Unique Aspects of Treating Endocrine Diseases in HIV-Positive Patients

Amy H. Warriner, M.D.
Director, UAB 1917 Endocrinology Clinic
Division of Endocrinology, Diabetes and Metabolism
University of Alabama at Birmingham

Disclosures

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  • NIH
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  • Amylin
Objectives

• Gain knowledge on endocrine diseases with disparate presentations in HIV+ persons
• Recognize potential medication interactions specific to anti-retroviral medications
• Identify appropriate treatment approach and mechanisms for assessing treatment effects

HIV
The Impact of Highly Active Antiretroviral Therapy (HAART) on HIV Mortality

Palella, NEJM, 1998

Slide Courtesy of Todd Brown
Persons Living with HIV in the US

<table>
<thead>
<tr>
<th>Data for 34 states</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at end of year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;13</td>
<td>3,996</td>
<td>3,568</td>
<td>3,119</td>
<td>2,736</td>
</tr>
<tr>
<td>13–14</td>
<td>1,116</td>
<td>1,207</td>
<td>1,242</td>
<td>1,159</td>
</tr>
<tr>
<td>15–19</td>
<td>3,864</td>
<td>4,286</td>
<td>4,828</td>
<td>5,400</td>
</tr>
<tr>
<td>20–24</td>
<td>13,699</td>
<td>14,307</td>
<td>15,347</td>
<td>16,905</td>
</tr>
<tr>
<td>25–29</td>
<td>38,381</td>
<td>30,081</td>
<td>31,659</td>
<td>33,857</td>
</tr>
<tr>
<td>30–34</td>
<td>59,564</td>
<td>48,057</td>
<td>48,931</td>
<td>47,390</td>
</tr>
<tr>
<td>35–39</td>
<td>62,730</td>
<td>60,663</td>
<td>78,206</td>
<td>76,565</td>
</tr>
<tr>
<td>40–44</td>
<td>102,941</td>
<td>106,420</td>
<td>108,069</td>
<td>107,023</td>
</tr>
<tr>
<td>45–49</td>
<td>82,943</td>
<td>89,050</td>
<td>95,752</td>
<td>103,025</td>
</tr>
<tr>
<td>50–54</td>
<td>53,903</td>
<td>60,030</td>
<td>67,082</td>
<td>74,582</td>
</tr>
<tr>
<td>55–59</td>
<td>28,027</td>
<td>33,023</td>
<td>38,186</td>
<td>43,565</td>
</tr>
<tr>
<td>60–64</td>
<td>13,303</td>
<td>15,309</td>
<td>17,705</td>
<td>20,642</td>
</tr>
<tr>
<td>≥65</td>
<td>19,512</td>
<td>12,361</td>
<td>14,363</td>
<td>16,982</td>
</tr>
</tbody>
</table>
Co-morbidities Reported with Increased Frequency Among HIV+ patients in the cART Era

- Lipodystrophy
- Diabetes Mellitus
- Cardiovascular Disease
- Malignancy
- Renal Dysfunction
- Cognitive Dysfunction
- Low Bone Mineral Density

- Adrenal Insufficiency
- Iatrogenic Cushing's
- Male Hypogonadism
Lipodystrophy
Lipodystrophy

Treatment strategies for adipose tissue changes in HIV-infected individuals

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Effect</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipodystrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switching antiretroviral therapy</td>
<td>X</td>
<td>Switching from stavudine or indinavir to abacavir or nevirapine or efavirenz</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>X</td>
<td>Effect and clinical significance of lipodystrophy apparent due to increased risk of cardiovascular disease. Patients tolerate well. Increased levels of triglycerides, decreased levels of HDL cholesterol, increased levels of LDL cholesterol.</td>
</tr>
<tr>
<td>Fibrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fat-releasing agents</td>
<td>X</td>
<td>Prevent adverse effects include lipodystrophy with concomitant use of medications that inhibit HMG-CoA reductase inhibitors (statins) and insulin-sensitizing agents (thiazolidinediones).</td>
</tr>
<tr>
<td>Lipoproteins</td>
<td>X</td>
<td>No effect on adipose tissue, but may improve metabolic resistance and adipocyte function.</td>
</tr>
</tbody>
</table>

Lipoproteins

Switching antiretroviral therapy X Overall: mixed results for reducing triglyceride plus restoring lipoproteins plus restoring as one small study.

Lipid changes

Moderate X Non-severe lipodystrophy

Growth hormone X Because of safety concerns.

Thiazolidinediones X FDA approved 2001, long-term benefits and side effects uncertain.

Lipodystrophy (hereditary lipodystrophy) X Can occur spontaneously.


Lipid Changes

- 1989: Triglyceride levels are higher in AIDS > HIV-positive > HIV-negative

## Lipid Changes

**Table 1. Plasma lipid and Apo lipoprotein levels**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HIV+</th>
<th>AIDS</th>
<th>AIDS vs control</th>
<th>HIV+ vs control</th>
<th>AIDS vs HIV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>1.15 ± 0.122</td>
<td>1.24 ± 0.187</td>
<td>2.25 ± 0.381</td>
<td>&lt;0.0005 NS</td>
<td>&lt;0.001 NS</td>
<td>&lt;0.001 NS</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>4.73 ± 1.72</td>
<td>3.80 ± 2.05</td>
<td>3.06 ± 2.05</td>
<td>&lt;0.02 NS</td>
<td>&lt;0.03 NS</td>
<td>&lt;0.001 NS</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.17 ± 0.055</td>
<td>0.80 ± 0.045</td>
<td>0.80 ± 0.045</td>
<td>&lt;0.0001 NS</td>
<td>&lt;0.0001 NS</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.078 ± 0.030</td>
<td>0.607 ± 0.031</td>
<td>0.621 ± 0.040</td>
<td>&lt;0.0001 NS</td>
<td>&lt;0.0001 NS</td>
<td>NS</td>
</tr>
<tr>
<td>Apo A-I (mg/dL)</td>
<td>0.086 ± 0.046</td>
<td>0.141 ± 0.021</td>
<td>0.163 ± 0.027</td>
<td>&lt;0.025 NS</td>
<td>&lt;0.006 NS</td>
<td>NS</td>
</tr>
<tr>
<td>Apo B-100 (mg/dL)</td>
<td>124 ± 8.24</td>
<td>96.4 ± 4.50</td>
<td>86.8 ± 5.46</td>
<td>0.002 ± 0.001 NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>2.13 ± 0.109</td>
<td>2.34 ± 0.106</td>
<td>2.15 ± 0.265</td>
<td>0.0025 NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Apo B-100 (mg/dL)</td>
<td>74.5 ± 4.28</td>
<td>58.0 ± 3.28</td>
<td>58.5 ± 6.46</td>
<td>&lt;0.05 NS</td>
<td>&lt;0.025 NS</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>71.5 ± 6.56</td>
<td>59.5 ± 0.76</td>
<td>1.05 ± 0.129</td>
<td>&lt;0.002 NS</td>
<td>&lt;0.001 NS</td>
<td>NS</td>
</tr>
<tr>
<td>FFA (nmol/mL)</td>
<td>1193 ± 84</td>
<td>1248 ± 96</td>
<td>1480 ± 77</td>
<td>&lt;0.05 NS</td>
<td>NS</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

* n = 16 for controls, n = 14 for HIV+, and n = 15 for AIDS, except for FFA, where n = 14 for HIV+ and n = 15 for AIDS.

Lipid Changes

Changes in Lipid Levels Associated With Antiretroviral Drugs

Effect on Triglyceride Level

- Substantially increase
- Marked increase
- Marked decrease
- Likely neutral

Effect on High-Density Lipoprotein Cholesterol Level

- Substantially increase
- Marked increase
- Marked decrease
- Likely neutral

Effect on Low-Density Lipoprotein Cholesterol Level

- Most PI- and NNRTI-based regimens
- Non-nucleoside-based INSTI, neutral
- Likely neutral

Note: Arrows indicate effect as follows: ||||, very large increase; ||, moderate increase; 1, mild increase; --, no change; J, mild decrease. NNRTI indicates non-nucleoside reverse transcriptase inhibitors.


Lipids: Treatment

Obtain fasting lipid profile, prior to starting antiretrovirals and within 3-6 months of starting new regimen

- Count number of CVD risk factors and determine level of risk. If ≥2 risk factors, perform a 10-year risk calculation

- Intervene for modifiable nontarget risk factors, including diet and smoking

- If above the lipid threshold based on risk group (see table 2) despite vigorous lifestyle interventions, consider altering antiretroviral therapy or lipid-lowering drugs

IF LIPID-LOWERING DRUGS ARE NECESSARY

- Serum LDL cholesterol above threshold, or triglycerides ≥500 mg/dL, with elevated non-HDL cholesterol: STATIN (pravastatin or simvastatin, see table 4)

- OR Serum triglycerides >500 mg/dL; FIBRATE (gemfibrozil or fenofibrate, see table 4)

Dietary Intervention


http://www.plosone.org/article/info:doi/10.1371/journal.pone.0038121

Figure 3. Forest plot for effect of various dietary interventions on triglyceride levels (mmol/l).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SD</td>
<td>Total</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Omega 3 intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malakootian et al. 2011</td>
<td>2.45</td>
<td>1.99</td>
<td>38</td>
<td>2.25</td>
</tr>
<tr>
<td>Flack 2006</td>
<td>0.87</td>
<td>12</td>
<td>2.89</td>
<td>1.32</td>
</tr>
<tr>
<td>Lister 2012</td>
<td>1.14</td>
<td>43</td>
<td>1.81</td>
<td>1.06</td>
</tr>
<tr>
<td>Sanchez 2009</td>
<td>-0.42</td>
<td>1.24</td>
<td>12</td>
<td>-0.62</td>
</tr>
<tr>
<td>Simard 2009</td>
<td>0.11</td>
<td>103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: TAU² = 0.67; CHI² = 6.97, df = 6 (P = 0.22); I² = 10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.23 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


http://www.plosone.org/article/info:doi/10.1371/journal.pone.0038121
Lipids: Treatment

- Pravastatin
- Atorvastatin
- Rosuvastatin
- Fenofibrate
- Gemfibrozil
- Omega-3-Fatty Acids
- Niacin
- Bile acid sequestrants

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### Table 4. Findings of selected prospective studies of lipid-lowering drugs in HIV-infected subjects.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study design</th>
<th>Lipid lowering drug</th>
<th>Lipid-lowering agents</th>
<th>Baseline lipid values, mg/dL</th>
<th>Main results</th>
</tr>
</thead>
</table>

*NOTE* - LDL-C = low-density lipoprotein cholesterol level; HDL-C = high-density lipoprotein cholesterol level; TC = total cholesterol level; TG = triglyceride level

* A = Active; ** = placebo.
Table 5. Considerations for antiretroviral drug effects on the metabolism of lipid-lowering drugs.

<table>
<thead>
<tr>
<th>Lipid-lowering drug, drug</th>
<th>Terminal</th>
<th>Nonterminal</th>
<th>Other PIa</th>
<th>Nevirapine</th>
<th>Efavirenz</th>
<th>Delavirdine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin:</td>
<td>Inhibition 1 AUC (concomitant)</td>
<td>Inhibition 1 AUC (concomitant)</td>
<td>Inhibition 1 AUC (concomitant)</td>
<td>Probably none</td>
<td>Unknown</td>
<td>Inhibition 1 AUC (concomitant)</td>
</tr>
<tr>
<td>Lovastatin:</td>
<td>Inhibition 1 AUC (concomitant)</td>
<td>Inhibition 1 AUC (concomitant)</td>
<td>Inhibition 1 AUC (concomitant)</td>
<td>Probably none</td>
<td>Unknown</td>
<td>Inhibition 1 AUC (concomitant)</td>
</tr>
<tr>
<td>Fluvastatin:</td>
<td>Inhibition 1 AUC (lute with caution)</td>
<td>Inhibition 1 AUC (lute with caution)</td>
<td>Inhibition 1 AUC (lute with caution)</td>
<td>Probably none</td>
<td>Probably none</td>
<td>Inhibition 1 AUC (lute with caution)</td>
</tr>
<tr>
<td>Fenofibrate:</td>
<td>Inhibition of metabolism, possible reduced effect</td>
<td>Inhibition of metabolism, possible reduced effect</td>
<td>Inhibition of metabolism, possible reduced effect</td>
<td>Probably none</td>
<td>Probably none</td>
<td>Inhibition 1 AUC (lute with caution)</td>
</tr>
<tr>
<td>Gemfibrozil:</td>
<td>Inhibition of metabolism, possible reduced effect</td>
<td>Inhibition of metabolism, possible reduced effect</td>
<td>Inhibition of metabolism, possible reduced effect</td>
<td>Probably none</td>
<td>Probably none</td>
<td>Inhibition 1 AUC (lute with caution)</td>
</tr>
</tbody>
</table>

NOTE: Adapted from [13], used with permission. AUC, area under the curve; PI, protease inhibitor.


Growth Hormone

- GH is lower in HIV+ patients with increased visceral adipose tissue (VAT)
- GH treatment
  - Decreases VAT
  - Lipids improve
  - Risk of DM and Malignancy
Growth Hormone


Tesamorelin

Falutz et al. JCEM. Sept 2010; 95(9): 4291-4304.

FIG. 2. Percent change from baseline in VAT and SAT at 26 (A) and 52 (B) weeks. Data are mean ± SEM. **, P < 0.001 vs. placebo; §, P < 0.001 vs. baseline and vs. T-T; †, P < 0.001 vs. baseline.
Insulin Resistance

From: Antiretroviral Therapy and the Prevalence and Incidence of Diabetes Mellitus in the Multicenter AIDS Cohort Study

Prevalence of Diabetes Mellitus Among 1278 Men at the Index Visit Between April and October 1999

Figure Legend:
Obesity

- Among 681 HIV+ patients newly started on cART
  - 44% overweight/obese at baseline
  - 64% overweight/obese 24 months after starting cART
- Increases were greater
  - Low CD4 at baseline
  - PI use


Diabetes Treatment
Diabetes Treatment Options

- **Metformin**
  - Lactic Acidosis
- **TZDs**
  - Fluid retention, bladder cancer, fracture risk
- **Sulfonylureas**
- **Incretin hormone-based treatment**
  - Saxagliptin – metabolized by CYP 3A4 system
- **Insulin**

Table 1. Summary of Treatment Strategies for Human Immunodeficiency Virus–Associated Cardiometabolic Abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lifestyle</th>
<th>Metformin</th>
<th>TZD</th>
<th>Lipid-Lowering Agents</th>
<th>GHRIH Analogue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid levels</td>
<td>May improve</td>
<td>No effect</td>
<td>May increase LDL-C level</td>
<td>Improve</td>
<td>Improve</td>
</tr>
<tr>
<td>Glucose homeostasis</td>
<td>Improve</td>
<td>Improve</td>
<td>Improve</td>
<td>No effect</td>
<td>Minimal effect*</td>
</tr>
<tr>
<td>Central obesity</td>
<td>Improve</td>
<td>May improve</td>
<td>No effect</td>
<td>No effect</td>
<td>Improve</td>
</tr>
<tr>
<td>Peripheral lipodystrophy</td>
<td>No effect</td>
<td>May Worsen</td>
<td>May Improve</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Safety</td>
<td>Excellent</td>
<td>Good</td>
<td>Fair</td>
<td>Good</td>
<td>Good</td>
</tr>
</tbody>
</table>

* GHRIH analogue therapy may modestly increase hemoglobin A1C levels over 6 months of treatment but shows no effect over 12 months.

Diabetes Treatment

Figure 1: Effects of insulin sensitizing drugs versus placebo or no treatment on fasting insulin and glucose levels in patients with HIV-associated lipodystrophy syndrome.

Figure 2: Effects of insulin sensitizing drugs versus placebo or no treatment on fasting lipid levels in patients with HIV-associated lipodystrophy syndrome.

Diabetes Treatment

Figure 3: Effects of insulin sensitizing drugs versus placebo or no treatment on body weight and morphology in patients with HIV-associated lipodystrophy syndrome.


Figure 4: Effects of rosiglitazone versus metformin on insulin sensitivity, lipid profile, and morphology in patients with HIV-associated lipodystrophy syndrome.

**Metformin**

*Fig. 2. Change in calcium score for participants randomized to metformin and/or lifestyle modification over 12 months.*


**Sitagliptin**

Goodwin et al. JCEM. Dec 2012. Epub.
Diabetes Treatment: HIV+ vs. HIV-

Table 2. Adjusted changes in hemoglobin A1c values compared with baseline by HIV infection status and duration of therapy.

<table>
<thead>
<tr>
<th>Duration of therapy (postbaseline)</th>
<th>Change from baseline, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 months</td>
<td>-1.11 (-0.36 to -1.20)</td>
</tr>
<tr>
<td>4-6 months</td>
<td>-1.23 (-1.05 to -1.41)</td>
</tr>
<tr>
<td>7-9 months</td>
<td>-1.15 (-1.08 to -1.22)</td>
</tr>
<tr>
<td>10-12 months</td>
<td>-1.04 (-0.97 to -1.22)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HbA1c, hemoglobin A1c.

*Absolute reduction in HbA1c (%).

†Of absolute reduction in HbA1c (%), with reference group patients without HIV infection.

Cortisol Excess

• Iatrogenic
  • Ritonavir

Adrenal Insufficiency

• Iatrogenic
• HIV
• Fungal
• Viral
Hypogonadism

Endocrine Society Clinical Practice Guidelines

- Recommend testosterone replacement in HIV+ patients with low T and weight loss
- 20-25% HIV+ on cART have low Testosterone
  - Associated with weight loss, progression to AIDS, wasting, depression, loss of muscle mass and exercise capacity

Erectile Dysfunction

- PDE-5 inhibitor concentrations
  - Significantly increased with some Protease inhibitors:
    - Ritonavir, Atazanavir, Darunavir
  - Decreased with some NNRTIs
    - Etravirine

Osteoporosis
Prevalence of Osteoporosis in HIV-infected Patients vs HIV-uninfected Controls: A Meta-analysis

Overall prevalence of osteoporosis in HIV-infected patients 15%

Fractures in HIV+ Persons

- Fractures per 100 persons:
  - 2.87 HIV+ vs. 1.77 HIV-
Prevention

- Calcium and Vitamin D
- Resistance Exercise
- Lifestyle changes
- Identification of Other Disease Processes
  - Hypogonadism
  - Thyroid Disease
  - Cortisol Excess
- Other Medications

Prevalence of Vitamin D Deficiency in 87 Subjects Initiating ART in Cleveland

<table>
<thead>
<tr>
<th>Vitamin D Level</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 32 ng/mL</td>
<td>84%</td>
</tr>
<tr>
<td>≤ 20 ng/mL</td>
<td>56%</td>
</tr>
<tr>
<td>≤ 15 ng/mL</td>
<td>33%</td>
</tr>
</tbody>
</table>


Slide Courtesy of Todd Brown
Vitamin D Metabolism

- Alteration of 25-hydroxylation
  - PIs inhibit CYP450 enzymes
  - NNRTIs induce CYP450 enzymes
- Alteration of 1-alpha hydroxylation
  - Direct PI effect
- Shunting of 1,25 (OH)2 Vitamin D to T-lymphocyte production

Change in 25OHD with ART-initiation: EFV vs non-EFV

Adjusted* Mean Difference(SEM): 
-5.1 ± 1.5 ng/mL, p=0.001

*Adjusted for baseline 25(OH)D, race, season


Slide Courtesy of Todd Brown
Vitamin D Recommendations

Osteoporosis Treatments

- Bisphosphonates
  - Alendronate
  - Ibandronate
  - Risedronate
  - Zoledronate
- SERMs/Estrogen
- Teriparatide
- Denosumab
Osteoporosis Treatment in HIV+ Persons: Alendronate


Conclusions

• Metabolic changes in HIV+ persons are multifactorial: virus, medications, lifestyle
• Diagnosis of endocrine diseases is similar to the HIV- population but the diseases differ in prevalence
• Treatment of endocrine diseases are similar to treatment recommendations for HIV- persons but may have different effects and possible drug-drug interactions must be considered

Thank you!

Questions?