Cardiovascular Risks of Antiretroviral Therapy

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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

Myocardial Infarction

Stroke

Heart Failure

Relative risk HIV+ vs. HIV-negative


Men  Women

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)

*Treatment Effect* = 0.25 units  
*P*-value = 0.19

*immediate vs. deferred, adjusted for baseline*
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
Population attributable fractions (PAFs) for myocardial infarction

- Total Cholesterol: 44%
- Hypertension: 42%
- Smoking: 37%
- HCV+: 13%
- CD4 <200: 12%
- VL >400: 4%
- Diabetes: 3%
- Stage IV CKD: 2%
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)

Friis-Moller et al. NEJM 2007
Protease Inhibitors

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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, Lancet 2008*
Abacavir

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

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 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
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
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

![Mean weight change from baseline to 48 weeks](chart.png)
Integrase Inhibitors

- RESPOND Cohort Analysis published July 2022
  - 17 cohorts in Europe & Australia
  - 29,000 PLWH

- Higher ASCVD risk $\rightarrow$ 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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