HIV and Metabolic Cases

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Disclosures

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Bones
Case: Ms. AG

- 58 year old Black female
- History of treated pulmonary TB
- Social History
  - Smokes cigarettes 1ppd
  - Drinks: 2-3 beers “most days”
    - Sometimes also wine on weekends
  - Exercise: none
  - Stable home environment
Case; Ms AG

• FH:
  – “All the women are hunched over”
  – “All the men die of heart attacks before age 60”

• PE: unremarkable
  – BMI = 21 kg/m²
Case: Ms AG

- Labs
  - CD4 = 333 cell/mm³
  - VL: 195,000 cells/mL
  - Hep B negative
  - TC: 288 mg/dL
    - LDL: 220, HDL 31, TG 183

- She is ready and able to start HAART
Audience: Particularly worried about her bones, you recommend:

1. TDF/FTC/EFV
2. TDF/FTC + RAL
3. TDF/FTC + LPV/r
4. TDF/FTC + ATV/r
5. ABC/3TC + EFV
6. Something else
Fragility Fractures in Women and Men over 50 years

Wasnich RD, Osteoporos Int 1997;7 Suppl 3:68-72 Images from the National Osteoporosis Foundation
Prevalence of Osteoporosis in HIV-infected Patients vs HIV-uninfected Controls: A Meta-analysis

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiel (2004)</td>
<td>5.03 (1.47, 17.27)</td>
</tr>
<tr>
<td>Brown (2004)</td>
<td>4.26 (0.22, 82.64)</td>
</tr>
<tr>
<td>Bruera (2003)</td>
<td>4.51 (0.26, 79.27)</td>
</tr>
<tr>
<td>Dolan (2004)</td>
<td>2.11 (0.54, 8.28)</td>
</tr>
<tr>
<td>Huang (2002)</td>
<td>3.52 (0.15, 81.92)</td>
</tr>
<tr>
<td>Knobel (2001)</td>
<td>5.13 (1.80, 14.60)</td>
</tr>
<tr>
<td>Loiseau-Peres (2002)</td>
<td>4.28 (0.46, 39.81)</td>
</tr>
<tr>
<td>Madeddu (2004)</td>
<td>29.84 (1.80, 494.92)</td>
</tr>
<tr>
<td>Tebas (2000)</td>
<td>3.40 (0.19, 61.67)</td>
</tr>
<tr>
<td>Teichman (2003)</td>
<td>17.41 (0.97, 313.73)</td>
</tr>
<tr>
<td>Yin (2005)</td>
<td>2.37 (1.09, 5.16)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>3.68 (2.31, 5.84)</td>
</tr>
</tbody>
</table>
BMD Decreases With Age

Relative influence on peak bone mass (men):
40% to 83% genetic; 27% to 60% environmental

0.5% to 1.0% reduction in bone volume/year

Osteoporosis in HIV-Positive Patients

- Osteoporosis and fractures are common in HIV-positive patients and will increase with aging

- **Risk factors** include
  - Pre-ART HIV disease severity ↓ CD4, ↑ HIV-1 RNA
  - ART (TDF, certain PIs, any ART initiation)
  - Traditional: smoking, alcohol, HCV, low T, low weight

- **Screening**: dual-energy x-ray absorptiometry should be considered in all HIV-positive postmenopausal women and in men aged older than 50 yrs (US)

Specific ARV

- TDF > other NRTIs
- PI vs other 3rd drug: data mixed/limited
  - vs EFV: Effect seen at spine, but not hip (A5224s)
- Recent trial A5257 compared ATV vd DRV vs RAL with TDF/FTC backbone
  - RAL better than PIs
ACTG 5257 (sub-study 5260s): BMD through week 96

Case: Ms AG

- You start her on TDF/FTC+EFV
- She gets enrolled into a study where they are measuring Vitamin D
- Vitamin D is 20 ng/mL
Audience: What should you consider next?

- A) continue her ART
- B) initiate Vitamin D at 400 IU/daily
- C) initiate Vitamin D at 50,000 IU/daily
- D) initiate Vitamin D 2000 IU+ Calcium supplement
EFV associated with decrease in Vitamin D: A5175

Havers PLOS One 2014
Calcium and Vitamin D: ACTG 5280

• Randomized, double-blind trial
  – patients initiating TDF/FTC/EFV
  – baseline vitamin D 10-75 ng/mL

• Intervention:
  – Vitamin D3 4000 IU/day
  – Calcium carbonate 1000 IU/day

Overton ET, et al. CROI 2014. Abstract 133
High Dose Vitamin D and Calcium Attenuates Bone Loss with Initiation of TDF/FTC/EFV

Overton, CROI, 2014

The lower and upper edges of the box indicate the first and third quartiles (the 25th and 75th percentiles); The line inside the box indicates the median value.
Bones Summary

• Good health maintenance:
  – Calcium
  – Vitamin D supplement (600-1200 IU)
  – Stop cigarettes
  – Decrease alcohol (≤ 2/day)
  – Weight bearing exercise

• Consider DXA scan

• Think about ARV selection
4: Lipids + CVD
Case: Mr. JW

- 54 yo Black male
- PMH:
  - CAD
    - 1 drug eluting stent (2012)
  - HTN
  - Hyperlipidemia
  - (No DM)
Case: Mr JW

• SH:
  – Former 1.5 ppd smoker (quit 2012)
  – 1 glass red wine, 4 times a week
  – No drugs
  – Exercises “occasionally”

• FH: CAD
Case: Mr JW

- PE: unremarkable
- Meds (all once daily)
  - Aspirin 81 mg
  - Lisinopril 40 mg
  - Atorvastatin 80 mg
  - Metoprolol XL 100 mg
  - herbal supplement
Case: Mr JW

• He is found to be HIV positive
• Labs
  – CD4 = 522 cell/mm³
  – VL: 88,000 cells/mL
  – Hep A+ B nonimmune
Audience: Given his CVD, you recommend

1. TDF/FTC/EFV
2. DRV/r + RAL
3. DRV/r + TDF/FTC
4. ABC/3TC + ATV/r
5. ABC/3TC + DTG
6. None: He doesn’t need to start HAART
ART effect on Lipids

Lake Lancet ID 2013

Change in Fasting lipid concentrations (mmol/L)

- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides
- Total cholesterol: HDL cholesterol
(1) ACTG 5257: ATV/r, RAL, DRV/r with TDF/FTC

Stratified by HIV-1 RNA < or ≥ 100,000 c/mL, participation in metabolic substudy, CV risk

Wk 96 after last patient enrolled

- ART-naive patients with HIV-1 RNA ≥ 1000 c/mL (N = 1809)
- AT/TV 300/100 mg QD + TDF/FTC (n = 605)
- RAL 400 mg BID + TDF/FTC (n = 603)
- DRV/RTV 800/100 mg QD + TDF/FTC (n = 601)

- Primary endpoints
  - 
  - Virologic failure: time to HIV-1 RNA > 1000 c/mL (at Wk 16 or before Wk 24) or > 200 c/mL (at or after Wk 24)
  - Tolerability failure: time to discontinuation of randomized component for toxicity
  - Composite endpoint: the earlier occurrence of either VF or TF in a given participant
  - Switch of regimens allowed for tolerability

ACTG 5257: Lipids at week 96

• DRV/r or ATV/r PI-containing regimens (vs. RAL)
  – significantly greater ➪
    • TC
    • LDL-C
    • TGs
  – Lipids remained stable or ➩ in RAL arm
  – Lipids changes in boosted PI arms similar

ACTG 5257: Carotid Intima-Media Thickening (IMT)

Stein J et al, J Am Coll Cardiol. 2014;63(12_S):. Abstract A1322
What did we learn about lipids?

• It's not straightforward.
• RAL better than PIs (provided: +TDF/FTC)
  – TC, LDL, TG
• Carotid IMT seems to worsen in all ARV
  – Didn’t necessarily follow lipids.
• With PIs, TDF/FTC is better than RAL
  – TC, LDL
    • But worse HDL, no difference in ratio.
What did we learn about lipids? (STRATEGY trials)

• EVG compared to PIs
  – Better for TG
• EVG compared to EFV
  – Better for LDL
  – Worse for HDL

Pozniak CROI 2014; Arribas CROI 2014
Bottom line

• TDF is better for lipids than other nRTIs
• With TDF: Integrase inhibitors seem better
• NNRTI: neutral overall (increase LDL, TG, HDL eith EFV but not total:HDL ratio)
• PIs
  – Use clinical judgment about entire patient
    • between ATV and DRV
Case: Mr JW

- He did not tolerate EFV and was switched to LPV/r+TDF/FTC
- 1 year later his LDL increased to 190mg/dL and his TG was 240
What would you do next?

- a) switch his LPV/r to ATV/r
- b) start simvastatin
- c) start atorvastatin
- d) both a and c
- c) not sure
## Guidance based on ATP III

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Goal LDL</th>
<th>Initiate Lifestyle Modification (LDL mg/dL)</th>
<th>Initiate Drug Therapy (LDL mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: Known CAD or CAD equivalent</td>
<td>&lt;100 or &lt;70</td>
<td>Any LDL</td>
<td>&gt;100 consider &gt;70</td>
</tr>
<tr>
<td>Moderately high risk: 2+ risk factors (10-20% 10 yr risk*)</td>
<td>&lt;130 or &lt;100</td>
<td>Any LDL</td>
<td>&gt;=130 consider &gt;100</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors (10yr risk &lt; 10%*)</td>
<td>&lt;130</td>
<td>&gt;=130</td>
<td>&gt;=160</td>
</tr>
<tr>
<td>Lower risk: 0-1 risk factor(s)</td>
<td>&lt;160</td>
<td>&gt;=160</td>
<td>&gt;=190</td>
</tr>
</tbody>
</table>
## Statins and ART

<table>
<thead>
<tr>
<th>Statin type</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>start 20mg (max 80mg)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>start 10mg (max 80mg; but most on ART max 40mg)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>start 5mg (max 40mg)</td>
</tr>
<tr>
<td>Lovastatin and Simvistatin</td>
<td>AVOID</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fibric acids for high TG &gt;500</th>
<th>gemfibroxil 600mg BID or fenofibrate 48-145mg qd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin</td>
<td>an option but can worsen insulin resistance</td>
</tr>
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</table>
Concomitant use of 2 to 3 lipid-modifying agents with HAART commonly seen

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary option</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated LDL-C or non-HDL-C, and triglycerides 200-500 mg/dL</td>
<td>• Atorvastatin</td>
<td>• Fluvastatin</td>
</tr>
<tr>
<td></td>
<td>• Pravastatin</td>
<td>• Fibrates</td>
</tr>
<tr>
<td></td>
<td>• (Rosuvastatin)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides &gt; 500 mg/dL</td>
<td>• Fibrates</td>
<td>• Niacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prescription</td>
</tr>
<tr>
<td></td>
<td></td>
<td>omega-3 fish oils</td>
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</table>

CV Summary

- Standard risk factors still dominate
  - Stop Smoking
  - Control HTN
  - Watch for and control DM
  - Exercise
  - TREAT Lipids

- Consider ARVs that may be better
  - TDF seems to lower lipids
  - INSTIs seem to have better lipid profiles
CV Summary

• Add Aspirin when appropriate
• Proper diet
• Exercise
• (Enjoy a drink)
• Mr JW now complains of polydipsia, polyphagia and fatigue for the past 2 months
What should you do next?

- a) send a HgBA1c
- b) send a fasting sugar
- c) have him do a oral glucose tolerance test
- d) send a random blood sugar
Multiple Factors May Contribute to Diabetes in HIV

- Lipoatrophy/visceral fat accumulation
- Genetic factors
- PIs/NRTIs
- Liver disease (HCV, steatosis)
- Age
- Cytokines
- Meds/opiates
- Free fatty acids
- Low testosterone?
- Obesity

Insulin resistance β-cell dysfunction
ADA Definitions of Diabetes: 2013

1. HbA1c ≥ 6.5%* or
2. Fasting plasma glucose ≥ 126 mg/dL* or
3. Plasma glucose ≥ 200 mg/dL when measured 2 hrs after 75-g oral glucose tolerance test * or
4. Random plasma glucose ≥ 200 mg/dL with polyuria and polydipsia

*Should be confirmed on repeat testing.

DA Guidelines 2013.
HbA1c Underestimates Glycemia in HIV-Infected Persons

- Prospective cross-sectional study of 100 HIV-infected adults with type 2 diabetes (77%) or fasting hyperglycemia (23%)

Diabetes Screening

• How?
  – Fasting glucose
  – If 100-125 mg/dL, consider 75-g OGTT

• When?
  HIVMA/IDSA:
  – Fasting glucose every 6-12 mos in all patients
  – Consider testing 1-3 mos after starting or modifying ART

Healthy eating, weight control, increased physical activity

Step 1: Monotherapy

Step 2: Dual therapy

Step 3: Combination therapy

Step 4: Complex insulin strategies

Metformin

- Sulfonylurea
  - Thiazolidinediones
    - DPP-4 inhibitors
      - GLP-1 receptor agonist
        - Insulin (usually basal)

- TZD
  - SU
    - DPP-4-i
      - GLP-1-RA
        - Insulin

- Insulin

- Insulin (multiple daily doses)

HbA1c Goal for the Prevention of Diabetes Complications

< 7%

Individualization is key:

Tighter control (HbA1c 6.0% to 6.5%): younger, healthier

Looser control (HbA1c 6.5% to 8.0%+): older, hypoglycemia prone, comorbidities

Should HbA1c goal be lower in HIV-positive patient if it underestimates glycemia?

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• HIVSAC organizers
THANK YOU!