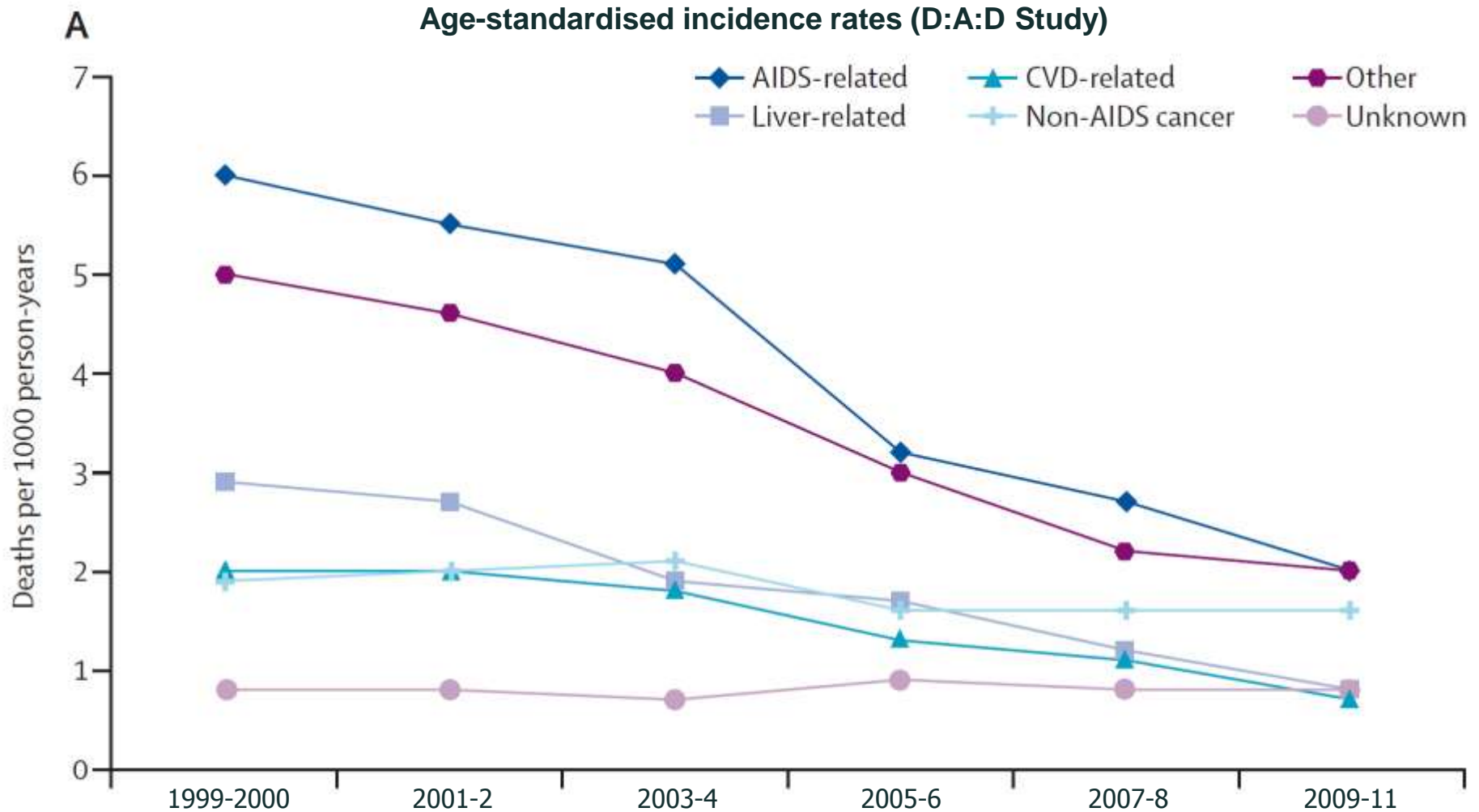


Cardiovascular risk
A key long-term comorbidity for HIV+

Dr Graeme Moyle

Chelsea and Westminster Hospital
London, United Kingdom

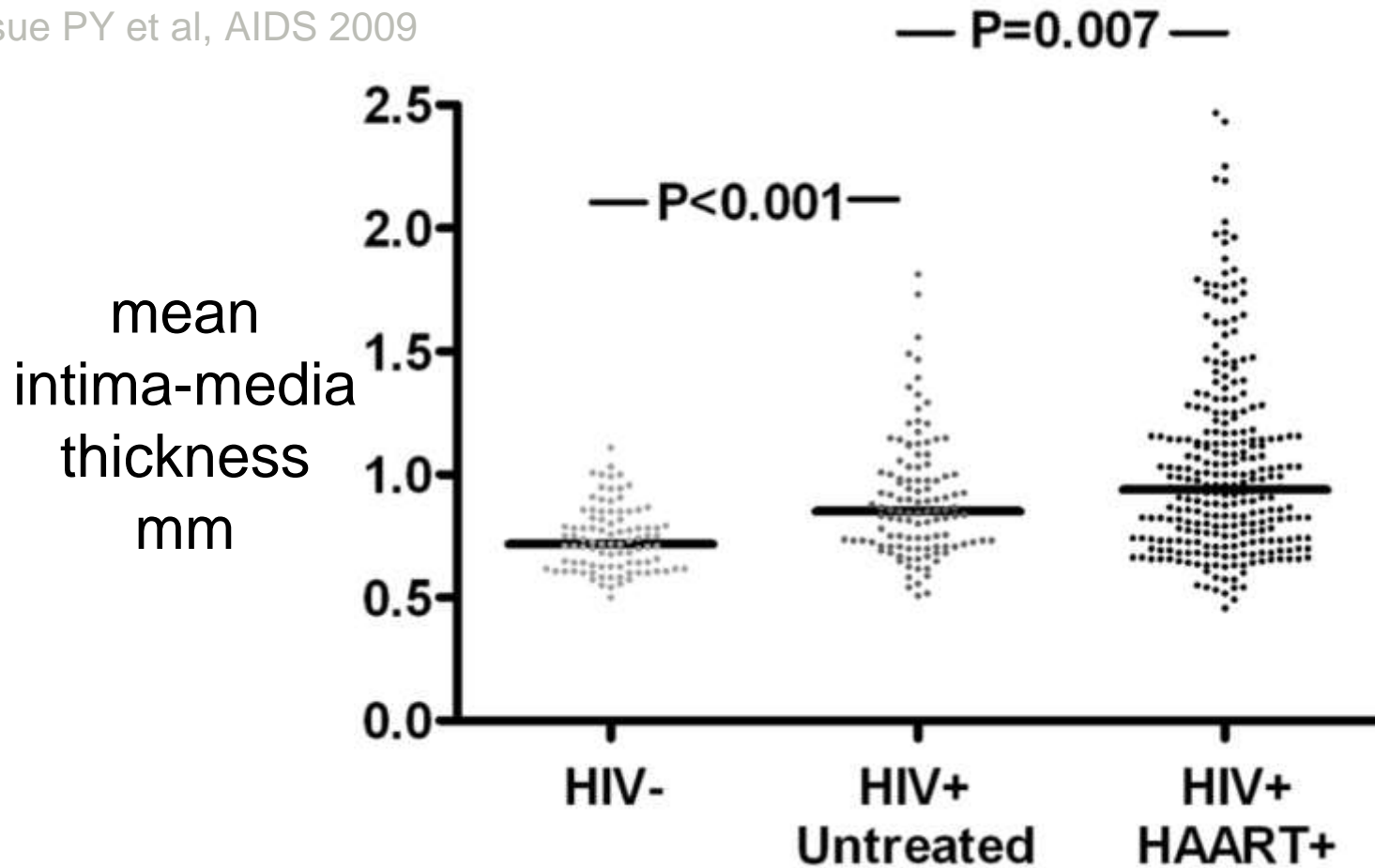
All-cause (both AIDS and non-AIDS) mortality has decreased with cART



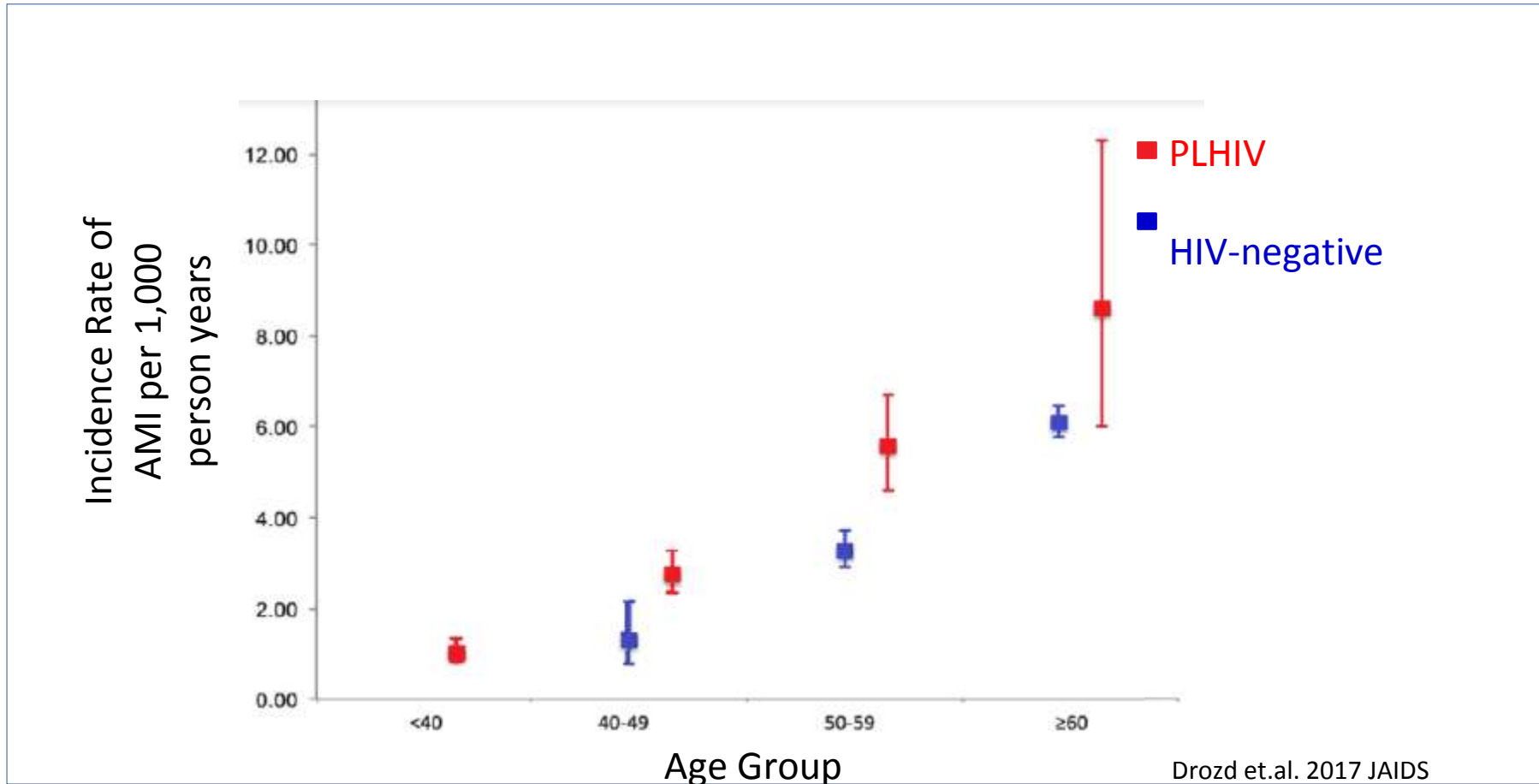
ICD-10 (until 2004)
CoDe (from 2004 on)

SCOPE cohort: subclinical atherosclerosis in HIV

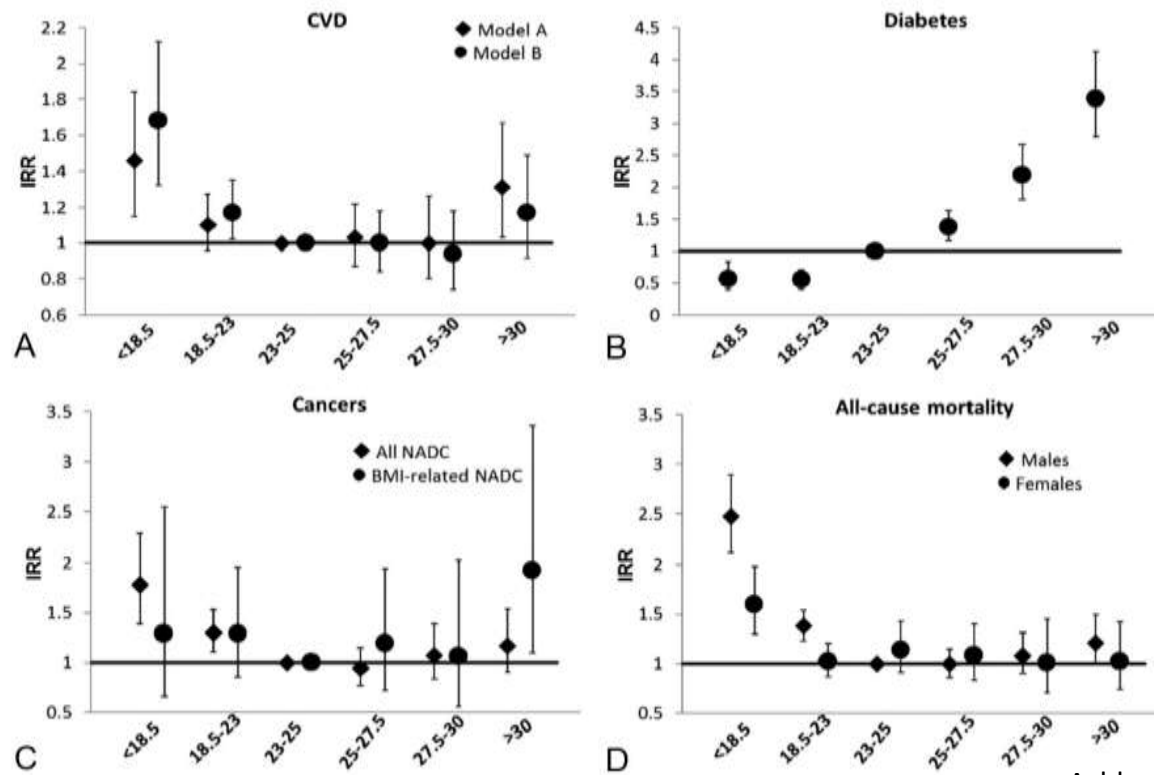
Hsue PY et al, AIDS 2009



HIV is associated with a relative increase in cardiovascular events



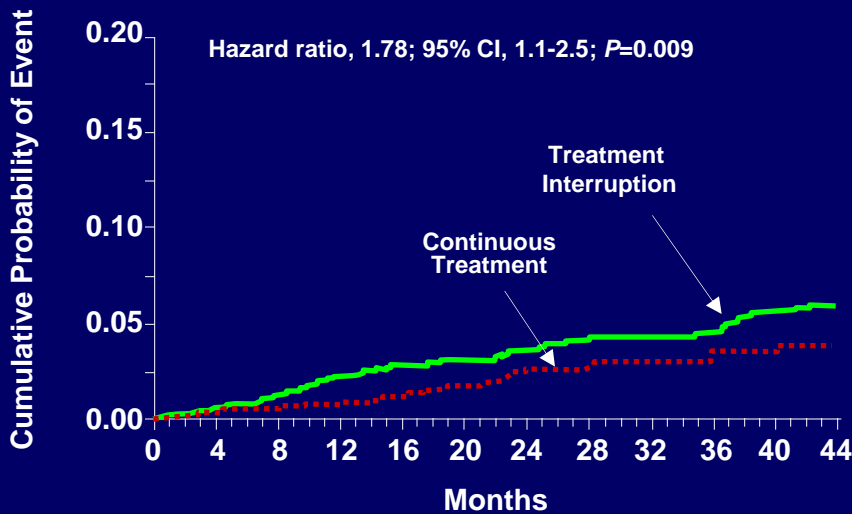
“U-shaped” relationship between BMI and poor outcomes in PLHIV



SMART Study: HIV Viremia Can Contribute to CV Risk

N=5472 HIV-infected patients with a CD4+ cell count >350mm³

Major Cardiovascular, Renal, or Hepatic Disease



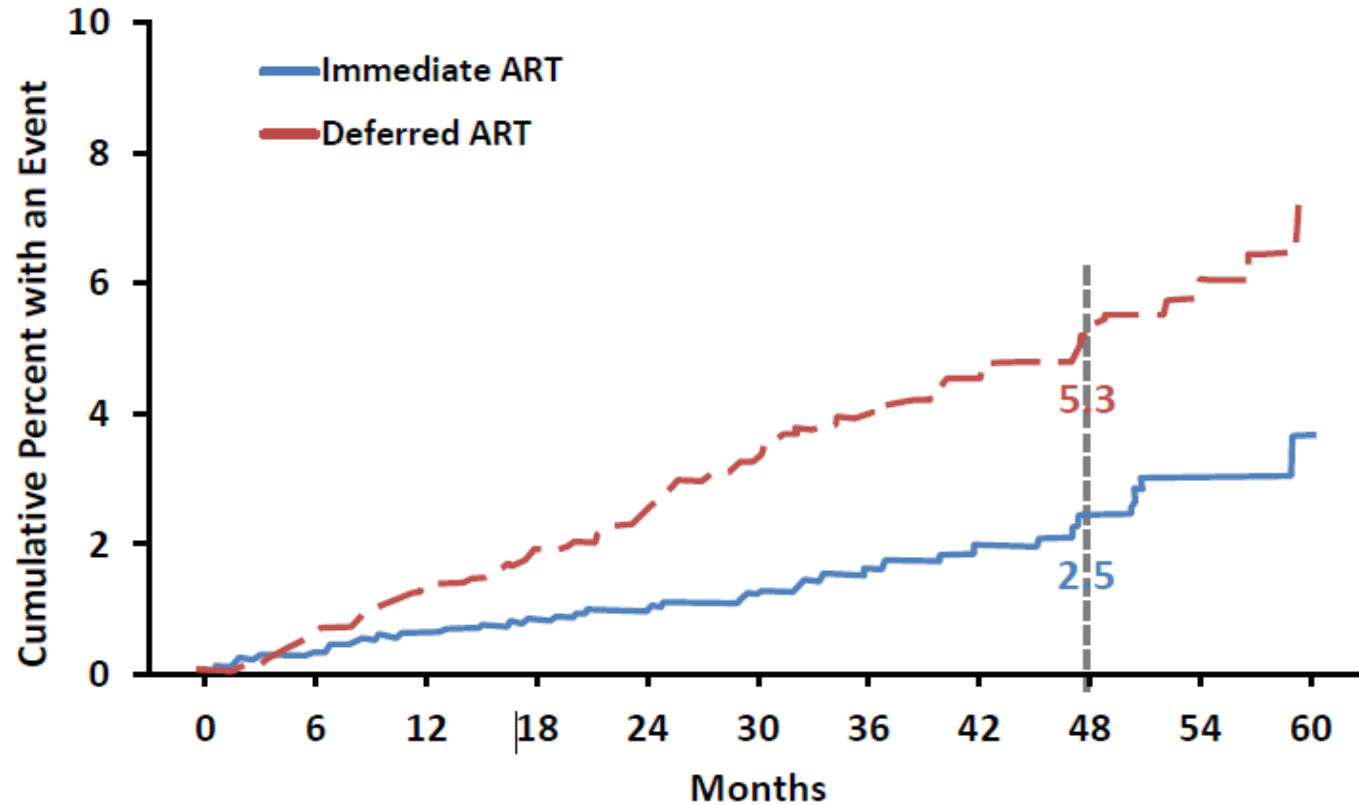
No. at Risk	0	4	8	12	16	20	24	28	32	36	40	44
Treatment Interruption	2720	2070	1663	1292	1041	867	693	543	443	375	273	157
Continuous Treatment	2752	2077	1692	1307	1070	899	713	563	462	380	282	165

Endpoint	Hazard Ratio (95%CI)*	P Value
Death, any cause	1.8 (1.2-2.9)	0.007
Major cardiovascular, renal or hepatic disease	1.7 (1.1-2.5)	0.009
Fatal or non-fatal CVD	1.6 (1.0-2.5)	0.05

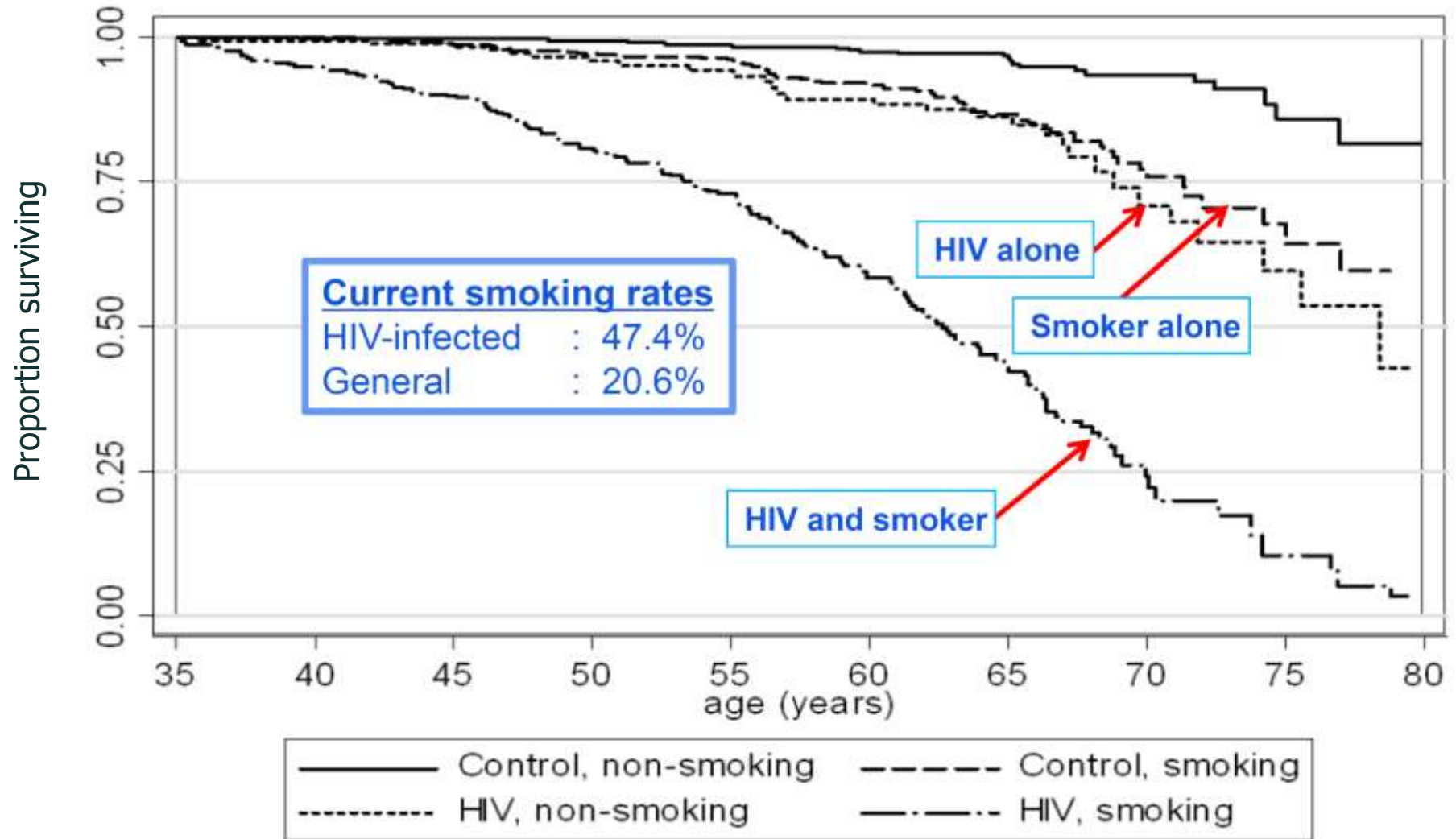
*Treatment Interruption vs. Continuous Treatment

START Study: Primary Endpoint

	Immediate ART	Deferred ART
No. with Event (%)	42 (1.8%)	96 (4.1%)
Rate/100PY	0.60	1.38
HR (Imm/Def)	0.43 (95% CI: 0.30 to 0.62, p<0.001)	



Higher impact of smoking than that of HIV infection in mortality of HIV-infected Persons



Cardiovascular risk: calculation

- Framingham risk score
- AHA/ACC pooled cohort equations CV risk calculator (PCE)
- DAD model
 - includes age, gender, BP, smoking, FH, DM, TC, HDL, CD4, cumulative exposure to PIs and NRTIs, current use of ABC
 - predicted risk more accurately than Framingham

Non-modifiable risk factors common to CKD and CVD

Non-modifiable risk factors	CKD	CVD
Advancing age ^{1,2}	+	+
Gender ^{1,2}	+ (female)	+ (male)
Family history ^{3,4}	+	+
Ethnicity ^{4,5}	+ (Black/Asian)	+ (Asian)

1. Booth GL, et al. Lancet 2006;368:29-36; 2. Mocroft A, et al. AIDS 2010;24:1667-78;
3. Hunt SC, et al. Am J Prev Med 2003;24:136-42;
4. NICE CKD Guidelines 2008. <http://www.nice.org.uk/nicemedia/pdf/CG073NICEGuideline.pdf>;
5. NICE CVD Guidelines 2010. <http://www.nice.org.uk/nicemedia/live/13024/49273/49273.pdf>

Many modifiable risk factors are common to CKD and CVD

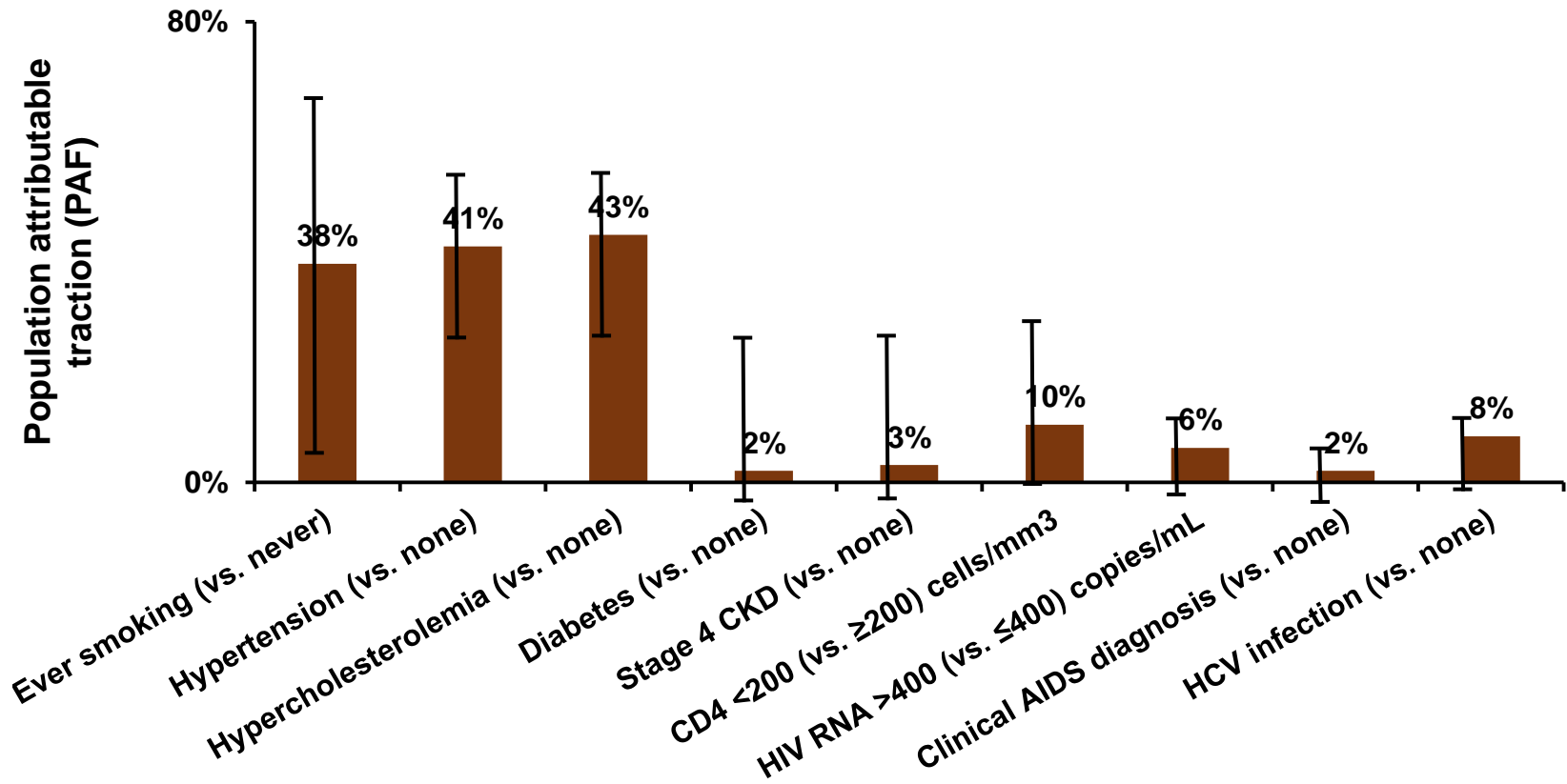
Major modifiable risk factors	CKD	CVD
Diabetes ^{1,2}	+	+
Hypertension ^{1,2}	+	+
Dyslipidaemia/abnormal lipids ^{1,3}	+	+
Smoking ^{1,4}	+	+
HIV disease ⁵⁻⁷	+	+
Metabolic syndrome ^{8,9}	+	+
Hepatitis C virus infection ^{2,10}	+	+
Obesity ^{1,11}	+	+

1. NICE CVD Guidelines 2010. Available at <http://www.nice.org.uk/hasmedia/1104/6921349273.pdf>
2. Meuwert A, et al. AIDS 2010;24:1647-78. 3. CKD in adults. In: [NICE CKD Guidelines](http://www.nice.org.uk/hasmedia/1104/6921349273.pdf)
4. NICE CKD Guidelines <http://www.nice.org.uk/hasmedia/1104/6921349273.pdf>
5. SMART Study Group. N Engl J Med 2006;355:251-262. 6. <http://www.nice.org.uk/hasmedia/1104/6921349273.pdf>
7. Campbell L, et al. HIV Med 2009;10:329-36. 8. WHO CVD Guidelines http://www.who.int/collab/infocis/ckd/ckd_guidelines.pdf
9. Royal College of Physicians CVD Guidelines <http://www.rcplondon.ac.uk/resources/publications/cvd-guidelines>
10. ButtAA, et al. Clin Infect Dis 2009;49:225-32. 11. Z. JH & Sharma KJ. Am Soc Nephrol 2010;21:406-12

NA-ACCORD:

Contributions to MI Risk in HIV+ Subjects

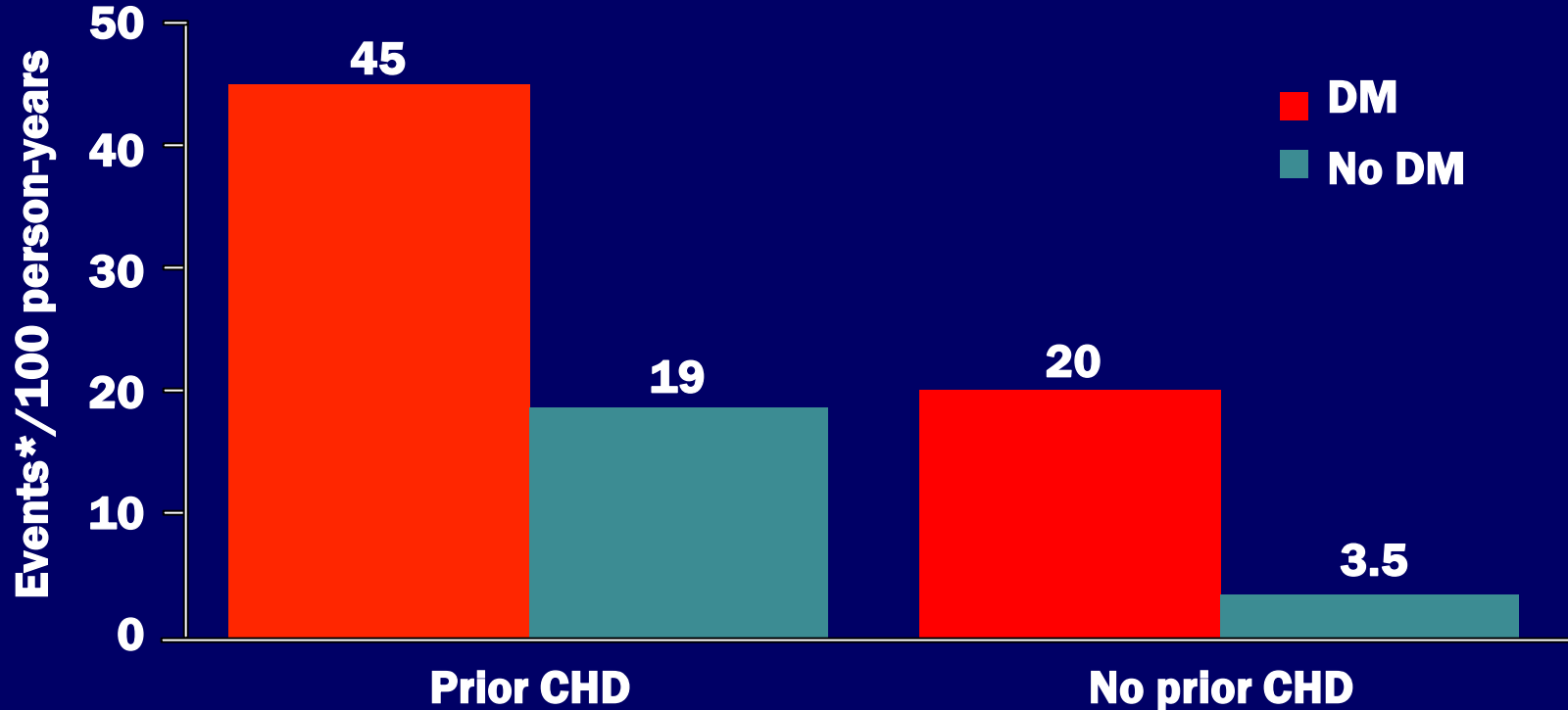
Population attributable fractions and 95% confidence intervals for traditional and HIV-related factors, and hepatitis C virus infection, NA-ACCORD (1 Jan 2000 – 31 Dec 2013)



Population attributable fractions have been adjusted for all the risk factors in the figure, as well as age, sex, race, HIV transmission risk, diabetes, and stage 4 chronic kidney disease.

Diabetes Mellitus: Risk of Myocardial Infarction

East-West Study



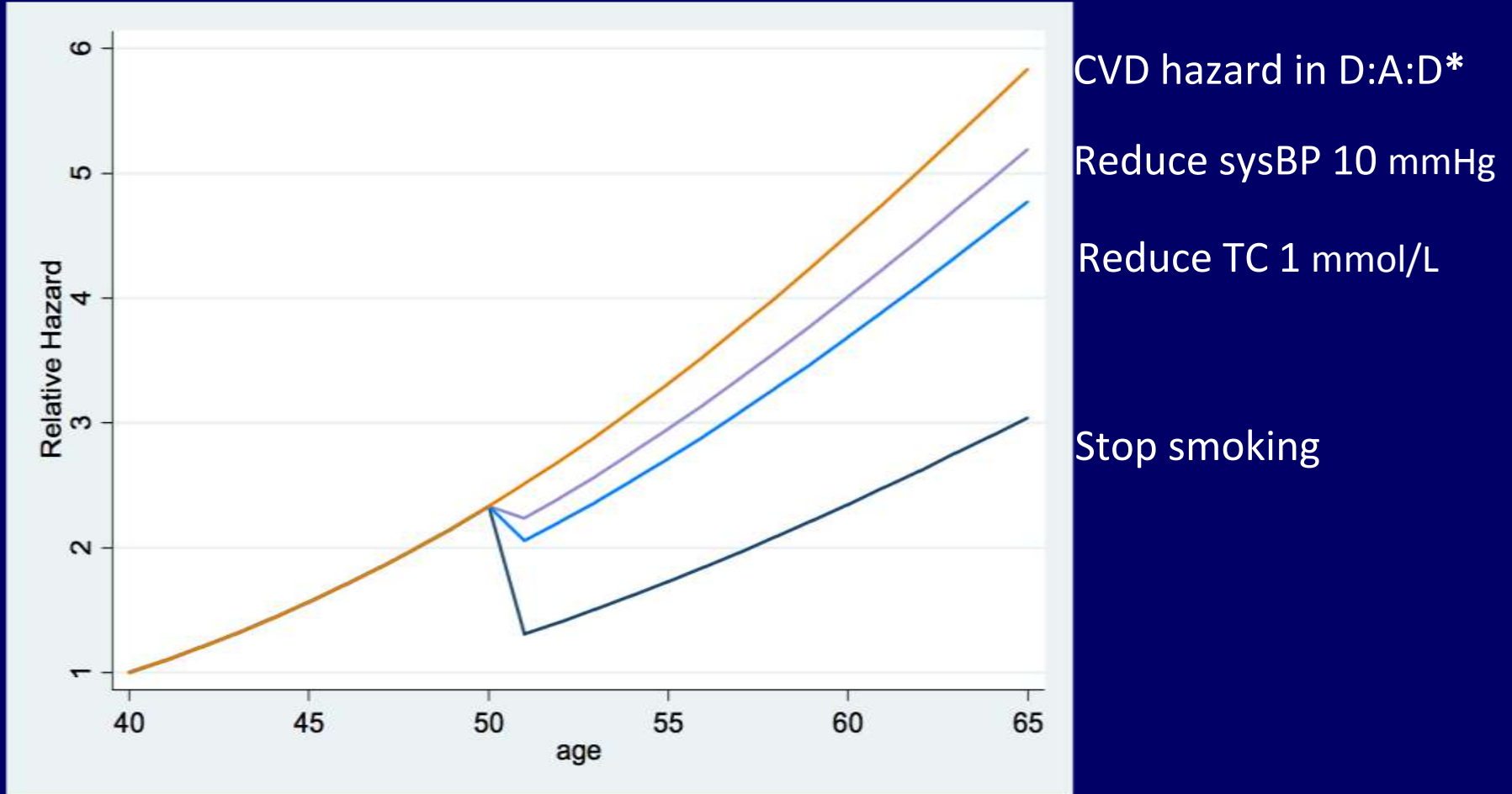
Patients with DM but no CHD experience a similar rate of MI as patients without DM but with CHD

*Fatal or non-fatal MI

CHD=Coronary heart disease, DM=Diabetes mellitus, MI=Myocardial infarction

Source: Haffner SM et al. *NEJM* 1998;339:229-234

CV Risk Modification in HIV



*relative to 40 y.o. HIV+ male

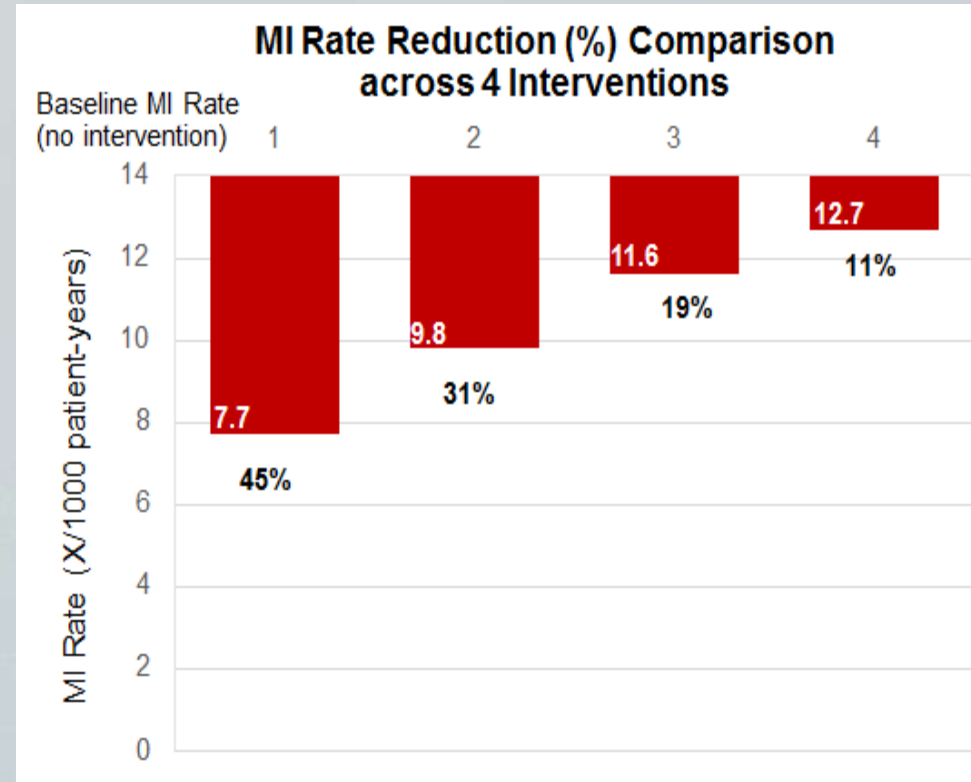
Petoumenos K for D:A:D . 20th CROI 2013.

NNT to Harm with MI: ABC in D:A:D

Risk	Underlying 5 year risk (%)	5 year NNH	Underlying 10 year risk (%)	10 year NNH
Low (40 yo non-smoker with good lipids and BP)	0.1	1111	0.3	370
Smoker	0.4	277	1.5	92
Smoker and DM	1.1	101	3.1	35
Smoker and raised lipids	3.1	35	7.5	14
Previous CVD	5	22	10	14

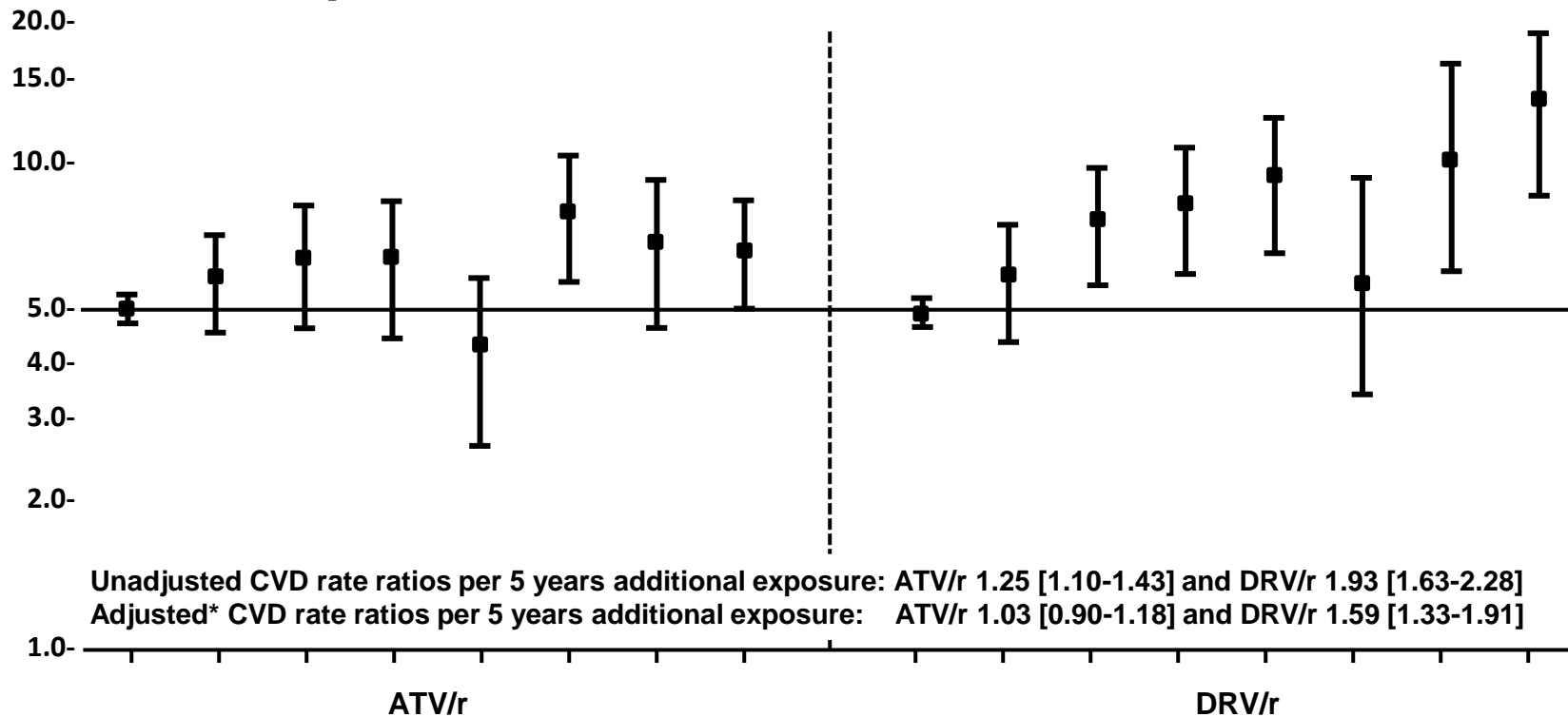
Impact on CV risk of selected interventions

Intervention Type	
HIV+ Patient Base Case Profile: 50 years old, Male, On Abacavir, Smoker, w/ Hypertension, w/ Hyperlipidemia	
1	Abacavir substitution with an alternative antiviral without association to higher MI rate [1][2][3]
2	Prescribing anti-hyperlipidemia medication [4][8]
3	Prescribing anti-hypertensive medication [4][7][8]
4	Counseling including standard treatment for smoking cessation such as nicotine patch and varenicline [4][5][6]



D:A:D:

Cumulative Exposure to DRV/r Increase MI Risk



Cumulative Years of Drug Exposure

	0	0-1	1-2	2-3	3-4	4-5	5-6	>6	0	0-1	1-2	2-3	3-4	4-5	5-6	>6
Events	824	75	49	41	26	46	34	62	909	52	51	44	39	17	18	27

*Adjusted for gender, race, HIV exposure group, enrolment cohort, baseline date, prior CVD, nadir CD4 count, current CD4 count**, dyslipidaemia**, BMI**, diabetes**, eGFR**, age (all as fixed variates at baseline), HBV, HCV, smoking, family history of CVD, VL., hypertension, AIDS, cumulative exposure to darunavir/r, atazanavir/r, lopinavir/r & indinavir & recent exposure to abacavir (≤6 months) (all as time-updated variables).

**Factors considered to potentially lie on the causal pathway between PI/r exposure and CVD and values hence fixed at baseline.

ART classes and dyslipidaemia

- **NRTIs**

 - TDF preferred (switching to TAF reduces lipid effect)

 - ABC associated with MI risk

- **NNRTIs**

 - RPV, DOR preferred over EFV

- **PIs**

 - ATV preferred even when boosted over LPV/rr

 - DRV/r associated with MI risk

- **InSTIs**

 - Lipid neutral but no CV risk. Weight gain risk?

NEAT 022: Switch from PI/r- to DTG-based Regimen in Subjects with Elevated CV Risk

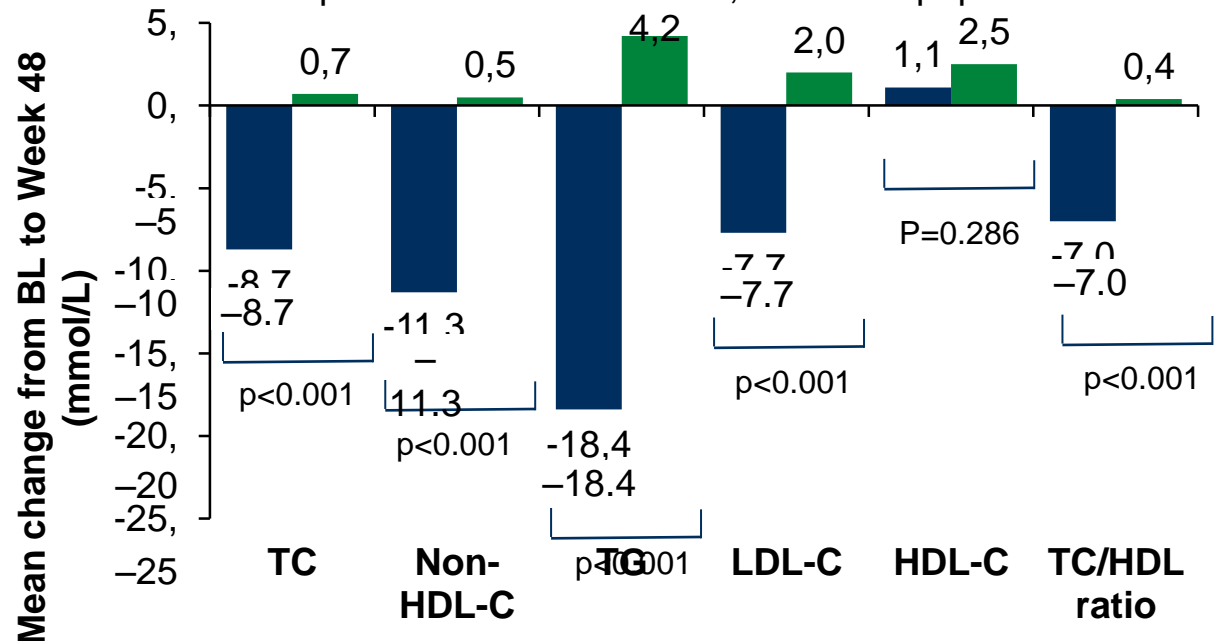
Switching from a PI/r-based regimen to a DTG-based regimen improved lipid profile versus continuing a P-based regimen in virologically suppressed patients with elevated CV risk*

- NEAT 022: randomised, open-label non-inferiority trial over 96 weeks in treatment-experienced patients, designed to investigate lipid parameters in subjects with elevated CV risk*
 - Changes in plasma lipids from BL to Week 48 were primary (TC) and secondary (other lipids) endpoints
 - Co-primary endpoint: % of patients free of therapeutic failure at Week 48, in the ITT population

DTG† (n=205)

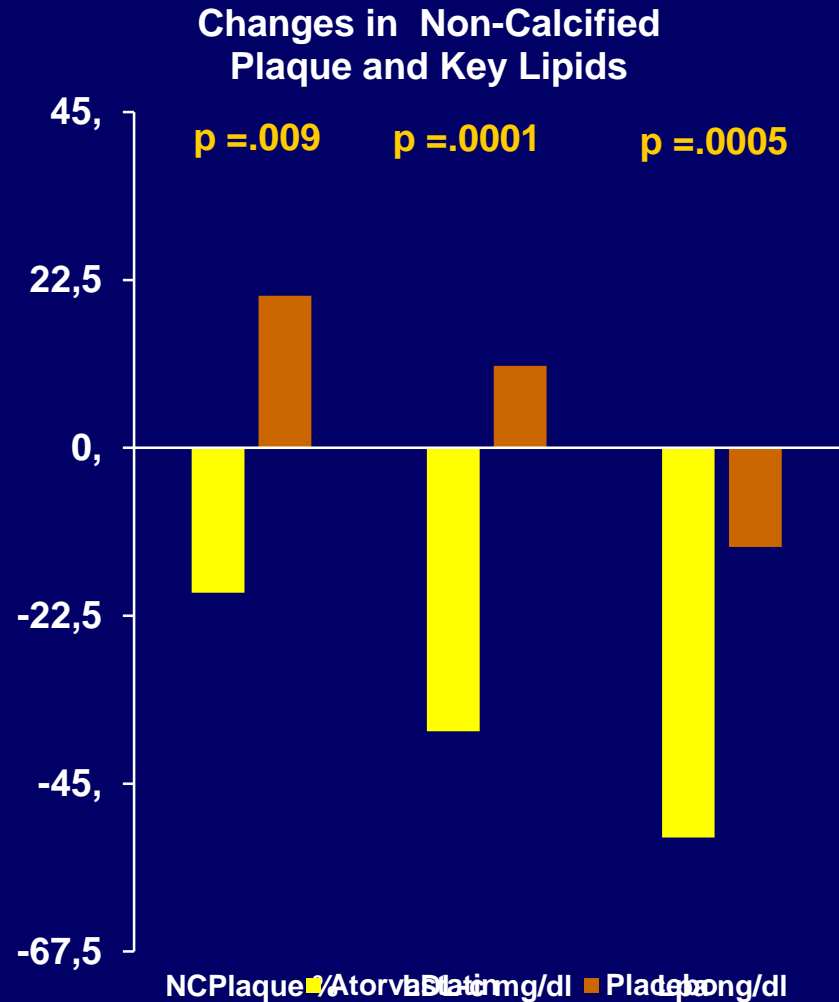
PI/r† (n=210)

- **TC and other lipid fractions (except HDL-C) improved significantly ($p < 0.001$) from BL with DTG.**
- **Virologic suppression was maintained after switch to DTG**



Atorvastatin vs Pbo for Non-Ca++ Coronary Plaques

- 40 HIV-infected pts with subclinical coronary atherosclerosis and low density lipoprotein (LDL) cholesterol <130mg/dL
- Coronary atherosclerotic plaque as assessed by coronary computed tomography angiography
- Statin therapy was well-tolerated, with low incidence of clinical adverse events or laboratory abnormalities

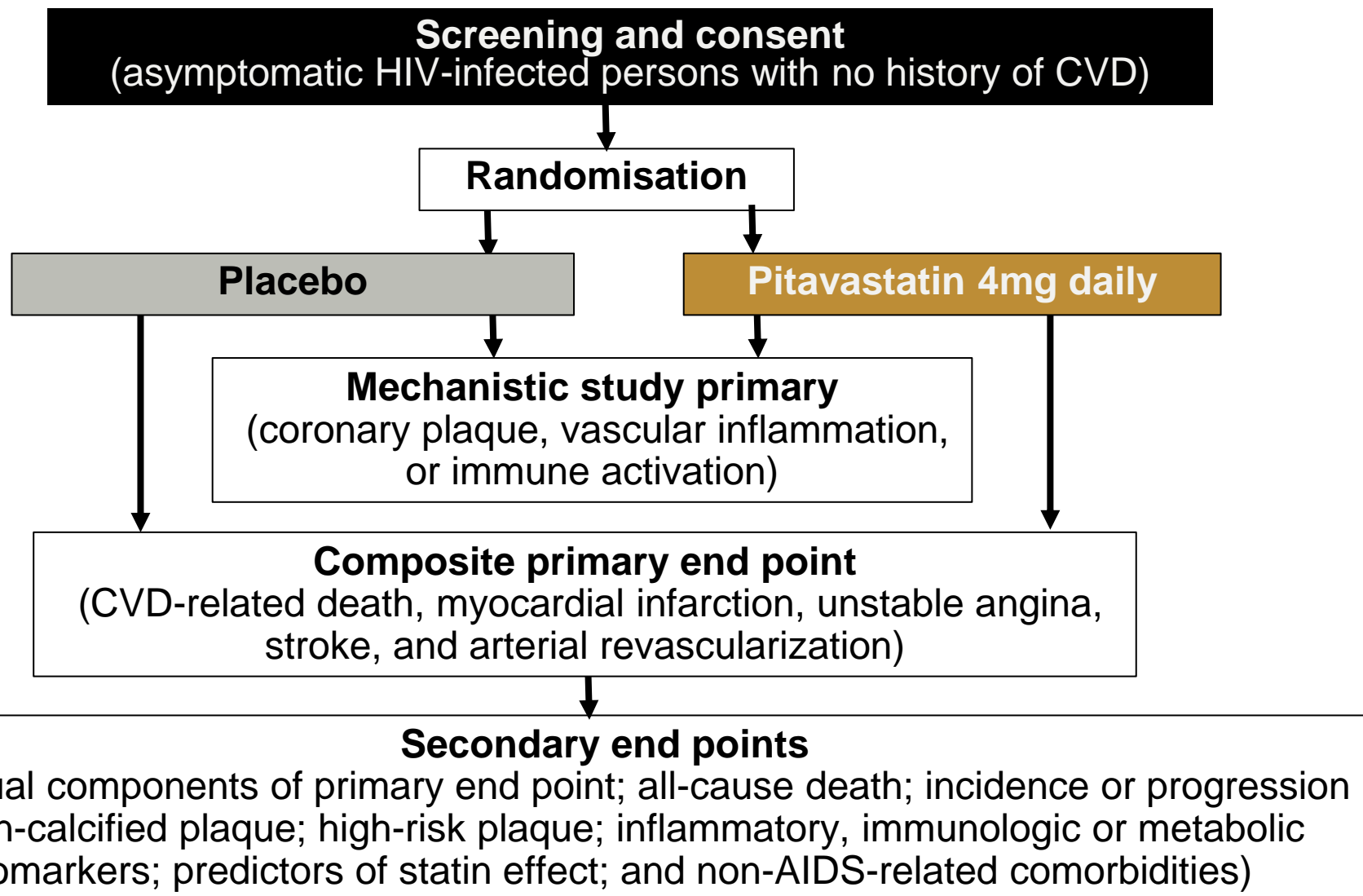


Beware of Drug Interactions

- ⊕ Boosters and statins esp simva-, fluva-statin
- ⊕ DRV induction and Atorva- and Rosuva-
- ⊕ Boosters and Ca Channel blockers e.g. amlodepine, diltiazem
- ⊕ Inducers (EFV>NVP) and statins, Ca Channels
- ⊕ DTG and metformin (+75%)

REPRIEVE: trial design (n=6500)

<http://reprievetrial.org/overview/>



Management principles in HIV-infected persons

- Same risk reduction strategies as general population
 - aspirin (?), statin, BP control, management of DM
- Screen for DM and dyslipidaemia at baseline and every 3 to 6 and 6 to 12 months respectively
- Use InSTI and avoid ABC in treatment naïve with increased cardiovascular risk
- Switch PI to InSTI has modest benefit on dyslipidaemia in treatment experienced
- atorvastatin, pitavastatin and rosuvastatin are statins of choice for dyslipidaemia on ART