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Metabolic Complications Associated with the Treatment of HIV-Infected Persons

Sponsorship
Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ), UMDNJ-Center for Continuing & Outreach Education. This activity is supported by an educational grant from NJDHSS Division of HIV/AIDS Services through a MOA titled “Education and Training for Physicians and other Healthcare Professionals in the Diagnosis and Treatment of HIV/AIDS.”

Target Audience
This activity is designed for physicians and nurses, and for other health care professionals in New Jersey who are involved in the care of persons with HIV/AIDS.

Statement of Need
The medical management of HIV has been revolutionized by the use of highly active antiretroviral therapy (HAART). In the pre-HAART era, HIV typically led to death within ten years. Treatment of HIV with HAART can extend the lifespan of HIV-infected persons several decades. A major challenge that has arisen out of this success is the management of the side effects of antiretroviral therapy. Antiretroviral therapy (ART) commonly causes various complications, some of which may be life threatening.

Abnormalities such as dyslipidemia, insulin resistance states, and lipodystrophy syndromes have become common metabolic complications associated with the treatment of HIV-infected persons, and may eventually lead to an epidemic of cardiovascular disease and diabetes among HIV-infected patients. Management of these complications has therefore become an integral component of HIV care.

Learning Objectives
Upon the completion of this activity, participants should be able to:
1. Describe metabolic complications associated with the use of antiretroviral agents.
2. Identify the risks and appropriate management of dyslipidemia for patients on antiretroviral agents.

Method of Instruction
Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the post-test which consists of a series of multiple-choice and True/False questions.

Upon completing this activity as designed and achieving a passing score of 70% or more on the post-test, participants will receive a credit letter and the test answer key four (4) weeks after receipt of the post-test, registration, and evaluation materials. Estimated time to complete this activity as designed is 1.25 hours.

Accreditation
Physicians: UMDNJ-Center for Continuing & Outreach Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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This activity is awarded 1.25 contact hours (60 minute CH).
Provider approved by the California Board of Registered Nursing, Provider Number CEP 13780.

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Review: This activity was peer reviewed for relevance, accuracy of content, and balance of presentation by Patricia Kloser, MD, MPH; and Brenda Christian, MED, PA-C; and pilot tested for relevance and time required for participation by Kinshasa Morton, MD; Bonnie Abedini, RN, MSN; Linda Berezny, RN, BA; and Mary C. Krug, RN, MSN, APN-C.

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Faculty Disclosure Declarations
The following have no financial relationships to disclose: faculty: Mark J. Fussa, DO and Sindy M. Paul, MD, MPH, FACP; and reviewers: Patricia Kloser, MD, MPH; Brenda Christian, MED, PA-C; Kinshasa Morton, MD; Bonnie Abedini, BSN, MS; Linda Berezny, RN, BA; and Mary C. Krug, RN, MSN, APN-C; and New Jersey AIDSLine editor Kimi Nakata, MSW, MPH.

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

1. Describe metabolic complications associated with the use of antiretroviral agents.
2. Identify the risks and appropriate management of dyslipidemia for patients on antiretroviral agents.

Introduction

The medical management of HIV has been revolutionized by the use of highly active antiretroviral therapy (HAART). In the pre-HAART era, HIV typically led to death within ten years. Treatment of HIV with HAART can extend the lifespan of HIV-infected persons by several decades. A major challenge that has arisen out of this success is the management of the side effects of antiretroviral therapy. Antiretroviral therapy (ART) commonly causes various complications, some of which may be life threatening.

This article focuses on some of the more common metabolic complications associated with the treatment of HIV-infected persons, such as dyslipidemia, insulin resistance states, and lipodystrophy syndromes. These abnormalities may eventually lead to an epidemic of cardiovascular disease and diabetes among HIV-infected patients. Management of these complications has therefore become an integral component of HIV care.

HIV causes lipid changes even in the absence of HAART. Low total cholesterol, low high-density lipoprotein cholesterol (HDL), low LDL (low-density lipoprotein), and high triglycerides were commonly seen in the pre-HAART era. Initiation of HAART reverses some of these effects. HDL rises to levels lower than that of the general population. Total cholesterol (including LDL and very-low-density lipoprotein (VLDL)) and triglycerides are all increased by ART. HAART causes an increase of the atherogenic small, dense LDL-2 particle. Of concern is that elevated triglycerides, low HDL, along with small LDL size, comprise the atherogenic dyslipidemia phenotype that is associated with premature atherosclerosis.
A comprehensive approach to the management of HIV-infected patients must take into consideration cardiac and metabolic consequences. A large prospective cohort study demonstrated that HIV-infected patients on HAART suffer cardiac events at an increased rate. The Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) Study Group has followed more than 23,000 HIV-infected individuals to assess whether exposure to antiretroviral therapy increases the incidence of myocardial infarction and other cardiovascular events. Of note, the incidence of traditional risk factors in this relatively young cohort was substantial – 56% had a smoking history, 2.8% were diabetic, 7.2% had high blood pressure, and 45.9% had dyslipidemia. In their initial reporting, 126 patients had had a myocardial infarction (MI) (incidence of 3.5 events per 1000 person-years), 38 patients had a stroke, and 39 patients required cardiac intervention. The incidence of cardiac and cerebrovascular events, including myocardial infarction and other cardiovascular events, increased with increasing exposure to HAART. After adjustment, the relative risk for MI was 1.16%. This leads to a doubling of cardiac risk after five years of exposure to HAART. Overall, the absolute risk of MI remained low, and HAART contributed only partially to the apparent excess risk.4,5

The use of HAART is only one of several factors that contribute to cardiovascular disease in HIV-infected individuals. The following modifiable risk factors for coronary heart disease are targets for risk modification: dyslipidemia, hypertension, cigarette use, diabetes, overweight/obesity (BMI >25/30 kg/m²), inactivity, and atherogenic diet. Older age, male sex, and family history of premature CHD (<55 years old in a first degree male relative or <65 years old in a first degree female relative) are non-modifiable risk factors.6 Other authors have suggested that HIV-infected individuals utilize elicit substances like cocaine and methamphetamine that increase cardiac stress, though this is unproven.7 Additionally, interactions between drugs, host, and virus means that metabolic complications are often not the sole consequence of medication.

The D:A:D Study demonstrated that despite the frequent use of lipid lowering agents like statins and fibrates, the risk factor profile among their HIV-infected cohort worsened from 1999 to 2006. This detrimental change in risk factors was partly caused by the aging of the HIV-infected population; as people aged, they also developed diseases like hypertension and diabetes. Over that period of time the incidence of MI remained stable, suggesting that worsening risk factors may have negated the benefits of risk reduction.8 Interestingly, the Framingham Cardiac Risk Calculator consistently underestimates the number of events predicted in the D:A:D cohort. This suggests that a lower threshold for intervention (diet, switch, or lipid lowering drugs) should be considered in HIV-infected persons.3
Management of Dyslipidemia

The National Cholesterol Education Program has produced guidelines, which should be used to guide therapy for dyslipidemia in HIV-infected patients. The NCEP guidelines were updated in 2004 to provide an option for more aggressive lipid lowering therapy in high risk individuals. These reports can be accessed at: www.nhlbi.nih.gov/guidelines/cholesterol/index.htm.

LDL is the main target of intervention to decrease the risk of CHD. LDL can be calculated as:

\[ \text{LDL} = \text{total cholesterol} - \left( \text{HDL} - \frac{\text{triglycerides}}{5} \right) \]

Determination of an individual's ten-year risk for developing coronary heart disease is an integral first step set forth in the NCEP guidelines. Three strata based on a ten-year risk guide target LDL levels.

- CHD or CHD equivalents have a >20% risk of experiencing a cardiac event within 10 years. The target LDL is <100 (with an optional target of <70 in very high-risk patients).
- CHD equivalents are: other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease); diabetes; and multiple risk factors that confer a 10-year risk for CHD >20%.

The second category includes patients with 2+ risk factors but a ten-year risk of <20%. The target LDL is <130.

- In this instance, only age, family history of CHD, smoking history, hypertension, and low HDL cholesterol are applicable.
- The Framingham Tool is used to calculate 10 year CHD risk. It can be accessed online at http://hp2010.nhlbihin.net/atp3ii/calculator.asp?usertype=prof
- Ten-year Framingham risk is based on age, total cholesterol, HDL cholesterol, gender, smoking history, and systolic blood pressure.

The third category includes patients with 0-1 risk factors. They generally have a 10-year risk of <10%. The target LDL is <160. Framingham scoring is not necessary.

The D:A:D Study demonstrated that despite the frequent use of lipid lowering agents like statins and fibrates, the risk factor profile among their HIV-infected cohort worsened from 1999 to 2006. This detrimental change in risk factors was partly caused by the aging of the HIV-infected population; as people aged, they also developed diseases like hypertension and diabetes. Over that period of time the incidence of MI remained stable, suggesting that worsening risk factors may have negated the benefits of risk reduction.6
NCEP guidelines recommend that all patients with an elevated LDL be evaluated for remeasurable secondary causes. These causes include: diabetes mellitus, hypothyroidism, nephrotic syndrome, liver disease, chronic kidney disease, and drugs (including progestins, steroids, and protease inhibitors).9

The LDL treatment goals for HIV-infected individuals are the same as for the general public. In all cases of dyslipidemia, therapeutic lifestyle changes (TLC) should be employed. TLC includes smoking cessation, regular exercise, adhering to a diet high in omega-3 fatty acids, low in total and saturated fats, high in fiber, and fresh fruits and vegetables. If LDL remains above goal after 6 weeks of TLC, intensification is warranted.9

Two main treatment approaches are available to attain NCEP goals for patients on HAART therapy – treatment switching and the addition of lipid lowering agents. Several studies suggest that lipid-lowering therapy rarely attains NCEP goals, and in many instances a combination of drug therapy and switch therapy is required.3

Therapeutic switching is based on the different effects that various antiretrovirals have on cholesterol and triglycerides. Thirty-one antiretroviral agents in various formulations have been approved for the treatment of HIV. Many of these have fallen out of favor and are no longer in routine use. Those which remain fall into one of six classes, each of which may have a different effect on metabolic parameters. Even within a single class, there is variability, for instance, the protease inhibitor ritonavir causes substantial and unfavorable elevations in serum lipids, while the newer protease inhibitor atazanavir has a neutral effect on lipids.3

The D:A:D Study Group compared the risk of MI in patients taking a protease inhibitor-based regimen to those on a non-nucleoside reverse transcriptase inhibitor based regimen. The incidence of MI increased in both groups through a median of 4.5 years of follow-up. However, the relative rate for patients exposed to PIs was 1.16, which was significant, versus 1.05 (NS) for patients exposed to NNRTIs. Protease inhibitors can cause marked elevations in total cholesterol, LDL cholesterol, and triglycerides. NNRTIs cause more modest increases in total cholesterol, LDL triglycerides, and HDL.2 The questions then become: 1) Do all protease inhibitors have the same effect on lipids? 2) Is it safe and effective to use a PI-sparing regimen?

Among protease inhibitors, ritonavir is associated with the greatest increases in lipids. Both the IAS-USA and the USDHHS guidelines for the treatment of HIV list ritonavir-boosted PIs as recommended treatment options (NNRTIs are also an option in both guidelines; in the USDHHS guidelines alternatives include two unboosted PIs). Obviously exposure to ritonavir happens commonly in the HAART era. Data is pending regarding the effect of lower doses of ritonavir, as used to boost another PI, on lipids and HDL. In the AI424-089 study, atazanavir (ATV), a protease inhibitor with a neutral effect on lipids, was examined with and without ritonavir(r). ATV/r was associated with greater increases in total cholesterol and LDL cholesterol than ATV alone. The difference in effect on HDL cholesterol was negligible. A review of available data shows that of the protease inhibitors, ATV has the smallest impact on lipids, followed by ATV/r. Boosted saquinavir given once or twice daily and boosted fosamprenavir given daily each have a moderate impact on lipids. Lopinavir/ritonavir and twice daily fosamprenavir with ritonavir have the greatest impact among commonly prescribed PIs.3

Research Studies on Safety and Effects Of Highly Effective Antiretroviral Treatment

**D:A:D:** The Data Collection of Adverse Events of Anti-HIV Drugs Study Group assessed the effect of either a protease inhibitor based regimen or a non-nucleoside reverse transcriptase inhibitor based regimen on the incidence of myocardial infarction and other cardiovascular events.

**POWER:** Performance Of TMC114/r. When evaluated in treatment-experienced patients with PI resistance (1 and 2 (TMC114-C213 and TMC114-C202) studies. In the 24-week primary efficacy analyses, patients receiving one of four darunavir-ritonavir doses plus an optimized background regimen demonstrated better antiviral activity than control PIs (CPIs) in treatment-experienced patients.

**SMART:** The Strategies for Management of AntiRetroviral Therapy Study Group compared two strategies in nearly 6,000 people worldwide: continuous treatment vs. regularly interrupted treatment (strategic treatment interruption) guided by increases in CD4 counts. The study was stopped early when, despite expectations of benefits in, the data showed that people who interrupted treatment had higher rates of illness and death.

**SWAN:** The SWitch to ANother Protease Inhibitor study was a 48-week, open-label trial. In patients with virologic suppression who were receiving other PIs, switching to a once-per-day regimen containing atazanavir provides better maintenance of virologic suppression, a comparable safety profile, and improved lipid parameters, compared with those for patients who continued their prior PI-based regimen.
**Management of Hyperlipidemia for Patient on Antiretroviral Agents**

*Debbie Mohammed, MS, APRN, BC, ACRN, MPH; UMDNJ-University Hospital*

**JF is a 64-year-old African American male** who was diagnosed in October 2000 with HIV infection contracted through heterosexual contact. He has a history of bilateral pneumonia, oral thrush and hypertension managed with Diovan HCT 320/25mg, 1 tablet daily. He has a history of smoking cigarettes in the past; he denies alcohol and illicit drug use. He sees the onsite nutritionist for education regarding his diet regularly and he takes the bus or walks to where he needs to go locally.

**TABLE 1**

<table>
<thead>
<tr>
<th>Labs</th>
<th>7/02</th>
<th>11/02</th>
<th>3/03</th>
<th>2/04</th>
<th>2/06</th>
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<td>218</td>
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<tr>
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<td>97</td>
<td>186</td>
<td>93</td>
<td>86</td>
<td>117</td>
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<tr>
<td>LDL</td>
<td>145</td>
<td>133</td>
<td>119</td>
<td>85</td>
<td>105</td>
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<td>(0-130)</td>
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<tr>
<td>HDL</td>
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<td>GFR mLs/min</td>
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<td>49</td>
<td>&gt;60</td>
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<td>&gt;60</td>
<td>&gt;60 mLs/min</td>
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<td>CD4+</td>
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<td>288</td>
<td>301</td>
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</table>

- In July 2002, JF’s antiretroviral regimen included Agenerase 150 mg po BID with Norvir 100 mg po BID, and Epivir/Ziagen also BID. His total cholesterol level and LDL were noted to be rising. He was started on Pravachol 40 mg orally once/day which was increased 4 months later to 80 mg orally. His cholesterol and LDL levels then began decreasing.

- In February 2004, his regimen was switched to Lexiva 700mg/Norvir 100 mg po BID and Truvada to simplify his medication regimen.

- In February 2006, his cholesterol and LDL were noted to be rising and Zetia 10 mg po OD was started with excellent results noted. However, in August 2007 his GFR was noted to be <49 mLs/min. His HAART was held pending diagnostic studies for kidney disease, which were unremarkable. His GFR spontaneously increased to >60 mLs /min.

- A decision was made in September 2007 to restart HAART, changing regimens using his genotype from June 2001, as the change was due to side effects rather than virologic failure. Mutations included L100L, K103N, G190A/G indicating resistance to NNRTIs. His current regimen is 2 tabs of Prezista 300mg/Norvir 100mg BID, Epzicom 1 tablet po OD, and Fuzeon 90 mg SC BID. Pravachol was discontinued because of the potential for drug interaction with Prezista.

- His GFR has remained >60 mLs/hr. and he is scheduled for a repeat lipid profile with his next set of labwork. His CD4+, HIV viral load and BMI have remained stable over the past six years.

- This patient will continue to require close monitoring of all his lab values.
SWITCHING THERAPY to an atazanavir-based regimen has been assessed. Atazanavir (ATV) is a once daily protease inhibitor that is a recommended component of HAART. ATV can be given either unboosted as a 400 mg dose or as a 300 mg dose boosted with 100 mg of ritonavir. Given the less lipophilic effects of atazanavir, AL424-900 assessed the safety and efficacy of a switch from a more lipophilic protease inhibitor to ATV or ATV/r. Thirty-three treatment-experienced patients with severe dyslipidemia were switched to ATV or ATV/r and followed for 48 weeks. A statistically significant 45.6% decrease in triglycerides and 17.9% decrease in total cholesterol occurred by 24 weeks of therapy, and the change was robust through 48 weeks of atazanavir therapy. Changes in HDL cholesterol and LDL were not statistically significant. After 48 weeks, a re-increase in triglyceride to levels still below baseline was seen while total cholesterol remained lower. The authors noted a coincident increase of patients who were receiving boosted atazanavir at the time, with ritonavir possibly leading to the increase in triglycerides.

Several studies have examined the effect of replacing PIs altogether. The LipNEFA study was a prospective open-label trial that followed 69 patients who were switched from various PI regimens to a nelfinivirus (NFV), efavirenz (EFV), or abacavir (ABC) containing regimen. This study demonstrated a benefit in lipid profiles by switching to a PI-sparing regimen. Seventy percent of enrollees had lipid abnormalities at baseline. Anthropomorphic examinations, lipid levels, and insulin levels were serially followed for 24 months. The ABC arm demonstrated significant decreases in total cholesterol and non-HDL cholesterol. The NNRTI arms had significant improvements in HDL cholesterol, leading to a more cardioprotective TC:HDL ratio. In all 3 treatment arms, triglycerides initially dropped, only to rebound during the second year of the study. The authors point to continued use of stavudine in the backbone as a potential explanation for the triglyceride rebound.

Switching therapy may be considered to meet NCEP goals for the management of dyslipidemia. If heavily treatment experienced patients with limited therapeutic options are prescribed switch therapy, careful follow-up must be assured to avoid virologic breakthrough. Planned treatment interruption is not safe, as demonstrated in the SMART Study, a large prospective trial.

Dyslipidemia may be treated by adding lipid lowering drugs if TLC and switching do not work. A statin should be used to treat isolated hypercholesterolemia. There are many important interactions between antiretroviral agents and statins which can lead to toxicity. Recommended statins include pravastatin, low-dose atorvastatin, fluvastatin, or rosuvastatin. A fibrate should be used to treat isolated hypertriglyceridermia, typically if the level is in excess of 400 mg/dL. Two fibrates, micronized fenofibrate (Tricor) and gemfibrozil (Lopid) are available. Fish oil also has a significant impact on triglycerides. Both fibrates and fish oil can raise LDL. Niacin can decrease triglycerides and increase HDL, but can also exacerbate insulin resistance. Bile acid sequestrants are relatively contraindicated in HIV because of unknown effects of these agents on the absorption of antiretroviral agents. Ezetimibe is a brush border inhibitor that can lower LDL, especially in combination with statins. In a recent study (ENHANCE), ezetimibe failed to show any improvement in thickness of coronary plaques when paired with simvastatin, as compared to simvastatin alone. However, the combination pill did result in significant reductions in LDL compared with simvastatin alone.

Calza compared the addition of lipid lowering agents to switch therapy to see which approach was more effective in improving dyslipidemia. In a randomized, open-label trial, 142 patients with mixed hyperlipidemia on PIs were randomized to receive nevirapine (NVP), efavirenz (EFV), pravastatin, or bezafibrate. At 12 months, decreases in triglycerides, total cholesterol, and LDL were significantly greater with both lipid lowering arms than with the switch arms. At 12 months the proportion of enrollees with normal triglycerides (50.7%) was greater in those on lipid lowering therapy than those who had switched to a PI sparing regimen. Similarly, the proportion of those with normal LDL by NCEP guidelines was higher after additive therapy (49.2%). It is perhaps important to note that only half of the patients enrolled in the most efficacious arm of this trial attained goals for dyslipidemia. This suggests that a combination of switch therapy and additive therapy may ultimately be necessary to manage dyslipidemia.

Disorders of Glucose Metabolism

Insulin resistance is a risk factor for development of CHD and can lead to the metabolic syndrome and diabetes. Impaired glucose tolerance is defined as either a fasting blood sugar between 100 mg/dL and 125 mg/dL, or a blood sugar of 140 mg/dL to 199 mg/dL two hours after a 75 gram glucose challenge. Diabetes is diagnosed when fasting blood sugar exceeds 126 mg/dL or a two hour glucose challenge test yields blood sugars greater than 200 mg/dL. Insulin resistance develops when insulin becomes less effective at stimulating target tissues, leading to a hyperinsulinemic state.

The pathogenesis of insulin resistance states is varied. Lipodystrophy syndrome can lead to disorders of glucose metabolism. Among a variety of effects on the glucose metabolic pathways, protease inhibitors can induce insulin resistance through inhibition of peripheral GLUT-4 transporters. As is the case with dyslipidemia, there are variable effects on glucose metabolism within the PI class. Atazanavir and possibly saquinavir have little or no effect on GLUT-4. Lopinavir and indinavir may have short-term effects on insulin sensitivity, but long-term suppression of GLUT-4 is required to markedly alter glucose metabolism. Lopinavir/ritonavir was compared to boosted atazanavir to assess their relative contributions to insulin resistance. Both agents led to some abnormalities in glucose uptake, with lopinavir/ritonavir causing more dysfunctional uptake. The clinical significance of this finding is unclear. However, the effect of HAART on glucose metabolism can be striking; impaired glucose tolerance was seen in 35% of HIV-infected patients in one study conducted in 2001; in another study, diabetes was 3.1 times as likely to develop in men receiving HAART for only three years.
Disorders of glucose metabolism can be addressed in several ways. Substitution of a protease inhibitor-based regimen with nevirapine, efavirenz, or abacavir has led to short-term improvements in glucose metabolism and can be considered in the appropriate setting. Generally, the management of glucose abnormalities in HIV-infected patients should be approached as it would be for the general population. Whenever possible, lifestyle modification should be stressed. Other risk factors for the development of CHD should be identified and remedied.

Medications are reserved for patients who have established diabetes. Metformin is a diabetic medication that improves insulin uptake in the periphery. It is unclear whether metformin forestalls the development of diabetes in patients with insulin resistance. Metformin can cause lactic acidosis and should be used cautiously in people receiving an NRTI. It is contraindicated for individuals with a serum creatinine >1.5. Because it is associated with modest weight reduction, metformin may exacerbate lipoatrophy. Thiazolidenediones (TZDs) improve insulin sensitivity in diabetics and HIV lipodystrophy. Both are known to cause weight gain and fluid retention and recent data suggests they may have detrimental cardiovascular effects. Pioglitazone has been associated with exacerbations of Stage 3 and 4 congestive heart failure. Rosiglitazone has been associated with exacerbations of Stage 3 or 4 CHF and coronary ischemia. These findings should be taken into account in the treatment of HIV-infected persons. Sulfonlyureas improve plasma glucose by increasing insulin secretion of pancreatic beta cells. Insulin is effective and inexpensive and may be used to treat diabetes. Exenatide is an injectable agent for the treatment of Type 2 diabetes that binds to glucagon-like peptide-1 receptors, leading to increased insulin secretion and reduced serum glucose levels. It has not been well studied in HIV-infected individuals.

Lipodystrophy Syndromes

Clinicians and patients began noticing fat distribution abnormalities shortly after the advent of HAART – particularly in regimens that combined NRTIs with protease inhibitors. Lipodystrophy occurs in the abdomen, dorsocervical fat pad (“buffalo hump”), neck, or breasts. Lipodystrophy involves the loss of subcutaneous fat in the face, extremities, abdomen, or buttocks. In addition to possible negative impacts on lipid profiles and truncal obesity, lipodystrophy may lead to psychological distress. Some patients are reluctant to start or continue antiretroviral therapy because of the body changes that can be encountered. Storage of fatty acids and impaired fatty acid oxidation in lipodystrophy may lead to hepatic steatosis and insulin resistance. Body fat abnormalities have been reported in 40%-50% of HIV-infected patients and are more common in patients on HAART.

Lipodystrophic changes are apparent in roughly 25% of HIV-infected patients after two years of treatment. Studies of body composition have outlined the mechanisms by which lipodystrophy occurs. During the first few months of treatment, there is a tendency towards increases in limb fat, followed by a steady decline over years, causing lipoatrophy. Concurrently, truncal fat increases and remains relatively stable for years, possibly leading to truncal obesity (lipoin accumulation).

Lipoatrophy is strongly associated with two NRTI/PI regimens. Among NRTIs, the association is particularly strong with stavudine and is more prevalent when stavudine is used in combination with didanosine. NRTIs cause lipoatrophy via inhibition of mitochondrial DNA polymerase. Additional mechanisms by which NRTIs promote lipoatrophy include: inhibition of adipogenesis, inhibition of adipocyte differentiation, and promotion of lipolysis. NRTIs may exert a synergistic toxic effect on adipocytes when used with protease inhibitors. Protease inhibitors are not associated with lipoatrophy when used by themselves. Additional risk factors for lipoatrophy are older age, nadir CD4+ count <200/µL, and lower body weight. Metformin may exacerbate lipoatrophy. Lipoin accumulation is associated with protease inhibitors, but can also occur in patients who are PI-naive. Risk factors for fat accumulation are older age, obesity/higher BMI, caucasian race, and lower nadir CD4+ count. Screening for lipoatrophy is largely subjective. Clinical trials have used DEXA, CT, and MRI, but the routine use of these modalities as screening tools is hampered by their expense. Objective measures may not be more sensitive than patient reporting and physical exam.
There is no objective measure for facial lipoatrophy. Screening for lipoaccumulation can involve anthropomorphic measurements. A waist/hip ratio of >0.85 in women or >0.95 in men is abnormal, as is a waist circumference of >88 cm in women or >102 cm in men. A CT or MRI can detect increases in visceral adipose tissue, but the clinical utility of this finding is often unclear.12, 13, 17

Several approaches to the management of lipoatrophy are available, but resolution is often disappointingly incomplete. Switch therapy has been investigated. Substituting tenofovir or abacavir for stavudine may lead to modest improvements in lipoatrophy. Modifying therapy from a thymidine-analogue containing regimen to a regimen with abacavir or no NRTIs at all may reverse lipoatrophy. Lopinavir/ritonavir monotherapy may worsen lipids, and should only be used with caution, if at all. TZDs may increase subcutaneous fat, but studies have yielded mixed results for the treatment of lipoatrophy. Reconstructive procedures may provide substantial cosmetic benefits. Polylactic-L-acid is FDA approved for the treatment of lipoatrophy, but its use is limited by cost. Other procedures that have been utilized include placement of silicone implants and fat transplantation.12, 13

The treatment of lipoaccumulation can be similarly vexing. If obesity is present, it presents an obvious target for intervention through diet and exercise. Metformin has been associated with weight loss and may lead to decreased subcutaneous fat. Studies assessing its use for lipoaccumulation have provided conflicting results. Topical testosterone supplementation may lead to mild-to modest decreases in subcutaneous abdominal and limb fat. Growth hormone can reduce total fat and visceral fat. Side effects of growth hormone therapy may include insulin resistance. Surgical options include resection of fatty tissue or liposuction, but re-growth of fatty tissue may occur.13

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**Case**

**Treatment of glucose intolerance & lipodystrophy in patient on antiretroviral agents**

*Patricia C. Kloser, MD, MPH*

EL is a 55-year-old woman with a family history of diabetes. She was diagnosed with advanced AIDS in 1996, with a CD4+ count of 14, and went on her first antiretroviral regimen, Crixivan and Combivir, which she credited with saving her life. Her family had many social and medical problems, contributing to her determination to manage her own care with as little change as possible. However, after about 5 years on the regimen, her weight had increased from 138 to over 200, and she had developed elevated glucose. She was diagnosed with non-insulin-dependent diabetes. She also developed pancreatitis and lipodystrophy.

The physician enlisted the help of a nutritionist to help EL change her diet and manage both the diabetes and pancreatitis. EL was able to lose weight to a healthier 148, though she continues to struggle with this. She also learned when she needed to take medication for her pancreatitis. Her physician finally convinced her that it was dangerous to continue on her old HAART regimen, and she switched to a new regimen, dropping Crixivan because of its effects on her metabolism. The new regimen is Reyetaz + Norvir + AZT + 3TC, with a careful dosing schedule to administer epivir three times per week after dialysis, to maintain therapeutic drug levels. Her abnormal lipid profile and diabetes improved.

EL found lipodystrophy very dismaying, as she was working hard to achieve and maintain a healthy weight and figure. She had surgery for her buffalo hump, through a collaboration with a plastic surgeon in another hospital, and was very relieved with the outcome. Her pancreatitis has resolved, and her diabetes has remained under control for several years.

Two years ago, she was admitted to the CCU with a heart attack and developed renal failure, becoming dialysis dependent. She just got her vascular shunt, and now wants to go on the kidney transplant list. She meets the medical criteria for transplant for HIV patients of a CD4+ level over 200 and undetectable VL. Her CD4+ is now >700, and her VL is undetectable.

As her physician, I paused to consider: what is the most amazing thing about this patient?
- That she is still alive, having been diagnosed with HIV in the early 1990s and AIDS in 1996?
- That she was able to lose weight and control her diabetes by diet alone?
- That she is seeking a kidney transplant?
- That she is not depressed despite AIDS, pancreatitis, diabetes, renal failure, lipodystrophy, coronary artery disease, obesity history, and painful low back disease?
- Or— that she was finally convinced to change her HAART to Reyetaz, Norvir, AZT, 3TC, when she had already had an undetectable viral load and high CD4+ count?

The greatest challenge was to change her HAART regimen, because EL had managed her HIV care and many co-morbidities through her determination to maintain a full independent life and to make her own decisions. It was difficult for her to believe that the treatment which had saved her life was the cause, in the long run, of many other medical problems.
Lipodystrophy and its management in patients on antiretroviral agents.

Debbie Mohammed, MS, APRN, BC, ACRN, MPH; UMDNJ-University Hospital

SJ is a 60-year-old man with HIV/AIDS, who was diagnosed in 1995. His risk factor was a blood transfusion. He has a history of opportunistic infections with bartonella, *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii*), and *Candida*. He has generally been adherent to antiretroviral medications as prescribed since 1995. Not surprisingly, he has a multidrug resistant HIV virus. His current antiretroviral regimen includes: Prezista 300mg with Norvir 100mg orally twice/day, Isentress 400mg po twice daily, Truvada 1 tablet daily and Videx EC 250 mg orally, daily since January 2008. Current CD4+ count is 814 cells (25%), and HIV viral load is <50 copies. His weight is appropriate for his height. He denies smoking, alcohol or illicit drug use and is not sexually active. He has Medicaid and Medicare insurance coverage. His medical history is significant for hypothyroidism, diabetes mellitus, and hyperlipidemia, depression without suicidal ideation, benign prostatic hypertrophy, GERD and sleep apnea.

In the summer of 2007, SJ attended a support group where he learned about lipodystrophy and became very concerned about his facial appearance. In addition, he reports that he is not sleeping well and feels tired all the time. He reports that his neck hurts when he turns his head from side to side or bends forward.

On physical exam, it was noted that SJ had severe loss of subcutaneous fat in his face, with submental hypertrophy, mild central adiposity, and loss of subcutaneous fat from his arms and legs with prominent veins. He was unable to touch his chin to his neck and able to turn his head only slightly to the sides.

SJ had a surgical evaluation for the submental hypertrophy and was subsequently offered a rhytidectomy with the full support of his psychiatrist. After the surgery, SJ was able to sleep better at night and was less tired during the day. He now has free range of motion to his neck.

However, SJ is still dissatisfied with his facial appearance. He has been referred to a plastic surgeon for possible use of injectable facial filler. He is requesting growth hormone to manage his lipodystrophy. The next steps to resolving his issues are still being evaluated in clinical trials. Hopefully one day soon we may have the answers on the best ways to manage a patient with this side effect to medications.

**Consultation with Dr. Kloser:**

**What can we learn from SJ’s history, and what are the next steps?**

**Do you believe that SJ was infected via blood transfusion?**

a. Yes, it is still very common to be infected via blood products.
b. No, but many people feel more comfortable with this explanation as it “absolves” them of sexual or illicit drug labels.
c. Yes, he was diagnosed in 1995 and most people who contract HIV via infected blood products live a long time.
d. No, it is impossible for anyone in a developed country to be infected via blood products.

*The most likely answer is b. It may be difficult to have honest discussions with JS about reducing HIV transmission risks.*

**What could help SJ to improve his self image?**

b. Cosmetic fillers.
c. Psychotherapy, both group and individual.
d. Antidepressant medication.
e. All of the above.

*Any or all of these interventions would be helpful to SJ in coping with the metabolic effects of his antiretroviral medications.*
Conclusion

With the advent of HAART, it is now possible to durably suppress HIV replication. Many HIV-infected patients will see their lifespan measured in decades. In HIV, to prolong life requires uninterrupted therapy with toxic agents. Unforeseen metabolic consequences of antiretroviral therapy have emerged, creating challenges for clinical management of HIV-infected patients. Intervention to ameliorate the present and future effects of antiretroviral therapy is necessary to prevent a potential epidemic of cardiac mortality and diabetes in the HIV population. The management of these complications remains unsettled in many ways. There is current multidisciplinary research on the metabolic effects of both established and new HIV medications, aimed at further improvements in preventing and managing these potentially fatal side effects.

Metabolic Complications Associated with the Treatment of HIV-Infected Persons

REFERENCES


