Metabolic Complications of HIV (and Antiretroviral Therapy)

October 25, 2012

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Disclosure Information

Research Support: Pfizer to Weill Cornell Medical College (pneumococcal vaccine clinical trial)

Consultant: Gilead Sciences; Pfizer; SIGA Technologies
Overview

• “Lipodystrophy”
• Diabetes mellitus
• Bone disease
Terminology

- Lipodystrophy
- Fat redistribution

- Lipoatrophy = loss of subcutaneous fat
  – Diffuse but most prominent in face, extremities, buttocks
- Lipohypertrophy = gain of fat (visceral abdominal tissue, other)

Switching from d4T or ZDV to ABC or TDF Improved Limb Fat in RAVE Study

Change in Limb fat (g)

Abacavir (n=53)
Tenofovir (n=52)

p = 0.37

Baseline ~3 kg limb fat

Moyle et al, AIDS 2006;20:2043-50

Abdominal MRI Scans

Control subject
Increased VAT

Courtesy of Ellen Engelson, Donald Kotler
I have patients in my practice/clinical setting who have abdominal fat accumulation that seems to be pathologic.

1. Yes
2. No

Case

- 58 y.o. former competitive body builder dx with HIV in 1990 (nadir CD4 ~100)
- Initiated AZT monox in 1990 and multiple regimens since then including d4T, every available PI
- Currently on TDF/FTC/ATV/r
- HIV RNA < 20; CD4 345
- On pioglitazone for diabetes (HgA1c = 6.4)
Intervention to reduce visceral adiposity in this patient is appropriate

1. Yes
2. No
3. Not sure
Rationale for Treatment of Visceral Obesity

- Reduce cardiovascular risk
  - Direct, indirect effects
  - General population: effects of liposuction\(^1\) and omentectomy\(^2\) on metabolic parameters
- Reduce risk of diabetes mellitus
- Improve quality of life
  - Maximize adherence to antiretrovirals
- ? Reduce risk of hepatic fibrosis (NASH)
- ? Improve bone mineral density


FRAM: Low Limb Muscle Mass and Central Adiposity Associated with 5 Year Mortality

\[
\begin{array}{ccc}
\text{Lower Odds of Death} & \text{Higher Odds of Death} & \text{Odds Ratio (95\% CI)} \\
\hline
\text{Arm SM:} & & \\
Tertile 1 & & \\
Tertile 2 & & \\
Tertile 3 & & \\
\text{LegSM:} & & \\
Tertile 1 & & \\
Tertile 2 & & \\
Tertile 3 & & \\
\text{VAT:} & & \\
Tertile 1 & & \\
Tertile 2 & & \\
Tertile 3 & & \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>reference</td>
<td>0.59 (0.35, 0.99)</td>
<td>0.51 (0.25, 1.04)</td>
</tr>
<tr>
<td>reference</td>
<td>0.92 (0.54, 1.57)</td>
<td>0.42 (0.21, 0.84)</td>
</tr>
<tr>
<td>reference</td>
<td>1.77 (1.03, 3.03)</td>
<td>2.12 (1.13, 3.98)</td>
</tr>
</tbody>
</table>

ACTG 5224s: Visceral Fat Change by Regimen in A5202

CT Results: Mean percent change in VAT (ITT, Week 96)

- ATV/r led to greater gains in weight (1.1kg more), trunk fat and a trend to greater gain in VAT than EFV. No differences between NRTIs


Nocturnal Pulse Secretion of GH is Reduced in HIV Lipodystrophy

~40% of men with LD have reduced peak GH response to GHRH-arginine (18% deficient using stringent criterion)

1Reitschel et al. JCEM, 2001;86:504-10. 2Koutkia et al JCEM, 2005;90:32-8
The approach that is likely to lead to the greatest reduction in visceral fat is....

**On: TDF/FTC/ATV/r**

1. Diet and exercise
2. Changing ATV/r to raltegravir
3. Starting tesamorelin
4. Adding metformin
5. Referring for liposuction
6. None of the above

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### Lifestyle Interventions

- Mostly small studies of exercise interventions
- RCT of supervised home-based aerobic & progressive resistance training x 16 w in 40 women with WHR ≥ 0.85 & fat redistribution\(^1\)
  - WC ↓ 1.0 cm but NS change in VAT, lipids
- Single arm study of individualized light aerobic training x 4 m in 17 “lipodystrophic” pts (15 w/ lipohypertrophy)\(^2\)
  - VAT ↓ 12%, TC 23%, TG 43%, HDL ↑ 6%
- RCT of intensive lifestyle intervention (weekly sessions w/dietician) x 6 m in 34 pts w/ metabolic syndrome\(^3\)
  - WC ↓ 2.6 cm but NS change in lipids, HOMA-IR

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37 women with abdominal obesity (16 on ATV) randomized to immediate or delayed (wk 24) switch to RAL

Lake JE et al, AIDS Patient Care STDs. 2012 Jul 23. [Epub ahead of print]

Metformin 500 mg bid Decreases Abdominal Fat But Non-Selectively

- Elevated WHR, fat gain/loss in at least 1 area, IGT &/or insulin > 15 μIU/ml

10/21/2012

### Phase III Trial of Tesamorelin

- N = 404 randomized 2:1 to tesamorelin x 26 w then re-randomized (T to T or P x 26 w; P to T x 26 w)

Falutz J et al, JAIDS 2010;53:311-22

### Metabolic & Adverse Effects of Tesamorelin

- IGF-1 ↑ 86%
- Trends for modest ↓ TG, TC:HDL
  - Original phase III trial\(^1\): significant ↓ TG, TC, TC:HDL
- Minimal adverse effects on glucose (8% FBG ≥ 125 at baseline)
- Injection site erythema (14%), pruritus (10%), hypersensitivity skin reaction (3%)
- 49% with IgG to tesamorelin at week 26
  - NS difference in IGF-1 or VAT by presence of Ab

\(^1\) Falutz J et al, JAIDS 2010;53:311-22
Limitations of Current Approaches

- Challenge to selectively reduce visceral fat without worsening lipoatrophy that may co-exist
- Safety profile, especially with prolonged use; cost
- Reaccumulation of fat with cessation of interventions (rhGH, tesamorelin)
  - Intermittent therapy? Induction-maintenance?
- What is the minimal amount of reduction for clinical benefit?

Overview

- “Lipodystrophy”
- Diabetes mellitus
- Bone disease
Adjusting for age & sex, the incidence of diabetes mellitus is increased in HIV-infected patients relative to the general population

1. True
2. False
3. Don’t know

Epidemiology of DM in HIV-Infected Patients

• Prevalence varies by population
  • Genetics, obesity, HCV, type of ART, ascertainment
  • Definition of DM varies by cohort study
• Evidence that it varies by HIV status is conflicting

Multiple Factors May Contribute to Diabetes in HIV

- Lipoatrophy/Visceral Fat Accumulation
- Genetic Factors
- Protease inhibitors/NRTIs
- Liver disease (HCV, steatosis)
- Insulin Resistance
- β-cell Dysfunction
- HIV?
- Age
- Cytokines
- Lower testosterone?
- Obesity
- Meds/Opiates
- Free fatty acids

In the general population, a hemoglobin A1c value of 7.0% is consistent with an average plasma glucose of 172. In HIV patients….

1. It should also be ~172
2. It is likely < 172
3. It is likely > 172
4. I don’t know
Is HbA1c Accurate in HIV-Infected Patients?

• Non-enzymatic glycation of hemoglobin occurs continuously in proportion to ambient glucose concentration over ~120 day lifespan of the rbc
  – ↓rbc lifespan = less opportunity for glycation

• Case series and cross-sectional study suggest A1c underestimates glycemic control, possibly due to hemolysis\(^1,2\)


NIH Study

• Prospective study: relationship between HbA1c and fasting and non-fasting glucose values
  – 100 HIV-infected adults with DM or impaired fasting glucose and 200 HIV-uninfected controls matched on sex, race, and age

• A1c underestimated mean glucose (calculated from 1 fasting and 1 non-fasting sample) in HIV-infected subjects by 29 mg/dL
  – Discordance associated in multivariate analysis with MCV and NRTI use, specifically abacavir.
  – Haptoglobin not independently associated with glucose-A1C discordance

HbA1c in WIHS

• Repeated measures of paired fasting glucose and HbA1c values in 315 HIV-infected and 109 HIV-uninfected participants with DM in the WIHS
• For the same fasting glucose concentration, an HIV-infected woman had on average 0.987 times as much Hb A1c (that is, 1.32% lower; 95% CI 0.97-0.99) as an HIV-uninfected woman
  – E.g. HIV+ woman with HbA1c of 8.00% would be equivalent to an HIV-uninfected woman with HbA1c of 8.11%

Glesby MJ et al, Antivir Ther 2010;15:571-7

ADA Goals in HIV+ Pts in Chicago

ADA Goals in HIV+ Pts in Chicago


- Documented foot exam 18%
- Urinalysis 60%
- ASA 44%
- Statin 45%
- ACE-I/ARB 62%

% Meeting ADA Goals

- Adherence rates to ADA guidelines: 47% for retinopathy screening and 19% for nephropathy screening

Overview

- “Lipodystrophy”
- Diabetes mellitus
- Bone disease

Bone Remodeling

1. Continuous renewal of bone to maintain biomechanical properties
2. Maintain mineral (calcium) homeostasis

Formation and resorption are normally coupled

Osteoporosis: Resorption > Formation
Case

- A 52 year-old white man with well controlled HIV infection presents for routine care
- His CD4 count is 920 cells/mm$^3$ and viral load < 50 copies/ml on TDF/FTC/EFV x 4 years
  - Nadir CD4 = 180 cells/mm$^3$
- He is 5 feet tall and weights 110 lbs (50 Kg; BMI = 21.6 kg/m$^2$)
- He smokes ½ pack per day of cigarettes and does not exercise regularly

Assuming there are no reimbursement issues, would you screen this patient for osteoporosis with a DEXA scan?

1. Yes
2. No
3. Maybe/Not sure

- 33%
- 33%
- 33%
Meta-analysis: Prevalence of Osteoporosis in HIV-infected Patients vs. Uninfected Controls

Overall prevalence of osteoporosis in HIV-infected patients = 15%

Overall (95% CI) 3.68 (2.31, 5.84)


T- and Z-Scores

T-score: number of standard deviations above or below the mean BMD of normal young adults (~age 30)

Z-score: number of standard deviations above or below the mean BMD of adults of same age
WHO Diagnostic Criteria (Post-Menopausal Women)

<table>
<thead>
<tr>
<th>T-Score</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-1 and above</td>
</tr>
<tr>
<td>Low bone mass (osteopenia)</td>
<td>-1 to -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>&lt; -2.5</td>
</tr>
</tbody>
</table>

- Can also base dx on history of fragility fracture
- Men < age 50 and pre-menopausal women:
  
  Z-score < -2.0 = “below the expected range for age”

![Diagram showing various factors affecting bone health]
Increased Prevalence of Fracture in HIV+

HIV+ women: higher prevalence of vertebral & wrist; HIV+ men: vertebral, wrist, & hip

Higher prevalence among HIV+ black & white women; HIV+ white men

n = 8,525 HIV+, n = 2,208,792 HIV- at BWH & MGH 1996-2008

Triant VA et al, J Clin Endocrin Metab 2008;93:3499-3505

BMD Decreases ~2-6% in Short Term with Diverse Regimens

BMD is Stable Over Time in HIV+ Women

![Graph showing BMD stability over time](image)

Dolan SE. J Clin Endocrinol Metab 2006;91:2938-45

IDSA/HIVMA Primary Care Guidelines

- Obtain baseline bone densitometry in postmenopausal women ≥ 65 and younger postmenopausal women with ≥ 1 risk factor for bone loss
- Routine screening not recommended for those without other risk factors but should be considered for those ≥ 50 especially if they have ≥ 1 risk factor for premature bone loss

Other Guidelines

- National Osteoporosis Foundation
  - Men ≥ 70, women ≥ 65 or either ≥ 50 if risk factors

- EACS
  - Consider DXA in:
    - Postmenopausal women
    - Men ≥ 50 years
    - History of low impact fracture or high risk for falls
    - Clinical hypogonadism
    - Oral glucocorticoid use (minimum 5 mg prednisone equivalent for > 3 months)

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Expert Opinion

- Consider HIV as a risk factor….
- Therefore check baseline DXA on postmenopausal women and men > 50

Bone Disease in HIV Infection: A Practical Review and Recommendations for HIV Care Providers
Grace A. McConnell,† Pablo Tabas,† Elizabeth Shase,‡ Michael T. Yin,† E. Turner Grulton,§ Jeannie S. Huang,∥ Grace M. Aldrovandi,∥ Sandra W. Cardenas,∥ Jorge L. Santana,∥ and Todd T. Brown

Bone Loss in the HIV-Infected Patient: Evidence, Clinical Implications, and Treatment Strategies
Vanessa Walker Harris and Todd T. Brown
J Infect Dis. 2012;205S391-8
Evaluation for Secondary Causes of Osteoporosis

<table>
<thead>
<tr>
<th></th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>25-OH vitamin D</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Men: Free testosterone.</td>
</tr>
<tr>
<td></td>
<td>Women: menstrual hx, estradiol, FSH, prolactin</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Serum calcium, phosphate, albumin, Cr, iPTH</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>TSH; free T4</td>
</tr>
<tr>
<td>Idiopathic hypercalciuria</td>
<td>24 hr urine calcium</td>
</tr>
<tr>
<td>Phosphate wasting</td>
<td>Fractional excretion of phosphate</td>
</tr>
<tr>
<td>Celiac sprue</td>
<td>Anti-tissue transglutaminase (IgG, IgA)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>CBC, SPEP</td>
</tr>
<tr>
<td>Mastocytosis</td>
<td>Serum tryptase</td>
</tr>
</tbody>
</table>

Adapted from: Walker Harris V, Brown TT. J Infect Dis. 2012;205S391-8

Who to Treat for Osteoporosis?

**NOF Guidelines**

- Hip or vertebral fracture
- T-score ≤ -2.5 at femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) AND a 10-year probability of a hip fracture ≥ 3% OR a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm (FRAX®)
- Clinician’s judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels

U.S. data suggest it’s cost-effective to treat if 10 yr probability of hip fx is > 3% or more or major osteoporotic fx is > 20%

Tosteson ANA et al. Osteoporos Int 2008;19:437-47

Not validated in HIV-infected patients

Treatment of Osteoporosis: General Measures

- IOM: Elemental calcium 1000 mg/d for men/women age 31-50, 1000 mg/d for men age 51-70, 1200 mg/d for women age 51-70
  - Dietary sources optimal; concerns about CV events with supplementation
- Weight bearing & muscle strengthening exercise x 30 mins, at least 3 d/week
- Smoking cessation; limit alcohol; reduce fall risk
- Vitamin D supplementation

Treatment of Osteoporosis: Medical Therapy

- Bisphosphonates: Alendronate 70 mg weekly and zoledronate 4 mg yearly appear safe/efficacious in short-term studies of HIV+ pts
  - Consider stopping temporarily or permanently after 5 years
- Other: raloxifene, estrogen, teriparatide—no data in HIV
- Denosumab (monoclonal Ab against RANKL)
  - May decrease monocyte & dendritic cell function


Do you routinely check vitamin D levels on your HIV-infected patients?

1. Yes
2. No
3. Only pts that I think are at high risk of being deficient
### Pleiotropic Effects of Vitamin D

<table>
<thead>
<tr>
<th>Organ system/Disease</th>
<th>Consequences of Low Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone/Skeleton</td>
<td>Low bone mineral density&lt;br&gt;Poor bone remodeling&lt;br&gt;Rickets/osteomalacia/osteoporosis&lt;br&gt;Fragility fractures, mortality</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Muscle weakness&lt;br&gt;Falls, fractures, mortality</td>
</tr>
<tr>
<td>Brain</td>
<td>Depression&lt;br&gt;Progression of Alzheimer’s</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Beta cell dysfunction&lt;br&gt;Insulin resistance, diabetes</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Atherosclerosis, CV events</td>
</tr>
<tr>
<td>Renal</td>
<td>Poor calcium resorption; hypertension</td>
</tr>
<tr>
<td>Malignancy</td>
<td>↑ risk of prostate, colon, breast ca</td>
</tr>
<tr>
<td>Immune system</td>
<td>Poor antigen presentation, dysregulated innate immunity &amp; T-cell proliferation/function</td>
</tr>
</tbody>
</table>

Adapted from: Overton ET, Yin MT, Curr Infect Dis Rep 2011;13:83-93

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**UV light on skin** → Vit D₃ (cholecalciferol) → **Liver** → 25(OH)D₃ (calcidiol) → **Kidneys** → 1,25(OH)₂D₃ (calcitriol) → **Target tissues**

- **Diet supplementation** → Vit D₂ (ergocalciferol) → **Liver** → 25(OH)D₃ (calcidiol) → **Kidneys** → 1,25(OH)₂D₃ (calcitriol) → **Target tissues**

**Efavirenz** → Induction of 24 hydroxylase

**Tenofovir** → Inhibition of 1-alpha hydroxylase

**Pis** → Inhibition of 25 hydroxylase

**Calictroic acid** (Inactive metabolite)

Overton ET, Yin MT, Curr Infect Dis Rep 2011;13:83-93
Screening for Vitamin D

- Institute of Medicine: no routine screening
- Endocrine Society
  - Recommend screening for vitamin D deficiency only in individuals at risk for deficiency (including receipt of “AIDS medications”)
- EACS
  - Check vitamin D status in patients with history of: low BMD and/or fracture, high risk for fracture, chronic kidney disease
  - Consider assessment of vitamin D status in patients with other factors associated with lower vitamin D levels (Dark skin, dietary deficiency, avoidance of sun exposure, malabsorption, obesity, chronic kidney disease, some antiretrovirals (i.e. efavirenz)

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Vitamin D Supplementation

<table>
<thead>
<tr>
<th>Vitamin D Level</th>
<th>Supplementation Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30 ng/ml</td>
<td>1000 IU/day vitamin D₃</td>
</tr>
<tr>
<td>21-29 ng/ml (insufficiency)</td>
<td>2000 IU/day vitamin D₃</td>
</tr>
<tr>
<td>15-19 ng/ml (deficiency)</td>
<td>Ergocalciferol 50,000 IU/week x 8 weeks or 6000 IU/day vitamin D₃ * Then maintenance 2000 IU/day vit D₃</td>
</tr>
<tr>
<td>&lt; 15 ng/ml (severe deficiency)</td>
<td>Ergocalciferol 50,000 IU 1-2x/week x 8-12 weeks or 6000 IU/day vitamin D₃ * Then maintenance 2000 IU/day vitamin D₃</td>
</tr>
</tbody>
</table>

*Recheck 25(OH)D after ergocalciferol with goal > 30 ng/ml.

<table>
<thead>
<tr>
<th>Summary</th>
</tr>
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<tbody>
<tr>
<td>• Lipohypertrophy is of clinical significance with limited options for intervention</td>
</tr>
<tr>
<td>• The risk of diabetes mellitus in HIV-infected patients may or may not be increased relative to the general population</td>
</tr>
<tr>
<td>– Hemoglobin A1c may not be as accurate</td>
</tr>
<tr>
<td>• HIV-infected pts are at increased risk of decreased bone mineral density</td>
</tr>
<tr>
<td>– Screening post-menopausal women &amp; men &gt; 50 yrs old is reasonable</td>
</tr>
<tr>
<td>– Role of screening for vitamin D deficiency is less clear</td>
</tr>
</tbody>
</table>