Welcome to Metabolic Complications in HIV Care and Treatment: Improving Practice Through Case Studies. This educational activity is presented and certified by the Discovery Institute of Medical Education (DIME). This activity is supported by an educational grant from Bristol-Myers Squibb Company.

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The faculty for this activity is Kathleen Squires, MD. Dr. Squires is Director of Infectious Diseases and Environmental Medicine and Professor of Medicine at Thomas Jefferson University in Philadelphia, Pennsylvania.
Educational Objectives

- Identify two major metabolic complications associated with HIV therapy
- Describe the pathogenic mechanisms involved in these complications
- Define strategies to manage metabolic complications of HIV therapy

The educational objectives of this activity are to identify two major metabolic complications associated with HIV therapy, to describe the pathogenic mechanisms involved in these complications, and to define strategies to manage metabolic complications of HIV therapy.
Antiretroviral therapy (ART) and HIV infection have been associated with a range of metabolic abnormalities. The metabolic disturbances and morphologic changes which are related to ART, however, are not completely understood. There are many causes, which may include viral factors, host factors, or direct and indirect effect of the agents which make up ART.

Some of the metabolic effects appear to be class related, and within classes there are drug-specific differences in the metabolic effects of these antiretroviral agents. While metabolic effects may be interrelated, the mechanism of these connections really remains unclear at this time.
So in terms of the morphologic disturbances that we see associated with HIV infection itself, as well as with the agents which are used as part of ART, we see two major categories. The first is adipose accumulation. It has also been called and you might see it labeled in the literature as lipohypertrophy. This constitutes accumulation of fatty tissue, and we see that happening in the abdominal area. Either we see increased subcutaneous fat deposits or what has been described in the literature as accumulation of fat around the visceral organs.

The other places on the body where we have seen this is dorsocervical fat enlargement, also known as the buffalo hump. We have also seen breast enlargement. Primarily this has been a problem in HIV-infected women, but we have certainly seen it in men as well.

The other major category is lipoatrophy. This is characterized by wasting, subcutaneous wasting of fat, and it's manifested in the extremities, in the face, and in the buttocks.

Despite the fact that I've said there are two categories, in an individual you may see one or the other of these categories predominating, or in some individuals you can actually see some element of adipose accumulation as well as subcutaneous fat wasting.
In terms of the metabolic changes associated with HIV infection itself, as well as with ART, a number of disturbances have been documented, and you will see reviews of studies in the literature.

The first is altered glucose metabolism. This has been manifested as insulin resistance, impaired glucose tolerance, or overt diabetes mellitus in some of our patients. One category that has been seen very commonly is dyslipidemia, which is really characterized as serum metabolic disturbances, specifically increases in triglycerides, a decrease in HDL, and increases in LDL.

Another disturbance which is seen fairly uncommonly, but has a high rate of morbidity and mortality, is hyperlactatemia, but more specifically lactic acidosis. This is a rare complication. It is associated with long-term use of nucleoside reverse transcriptase inhibitors (NRTIs). As I mentioned, when we see lactic acidosis, it is a very severe complication, associated with a very high rate of morbidity and mortality.

Lastly, we are seeing bone disease in HIV-positive patients, and that covers a spectrum of osteonecrosis, which has been reported. The most common joint involved is the hip, but we have certainly seen other joints involved as well. And then the spectrum of osteopenia and osteoporosis.

For this particular category it is unclear at the present time whether it’s HIV infection itself, in the kind of inflammatory state that is associated with HIV infection, and/or the drugs, the agents, that are causing this spectrum of bone disease that we’re seeing in HIV-positive patients. But certainly this is something that has been reported over the past several years.
In terms of dyslipidemia and HIV infection, lipid abnormalities are common complications of HIV itself, as well as ART. Why do we see this? What’s the pathogenesis? It is felt to be that the inflammatory response we see to HIV infection may be proatherogenic, that some of the cytokines we see elevated in HIV-positive patients may actually be adding to these elevations in serum lipids.

Elevations in triglycerides, LDL, and total cholesterol are commonly seen in patients who are receiving ART. The dyslipidemia which is associated with HIV infection and with ART appears to increase the risk of cardiovascular disease (CVD). So clearly, as our patients are on ART and are living for longer periods of time, we need to carefully assess for baseline risk factors for CVD and then follow up these patients very carefully over the ensuing years.
Dyslipidemia and ART

• PIs have been implicated as a major cause of ART-related dyslipidemia
  – Different PIs have various effects on lipid metabolism
  – Genetic susceptibility has been found to play an important role
• NRTIs appear to be associated less with dyslipidemia than PIs
  – However, some NRTIs (stavudine [d4T], didanosine [ddl], azidothymidine [AZT]) are associated with dyslipidemia
• NNRTIs are least associated with dyslipidemia
  – Efavirenz (EFV) is shown to have a modest effect on total cholesterol

In terms of thinking about the drugs, we’ve talked a little bit about the proatherogenic profile of HIV infection and the inflammatory state that we see, specifically in untreated HIV infection. That’s a contribution of the drugs that we use in treating [HIV] therapy. In this setting PIs, or protease inhibitors, have been implicated as a major cause of ART-related dyslipidemia.

We know that across a class of PIs, different agents have various effects on lipid metabolism. Some drugs (for instance, ritonavir) are very closely associated with triglyceride elevations. At the other end of the spectrum perhaps is a drug such as atazanavir, which is felt, especially when it is given unboosted, to be lipid neutral.

We have also seen a genetic susceptibility in the setting of patients who have certain genetic background who receive some of these drugs. They may have an increased propensity because of this genetic background to experience elevations in their lipids.

Now in terms of NRTIs, or nucleoside reverse transcriptase inhibitors, they appear to be less associated with dyslipidemia than the PIs; however, across this class of agents, there are some, specifically stavudine, didanosine, and azidothymidine, or AZT, which have been associated with dyslipidemias, specifically elevations in triglycerides.

The third class that we are using as first-line therapy in treatment-naive patients—those would be the nonnucleoside reverse transcriptase inhibitors (NNRTIs). They are least associated of all of these three classes with dyslipidemia.

So across the two drugs in this class that are currently FDA approved, efavirenz and nevirapine; out of the two, efavirenz has been shown to have a modest effect on total cholesterol. In contrast, nevirapine is felt to be completely lipid neutral.
Turning to the topic of insulin resistance, we do know that ART has been associated with an increased incidence of insulin resistance and glucose intolerance. There are several mechanisms which may underlie the phenomenon of insulin resistance that we see in HIV positive patients.

We do know that some of the antiretroviral agents, specifically from the NRTI class as well as the PI class, can cause insulin resistance. These observations have come from very carefully done studies in normal volunteers who have received short courses of these agents. Their serum insulin levels, as well as glucose homeostasis, have been followed up, and we have seen that the drugs are directly involved in causing insulin resistance.

We also know that there may be indirect consequences of fat redistribution. For instance, we know in HIV-negative patients who have lipoatrophy that there is an association between lipoatrophy and insulin resistance.

We know that the chronic inflammatory changes induced by HIV and these elevated cytokine levels that I spoke to a little while ago can be associated with insulin resistance. And finally, hepatic steatosis, which is seen commonly in HIV-infected patients, is also associated with the development of insulin resistance. So there are many mechanisms whereby the insulin resistance that has been documented in HIV-positive patients may be occurring.
Now we’re going to turn to considering the management of hyperlipidemia, one of the metabolic complications seen in association with HIV infection.
So let's start talking about the patient. He's a 45-year-old, HIV-positive man who is about 6 feet tall and weighs 180 lb. And a year and a half ago he had CD4+ cell counts which were ranging from 300 to 350.

At that time he started a HAART-based regimen of efavirenz plus tenofovir and emtricitabine in a coformulated medication. At the current time his CD4+ count is 650 and his viral load is <50 copies/mL. At least in terms of the aim of ART, he has had a very nice response in terms of a nice rise in his CD4+ cell counts and has an undetectable plasma viral load.

His baseline and on-treatment lipid profiles show that he has mild hypercholesterolemia and borderline LDL.
Certainly in terms of looking at the issue of his CVD profile, he doesn’t smoke cigarettes, he drinks a glass of wine several times a week, he follows a regular aerobic exercise program. He tells you that his diet is heart smart.

He has a history of hypertension, which is controlled on lisinopril and hydrochlorothiazide, and in terms of his family history, there is hypertension and coronary artery disease. Both his father and his brother have had both conditions, and both have undergone angioplasty and require ongoing medical management.
Current Presentation

• Recent fasting lipid profile
  – Total cholesterol: 268 mg/dL – Triglycerides: 189 mg/dL
  – HDL: 49 mg/dL – LDL: 178 mg/dL

• All other safety labs WNL

• Recent ECG shows RBBB
  – No change from prior ECG

• He is concerned that he may have increased risk of cardiac vascular disease (CVD); told he needs treatment for hypercholesterolemia

At the time that he comes in to see you, he has had a fasting lipid profile done, his total cholesterol is 268, his triglycerides are 189, his HDL is 49, and his LDL is 178. All of his other safety labs are within normal limits.

He has had an ECG, which shows a right bundle-branch block, and this is stable from previous tracings. He is a very intelligent man, and certainly in light of his family history, he really is worried about his risk for CVD. He has also been told, based on these lipid profiles that he’s been undergoing, that he needs treatment for his hypercholesterolemia.
What I have on this slide is the way that you can actually assess your patient for their risk for CVD. This is a chart from the Framingham study.

As I'm sure most people are aware, this is a study that has been ongoing for the past couple of decades. The investigators have followed up a cohort of men and women in Framingham, Massachusetts, and assessed them for a number of characteristics in terms of risk of CV.

And as you can see, age, blood pressure, cigarette use, diabetes, total cholesterol, and HDL cholesterol have been the major factors shown in this study to be associated with risk for CVD.

Listed on the chart is the relative risk for each of these factors for men and for women. For each box there is a referent, which means “normal.” So, for instance, let’s look at blood pressure. A normal is given a relative risk of 1, and then as the type of blood pressure or the amount of hypertension that the patient has [rises], the relative risk for CVD rises.

There is actually a website where you can do a cardiovascular risk profile for all of your patients, which should be done at baseline, and, especially for patients who have an increased baseline risk of CVD, followed up at regular intervals.

So if we look down these risk factors, you can see that cigarette use is far and away the single risk factor most highly associated with an increased risk of CVD. For total cholesterol, obviously the higher the total cholesterol, the higher the risk, and in contradistinction to age, blood pressure, cigarette use, diabetes, and total cholesterol, and HDL. In fact, higher levels of HDL are actually felt to be cardioprotective. As HDL levels rise higher, you can see there is actually a decreased risk for CVD.

For all of our patients we should be looking at this model, plugging in the factors and coming up with the risk profile for our patients, most specifically for patients who appear to have some baseline risk factors for CVD.
What do you advise at this time?

A. Begin pravastatin 20 mg/d
B. Begin atorvastatin 20 mg/d
C. Begin aspirin and omega-3 fish oil
D. Observe

Okay, so having said all of that, what are we going to advise at this time? You have a choice here of a couple of statins, pravastatin at 20 mg/d; we are going to begin atorvastatin at 20 mg/d, begin aspirin and omega-3 fish oil. Are we really not too worried about the parameters that I outlined and are we just going to observe this patient?

Please select your answer at this time.
Listed on this slide are the agents that are available for dyslipidemia. Now you can see, as you look down for each of these categories, the effect of the particular agents on either LDL, on triglycerides, or on HDL.

Most of the responses that you see here have been documented in HIV-negative patients. In some cases these drugs have been studied specifically in HIV-positive patients who manifest dyslipidemia, and what those studies overall have shown is that we certainly see the same effects that are listed on this slide for the various agents, but the effect is not as robust. In other words, the effect of these agents in HIV-positive patients who have, or manifest, hyperlipidemia is muted compared to the effects seen in HIV negative patients.

Now I would like to talk about several of these agents or the classes, and let’s start with the statins. We recognize that the major effect for statins is their ability to lower LDL. Again, there are a number that have been studied specifically in HIV infection, and I will speak to that issue in a little while.

Niacin, on the other hand, has been used predominantly for triglycerides, but also, of all of the agents on this table, is really the only agent that has been shown to affect to any large extent HDL; in other words, to help elevate HDL levels.

Fibrates—the major effect is to lower triglycerides, as you can see on this table.

For the other agents, the bile acid sequestrants, there’s ezetimibe and fish oil. They don’t have as profound an effect as the three classes that I spoke about; however, they do have a role in the treatment of hyperlipidemia. In many cases these drugs will be added after the first three classes have been tried and you have not been able to get the maximal effect that you are trying to achieve.

Bile acid sequestrants act predominantly by lowering LDL, ezetimibe primarily again by lowering LDL levels, and fish oil primarily by lowering triglyceride levels.
Decision

• You decide to prescribe pravastatin 20 mg/d

You’ve decided, after considering all of the classes, and remembering the levels of lipids—serum lipids—that this patient had, that you’ve decided to prescribe pravastatin at a dose of 20 mg/d.
Lipid-Lowering Agents: Use in HIV-Infection

- Rank determined by pharmacokinetic studies in normal volunteers

<table>
<thead>
<tr>
<th>Recommended¹,²</th>
<th>Alternative³,⁴</th>
<th>Contraindicated⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrates</td>
<td>Fibrate + statin</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Atorvastatin</td>
<td>Lovastatin</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td></td>
<td></td>
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<tr>
<td>Rosuvastatin?</td>
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What do we know specifically about the use of the various statins in HIV-positive patients?

What’s listed on this slide is the breakdown across this class by drugs, statins that are specifically recommended in the treatment of HIV-infected patients, some kinds of alternatives, and then specifically some statins that are contraindicated.

And the reason that there is this kind of breakdown is that many of these—most of these—agents listed on this slide are metabolized or are substrates of the P450 enzyme system. And as you are aware, for our two major classes of drugs, which act as the backbones for HIV infection—those being the NNRTIs and the PIs—these drugs are also substrates and/or [are] metabolized by the P450 enzyme system.

So you would expect that there would be drug–drug interactions, and, in fact, there are substantive drug–drug interactions between statins, various statins and various antiretroviral agents.

Hence, the reason for the two drugs that are contraindicated, simvastatin and lovastatin. For instance, simvastatin; when it was studied in PK studies with saquinavir and ritonavir, what they saw was that the serum levels of simvastatin were really substantially elevated when coadministered with this particular PI-containing regimen. And because of the side effects that we know that are associated with the statin class—CPK elevations, myopathy, rhabdomyolysis—it really is not recommended to coadminister simvastatin with PIs.

In contradistinction, for the drugs that are in the recommended class, pravastatin, fluvastatin, and I have a question again with rosvuastatin, but specifically for pravastatin and fluvastatin, these drugs in formal PK studies have been shown to have the least effect in terms of drug–drug interactions and are the recommended drugs when you are going to use statins in HIV-infected patients. And the alternatives, they kind of lie in the middle there in terms of the drug–drug interactions that you might see.

The standard way of handling these drugs is to use a recommended statin, and in general you want to start with the lowest dose of the drug and titrate upward while you follow up with the patient carefully in terms of clinical signs and symptoms.
Evolution

• 8 weeks later, his fasting lipid profile is:
  – Total cholesterol: 239 mg/dL
  – Triglycerides: 164 mg/dL
  – HDL: 47 mg/dL
  – LDL: 144 mg/dL

• The patient is concerned that he has not had the reduction in TC and LDL to meet the levels outlined in the NCEP ATP III guidelines

For this particular patient, 8 weeks later, after he started his pravastatin, his fasting lipid profile now is: his total cholesterol is 239, his triglycerides are 164, his HDL is 47, and his LDL is 144. So we have seen some movement here in terms of his lipid profile.

However, as I mentioned, this is a very with-it guy, especially in terms of CVD, and he is concerned that he has not had the reduction in total cholesterol and LDL to meet the levels that are outlined in the National Cholesterol Education Project ATP III guidelines. And I will go over what those guidelines are in just a little while.
What are you going to do at this point? Are you going to discontinue his pravastatin so he’s on a statin—we did get some effect, but discontinue it? Continue the therapy for 8 more weeks? Increase the pravastatin dose? As I mentioned, we typically start with a low dose and titrate upwards. Are we going to switch to fluvastatin? Or another alternative here would be to switch his ART.

I haven’t really talked much about that issue to date, but you might think about switching from an antiretroviral agent which is felt to have some effect on cholesterol and triglycerides, in terms of elevating it, to perhaps an agent which is felt to be more lipid friendly or lipid neutral. And so in this case he’s on efavirenz, which is an NNRTI, switch him to now a boosted PI, but specifically [the] PI atazanavir, which is felt to be more lipid friendly.
Listed on this slide is concomitant use of statins, and you can see the ones that are mentioned on this slide, and efavirenz. And I included this because this gentleman is on an efavirenz-containing regimen, and so I wanted to give you an idea from studies that have been published or presented at conferences, what we see in terms of combining a statin with an antiretroviral agent.

So the drugs that have been studied here are simvastatin, atorvastatin, and pravastatin, and clearly, as I mentioned to you, simvastatin is a drug that we don’t really want to use because of the drug–drug interactions, but this is a study from several years ago now.

And you can see what can be achieved here in terms of reduction from baseline LDL cholesterol with these agents. And while there is a modest reduction, you do see reductions in LDL cholesterol across all three of these agents in combination with efavirenz.
Now the other alternative, one that I mentioned when discussing the possible strategies that you were going to choose, is instead of using a lipid-lowering agent, look at the strategy of antiretroviral class switching.

So in other words, switch from a drug that the patient is on and has manifested this dyslipidemia, to another drug in the class, in this case it would be the same class, or to a drug in another class that is felt to be more lipid friendly or more lipid neutral type of agent.

Now this is a study again published a few years ago in patients who were participating in phase 2 atazanavir trials. They were randomized to either nelfinavir, one of the older PIs available to us, or atazanavir. In patients in those particular trials who experienced dyslipidemia on nelfinavir, they had the ability to switch to atazanavir.

And here, showing the difference in these lipid parameters at the time that they made the switch, and then 12 weeks later, demonstrating that for patients who switch from nelfinavir to atazanavir, for total cholesterol, for LDL cholesterol, and for triglycerides, you do see a decrease in the serum levels of these particular parameters. For HDL cholesterol, there is really not much of a change, but at least no continued decline in HDL cholesterol.

So it’s another strategy, another way of trying to get to the issue of successfully dealing with a dyslipidemia that your patient is manifesting.
Decision

Since the patient is on an EFZ-based antiretroviral regimen, you increase his pravastatin dose to 40 mg/d.

What was decided to do in this case was: he is on the efavirenz-based antiretroviral regimen and a relatively modest dose of pravastatin, so the decision here was made to increase the dose of pravastatin to 40 mg/d.
Evolution

- 8 weeks later, his fasting lipid profile is:
  - TC: 222 mg/dL  
  - TG: 176 mg/dL  
  - HDL: 49 mg/dL  
  - LDL: 126 mg/dL
- The pravastatin dose is increased to 80 mg/d
- 8 weeks later, the fasting lipid profile is:
  - TC: 202 mg/dL  
  - TG: 170 mg/dL  
  - HDL: 50 mg/dL  
  - LDL: 108 mg/dL

Eight weeks after that, you can see his total cholesterol is 222, his triglycerides are 176, his HDL is 49, and his LDL is 126. So we have seen continued evolution or continued decline in his parameters and his HDL— not markedly elevated, but at least a little bit higher than it was previously.

Now the pravastatin dose is increased to 80 mg, which as we know is really the top of the dosing level that you can give, and in another 8 weeks, his total cholesterol has decreased to 202, his triglycerides to 170, his HDL is now 50, and his LDL is 108.

So, over time we’re seeing a continued decline, specifically in his LDL cholesterol and his total cholesterol.
What should be your management goals for this patient—current TC 202 mg/dL, LDL 108 mg/dL?

A. Total cholesterol <200 mg/dL, LDL <130 mg/dL
B. Total cholesterol <200 mg/dL, LDL <100 mg/dL
C. Total cholesterol <200 mg/dL, LDL as low as possible
D. Something else

So what should your management goals for this patient be in terms of his dyslipidemia? Let’s remember that his current total cholesterol is 202 and his LDL is 108. So in terms of the categories here, what we’re looking at is the effect on LDL. So what are we trying to achieve, LDL of less than 130, of less than 100, really to get the LDL as low as possible, or is this the wrong parameter and is there something else that we should be thinking about and following?
Well, listed here on this table are the NCEP ATP III recommendations. And as you can see here, really the goal, the parameter that we want to follow in terms of cardiovascular risk is LDL. And as you can see, depending on the risk category of the patient, there is a different goal in terms of LDL—the serum level of LDL cholesterol that you want to achieve for your patient.

So specifically for patients who have a history of coronary heart disease, or really the risk equivalent to established coronary artery disease, your LDL goal should be to get the level to less than 100. For patients who have two or more risk factors out of that Framingham score that I discussed previously and a 10-year risk factor of <20%, the goal is 130. And for 0–1 risk factors, the goal is 160.

For this patient, really the goal should be around 100, if possible, because he does have risk equivalent in terms of both the family history as well as the other, his hypertension, and so on and so forth. So for this particular patient, if it would be possible to achieve a goal of 100, that really would be where we want to go.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>LDL at Which To Initiate therapeutic Lifestyle Change</th>
<th>LDL at Which to Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease or risk equivalent</td>
<td>&lt;100</td>
<td>≥100</td>
<td>≥130</td>
</tr>
<tr>
<td>≥2 risk factors and 10-year risk &lt;20%</td>
<td>&lt;130</td>
<td>≥130</td>
<td>10-year risk 10%–20% ≥130 10-year risk &lt;10%:≥160</td>
</tr>
<tr>
<td>0–1 risk factors</td>
<td>&lt;160</td>
<td>≥160</td>
<td>≥190</td>
</tr>
</tbody>
</table>
Listed on this slide gives you two websites. The first one is the Framingham cardiovascular risk equation. As I mentioned, you really should be assessing at baseline the cardiovascular risk profile for your patient, and all you do is go to that website and plug in the various parameters that are asked for, and you can come out with a prediction of the 10-year risk and have a discussion with the patient.

The other website that I placed on here, and I think it’s very important because you are managing HIV-positive patients, is to look at the assessment of risk of HIV progression. And this is another website where, like the cardiovascular equation, there will be a number of parameters. Now they are linked to HIV disease, to be able to put into perspective the patient’s risk of HIV progression. And really when you are thinking about management of dyslipidemia, you have to put it into the context of the patient’s HIV infection and balancing trying to decrease the risk of HIV progression with obviously controlling dyslipidemia and controlling the risk of CVD.
Well, now we are going to consider lipoatrophy and insulin resistance and how we would try to manage that in an HIV-infected patient. For our patient, we have a 45-year-old male who is a nonsmoker who was diagnosed with HIV infection in 1997. His CD4+ cell count was 300, and his viral load was 50,000 copies.
Case

- 45-year-old male, nonsmoker, diagnosed with HIV infection in 1997
  - CD4+ 300 cells/mm³, VL 50,000 copies/mL
- Pertinent history
  - Family history of diabetes mellitus, cardiovascular and cerebrovascular disease
  - Social history
    - No tobacco use
    - Former dancer and gymnast, works as a personal trainer

In terms of his history, he has a family history of diabetes mellitus [and] cardiovascular and cerebrovascular disease. And in terms of his social history, he doesn’t smoke, as I mentioned, is a former dancer and a gymnast, and he works as a personal trainer.
Like our first patient, [he] is very in tune with his disease and his infection and wants to be as proactive as possible, and so he signed up to be in an observational study for a nutritional assessment. And so what’s listed on this particular table is not something that you are going to be doing on a regular basis with your patients in your practice setting, but these are parameters that we’re going to consider as we go through the case because they are indicative of some of the changes, body habitus changes, that we see in patients with HIV infection.

So you can see here that his BMI is 22½, really a very kind of optimal BMI for this man who is 45 years old. His waist/hip ratio is .85. The next three parameters were measured by a DEXA scan: his total body fat is 14 %, his extremity fat is 12%, his truncal fat is 15%. Clearly he is an athlete.

His triglycerides, on the other hand, are 325, his total cholesterol is 185, his HDL cholesterol is 35, and his glucose is 85. So his triglycerides, his total cholesterol, and his HDL are really what we see sometimes in untreated HIV infection, specifically the elevation in triglycerides and the relatively low HDL cholesterol.
This was in 1997 when he was diagnosed. It was recommended to him that he start therapy, and he started indinavir, a PI, stavudine, and lamivudine, which was a very commonly used HAART-based regimen at the time.

Six months later his CD4+ cell count is 435 and his viral load is <500 copies/mL, and again at that time, that was the lower limit of detection for that particular assay. So he’s had a desired response in terms of his immunologic response and his virologic response. He has gained 12 pounds and he feels well.
Month 6 Nutritional Assessment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Month 6</th>
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</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>22.5</td>
<td>24.1</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.85</td>
<td>0.87</td>
</tr>
<tr>
<td>Total body fat (DEXA)</td>
<td>14%</td>
<td>18%</td>
</tr>
<tr>
<td>Extremity fat (DEXA)</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Truncal fat (DEXA)</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>325</td>
<td>300</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>185</td>
<td>225</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>85</td>
<td>106</td>
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Six months later, he’s in this observational study, and his parameters here, his nutritional assessment is reperformed. His BMI has increased to 24 and his waist/hip ratio has not changed to an appreciable extent; however, you can see in terms of his total body fat, his extremity fat and his truncal fat, he has seen an increase here. His triglycerides are 300, so essentially unchanged. His total cholesterol, however, has increased to 225, his HDL is the same at 35, and his glucose now is 106, and these parameters are fasting parameters.

So we have seen an elevation in his glucose and we have seen some increase in total body fat here.
Month 12 Follow-up

- 5-lb weight loss since month 6, but patient clinically well and exercising regularly
- Laboratory values:
  - Random blood glucose 185 mg/dL
  - Fasting glucose 140 mg/dL, 125 on repeat
  - HbA₁c mildly elevated at 6.2%
  - Serum lipids unchanged

So now 12 months later he has actually lost 5 pounds since the 6th month, but he is clinically well and he is exercising regularly. Remember, this is a gentleman who is a personal trainer and very attuned to physical fitness.

His laboratory values— he has a random blood glucose of 185, he has a fasting glucose of 140, which is 125 on repeat, and his HbA1C is mildly elevated at 6.2%. His serum lipids are unchanged, so he has hypertriglyceridemia and hypercholesterolemia, and those values are relatively stable.
On this table, we see this nutritional assessment extended through month 12, and those values that I just told you about are reflected in this table. So you now see his glucose is at 125, his triglycerides are at 300, and the other values are relatively unchanged in terms of his BMI and his waist/hip ratio.

However, what you can see now is that between baseline and month 6, he had increase in total body fat, and now a year later, 6 months later, he is down to baseline for extremity fat, actually less than baseline at 10 %.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>22.5</td>
<td>24.1</td>
<td>23.1</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.85</td>
<td>0.87</td>
<td>0.89</td>
</tr>
<tr>
<td>Total body fat (DEXA)</td>
<td>14%</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Extremity fat (DEXA)</td>
<td>12%</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Truncal fat (DEXA)</td>
<td>15%</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>325</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Total (mg/dL)</td>
<td>185</td>
<td>225</td>
<td>225</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>85</td>
<td>106</td>
<td>125</td>
</tr>
</tbody>
</table>
First of all, let’s talk about diabetes—so does this patient meet the criteria for diabetes?

Does this patient meet the criteria for diabetes?

A. Yes
B. No
What we see reflected in this table are the diagnostic criteria for patients who have impaired glucose tolerance or diabetes, and the values on the table are generated based on an oral glucose tolerance test.

So for random and fasting levels that there are some differences between patients who meet the diagnostic criteria for impaired glucose tolerance or for diabetes, and then you can see the values that are listed for glucose tolerance tests. And again, breaking it up between patients who have impaired glucose tolerance and frank diabetes.

Our patient, who has had fasting levels 2 times of 126 or above, really 125 and 140, really does meet the diagnostic criteria for diabetes.
How will you manage his diabetes?

1. Diet/exercise
2. Add metformin
3. Add rosiglitazone
4. A combination of the above
5. Stop/switch therapy

How are we going to manage his diabetes? Are we going to think about diet and exercise, add metformin, add rosiglitazone, or a combination of the above? Or because we think that the drugs might be exacerbating or actually leading to diabetes, do we think about stopping his therapy altogether or at least switching the agents that he is currently receiving?
There are a number of modalities for the treatment of diabetes, and those modalities account for whether patients are HIV-positive or HIV-negative. What I am going to try and do over the next several slides is outline for you across those modalities what we know about the use of them in HIV-positive patients.

In this slide—this is really looking at the issue of diet and exercise for weight loss but also to treat at least as one of the treatment parameters for diabetes. This is a study that was presented several years ago looking at obese HIV-positive women. It’s a prospective longitudinal study. They were given a 1200-calorie diet with nutrition counseling, and they underwent exercise with a personal trainer, and you can see what that entailed on the slide here.

They underwent whole-body MRI and DEXA scanning and they also had frequently sampled, insulin-stimulated intravenous glucose tolerance testing.
Listed on this slide are the changes in those parameters that were seen at baseline vs week 12. And when we look out across these, we can see that if we’re looking in terms of weight and we’re looking in terms of visceral adipose tissue, subcutaneous adipose tissue, we do see a decrease over the 12 weeks of the study, and all of these parameters are significantly different than the parameters at baseline.

If we then turn to look at insulin sensitivity, however, or fasting insulin, or fasting glucose, we really do not see much of a change, and in none of these cases does the change between baseline and week 12 reach statistical significance.

So, despite the fact that we do see differences in the body habitus, we really don’t see a marked response here in terms of parameters that we’re particularly interested in here in terms of impaired glucose tolerance and in terms of diabetes.
Pharmacologic Treatment of Insulin Resistance

• Metformin
  – Decreases insulin resistance >1 year
  – Decreases weight, diastolic pressure, tPA, and PAI-1

• Thiazolidinediones
  – Decrease insulin resistance
  – Increase triglycerides and cholesterol
  – Variable effects on body composition

• However, insulin resistance does not return to normal

Turning away now from diet and exercise, let's talk about pharmacologic treatment of insulin resistance. What drugs, what agents do we have to treat that? And the first agent is metformin. In studies it has been shown to decrease insulin resistance over a 1 year of follow-up. It also decreases weight, diastolic pressure, and tPA and PAI-1, which are various enzymes that are associated with glucose metabolism.

The other agents, the so-called glitazones, have been shown to decrease insulin resistance, to increase triglycerides and cholesterol, and to have variable effects on body composition depending on what the baseline body composition of the patient was at the time these drugs were started. However, unfortunately, across these modalities, insulin resistance doesn’t really return to normal, but you will see some amelioration in insulin resistance.
Follow-up

- The patient takes metformin, modifies his diet, and increases his exercise
- HbA$_{1c}$ normalizes
- Body weight decreases 12 lb during next 6 months and BMI falls to 21.5
- There is obvious lipoatrophy
- Patient develops nephrolithiasis and switches to NFV with maintenance of virologic control
- Metformin is discontinued and glucose and HbA$_{1c}$ remain normal

What we have decided with this patient is to take a kind of multimodular or modality approach. He starts on metformin, he modifies his diet, and he increases his exercise, something that we would hope all of our patients would do. His HbA1C normalizes, his body weight decreases 12 lbs over the next 6 months, and his BMI, which has increased to about 24, has now fallen to 21.5.

However, over this time period, and remember now we followed him up for a year on these drugs, he has obvious lipoatrophy. The patient has another complication directly related to the antiretroviral agent that he is on, indinavir, and he develops nephrolithiasis, kidney stones, and he is switched in that setting to nelfinavir, with maintenance of virologic control.

Again, he was switched on his antiretroviral agents, not to deal with the dyslipidemia, the insulin resistance, and so forth, but because of a known complication of one of his antiretrovirals. His metformin is discontinued and his glucose and his HbA1C remain normal.

So he’s on indinavir and metformin, maybe some interaction here in terms of nephrolithiasis, and so the metformin is discontinued.
So what are we going to do now? He’s on a nelfinavir-containing regimen. Are you going to switch him to a PI-sparing therapy? Are you going to switch him from stavudine, from the D4T that he’s on to abacavir, another NRTI? Are you going to switch the D4T to tenofovir, one of the newest NRTIs that we have available? Are we going to switch both the D4T and the nelfinavir, or are we going to continue the present regimen?
What I am going to do over the next few slides is to summarize for you the studies that have been performed to look at the issue of lipoatrophy and various interventions that might treat this particular dyslipidemia or particular lipid abnormality.

For the first intervention, what has been employed here is to switch a patient off a drug, specifically here, stavudine, NRTI, or zidovudine, another nucleoside analogue. Both of these agents [are] felt to be associated with lipoatrophy, and switch them to other drugs in the class, specifically abacavir or tenofovir, which are not felt to cause to any appreciable extent lipoatrophy.

Summarizing across a number of studies that have been performed, there are small but significant increases in peripheral fat. However, it can take several years for the patient to return to his or her baseline status.

There have also been studies using uridine, which affects mitochondrial stores. And what we see here is about an increase of about a kilogram in limb fat over 12 weeks. But this is really kind of preliminary and only one study has really shown this effect.

The last two rows here deal with the use of statins and glitazones for the treatment of lipoatrophy. And for a statin, specifically here pravastatin, we have seen in a study [an] increase in total limb fat and subcutaneous fat; however, this really has been a secondary outcome because statins are used primarily for their effect on LDL cholesterol.

Lastly, we have seen the use of rosiglitazone in a number of trials now—most of the trials have demonstrated that you see no change in limb fat—in one, limb fat was increased—but overall these two latter categories of the use of statins or the use of glitazones really don’t appear to be the state of the art in terms of treatment of lipoatrophy at the current time.
Treatment Interventions for Lipoatrophy: New Studies

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone¹</td>
<td>• Increased limb fat of 0.3 kg over placebo ($P=0.051$)</td>
</tr>
<tr>
<td></td>
<td>• Thigh circumference and tricep skin fold increase</td>
</tr>
<tr>
<td></td>
<td>• No benefit in patients taking d4T</td>
</tr>
<tr>
<td>Metformin²,³</td>
<td>• No benefit for fat distribution or dyslipidemia in 2 studies</td>
</tr>
<tr>
<td></td>
<td>• Trend toward decrease in appendicular fat</td>
</tr>
<tr>
<td>Rosiglitazone³</td>
<td>• Increased lower extremity fat ($P=0.034$)</td>
</tr>
<tr>
<td>Rosiglitazone + Metformin³</td>
<td>• No benefit</td>
</tr>
<tr>
<td>Testosterone⁴</td>
<td>• Decrease in subcutaneous fat</td>
</tr>
<tr>
<td></td>
<td>• No effect on visceral fat</td>
</tr>
</tbody>
</table>


Just to round out some of the newer studies now, looking again with some glitazones—pioglitazone, rosiglitazone, the combination of rosiglitazone and metformin. Metformin, which this gentleman was given, really in terms of his glucose intolerance or his diabetes is not really for lipoatrophy, or lastly, for testosterone.

You can see, if you go over all of those outcomes, that in isolated studies we have seen some benefit in terms of increased limb fat—for instance, in the one study with pioglitazone—but relatively disappointing results overall.
Data from a specific study, the so-called TARHEEL study, in which patients who were on a stavudine (or D4T)-containing regimen were switched away from that NRTI to other NRTIs in the same class, here abacavir or AZT.

What you can see at baseline is at the time that they were on the D4T-containing regimen, and then 48 weeks later, what you can see is the percent change from baseline in arm fat, leg fat, and trunk fat, demonstrating that over the 48 weeks of follow up, you did see increases in each of these parameters when you removed an agent considered to be strongly associated with lipoatrophy.

Well, these look like impressive changes. What I can tell you though is that typically in the individual the changes are actually very modest, and sometimes you can’t even visually appreciate the change, and it will take several years before there is enough regaining of the fat reflected in the body habitus.
This is another study, the so-called MITOX study, and this is a longer period of time at follow up, at least in the graph, of 72 weeks. These are patients who were switched from D4T or from zidovudine. Both of these drugs are NRTIs of the thymidine class, and both have been associated with lipoatrophy—specifically, the stavudine drug has been most closely associated with lipoatrophy. And these patients were switched from either of those drugs to abacavir.

To summarize on the slide here, you can see the results, an increase in limb fat for patients after they switched. The best one was for the patients who switch from baseline to abacavir. Through 72 weeks of follow up you can see an increase of over 1 kg in body weight—I should say in limb fat weight. However, that is kind of a modest change, and it would take several years for that kind of change to be manifested if you are visually inspecting the patient.
Follow-up

- The patient switches from NFV to EFZ
- Despite initial perception of improvement, body composition does not change over 9 months
- The patient then changes from d4T to ABC
- After 12 months there is mild improvement on body composition study, but the changes are not perceptible

Now back to our patient. He actually switches from nelfinavir to efavirenz. So he switches from a PI-containing regimen to an NNRTI-containing regimen. And despite the initial perception of improvement, his body composition doesn’t really change over the ensuing 9 months. And then he changes another part of his regimen. Specifically, he changes from stavudine or D4T to abacavir.

I just want to put this into context because if we were managing this patient today, most likely a PI-based regimen would not be a nelfinavir-containing regimen, so—just to kind of deal with that issue. But the other thing is that while we typically do kind of stagger changes in therapy, in this particular setting the patient has lipoatrophy. He is on agents that we associate with lipoatrophy or at least with some element of insulin resistance, and so in this particular patient’s case, we might not have staggered therapy but we might have changed both components of the regimen. So there is more than one way of handling this particular situation.

In any case, for this gentleman, after another 12 months, there is mild improvement on the body composition study, but the changes for him or to him are really not perceptible.
Question 4
What would you do now?

1. Restart metformin
2. Add rosiglitazone
3. Give growth hormone
4. Continue current regimen and reassess in 6 months
5. Something else

So what are you going to do now? Are you going to restart the metformin which was stopped several years ago when he developed nephrolithiasis? Are you going to add rosiglitazone? Are you going to give him growth hormone? I really didn’t speak to the issue of growth hormone here, but that has been used for a number of problems, lipoatrophy being one of them. Are you going to continue the current regimen and reassess in 6 months, or are you going to try something else?
Conclusion

- The patient continues on his current regimen
- After an additional 6 months, there is no perceptible change in his lipoatrophy
- He decides to explore reconstructive surgery using polylactic acid

In this particular patient’s case, as I mentioned, there is no one really tried and true method that is going to restore this gentleman’s subcutaneous fat. He has been seeing some modest changes over the time period, and for a number of reasons he continues on his current regimen. The other alternatives—and I outlined what you could hope to gain with these alternatives—didn’t appear to add a lot of additional benefit for this gentleman.

After an additional 6 months, there is again no perceptible change in his lipoatrophy, and at this point in time he decides to explore reconstructive surgery using polylactic acid, which is injected subcutaneously to try and fill out that area. This is something that has been approved by the FDA, and for patients who can afford this, this has become a popular way of dealing with lipoatrophy, especially lipoatrophy that involves primarily the face. And there are some studies in the literature, many of them uncontrolled studies, documenting some modest improvement.
Summary

- Dyslipidemia and body habitus changes continue to be concerns in the management of HIV disease
- Body habitus changes have been most problematic to patients because they often render the patient visibly identifiable as having HIV
- Lipoatrophy may become less of a problem as newer agents and newer classes of drugs become available
- Dyslipidemia, however, will continue to be a problem for the foreseeable future
- As far as possible, treatment regimens should be designed to minimize drug-related lipid perturbations
- As patients live longer on HAART, CVD and dyslipidemia must be given careful consideration in the management of HIV disease

The whole topic of dyslipidemia and body habitus changes continues to be a considerable concern for both patients, as well as their providers. Body habitus changes have really been most problematic to patients because in many cases, especially having [those] problems with lipoatrophy, changes can unmask the patient as having underlying HIV infection.

Fortunately, as we have more recent agents and newer agents and newer classes of agents available to us, it really does look like lipoatrophy, especially for those patients who are starting therapy at this point in time with these newer agents, may become less of a problem, which clearly will be a major benefit to patients.

In terms of dyslipidemia, and specifically perturbations in serum lipids, this area will continue to be a problem for the foreseeable future. Some of our newer agents do have a better lipid profile, and specifically for patients who look like they have a baseline, an elevated baseline risk of CVD, part of the decision analysis about what antiretroviral agents or combination of agents to give a patient should take into close consideration the cardiovascular risk profile for the patient. A regimen should be devised to try and minimize adding yet another risk factor, in this case elevated LDL cholesterol, and total cholesterol, and decreased HDL cholesterol.

So the management of HIV infection is complicated, and we have yet another factor now to think about as our patients are living for longer periods of time—ie, CVD and dyslipidemia—and careful consideration needs to be paid to these factors.