Cardiovascular Risks of Antiretroviral Therapy

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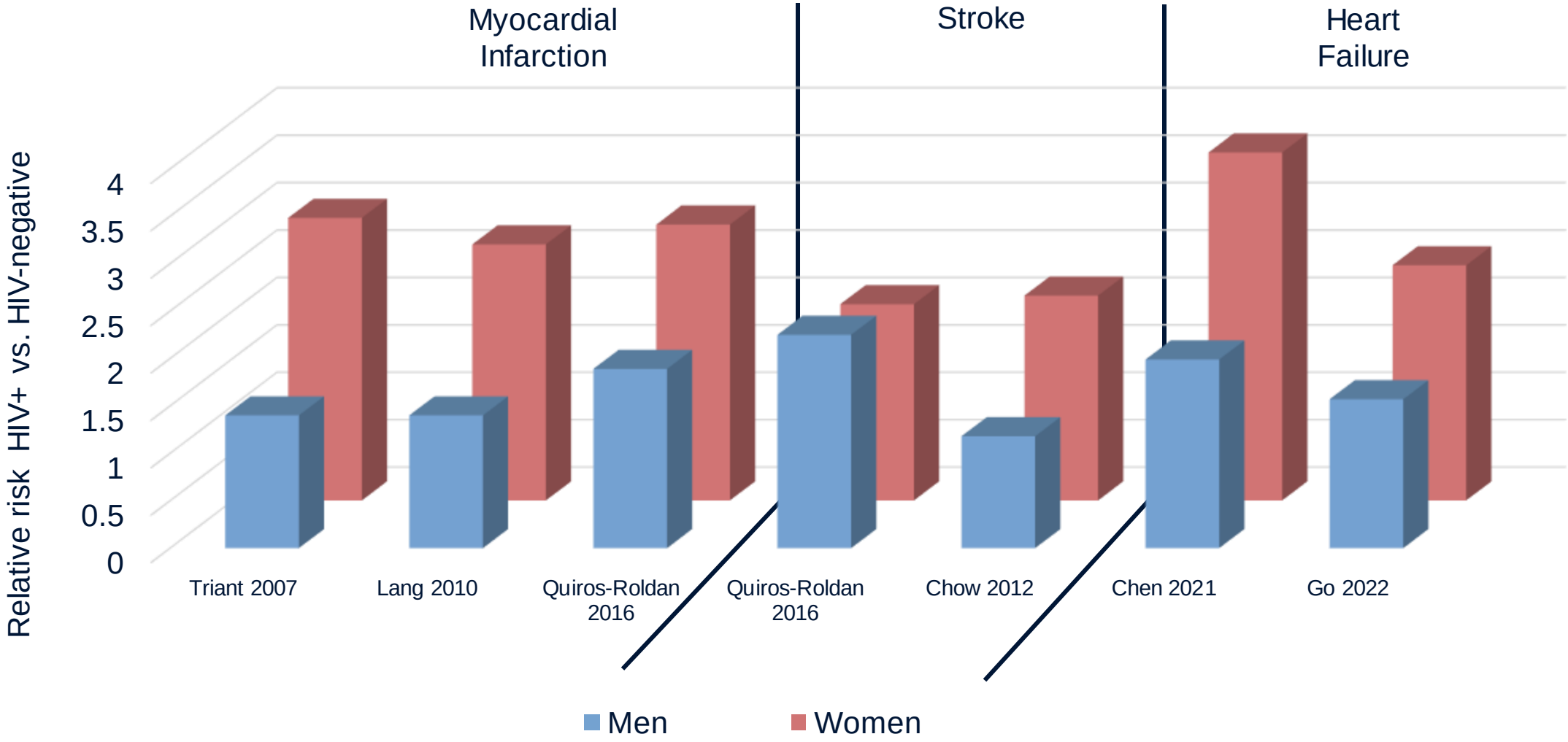
AETC AIDS Education & Training Center Program Mountain West

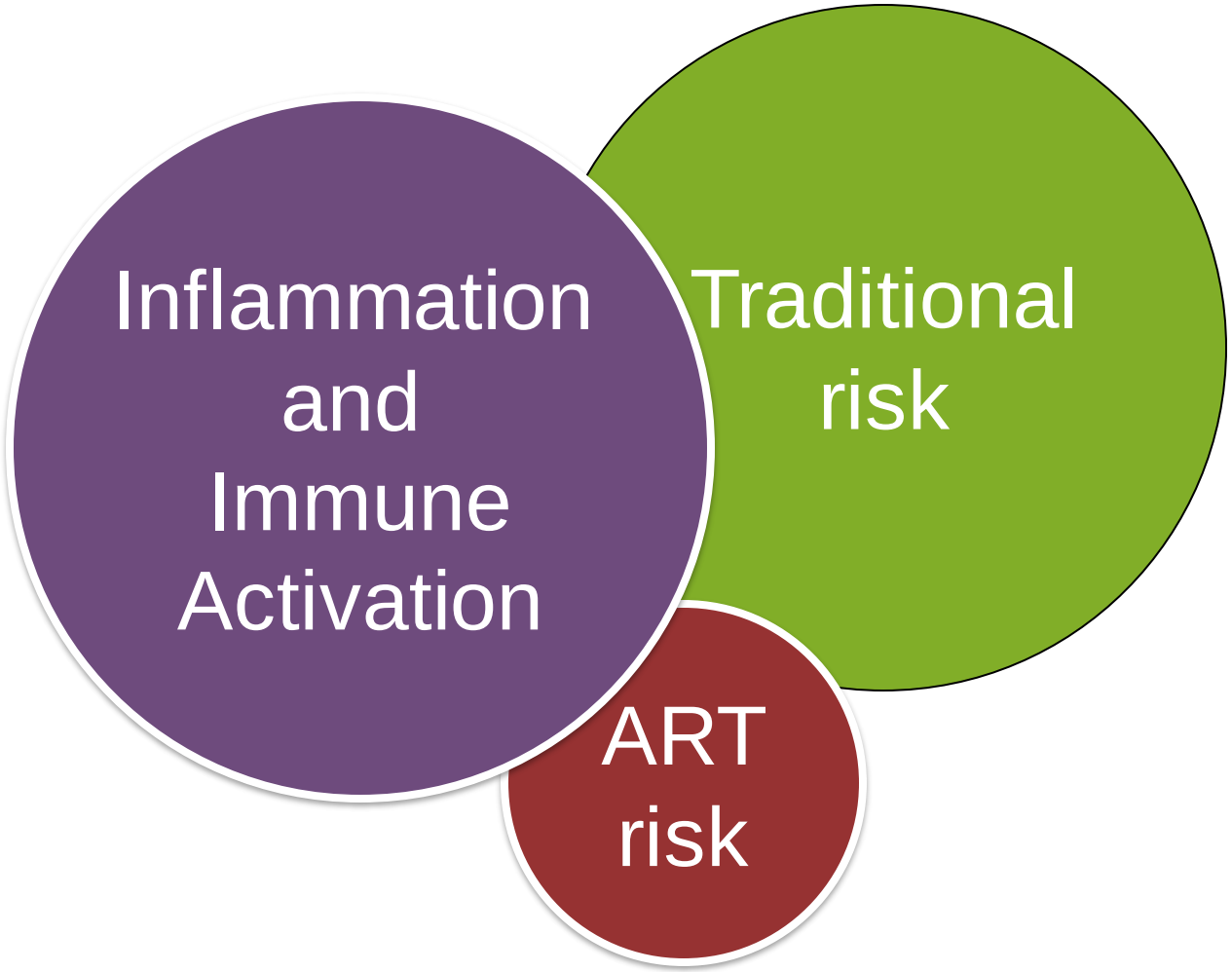
Outline

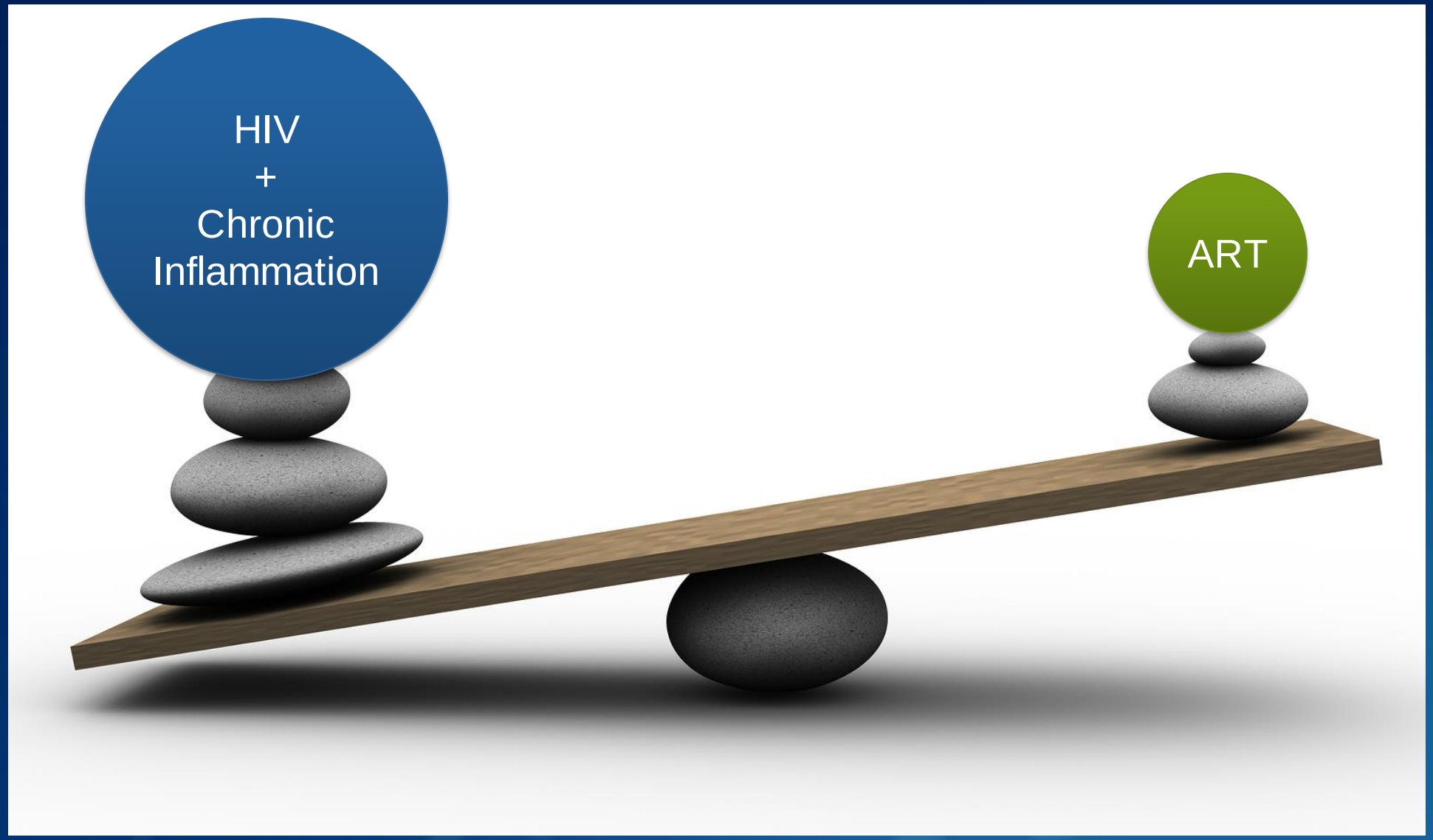
- Epidemiology and domains of cardiovascular risk for people living with HIV (PLWH)
- Evidence for drug or class risk
  - Protease Inhibitors
  - Abacavir
  - Tenofovir
  - Integrase Inhibitors
- My approach to mitigating risk

Cardiovascular risk in PLWH



Kentoffio et al, Curr Opin HIV/AIDS, In Press


Inflammation and Immune Activation
Traditional risk
ART risk


HIV
+
Chronic
Inflammation
ART

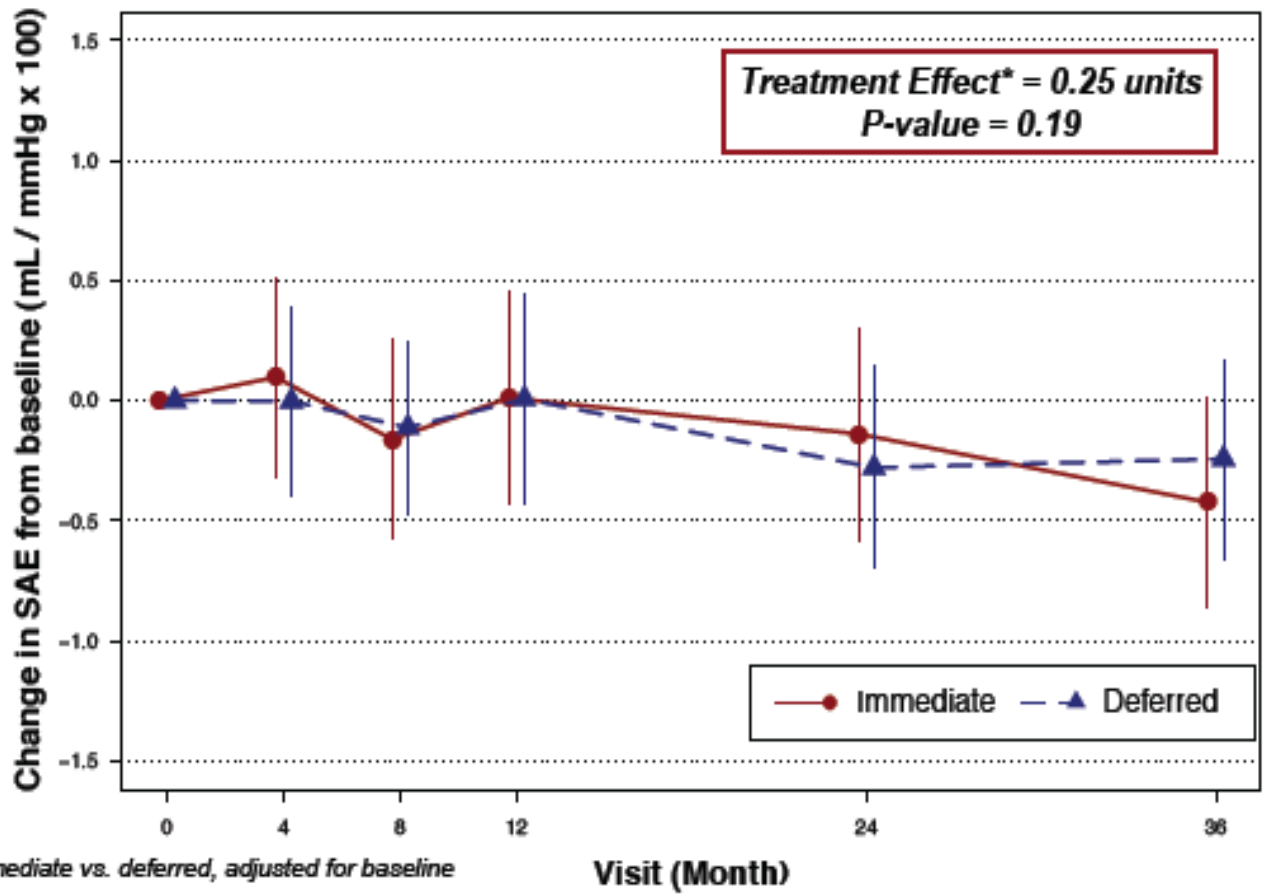
START: No Difference in Cardiovascular Outcomes with Early vs. Delayed ART

Cardiovascular Events (Early vs. Delayed):

HR 0.84 (0.4-1.8)
P=0.65

Why?

Small Artery Elasticity (higher better)



START

insight

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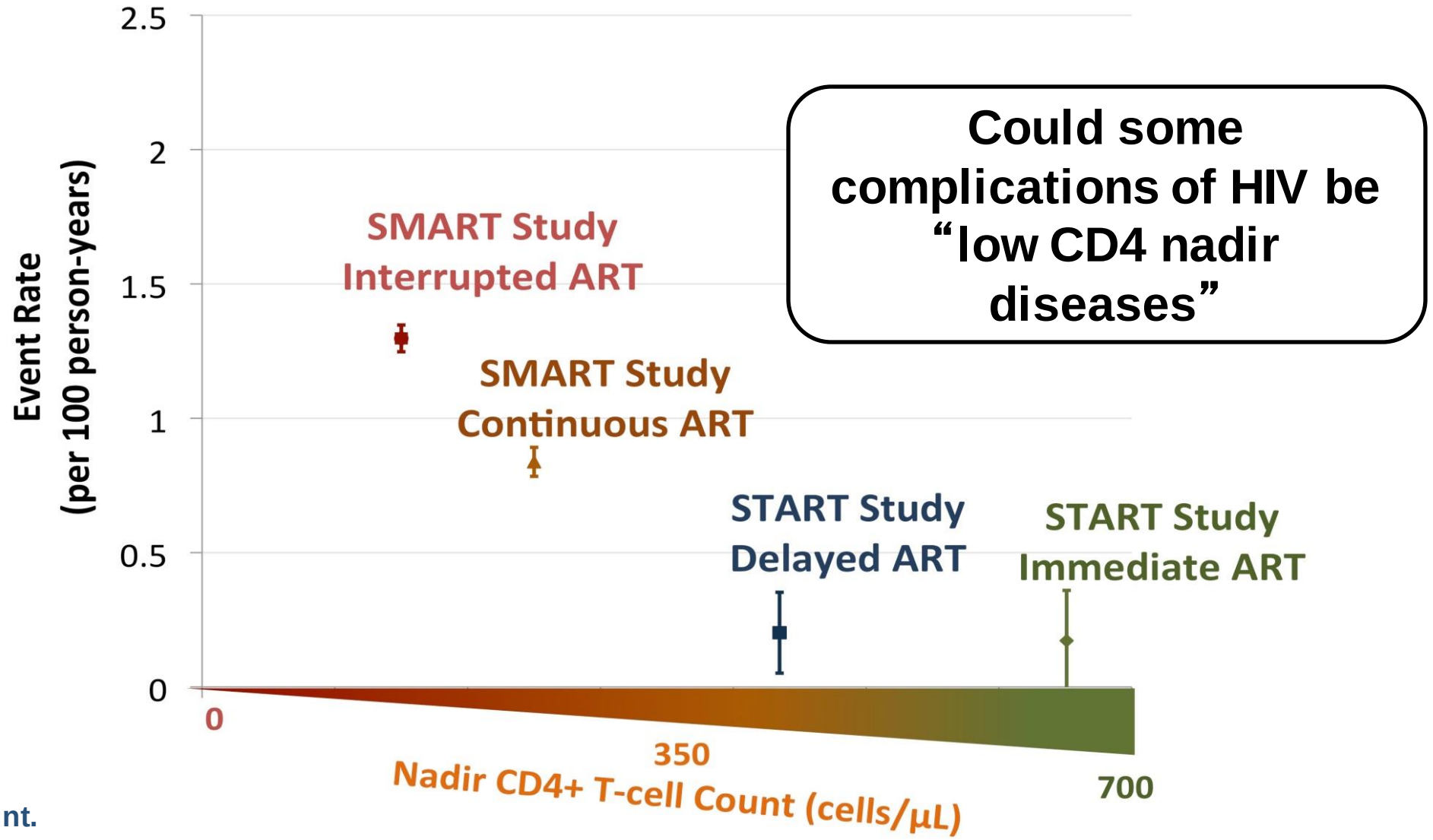
Adapted from P Hunt
START, NEJM, 2015 and Baker, Open Forum Inf Dis 2016

Cardiovascular Complications Much Lower in START than SMART: Role of CD4 nadir



Could some complications of HIV be "low CD4 nadir diseases"

Adapted from P Hunt.
Hunt et al, J Inf Dis 2016

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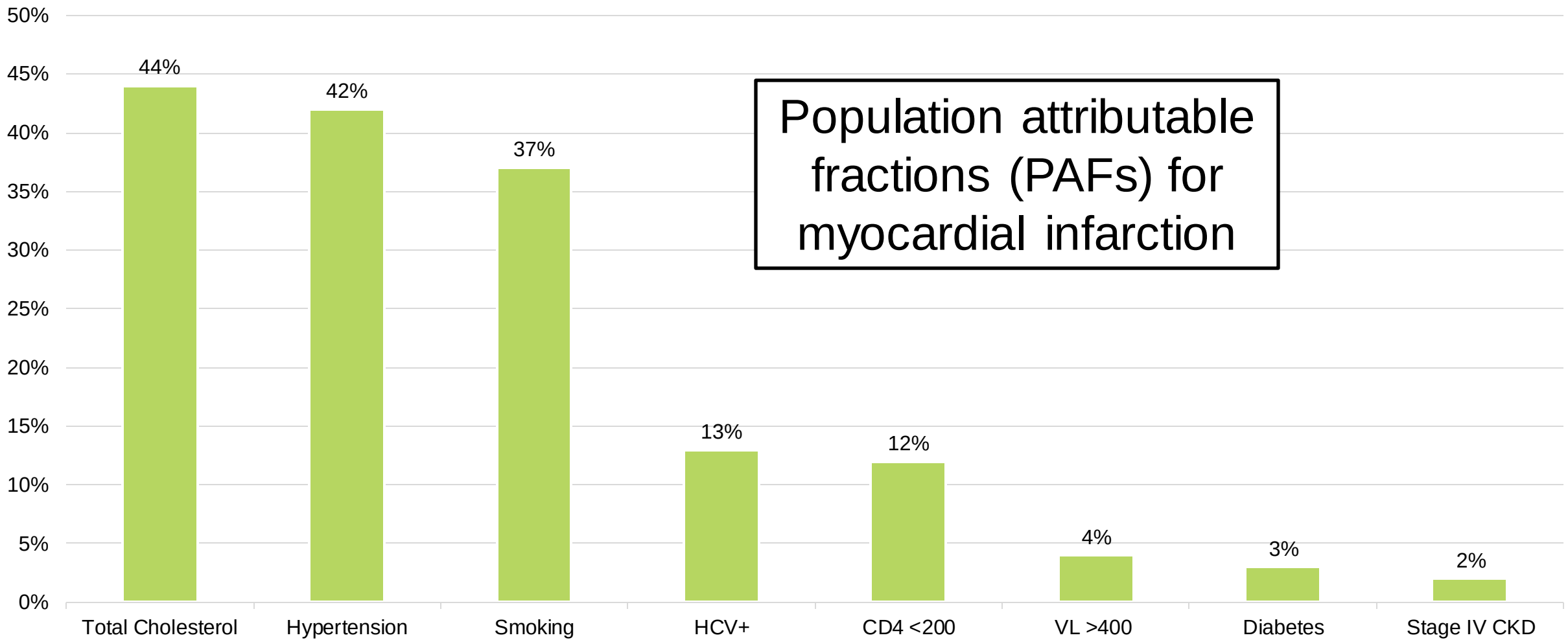


Population attributable fractions (PAFs) for myocardial infarction

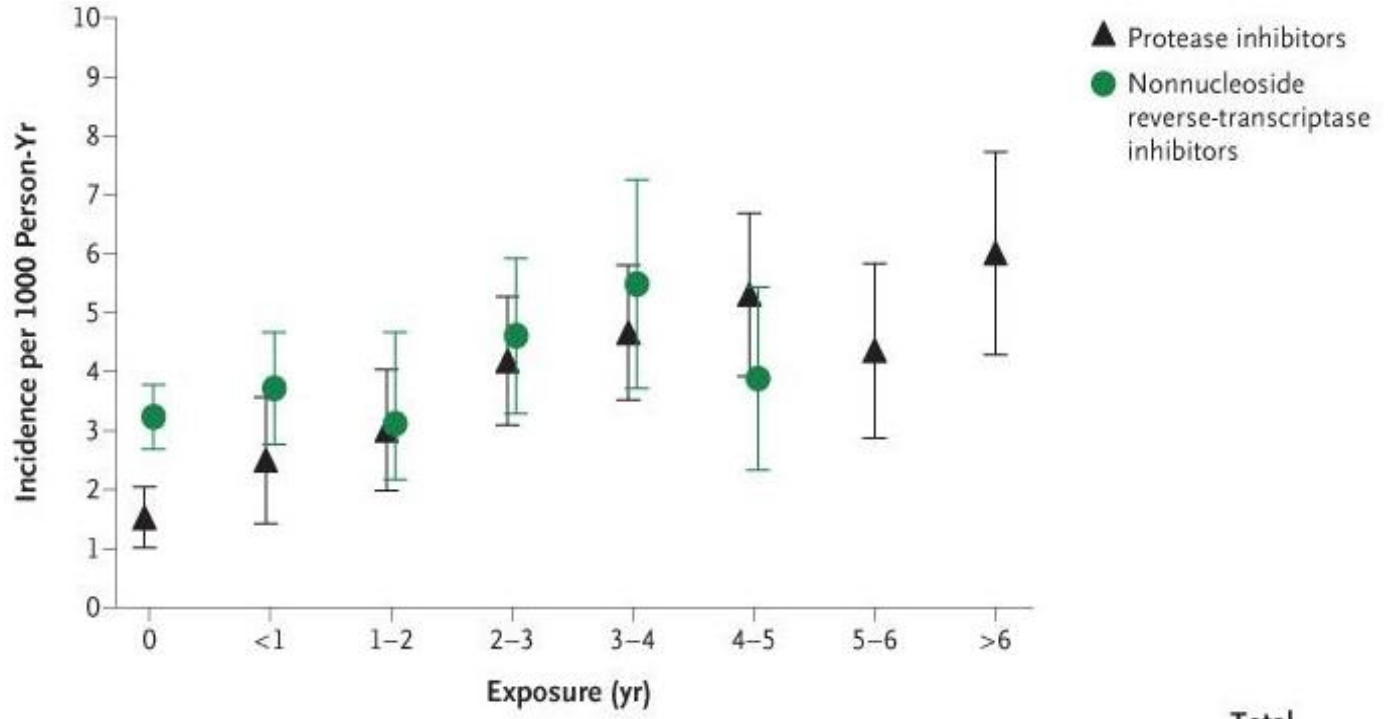
Althoff et al. Lancet HIV 2019

ART AND CVD RISK

Evidence for Drug or Class Risk

Protease Inhibitors

- 2007 Original D:A:D drug class analysis
- Myocardial Infarction
- 1999-2006
- Indinavir, Saquinavir, Lopinavir, etc…
- Likely limited Atazanavir (2003) and no Darunavir (2006)
- PI's associated with RR 1.16 per yr (cumulative)



									Total
Protease Inhibitors									
No. of events	33	21	33	57	64	57	33	47	345
No. of person-yr	21,623	8410	10,947	13,616	13,742	10,734	7576	7821	94,469
Nonnucleoside Reverse-Transcriptase Inhibitors									
No. of events	136	59	42	47	37	24	—	—	345
No. of person-yr	42,013	15,866	13,476	10,204	6739	6172	—	—	94,469

Friis-Moller et al. NEJM 2007

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Protease Inhibitors

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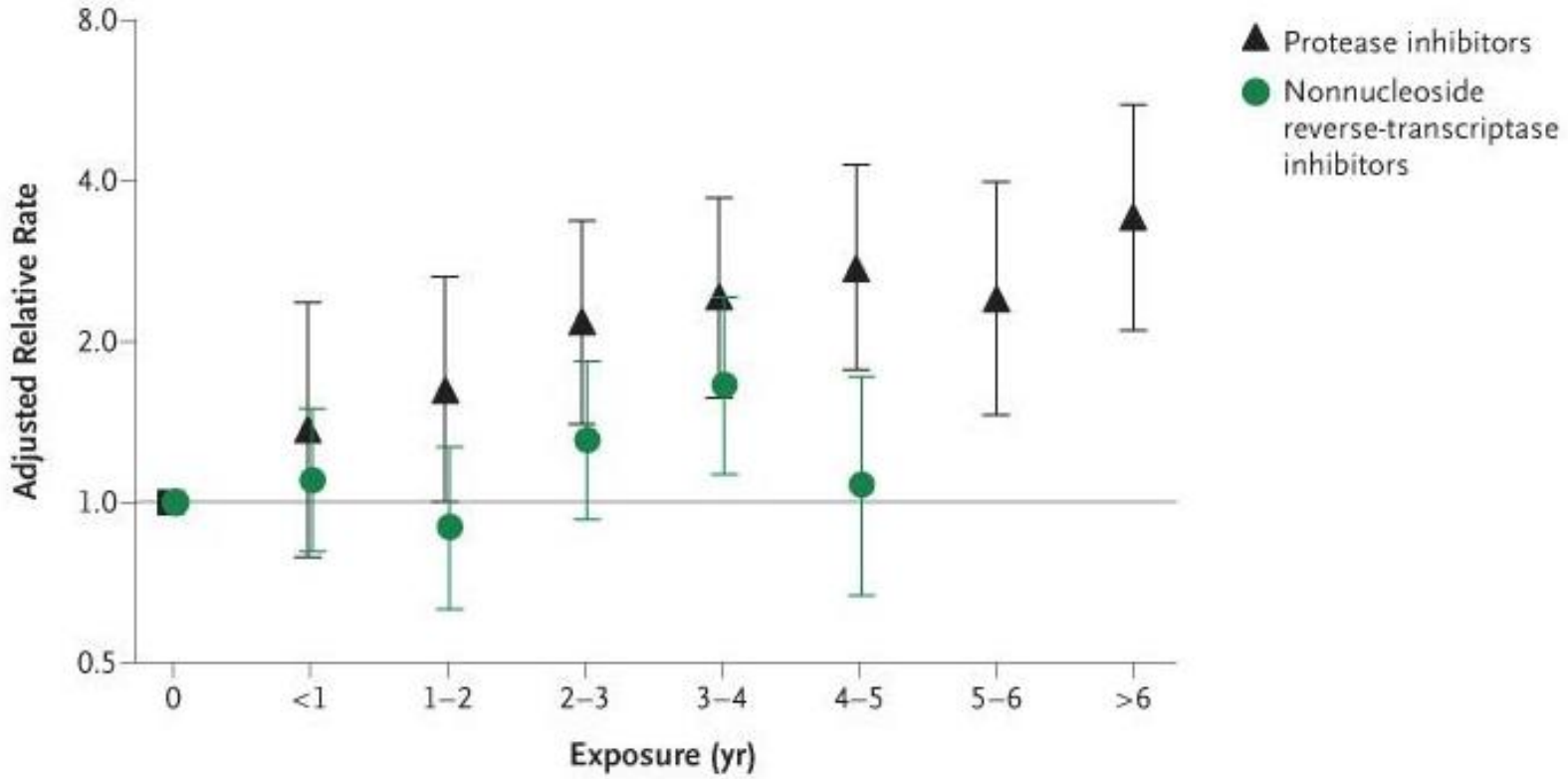

Friis-Moller et al. NEJM 2007

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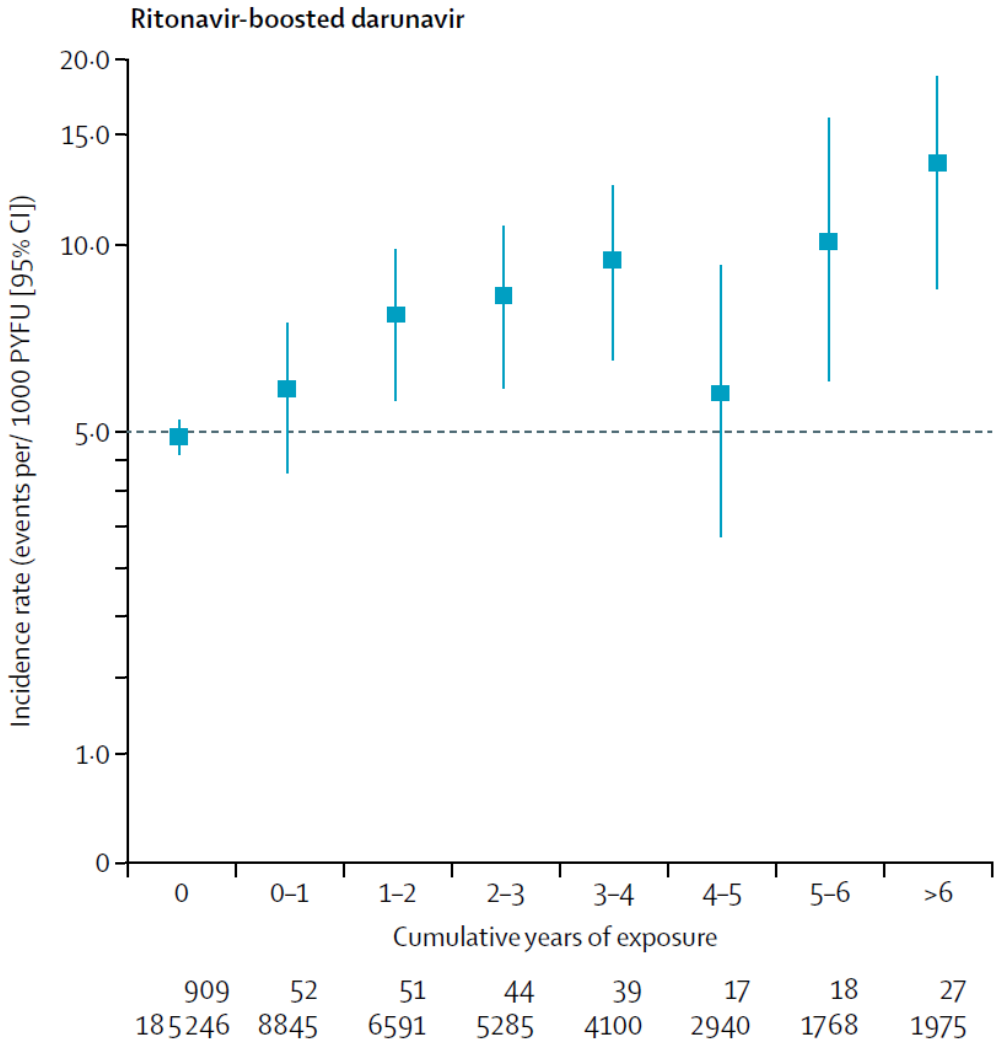
Protease Inhibitors

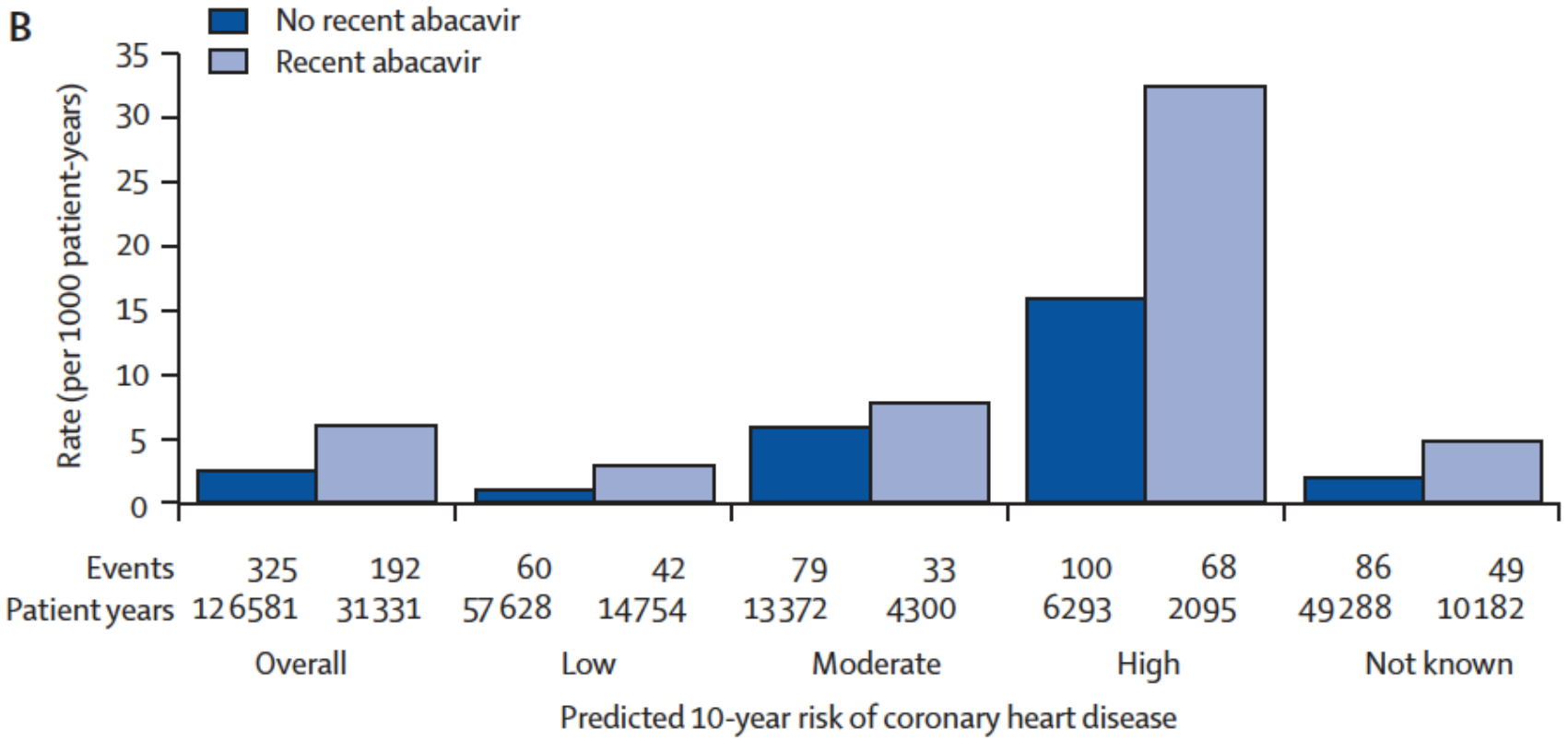
- Updated darunavir vs. atazanavir
- Cardiovascular Disease (40% MI, 33% stroke, 48% PCI/CABG; could have >1)
- 2009-2016
- Darunavir was associated with an adjusted incidence rate ratio of 1.59 (95% CI 1.33-1.91) per 5-years exposure
- Atazanavir was not (aIRR 1.03 (0.90-1.18)



Ryom et al, Lancet 2018

Abacavir

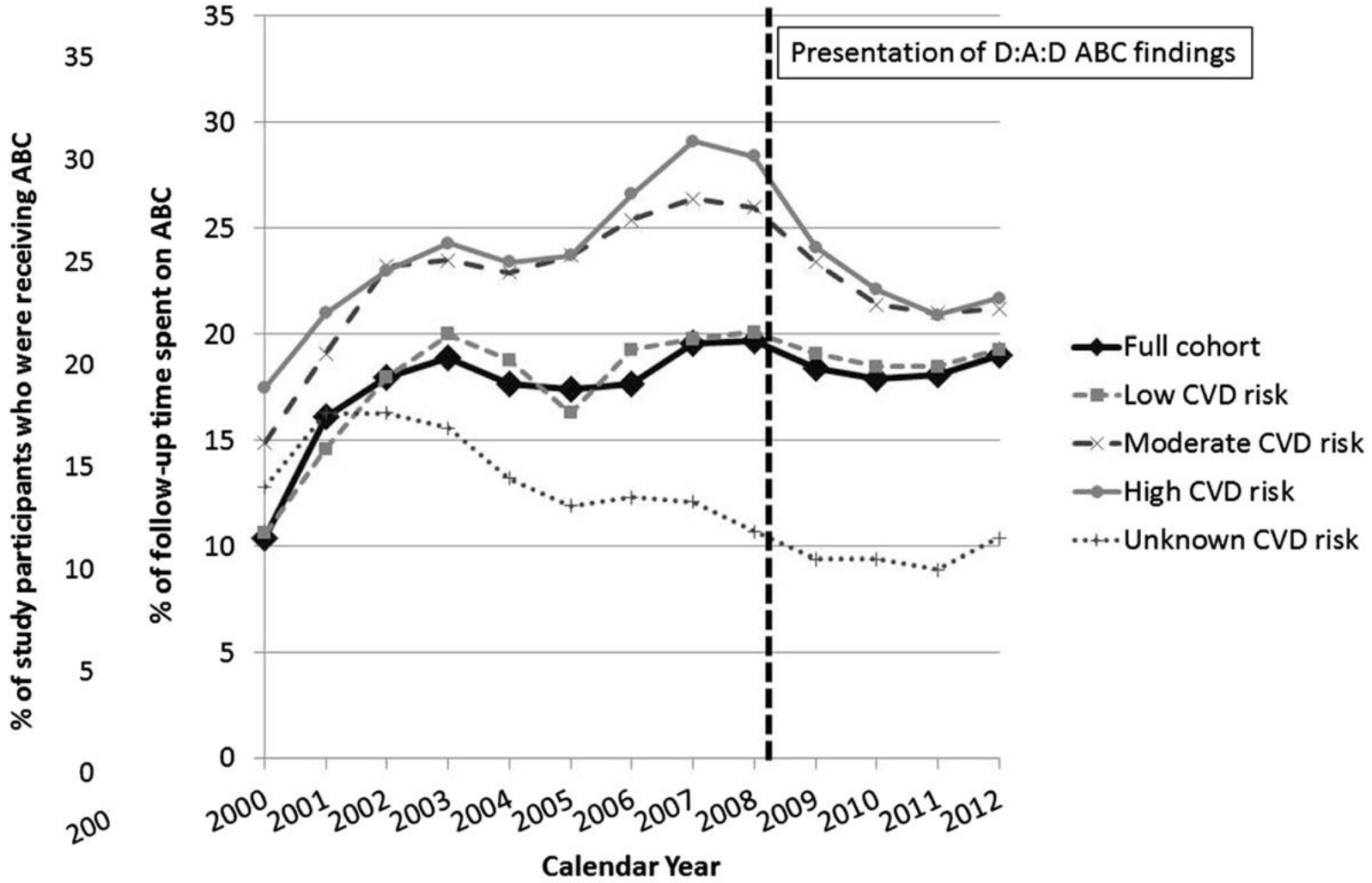
- Original D:A:D study of NRTI risk
- Recent (<6 months)—but not cumulative—use associated with risk (RR 1.9 for abacavir and 1.5 for didanosine)



Sabin et al, Lanc

Abacavir

- Adjusted RR of MI while on ABC ~2.0
- No difference in pre- vs. post-2008 periods



Sabin et al, BMC Med 2016

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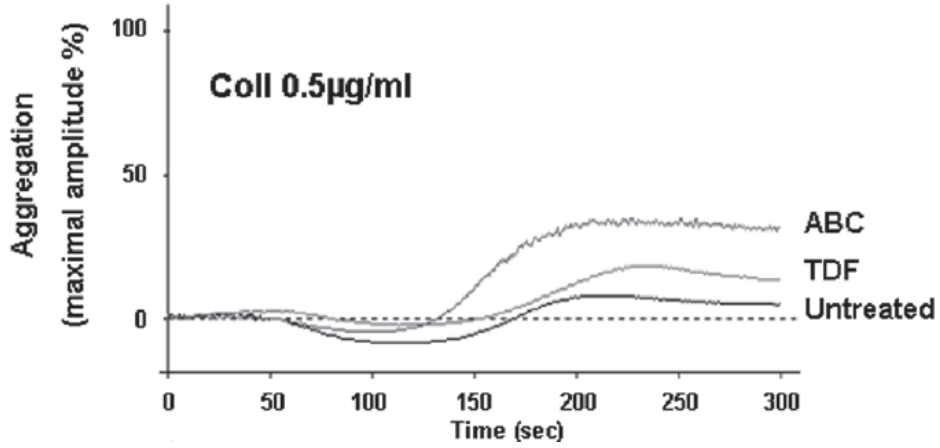
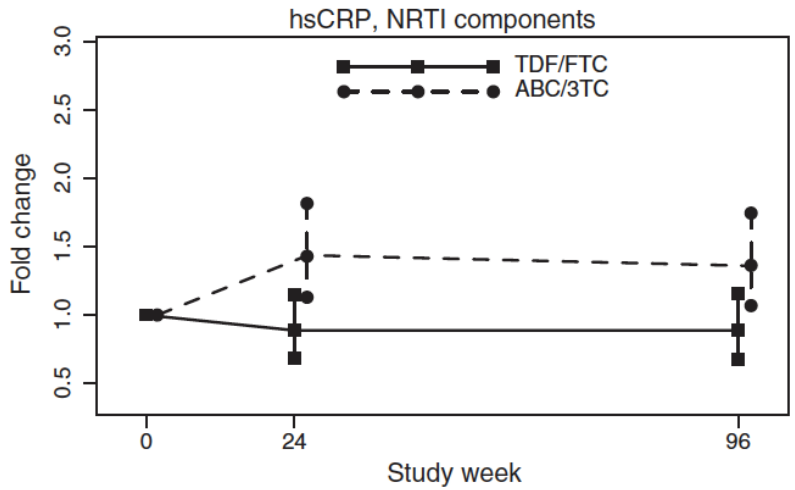
Abacavir

- Mechanisms?
  - Platelet reactivity
  - Inflammation
- D:A:D analysis of recurrent MI
  - NO increased risk of continued abacavir use after first MI
    - Cumulative post-MI exposure RR 0.86 (95% CI 0.68-1.10)
    - Recent post-MI exposure RR 1.19 (0.82-1.71)
  - ? Role of aspirin



* Higher platelet aggregation by light transmission aggregometry after stimulation in ABC treated patients compared to TDF

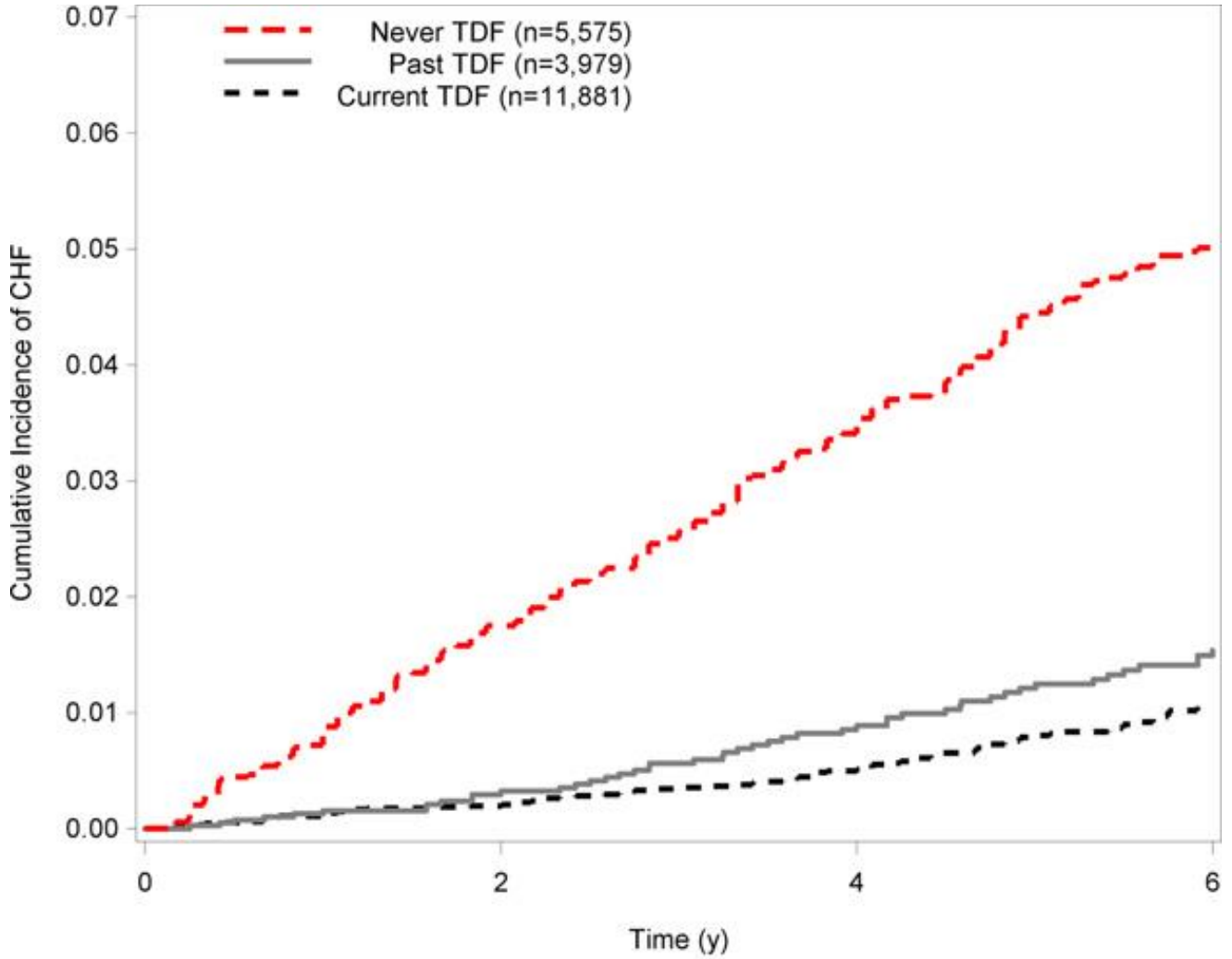


* More inflammation? Higher hsCRP with ABC vs. TDF in A5224s

Falcinelli et al, Thromb Haemost 2013; McComsey et al, AIDS 2012; Sabin et al, AIDS 2017

Tenofovir

- Tenofovir disoproxil fumarate (TDF) associated with 30-50% ***lower*** risk of heart failure in VA study
  - Contrary to hypothesis of tenofovir → kidney damage → HF risk
- ? Phosphaturia → reduced fibroblast growth factor → lower HF risk
- ? Lipid effects → reduced MI risk



Chen et al, J Am Heart Assoc 2017

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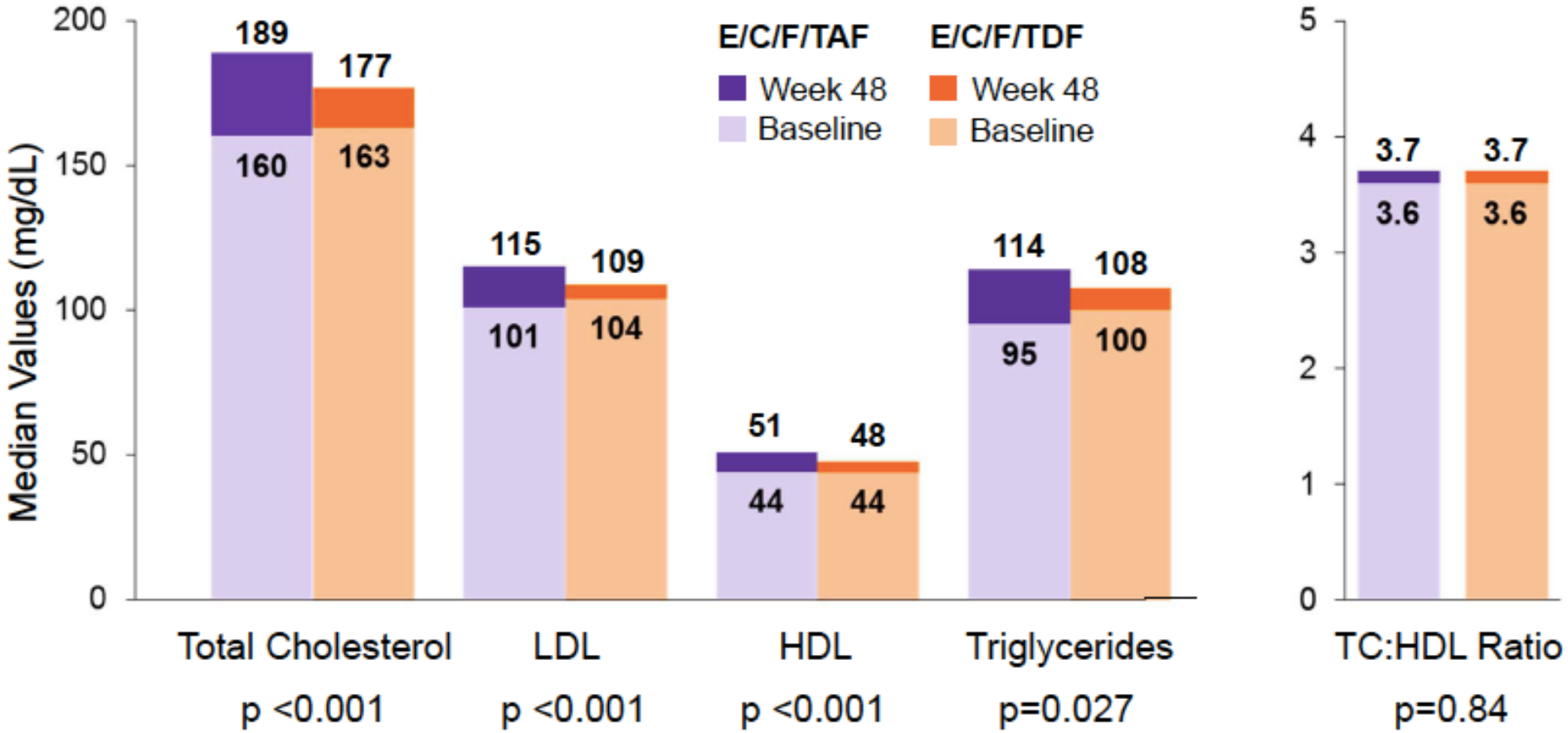
Tenofovir

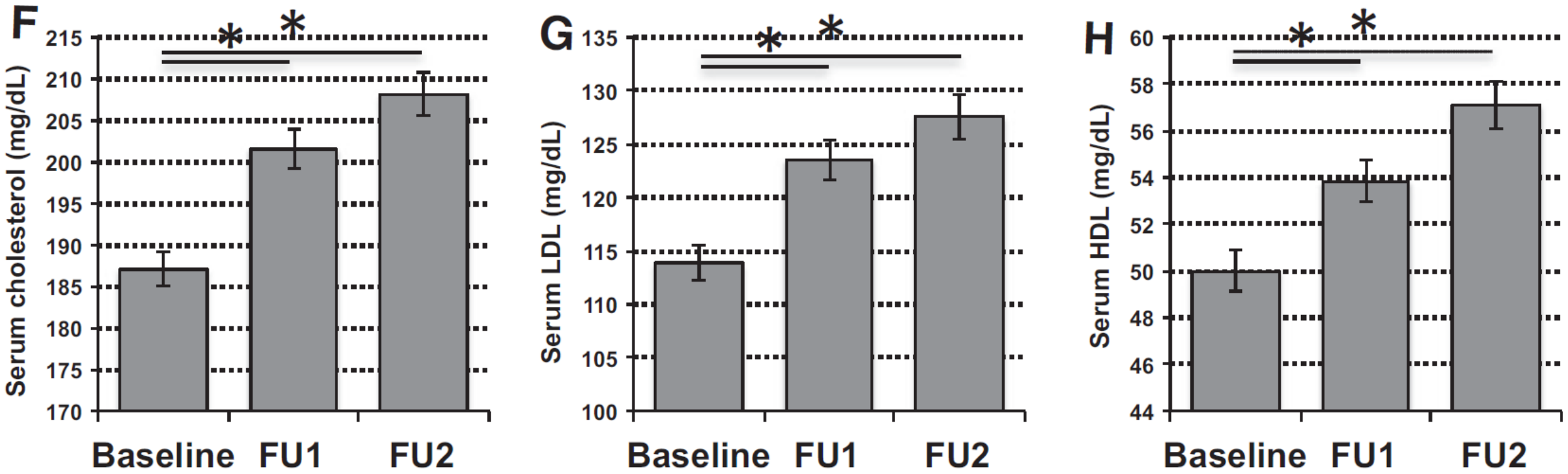
- Lipid effects in 2 Gilead trials of TAF vs. TDF



Sax et al, Lancet 2015

Tenofovir

- Switching TDF → TAF results in adverse lipid effects in real world
- Switching back to TDF reverses those effects



Schwartz-Zander, HIV Med 2020; Milinkovic et al, AIDS 2019

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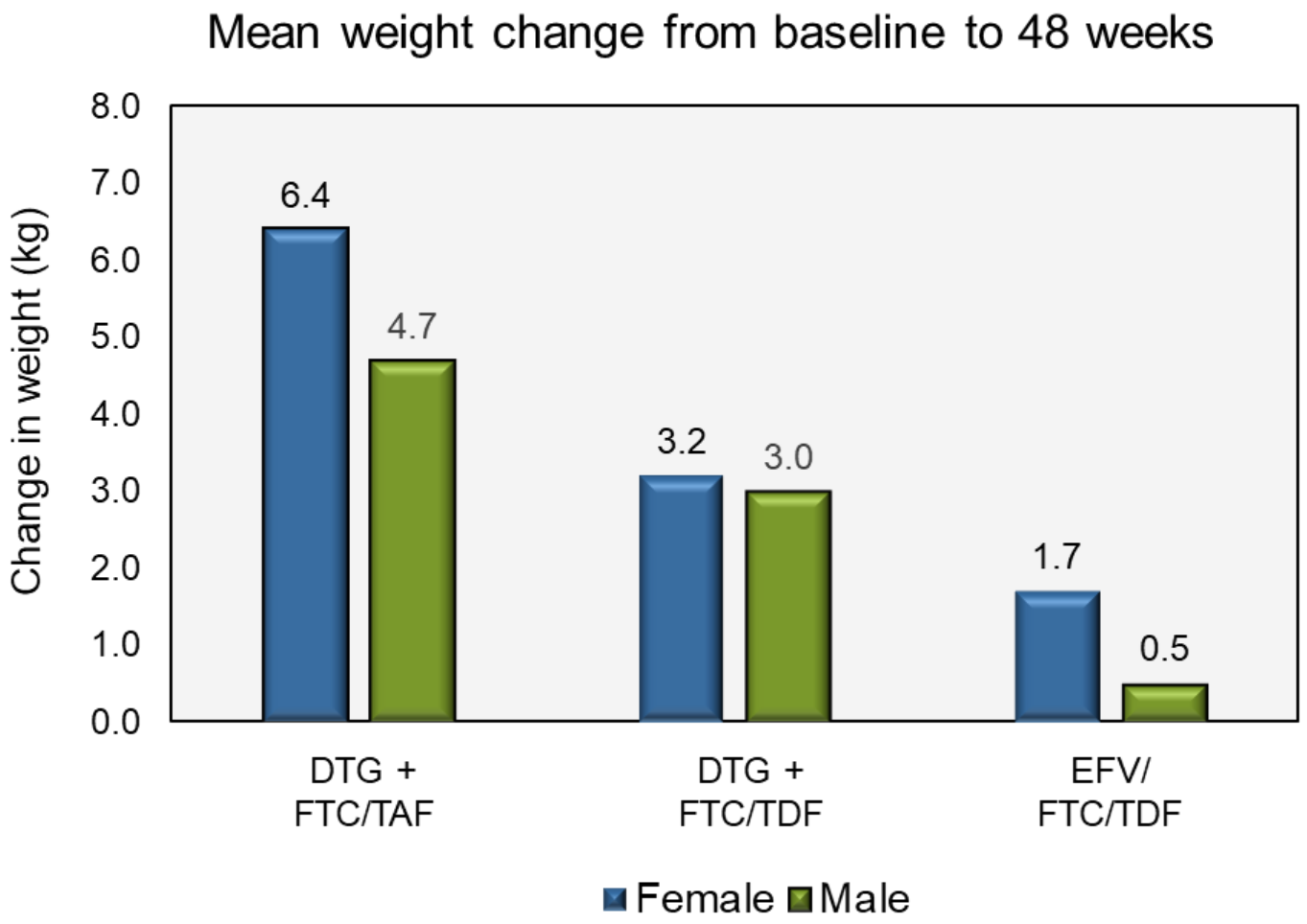
ADVANCE Trial
Comparison of Three First-Line Regimens

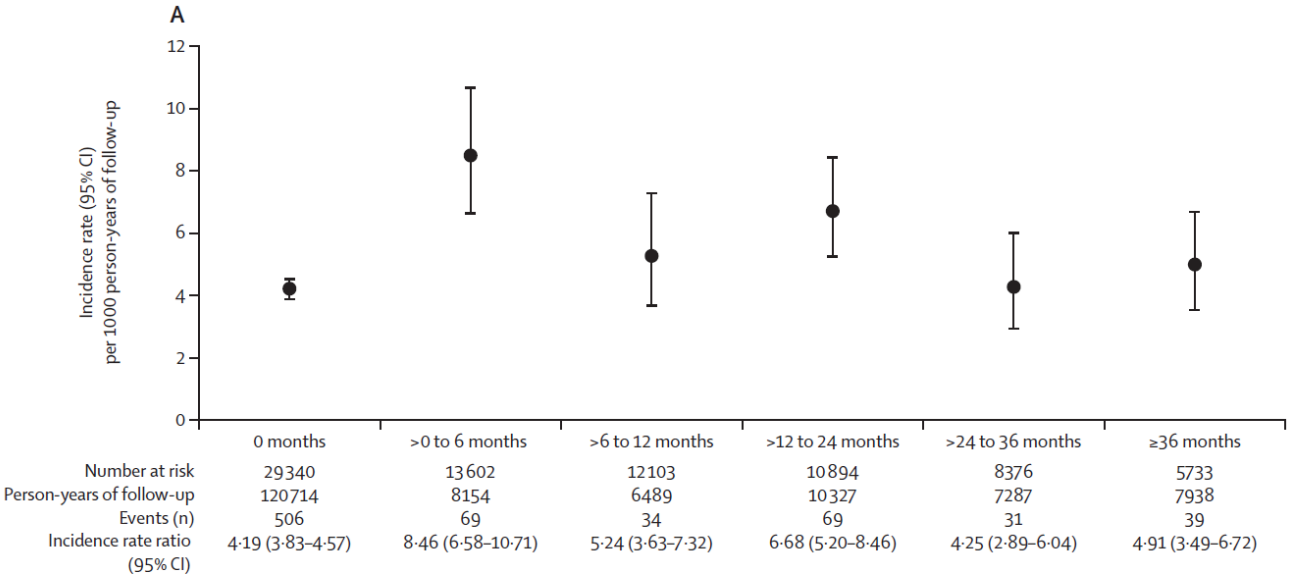
- Phase 3 RCT in South Africa
- Initial ART:
  DTG + FTC/TDF
  DTG + FTC/TAF
  EFV/FTC/TDF
- DTG arms non-inferior with fewer discontinuations
- TAF led to fewer bone/renal AE's
- Weight change more with TAF and INSTI

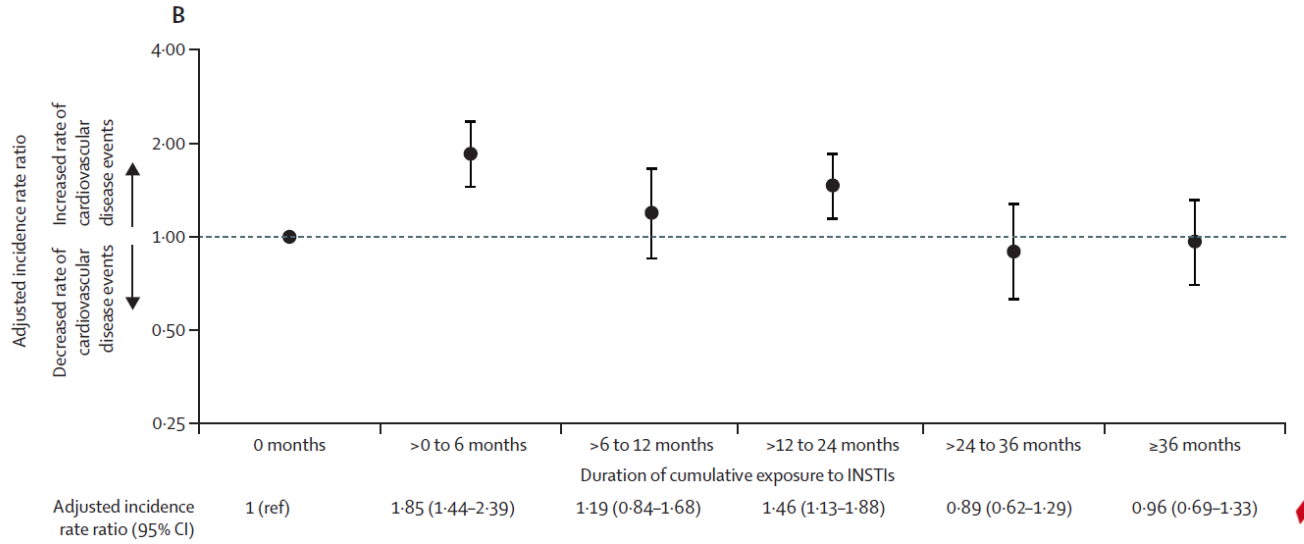


Slide adapted from B. Wood. Ventner WDF et al. NEJM, August 2019.

Integrase Inhibitors

- RESPOND Cohort Analysis published July 2022
  - 17 cohorts in Europe & Australia
  - 29,000 PLWH
- Higher ASCVD risk → more likely to get INSTI
- Composite CVD (same outcome as DRV vs. ATV analysis)
  - 748 events (less than 1157 in DRV vs. ATV)
- Early (0-24 months) use associated with increased risk





Neesgaard et al, Lancet HIV 2022

My approach to mitigating risk

- First and foremost:
  1. Traditional risk factors
  2. Traditional risk factors
  3. Traditional risk factors
- Switching ART
  - In my experience, a drug interaction is a more compelling reason to switch ART (e.g. in order to prescribe higher potency statin) than CVD risk per se
- Abacavir
  - If compelling indication, then I consider aspirin use after weighing risk/benefit and shared decision making with patient
- Clinics need more comprehensive solutions to manage metabolic effects of contemporary ART

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Acknowledgment

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