HIV Infection and Cardiovascular Disease

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Disclosures

- None

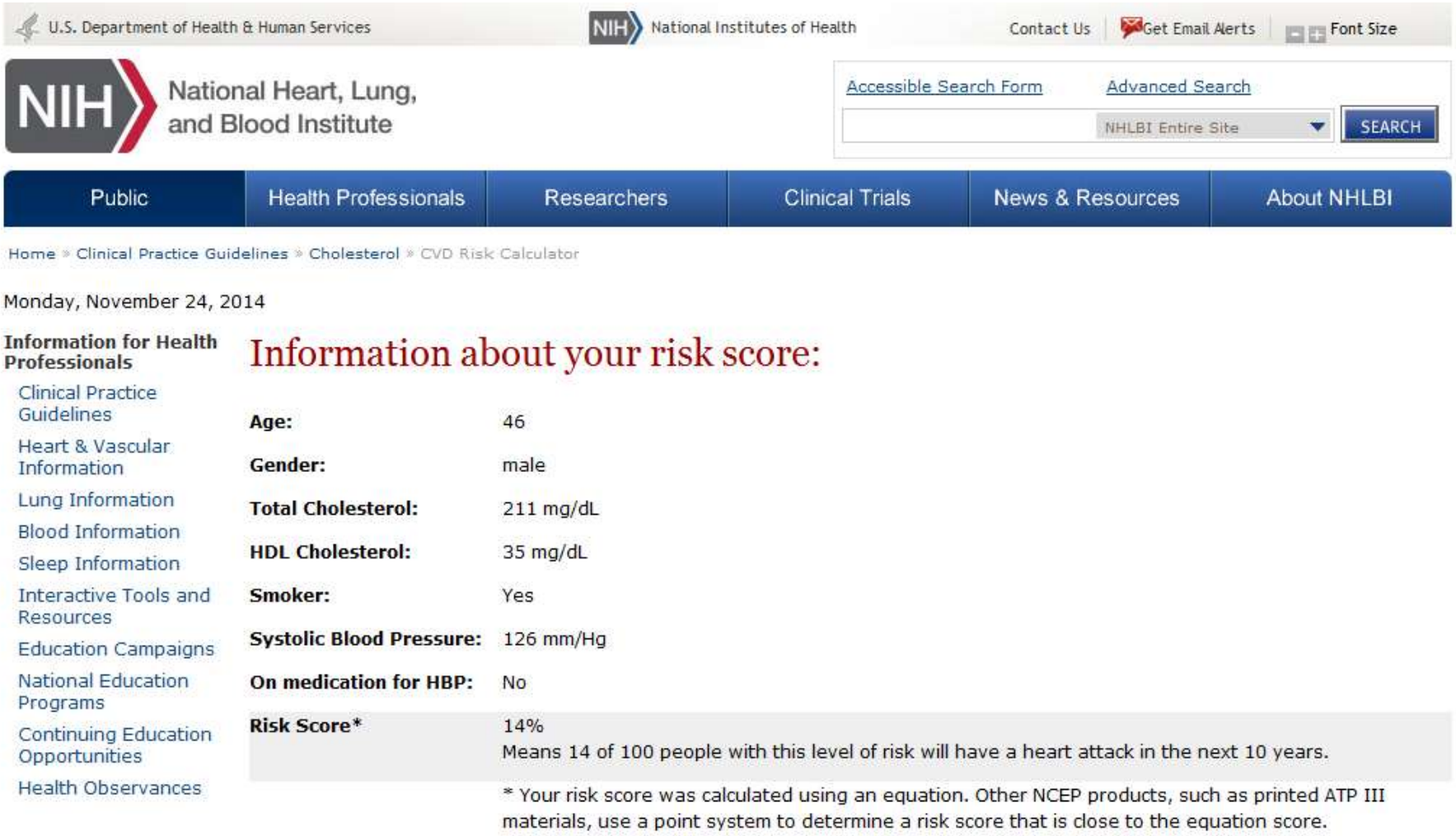
Outline

- Context of HIV and CVD
- Pathophysiology of HIV and CVD
  - Role of traditional risk factors and ART
  - Role of inflammation/immune activation
- Management of CVD in HIV
  - CVD risk prediction
  - CVD prevention
    - Novel risk factors
    - Traditional risk factors

Case

- 46 year old man diagnosed with HIV 3 years ago
- CD4 800 and HIV RNA undetectable on abacavir/lamivudine/darunavir/ritonavir
- No other significant medical history
- Smokes one pack per day despite numerous quit attempts
- BP 126/74
- TC 211, LDL 147, HDL 35, TG 194

Framingham Risk Score



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Information about your risk score:

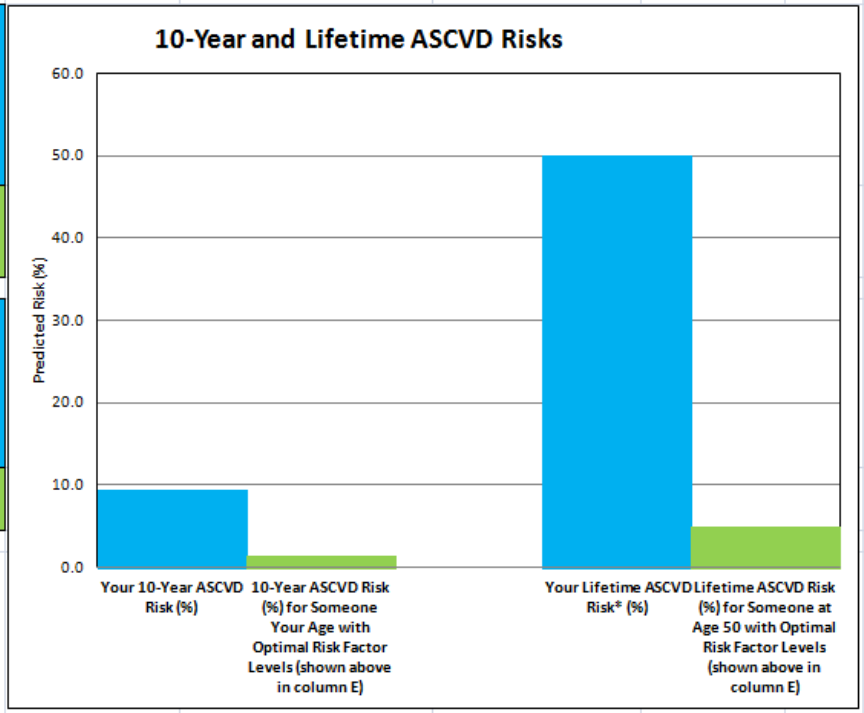
Age:	46
Gender:	male
Total Cholesterol:	211 mg/dL
HDL Cholesterol:	35 mg/dL
Smoker:	Yes
Systolic Blood Pressure:	126 mm/Hg
On medication for HBP:	No
Risk Score*	14% Means 14 of 100 people with this level of risk will have a heart attack in the next 10 years.

* 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.

ACC/AHA Risk Score

Risk Factor	Units	Value	Acceptable range of values	Optimal values
Sex	M (for males) or F (for females)	M	M or F	
Age	years	46	20-79	
Race	AA (for African Americans) or WH (for whites or others)	WH	AA or WH	
Total Cholesterol	mg/dL	211	130-320	170
HDL-Cholesterol	mg/dL	35	20-100	50
Systolic Blood Pressure	mm Hg	126	90-200	110
Treatment for High Blood Pressure	Y (for yes) or N (for no)	N	Y or N	N
Diabetes	Y (for yes) or N (for no)	N	Y or N	N
Smoker	Y (for yes) or N (for no)	Y	Y or N	N

Your 10-Year ASCVD Risk (%)	9.4
10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)	1.3
Your Lifetime ASCVD Risk* (%)	50.0
Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (shown above in column E)	5.0



*This is the lifetime ASCVD risk for an individual at age 50 years with your risk factor levels. In rare cases, 10-year risks may exceed lifetime risks given that the estimates come from different approaches. While 10-year risk estimates are derived from methods and data using continuous variables, the reported estimate of lifetime risk is based on assigning each person into one of 5 mutually exclusive sex-specific groups, as per Lloyd-Jones et al., Circulation

For patients and the public: *This is the

Case

- Which intervention would you prioritize to reduce his cardiovascular risk?

  A. Switch off abacavir

  B. Assist in quitting smoking

  C. Start a statin

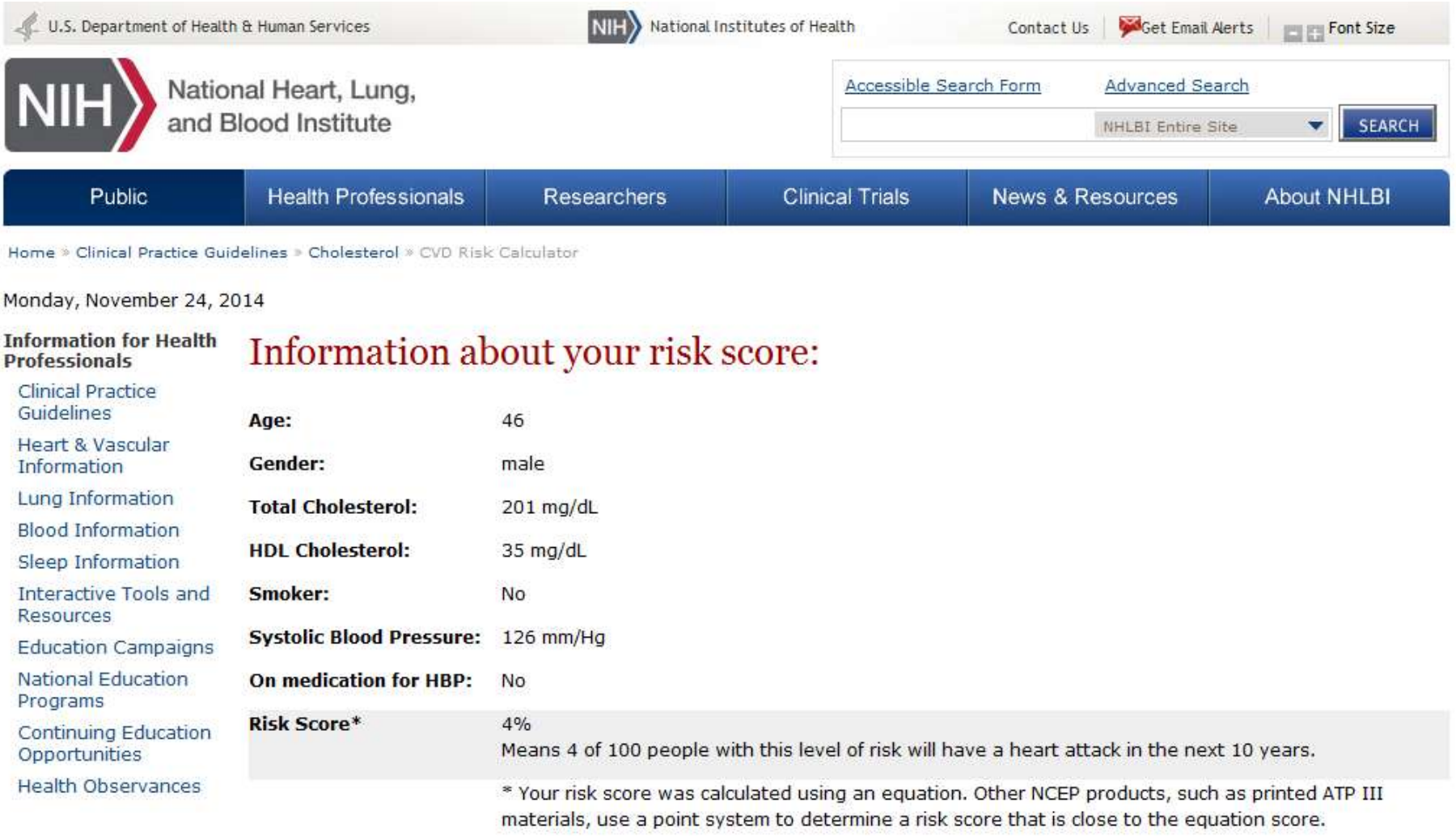
  D. Switch off ritonavir

  E. Start ASA

Case

- He starts to exercise and quits smoking.
- TC 201, LDL 127, HDL 35, TG 194

Framingham Risk Score



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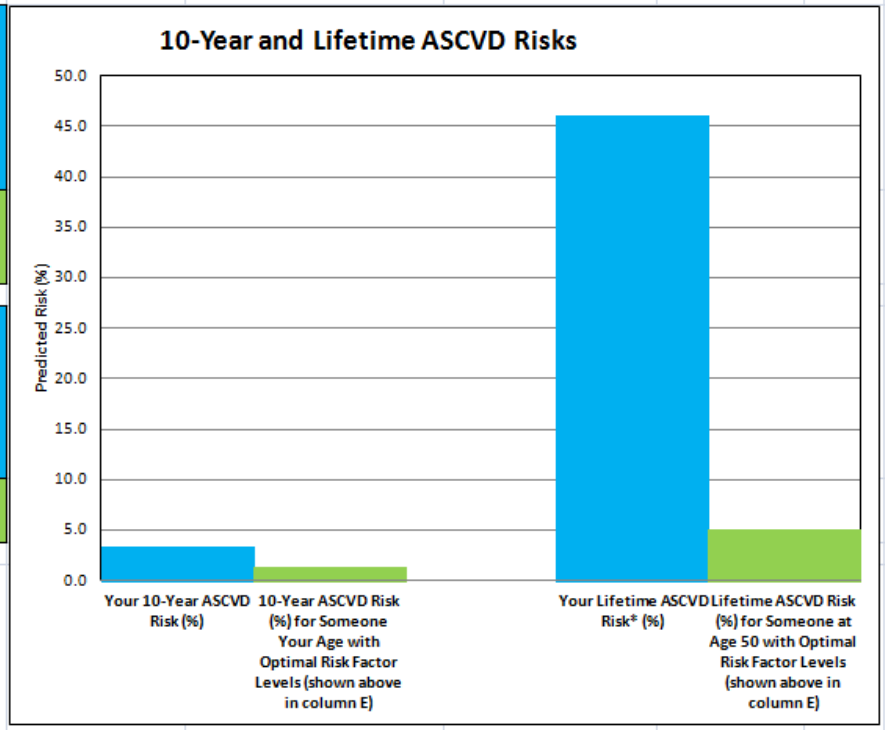
Information about your risk score:

Age:	46
Gender:	male
Total Cholesterol:	201 mg/dL
HDL Cholesterol:	35 mg/dL
Smoker:	No
Systolic Blood Pressure:	126 mm/Hg
On medication for HBP:	No
Risk Score*	4% Means 4 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.

ACC/AHA Risk Score

	A	B	C	D	E	F	H	I
1			Enter patient values in this column					
2	Risk Factor	Units	Value	Acceptable range of values	Optimal values			
3	Sex	M (for males) or F (for females)	M	M or F				
4	Age	years	46	20-79				
5	Race	AA (for African Americans) or WH (for whites or others)	WH	AA or WH				
6	Total Cholesterol	mg/dL	201	130-320	170			
7	HDL-Cholesterol	mg/dL	35	20-100	50			
8	Systolic Blood Pressure	mm Hg	126	90-200	110			
9	Treatment for High Blood Pressure	Y (for yes) or N (for no)	N	Y or N	N			
10	Diabetes	Y (for yes) or N (for no)	N	Y or N	N			
11	Smoker	Y (for yes) or N (for no)	N	Y or N	N			
12								
13	Your 10-Year ASCVD Risk (%)	3.4						
14	10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)	1.3						
15								
16	Your Lifetime ASCVD Risk* (%)	46.0						
17	Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (shown above in column E)	5.0						
18								



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For patients and the public: *This is the

Case

- Which intervention would you prioritize now to reduce his cardiovascular risk?

  A. Switch off abacavir

  B. Start a statin

  D. Switch off ritonavir

  E. Start ASA

Outline

- Context of HIV and CVD
- Pathophysiology of HIV and CVD
  - Role of traditional risk factors and ART
  - Role of inflammation/immune activation
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  - CVD prevention
    - Novel risk factors
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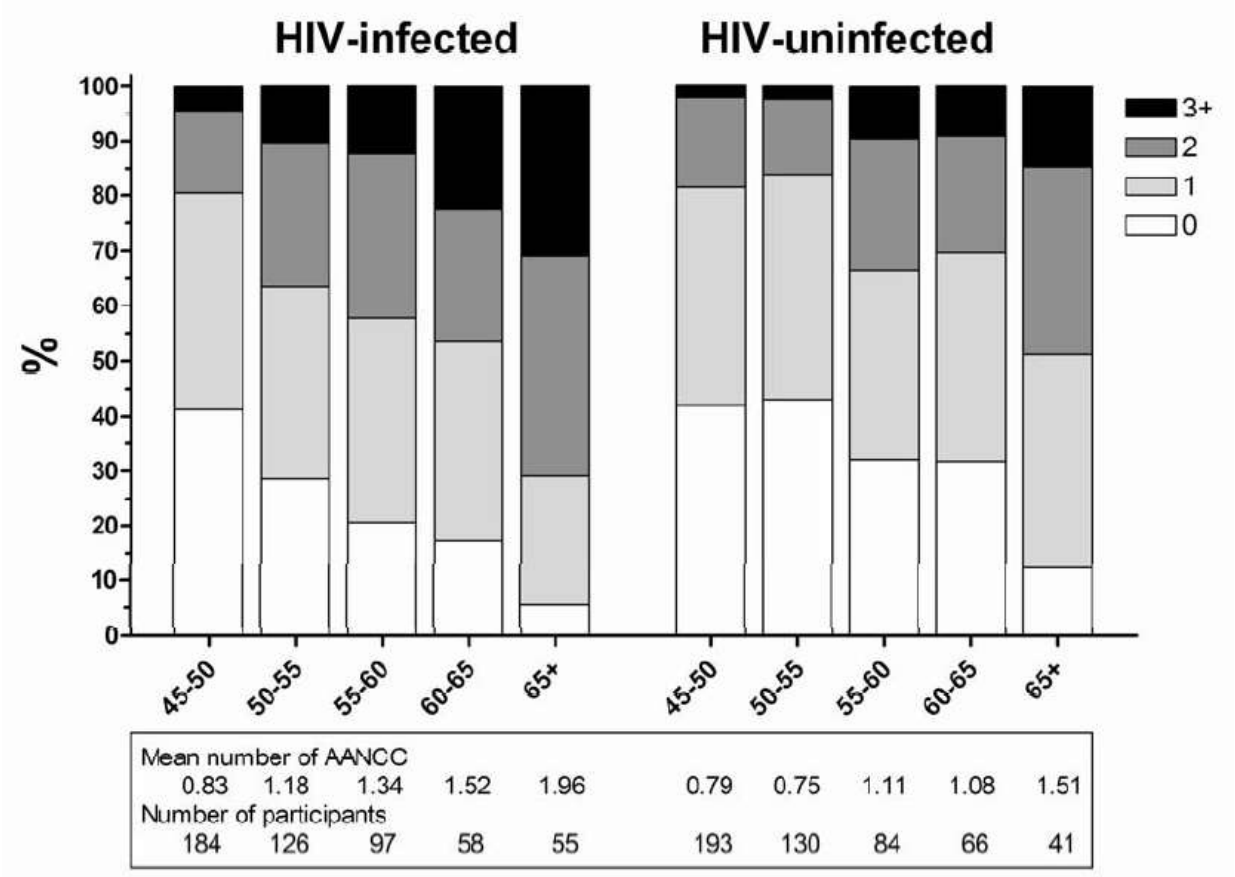
Non-Communicable Disease Complications in HIV



Aging-associated noncommunicable comorbidities (AANCC) include:
HTN, MI, PAD, CVA, angina, DM2, COPD, CKD, non-AIDS cancer, fracture/osteoporosis

Schouten CID 2014.

HIV and Risk of Acute Myocardial Infarction

Study	Year	Population	N (HIV)	Primary Result	Effect Size
Klein	2002	Kaiser	4159	↑ MI and CHD in HIV vs. control	1.5 (MI) 1.7 (CHD)
Currier	2003	CA Medicaid	28513	↑ CHD in HIV (age 18-33) vs. control	2.06
Triant	2007	Partners	3851	↑ MI in HIV vs. control	1.75
Obel	2007	Danish cohort	3953	↑ CHD in HIV (on ART) vs. control	2.12
Lang	2010	FHDH	74958	↑ MI in HIV vs. 3 population registries	1.5
Durand	2011	Quebec	7053	↑ MI in HIV vs. 4:1 matched control	2.11
Freiberg	2013	VA	27350	↑ MI in HIV vs. 2:1 matched control	1.48
Silverberg	2014	Kaiser	22081	↑ MI and CHD in HIV vs. 10:1 matched control	1.4

Klein JAIDS 2002; Currier JAIDS 2003; Triant JCEM 2007; Obel HIV Med 2010; Lang AIDS 2010; Durand JAIDS 2011; Freiberg JAMA Intern Med 2013; Silverberg JAIDS 2014.

CVD Incidence by Gender and Age

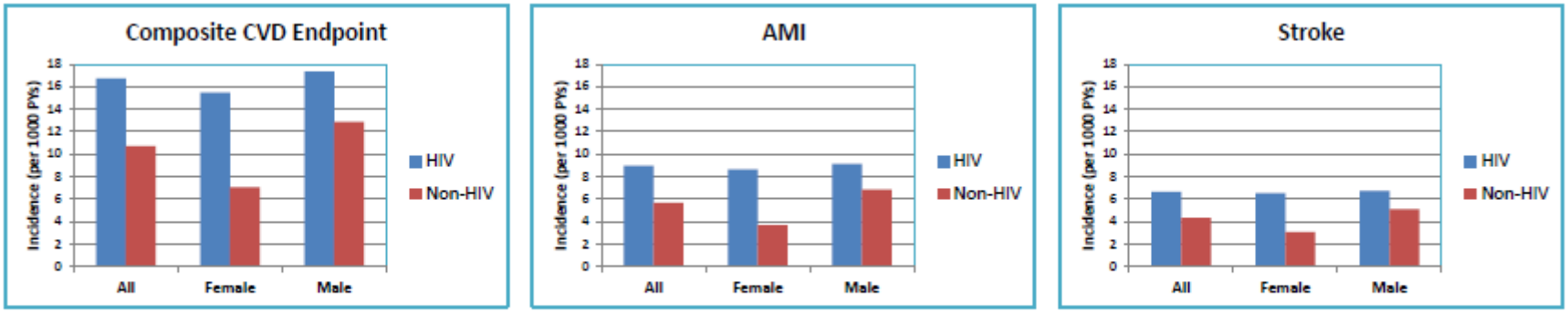


Figure 1: CVD Incidence Rates by Gender. Incidence rates per 1000 PYs are shown for the composite CVD endpoint (including AMI, stroke, angina or coronary revascularization) and for AMI and stroke individually. For each outcome, incidence rates are shown comparing HIV to control groups in all patients and within each gender. All differences in incidence rates comparing HIV to control groups are statistically significant.

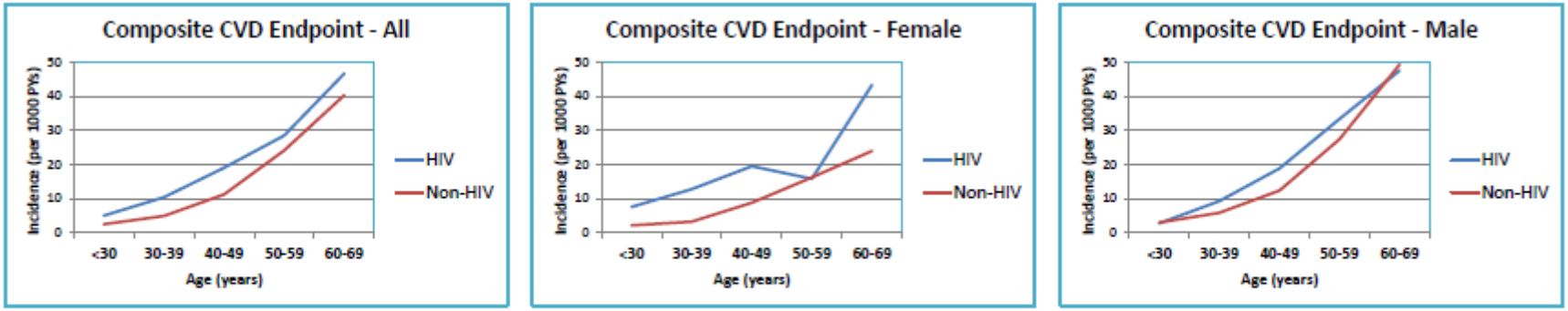
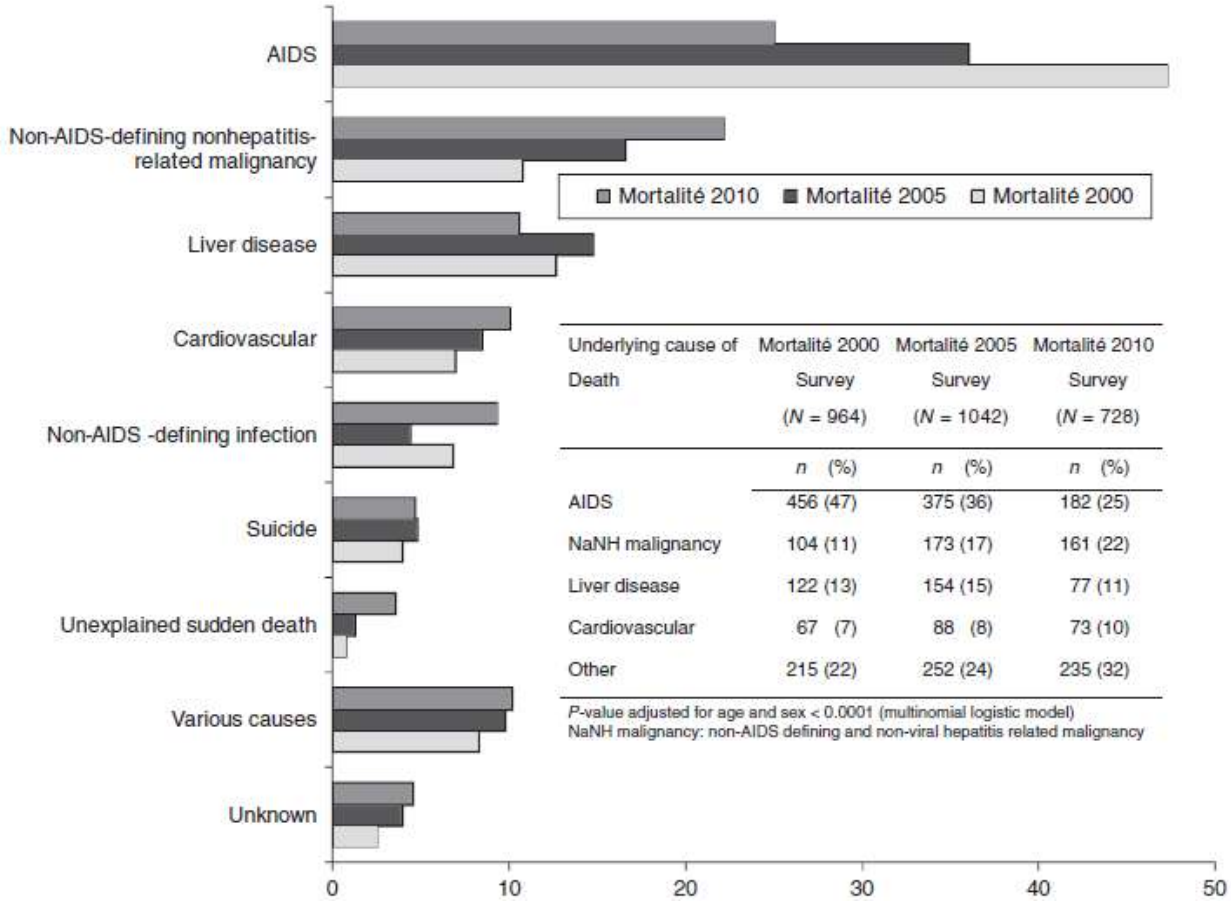


Figure 2: CVD Incidence Rates by Age Group. Incidence rates per 1000 PYs are shown for the composite CVD endpoint (including AMI, stroke, angina or coronary revascularization). For the overall group and each gender, incidence rates are shown comparing HIV to control groups according to age group.

- Increased relative risk in patients traditionally considered low risk
- May reflect the different distribution of CVD risk factors in HIV

Triant CROI 2014, abstract 738.

CVD Mortality in HIV



Underlying cause of Death	Mortalité 2000 Survey (*N* = 964)	Mortalité 2005 Survey (*N* = 1042)	Mortalité 2010 Survey (*N* = 728)
	n (%)	*n* (%)	*n* (%)
AIDS	456 (47)	375 (36)	182 (25)
NaNH malignancy	104 (11)	173 (17)	161 (22)
Liver disease	122 (13)	154 (15)	77 (11)
Cardiovascular	67 (7)	88 (8)	73 (10)
Other	215 (22)	252 (24)	235 (32)

P-value adjusted for age and sex < 0.0001 (multinomial logistic model)
NaNH malignancy: non-AIDS defining and non-viral hepatitis related malignancy

Morlat AIDS 2014.

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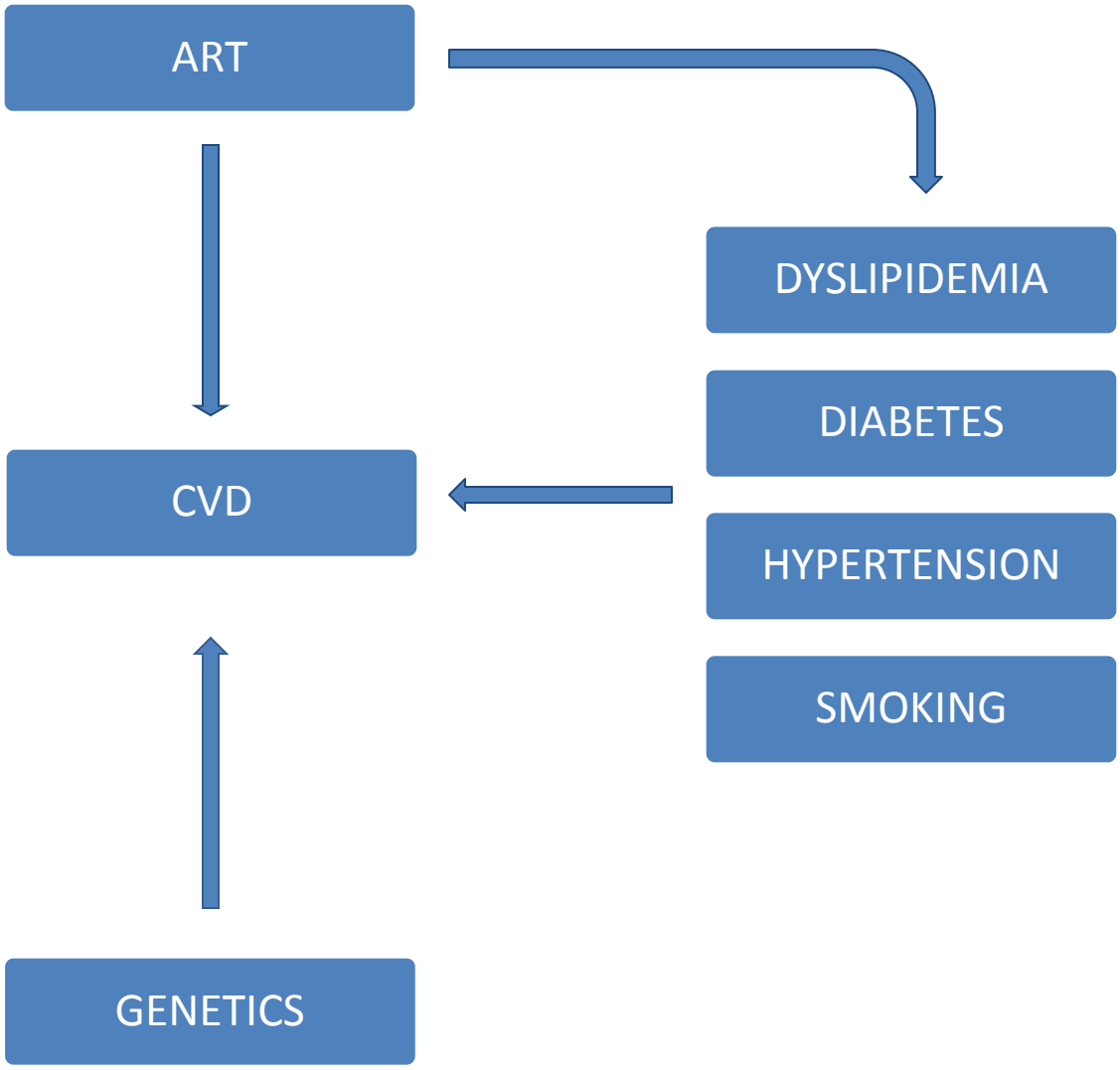
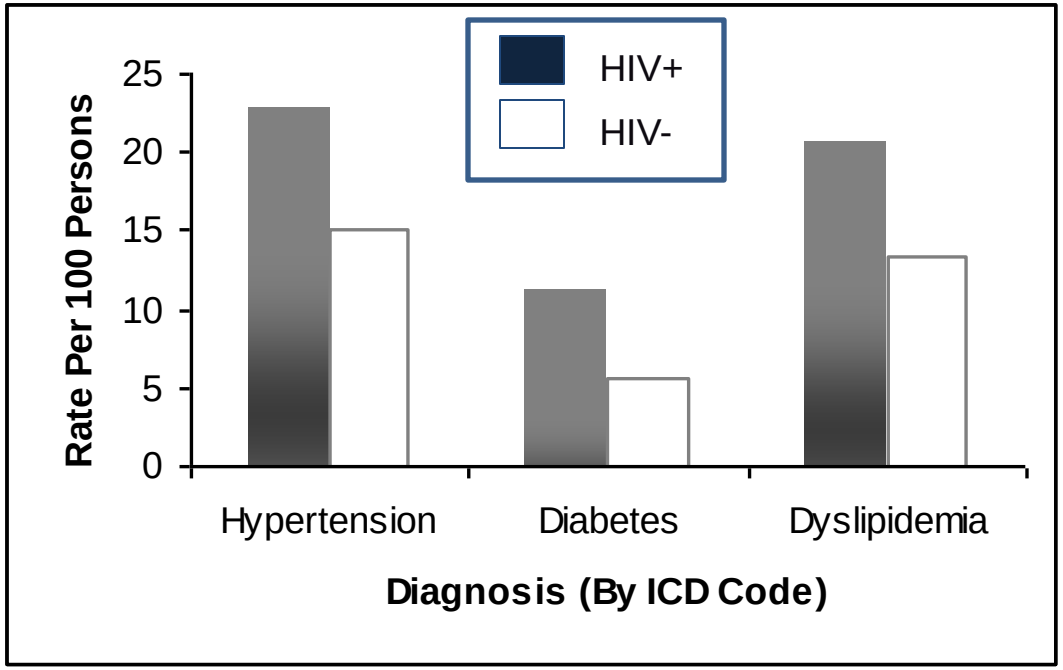
  - CVD prevention
    - Novel risk factors
    - Traditional risk factors

Pathophysiology of HIV-Associated CVD

- Early (1990s-early/mid 2000s) understanding of heightened CVD risk
- Traditional CVD risk factors
  - Elevated rates observed in HIV
- ART
  - Select PIs
  - Abacavir (debated)
  - Effects on CVD risk factors versus other effects



Traditional CVD Risk Factors in HIV

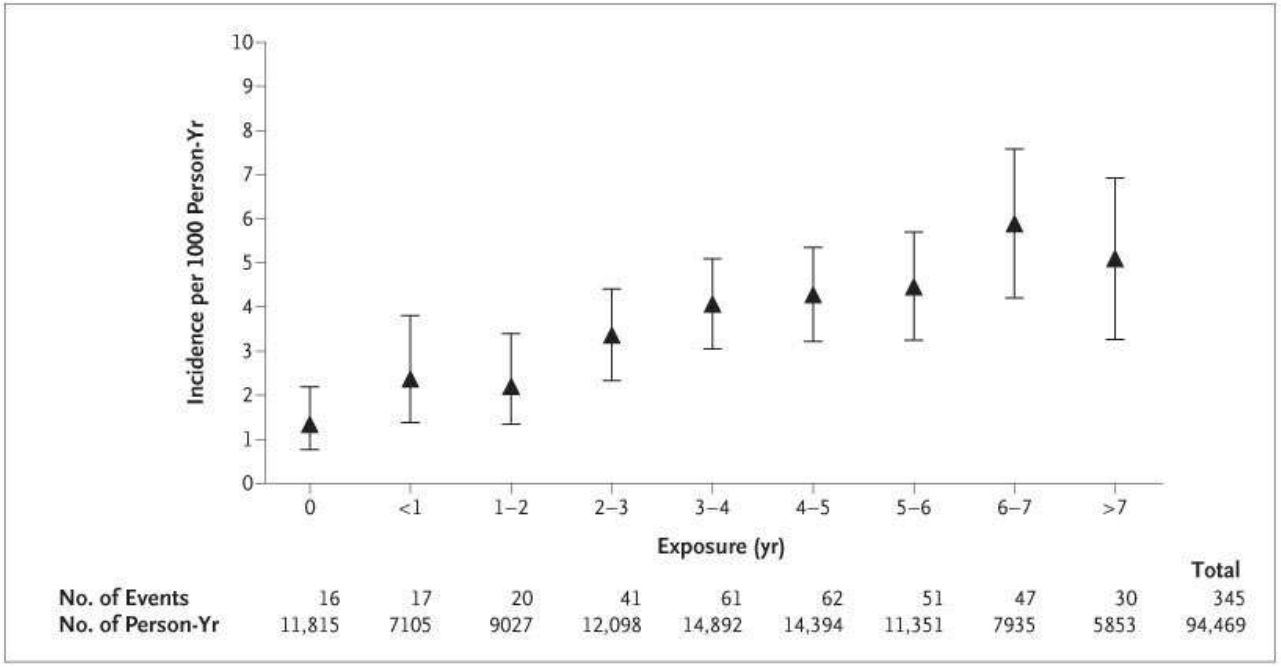


Smoking in HIV

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

Triant JCEM 2007; Burkhalter Nicotine Tob Res 2005; Friis-Moller AIDS 2003; Mamary AIDS Pt Care STDs 2002; Gritz Nicotine Tob Res 2004; Vittecoq AIDS 2003; Savès CID 2003; Lifson AJPH 2010.

AMI Incidence Increased with ART/PIs

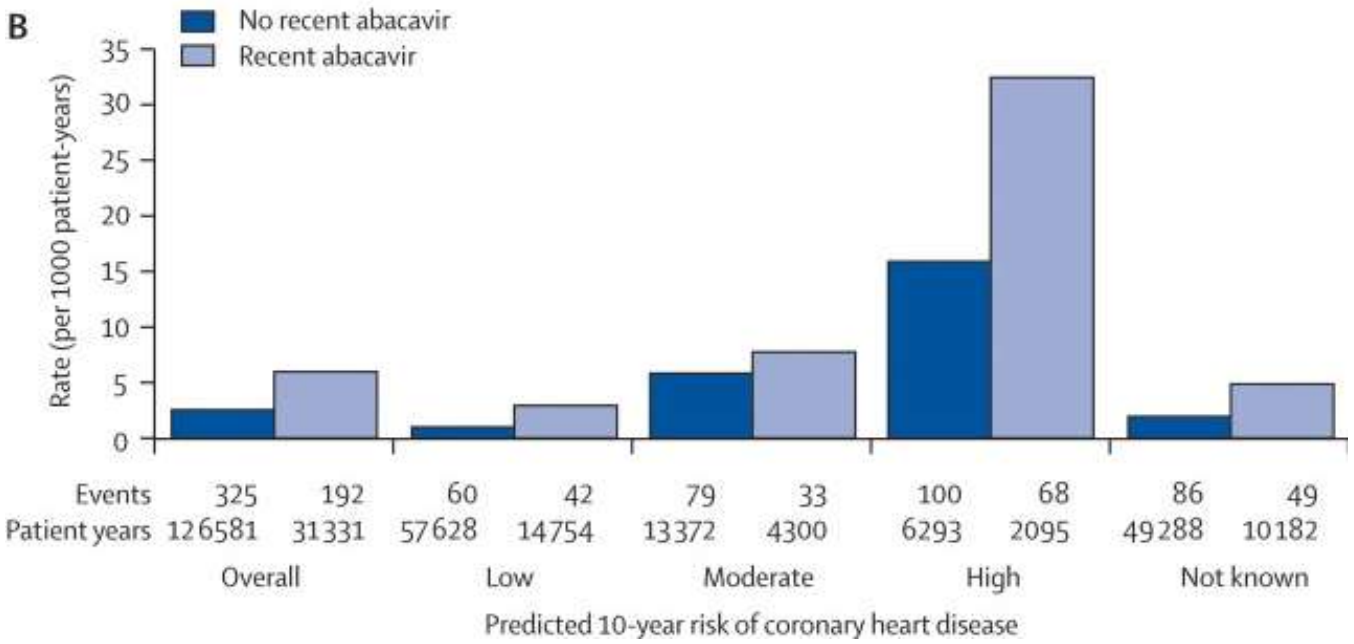


										Total
No. of Events	16	17	20	41	61	62	51	47	30	345
No. of Person-Yr	11,815	7105	9027	12,098	14,892	14,394	11,351	7935	5853	94,469

- D:A:D - prospective observational cohort of 33,347 patients
- Relative risk of AMI 1.16 per year ART exposure
- PIs but not NNRTIs conferred increased risk

Friis-Moller NEJM 2007.

AMI Incidence Increased with Abacavir



- MI event rate increases as predicted CHD risk increases
- Within each predicted CHD risk category, MI rates higher with abacavir use
- Relative risk greater at lower predicted CHD risk

Sabin Lancet 2008;371:1417-1426; Worm JID 2010;201:318-330.

The Ongoing Abacavir Saga

Study	N	Design	Effect	Effect Size
D:A:D	33347	observational cohort	Yes	RR 1.90
SMART	2752	observational RCT	Yes	HR 4.3
GSK	14174	pooled RCTs	No	RR 0.81
STEAL	357	RCT	Yes	HR 0.12 (TDF)
Danish	2952	prospective cohort	Yes	RR 2.00
FHDH	1173	nested case-control	No	OR 1.27
VA (original)	19424	observational cohort	No	HR 1.18/yr
Quebec	7053	nested case-control	Yes	OR 1.79
Meta-analysis	9233	28 RCT meta-analysis	No	RR 0.73
FDA Meta-analysis	5028	26 RCT meta-analysis	No	OR 1.02
ALLRT	5056	ACTG RCTs	No	HR 0.7
VA	10931	observational cohort	Yes	HR 1.48

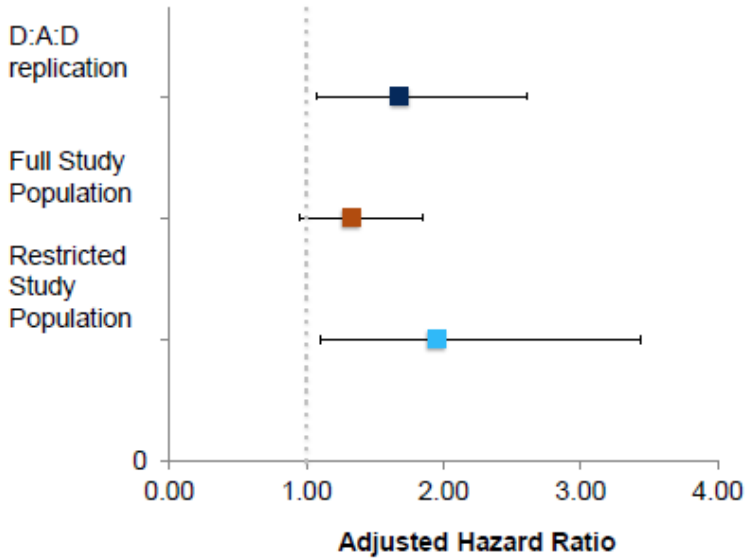
Sabin Lancet 2008;371:1417-1426; SMART/INSIGHT/DAD AIDS 2008;22:F17-F24; Brothers JAIDS 2009;51:20-28; Martin CID 2009;49:1591-1601; Obel HIV Med 2010;11:130-136; Lang Arch Int Med 2010;170:1228-1238; Bedimo CID 2011;53:84-91; Durand JAIDS 2011;epub; Cruciani AIDS 2011;57:245-53. Ding CROI 2011. Abstract 808; Ribaudo CID 2011;52:929-40; Choi AIDS 2011;25:1289-1298.

Abacavir Risk in NA-ACCORD

- 7 North American cohorts
- 16,733 patients (64,607 PYs)
- 301 incident MIs
- Increased risk for MI associated with recent ABC use:
  - Statistically significant in models analogous to those used in the D:A:D
  - Not statistically significant in models more fully adjusted for traditional CVD risk factors
  - Statistically significant in models restricted to ART naïve patients observed to initiate ART

Figure 2. Adjusted hazard ratios for MI among persons with recent ABC use (vs. no recent ABC use): replication of the D:A:D model, NA-ACCORD model in the Full study population, and NA-ACCORD model in the Restricted study population

Point estimates for ABC association with MI range from 1.33 in the NA-ACCORD full model to 1.95 in the restricted model.



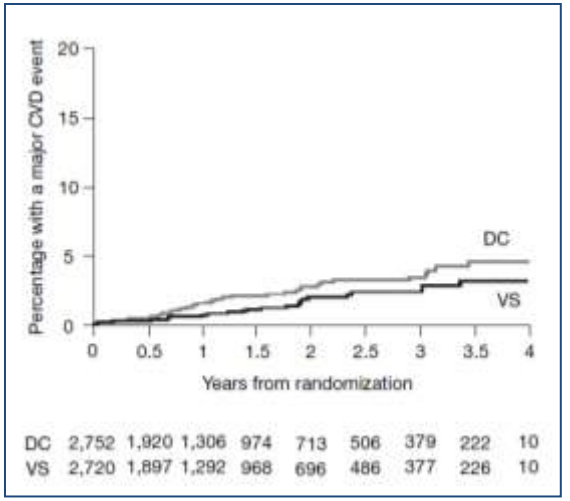
Palella CROI 2015, abstract 749LB

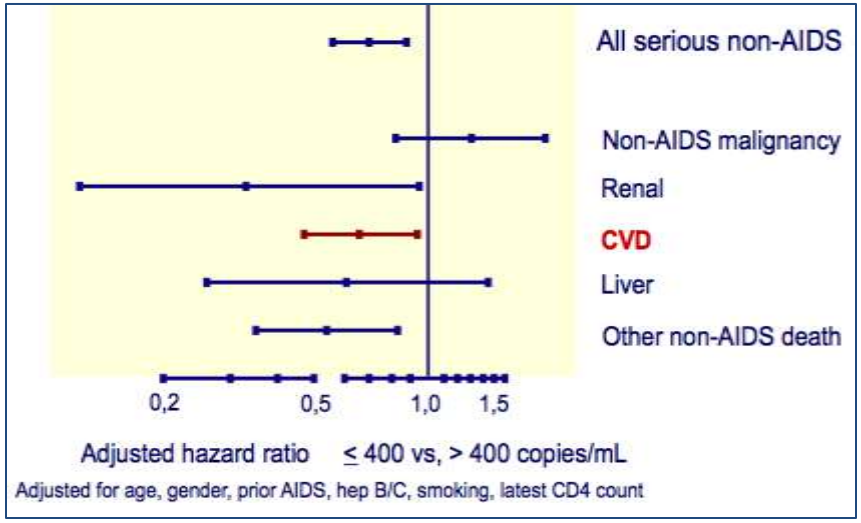
Role for Novel Risk Factors in HIV-Associated CVD Risk

- Increased AMI risk persists despite accounting for established CVD risk factors and ART use
  - Traditional risk factors only account for 10-25% of risk in large cohorts
  - Persistent 40-80% increased risk in HIV-infected patients
- Persistently increased risk thought to be driven by HIV-specific inflammation and immune activation, supported by extensive data
  - SMART study
  - Biomarkers of inflammation linked to surrogate markers of CVD
  - Vulnerable plaque and arterial inflammation linked to monocyte activation
  - Low CD4 and high viral load linked to CVD events
- In treated and suppressed HIV patients:
  - Reduced but persistent inflammation/immune activation and CVD risk

SMART, Inflammation and CVD

- 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



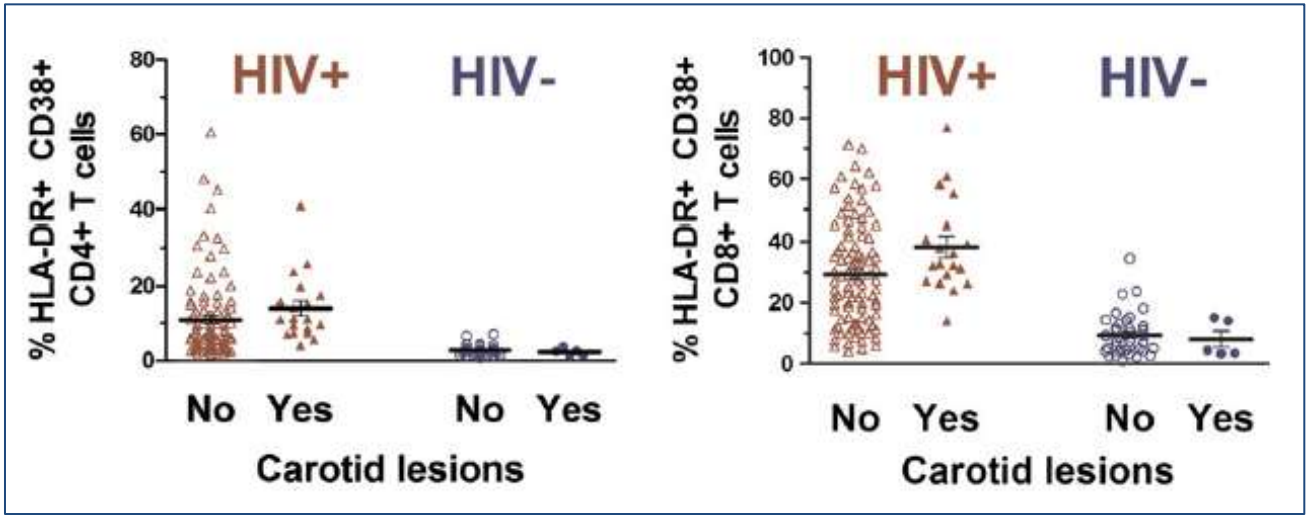


- Inflammatory markers IL-6 and d-dimer increased 1 month after treatment interruption in SMART
- Baseline hsCRP, IL-6, and d-dimer strongly correlated to overall mortality

El-Sadr NEJM 2006; Phillips AIDS 2008; Kuller PLoS 2008.

Immune Activation Linked to Vascular Lesions

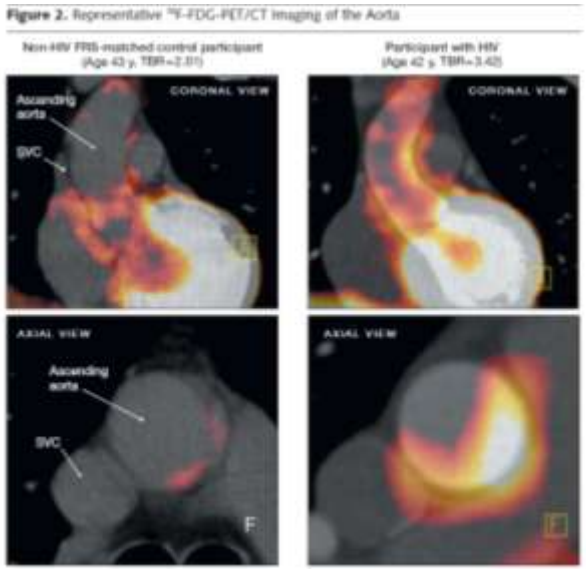
- Increased immune activation in HIV women vs. controls
- Higher frequencies of activated T cells associated with carotid artery lesions within HIV patients
- Effect present even among virologically suppressed patients

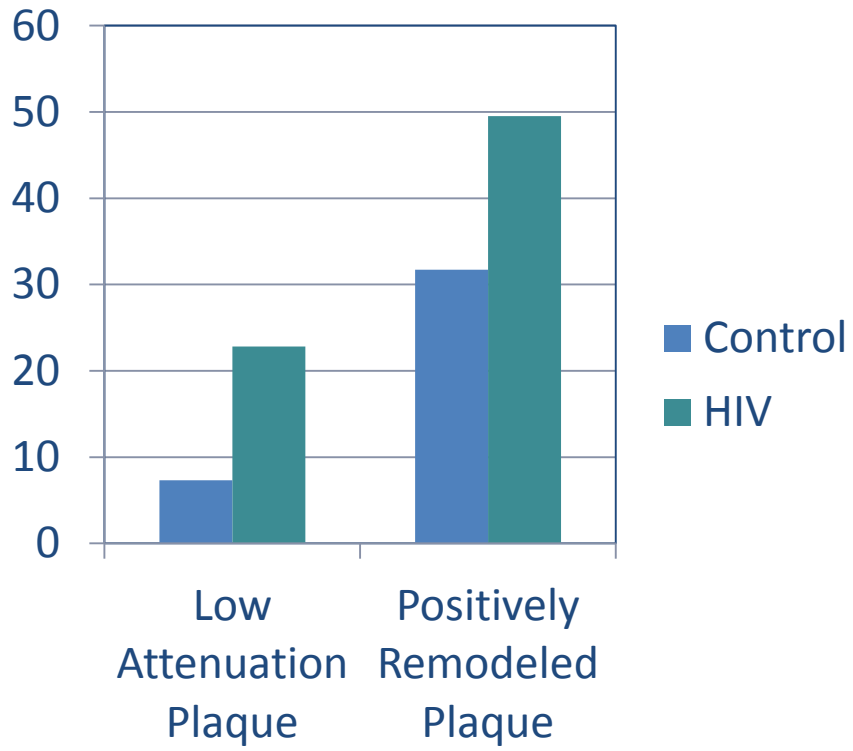


Kaplan JID 2011.

Immune Activation Associated with Vulnerable Plaque and Arterial Inflammation

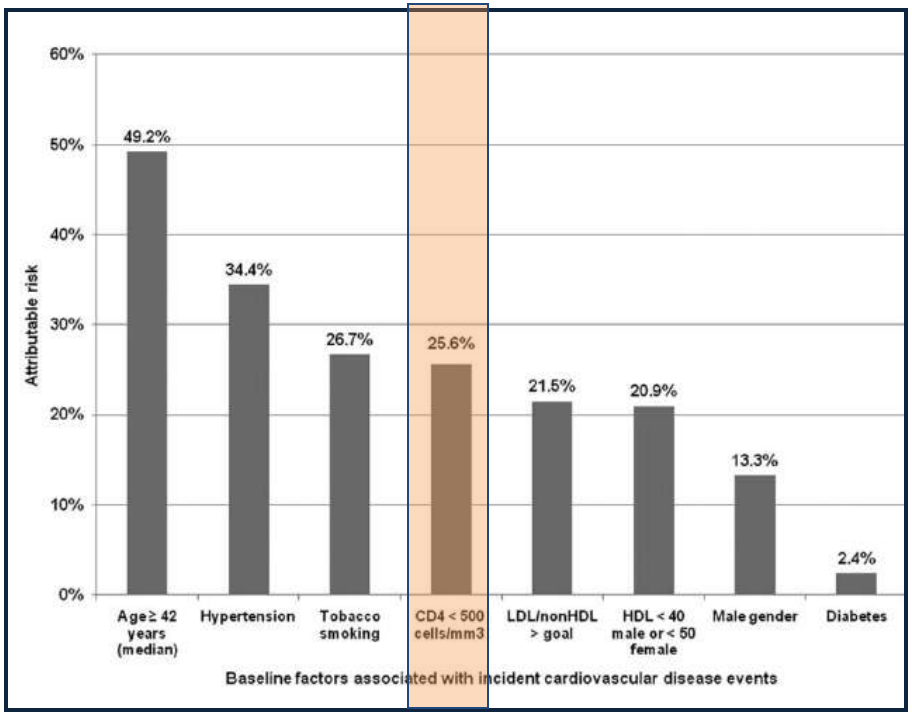
- Immune activation markers, including markers of monocyte activation (sCD163), are significantly linked to:
  - Presence of non-calcified vulnerable plaque
  - High-risk morphology plaque
  - Arterial inflammation (aortic TBR)

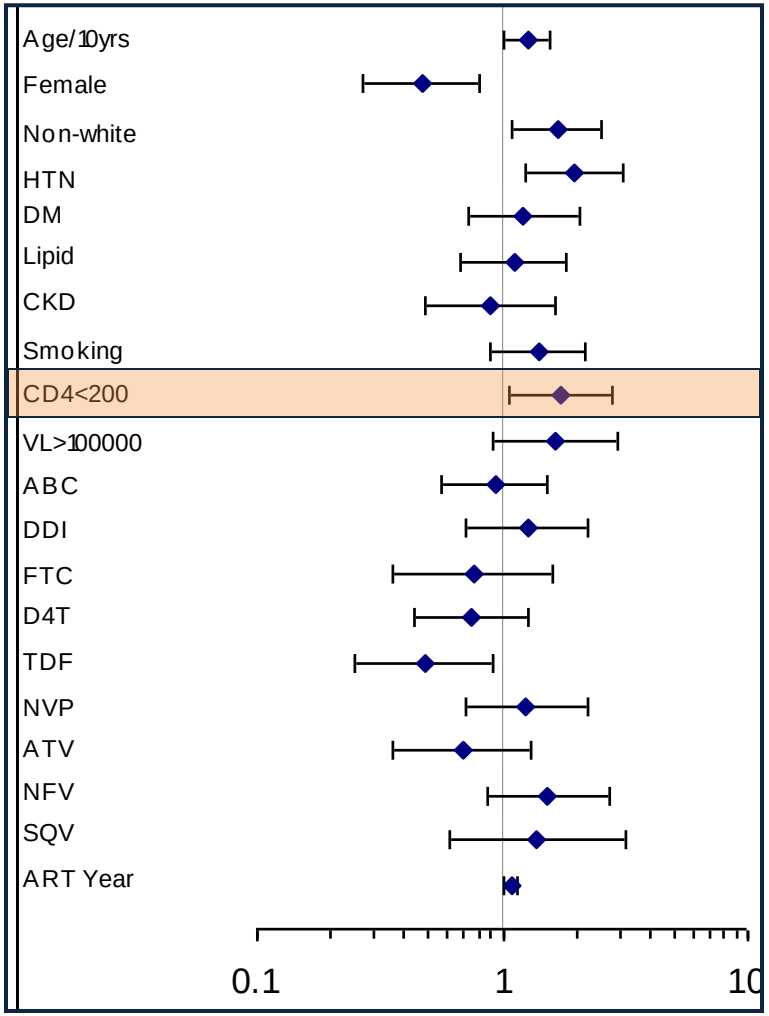




Burdo JID 2011; Zanni AIDS 2013; Subramanian JAMA 2012.

Decreased CD4 Count Linked to CVD





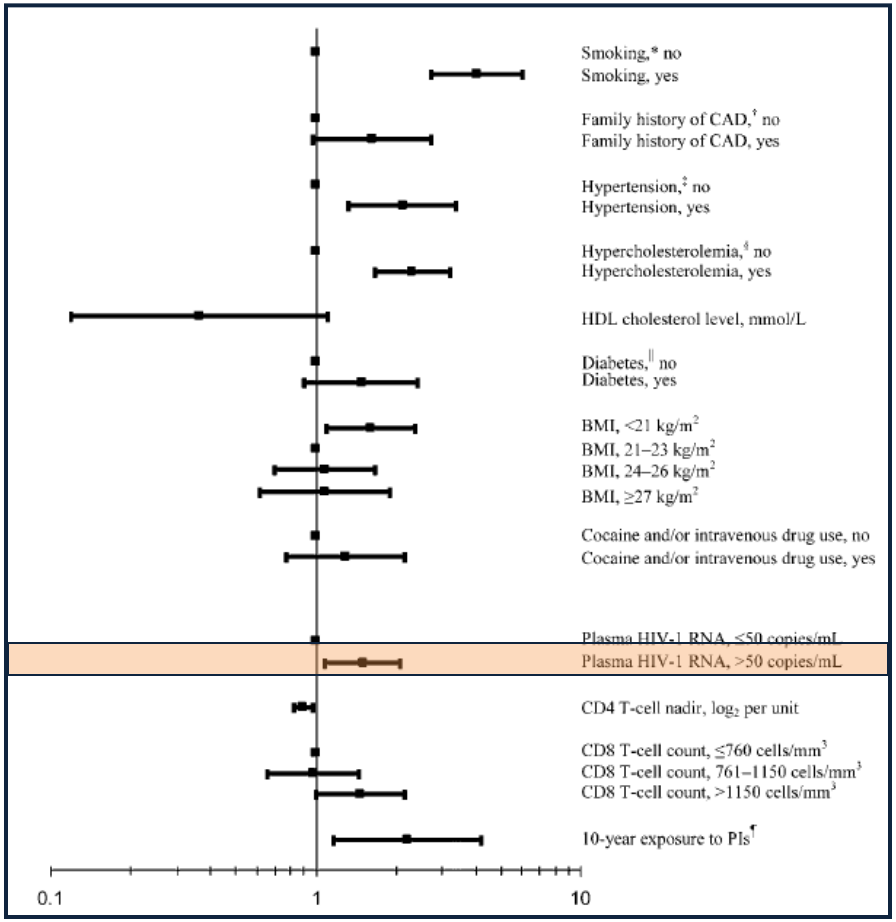
- CD4 <500 associated with CVD events independent of CVD risk factors or ART
- CD4 <200 independently associated with AMI with OR of 1.74

Lichtenstein CID 2010; Triant JAIDS 2010.

Increased HIV RNA linked to CVD

TABLE 4. HRs for Stroke in HIV-Stratified Models

	HIV (n = 2255) HR (95% CI)	P
Female gender	0.97 (0.50 to 1.89)	0.921
Age	1.06 (1.03 to 1.09)	<0.001
CD4 count (cells/mm^3)*	0.97 (0.90 to 1.05)	0.477
HIV RNA (copies/mL)†	1.10 (1.04 to 1.17)	0.001
CNS infection/malignancy	2.75 (1.26 to 6.03)	0.011



- Increased HIV viral load linked to ischemic stroke events
- Detectable viral load (>50) associated with increased risk myocardial infarction with odds ratio of 1.51

Chow JAIDS 2014; Lang CID 2012.

Decreased CD4 Count and Increased HIV RNA Increases CVD Risk in HIV

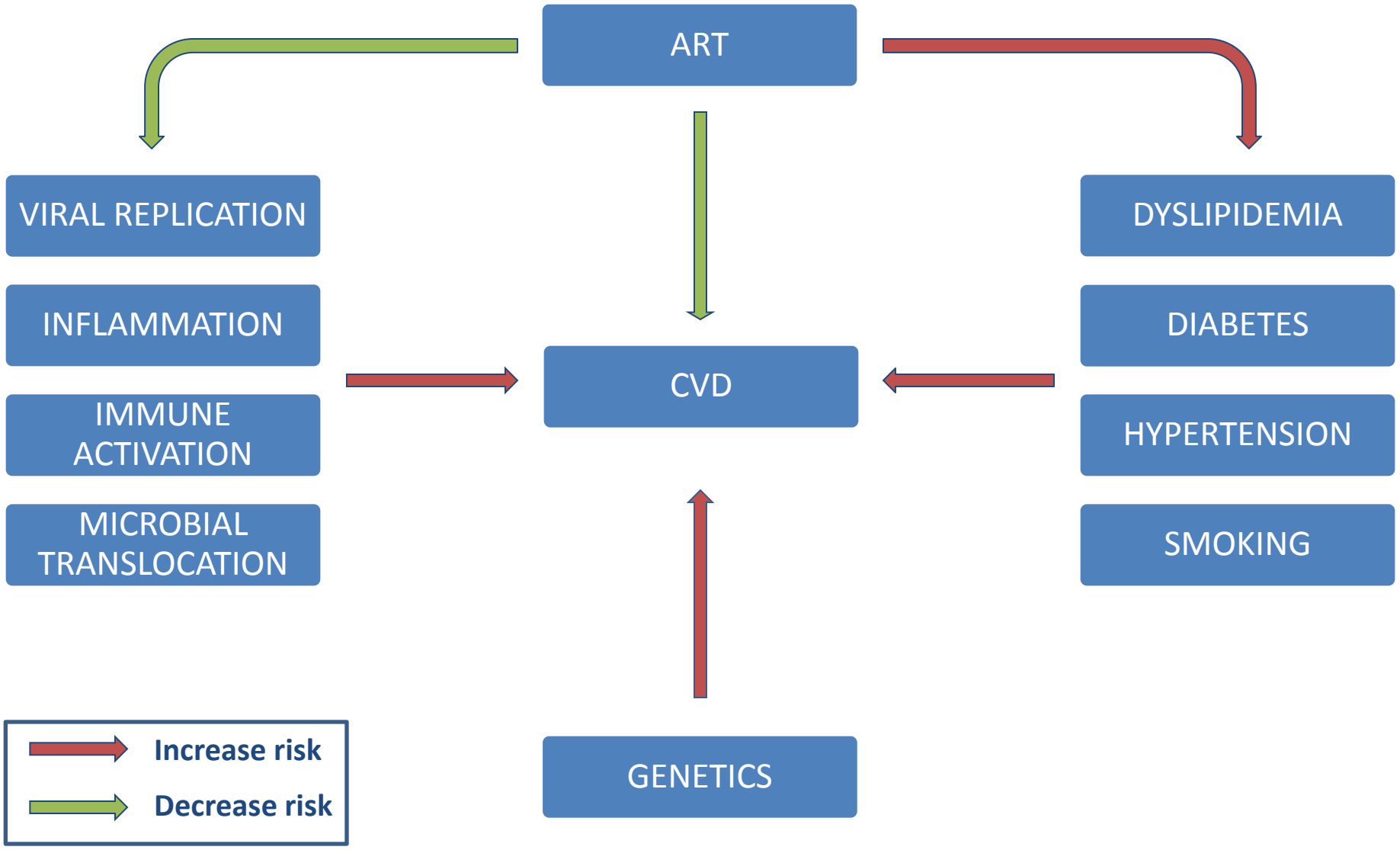
Table 4. Time-Updated Analyses Assessing the Association of HIV-1 RNA and CD4 Cell Count Values and the Risk of AMI in Separate Models[a]

Category	HR (95% CI)	*P* Value[b]
HIV-1 RNA		
Uninfected	1 [Reference]	
≥500	1.75 (1.40-2.18)	.05
<500	1.39 (1.17-1.66)	
CD4 cell count		
Uninfected	1 [Reference]	
<200	1.88 (1.46-2.40)	.04
≥200	1.43 (1.21-169)	

- AMI risk in recent VA study by CD4 and HIV RNA status
- HIV RNA≥500 and CD4<200 associated with increased AMI risk
- **AMI risk persists in patients achieving virologic suppression**

Freiberg JAMA IM 2013.

Pathophysiology of HIV-Associated CVD



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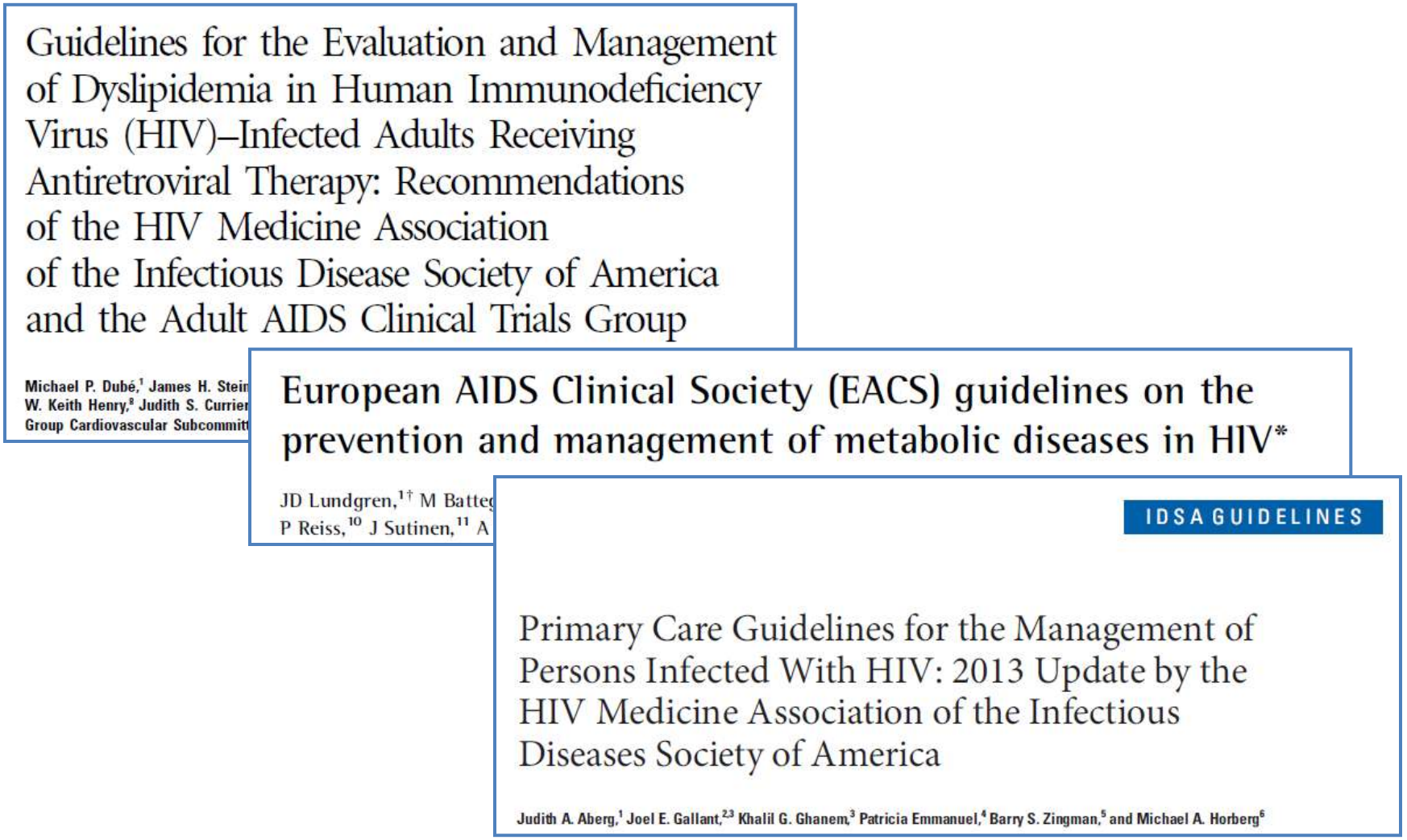
Challenges in Management of HIV-Associated CVD

- Understanding of mechanism has not yet translated into tailored clinical interventions
  - Area of intensive investigation
- Unclear applicability of general population guidelines
- Limitations of HIV-specific CVD guidelines

Intervention	Traditional Risk Factors	Novel Risk Factors
Statins		
ASA		
ART		
Immunomodulatory agents		
Smoking cessation		
Diabetes management		
HTN management		

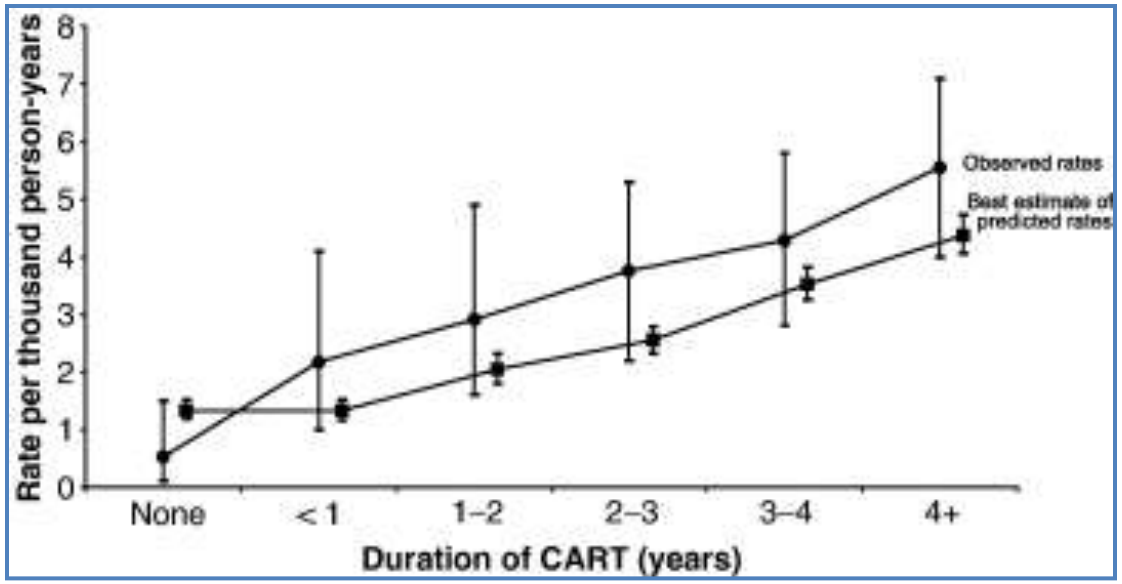
HIV-Specific CVD Guidelines



Dube CID 2003; Lundgren HIV Med 2008; Aberg CID 2014.

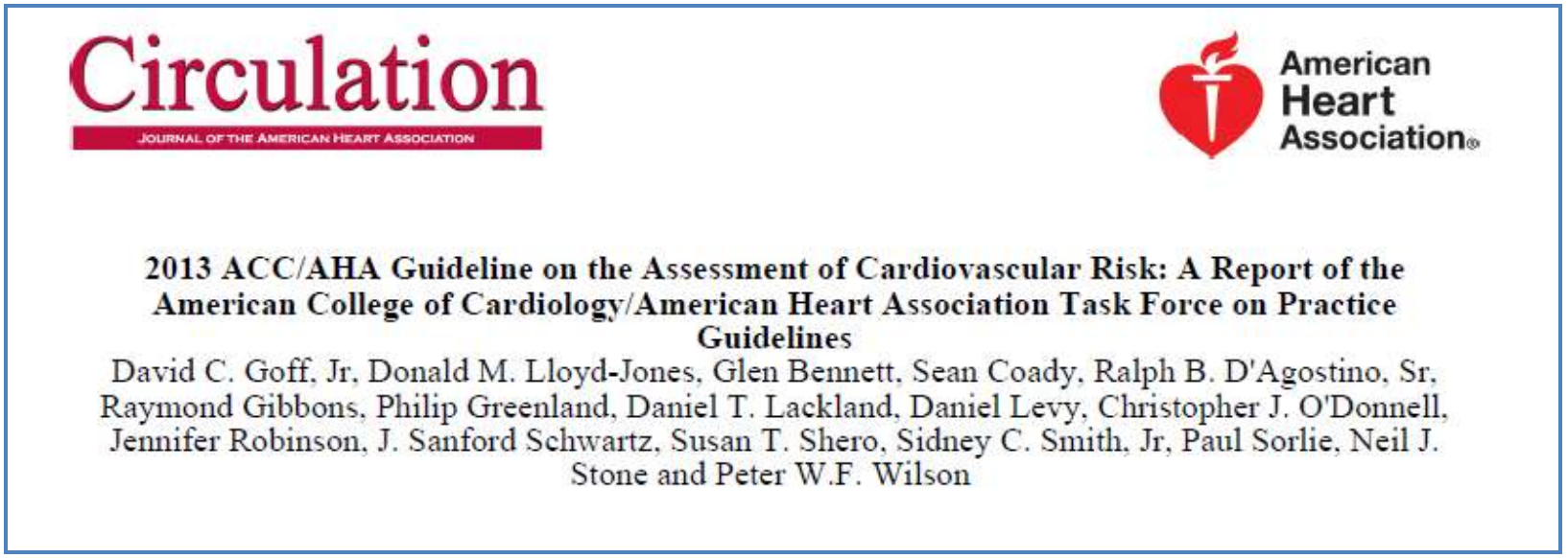
CVD Risk Prediction in HIV

- CVD risk prediction tools designed for the general population may **underestimate** risk in HIV
  - Novel HIV-specific risk factors not accounted for
- Framingham Risk Score underestimates risk in HIV (AMI and stroke)
- HIV-specific risk prediction tool developed but not externally validated



Law HIV Med 2006; Mateen Neurology 2013.

New Cardiovascular Risk Guidelines Add Complexity to HIV-Specific Risk Prediction

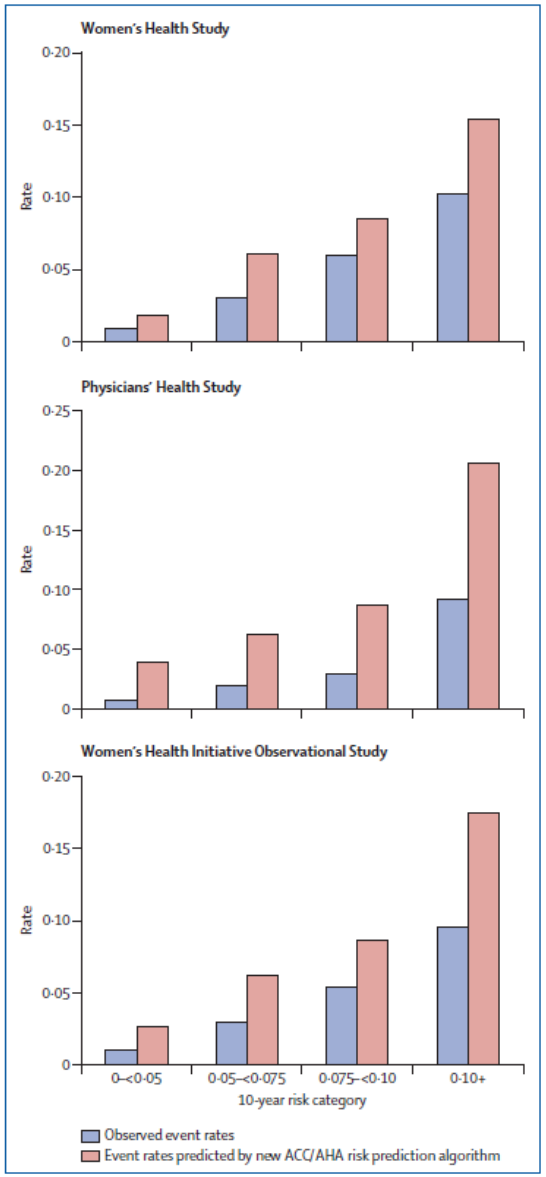


- New ACC/AHA guidelines on CVD risk estimation released in 2013
- New CVD risk prediction equation employed (Pooled cohorts equation)
- Reports of **overestimation** of risk in the general population

Goff Circulation 2014.

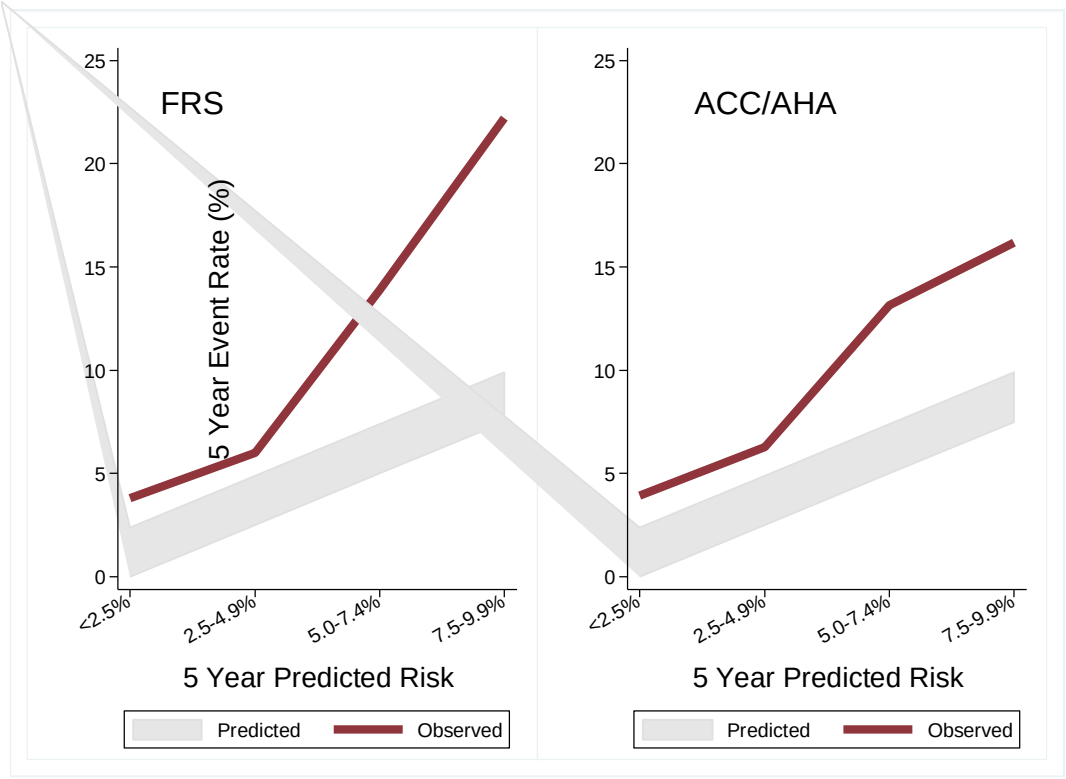
2013 ACC/AHA Calculator Overestimates Risk

- 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 studies from Women's Health Study and MESA also observed overestimation of risk



Ridker Lancet 2013; Cook JAMA IM 2014, Kavousi JAMA 2014; DeFilippis, Annals 2015.

FRS and ACC/AHA Underestimate CVD Risk in HIV



- Partners HIV longitudinal cohort, 2239 patients
- ACC/AHA risk score and FRS underestimate CVD risk in HIV
  - 5-year observed versus predicted event rates

Regan CROI 2015, abstract 751.

What are the Implications for CVD Risk Prediction in HIV?

- Unknown accuracy of FRS and new ACC/AHA calculator in HIV
- New ACC/AHA risk score overestimates risk in general population but may underestimate risk in HIV
- In HIV, risk scores discordant in approximately 19%
  - FRS assigns low risk and ACC/AHA high risk in 99% of discordant cases

Clinical strategy

- Consider calculating both Framingham Risk Score and ACC/AHA risk score
- Patients in high-risk category by at least one score (>10% for FRS and >7.5% for ACC/AHA) merit:
  - Suppressive ART if not already treated
  - Strong consideration of statin
  - Aggressive CVD risk factor reduction

Preliminary data, Partners HIV cohort.

Management of Dyslipidemia in HIV

- Dyslipidemia in HIV:
  - Prevalent, with higher rates than control patients
  - Distinctive pattern of low HDL and high TG
  - May be more difficult to treat with statins
  - Drug interactions with ARVs important
- Statins are mainstay of treatment and may reduce both traditional and non-traditional risk factors
- Statins in HIV:
  - Effectively lower LDL
  - Decrease immune activation (T cell and monocyte)
  - Contribute to immune reconstitution independent of ART
  - Decreased mortality in HIV observational cohort

Hadigan CID 2001; Riddler JAMA 2003; Silverberg Ann Int Med 2009; Funderburg, CROI 2014 abstract 335; Eckard JID 2014; Drechsler CROI 2014 abstract 308; Moore PLoS One 2011.

Paradigm Shift in Cholesterol Treatment for General Population

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Neil J. Stone, Jennifer Robinson, Alice H. Lichtenstein, C. Noel Bairey Merz, Conrad B. Blum, Robert H. Eckel, Anne C. Goldberg, David Gordon, Daniel Levy, Donald M. Lloyd-Jones, Patrick McBride, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Karol Watson and Peter W.F. Wilson

Circulation. published online November 12, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

- New cholesterol/statin guidelines released November 2013
- Replaced NCEP ATP-III
- Controversial new approach to treating cholesterol

Stone Circulation 2014.

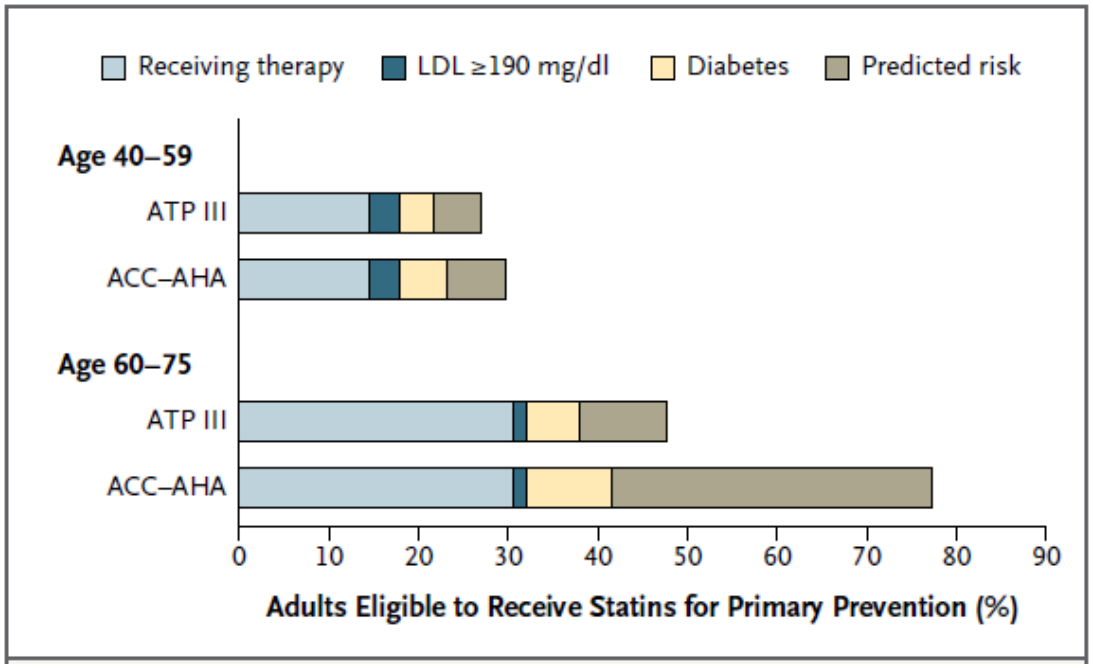
2013 ACC/AHA Cholesterol Treatment Guidelines

- Statin initiation: 4 major benefit groups
  - Clinical ASCVD
  - LDL ≥ 190 mg/dL
  - DM age 40-75
  - Estimated 10-year ASCVD risk ≥ 7.5%
- No LDL treatment targets
- No non-statin therapies
- New risk calculator to estimate 10-yr ASCVD risk
- Recommend increased statin treatment in general population

Stone Circulation 2014.

Increased Statin Use in the General Population with New Guidelines

- 12.8 million additional adults eligible for statin therapy
  - 43 → 56 million US adults
- Increase driven by 10-year predicted risk
- Greatest increase in men and older patients



Pencina NEJM 2014.

2013 ACC/AHA Cholesterol Treatment Guidelines

Focused on fixed dose statin RCTs to reduce atherosclerotic CVD risk

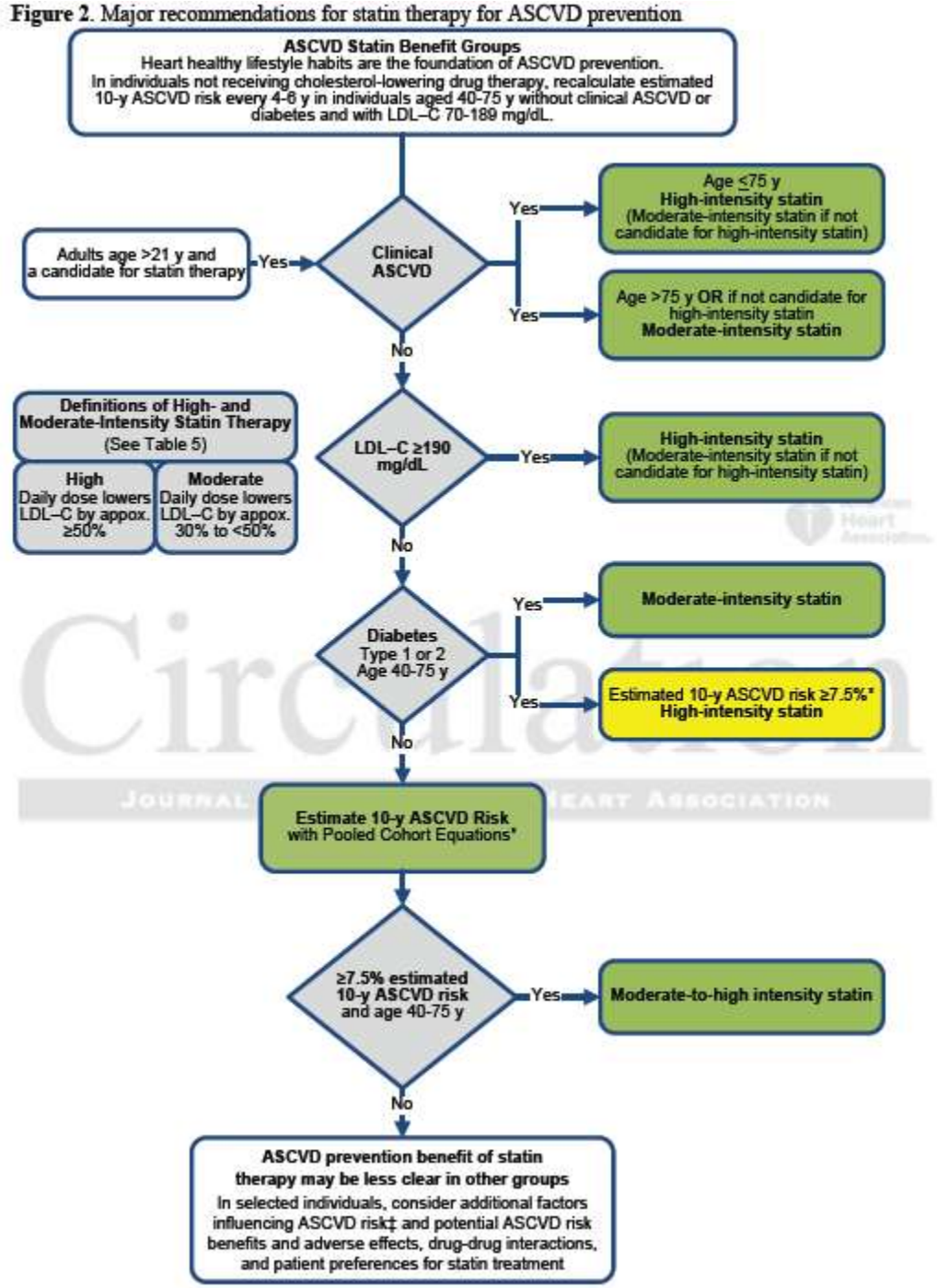
3 years deliberation

Why treat-to-target was abandoned

- Inadequate RCT data on what target
- Unknown magnitude of ASCVD risk reduction
- Potential adverse effects from multidrug therapy

Critique

- Scope limited to RCTs
- Abandonment of LDL targets
- Increase in patients eligible for statins
- Discordance of risk calculators



Stone Circulation 2014.

Limitations of New Cholesterol Guidelines in HIV

Future Updates to the Blood Cholesterol Guideline

CQs for future guidelines could examine:

1. the treatment of hypertriglyceridemia;
2. use of non-HDL-C in treatment decision-making;
3. whether on-treatment markers such as Apo B, Lp(a), or LDL particles are useful for guiding treatment decisions;
4. the best approaches to using noninvasive imaging for refining risk estimates to guide treatment decisions;
5. how lifetime ASCVD risk should be used to inform treatment decisions and the optimal age for initiating statin therapy to reduce lifetime risk of ASCVD;
6. subgroups of individuals with heart failure or undergoing hemodialysis that might benefit from statin therapy;
7. long-term effects of statin-associated new onset diabetes and management;
8. efficacy and safety of statins in patient groups excluded from RCTs to date (e.g., HIV positive or solid organ transplant); and
9. role of pharmacogenetic testing.

8. Limitations

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. These patient groups include younger adults (<40 years of age) who have a low estimated 10-year ASCVD risk, but a high lifetime ASCVD risk based on single strong factors or multiple risk factors. 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 Circulation 2014.

Further Challenges in Applying New Cholesterol Guidelines to HIV

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg	**Atorvastatin 10 *(20)* mg**	~~*Simvastatin 10 mg*~~
Rosuvastatin 20 *(40)* mg	**Rosuvastatin (5) 10 mg**	**Pravastatin 10–20 mg**
	~~**Simvastatin 20–40 mg‡**~~	~~**Lovastatin 20 mg**~~
	Pravastatin 40 *(80)* mg	*Fluvastatin 20–40 mg*
	~~**Lovastatin 40 mg**~~	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg bid	
	Pitavastatin 2–4 mg	

Dose-adjustment in HIV (with PIs)

Contraindicated in HIV (with PIs)

Awaiting further study in HIV

Stone Circulation 2014.

Unclear Applicability of New Cholesterol Guidelines in HIV

- HIV patients excluded from RCTs
- Different mechanism of CVD
- Different typical cholesterol profile
- Unclear role of new ACC/AHA risk calculator
- Statin intensity definition not directly applicable

Clinical strategy

- In HIV, still likely that statins will be effective in risk groups outlined by guidelines
  - Traditional risk factors remain important in HIV
  - Risk scores may underestimate risk in HIV

REPRIEVE Hypothesis

Statins will prevent cardiovascular disease in HIV-infected patients, particularly among the large group with minimal traditional risk and not meeting current guidelines for clinical use of statins but at risk for CVD based on unique pathophysiology of vulnerable plaque morphology and inflammation

Personal communication, Grinspoon 2014.

Management of Dyslipidemia in HIV

Clinical strategy

- Check fasting lipids
  - At HIV diagnosis
  - Prior to and within 1-3 months after starting or changing ART
  - Every 6-12 months
- Consider starting statin based on ACC/AHA cholesterol guidelines
- Consider therapy with:
  - Statin if LDL above ATPIII goal or TG 200-500 with elevated non-HDL
  - Fibrate if TG>500
- 2013 HIV primary care guidelines includes detailed statin-ARV interaction chart
- Await REPRIEVE results

Statin	Level w/ PI	Use
Pravastatin	--	
Atorvastatin	↑	
Simvastatin	↑↑	
Lovastatin	↑↑	
Rosuvastatin	↑	
Pitavastatin	?	

Can use safely

Use with caution/low dose

Contraindicated

Accruing data

Dube CID 2003; Aslangul AIDS 2010; ATPIII JAMA 2001; Singh CID 2011; Mutimura AIDS Res Hum Retro 2008; Aberg CID 2014.

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

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.

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.

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%

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.

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.

Ann Intern Med 2009.

Aspirin Use in HIV Infection

- ASA may modulate traditional and novel CVD risk factors
- ASA significantly underused in HIV patients meeting criteria for its use
  - 31% met criteria yet 1.6% received ASA
  - Less than 1 in 5 received ASA in US clinic
- ASA use rates lower in HIV versus non-HIV
- Unclear role of ASA in primary prevention of AMI or stroke for HIV patients
  - Decreases immune activation and platelet activation in HIV
  - Preliminary data suggests ASA may not confer same benefit in HIV

Clinical strategy

- Reasonable to use ASA if known CVD or high predicted CVD risk (ATPIII or ACC/AHA) and low bleeding risk
- Should be used in combination with other CVD risk reduction methods
- Interventions targeted at HIV-specific inflammation and immune activation may better reflect pathogenesis and reduce CVD

Tornero JAIDS 2010; Burkholder CID 2012; Suchindran OFID 2014.; O'Brien JAIDS 2013.

Role of ART in CVD Risk

- **Paradigm shift** in role of ART in relation to CVD risk in HIV
- CVD-related benefit from virologic suppression and immune reconstitution achieved by treating HIV thought to outweigh possible proatherogenic effects of individual medications
- **START trial** will be first RCT to assess rates of comorbidities including CVD by early versus deferred ART initiation

Clinical strategy

- Treat HIV to reduce inflammation, immune activation, and associated cardiovascular risk
- Consider underlying CVD risk when selecting specific drugs, as individual ART medications may have varying risk

Thompson JAMA 2010; clinicaltrials.gov NCT00867048.

HIV Treatment Guidelines and CVD Risk

- 2010 IAS-USA HIV treatment guidelines
  - Recommended initiation of ART specifically for patients with high cardiovascular risk regardless of CD4 count
  - Endorse aggressive management of modifiable CVD risk factors

- 2012 DHHS HIV treatment guidelines
  - Recommend antiretroviral therapy for all HIV-infected individuals
  - *The recommendation to initiate therapy at CD4 count >500 cells/mm3 (BIII) is based on growing awareness that untreated HIV infection or uncontrolled viremia may be associated with development of many non-AIDS defining diseases, including* ***cardiovascular disease*** *(CVD), kidney disease, liver disease, neurologic complications, and malignancy*

Thompson JAMA 2010; ACCF/AHA/ACP Circulation 2009;
http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf

Further Management of Novel Risk Factors in HIV-Associated CVD

- Targeting inflammation and immune activation with established anti-inflammatory therapies or novel immunomodulatory agents may decrease CVD risk in HIV
- Management strategies include:
  - Existing therapies to decrease inflammation (statins, ASA)
  - ART to decrease inflammation
  - Tailored immunomodulatory therapies

Novel Interventions Targeting Inflammation and Immune Activation

- ART treatment intensification
  - No effect of raltegravir intensification on flow mediated dilatation (FMD) or viral replication markers
- Methotrexate
  - Anti-inflammatory used in auto-immune disorders
  - Associated with decreased CVD risk in general population
  - RCT underway to assess the effect of low-dose methotrexate on inflammatory markers and endothelial function in treated and suppressed HIV
- CCR5 antagonists
  - Theoretical role in preventing/delaying atherosclerosis
  - Maraviroc slowed atherosclerosis progression in mice
  - Potential cardioprotective effect in HIV

Hatano JAIDS 2012; Gandhi JAIDS 2012; Stein JAMA 2012; Jones Br J Pharmacol 2011; Cipriani Circulation 2013.

Novel Interventions Targeting Inflammation and Immune Activation

- Further potential immunomodulating therapies
  - Rifaximin
    - Marginal decrease in T cell activation
  - Sevelamer
    - Did not decrease inflammation, immune activation or microbial translocation but decreased LDL and soluble tissue factor
  - Mesalamine
    - Did not decrease immune activation or microbial translocation
  - Pentoxifylline
    - Did not improved endothelial function (FMD) and increased inflammatory biomarker (sTNFR1)
- Hydroxychloroquine
  - Anti-inflammatory used in auto-immune disorders
  - RCT did not show reduction in immune activation
  - Unanticipated decline in CD4 and increased viral replication in hydroxychloroquine-treated

Tenorio CROI 2014 abstract 339; Sandler JID 2014; Somsouk CROI 2014 abstract 341; Gupta PLoS One 2013; Paton JAMA 2012.

Current HIV/CVD Management Principles: Smoking

- Priority for all HIV-infected patients
- HIV patients cited as priority in 2008 clinical practice guideline *Treating Tobacco Use and Dependence*
- HIV-specific smoking cessation interventions differ in efficacy

Clinical strategy

- Apply guidelines for general population to all HIV smokers
  - Routine screening integrated into HIV primary care
  - Strong, brief, intensive repeated counseling
  - Pharmacologic interventions (varenicline safe and effective in HIV)
- Consider systematic approaches to identify HIV smokers and ensure smoking cessation interventions applied

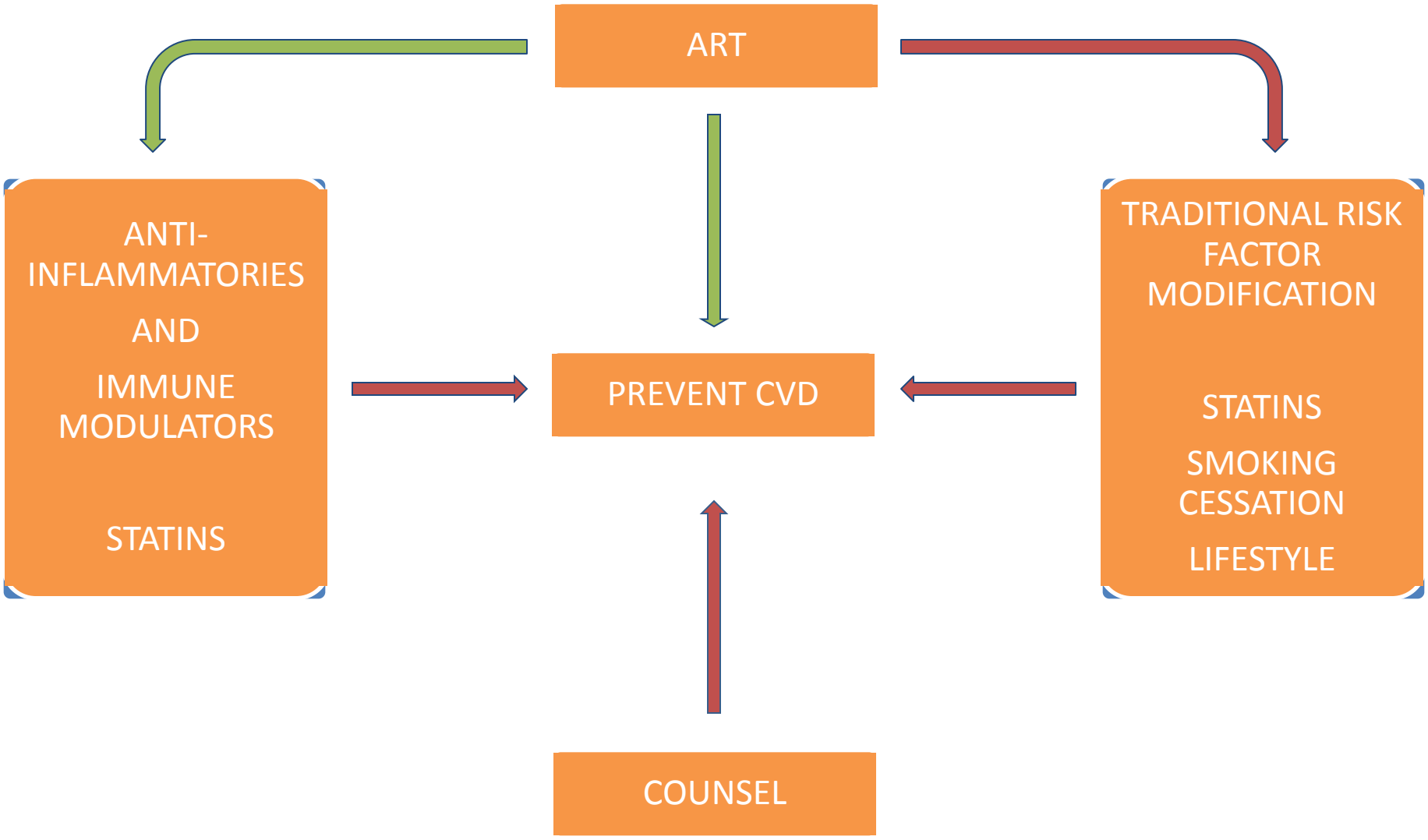
Etzi Antivir Ther 2006; Tashima CROI 2009 abstract 148; Tornero JAIDS 2009; Treating Tobacco Use and Dependence DHHS 2008.

Current HIV/CVD Management Principles: Diabetes and Hypertension

- Check fasting glucose or HbA1C at HIV diagnosis, 1-3 months after starting or changing ART, and every 6-12 months
- HbA1C may be used for screening
  - Consider cutoff 5.8%
  - HbA1C may underestimate glycemia in HIV
- Check HbA1C every 6 months in DM
- Lifestyle intervention recommended
  - Shown to decrease HbA1C for HIV patients
- Check blood pressure annually
- Follow existing JNC8 (2014 Hypertension Guideline) for general population
  - No HIV-specific guidelines
- Consider drug interactions
  - Use of some calcium-channel blockers contraindicated with protease inhibitors

Fitch AIDS 2006; Aberg CID 2014; Lundgren HIV Med 2008; Chobanian Hypertension 2003; CROI 2014 abstract 769; James JAMA 2014.

Prevention of HIV-Associated CVD



Management of CVD in HIV: Key Questions

- Are the new ACC/AHA risk calculator and cholesterol guidelines applicable and accurate in HIV?
- What is the role for statins in HIV?
- Will tailored immunomodulatory agents further decrease CVD risk in HIV?
- Are CVD prevention strategies similar in critical subgroups, including HIV-infected women and patients in resource-limited settings?
- Should HIV be considered a cardiovascular risk equivalent?

Management of CVD in HIV: Key Principles

- Significant impact of CVD in HIV populations anticipated
- Pathophysiology driven in large part by HIV-related immunologic and inflammatory changes
- Current treatment paradigms do not reflect this pathophysiology
- Recommended strategies
  - Build CVD risk assessment into practice
  - Manage traditional CVD risk factors aggressively (e.g. smoking)
  - Start appropriate statin if candidate by general population guidelines
  - Low threshold for diagnostic workup in traditionally low-risk groups
  - Treat HIV to reduce CVD risk
- Intensity and consistency of HIV care provide opportunity to prevent and manage chronic disease complications