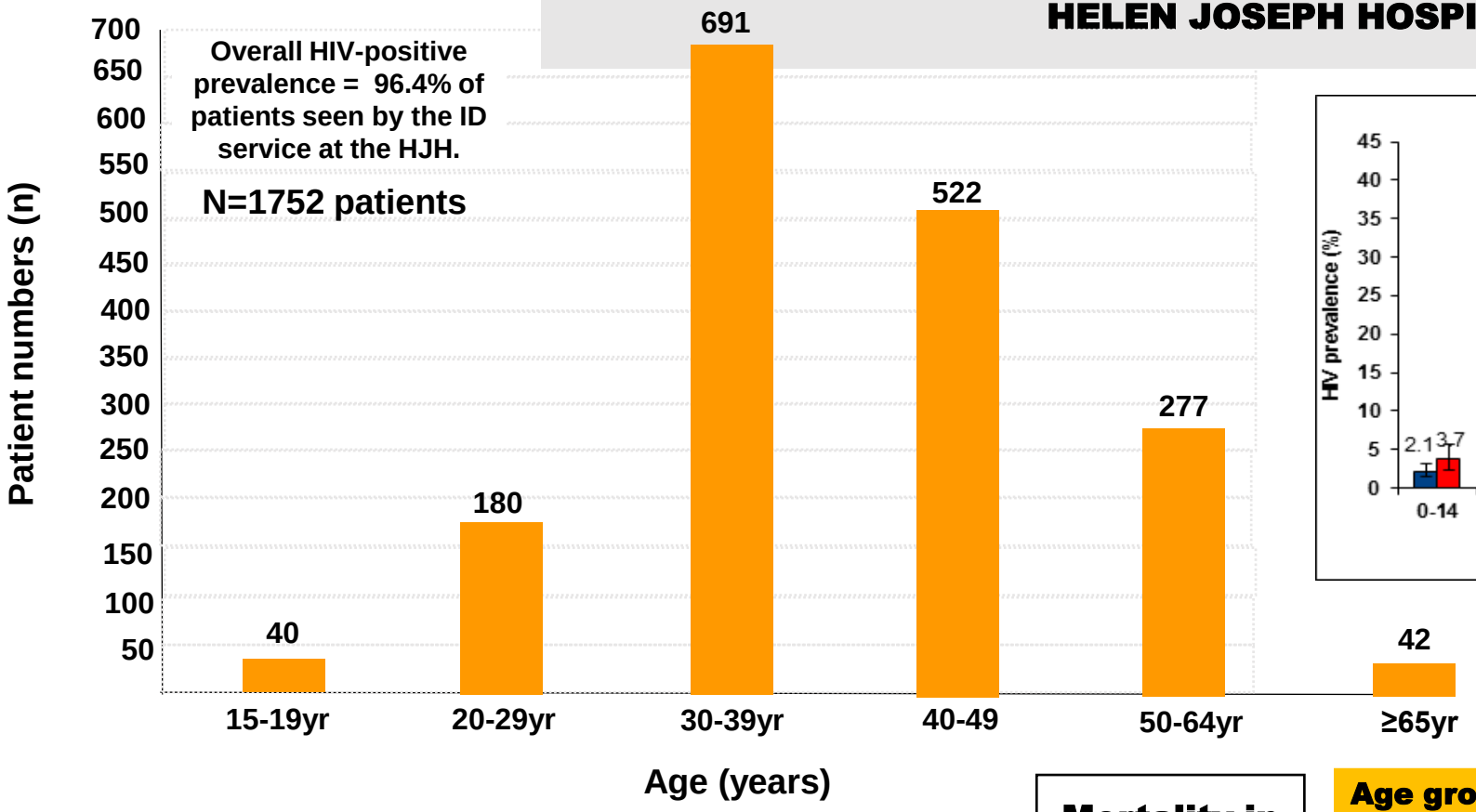
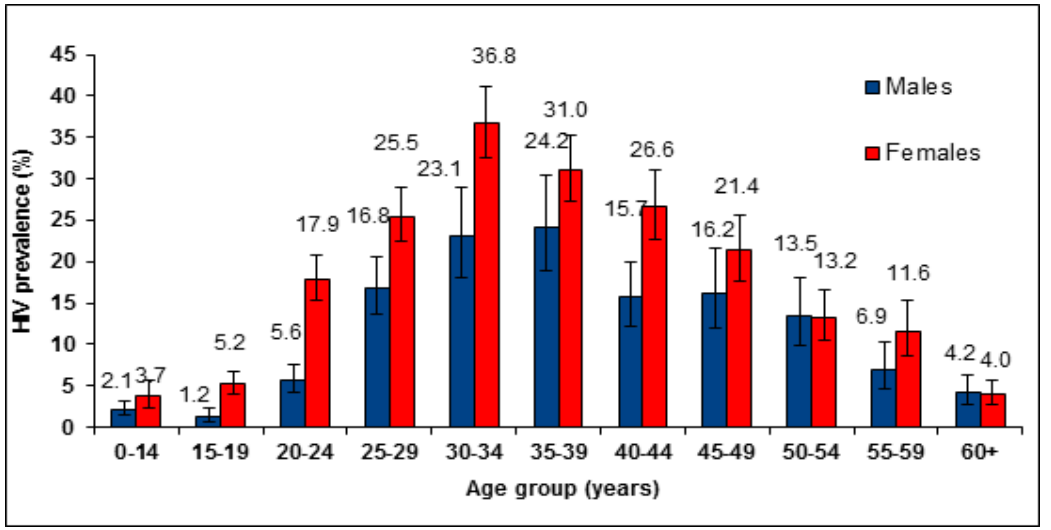
HIV, HYPERTENSION and CARDIOVASCULAR DISEASE

Dr David Spencer Right to Care
Helen Joseph Hospital
Johannesburg
April 2016

HIV-POSITIVE SUBJECTS REFERRED TO THE INFECTIOUS DISEASES UNIT, HELEN JOSEPH HOSPITAL, 2013-2015





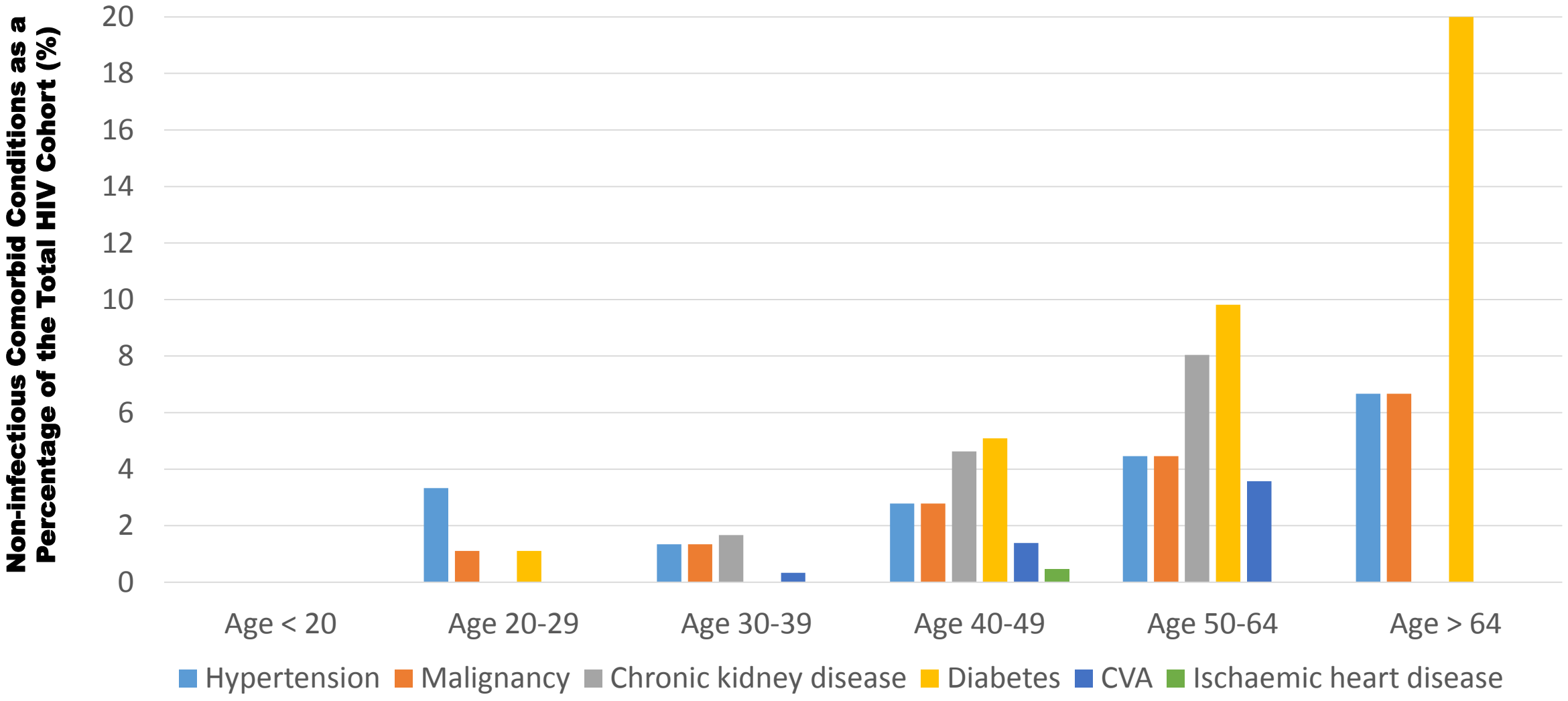
Whiteside A., Health Economics and HIV and AIDS Research Division (HEARD), University of KwaZulu-Natal. 2013

Nel J, Ive P, Spencer DC. Infectious Diseases Database ID Department. Helen Joseph Hospital, Johannesburg, SA. April 2016

Mortality in HIV+ve patients seen by the ID unit of the Helen Joseph Hospital

Age group	Number of Deaths (n)	Deaths (%)
15-19yr	2/40	5%
20-29yr	13/180	7%
30-39yr	73/691	10.5%
40-49yr	66/522	12.6%
50-64yr	29/277	10.5
≥65yr	5/42	11.9

Comorbidities (%) in HIV-infected patients seen in the Infectious Diseases Programme, Helen Joseph Hospital, 2015



Nel J. Database. ID Department, Helen Joseph Hospital, Johannesburg, SA. April 2016

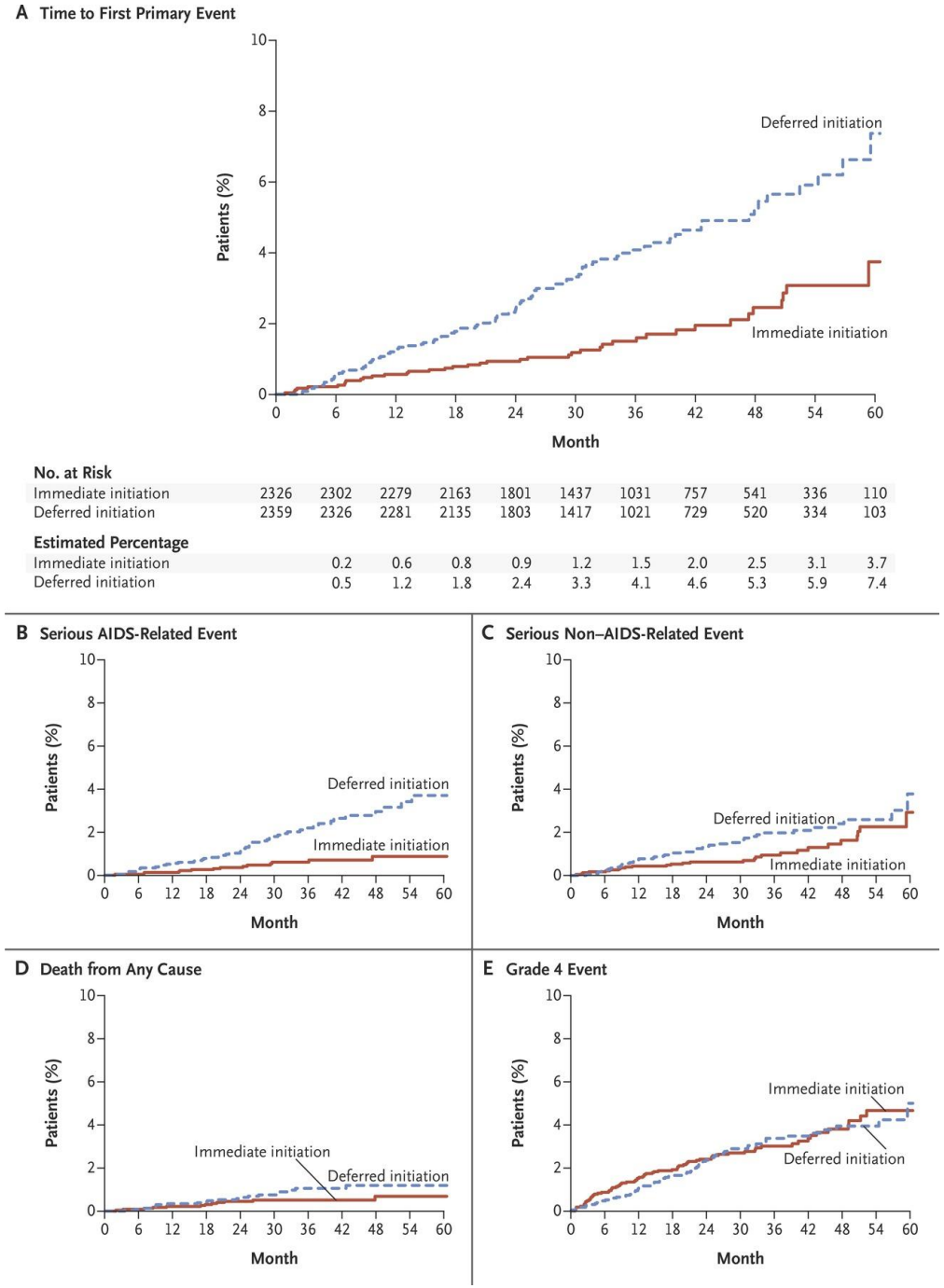


Figure. Primary and Secondary End Points to the START Study.

Shown are Kaplan-Meier estimates of the cumulative percentages of patients with the composite primary end point – a serious AIDS-defining or serious non-AIDS-related event, including death – in the two study groups (Panel A). Secondary end points included serious AIDS-related events (Panel B), serious non-AIDS-related events (Panel C), death from any cause (Panel D) and grade 4 events (Panel E). Grade 4 events were defined as potentially life-threatening symptomatic events that were not attributable to AIDS and that required medical intervention.

THE START STUDY

The INSIGHT START Study Group (Jens Lundgren et al).
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection.
N Engl J Med 2015 (August 27); 373: 795-807

THE HEART OF SOWETO STUDY

Cohort drawn from consecutive referrals to the cardiac unit at the CHBH in Soweto from Jan.1-Dec 31, 2006

N = 45 400 in-patients in the Department of Medicine of the CHBH in 2006

Sliwa K, Wilkinson D, Hansen C, et al. Spectrum of heart disease and risk factors in a black urban populations in South Africa (the Heart of Soweto Study): a cohort study. *Lancet* 2008; 371: 915-22

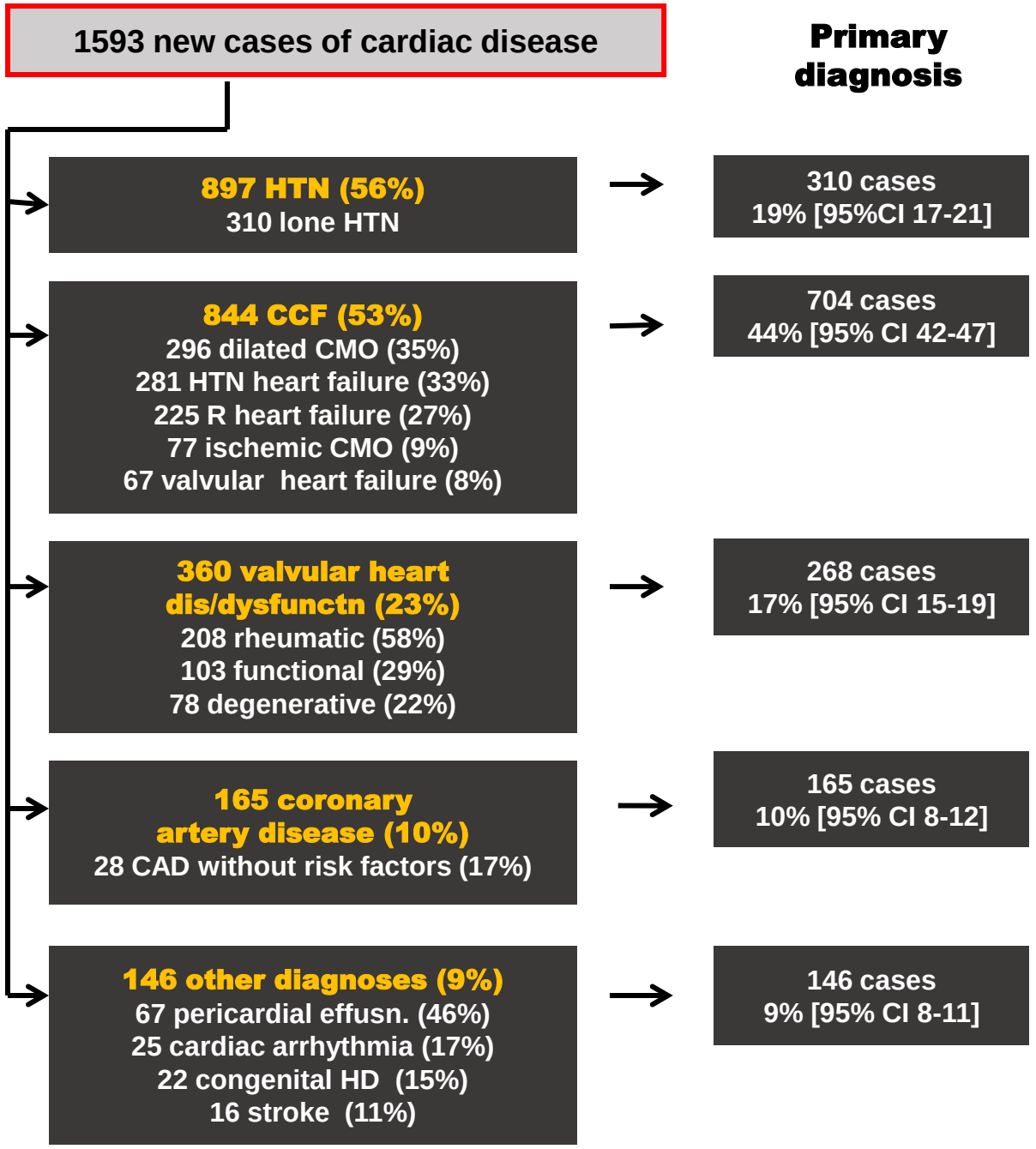
Study population:

N = 4162 confirmed with cardiovascular disease

N = 1593 (38%) newly diagnosed

N = 2569 (62%) previously diagnosed and on treatment

N = 74 (5%) HIV-positive



THE HEART OF SOWETO STUDY (2006)

Profile	All (n=1593)	HTN (n=310)	CCF (n=704)	Valve dis (n=268)	CAD (n=165)	Other (n=146)
Age (yr)	**52.8 (17.1)**	**58.3 (15.3)**	**55.1 (16.2)**	**45.7 (18.2)**	**56.7 (12.4)**	**38.0 (16.6)**
Black African	1359 (85%)	265 (86%)	640 (91%)	243 (91%)	77 (47%)	134 (92%)
Women	939 (59%)	199 (64%)	409 (58%)	179 (67%)	68 (41%)	84 (58%)
High cholesterol	**159 (22%)**	**54 (38%)**	**45 (17%)**	**16 (21%)**	**37 (35%)**	**7 (20%)**
Smoker	661 (41%)	112 (36%)	327 (46%)	84 (31%)	84 (51%)	54 (37%)
Renal dysf.	115 (10%)	23 (10%)	51 (10%)	20 (8%)	16 (11%)	5 (5%)
Anemia	156 (13%)	30 (12%)	64 (11%)	22 (12%)	7 (6%)	33 (28%)
Diabetes	**165 (10%)**	**41 (13%)**	**66 (9%)**	**13 (5%)**	**35 (21%)**	**10 (7%)**
HIV+ve*	**74 (5%)**	4 (1%)	35 (5%)	10 (4%)	2 (1%)	**23 (16%)**
NYHA Class III/IV	486 (31%)	84 (27%)	255 (36%)	63 (24%)	32 (19%)	52 (36%)

*** HIV test = only "if clinically indicated and consent given"**

Sliwa K, Wilkinson D, Hansen C, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. Lancet 2008; 371: 915-22

The clinical spectrum of heart disease in the Sowetan population is changing:

Atherosclerotic disease was once 'absent' from this group. In this study it accounted for 14% overall cardiac disease.

In addition, the scope of cardiac disease is uniquely broadened by the presence of TB and HIV

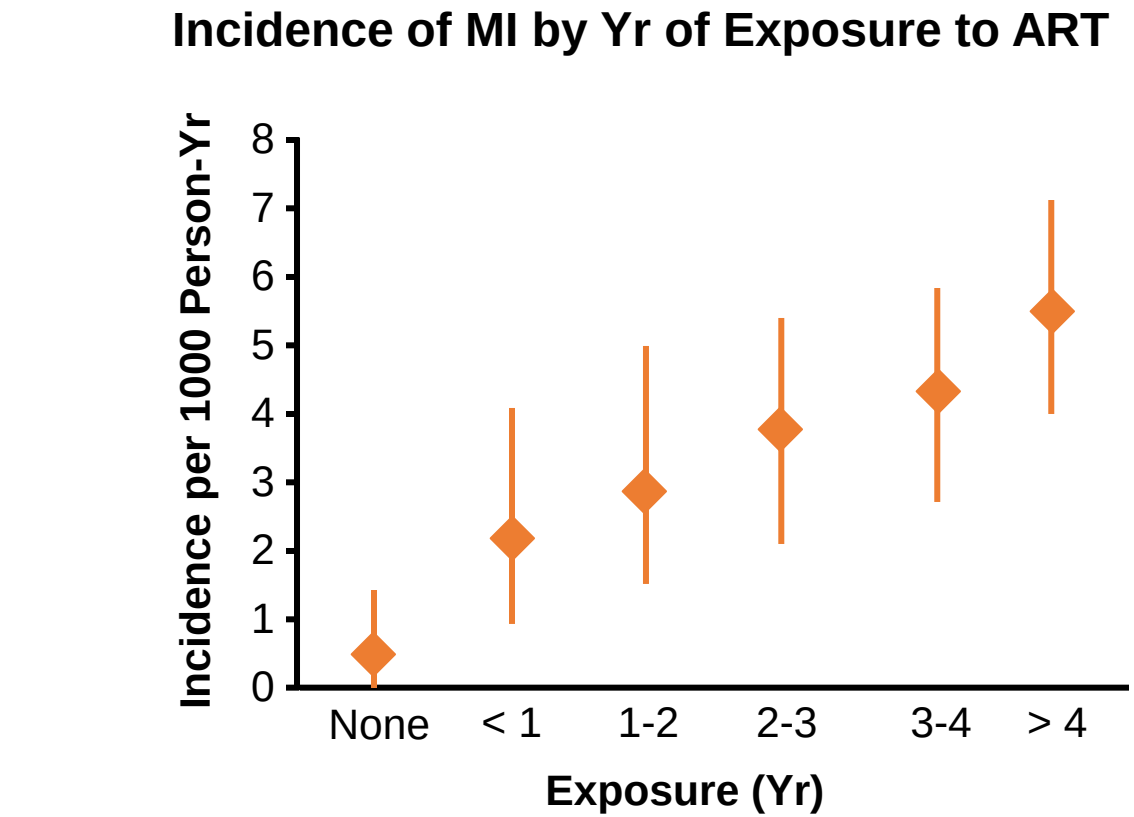
e.g. TB pericardial effusion,
HIV-related cardiomyopathy,
and disease that has resulted from the use of antiretroviral therapy.

THE HEART OF SOWETO STUDY

Sliwa K, Wilkinson D, Hansen C, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. Lancet 2008; 371: 915-22

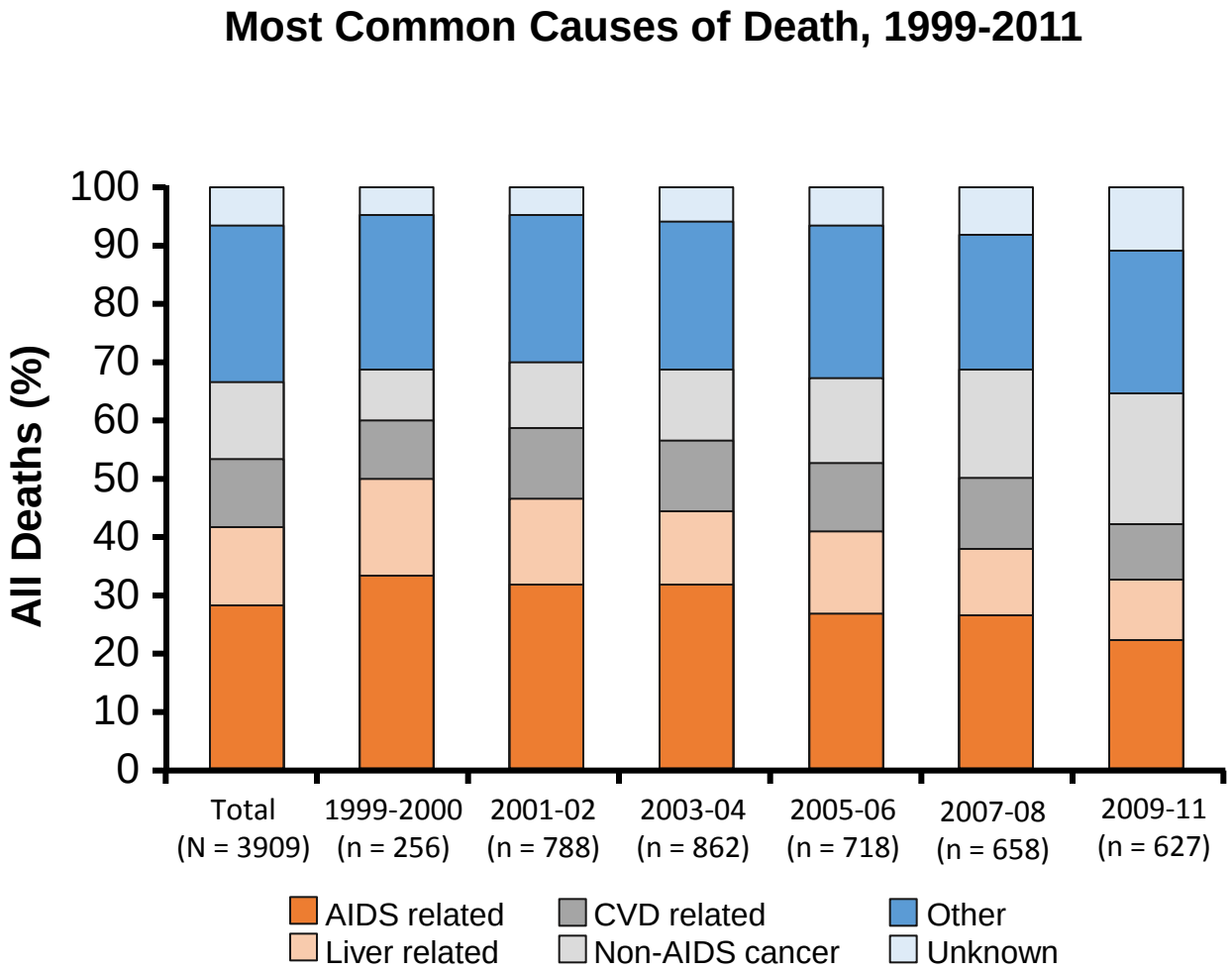
D:A:D: Incidence of MI Increases With Exposure to Combination ART

D:A:D Study.
N Engl J Med.
2003;349:1993-2003.



Events, n	3	9	14	22	31	47
Person-yrs, n	5714	4140	4801	5847	7220	8477

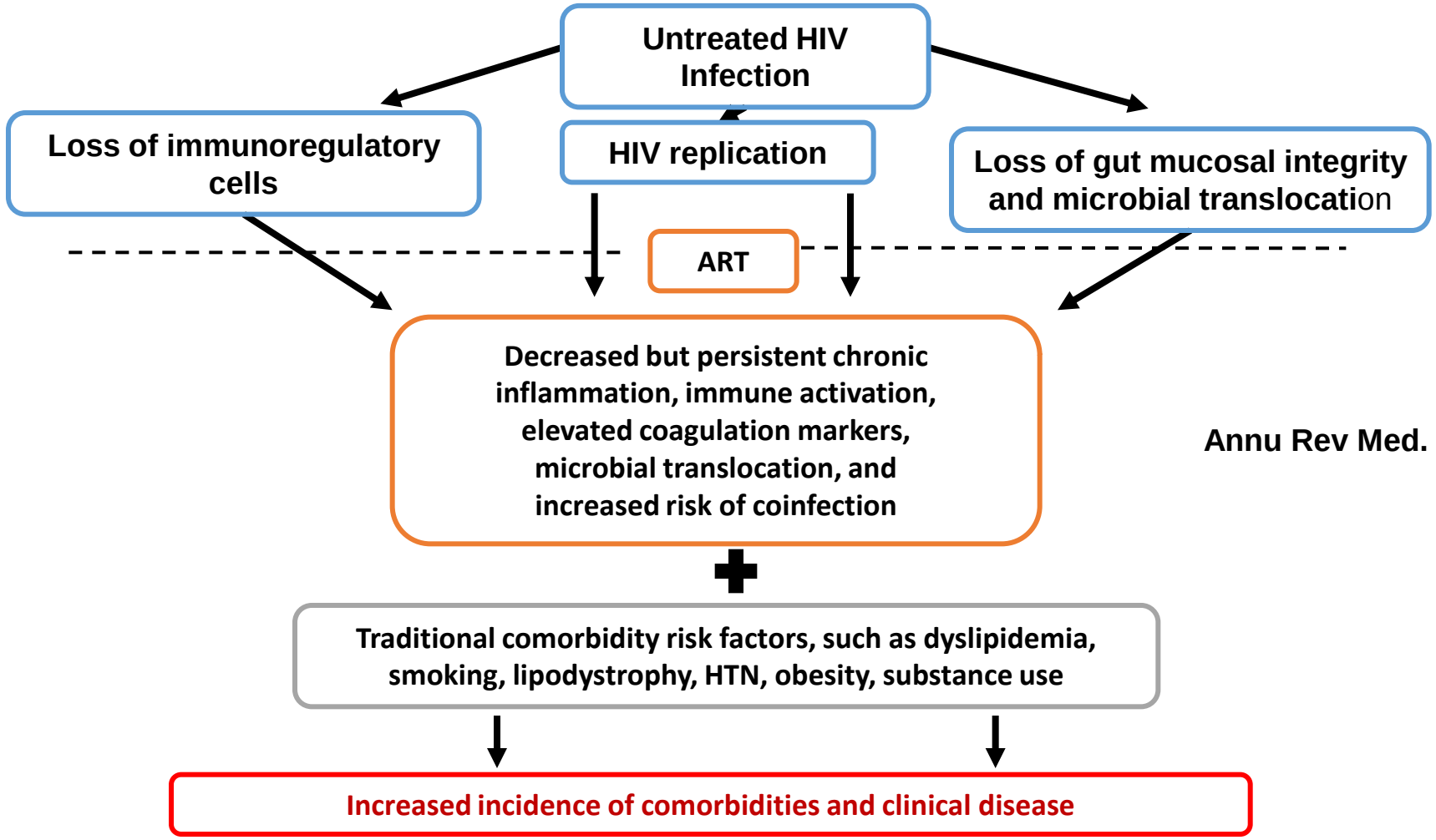
D:A:D: CVD Deaths Decreased in Era of Modern ART



The DATA COLLECTION on ADVERSE EVENTS Of ANTI-HIV DRUGS = D:A:D STUDY

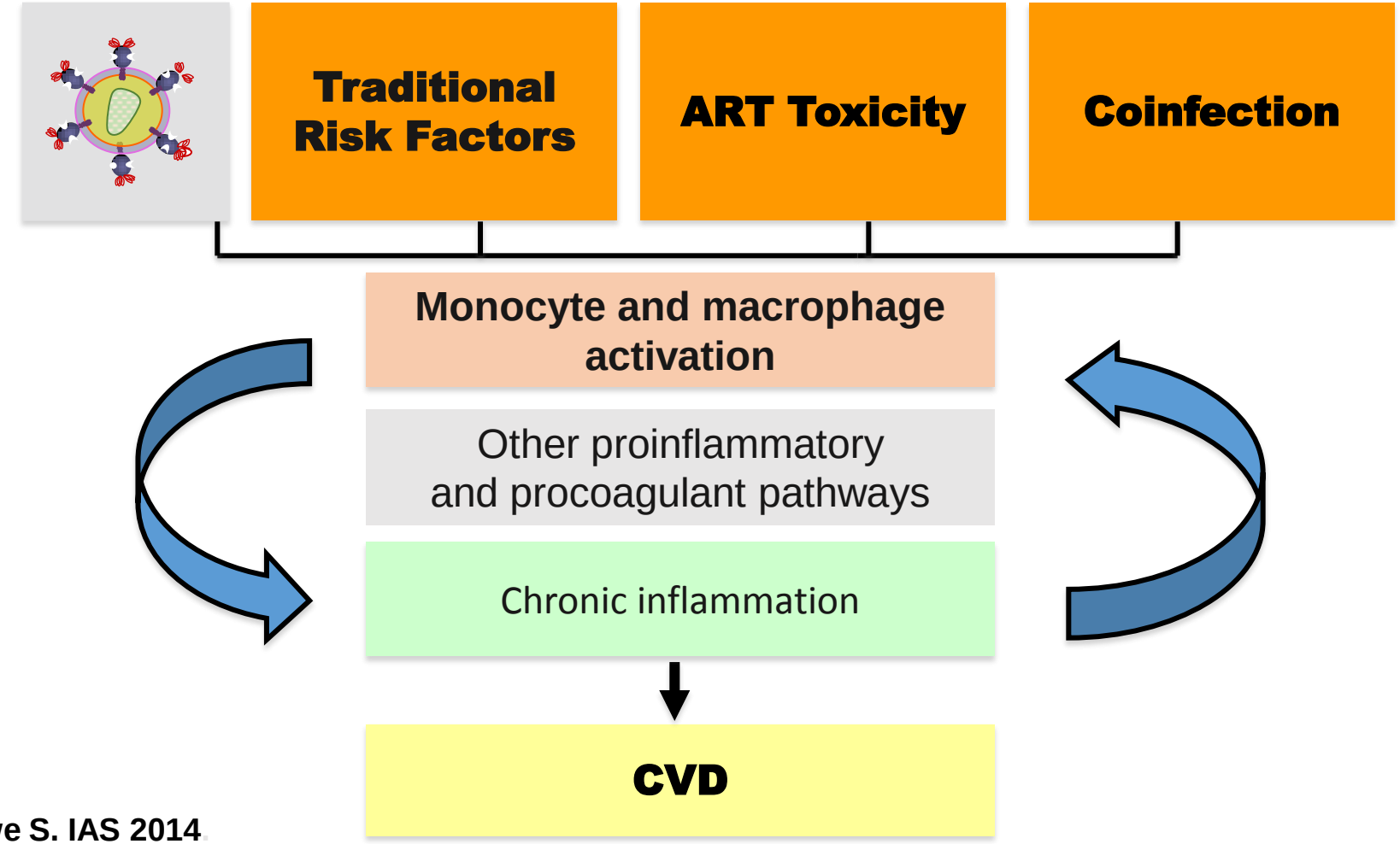
Smith C, et al Lancet. 2014:384:241-248.

Chronic Inflammation and Increased Risk for Comorbidities in HIV-Positive Pts



Deeks SG.
Annu Rev Med. 2011;62:141-155.

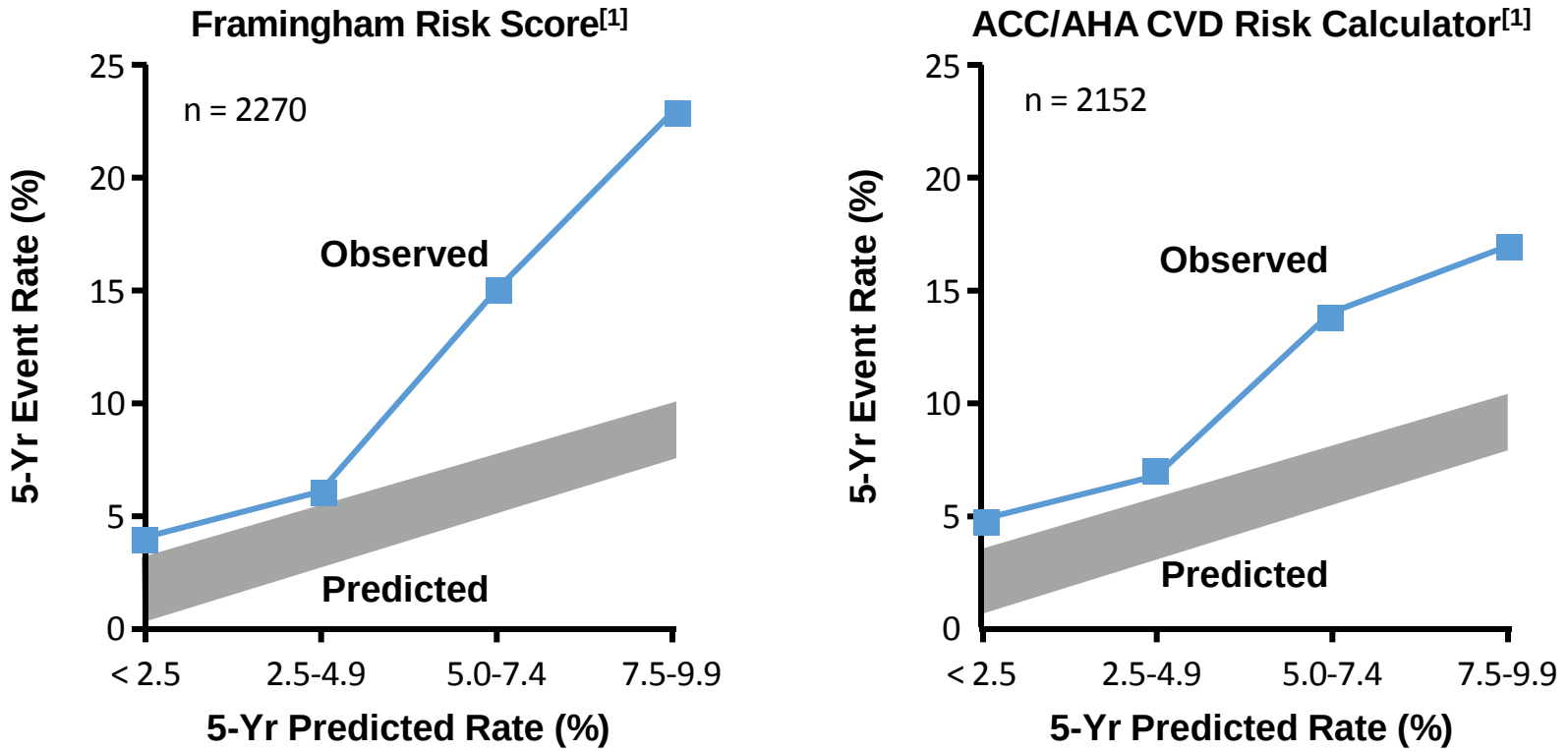
Factors Contributing to CVD in HIV-Positive Pts



Crowe S. IAS 2014

CVD Outcomes Underestimated in HIV-Positive Pts by Risk Calculators

- **CVD risk scores calculated with data from 2006-2009 for pts in Partners HealthCare System Cohort[1]**

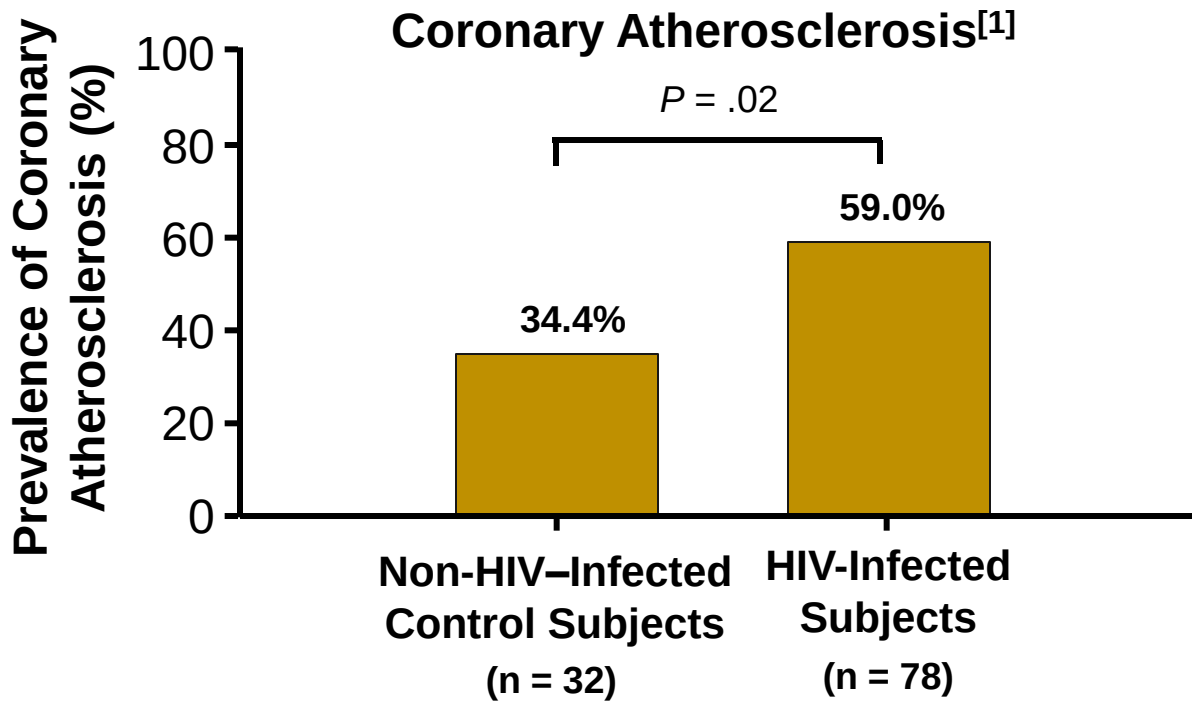


- **An outpatient study cohort (n = 2392) had similar findings of underestimated CVD risk (15% to 25%)[2]**

1. Regan S, et al. CROI 2015. Abstract 751. 2. Thompson-Paul A, et al. CROI 2015. Abstract 747.

CT Angiography in HIV

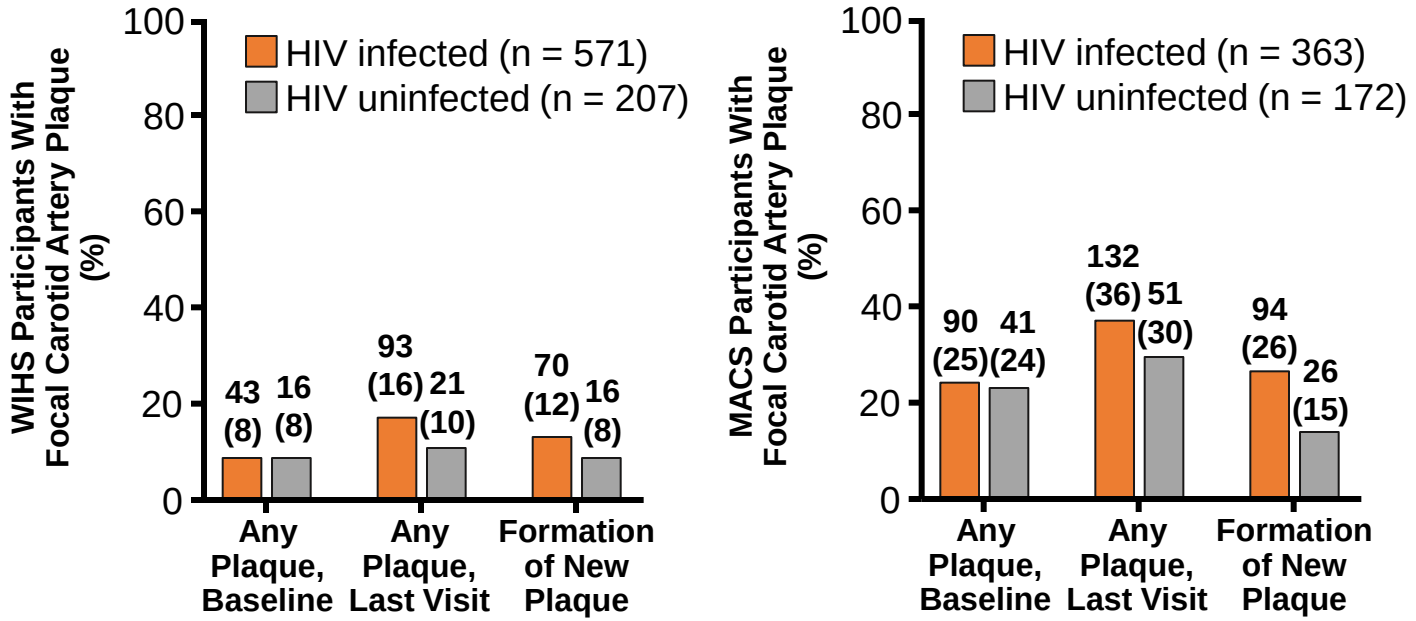
- **Asymptomatic HIV-positive pts had higher prevalence and degree of coronary atherosclerosis vs uninfected controls[1]**
- **Among ART-treated HIV-infected pts, plasma sCD163 significantly higher (*P* = .02) and correlated with non-calcified plaque[2]**



1. Lo J, et al. AIDS. 2010;24:243-253. 2. Burdo TH, et al. J Infect Dis. 2011;204:1227-1236.

HIV and Carotid IMT in MACS/WIHS Cohorts

- 1.6-fold greater risk of new plaque formation in HIV-positive vs HIV-negative individuals (RR: 1.61; 95% CI: 1.12-2.32), adjusting for cardiometabolic factors
- Increased plaque occurred even among persistently virologically suppressed HIV-positive individuals vs uninfected individuals (RR: 1.56; 95% CI: 1.07-2.27)
- HIV-positive individuals with BL CD4+ ≥ 500 cells/mm^3 had plaque risk not statistically different from uninfected individuals



Hanna D, et al. *Clin Infect Dis*. 2015;[Epub ahead of print].

SOUTH AFRICA: GROBBLERSDAL, LIMPOPO

Methods: Cross-sectional Study of cardiovascular risk factors including Carotid Intimal-Media Thickness (CIMT) among HIV+ve clinic attenders.

RESULTS:

N=904 HIV+ve patients were screened
Female n=626 (69%)

Age = 40.7yr (median), IQR, 34.8-48.0

ART= >85% were on ART of whom
68% (n=539) had an undetectable vl.
CD4=388 (median)

Hypertension + obesity = 20%

Smokers: women 14% males 36%

Diabetes mellitus =5%

Patients on treatment for HPT n=46/205 (22%)

Carotid Intimal-Media Thickness n=866 patients

Females: 0.589mm (mean), IQR 0.524-0.678)
Males: 0.609mm (mean), IQR, 0.547-0.745)

INTERPRETATION:

Those with increased intimal thickness in the HIV+ve cohort appeared to reach a threshold CIMT value of 0.78mm more than a decade earlier than counterparts in a European reference group.

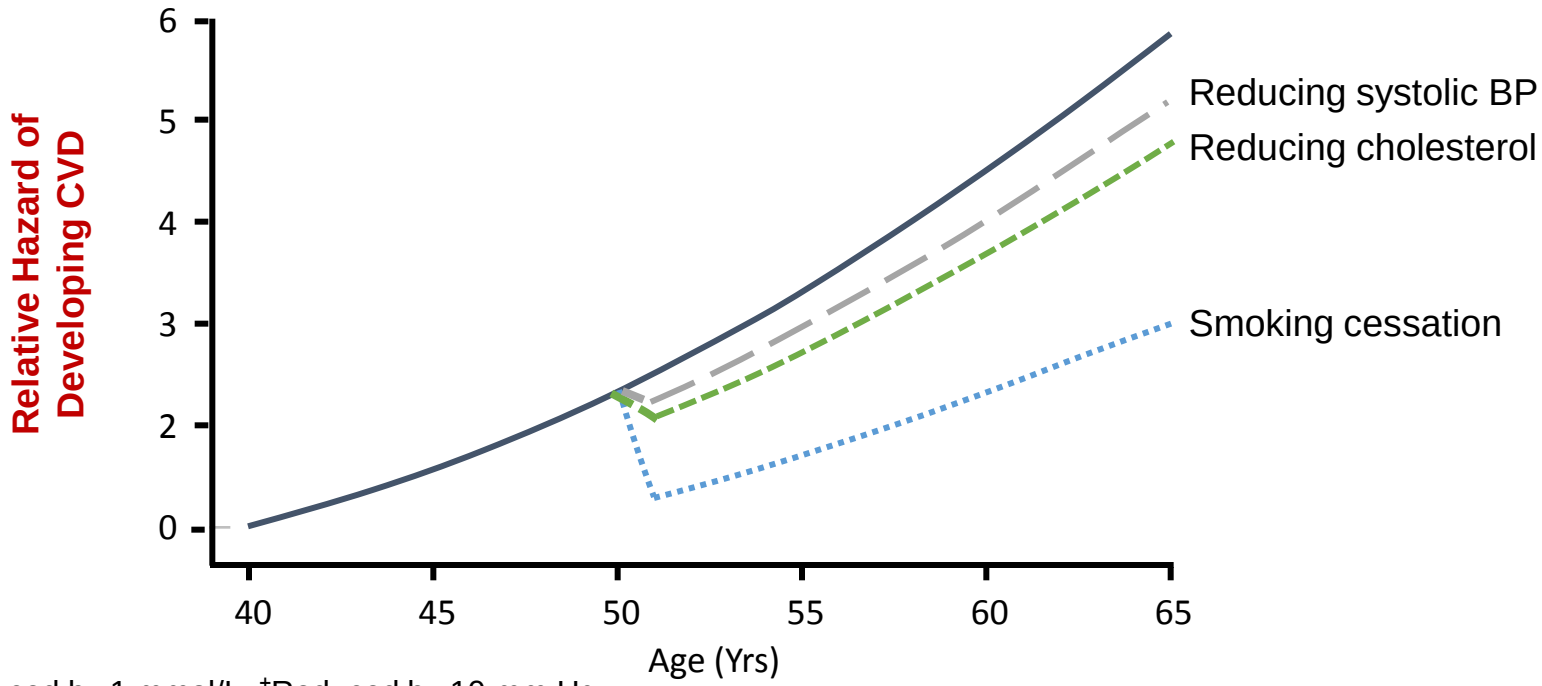
Overall, 12% of subjects (106/866) had subclinical evidence of atherosclerosis

Schoffelen AF, de Groot E, Templeman HA, et al. Carotid Intima Media Thickness in Mainly Female HIV-Infected Subjects in Rural South Africa: Association With Cardiovascular but Not HIV-Related Factors. *Clin Infect Dis* 2015 (15 Nov); 61; 1606-14

Reducing CVD Risk Factors Can Decrease Risk of CVD in Older HIV+ Pts

- **Effective treatment of modifiable risk factors, such as smoking, cholesterol, and BP can significantly reduce an individual's CVD risk**

Model for Change in Relative Risk of CVD From Smoking Cessation, Reducing Cholesterol,* or Reducing Systolic BP† in a Cohort of 24,323 HIV-Positive Pts Without Prior CVD (D:A:D Study)

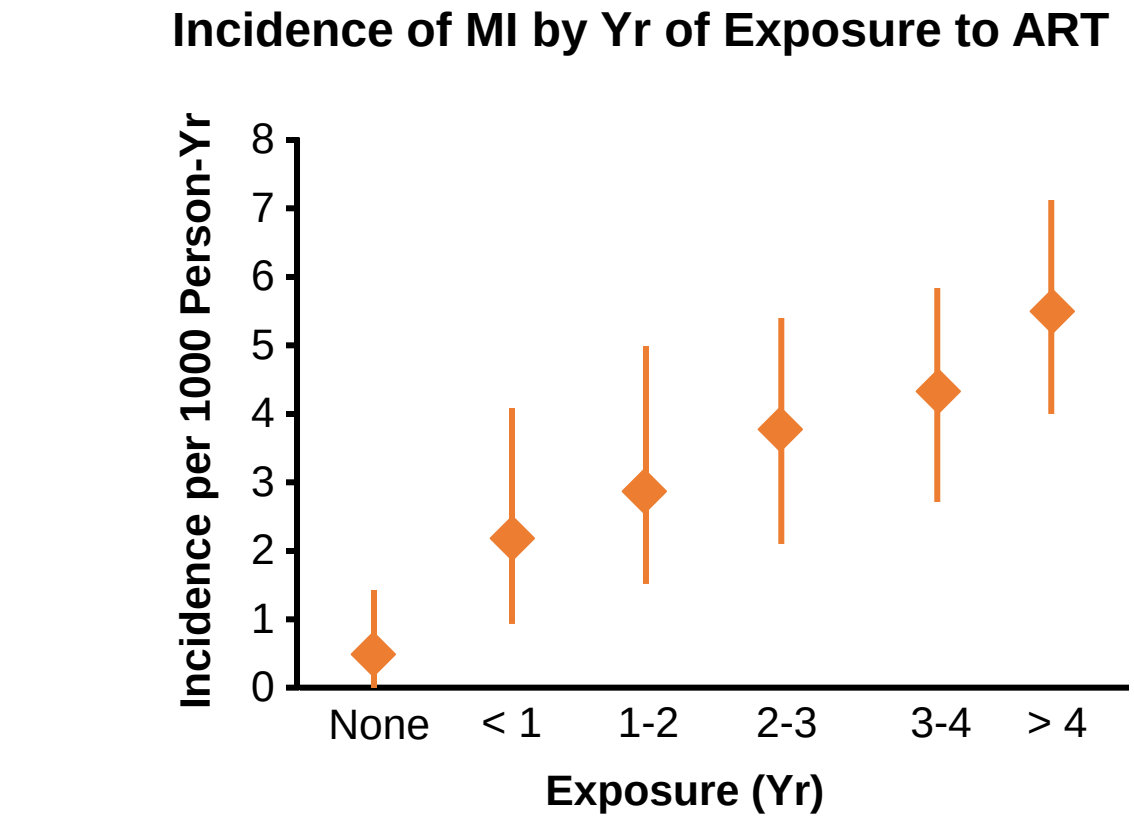


*Reduced by 1 mmol/L. †Reduced by 10 mm Hg.

Petoumenos K, et al. HIV Med. 2014;15:595-603.

D:A:D: Incidence of MI Increases With Exposure to Combination ART

D:A:D Study.
N Engl J Med.
2003;349:1993-2003.



Events, n	3	9	14	22	31	47
Person-yrs, n	5714	4140	4801	5847	7220	8477

CVD in SMART Trial of Immediate vs Deferred ART

- Outcomes including CVD (ART Better than no ART)

Endpoint*	Drug Conservation Group (N = 2720)		Viral Suppression Group (N = 2752)		HR for Conservation Group vs Viral Suppression Group (95% CI)	*P* Value
	Participants With Event, n	Event Rate (per 100 Person-Yr)	Participants With Event, n	Event Rate (per 100 Person-Yr)		
Primary endpoint	120	3.3	47	1.3	2.6 (1.9-3.7)	< .001
▪ Death from any cause	55	1.5	30	0.8	1.8 (1.2-2.9)	.007
Opportunistic disease						
▪ Serious	13	0.4	2	0.1	6.6 (1.5-29.1)	.01
▪ Nonserious	63	1.7	18	0.5	3.6 (2.1-6.1)	< .001
Major CV, renal, or hepatic disease	65	1.8	39	1.1	1.7 (1.1-2.5)	.009
▪ Fatal or nonfatal CVD	48	1.3	31	0.8	1.6 (1.0-2.5)	.05
▪ Fatal or nonfatal renal disease	9	0.2	2	0.1	4.5 (1.0-20.9)	.05
▪ Fatal or nonfatal liver disease	10	0.3	7	0.2	1.4 (0.6-3.8)	.46
Grade 4 event	173	5.0	148	4.2	1.2 (1.0-1.5)	.13
Grade 4 event or death from any cause	205	5.9	164	4.7	1.3 (1.0-1.6)	.03

*Numbers of individual events of each type do not sum to the total number because some participants had more than 1 event. Endpoint definitions are listed in the Supplementary Appendix. Grade 4 events were determined on the basis of toxicity grades developed by the Division of AIDS of the NIAID.

El Sadr W, et al. N Engl J Med. 2006;355:2283-2296.

ART and Effects on Lipids

TDF

RAL
DTG

RPV
ETV

ABC

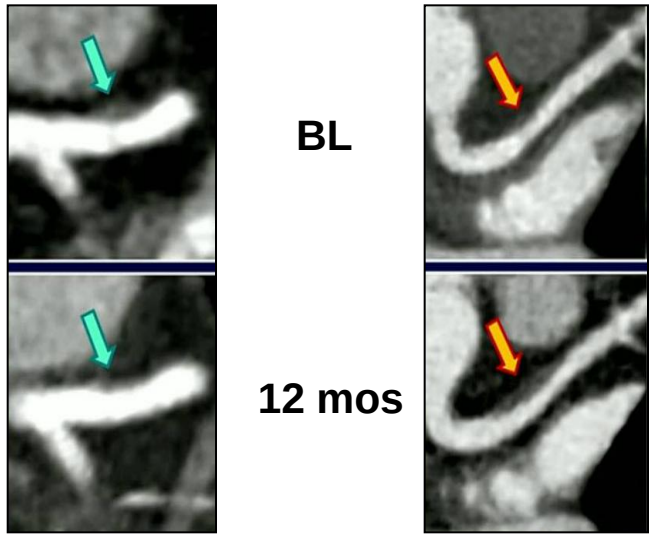
EFV

ATV/RTV or ATV/COBI
DRV/RTV or DRV/COBI
EVG/COBI

Randomized Trial of Statin Therapy and Coronary Plaque Progression

- **Randomized 12-mo trial in HIV+ pts on stable ART with LDL < 130 and ≥ 1 coronary plaque**
  - Atorvastatin 20 mg (↑ to 40 mg at 3 mos) (n = 19) vs
  - Placebo (n = 21)
- **Statin therapy reduced progression of coronary plaques**
  - Reduced overall plaque volume, including lipid-laden plaques
  - Reduced high-risk morphology plaques
- **Statin therapy safe and well tolerated**

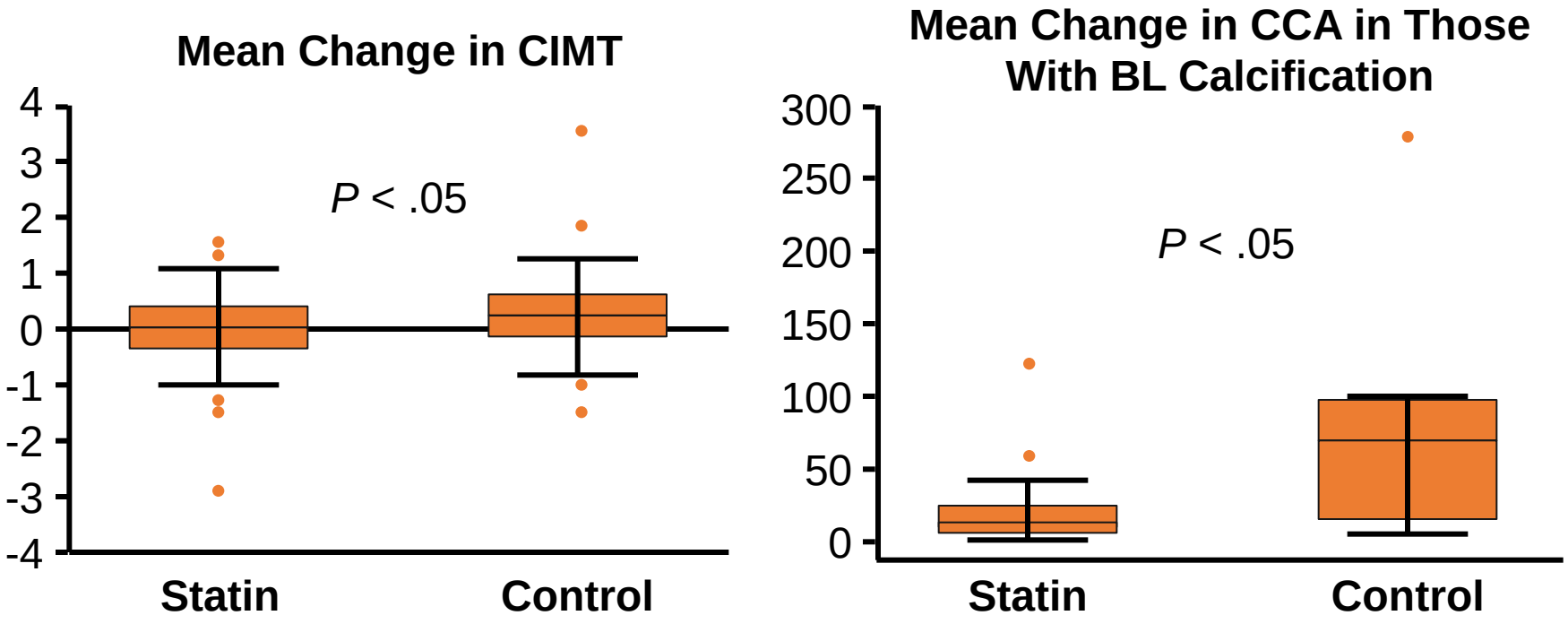
Plaque Progression in Proximal Left Anterior Descending Coronary Artery With Atorvastatin or Placebo



Lo J, et al. CROI 2015. Abstract 136.

Rosuvastatin Effects on Carotid Intimal Thickness and Coronary Calcium Score

- SATURN-HIV: double-blind, randomized, placebo-controlled trial of rosuvastatin in HIV-positive pts (N = 147)



Longenecker T, et al. CROI 2015. Abstract 137.

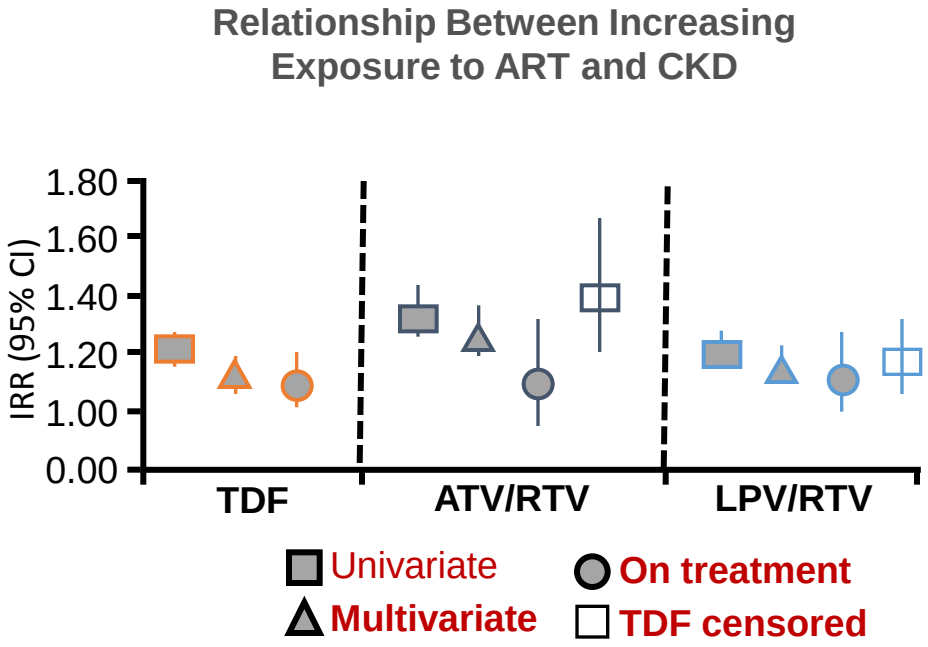
D:A:D: ART Exposure and Risk of CKD

- Retrospective analysis of pts with baseline eGFR > 90/mL/min (N = 23,560)
- Multivariate analysis: exposure to TDF, ATV/RTV, and LPV/RTV significantly associated with CKD development

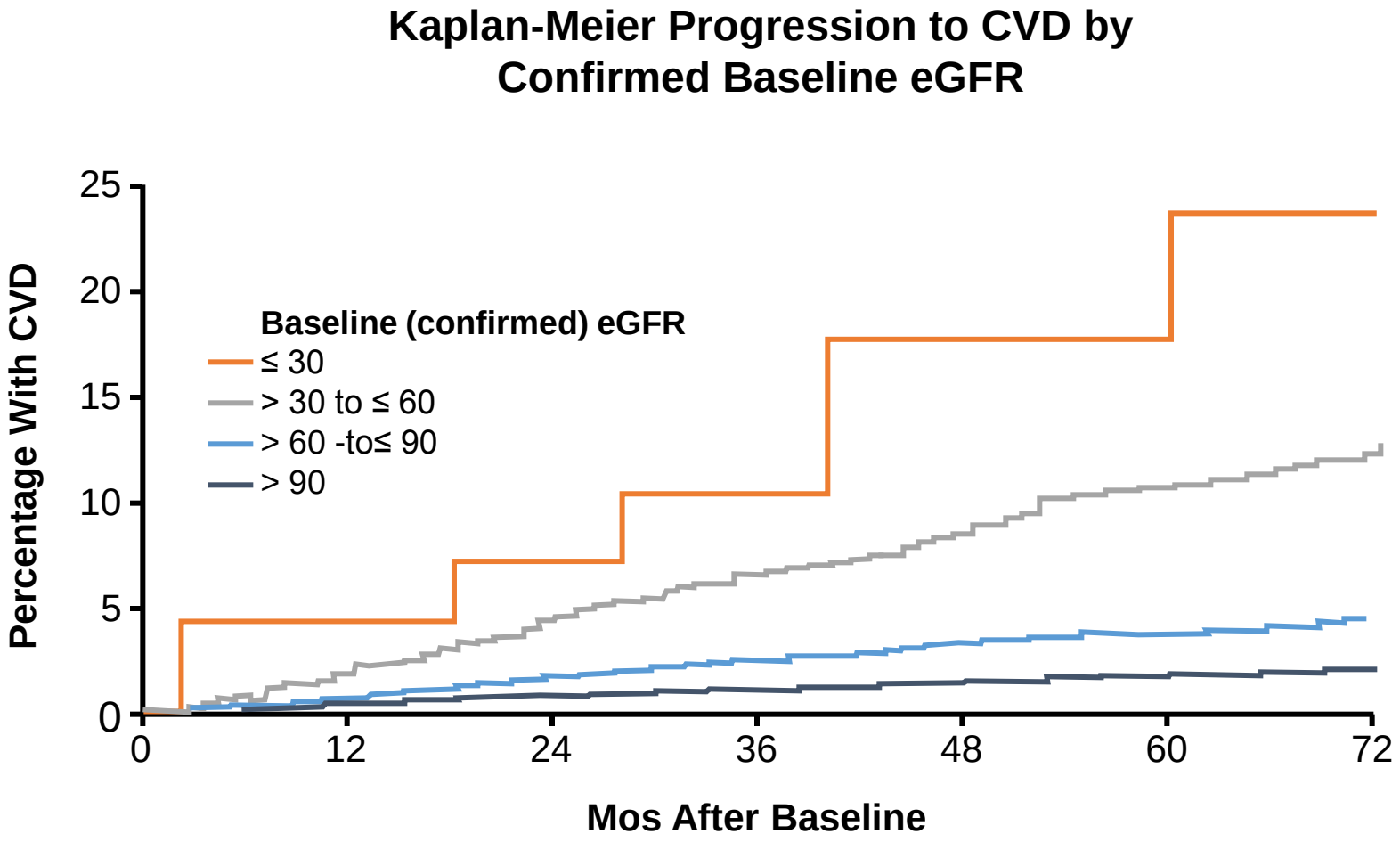
CKD Risk by Yrs of ARV Exposure, IRR (95% CI)			
Drug	**1 Yr**	**2 Yrs**	**5 Yrs**
TDF	1.12 (1.06-1.18)	1.25 (1.12-1.39)	1.74 (1.33-2.27)
ATV/RTV	1.27 (1.18-1.36)	1.61 (1.40-1.84)	3.27 (2.32-4.61)
LPV/RTV	1.16 (1.10-1.22)	1.35 (1.21-1.50)	2.11 (1.62-2.75)

Mocroft A, et al. CROI 2015. Abstract 142.

- Association with TDF or LPV/RTV and CKD remains when excluding those who stopped drugs during or before study entry
- When TDF exposure censored, CKD risk per yr of ATV/RTV or LPV/RTV exposure increased substantially
- CKD risk ↓ with time after stopping TDF



D:A:D: Renal Disease and CVD



Ryom L, et al. CROI 2015. Abstract 742.

Studies Addressing Abacavir and MI

Study	Association?	Description
D:A:D[1]	✓	Cohort collaboration (prospective)
Danish HIV Cohort[2]	✓	Cohort (linked with registries)
Montreal study[3]	✓	Nested case-control study
SMART[4]	✓	Post hoc subgroup analysis of RCT (use of ABC not randomised)
STEAL[5]	✓	Preplanned secondary analysis of RCT (use of ABC randomised)
Desai et al[6]	✓	Cohort (retrospective)
Swiss HIV Cohort[7]	✓	Cohort (prospective)
FHDH ANRS CO4[8]	?	Nested case-control study
NA-ACCORD[9]	?	Cohort (retrospective)
VA Clinical Case Registry[10]	✗	Cohort (retrospective)
Brothers et al. analysis[11]	✗	Post hoc meta-analysis of RCTs
ACTG A5001/ALLRT[12]	✗	Post hoc meta-analysis of RCTs
FDA meta-analysis[13]	✗	Post hoc meta-analysis of RCTs

1. Friis-Møller N, et al. N Engl J Med. 2003;349:1993-2003. 2. Obel N, et al. HIV Med. 2010;11:130-136. 3. Durand M, et al. J Acquir Immune Defic Syndr. 2011;57:245-253. 4. Phillips AN, et al. Antiv Ther. 2008;13:177-187. 5. Martin A, et al. AIDS. 2010;24:2657-2663. 6. Desai M, et al. Clin Infect Dis. 2015;[Epub ahead of print]. 7. Young J, et al. J Acquir Immune Defic Syndr. 2015;[Epub ahead of print]. 8. Lang S, et al. AIDS. 2010;24:1228-1230. 9. Palella F, et al. CROI 2015. Abstract 749LB. 10. Bedimo RJ, et al. Clin Infect Dis. 2011;53:84-91. 11. Brothers CH, et al. J Acquir Immune Defic Syndr. 2009;51:20-28. 12. Ribaudo HJ, et al. Clin Infect Dis. 2011;52:929-940. 13. Ding X, et al. J Acquir Immune Defic Syndr. 2012;61:441-447.

EACS: On-Treatment Monitoring of Pts With Cardiovascular Complications

	Assessment	At HIV Diagnosis	Prior to Starting ART	Follow-up Frequency	Comment
Cardiovascular disease	**Risk assessment (Framingham score)**	+	+		**Should be performed in all men > 40 yrs of age and women > 50 yrs of age without CVD**
	ECG	+	+/-	Annual	**Consider baseline ECG prior to starting ARVs associated with potential conduction problems**
Hypertension	**Blood pressure**	+	+	Annual	

EACS Guidelines v. 7.1 November 2014.

Drug–Drug Interactions With ART and CVD and Antihypertensive Therapy

Antiretroviral	Contraindicated	Titrate Dose
ARV/RTV or DRV/RTV	**Lercanidipine** **Dabigatran***	Amlodipine, diltiazem, felodipine, lacidipine, nicardipine, nifedipine, nisoldipine, verapamilo, indapamide, doxazosin, amlodipine, diltiazem, verapamil, warfarin
EFV		**Lercanidipine, a**mlodipine, diltiazem, felodipine, lacidipine, nicardipine, nifedipine, nisoldipine, verapamilo, **indapamide, doxazosin**
EVG/COBI	**Lercanidipine** **Dabigatran***	Amlodipine, diltiazem, felodipine, lacidipine, nicardipine, nifedipine, nisoldipine, **verapamilo, indapamide, doxazosin, amlodipine, diltiazem, verapamil, warfarin**

DTG, RAL, ABC, FTC, 3TC, and TDF have no significant interactions.
***If CrCl < 50 mL/min.**

DHHS Guidelines. April 2015. EACS Guidelines v. 7.1 November 2014. Dolutegravir [package insert].

ART Considerations for Patients With Cardiovascular Complications

- **DHHS considerations**
  - Consider avoiding ABC, LPV/RTV

- **Drug–drug interactions** occur between calcium channel blockers and ART components

Conclusions: Managing CV Risk in HIV Pts

- Rates of CVD higher in HIV-infected pts vs general population
- CVD risk can be assessed by considering
  - Traditional risk factors
  - HIV-related factors
- Starting ART early can mitigate CV risk even though certain ART drugs may increase lipids
- Statins have been shown to be effective in reducing CV risk in pts without HIV infection and should be used as indicated in HIV-infected pts