

# **The Role of Aspirin in HIV & Aging: Pro-Standpoint**

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6<sup>th</sup> International Conference on HIV and Aging  
October 6, 2015

# Disclosures

- None

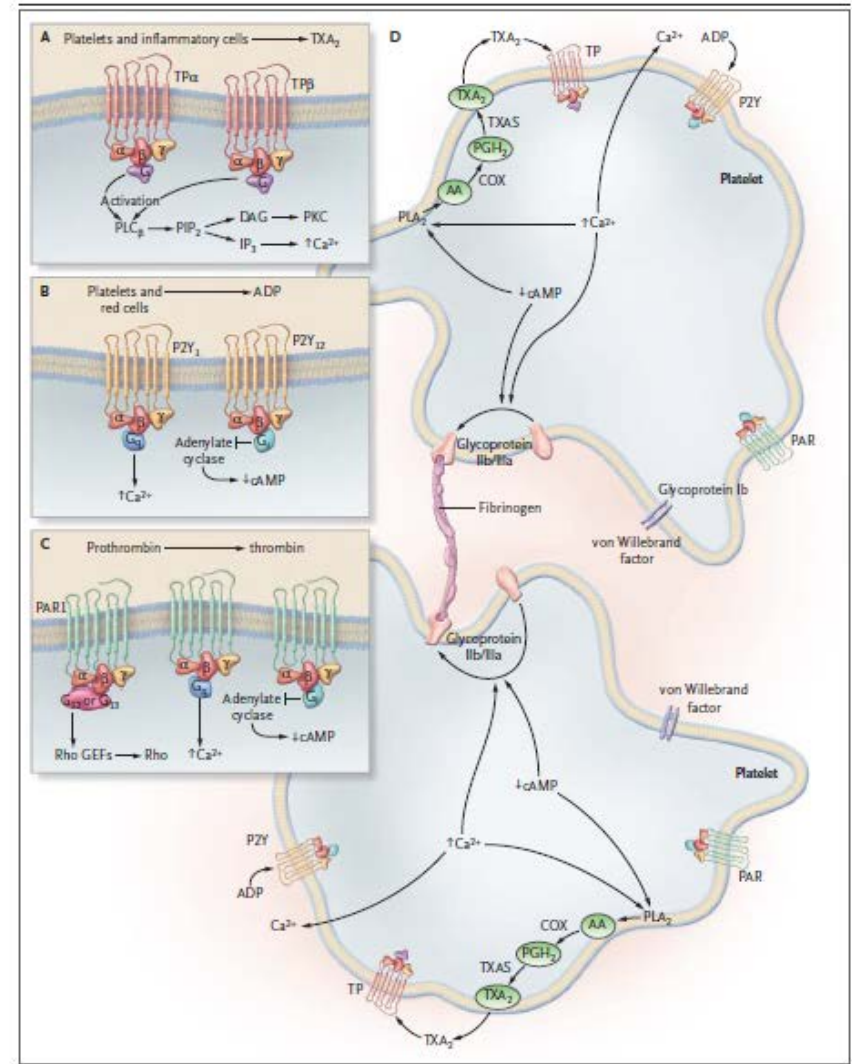
# Questions for Debate

**Should aspirin (ASA) be considered in HIV-infected persons with 10-year risk of atherosclerotic cardiovascular disease (ASCVD) >7.5%?**

**Is a randomized controlled trial of ASA to prevent vascular events in HIV indicated?**

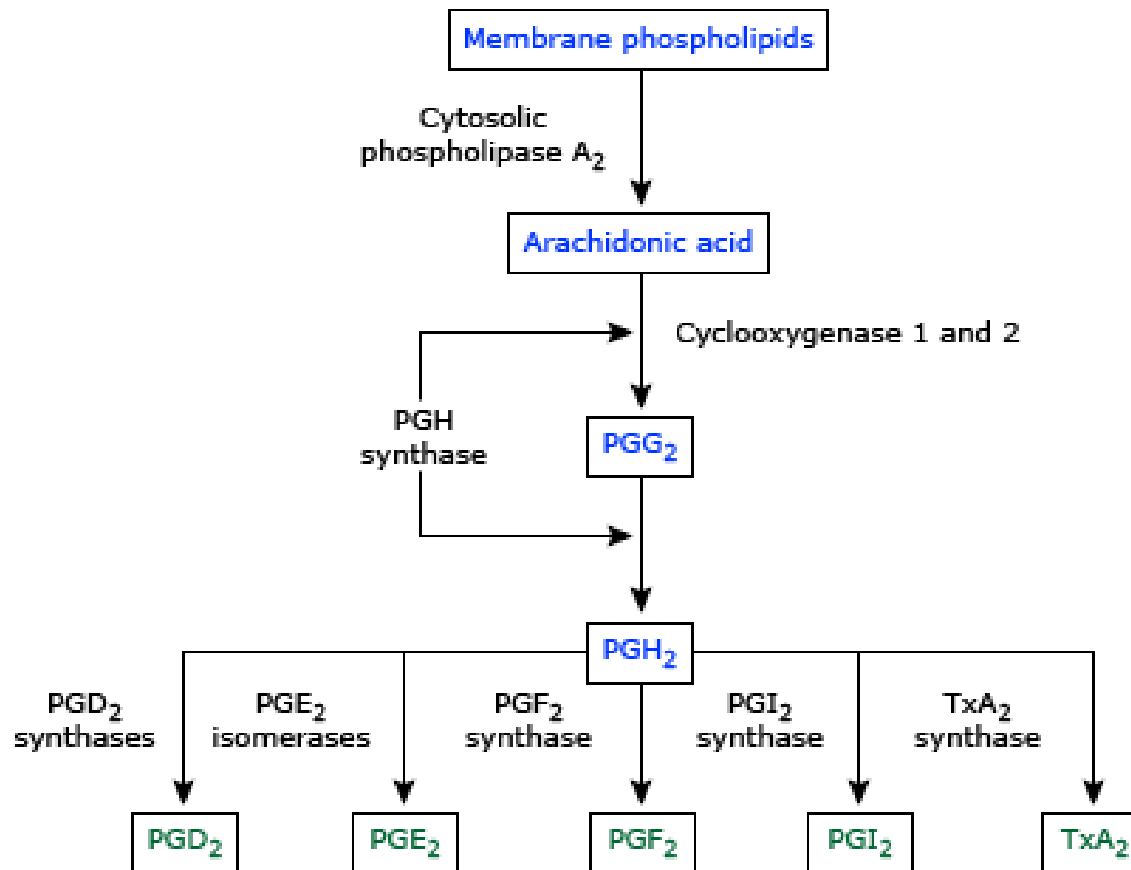
# Aspirin Mechanism of Action

- Nonsteroidal anti-inflammatory drug (NSAID)
- Anti-inflammatory, antithrombotic, antipyretic, and analgesic
- Antithrombotic effect: inhibits platelet production of thromboxane  $A_2$  ( $TXA_2$ ) → decreases platelet aggregation
- Antipyretic/analgesic: inhibits COX-1 and COX-2 → blocks prostaglandin production
  - COX-1 involved in platelet aggregation
  - COX-2 expressed in inflammation
- Anti-inflammatory: mechanism in part prostaglandin-related



# Aspirin Mechanism of Action

## Prostaglandin and thromboxane synthesis



# Aspirin Mechanism of Action

- Anti-inflammatory effects via prostaglandin-independent actions
  - Inhibition of expression of inducible nitric oxide synthase and generation of nitric oxide
  - Inhibition of activation of NF-kappa B, transcription factor involved in inducible expression of factors including IL-6 and TNF
  - Inhibition of neutrophil activation and adhesiveness
- Higher doses required for anti-inflammatory than antithrombotic effect as COX-2 is inhibited less efficiently than COX-1

# Aspirin for Primary Prevention of CVD

Population	Men Age 45–79 Years	Women Age 55–79 Years	Men Age <45 Years	Women Age <55 Years	Men and Women Age ≥80 Years
Recommendation	Encourage aspirin use when potential CVD benefit (MIs prevented) outweighs potential harm of GI hemorrhage	Encourage aspirin use when potential CVD benefit (strokes prevented) outweighs potential harm of GI hemorrhage	Do not encourage aspirin use for MI prevention	Do not encourage aspirin use for stroke prevention	No Recommendation
	Grade: A		Grade: D		Grade: I (insufficient evidence)

How to Use This Recommendation	<p>Shared decision making is strongly encouraged with individuals whose risk is close to (either above or below) the estimates of 10-year risk levels indicated below. As the potential CVD benefit increases above harms, the recommendation to take aspirin should become stronger.</p> <p>To determine whether the potential benefit of MIs prevented (men) and strokes prevented (women) outweighs the potential harm of increased GI hemorrhage, both 10-year CVD risk and age must be considered.</p> <table border="1"> <thead> <tr> <th colspan="4">Risk Level at Which CVD Events Prevented (Benefit) Exceeds GI Harms</th> </tr> <tr> <th colspan="2">Men</th> <th colspan="2">Women</th> </tr> <tr> <th>Age</th> <th>10-Year CHD Risk</th> <th>Age</th> <th>10-Year Stroke Risk</th> </tr> </thead> <tbody> <tr> <td>45–59 years</td> <td>≥4%</td> <td>55–59 years</td> <td>≥3%</td> </tr> <tr> <td>60–69 years</td> <td>≥9%</td> <td>60–69 years</td> <td>≥8%</td> </tr> <tr> <td>70–79 years</td> <td>≥12%</td> <td>70–79 years</td> <td>≥11%</td> </tr> </tbody> </table> <p>The table above applies to adults who are not taking NSAIDs and who do not have upper GI pain or a history of GI ulcers. NSAID use and history of GI ulcers increase the risk for serious GI bleeding events considerably and should be considered in determining the balance of benefits and harms.</p> <p>NSAID use combined with aspirin use approximately quadruples the risk for serious GI bleeding events compared with the risk with aspirin use alone. The rate of serious bleeding in aspirin users is approximately 2 to 3 times greater in patients with a history of GI ulcers.</p>	Risk Level at Which CVD Events Prevented (Benefit) Exceeds GI Harms				Men		Women		Age	10-Year CHD Risk	Age	10-Year Stroke Risk	45–59 years	≥4%	55–59 years	≥3%	60–69 years	≥9%	60–69 years	≥8%	70–79 years	≥12%	70–79 years	≥11%
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- USPSTF most recent published recommendation statement

# Aspirin for Primary Prevention of CVD



U.S. Preventive Services  
TASK FORCE



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## Draft Recommendation Statement

*Aspirin to Prevent Cardiovascular Disease and Cancer*

This opportunity for public comment expires on October 12, 2015 at 8:00 PM EST

- USPSTF recently released new draft recommendation statement on low-dose aspirin use for primary prevention of CVD and colorectal cancer



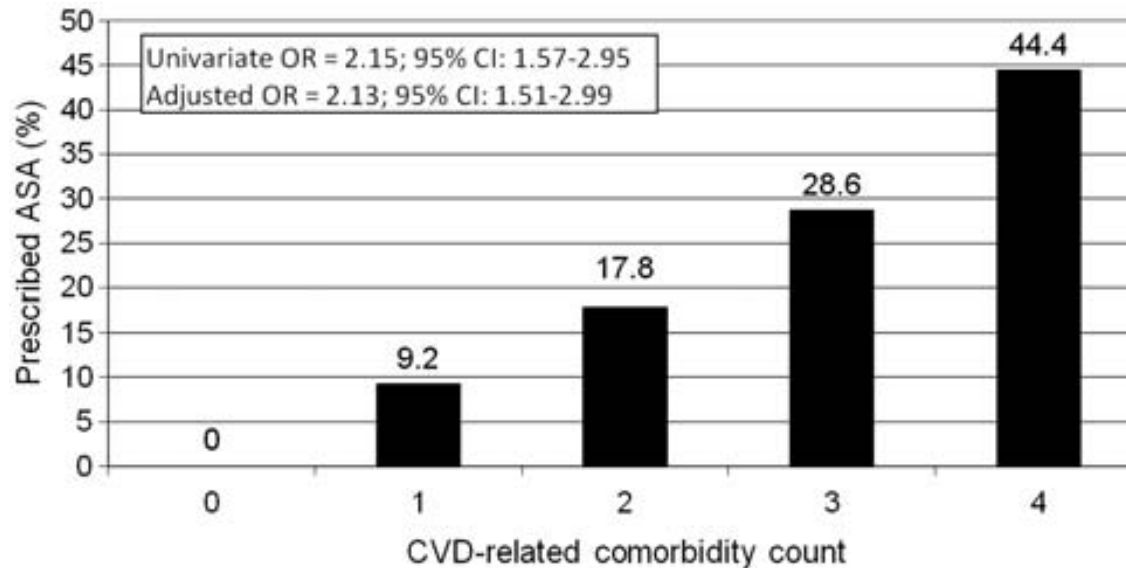
# Aspirin for Primary Prevention of CVD

Draft: Recommendation Summary		
Population	Recommendation	Grade (What's This?)
Adults ages 50 to 59 years	The USPSTF recommends low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer in adults ages 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	<b>B</b>
Adults ages 60 to 69 years	The decision to use low-dose aspirin to prevent CVD and colorectal cancer in adults ages 60 to 69 years who have a greater than 10% 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to use low-dose aspirin.	<b>C</b>
Adults younger than age 50 years	The current evidence is insufficient to assess the balance of benefits and harms of aspirin use to prevent CVD and colorectal cancer in adults younger than age 50 years.	<b>I</b>
Adults age 70 years and older	The current evidence is insufficient to assess the balance of benefits and harms of aspirin use to prevent CVD and colorectal cancer in adults age 70 years and older.	<b>I</b>

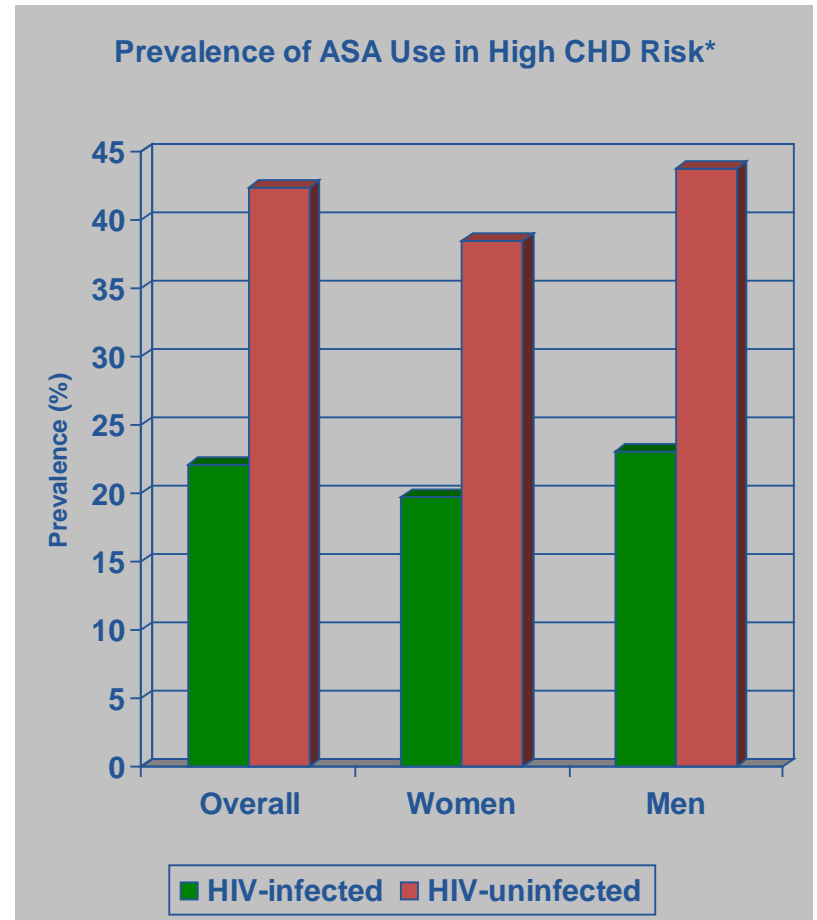
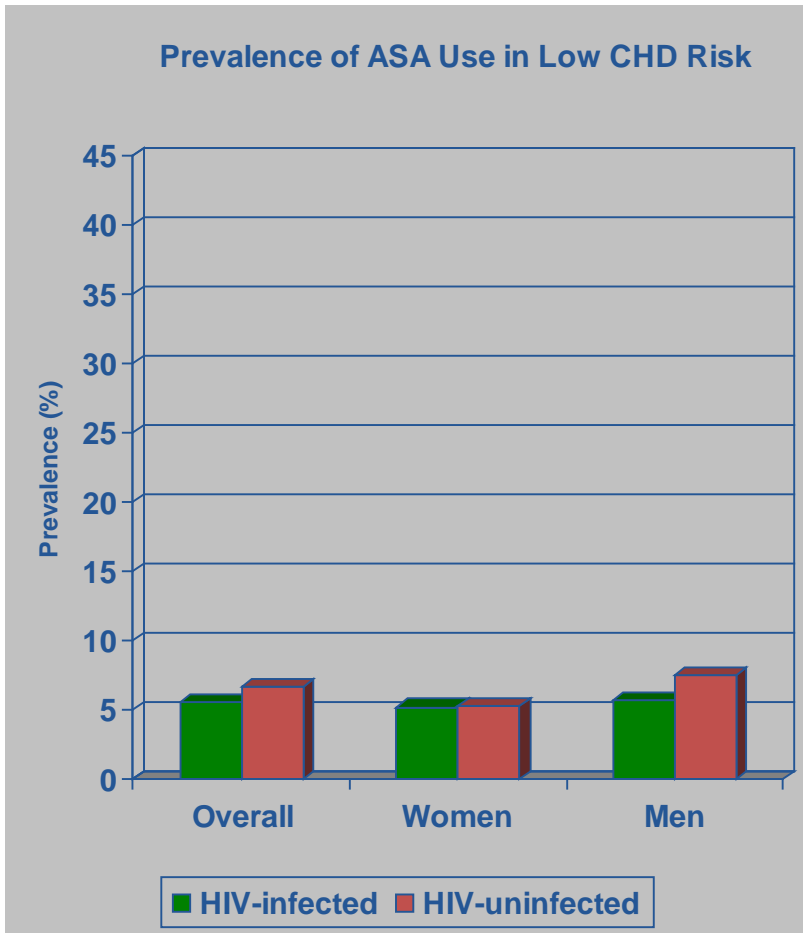
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# Aspirin Underused in HIV

- Fewer than 1 in 5 patients (17%) who qualified to receive ASA for primary prevention received it in large HIV clinic
  - 2009 US Preventive Services Task Force Guidelines
  - Odds of ASA use increased with each additional CVD risk factor
- In another study, 31% of patients met criteria for ASA yet 1.6% received it



# Aspirin Use in HIV Lower than Controls



# Pro-Standpoint

**Aspirin should be considered in HIV-infected persons with 10-year risk of atherosclerotic cardiovascular disease (ASCVD) >7.5%?**

- **Aspirin should be used more aggressively in HIV patients than in comparable general population patients**

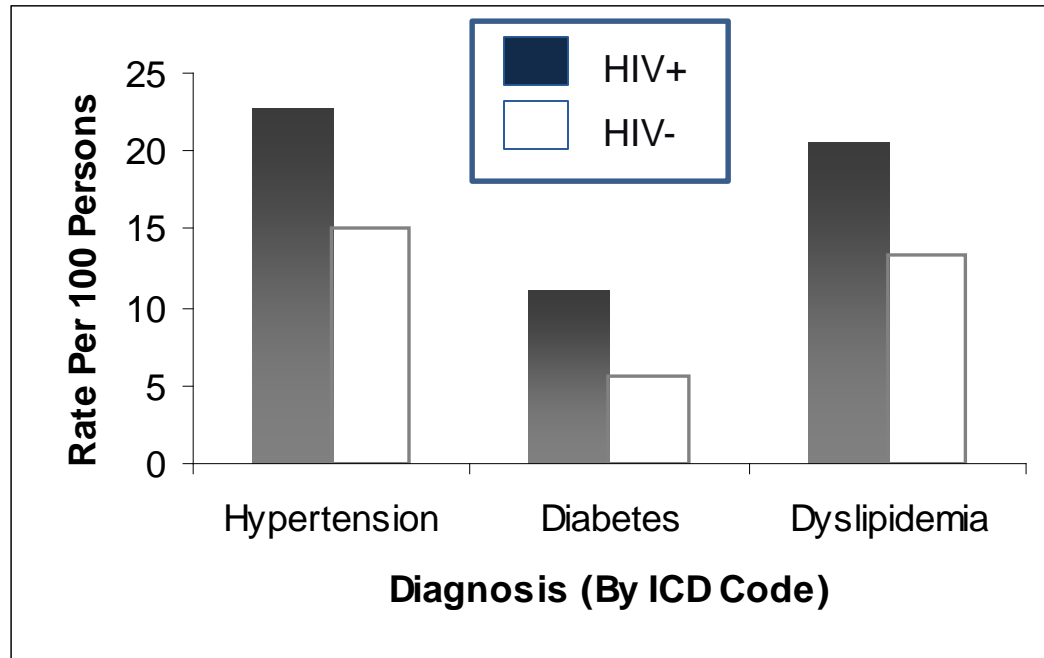
# Pro-Standpoint

- HIV patients have traditional and novel CVD risk factors that can be modulated by ASA
  - Increased rates of traditional CVD risk factors
  - Novel CVD risk factors related to inflammation and immune activation
- ASA has been shown to be an effective antithrombotic and anti-inflammatory in HIV
  - Increased platelet dysfunction and immune activation in HIV
  - ASA decreases platelet dysfunction and immune activation in HIV
- CVD risk prediction algorithms may underestimate risk in HIV
  - Traditional CVD risk factors may not be appropriately weighted
  - Novel CVD risk factors are not captured
  - Different thresholds may be needed in HIV

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# Elevated Rates of Traditional CVD Risk Factors in HIV

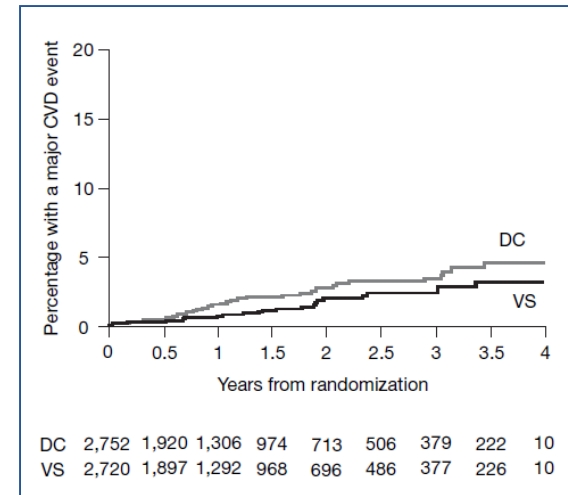
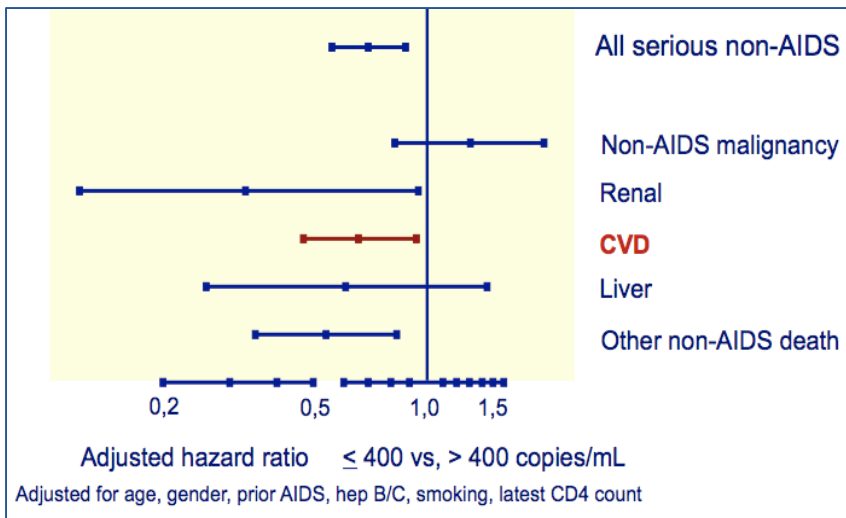


## Smoking in HIV

- Heightened rates
  - 56% (D:A:D)
  - 54% (SFGH)
  - 47% (US cohort)
  - 69% (French cohort)
- 85% lifetime history
- Significantly higher than non-HIV patients

# Novel CVD Risk Factors in HIV: Inflammation and Immune Activation

- SMART study showed increased CVD event rates in drug conservation (episodic treatment) vs. viral suppression (continuous treatment) group
  - HR=1.57, P=0.05
  - Primary endpoint recurrent OI/death



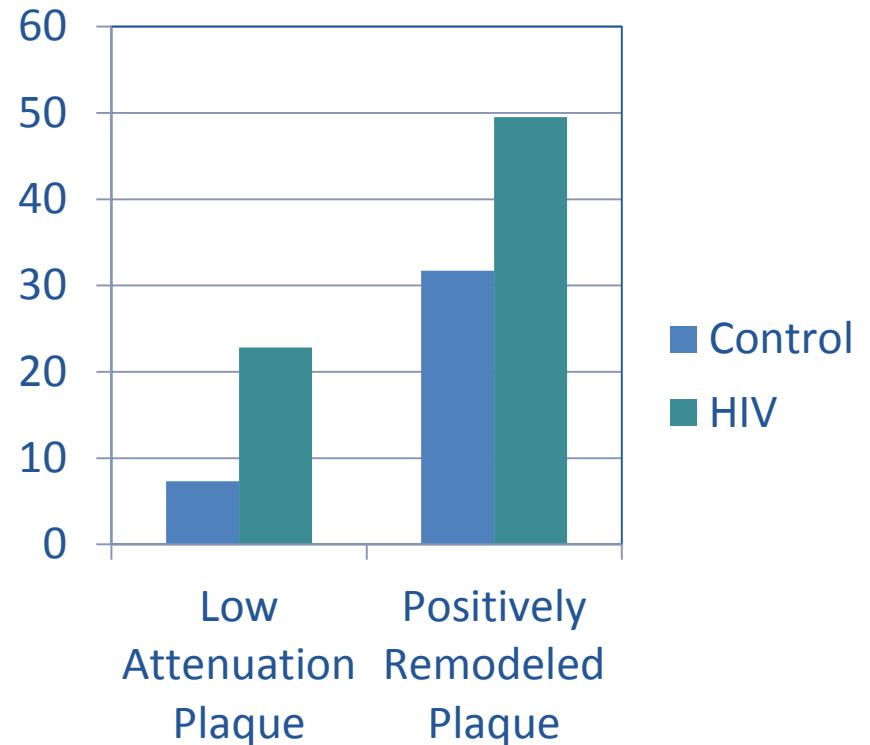
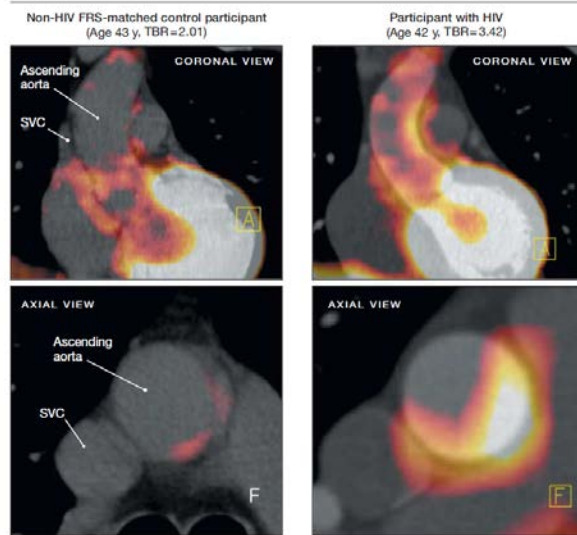
- Inflammatory markers IL-6 and d-dimer increased 1 month after treatment interruption in SMART
- Baseline hsCRP, IL-6, and d-dimer strongly correlated to overall mortality



# Novel CVD Risk Factors in HIV: Monocyte Activation

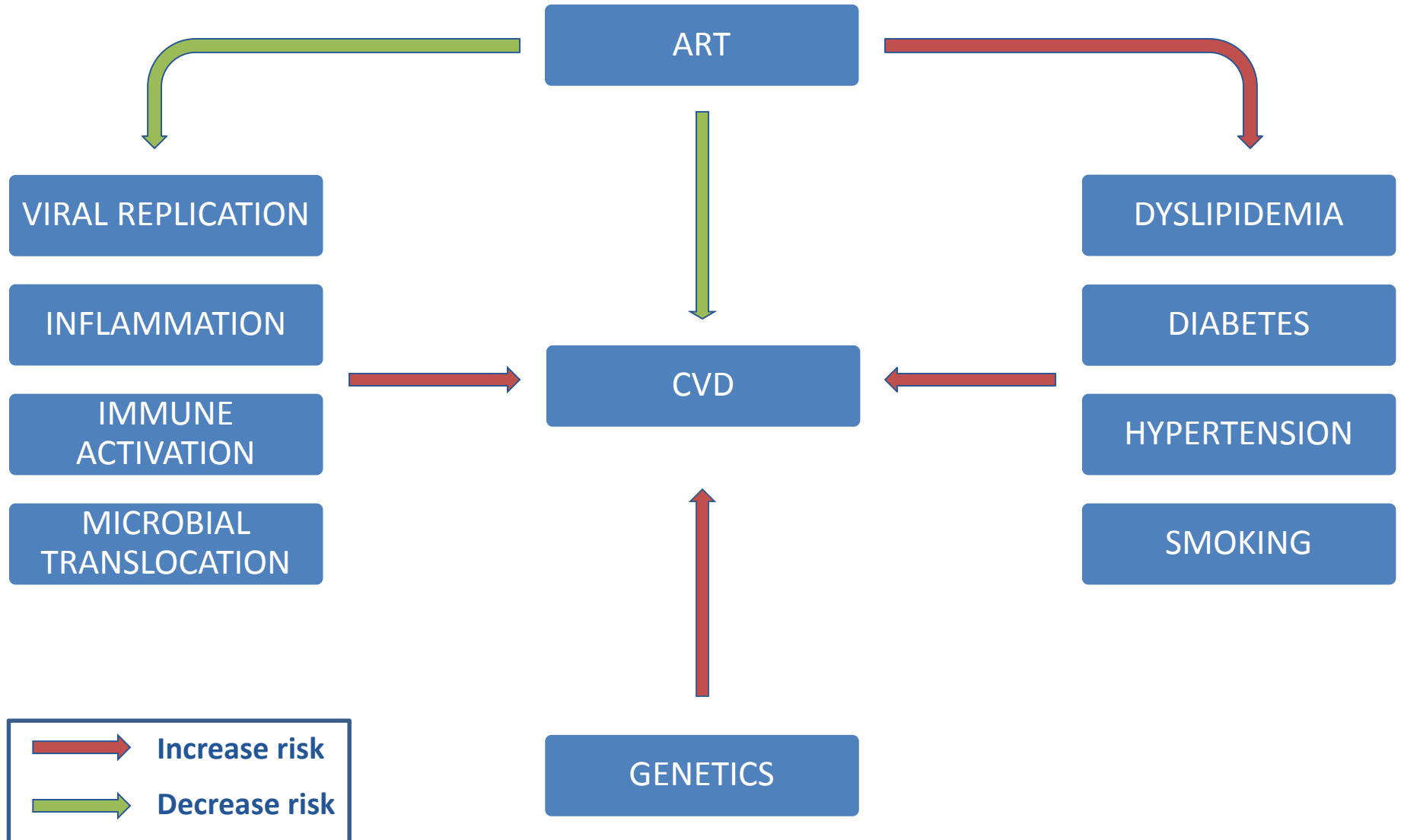
- Immune activation markers, including markers of monocyte activation (sCD163), are significantly linked to:
  - Presence of non-calcified vulnerable plaque
  - High-risk morphology plaque
  - Arterial inflammation (aortic TBR)

Figure 2. Representative <sup>18</sup>F-FDG-PET/CT Imaging of the Aorta



**% subjects with vulnerable plaque**

# Pathophysiology of HIV-Associated CVD



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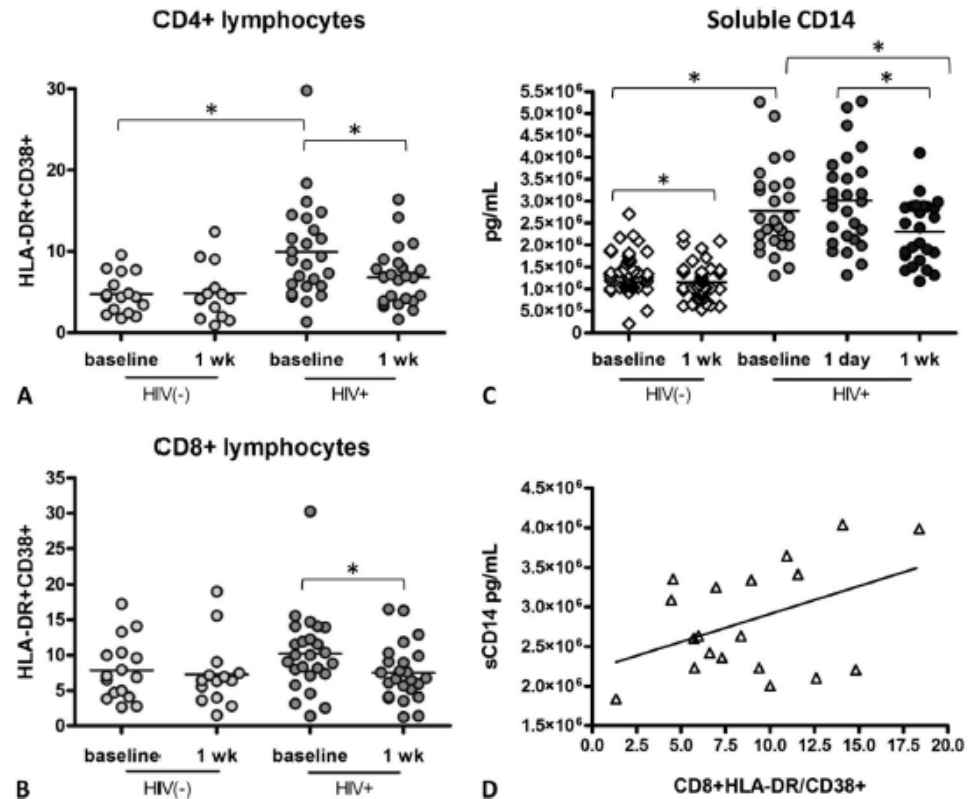
# Platelet Activation Increased and Linked to Immune Activation in HIV

- Platelet activation increased in HIV patients versus controls
  - As measured by P-selectin and CD63
- Platelet aggregation in response to some platelet agonists increased in several studies
- Platelets in HIV patients have lower threshold to activation
  - Dose-dependent hyper-reactivity
- HIV-activated platelets in turn activated monocytes
  - Direct role for activated platelets in immune activation

# Aspirin Decreases Platelet Activation and Immune Activation in HIV

## 1 week of low-dose ASA:

- Decreased percent platelet aggregation similarly in HIV and control patients in response to all except one agonist
- Attenuated T cell and monocyte activation
- ASA may decrease immune activation in HIV
  - Directly through inflammatory pathways
  - Indirectly through inhibition of platelet activation



# ACTG Aspirin Study

- **Modulation of Immune Activation by Aspirin**
- Interventional study assessing changes in immune activation with 12 weeks of ASA therapy
- Primary outcome change in sCD14 from baseline to week 12
- Secondary outcomes multiple immune, inflammatory and thrombotic markers

# Abacavir and Platelet Dysfunction

- Platelet reactivity increased in patients on abacavir-containing ART versus non-abacavir-containing ART
- Abacavir associated with platelet hyperreactivity
  - Competitively inhibits guanylyl cyclase
- Abacavir associated with reversible platelet dysfunction
  - Decreased ADP responsiveness and integrin  $\beta 3$  and platelet receptor levels
  - Suggests presence of immature platelets

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# New CVD Risk Assessment Guidelines

**Circulation**  
JOURNAL OF THE AMERICAN HEART ASSOCIATION



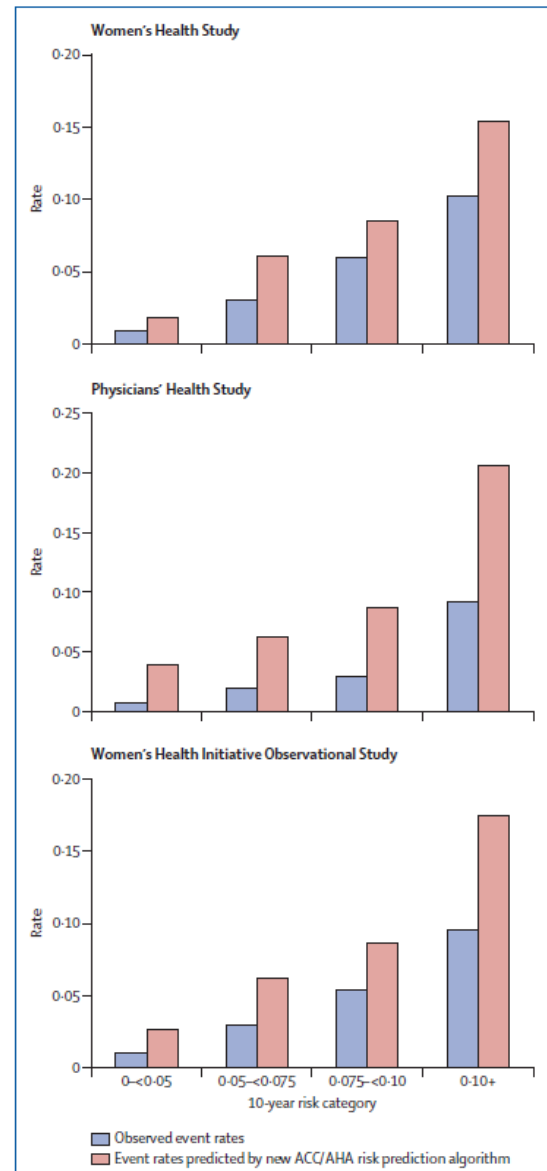
**2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines**

David C. Goff, Jr, Donald M. Lloyd-Jones, Glen Bennett, Sean Coady, Ralph B. D'Agostino, Sr, Raymond Gibbons, Philip Greenland, Daniel T. Lackland, Daniel Levy, Christopher J. O'Donnell, Jennifer Robinson, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Paul Sorlie, Neil J. Stone and Peter W.F. Wilson

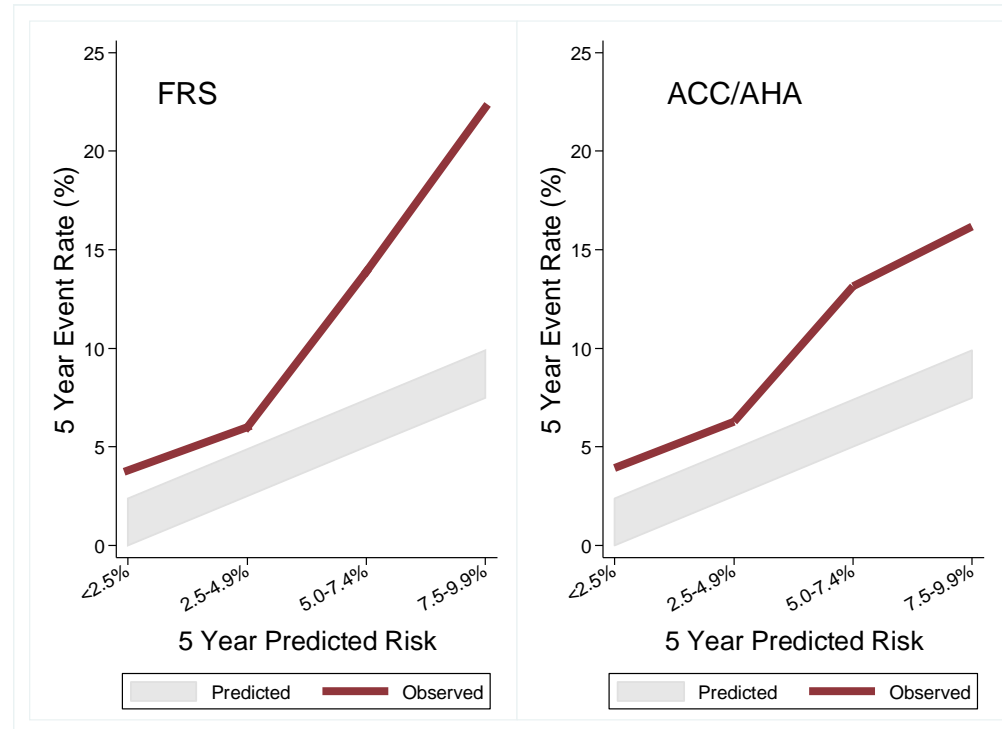
- New ACC/AHA guidelines on CVD risk estimation released in 2013
- New CVD risk prediction equation employed (Pooled cohorts equation)
- Reports of **overestimation** of risk in the general population

# ACC/AHA Calculator Overestimates Risk

- Primary prevention cohorts
- ACC/AHA risk prediction algorithm systematically overestimated observed risk in general population
- Degree of risk overestimation 75-150%
- Overestimation observed by guideline developers in 2 additional external validation cohorts
- Recent study from Women's Health Study also observed overestimation of risk



# CVD Risk Prediction Algorithms Underestimate Risk in HIV



- Partners HIV longitudinal cohort, 2239 patients
- Algorithms **underestimate** CVD risk in HIV, comparing observed to predicted rates
- To identify HIV patients at a target predicted CVD risk category, a lower threshold may need to be used (e.g. use 7.5% in HIV vs 10% in the general population)

# CVD Outcome Rates by Predicted Risk Category in HIV Cohort

10-Yr ASCVD Risk	LDL	N	Events	Rate/1000P Y	95% CI LL	95% CI UL
<7.5	<130	645	40	15.556	11.411	21.208
	<160	735	45	15.287	11.414	20.474
	<190	755	46	15.211	11.393	20.307
<10	<130	754	48	15.996	12.054	21.226
	<160	865	54	15.542	11.903	20.292
	<190	892	55	15.332	11.771	19.969
<15	<130	850	60	17.800	13.821	22.926
	<160	990	70	17.677	13.986	22.344
	<190	1026	71	17.271	13.686	21.794
<17.5	<130	872	66	19.081	14.991	24.287
	<160	1020	77	18.884	15.104	23.610
	<190	1061	78	18.344	14.693	22.902
<20	<130	887	69	19.695	15.555	24.936
	<160	1044	83	19.991	16.122	24.790
	<190	1087	84	19.378	15.647	23.999

# Questions for Debate

**Should aspirin (ASA) be considered in HIV-infected persons with 10-year risk of atherosclerotic cardiovascular disease (ASCVD) >7.5%?**

**Is a randomized controlled trial of ASA to prevent vascular events in HIV indicated?**

# Aspirin Use in HIV: Conclusions

- Adhere to general population guidelines at minimum
- Consider lower threshold for ASA use than that used in general population if no contraindication
  - USPSTF draft recommendations: consider 7.5% as a threshold rather than 10 (ACC/AHA risk score)
  - Tailor based on gender, age, and predicted 10-year CVD risk
- Consider ASA use in HIV patients on abacavir-containing ART
- Use ASA in combination with other CVD risk reduction strategies
- A trial of ASA for CVD risk reduction in HIV would enhance current knowledge
  - Consider trial in combination with other immunomodulatory interventions
  - Consider marker of preclinical atherosclerosis as outcome
- **HIV patients merit aggressive CVD risk reduction as a population**