HIV, Aging, and Statins: Pros vs. Cons...

Priscilla Hsue, MD
Professor of Medicine
University of California, San Francisco
Disclosures

• Honoraria: Gilead, Amgen
The number of people 50 and older living with HIV in U.S has increased 77% from 2001 to 2005.¹

By the year 2015, HIV patients aged 50 and older will account for half of all HIV/AIDS cases in the U.S.¹

Chronic disease conditions such as cardiovascular disease are increasingly important health issues in this population.

¹[www.cdc.gov](http://www.cdc.gov)

- 1,876 deaths among 39,727 patients
- Non-AIDS related deaths accounted for 50.5%

Patient Case

• 78 y.o. male no HIV no prior cvd
• Cardiac Risk Factors
  – Blood pressure of 135/85
  – No cigarettes
  – LDL 189mg/dL, TC 262mg/dL, HDL 40mg/dL
  – Fasting glucose of 110 mg/dL
  – HOMA suggesting early insulin resistance
  – Weight of 195 pounds slowing increasing weight for past 10 years...
• Patient referred to Cardiology with dyspnea

Question: Do you prescribe a statin – Reasons why? Reasons not?
Patient Case with HIV

• 48 y.o. male with HIV
  – CD4 440 and VL UD
  – Treated with Lopinavir/RTV/Abacavir/Lamivudine
• Cardiac Risk Factors
  – Blood pressure of 135/90
  – Cigarette smoker
  – HDL of 32 mg/dL (0.83), TG 236 mg/dL (2.66), LDL-C 160 mg/dL (4.14), TC 244 mg/dL (6.31)
  – Weight of 135 pounds and slowing decreasing over past 10 years...
• Patient referred to Cardiology with dyspnea

Question: Do you prescribe a statin – Reasons why? Reasons not?
Reasons why to prescribe statin - Pros
Relation Between the Proportional Reduction in MAJOR VASCULAR EVENTS and Mean Absolute LDL-C Reduction in 14 Statin Trials

### Effects on MAJOR VASCULAR EVENTS Per Mmol/L LDL-C Reduction, Subdivided by Baseline Prognostic Factors

<table>
<thead>
<tr>
<th>Groups</th>
<th>Events (%)</th>
<th>Rate Ratio (CI)</th>
<th>RR (99% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post MI</td>
<td>3051 (21·2)</td>
<td>3860 (26·9)</td>
<td>0·79 (0·75 – 0·83)</td>
<td></td>
</tr>
<tr>
<td>Other CHD</td>
<td>1257 (19·3)</td>
<td>1581 (24·2)</td>
<td>0·80 (0·73 – 0·87)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2046 (8·5)</td>
<td>2553 (10·6)</td>
<td>0·78 (0·72 – 0·84)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>3454 (12·5)</td>
<td>4448 (16·2)</td>
<td>0·78 (0·74 – 0·82)</td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>2900 (16·6)</td>
<td>3546 (20·3)</td>
<td>0·81 (0·77 – 0·86)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5097 (14·9)</td>
<td>6504 (19·0)</td>
<td>0·78 (0·75 – 0·81)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1257 (11·7)</td>
<td>1490 (13·8)</td>
<td>0·83 (0·76 – 0·91)</td>
<td></td>
</tr>
<tr>
<td>Treated hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3925 (15·8)</td>
<td>4783 (19·2)</td>
<td>0·81 (0·77 – 0·85)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2429 (12·0)</td>
<td>3211 (15·9)</td>
<td>0·77 (0·73 – 0·82)</td>
<td></td>
</tr>
<tr>
<td>History of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1465 (15·6)</td>
<td>1782 (19·2)</td>
<td>0·79 (0·72 – 0·86)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4889 (13·7)</td>
<td>6212 (17·4)</td>
<td>0·79 (0·76 – 0·82)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤90</td>
<td>5191 (14·9)</td>
<td>6493 (18·6)</td>
<td>0·79 (0·76 – 0·83)</td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td>1154 (11·4)</td>
<td>1496 (14·8)</td>
<td>0·77 (0·80 – 0·84)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>6354 (14·1)</td>
<td>7994 (17·8)</td>
<td>0·79 (0·77 – 0·81)</td>
<td>p&lt;0.00001</td>
</tr>
</tbody>
</table>
Event Reduction Is Independent of Baseline LDL-C

<table>
<thead>
<tr>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin/more</td>
<td>Control/less</td>
</tr>
<tr>
<td><strong>All trials combined</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>910 (4.1%)</td>
<td>1012 (4.6%)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/L</td>
<td>1528 (3.6%)</td>
<td>1729 (4.2%)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3.0 mmol/L</td>
<td>1866 (3.3%)</td>
<td>2225 (4.0%)</td>
</tr>
<tr>
<td>≥3 to &lt;3.5 mmol/L</td>
<td>2007 (3.2%)</td>
<td>2454 (4.0%)</td>
</tr>
<tr>
<td>≥3.5 mmol/L</td>
<td>4508 (3.0%)</td>
<td>5736 (3.9%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10973 (3.2%)</td>
<td>13350 (4.0%)</td>
</tr>
</tbody>
</table>

99% or 95% CI

Cholesterol Treatment Trialists’ Collaboration, *Lancet* 2010;376:1670
## Risk Reduction According to Baseline Risk

### 5-year MVE risk at baseline

<table>
<thead>
<tr>
<th>Events (% per annum)</th>
<th>RR (CI) per 1.0 mmol/L reduction in LDL cholesterol</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin/more</td>
<td>Control/less</td>
</tr>
<tr>
<td><strong>Major coronary event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>50 (0.11)</td>
<td>88 (0.19)</td>
</tr>
<tr>
<td>≥5% to &lt;10%</td>
<td>276 (0.50)</td>
<td>435 (0.79)</td>
</tr>
<tr>
<td>≥10% to &lt;20%</td>
<td>1644 (1.29)</td>
<td>1973 (1.57)</td>
</tr>
<tr>
<td>≥20% to &lt;30%</td>
<td>1789 (1.93)</td>
<td>2282 (2.49)</td>
</tr>
<tr>
<td>≥30%</td>
<td>1471 (3.73)</td>
<td>1887 (4.86)</td>
</tr>
<tr>
<td>Overall</td>
<td>5230 (1.45)</td>
<td>6665 (1.87)</td>
</tr>
</tbody>
</table>

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Cholesterol Treatment Trialists' (CTT) Collaborators, *Lancet* 2012
Reduction in Cardiovascular Events Over 5 Years According to Risk Category and Amount of LDL-C Reduction

LDL-C reduction (mmol/L)

- ≥30%
- ≥20% to <30%
- ≥10% to <20%
- ≥5% to <10%
- <5%

Major vascular events avoided per 1000

Cholesterol Treatment Trialists' (CTT) Collaborators, *Lancet* 2012
CV Event Reduction with Statins...

- is proportional to LDL-C reduction
- applies to a broad population
- is independent of baseline LDL-C
- is independent of baseline risk

How does this translate to patient’s with HIV? Do statins lower LDL-C and do they reduce CV events and mortality?
## Doses of Statins Needed to Obtain 30-40% reduction of LDL-C

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose, mg/d</th>
<th>LDL Reduction %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovastatin</td>
<td>10*</td>
<td>39</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>40*</td>
<td>31</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40*</td>
<td>34</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20-40*</td>
<td>35-41</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>40-80</td>
<td>25-35</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5-10**</td>
<td>39-45</td>
</tr>
</tbody>
</table>

*Are available at doses up to 80mg. For every doubling of dose above std dose, an approximate 6% reduction in LDL is expected

** doses available up to 40mg

*Grundy SM Circulation 2004*
Lipid lowering in HIV vs. Uninfected Population

Slide from Vivek Jain UCSF
Potency of Statins in HIV

- Retrospective study of 700 patients in 2 large US clinics looked at HIV positive patients starting initial statin

- Both atorvastatin and rosvastatin did better than pravastatin in reducing total cholesterol, LDL, TGs and non-HDL cholesterol.

Table 3. Decrease in Plasma Lipid Concentrations After 12 Months of Statin Therapy Compared With Baseline by Individual Statin in Adjusted Analyses

<table>
<thead>
<tr>
<th>Statin</th>
<th>Total cholesterol (n = 502)</th>
<th>LDL-C (n = 468)</th>
<th>Triglycerides (n = 505)</th>
<th>Non-HDL-C (n = 433)</th>
<th>HDL-C (n = 460)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dL 95% CI P</td>
<td>mg/dL 95% CI P</td>
<td>mg/dL 95% CI P</td>
<td>mg/dL 95% CI P</td>
<td>mg/dL 95% CI P</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>25 16–34 Ref 12 5–19 Ref</td>
<td>12 5–19 Ref</td>
<td>24 –17 to 65 Ref</td>
<td>26 17–35 Ref</td>
<td>1.1 –.7 to 2.9 Ref</td>
</tr>
</tbody>
</table>
| Atorvastatin| 39 31–48 <.001              | 26 20–32 <.001 | 60 23–66 .06            | 39 31–47 .002       | .6 –1.1 to 2.2  
| Rosuvastatin| 43 31–55 .004              | 23 14–32 .01  | 83 29–137 .03           | 47 35–59 .001       | +.6 1.6 to 3.0 |

NOTE. Models were adjusted for baseline lipid values, age, race, sex, baseline antiretroviral therapy (none, protease inhibitor–based, or non-nucleoside reverse transcriptase inhibitor–based), and CD4+ cell count nadir. To convert total cholesterol, LDL-C, non-HDL-C, or HDL-C values to mmol/L, multiply by .0259. To convert triglyceride values to mmol/L, multiply by .0113. CI, confidence interval; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein; non-HDL-C, non-high density lipoprotein cholesterol.

Singh S, et al CID 2011
Slide from Dr. Vivek Jain, UCSF
Statin use and mortality in HIV

- Johns Hopkins HIV Clinical Cohort
  - 1538 pts on HAART (1998-2009) maintaining virological suppression, 238 (15.5%) on statin.
  - Follow to death or VL > 500 copies/ml
  - Statin use associated with relative hazard of 0.33 (95% CI 0.14, 0.76, p=0.009) after adjustment.
  - 85 deaths (7 in statin and 78 in non-statin – small numbers overall)
  - Malignancy, non-AIDS infections and liver failure prominent causes of death

No impact of statins on non-AIDS death in HIV –

- Retrospective study of 3601 HIV pts not on statin from ACTG ALLRT cohort studies, 95% on ART, 66% suppressed
- 15135 PY fu
- No reduction in non-AIDS events or death, statin use associated 25% increase risk of bacterial infection (non significant)
- 57% reduction in non-AIDS malignancies
- CA Kaiser cohort – statin use associated with risk of NHL vs. pts on non-statin lipid lowering tx

ET Overton et al CID 2013

Chao et al AIDS 2010
Danish and VA studies: non significant association of statins with mortality

• Danish study: 1738 Danish HIV pts who initiated ART with virologic suppression, 145 (8.3%) initiated statin
  – Statin use associated with non-significant reduced rate of death, adjusted mortality rate ratio only in models including treated suppressed pts only (aMRR 0.75, 95% CI 0.33-1.68)
  – No difference when individuals with virologic failure were included
  – Trend towards lower mortality among individuals with comorbidity diagnosed

• VA Study:
  – Cumulative exposure to statins in HAART (N=25884 and virologically suppressed, N=15943)
  – Cumulative exposure to statins associated with a trend toward reductions in non-AIDS complications and mortality, but p values not significant.

Rasumussen LD et al PLoS One 2013
Dreschsler H et al CROI 2013
• Statins may impact inflammation and inflammation may be a key issue in HIV
Jupiter study

- 17,802 subjects without known coronary disease or diabetes, with LDL-C <130 mg/dl and hs-CRP ≥2 mg/dl
- Randomized to rosuvastatin 20 mg/day or placebo
- Primary endpoint: CV death, MI, stroke, arterial revascularization, or hospitalization for unstable angina
- Study stopped after median follow-up of 1.9 years
- Primary endpoint occurred in 142 rosuvastatin and 251 placebo patients (HR 0.56, 95% CI 0.46-0.69)

Ridker P NEJM 2008
Many Age-associated Diseases Are More Common in Treated HIV Disease Than In Age-matched Uninfected Persons

- Cardiovascular disease
- Cancer (non-AIDS)
- Bone fractures/osteopenia
- Left ventricular dysfunction
- Liver failure
- Kidney failure
- Cognitive decline
- Frailty
- Immune system

Multiple factors likely explain this increased risk, including co-morbid conditions and antiretroviral drug toxicity

*Chronic inflammation is thought to underlie many of these conditions*
Atorvastatin associated with reductions in activated T lymphocytes

- 22 patients in a cross over trial
- 80mg atorvastatin or placebo, 4-6 week washout
- No effect on HIV-1 RNA
- Atorvastatin resulted in reductions in CD4+HLA-DR+ (-2.5%, \( p=0.02 \))
  reductions in CD8+HLA-DR+(-5%, \( p=0.006 \)) and CD8+HLA-DR+ T cells (-3%, \( p=0.03 \))

Clinical significance of this finding?

Ganesan A et al JID 2011; 203: 756-64.
Rosuvastatin in HIV did not impact inflammatory markers

- 147 HIV pts on stable ART, with LDL ≤ 130mg/dL and hsCRP > 2mg/L and/or expression of CD38 and HLA-DR antigens on ≥ 19% of CD8+ T cells at screening
- 24 weeks of rosuvastatin 10mg daily reduced Lp-PLA2 and LDL but did not impact inflammatory/coagulation markers (hsCRP, IL-6, D-dimer, fibrinogen).

Eckard A et al JID 2014
Saturn (“Jupiter-HIV”) vs. Jupiter

- LDL lowering higher in Jupiter
  - LDL decreased 28% in Saturn vs. 50% in Jupiter
- No impact on inflammatory markers in HIV
  - No impact on hsCRP in Saturn vs. 37% reduction vs. placebo in Jupiter

Will statins target the inflammatory pathways of interest in HIV?
Statins lower LDL which also impacts CV risk and mortality...

But rosuvastatin lowers LDL as well as hsCRP and does not directly address whether lowering inflammation alone reduces CV risk

Despite high dose statins tx, > 20% of individuals with ACS have a recurrent event in the next 30 months - need for tx to lower LDL more, other anti-inflammatory agents?

Cannon C et al NEJM 2004
• New guidelines and how they may impact HIV patients?
New ACC/AHA cholesterol treatment guideline published November 2013


Who to Treat: New US Guidelines

**Group 1**
Clinical ASCVD
CHD, stroke, and peripheral arterial disease, all of presumed atherosclerotic origin

**Group 2**
LDL-C ≥190 mg/dL (~5 mmol/L)

**Group 3**
Diabetes mellitus
+ age of 40–75 years
+ LDL-C 70–189 mg/dL (~1.8–5 mmol/L)

**Group 4**
ASCVD risk ≥7.5%
No diabetes
+ age of 40–75 years
+ LDL-C 70–189 mg/dL (~1.8–5 mmol/L)

# Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>Intensity</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↓ LDL-C ≥50%</td>
<td>↓ LDL-C 30 to &lt;50%</td>
<td>↓ LDL-C &lt;30%</td>
</tr>
<tr>
<td>High</td>
<td>Atorva 40-80 mg, Rosuva 20-40 mg</td>
<td>Atorva 10 mg, Rosuva 10 mg, Simva 20-40 mg, Pravas 40 mg, Lova 40 mg, Fluva XL 80 mg, Fluva 40 mg bid, Pitava 2-4 mg</td>
<td>Simva 10 mg, Prava 10-20 mg, Lova 20 mg, Fluva 20-40 mg, Pitava 1 mg</td>
</tr>
</tbody>
</table>

Statins in bold were evaluated in randomized controlled trials; those in italics were not.

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, p 34
Intensity of Treatment

• Known ASCVD: high-intensity statin*
• LDL-C >190 mg/dl: high-intensity statin*
• Diabetes, age 40-75, LDL-C 70-189 mg/dl: moderate-intensity statin unless score ≥7.5%, then high-intensity statin
• Patients aged 40-75, LDL-C 70-189 mg/dl with a global 10-year risk score of ≥7.5%: moderate to high-intensity statin

* Unless >75 years old or statin-intolerant, then use moderate-intensity statin

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
Patient Case

- 78 y.o. male no HIV no prior cvd
- Cardiac Risk Factors
  - Blood pressure of 135/85
  - No cigarettes
  - LDL 189mg/dL, TC 262mg/dL, HDL 40mg/dL
  - Fasting glucose of 110 mg/dL
  - HOMA suggesting early insulin resistance
  - Weight of 195 pounds slowing increasing weight for past 10 years...
- Patient referred to Cardiology with dyspnea

Question: what do guidelines recommend for this patient?
Using acc/aha calculator online...

Based on the data entered (assuming no clinical ASCVD and LDL-C 70-189 mg/dL):

- Gender: Male
- Age: 78
- Race: White/Other
- Total Cholesterol: 262
- HDL-Cholesterol: 40
- Systolic Blood Pressure: 135
- Hypertension Treatment: No
- Diabetes: No
- Smoker: No

**Not In Statin Benefit Group Due To Age > 75 Years**

Before initiating statin therapy, it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment. (IIa C)

http://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp
Other scenarios:

Group 1
Clinical ASCVD
CHD, stroke, and peripheral arterial disease, all of presumed atherosclerotic origin

Group 2
LDL-C ≥190 mg/dL (~5 mmol/L)

Group 3
Diabetes mellitus
+ age of 40–75 years
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Group 4
ASCVD risk ≥7.5%
No diabetes
+ age of 40–75 years
+ LDL-C 70–189 mg/dL (~1.8–5 mmol/L)

If you change age of patient to 75, he qualifies for moderate to high intensity statin due to 10 year ASCVD risk of 31%, making him a Group 4

Patient Case with HIV

- 48 y.o. male with HIV
  - CD4 440 and VL UD
  - Treated with Lopinavir/RTV/Abacavir/Lamivudine
- Cardiac Risk Factors
  - Blood pressure of 135/90
  - Cigarette smoker
  - HDL of 32 mg/dL (0.83), TG 236 mg/dL (2.66), LDL-C 160 mg/dL (4.14), TC 244 mg/dL (6.31)
  - Weight of 135 pounds and slowing decreasing over past 10 years...

- Patient referred to Cardiology with dyspnea

**Question:** Do you prescribe a statin – Reasons why? Reasons not?
Using online calculator...

<table>
<thead>
<tr>
<th>Estimator</th>
<th>Clinicians</th>
<th>Patients</th>
<th>About</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD Risk Estimator*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**10-Year ASCVD Risk**

- **15.8%** calculated risk
- **1.7%** risk with optimal risk factors**

**Lifetime ASCVD Risk**

- **69%** calculated risk
- **5%** risk with optimal risk factors

Recommendation Based On Calculation

Based on the data entered (assuming no clinical ASCVD and LDL-C 70-189 mg/dL):

- Gender: Male
- Age: 48
- Race: White/Other
- Total Cholesterol: 244
- HDL-Cholesterol: 32
- Systolic Blood Pressure: 135
- Hypertension Treatment: No
- Diabetes: No
- Smoker: Yes

**Moderate to High-Intensity Statin Recommended**
Other scenarios:

**Group 1**
Clinical ASCVD
CHD, stroke, and peripheral arterial disease, all of presumed atherosclerotic origin

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LDL-C ≥190 mg/dL (~5 mmol/L)

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ASCVD risk ≥7.5%
No diabetes
+ age of 40–75 years
+ LDL-C 70–189 mg/dL (~1.8–5 mmol/L)

If he stops smoking, his 10 year risk decreases to 6.8%, no longer part of Group 4, and guidelines suggest “consider moderate dose statin”

Other factors:

In selected individuals who are not part of the 4 statin benefit groups, additional factors to consider:

- LDL ≥ 160 (4.14mmol/l), FH CAD, hsCRP ≥ 2, CAC ≥ 300 or 75% percentile, ABI < 0.9, or elevated lifetime risk of CAD

“Clinicians often consider statins for the primary prevention of CAD in individuals who have HIV on PI; decisions about statin treatment could include a risk discussion that considers 10-year risk estimated with the NHLBI risk calculator as well as the harms associated with therapy…”
Threshold for starting preventive treatment with statins should be halved from a 20% risk over 10 years to a 10% risk.

Mark Baker, director of NICE’s Centre for Clinical Practice, said, “We also recommend that statins are now offered to many more people - the effectiveness of these medicines is now well proven and their cost has fallen.”

Doctors should prescribe atorvastatin 20 mg for the primary prevention of CVD and atorvastatin 80 mg for patients with established CVD or diabetes.

Standard CV risk scores underestimate risk in some groups of patients such as people being treated for HIV.

Wise J, *BMJ* 2014;348:g1518
Risk Calculators in HIV

• Risk predictors developed in non-HIV populations may not predict risk in HIV due to different etiologies
• HIV specific calculators – ie DAD validation pending, should inflammatory/immunologic parameter be included?
• MAGNIFICENT Consortium – Impact of genetic testing in HIV was additive to traditional risk factors, and ART

D’Agostino RB JID 2012
Friss-Moller N et al Euro Jl Preventive Cardiology 2010
Rotger M et al CID 2013
Should HIV be considered a CVD equivalent?

- Association of HIV to atherosclerosis similar to DM (FRAM study)
- Veterans Cohort: HR for HIV infection and acute MI similar DM
- Mildly elevated BP (SBP 120-139) was associated with a higher risk for MI in HIV

Should we treat HIV like DM, which would move all HIV patients into Group 3 - Diabetes, age 40-75, LDL-C 70-189 mg/dl: moderate-intensity statin unless score ≥7.5%, then high-intensity statin

Freiberg M JAMA IM 2013.
Armah K CID 2013
• Statins, HIV, Reasons not to prescribe, the cons...
Main Drugs That Increase the Risk of Myopathy and Rhabdomyolysis When Used With Statins

- fibrates (gemfibrozil > fenofibrate)
- niacin
- cyclosporin, tacrolimus
- protease inhibitors (aprenavir, indinavir, nelfinavir, ritonavir, saquinavir)
- calcium channel blockers (diltiazem, verapamil)
- macrolide antibiotics (azithromycin, clarithromycin, erythromycin)
- warfarin
- sildenafil
- digoxin
- amiodarone

Note: Not all of these drugs interfere with all statins. The severity of the interaction and thus the risk of myopathy varies widely among these drugs.

# Statin Choices: a review

<table>
<thead>
<tr>
<th>Statin</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>can use, just reduce dose to 10 or 20mg</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>X</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>can use, just less potent; use at lower doses</td>
</tr>
<tr>
<td></td>
<td>(particular caution with DRV)</td>
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<tr>
<td>Simvastatin</td>
<td>X</td>
</tr>
<tr>
<td>Fluvastatin</td>
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<tr>
<td>Rosuvastatin</td>
<td>can use at 5 or 10mg dose, infrequently used</td>
</tr>
<tr>
<td></td>
<td>b/c less accumulated data in HIV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PI’s</th>
<th>NNRTI’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins are metabolized by CYP3A4 system</td>
<td>EFV: raises CYP3A4 activity</td>
</tr>
<tr>
<td>All protease inhibitors downregulate CYP3A4</td>
<td>EFV → can reduce statin levels</td>
</tr>
<tr>
<td>PI’s → can boost statin levels to dangerous levels and trigger rhabdomyolysis</td>
<td></td>
</tr>
</tbody>
</table>
# Overview of Drug Interactions Between Lipid Lowering Agents and HIV Drugs

<table>
<thead>
<tr>
<th>Lipid Lowering Agents</th>
<th>Atazanavir</th>
<th>Darunavir</th>
<th>Fosamprenavir</th>
<th>Indinavir</th>
<th>Lopinavir</th>
<th>Nelfinavir</th>
<th>Ritonavir</th>
<th>Saquinavir</th>
<th>Efavirenz</th>
<th>Etravirine</th>
<th>Nevirapine</th>
<th>Maraviroc</th>
<th>Raltegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
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<td>Clofibrate</td>
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<td>Ezetimibe</td>
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<tr>
<td>Fenofibrate</td>
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<td>Fish oils</td>
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<td>Fluvastatin</td>
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<td>Gemfibrozil</td>
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<tr>
<td>Lovastatin</td>
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<tr>
<td>Pravastatin</td>
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<tr>
<td>Rosuvastatin</td>
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<tr>
<td>Simvastatin</td>
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</tbody>
</table>

www.hiv-druginteractions.org
Algorithm for Managing Elevated LDL-C in HIV Patients

Pt on PI

Avoid lovastatin/simvastatin
Atorvastatin at lower dose (start at 10mg and titrate up not to exceed 40 mg)
Pravastatin
Ezetimibe

If lipids remain high, consider changing PI to Atazanavir

Pt not on PI

Statin therapy per NCEP guidelines

How will the new guidelines impact HIV-infected individuals?

100% of UCSF residents put HIV pts admitted with MI on high dose atorvastatin without thinking about drug/drug interactions

Hepatic Enzyme Elevations and Statin Use

• Cholesterol lowering itself may affect hepatocyte membranes and result in minor ALT/AST elevations
• ALT and AST elevations usually disappear with continued treatment
• Minor elevations are not predictive of significant liver disease
• Acute liver failure has been reported with most cholesterol-lowering drugs, including statins, but it is uncertain whether the rate is higher than the background rate
• Monitoring ALT/AST is not effective in preventing acute liver failure because of its rarity and the poor predictive value of minor elevations

Tolman et al, Am J Cardiol 2002;89:1374
## Safety of Atorvastatin 80 mg in Clinical Trials

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Patients</th>
<th>↑ALT/AST &gt;3x ULN*</th>
<th>↑CK &gt;10x ULN*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newman et al*</td>
<td>variable 4,798</td>
<td>26 (0.6%)</td>
<td>2 (0.06%)</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>2 years 2,099</td>
<td>69 (3.3%)</td>
<td>NA</td>
</tr>
<tr>
<td>TNT</td>
<td>4.9 years 4,995</td>
<td>60 (1.2%)</td>
<td>0</td>
</tr>
<tr>
<td>IDEAL</td>
<td>4.8 years 4,439</td>
<td>61 (1.38%)</td>
<td>0</td>
</tr>
<tr>
<td>SPARCL</td>
<td>4.9 years 2,365</td>
<td>51 (2.2%)</td>
<td>2 (0.08%)</td>
</tr>
<tr>
<td>Total</td>
<td>variable 18,696</td>
<td>267 (1.43%)</td>
<td>4 (0.021%)</td>
</tr>
</tbody>
</table>

* Consecutive measurements; * Am J Cardiol 2006;97:61-67
FDA Safety Advisory on Statins
February, 2012

- Routine monitoring of liver enzymes in the blood, once considered standard procedure for statin users, is no longer needed. Such monitoring has not been found to be effective in predicting or preventing the rare occurrences of serious liver injury associated with statin use.
- Cognitive (brain-related) impairment, such as memory loss, forgetfulness and confusion, has been reported by some statin users.
- People being treated with statins may have an increased risk of raised blood sugar levels and the development of type 2 diabetes.
JUPITER Trial

- 17,802 subjects without known coronary disease or diabetes, with LDL-C <130 mg/dl and hs-CRP ≥2 mg/dl
- Randomized to rosuvastatin 20 mg/day or placebo
- Primary endpoint: CV death, MI, stroke, arterial revascularization, or hospitalization for unstable angina
- Study stopped after median follow-up of 1.9 years
- Primary endpoint occurred in 142 rosuvastatin and 251 placebo patients (HR 0.56, 95% CI 0.46-0.69)
- But, physician-diagnosed new-onset diabetes occurred in 270 rosuvastatin and 216 placebo patients (HR 1.25, 95% CI 1.05-1.49)

Statin Therapy and Incident Diabetes


ASCOT-LLA 7773 154 11.9 134 10.5 1.14 (0.89-1.46) 7.07%
HPS 14,573 335 9.2 293 8.0 1.15 (0.98-1.35) 13.91%
JUPITER 17,802 270 16.0 216 12.8 1.26 (1.04-1.51) 11.32%
WOSCOPS 5974 75 5.2 93 6.5 0.79 (0.58-1.10) 4.24%
LIPID 6997 126 6.0 138 6.6 0.91 (0.71-1.71) 6.53%
CORONA 3534 100 20.9 88 18.5 1.14 (0.84-1.55) 4.65%
PROSPER 5023 165 20.5 127 15.8 1.32 (1.03-1.69) 6.94%
MEGA 6086 172 10.8 164 10.1 1.07 (0.86-1.35) 8.03%
AFCAPS/TEXCAPS 6211 72 4.5 74 4.6 0.98 (0.70-1.38) 3.76%
4S 4242 198 17.3 193 16.8 1.03 (0.84-1.28) 8.88%
ALLHAT 6087 238 16.4 212 14.4 1.15 (0.95-1.41) 10.23%
GISSI HF 3378 225 34.8 215 32.1 1.10 (0.89-1.35) 9.50%
GISSI PREV 3460 96 27.5 105 30.6 0.89 (0.67-1.20) 4.94%

Overall (I² = 11.2% [95% CI 0.0-50.2%]) 1.09 (1.02-1.17) 100%
# Association Between Specific Statins and Development of Diabetes


## Table

<table>
<thead>
<tr>
<th>Statin</th>
<th>Placebo or Control</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>7773 154 134</td>
<td>1.14 (0.89-1.46)</td>
<td>7.07%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.14 (0.89-1.46)</td>
<td>7.07%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HPS</td>
<td>14,573 335 293</td>
<td>1.15 (0.98-1.35)</td>
<td>13.91%</td>
</tr>
<tr>
<td>4S</td>
<td>4242 198 193</td>
<td>1.03 (0.84-1.28)</td>
<td>8.88%</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>1.11 (0.97-1.26)</td>
<td>22.80%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JUPITER</td>
<td>17,802 270 216</td>
<td>1.26 (1.04-1.51)</td>
<td>11.32%</td>
</tr>
<tr>
<td>CORONA</td>
<td>3534 100 88</td>
<td>1.14 (0.84-1.55)</td>
<td>4.65%</td>
</tr>
<tr>
<td>GISSI HF</td>
<td>3378 225 215</td>
<td>1.10 (0.89-1.35)</td>
<td>9.60%</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>1.18 (1.04-1.33)</td>
<td>25.46%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>5974 75 93</td>
<td>0.79 (0.58-1.10)</td>
<td>4.24%</td>
</tr>
<tr>
<td>LIPID</td>
<td>6997 126 138</td>
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<td>PROSPER</td>
<td>5023 165 127</td>
<td>1.32 (1.03-1.69)</td>
<td>6.94%</td>
</tr>
<tr>
<td>MEGA</td>
<td>6086 172 164</td>
<td>1.07 (0.86-1.35)</td>
<td>8.03%</td>
</tr>
<tr>
<td>ALLHAT-LLT</td>
<td>6087 238 212</td>
<td>1.15 (0.95-1.41)</td>
<td>10.23%</td>
</tr>
<tr>
<td>GISSI PREV</td>
<td>3460 96 105</td>
<td>0.89 (0.67-1.20)</td>
<td>4.94%</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>1.03 (0.90-1.19)</td>
<td>40.91%</td>
</tr>
<tr>
<td>Lovastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>6211 72 74</td>
<td>0.98 (0.70-1.38)</td>
<td>3.76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.98 (0.70-1.38)</td>
<td>3.76%</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.09 (1.02-1.17)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Meta-Analysis of New-Onset Diabetes and First Major Cardiovascular Events in Trials Comparing Intensive- to Moderate-Dose Statin Therapy

<table>
<thead>
<tr>
<th>Incident Diabetes</th>
<th>Intensive Dose</th>
<th>Moderate Dose</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT–TIMI 22, 18 2004</td>
<td>101/1707 (5.9)</td>
<td>99/1688 (5.9)</td>
<td>1.01 (0.76-1.34)</td>
</tr>
<tr>
<td>A to Z, 17 2004</td>
<td>65/1768 (3.7)</td>
<td>47/1736 (2.7)</td>
<td>1.37 (0.94-2.01)</td>
</tr>
<tr>
<td>TNT, 15 2005</td>
<td>418/3798 (11.0)</td>
<td>358/3797 (9.4)</td>
<td>1.19 (1.02-1.38)</td>
</tr>
<tr>
<td>IDEAL, 16 2005</td>
<td>240/3737 (6.4)</td>
<td>209/3724 (5.6)</td>
<td>1.15 (0.95-1.40)</td>
</tr>
<tr>
<td>SEARCH, 5 2010</td>
<td>625/5398 (11.6)</td>
<td>587/5399 (10.9)</td>
<td>1.07 (0.95-1.21)</td>
</tr>
<tr>
<td><strong>Pooled odds ratio</strong></td>
<td>1449/16408 (8.8)</td>
<td>1300/16344 (8.0)</td>
<td>1.12 (1.04-1.22)</td>
</tr>
</tbody>
</table>

Heterogeneity: $i^2 = 0\%$; $P = .60$

<table>
<thead>
<tr>
<th>Incident CVD</th>
<th>Intensive Dose</th>
<th>Moderate Dose</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT–TIMI 22, 18 2004</td>
<td>315/1707 (18.4)</td>
<td>355/1688 (21.0)</td>
<td>0.85 (0.72-1.01)</td>
</tr>
<tr>
<td>A to Z, 17 2004</td>
<td>212/1768 (12.0)</td>
<td>234/1736 (13.5)</td>
<td>0.87 (0.72-1.07)</td>
</tr>
<tr>
<td>TNT, 15 2005</td>
<td>647/3798 (17.0)</td>
<td>830/3797 (21.9)</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>IDEAL, 16 2005</td>
<td>776/3737 (20.8)</td>
<td>917/3724 (24.6)</td>
<td>0.80 (0.72-0.89)</td>
</tr>
<tr>
<td>SEARCH, 5 2010</td>
<td>1184/5398 (21.9)</td>
<td>1214/5399 (22.5)</td>
<td>0.97 (0.88-1.06)</td>
</tr>
<tr>
<td><strong>Pooled odds ratio</strong></td>
<td>3134/16408 (19.1)</td>
<td>3550/16344 (21.7)</td>
<td>0.84 (0.75-0.94)</td>
</tr>
</tbody>
</table>

Heterogeneity: $i^2 = 74\%$; $P = .004$
Statin Use and DM in HIV:

• Retrospective study of statin use and risk of DM (abstract 766): pts with no statin at ART initiation
  – 5380 pts followed for 9.8 years, nadir CD4 214, 162 developed DM,
  – Statin use associated with 77% reduction in risk of DM (95% CI 0.08 to 0.63, p=0.004)
  – BMI> 30, TG, BL glucose, and use of D4T and DDI also associated.

• HIV Outpatient Study (Abstract 767)
  – 4962 pts followed for 49 months.
  – Statin use associated with incident DM (HR 1.1 per year, 95%CI 1.01-1.2, Hispanic race, and BMI≥ 30.

Spagnuolo V et al Abstract 766 CROI 2013
Lichtenstein K et al Abstract 767 CROI 2013
Guidelines use new ASCVD risk calculator

10-year risk (%) of ASCVD (non-fatal MI, CHD death, or fatal/non-fatal stroke) is calculated from simple parameters:

<table>
<thead>
<tr>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male or female)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Race (African-American or White/other)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
</tr>
<tr>
<td>Treatment for high BP (yes or no)</td>
</tr>
<tr>
<td>Diabetes (yes or no)</td>
</tr>
<tr>
<td>Smoker (yes or no)</td>
</tr>
</tbody>
</table>
• What is the impact of ART on cholesterol? forget statins, just switch ART...
Differential Effect of ART on Lipids

Slide from Dr. Vivek Jain UCSF

Green: No effect on lipids
Red: Worsening of lipid profile

NRTIs
- Tenofovir
- Abacavir
- D4T
- AZT

NNRTIs
- NVP
- Rilpivirine
- Etravirine
- EFV

PIs
- Darunavir
- Atazanavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Tipranavir

INSTIs
- Raltegravir
- Dolutegravir
- Stribalid
SPIRAL Study – PI to Raltegravir Switch

Substantial improvements in TG, TC, LDL, & HDL with switch from PI to RAL

Slide from Vivek Jain UCSF
Martinez E et al AIDS 2010
Switch to RGV vs. continuation of LPV/RTV – SWITCHMRK 1 and 2

Eron J et al Lancet 2010
PI → Complera (TDF/FTC/RPV) switch

**SPIRIT**

Changes from Baseline to Week 24 in Fasting Lipids

- TC: -25
- LDL: -16
- TG: 3
- HDL: -4

Graph showing changes in lipids with different treatment regimens.

Slide from Dr. Vivek Jain UCSF
Problems With Specific Statins

- Cerevastatin withdrawn from the market in 2001 due to high risk of rhabdomyolysis (52 deaths)
- Simvastatin has higher risk of myopathy than other currently available statins
- Rosuvastatin should probably not be used in patients with diabetes and CKD as a result of findings in PLANET I Trial
Statins- the cons…

• All statins slightly increase the risk of NOD
• Higher doses of potent statins cause slightly more NOD than lower doses of weaker statins
• CV risk reduction far exceeds the risk of NOD
• Hepatic enzyme monitoring is no longer recommended by the US FDA
• Simvastatin causes more myopathy than other statins. The 80 mg dose should be avoided and use with PIs is contraindicated
• Rosuvastratin should not be used in patients with diabetes and CKD (PLANET I)
Statins: unanswered questions in HIV

- No definitive studies demonstrating mortality and/or cvd benefit
- Unknown if ACSVD risk calculator applies in HIV, likely does not
- May not target the inflammatory pathways of interest in HIV
- Will not definitively answer the impact on inflammation (due to concomitant lowering of LDL)
- Drug-drug interactions
- Impact of new ART regimens on lipids and long term effects
- Are risks of DM same for HIV?
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• SFGH Cardiology
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  – Peter Hunt
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  – Rebecca Scherzer
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• University of Wisconsin – James Stein
• BWH Paul Ridker
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  – R01HL117713
  – U01 HL121819
  – K24AI112393
  – R56HL125034-01
  – R24A1067039
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Options: Rick Hecht
Pulm: Laurence Huang

SFGH Cardiology
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David Waters
Ann Bolger
John MacGregor
Chris Barnett

Hsue Research Team
Clinical:
Kristinalisa Maka
Courtney Carroll
Eric Secemsky
Dave Lange
Rushi Parikh
Vicki Parikh

SCOPE

Patients at SFGH

Vascular/US Tech:
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Craig Kalapus
Rina Donovan
Susan Takaki

UCSF Cardiology
Ethan Weiss
Zian Tseng

Dem
Mike McCune and team

VAMC
Carl Grunfeld, Harry Lampiris,
Rebecca Scherzer

Collaborators: MGH – Ahmed Tawakol; University of Colorado – Sonia Flores, UCLA-
Judith Currier; University of Wisconsin – James Stein; BWH-Stephen Chan; BWH –
Paul Ridker; University of Massachusetts – Jane Freedman; Boston University – Joe
Vita, NIAID – Irini Sereti