AETC AIDS Education & Training Center Program Mountain West

Revisiting Cardiovascular Risks of Abacavir: Insights from the REPRIEVE Trial

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Disclaimer

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Objectives

- Review evidence and current guidelines for abacavir (ABC) and cardiovascular disease (CVD) risk
- Discuss recent findings from REPRIEVE on CVD risk for ABC vs tenofovir (TFV)-based ART regimens
- Discuss how these results may impact your own practice and approach to ABC from a CV perspective

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Case

A 63-year-old man with HTN and dyslipidemia presents to your clinic to establish care for HIV. He has had well-controlled HIV for >10 years and currently has a CD4 359 and undetectable HIV RNA. He is currently on atorvastatin 20mg QD, losartan 50mg QD, and ABC/3TC/DTG.

He is interested in reducing his risk for cardiovascular disease and heard that ABC may impact this risk.

Poll: Would you consider changing his ART regimen? Y/N

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Current DHHS and IAS-USA Guidelines on ABC and CV Risk

- US DHHS (section last updated Sept 2024)
  - "Some data continue to support an association between ABC and an increased risk for serious cardiovascular events"
  - "ABC should be used with caution or avoided in people with cardiovascular disease or known high cardiovascular risk."
- IAS-USA (Dec 2024)
  - "People with or at high risk for cardiovascular disease who are receiving an abacavir-containing regimen should switch to a non–abacavir-containing regimen if an active regimen is available (evidence rating: AIIb)."

DHHS Guidelines 2025. Gandhi et al. JAMA 2025.

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Evidence for ABC and CV Risk

- First described in D:A:D study (2008): ABC associated with ~2x RR for MI
  - Potentially only recent exposure (6 mo) and not cumulative or past use
- Potential mechanism
  - Platelet aggregation/hyperreactivity + WBC recruitment => plaques
- Some controversy of ABC's higher risk of CVD
  - MI and broader CVD association reproduced in multiple studies + meta-analyses, while other studies did not show higher risk
  - Channeling bias
  - Used with older, more toxic ART drugs no longer widely used
- Knowledge gap: (1) no LMIC data, (2) contemporary ART drugs

Sabin et al. Lancet 2008. Worm et al. JID 2010. DHHS Guidelines 2025. Gandhi et al. JAMA 2025. Smith et al. OFID 2025.

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Cardiovascular Hazards of Abacavir- Versus Tenofovir-Containing Antiretroviral Therapies: Insights From an Analysis of the REPRIEVE Trial Cohort

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Smith et al. OFID 2025.

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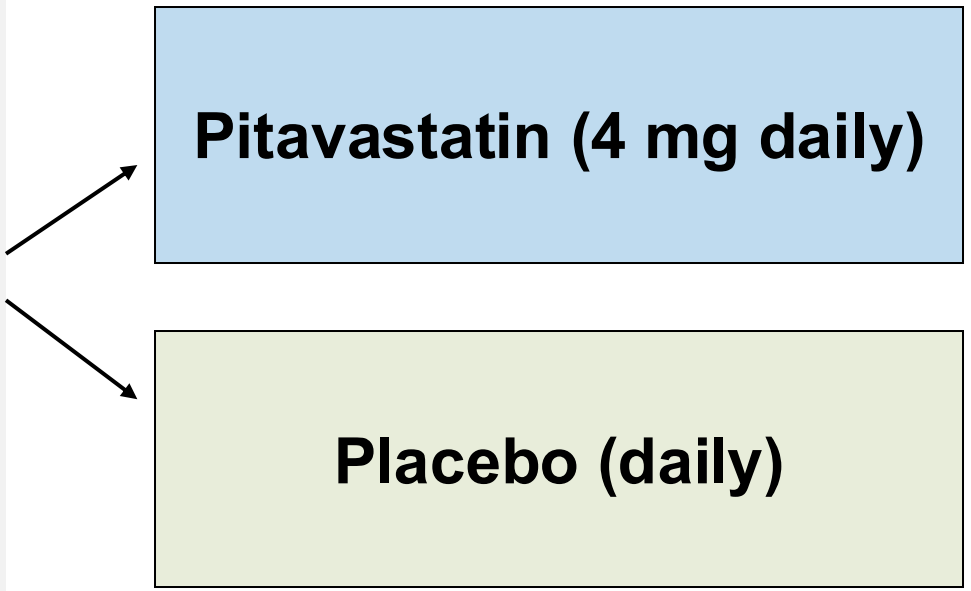
REPRIEVE Trial: Background

- **Background**
  - Phase 3, randomized, trial comparing daily pitavastatin versus placebo in persons with HIV who had low-moderate cardiovascular risk
- **Enrollment Criteria**
  - Age 40-75 years
  - Persons with HIV taking ART
  - CD4 count >100 cells/mm^3 at enrollment
  - eGFR >60
  - Low-moderate cardiovascular risk (10-year ASCVD risk score ≤15%)
  - At least one fully active agent available for HIV treatment



Source: NEJM 2023.

REPRIEVE Trial: Background

Study 3/2015 – 7/2019
Conducted in 12 Countries

7769 Participants Enrolled
- Women = 32%
- Mean age = 50 years

Findings
Pitavastatin had 35% reduction in major adverse CV events compared with placebo

DSMB Stopped Study

Source: NEJM 2023.

Sub-Study Methods

- Additional inclusion criteria for sub-study: taking ABC, TAF, TDF at entry
- Outcome: all adjudicated
  - Primary: time to first major adverse CV event (MACE) (MI, CVA/TIA, PAD, revascularization, CV death)
  - Secondary: time to first "hard" MACE (MI, CVA, CV death)
- Compared risk of outcomes by ABC vs TAF vs TDF groups using 2 approaches:
  - Goal: to "simulate" a clinical trial using existing data
  - Marginal structural Cox models adjusted for clinical and REPRIEVE study factors

  - *"Intention-to-treat" (ITT):* ignored any switches over follow-up
  - *"Modified ITT":* allowed 1 switch, additional weighting to reduce potential bias related to switching

Smith et al. OFID 2025.

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Key Results: Table 1 Highlights

- 6114 total participants in the sub-study cohort (79% of REPRIEVE)
  - Median follow up time: 5.6 years
  - ~50% 40-49y, 32% female at birth, ~2/3 non-White
  - ASCVD risk ~80% <7.5%, 87% CD4>350

  - TDF: 4274, ABC: 883, TAF: 957
    - ~70% ABC + TAF on INSTIs, 63% TDF on NNRTIs
  - NRTI switch: range 0-7 switch
    - 0 = 62%, 1 = 29%, ≥2 = 7.5%
    - Median time to first switch was ~2 years
- MACE: 183 first events
  - 5% ABC, 4% TAF, 2% TDF
  - 64% of first MACE occurred on the entry NRTI

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Event (Observed)	Adjustment	ABC vs TAF	ABC vs TDF	TAF vs TDF
MACE (183)	None	1.3 (.8–2.0)	2.5 (1.8–3.6)	2.0 (1.3–2.9)
	Baseline	1.5 (.9–2.3)	1.4 (.9–2.1)	0.9 (.6–1.5)
	Baseline + Switch	1.6 (.9–2.7)	2.0 (1.2–3.4)	1.2 (.7–2.2)
Hard MACE (121)	None	1.1 (.6–1.8)	2.5 (1.6–3.8)	2.3 (1.4–3.5)
	Baseline	1.2 (.7–2.1)	1.3 (.8–2.2)	1.1 (.6–1.9)
	Baseline + Switch	1.5 (.8–2.7)	1.8 (1.0–3.4)	1.2 (.6–2.4)
MI (57)	None	1.1 (.5–2.1)	3.7 (2.0–6.9)	3.5 (1.9–6.6)
	Baseline	1.4 (.7–2.8)	1.9 (.9–4.2)	1.4 (.6–3.1)
	Baseline + Switch	1.4 (.6–3.0)	3.5 (1.3–9.4)	2.5 (.9–7.0)
Stroke (50)	None	1.5 (.6–3.6)	2.1 (1.1–4.1)	1.4 (.7–3.1)
	Baseline	1.5 (.6–3.8)	1.1 (.5–2.5)	0.8 (.3–1.9)
	Baseline + Switch	2.9 (.9–9.8)	1.3 (.5–3.4)	0.5 (.1–1.5)
CV death (21)	None	0.9 (.2–3.6)	1.6 (.5–5.0)	1.8 (.6–5.5)
	Baseline	0.9 (.1–3.7)	1.1 (.3–3.8)	1.3 (.4–4.5)
	Baseline + Switch	0.9 (.2–4.4)	1.8 (.4–7.6)	1.9 (.4–8.7)

Sub-Study Conclusions

- Results generally align with earlier studies:
  - ABC associated with higher risk of first MACE (and components) compared to TFV, after adjustment for relevant clinical characteristics
  - TAF vs TDF had similar hazard of first MACE and components
- Limitations:
  - Anchor drug interactions with NRTI and impact on MACE
  - Evaluated existing NRTI exposure = survival bias, not a new user analysis
- Next REPRIEVE study: timing and duration of ABC on MACE
  - Poster at IAS 2024: https://doi.org/10.1002/jia2.26279

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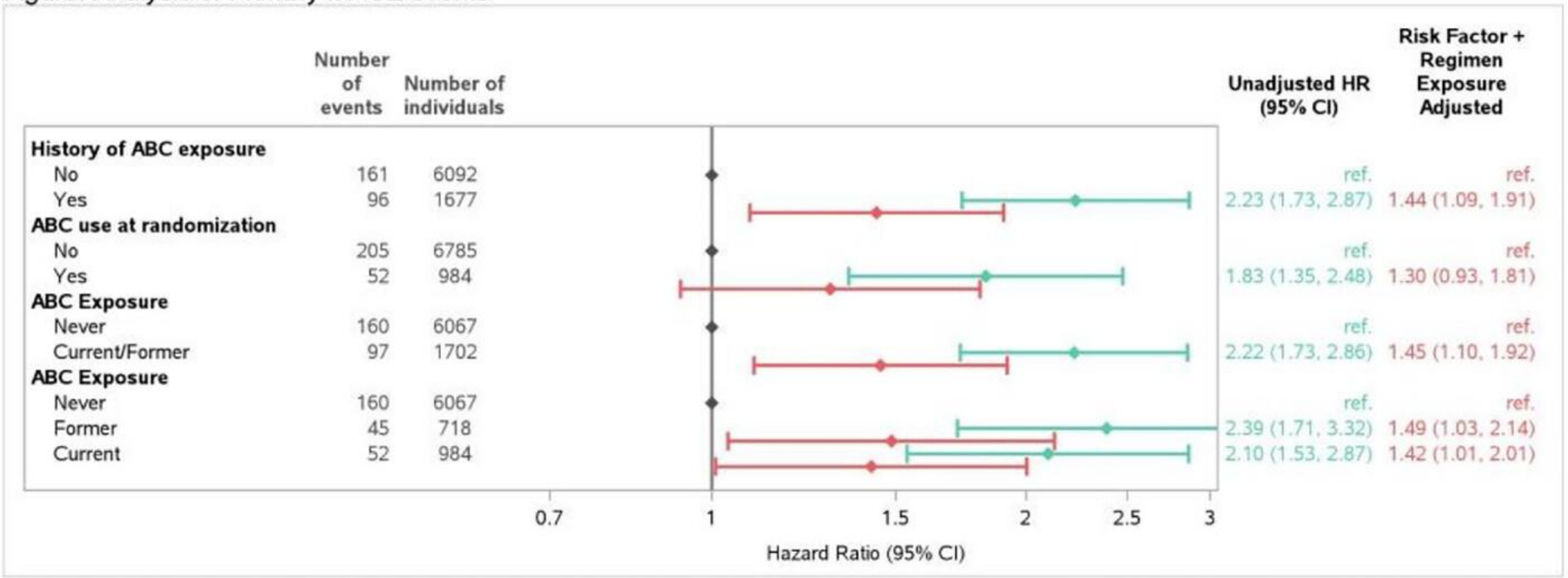
IAS 2024 Presentation: Abacavir is associated with elevated risk for cardiovascular events in the REPRIEVE trial

Figure: Analysis of Primary MACE events



Risk factor and regimen adjusted analysis adjusts for entry ART class (NRTI + NNRTI, NRTI + INSTI, NRTI + PI, NRTI-sparing, other NRTI-containing regimens), age, natal sex, race, global burden of disease region, family history of CVD, smoking, hypertension, BMI, substance use, nadir CD4, HIV viral load, creatinine clearance, fasting glucose and lipids.

Fichtenbaum et al. IAS 2024.

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Return to Case, Poll, and Discussion

A 63-year-old man with HTN and dyslipidemia presents to your clinic to establish care for HIV. He has had well-controlled HIV for >10 years and currently has a CD4 359 and undetectable HIV RNA. He is currently on atorvastatin 20mg QD, losartan 50mg QD, and ABC/3TC/DTG.

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Poll: Would you consider changing his ART regimen? Y/N

Discussion:

- Why did you choose to change or not change his ART?
- How would you counsel him on ABC?
- When or what groups would you consider using ABC in contemporary ART?

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Thank you!
Questions and Comments?

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