy*

<table>
<thead>
<tr>
<th>Switch Type</th>
<th>Outcomes</th>
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| PI to nevirapine or efavirenz (plus 2 NRTIs) | - Improved lipid profile with nevirapine  
- Improved quality of life/better adherence to therapy compared with PIs |
| PI to abacavir-based triple NRTI regimen | - Improved metabolic profile  
- Improved quality of life/better adherence to therapy compared with PIs |
| PI and stavudine switch | - Improved metabolic profile  
- Optimal ease of dosing  
- Improved quality of life/better adherence to therapy  
- Fat restoration  
- Fat sparing  
- Less chronic hyperlactatemia and mitochondrial DNA depletion |

* In patients with well-established virologic suppression. DNA = deoxyribonucleic acid; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

4. Joly V, Flandre P, Meiffredy V, et al. Assessment of lipodystrophy in patients previously exposed to AZT, ddI, or ddC, but naïve for d4T and protease inhibitors (PIs), and randomized between d4T/3TC/Indinavir and AZT/3TC/Indinavir (NOVAIR trial). Presented at 8th Conference on Retroviruses and Opportunistic Infections; February 4-8, 2001; Chicago, Ill.


8. Lonergan JT, Havlir D, Barber E, Matthews WC. Incidence of symptomatic hyperlactatemia in HIV-infected adults on NRTIs. Presented at 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Wash.


