Management of Metabolic Complications in the HIV Patient

Marshall J. Glesby, MD, PhD

Disclosures

• None
Overview

- Dyslipidemia
- Diabetes mellitus
- Osteopenia/Osteoporosis

Relative Risk of CVD Among People Living with HIV: A systematic review and meta-analysis

(a) Study | Relative risk (95% CI) | Weight
Obel (2007) | 1.39 (0.81, 2.39) | 4.72
Triant (2007) | 1.75 (1.51, 2.03) | 46.62
Lang (2010) | 1.50 (1.30, 1.73) | 48.67
Overall (I-squared = 18.4%, p = 0.294) | 1.61 (1.43, 1.81) | 100.00

(b) Study | Relative risk (95% CI) | Weight
Obel (2007) | 2.12 (1.62, 2.77) | 32.95
Benito (2002) | 2.40 (1.69, 3.41) | 20.54
Klein (2007) | 1.78 (1.43, 2.22) | 46.51
Overall (I-squared = 13.2%, p = 0.316) | 2.00 (1.70, 2.37) | 100.00

Case

• 50 yo man with HIV dx 1988
  – h/o PCP 1995 (nadir CD4 = 0)
  – Prior RTV, IDV, LPV/r
  – Currently on TDF/FTC/EFV with VL < 20, CD4 918
  – CHD risk factors: smoked minimally in H.S., no family hx premature CHD, + hypertension (off and on meds)

Lipids

• Long h/o elevated LDL-C on pravastatin
• On atorvastatin 20 mg/d while on LPV/r:  
  – TC 164, HDL 57, LDL 94, TG 67 mg/dL
• Developed mild myalgias
  – Switched to TDF/FTC/EFV and stopped atorvastatin
• LDL-C is in 140-190 range consistently, HDL ~60, TG < 110 mg/dL
• Sees local dietician, chiropractor
  – Prescribed liver-gall bladder flushes and raw food cleanses
  – Weight is stable
Follow-up Fasting Lipids

- TC 314, HDL 65, LDL 227, TG 112
- Repeated and similar

Lipid Changes at Week 144 in STARTMRK (with TDF/FTC)

N = ~280/arm

Rockstroh JK, Clin Infect Dis 2011;53:807-16
SWITCH-ER Study

- Randomized, double-blind, cross-over study of 57 subjects on EFV
  - RAL 400 mg bid + EFV placebo or
  - RAL placebo + EFV 600 mg daily
  - 2 weeks on each regimen

<table>
<thead>
<tr>
<th>Change on RAL</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>-16 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-18 mg/dL</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-8 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-4 mg/dL</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

Nguyen A, AIDS 2011;25:1481-87

Case Follow-Up

- Started rosuvastatin 10 mg/d
- Lipids 2 months later:
  - TC 170, HDL 62, LDL 89, TG 94
- Tolerated it well
• After 3 months on rosuvastatin, calls to say he developed paresthesias in his hands and feet like the neuropathy he had in the distant past on d4T
• He stopped rosuvastatin

Further History....

• He reports having started red yeast rice extract at the same time as the rosuvastatin
• Monacolin K has the same structure as lovastatin
Follow-up Lipids

- TC 271, HDL 59, LDL 171, TG 206 mg/dL
- You decide that risk stratification may be helpful
### Intended for use if there is not ASCVD and

<table>
<thead>
<tr>
<th>Race</th>
<th>Age</th>
<th>Total Cholesterol (mg/dL)</th>
<th>Systolic Blood Pressure</th>
<th>Treatment for Hypertension</th>
<th>Diabetes</th>
<th>Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>50</td>
<td>271</td>
<td>134</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>African American</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

**Optimal risk factors:**
- TC 170, HDL-C 50, SBP 110
- Not on meds for htn
- Not diabetic
- Not a smoker

*Intended for use if there is not ASCVD and LDL-C is < 190*
Based on the data entered (assuming no clinical ASCVD and LDL-C 70-189 mg/dL):

- Gender: Male
- Age: 50
- Race: White/Other
- Total Cholesterol: 271
- HDL-Cholesterol: 59
- Systolic Blood Pressure: 134
- Hypertension Treatment: No
- Diabetes: No
- Smoker: No

Not In Statin Benefit Group Due To 10-Year ASCVD Risk <5%

In individuals for whom after quantitative risk assessment a risk-
Limitations

The evidence-based recommendations in this guideline focus on patient groups who are well represented in RCTs and/or are highly likely to have high-risk genetic conditions, so the recommendations are designed to inform clinical judgment, not to replace it. However, there are other patient groups in whom a robust evidence base is lacking, but which may nevertheless include some persons in whom statin treatment should be considered (after taking patient preferences into account) based on the potential for ASCVD benefits exceeding the risk of adverse events or drug-drug interactions.

Clinician judgment is especially important for several patient groups for whom the RCT evidence is insufficient for guiding clinical recommendations.

Other groups include those with serious comorbidities and increased ASCVD risk (e.g., individuals with HIV, rheumatologic or inflammatory diseases, or who have undergone a solid organ transplant).

This guideline encourages clinicians to use clinical judgment in these situations weighing potential benefits, adverse effects, drug-drug interactions and patient preferences.

Stone NJ et al, Circulation 2013 [Epub ahead of print]
Framingham Risk Calculation

Information about your risk score:
Age: 50
Gender: male
Total Cholesterol: 271 mg/dL
HDL Cholesterol: 59 mg/dL
Smoker: No
Systolic Blood Pressure: 134 mmHg
On medication for HBP: No

Risk Score* 7%

Means 7 of 100 people with this level of risk will have a heart attack in the next 10 years.

* Your risk score was calculated using an equation. Other NCEP products, such as printed ATP III materials, use a point system to determine a risk score that is close to the equation score.

http://cvdrisk.nhlbi.nih.gov/

Observed MI Rates Track with Predicted Rates by Framingham Risk Equation in D:A:D Cohort

HIV-Specific Risk Calculator

• 3.7% risk of MI over 10 years


AHA/ACC Cholesterol Guidelines
November 2013

• Key Points
  – Specific LDL and non-HDL targets have been eliminated
  – Focuses on 4 groups of primary and secondary prevention patients
  – Within groups, discusses appropriate intensity of statin therapy
• Controversy remains over whether calculator overestimates risk….

Slide courtesy of John Farragon, PharmD
Four Statin Benefit Groups:

- Individuals with clinical atherosclerotic cardiovascular disease (acute coronary syndromes, h/o MI, stable/unstable angina, revascularization, stroke, TIA, PAD)
- Individuals with LDL-cholesterol levels $\geq 190$ mg/dL, such as those with familial hypercholesterolemia
- Individuals 40-75 years old with diabetes and LDL-C 70-189 mg/dL, without clinical ASCVD
- Individuals 40-75 years old without clinical ASCVD or diabetes but who have LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of $\geq 7.5\%$ (Pooled Cohort Equations)

<table>
<thead>
<tr>
<th>High-Intensity Statin</th>
<th>Moderate-Intensity Statin</th>
<th>Low-Intensity Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lower LDL-C by $\geq 50%$ on average</td>
<td>Daily dose lower LDL-C by 30-50% on average</td>
<td>Daily dose lowers LDL-C by $&lt; 30%$ on average</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
<td>Fluvastatin XL 80 mg</td>
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<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Fluvastatin 40 mg</td>
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<tr>
<td></td>
<td>Fluvastatin 20 mg</td>
<td>Fluvastatin 40 mg bid</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>
Cholesterol Guidelines

ASCVD Statin Benefit Groups
Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C ≥70-189 mg/dL.

Adults age >21 y and a candidate for statin therapy

Clinical ASCVD

Yes

Yes

No

Age <75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin

Definitions of High- and Moderate-Intensity Statin Therapy
(See Table 5)

High
Daily dose lowers LDL-C by approx. ≥50%

Moderate
Daily dose lowers LDL-C by approx. 30% to <50%

LDL-C ≥190 mg/dL

Yes

High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

No
Pitavastatin: Low Potential for Drug-Drug Interactions

- Minimally metabolized thru cytochrome P450
- DRV/r (800/100) decreased pitavastatin exposure by 26% but no effect on peak\(^1\)
  - No effect of pitavastatin on DRV or RTV
- LPV/r decreased pitavastatin AUC by 20% but no effect on peak\(^2\)
  - Minimal effect of pitavastatin on LPV/r

\(^{1}\)Yu CY, Clin Drug Invest 2014 [epub ahead of print]  \(^{2}\)Morgan RE, JAIDS 2012;60:158-64
Changes in lipid profiles before and after 12 weeks of treatment with pitavastatin (PTV) (2 mg) or atorvastatin (ATV) (10 mg).

doi:10.1371/journal.pone.0076298
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0076298

% Change in Lipids at Week 52

HIV+, LDL 130-220 and TG < 400 after 4 week washout/dietary stabilization

Sponseller CA, CROI 2014, 751LB
Rosuvastatin: Other Effects

• SATURN-HIV:
  – HIV on ART, VL < 1K, LDL < 130, CRP > 2 or CD8 CD38+DR+ ≥ 19%
  – Rosuvastatin 10 mg (n=72) or placebo (n=75)
• Bone: +0.6% incr at hip vs -0.6% (p=0.017)
  – Trochanter: 0.9% vs -0.7% (p=0.042) at wk 48
• HOMA-IR increased in rosuva arm
• Biomarkers: sCD14, Lp-PLA2, CD4 38+DR+, CD8 38+DR+, IP-10, oxLDL all decreased

McComsey, CROI 2014; abstr 134; 335; 750

Case Follow-Up

• My patient has not (yet?) agreed to restart a statin
• Recently started anti-hypertensive therapy
Abacavir and CV Disease: Update

- Large cohort study
- Prior CV risk
- ↓ channeling since 2008
- Results (to 2/1/13):
  - 941 MI / 367,559 p-yrs.
    - Current ABC use 0.47
    - No current ABC use 0.21
  - RR 1.98; no ∆ by time period or after adjustment for lipids/HTN/etc.

ACTG REPRIEVE Study

- HIV-infected who do not meet criteria for statin therapy
- Randomized to pitavastatin or placebo
- 5 year f/u
- Primary endpoint: Major adverse cardiac events (MACE)
- Cardiac CT substudy
Epidemiology of DM in HIV-Infected Patients

- Incidence/prevalence varies by population
  - Genetic factors, obesity, HCV, type of ART (treatment era), ascertainment
  - Definition of DM varies by cohort study
  - Not all studies adjust for risk factors such as family history, HCV
- Evidence that it varies by HIV status is conflicting
Multiple Factors May Contribute to Diabetes in HIV

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

Decreasing Incidence of DM at 47 French Clinical Sites

Capeau J et al, AIDS 2012; 26:303-14
Danish Nationwide Population-Based Cohort Study

N = 3,540 HIV+ Danish born vs 14,160 age/sex-matched controls


Diabetes in the WIHS (2000-06)

First visit after index visit at which any of the following occur:

**Definition I:**
- Anti-DM medication reported
- FG ≥126mg/dL
- DM reported + Anti-DM medication* or FG ≥126mg/dL*

**Definition II:**
- Anti-DM medication reported
- FG ≥126mg/dL
- DM reported + Anti-DM medication* or 2nd FG ≥126mg/dL*

**Definition III:**
- Anti-DM medication reported
- A1C ≥6.5%
- FG ≥126mg/dL
- DM reported + Anti-DM medication* or 2nd FG ≥126mg/dL* or A1C ≥6.5%

*Subsequent visit (s)
†current or subsequent visit

Why Screen HIV+ Patients?

- Why screen anyone?
  - Important public health problem
  - Asymptomatic period exists
  - Undiagnosed DM can cause progressive microvascular damage
  - Treatment exists
  - Lifestyle intervention may reduce risk of DM in those with prediabetes
- Why screen HIV+?
  - As above plus increased risk of cardiovascular and renal disease
Case

- 53 year-old African-American man, HIV+ for 20 years, on ART since 2000
- VL< 50 on TDF/FTC/ EFV
- Mild/moderate lipoatrophy and lipohypertrophy
- Strong family history of DM
- BMI 29 kg/m²
- Fasting Glucose 110 mg/dL (confirmed)
- Hb A1c 6.2%

ADA Definitions: 2013

**Diabetes Mellitus**

1. Hb A1c ≥ 6.5%
2. Fasting plasma glucose ≥ 126 mg/dL, confirmed by repeat testing
3. Plasma glucose 2 hours after 75 g oral glucose tolerance test ≥ 200 mg/dL
4. Random plasma glucose ≥ 200 mg/dL with polyuria and polydipsia

#1-3 should be confirmed on repeat testing
ADA Definitions: 2013

Increased Risk of Diabetes (Prediabetes)

1. Hb A1c 5.7-6.4%
2. Fasting plasma glucose 100-125 mg/dL
3. Plasma glucose 2 hours after 75 g oral glucose tolerance test 140-199 mg/dL

ADA. Diabetes Care 2013;36(supp1):S67-74

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 hemolysis¹,²

Caveat for the use of HgbA1c for diagnosis

“For conditions with abnormal red cell turnover……, the diagnosis of diabetes must employ glucose criteria exclusively”

ADA Clinical Practice Recommendations, 2012

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 Underestimates Glycemia in HIV-infected Persons**

![Graph showing glucose levels and HbA1c values for HIV-infected and control groups.]

*Kim, Diabetes Care, 2009*

**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 given glucose: HIV+ had 1.3% lower relative value of A1C compared to HIV-

![Bar chart showing HbA1c levels for HIV+ and HIV- groups.]

*Glesby MJ et al, Antivir Ther 2010;15:571-7*
Performance of HbA1c as Screening Test

Retrospective study of 395 HIV+ pts at Bellevue Hospital
Gold standard = FBG

Eckhardt BJ et al, AIDS Pt Care STDs 2012;26: 197-201

Diabetes Screening

- How?
  - Fasting Glucose
  - If 100-125 mg/dL, consider 75 g OGTT
  - HbA1c

- When?
  HIVMA/IDSA: Fasting glucose and/or HbA1c prior to and within 1-3 months after starting ART

Incident fractures in HIV-infected individuals: a systematic review and meta-analysis.
Shiau, Stephanie; Broun, Emily; Arpadi, Stephen; Yin, Michael  AIDS. 2013;27:1949-1957

### Meta-Analysis of Crude Incidence Rate Ratios of Fractures in HIV+ vs Controls

#### (a) All fractures

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arvikan et al. 2011</td>
<td>0.5%</td>
<td>1.10 [0.57, 2.19]</td>
<td></td>
<td>1.10 [0.57, 2.19]</td>
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<tr>
<td>Hansen et al. 2012</td>
<td>40.7%</td>
<td>1.58 [1.44, 1.78]</td>
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<td>1.58 [1.44, 1.78]</td>
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<tr>
<td>Yin et al. 2010</td>
<td>24.4%</td>
<td>1.29 [0.83, 1.97]</td>
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<td>1.29 [0.83, 1.97]</td>
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<tr>
<td>Young et al. 2011</td>
<td>21.1%</td>
<td>2.41 [1.64, 3.54]</td>
<td></td>
<td>2.41 [1.64, 3.54]</td>
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<tr>
<td><strong>Total</strong>: (95% CI)</td>
<td>100.0%</td>
<td><strong>1.40 [1.09, 1.79]</strong></td>
<td></td>
<td><strong>1.40 [1.09, 1.79]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.03$, $Q(3) = 3.83$ ($P = 0.57$), $I^2 = 0.00$

Test for overall effect: $Z = 3.30$ ($P = 0.001$)

#### (b) Fragility fractures

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hansen et al. 2012</td>
<td>20.7%</td>
<td>1.49 [0.70, 2.06]</td>
<td></td>
<td>1.49 [0.70, 2.06]</td>
<td></td>
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<tr>
<td>Valk et al. 2011</td>
<td>20.8%</td>
<td>1.27 [1.05, 1.56]</td>
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<td>1.27 [1.05, 1.56]</td>
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<tr>
<td>Walker-Hams et al. 2011</td>
<td>13.6%</td>
<td>1.09 [0.65, 1.80]</td>
<td></td>
<td>1.09 [0.65, 1.80]</td>
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<tr>
<td>Young et al. 2011</td>
<td>9.2%</td>
<td>1.09 [0.64, 1.88]</td>
<td></td>
<td>1.09 [0.64, 1.88]</td>
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<tr>
<td><strong>Total</strong>: (95% CI)</td>
<td>100.0%</td>
<td><strong>1.30 [1.03, 1.66]</strong></td>
<td></td>
<td><strong>1.30 [1.03, 1.66]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.46$, $Q(4) = 0.64$ ($P = 0.904$), $I^2 = 91$

Test for overall effect: $Z = 2.91$ ($P = 0.004$)

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A5202: Decrease in BMD at the Spine Occurs by 24 Weeks After Initiation

McComsey et al., J Infect Dis 2011;203:1791-801

Decrease in BMD at the Hip Occurs by 48 weeks

McComsey et al., J Infect Dis 2011;203:1791-801
Fractures After Antiretroviral Initiation

Fig. 1. Time-to-first fracture from antiretroviral therapy initiation in 3398 antiretroviral therapy-naive participants.

26 randomized ACTG ART trials with median f/u 5 yrs
Median age 39; 83% men, 48% white
Median nadir CD4 187

Yin, Michael; Kendall, Michelle; Wu, Xingye; Tassipoulos, Katherine; Hochberg, Marc; Huang, Jeannie; Glesby, Marshall; Bolivar, Hector; McComsey, Grace  AIDS 2013;26:2175-2184,

Fracture Rate is Higher Within First 2 Years After ART Initiation

Fig. 2. Fracture incidence rates (and 95% confidence intervals) by time since antiretroviral therapy initiation in 3398 ART-naive participants. Bar widths are proportional to the number of participants.

? Related to decline in BMD with initiation of ART or improved health status leading to decreased risk over time
**ACTG A5257 Substudy (n = 328)**

Mean Percentage Change in BMD over 96 Weeks by Treatment Regimen

- Total Hip
- Lumbar Spine
- Total Body

**Results:**
- ~50% reduction in bone loss with calcium/vitamin D (-1.5% vs -3.2% hip, -2.9% vs -1.4% L-spine)

Brown TT et al, CROI 2014; abstr 133

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**ACTG 5280: Vitamin D/Calcium for ART-related Bone Loss**

- Randomized, double-blind, placebo-controlled
- Pts. initiating TDF/FTC/EFV (N=145)
- Randomized to CaCO₃ 1000 mg + vit D 4000 IU daily or matching placebos

**Results:**
- ~50% reduction in bone loss with calcium/vitamin D (-1.5% vs -3.2% hip, -2.9% vs -1.4% L-spine)

Overton E, CROI 2014, abstr 133
Screening Recommendations

- IDSA/HIVMA\textsuperscript{1}: Baseline bone densitometry in post-menopausal women and men age $\geq 50$

- Expert opinion\textsuperscript{2}: As above but repeat every 2-5 years if results do not warrant medical treatment

\textsuperscript{1}Aberg JA et al, Clin Infect Dis. 2014;58:1-10.
\textsuperscript{2}McComsey G et al, Clin Infect Dis 2010;51:937-46
Summary

• HIV-infected patients are at increased risk of coronary heart disease
  – How to optimally manage lipids in the context of changing guidelines for the general population is uncertain

• Regular DM screening is important
  – Use HbA1c judiciously for diagnosis in HIV+ patients

• Fracture risk is increased in HIV-infected patients
  – Different antiretroviral regimens may affect bone density differently