Prevention of CVD: Time for a Polypill for HIV+ Persons

The Global Summit on Combination Polypharmacy for Cardiovascular Disease

Jim Neaton

25 September 2012

Outline

- Morbidity and mortality among HIV+ adults receiving effective antiretroviral therapy (ART)
- Evolution of thinking concerning HIV, ART and CVD
- Evolution of thinking concerning a polypill to prevent CVD for HIV+ adults
- A proposed factorial design
- Summary

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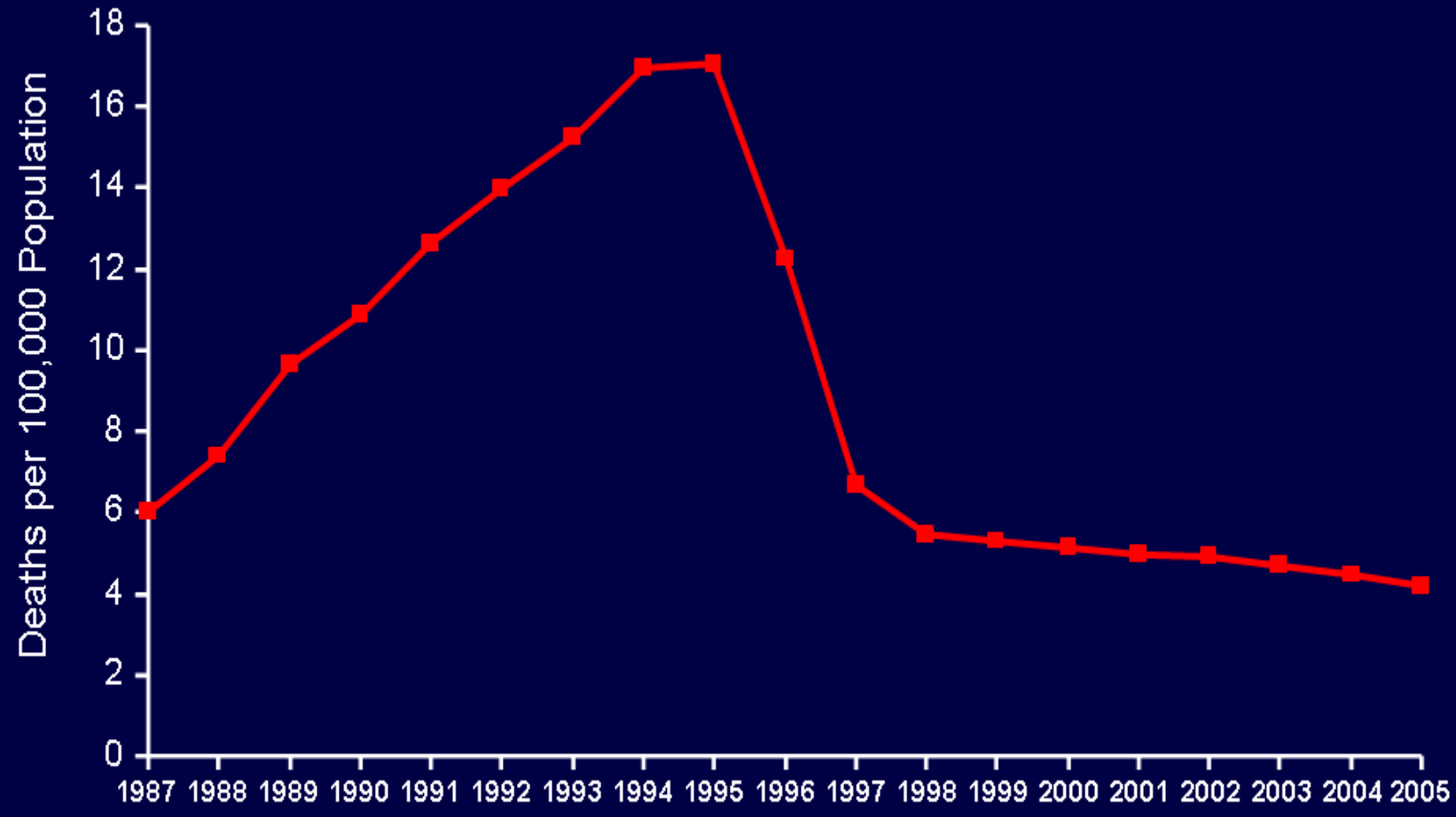
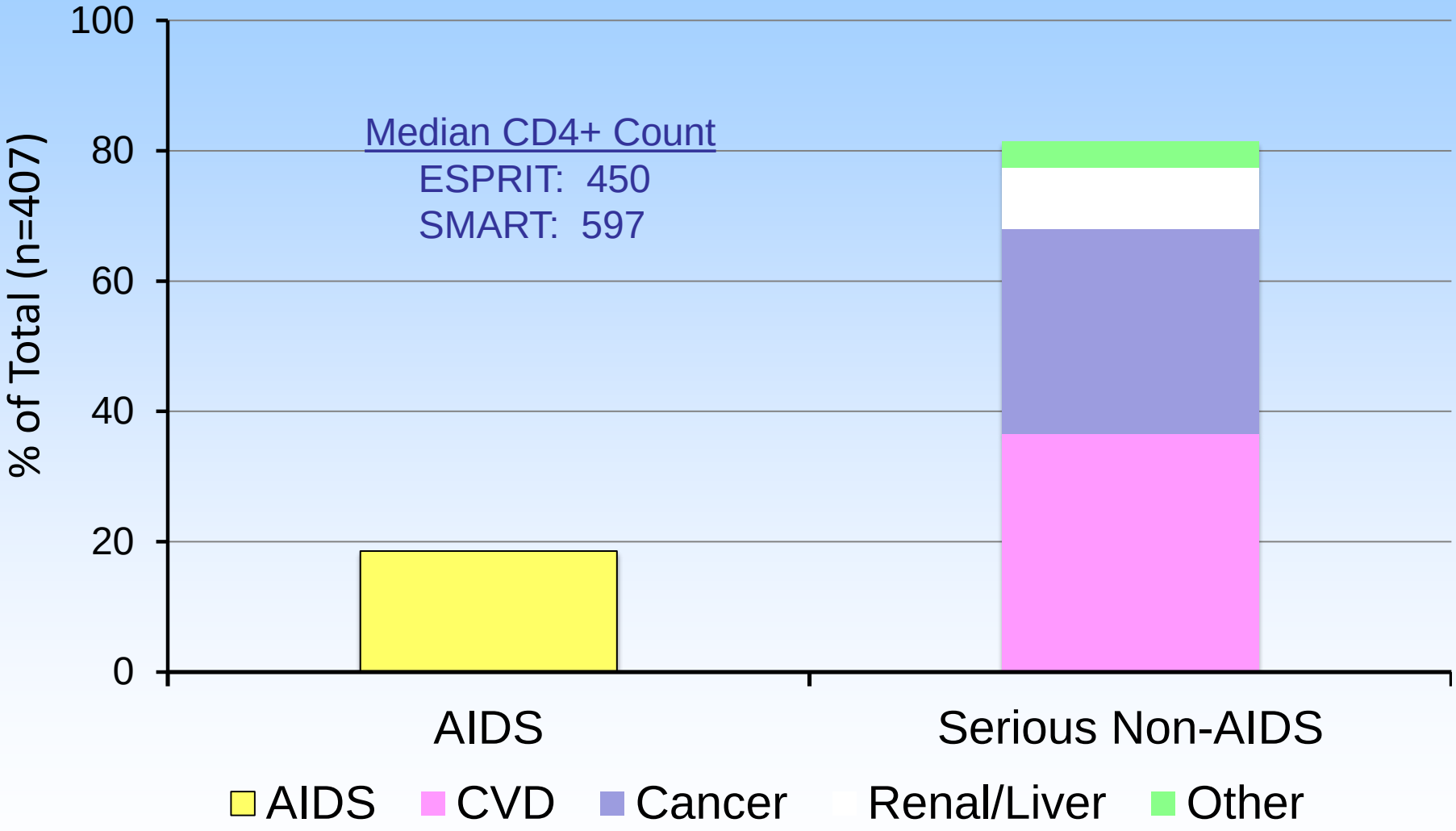
Trends in Annual Age-Adjusted* Rate of Death due to HIV Disease, United States, 1987–2005



Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for *ICD-10* rules instead of *ICD-9* rules.
*Standard: age distribution of 2000 US population

Morbidity and Mortality in SMART / ESPRIT Control Arms (N=4792)



INSIGHT SMART & ESPRIT Study Groups
AIDS 2010; 24(12):1877, NEJM 2006; 355:2283-2296 , Ann Int Med 2008; 149:289-299

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Evolution of Thinking: HIV, ART and CVD

- ART is associated with unintended adverse effects.
- Longer use of ART is associated with an increased risk of MI (and a CVD composite), risk is greatest for patients taking protease inhibitors.
- Between 2006 and 2008, findings from a trial called SMART and epidemiological investigations changed thinking about reasons for CVD risk.

Antiretroviral Therapy and Risk of Myocardial Infarction

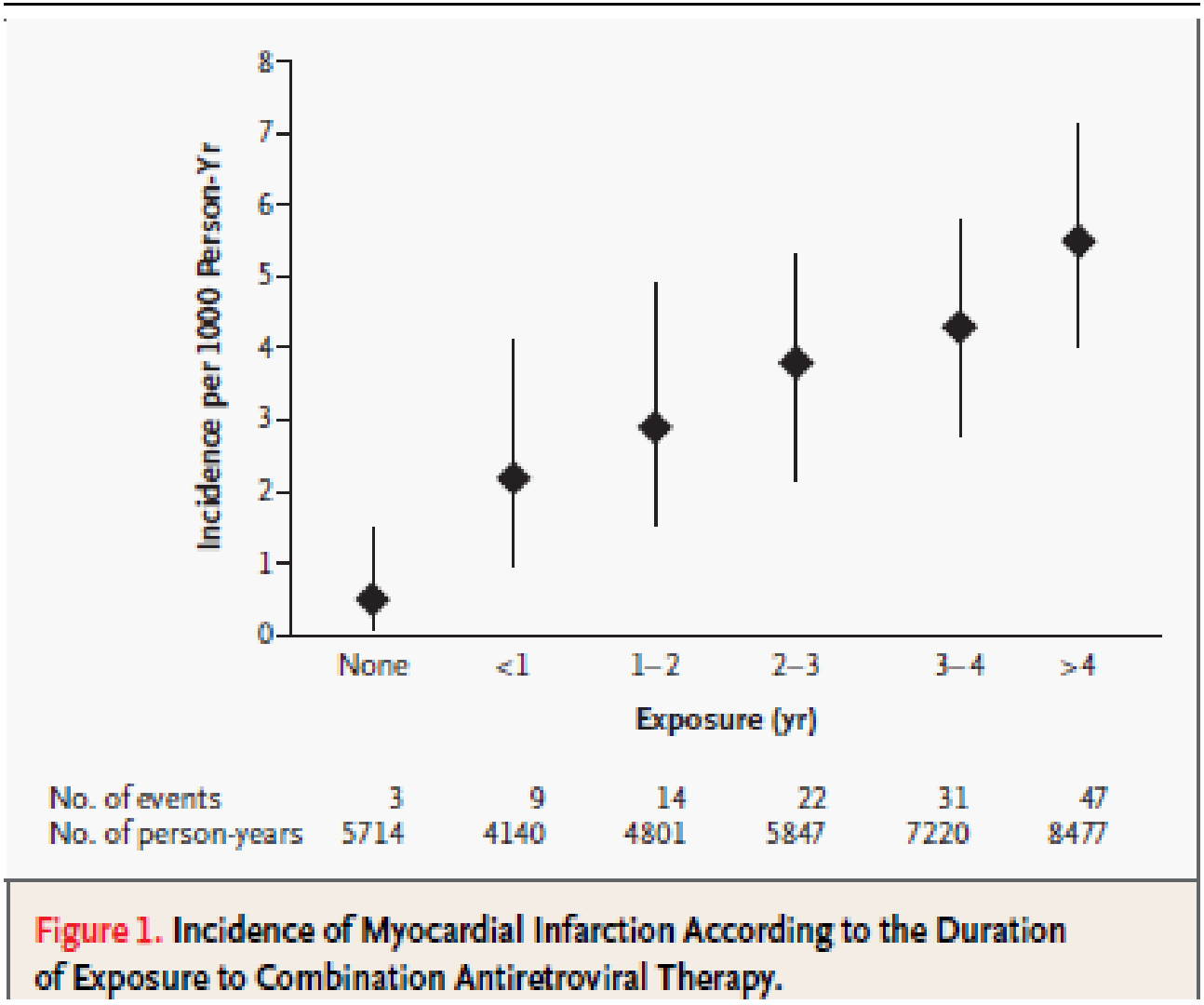

Figure 1. Incidence of Myocardial Infarction According to the Duration of Exposure to Combination Antiretroviral Therapy.

D:A:D Study; N Engl J Med 2003

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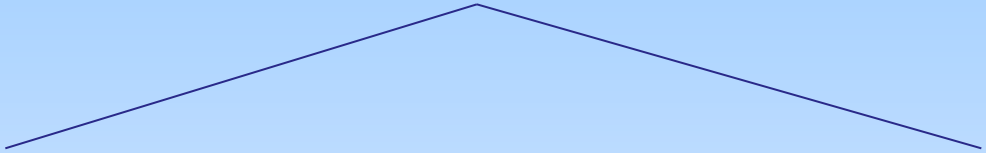
SMART Study Design

Participants with CD4+ count > 350



n = 2720

Virologic Suppression (VS) Strategy

[Continuous ART use]

n = 2752

Drug Conservation (DC) Strategy

[Stop or defer ART until CD4+ < 250; then *episodic* ART based on CD4+ cell count to increase counts to > 350]

SMART Study Group, N Engl J Med 2006 and Ann Intern Med 2008

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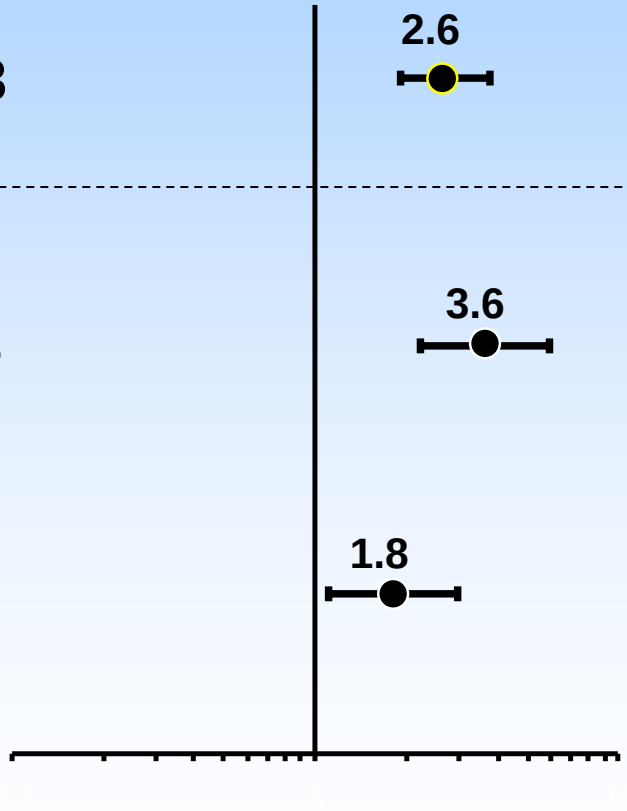
Main SMART Findings

Endpoints	No. of Patients with Events	Rate* DC	Rate* VS	Hazard Ratio (DC/VS) (95% CI)
AIDS or death	167	3.3	1.3	2.6
AIDS(fatal or non-fatal)	95	2.1	0.6	3.6
Non-AIDS deaths	72	1.3	0.7	1.8



◀Favors DC Favors VS ▶

* Per 100 person-years

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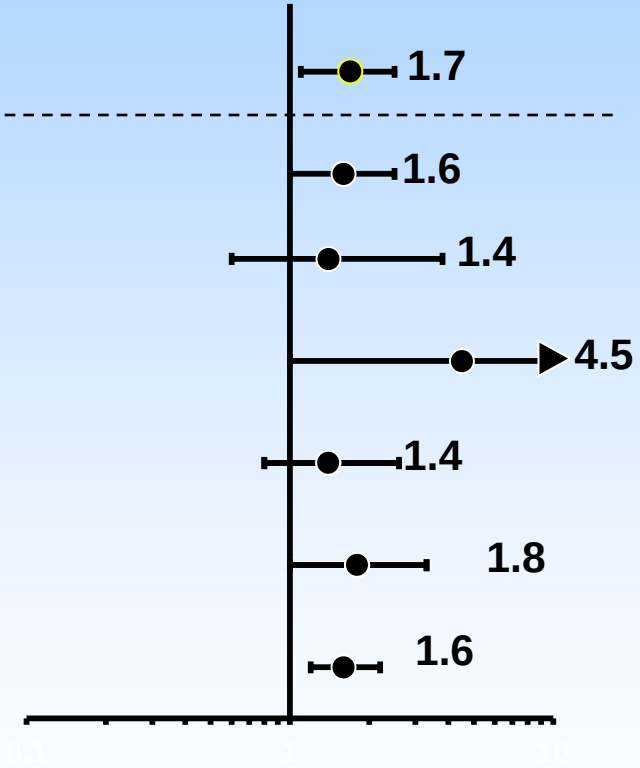
Serious Non-AIDS Outcomes in SMART

Endpoints	No. of Patients with Events	Rate DC	Rate VS	Hazard Ratio (95% CI)
Major CVD, hepatic or renal disease	104	1.8	1.1	1.7
CVD+	79	1.3	0.8	1.6
Hepatic (Cirrhosis)	17	0.3	0.2	1.4
Renal (ESRD)	11	0.2	0.1	4.5
NADM++	47	0.8	0.5	1.4
Other non-AIDS death	51	0.9	0.5	1.8
Any of the above	186	3.2	2.0	1.6



◀ Favors DC Favors VS ▶

+ MI (clinical or silent), stroke, surgery for CAD
++ Except non-melanoma skin

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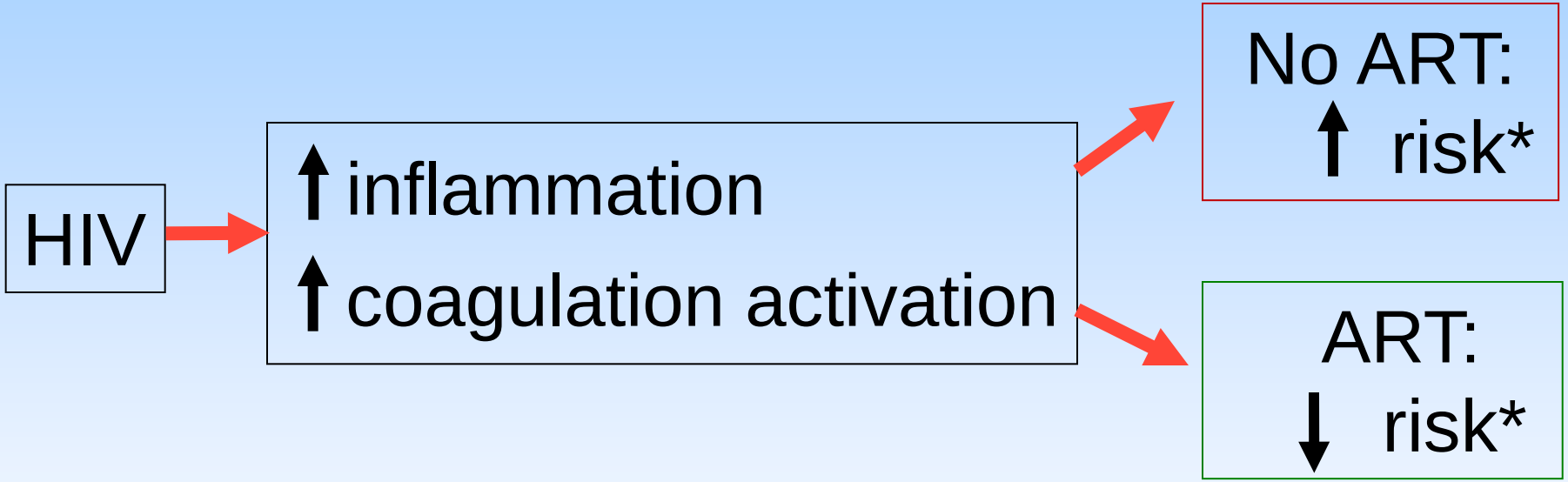
Hypothesis: ART reduces risk of non-AIDS events by dampening inflammation and coagulation



*: magnitude of absolute risk ↑ or ↓ depends on lifestyle, demographics, co-infections, host genetic

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Inflammatory and Coagulation Biomarkers and Mortality in Patients with HIV Infection

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Biomarker and All-Cause Mortality Associations

Baseline Level	OR ($4^{th}/1^{st}$ QRT) Univariate	*P-value*
D-dimer	**12.4**	<0.0001
IL-6	**8.3**	<0.0001
hsCRP	**2.0**	0.05

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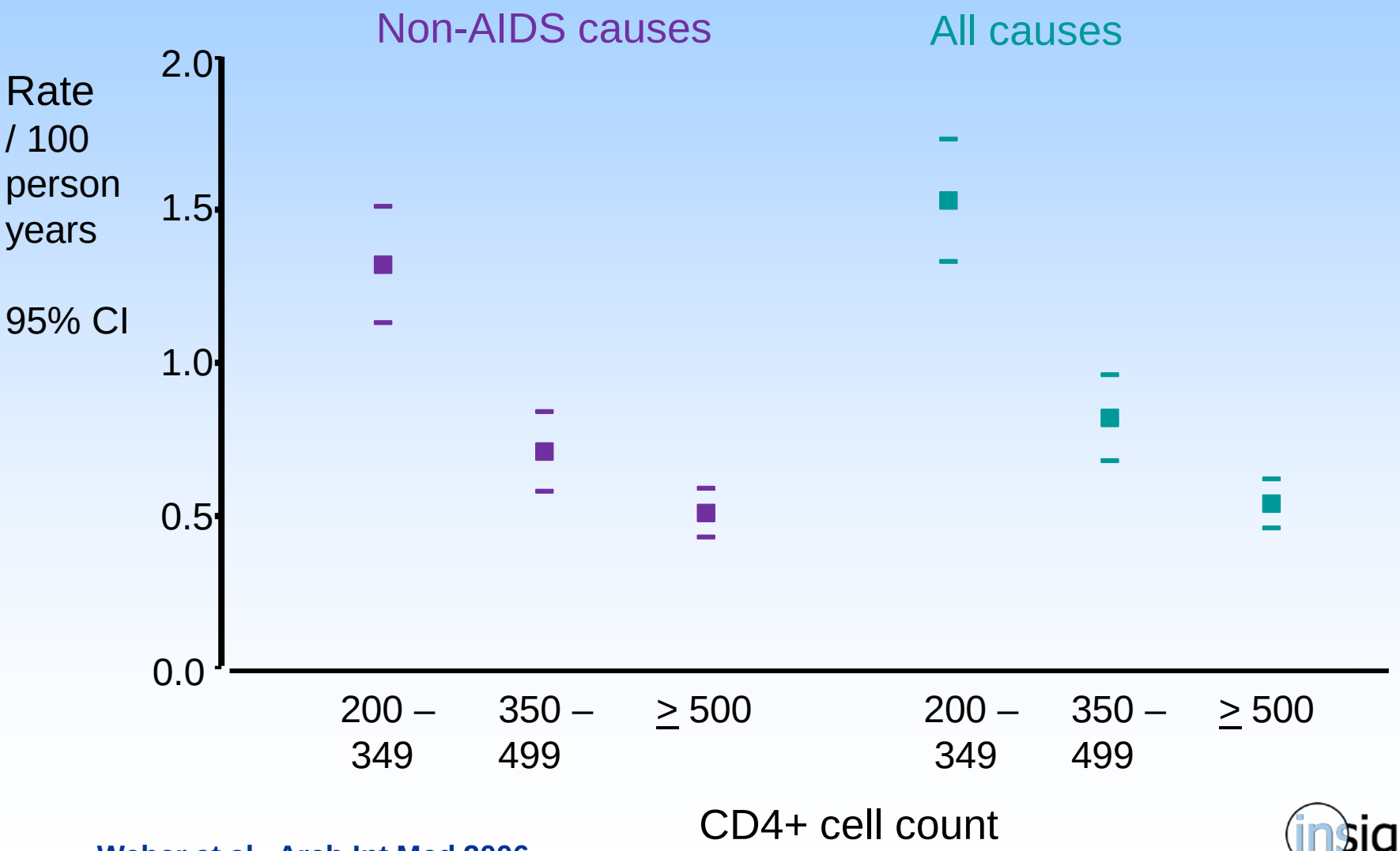
Biomarker Levels in SMART Compared with Participants CARDIA and MESA

Table 3. Biomarkers Levels in SMART Study Participants Receiving Antiretroviral Therapy (ART) Who Had an HIV RNA Level ≤400 Copies/mL and Percentage Differences in Levels Versus CARDIA and MESA Study Participants, as Cited in Table 2

	Participants 33–44 years of age			Participants 45–76 years of age		
Biomarker	No.	Median level (IQR)	% Diff. (*P*)	No.	Median level (IQR)	% Diff. (*P*)
hsCRP, μg/mL	140	2.13 (0.77–5.20)	40.2 (<.001)	293	2.83 (1.07–6.80)	37.8 (<.001)
IL-6, pg/mL	139	1.89 (1.15–3.42)	39.0 (<.001)	291	2.64 (1.55–4.14)	60.1 (<.001)
D-dimer, μg/mL	140	0.21 (0.15–0.46)	NA	293	0.29 (0.17–0.57)	49.1 (<.001)
Cystatin C, mg/dL	86	0.90 (0.78–0.97)	NA	130	1.00 (0.86–1.16)	20.9 (<.001)

Neuhaus et al., JID 2010

CD4+ Cell Count and Risk of Death: DAD Study



Weber at al Arch Int Med 2006

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Relative Risk (RR) for First Hospitalization for Ischemic Heart Disease: Patients with HIV Infection (N=3,953) versus Control Subjects (N=373,856) in Denmark by Treatment period (Obel CID 2007)

Treatment Period	Adjusted RR (95%CI)
Non-HAART	1.4 (0.8-2.4)
HAART period	2.1 (1.6-2.8)

RR not adjusted for smoking

See also Triant J Clin Endocrinol Metab 2007: RR=1.75 (p<0.0001) and Freiberg CROI abstract 2011: RR=1.94 (95% CI: 1.58-2.37)

Research Questions: HIV, ART and CVD

- √ What is the risk/benefit for CVD and other serious non-AIDS conditions of using ART early (when-to-start)?

- Given absolute risk of CVD among HIV+ adults on ART (approximately 1% per year), should BP and lipid-lowering treatment be initiated earlier than current guidelines indicate (polypill)?

- Given ongoing inflammation among HIV+ adults on ART, should adjunctive treatment targeted at inflammatory and coagulation pathways be used with ART?

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START Design

HIV-infected adults, ART-naive with CD4+ cell counts > 500 cells/mm^3

Early ART Group

Immediately initiate ART

N=2,000

Deferred ART Group

Defer ART until CD4+ <350 cells/mm^3 or symptoms develop

N=2,000

Primary endpoint: Serious AIDS & serious non-AIDS disease (375)

Current Status: 3000 of planned 4000 randomised

Babiker A, Clinical Trials 2012

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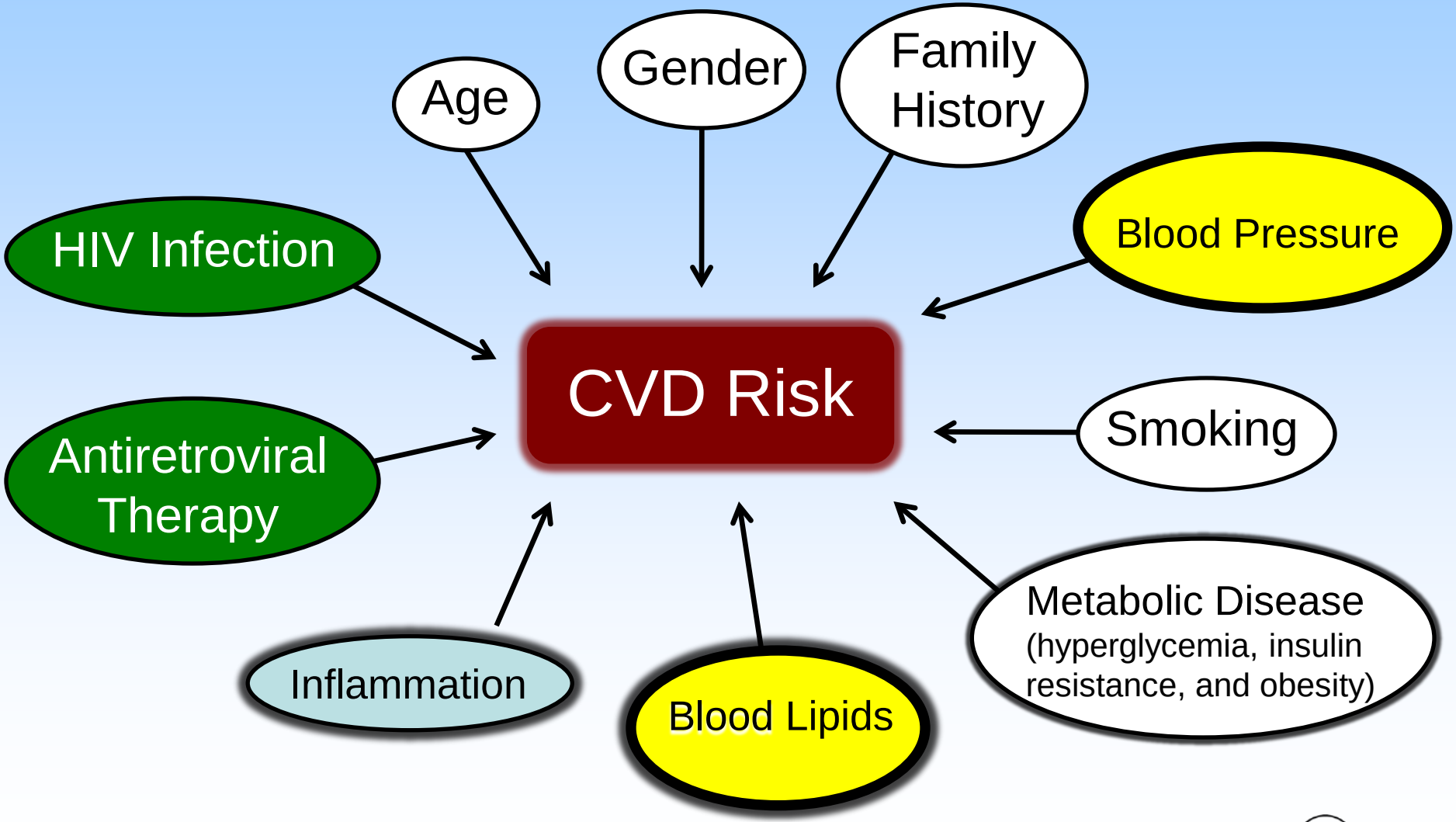
CVD Risk Factors:

In the setting of HIV infection



Adapted from A.Carr CCO/HIV 2008

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CVD Polypill Design: 2005

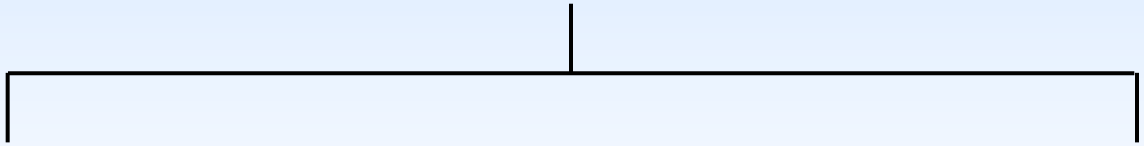
Patients with 5 year Framingham risk of CVD > 7.5%

OR

with 5 year Framingham risk >4.0%

AND

7+ years of prior ART and no indications/contraindications to treatment



Polypill*

(N = 4,000)

Placebo

(N = 4,000)

***aspirin, ACE inhibitor, diuretic, statin**

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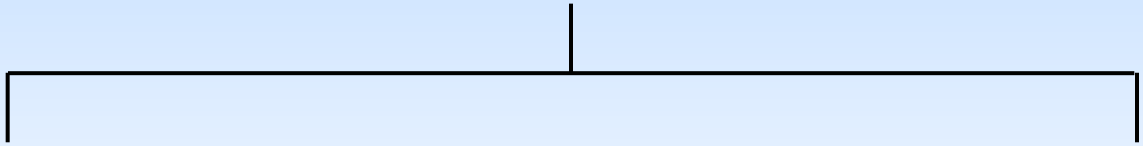
CVD Polypill Design: 2012

Patients on ART, 45+ years, CD4+ < 500 cells/mm^3 and no indications/contraindication to treatment



Polypill*
(N = 2,650)

Placebo
(N = 2,650)

Power = 0.80 to detect at 40% reduction in CVD

***ACE inhibitor, diuretic, beta-blocker, statin**

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Age-Specific Rates Per 100 Person Years of CVD and Serious Non-AIDS or All-Cause Mortality

SMART, ESPRIT and SILCAAT Control Group Patients with CD4 < 500 and Suppressed Viral Load

Age (years)	CVD	Serious-AIDS or All-Cause Mortality
45 - 54	0.98	2.21
55 +	1.58	4.40

CVD = MI, stroke, revascularization, heart failure, or CVD death

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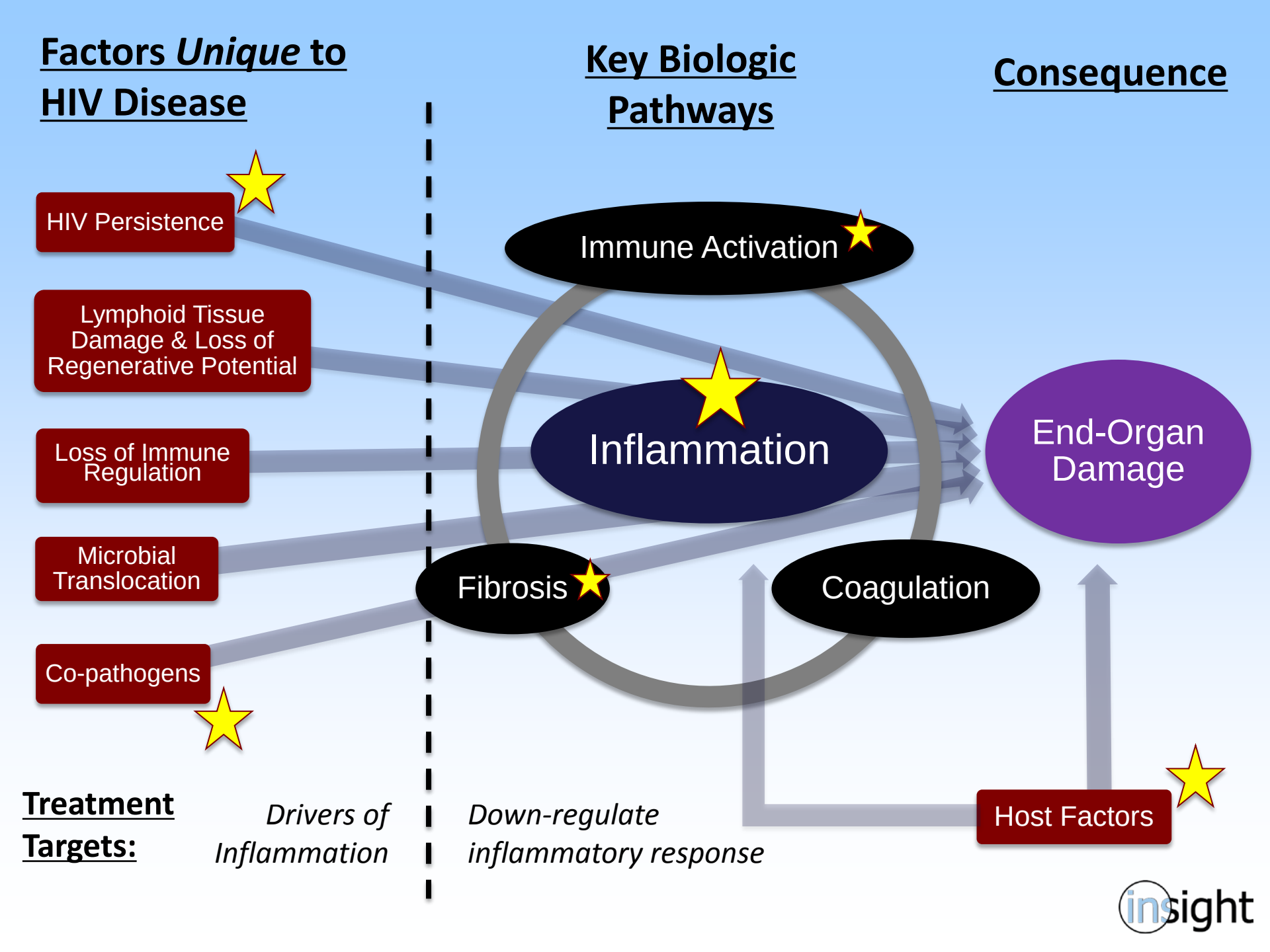
Factors *Unique* to HIV Disease
Key Biologic Pathways
Consequence
HIV Persistence
Lymphoid Tissue Damage & Loss of Regenerative Potential
Loss of Immune Regulation
Microbial Translocation
Co-pathogens
Immune Activation
Inflammation
Fibrosis
Coagulation
End-Organ Damage
Host Factors
Treatment Targets:
Drivers of Inflammation
Down-regulate inflammatory response
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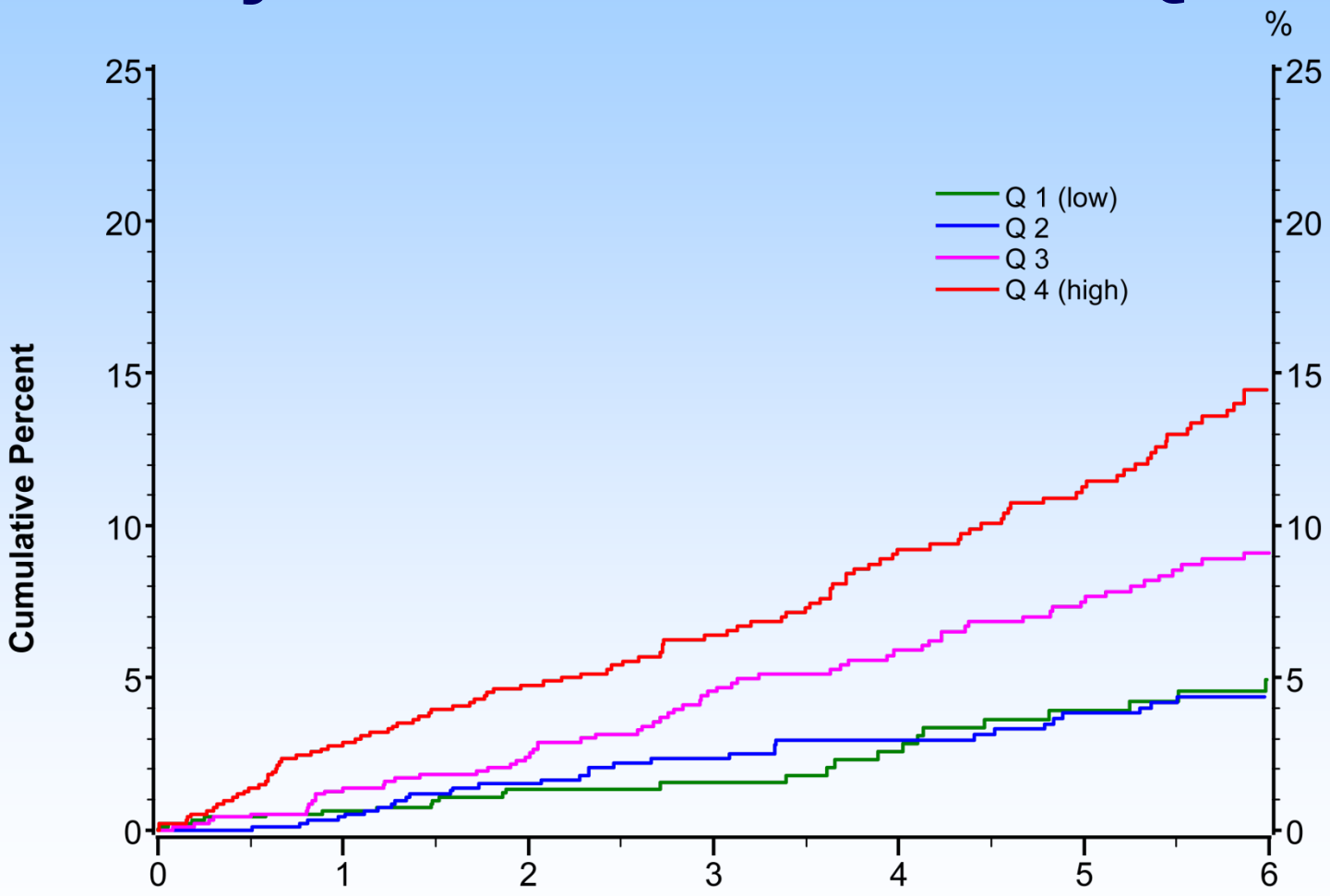
Serious Non-AIDS Event or Death by IL-6/D-dimer Score Quartile



At Risk:							
Q 1:	941	919	676	445	366	324	255
Q 2:	942	934	776	642	574	540	444
Q 3:	942	920	810	661	605	556	444
Q 4:	941	909	787	640	556	490	373

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2x7 Factorial Design: Stage 1 Drugs and Polypill

	Polypill	Placebo
Dolutegravir		
Valaciclovir		
Dabigatran*		
Metformin		
Methotrexate*		
Lactoferrin		
Aspirin		
Pooled Placebo		

Primary Endpoints:

Inflammation/coagulation:
IL-6/D-dimer score

Polypill:
ΔBP & Δcholesterol

**additional safety data required in HIV positive populations*

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2x2 Factorial Design: Winner of Stage 1 and Polypill

	Polypill	Polypill Placebo
Winner		
Winner Placebo		

Polypill primary endpoint: CVD

IL-6/D-dimer winner composite endpoint: serious non-AIDS (including CVD) or all-cause mortality

Summary

- CVD represents a large burden of the morbidity/mortality among HIV+ adults on effective ART
- HIV and ART are associated with ↑ risk of CVD
- Broadened use of BP and lipid-lowering treatment with a polypill may be an effective way to reduce risk of CVD
- A factorial design of a polypill and a drug that reduce inflammation and coagulation is a cost-effective way of addressing two approaches to risk reduction.

Acknowledgements

- Polypill 2005: Anthony Rodgers and Richard Grimm

- Polycap 2012: Ed Mills and Salim Yusuf

- INSIGHT team: Ab Babiker, Jason Baker, Alvaro Borges, Haitao Chu, Cal Cohen, Gary Collins, Al Cozzi-Lepri, Steve Deeks, Birgit Grund, Kathy Huppler-Hullsiek, Jens Lundgren, Jacquie Nuehaus, Jemma O'Connor, Andrew Phillips, Caroline Sabin, Deb Wentworth, Julian Wolfson

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