

Do Integrase Inhibitors or TAF *Cause* Weight Gain?

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Disclaimer

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Poll #1

Do integrase strand transfer inhibitors (INSTIs), like dolutegravir and bictegravir, directly cause weight gain?

A) Yes

B) No

Poll #2

Does tenofovir alafenamide (TAF) directly cause weight gain?

A) Yes

B) No

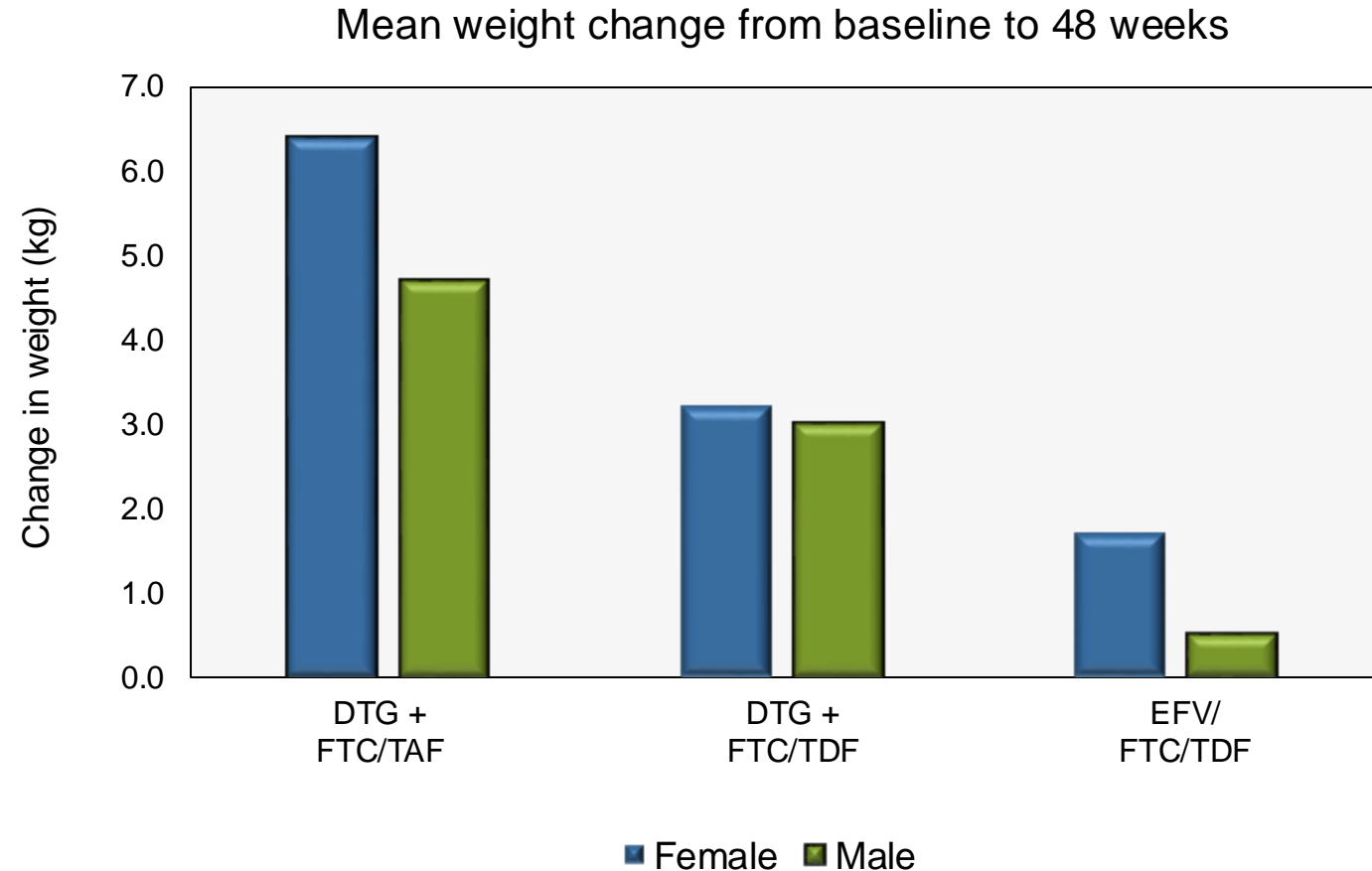
Latest Data on ART and Weight Change

- Summary of my take:
 - INSTIs and TAF are associated with more weight gain than older agents, but...
 - Does TAF *cause* weight gain? No
 - Does stopping TAF lead to weight loss? No
 - Do INSTIs *cause* weight gain? No
 - Does switching off an INSTI lead to weight loss? No
 - So what's the issue? TDF, efavirenz, and other older ARVs suppress or attenuate weight in ways we don't understand...

ADVANCE Trial

Comparison of Three First-Line Regimens

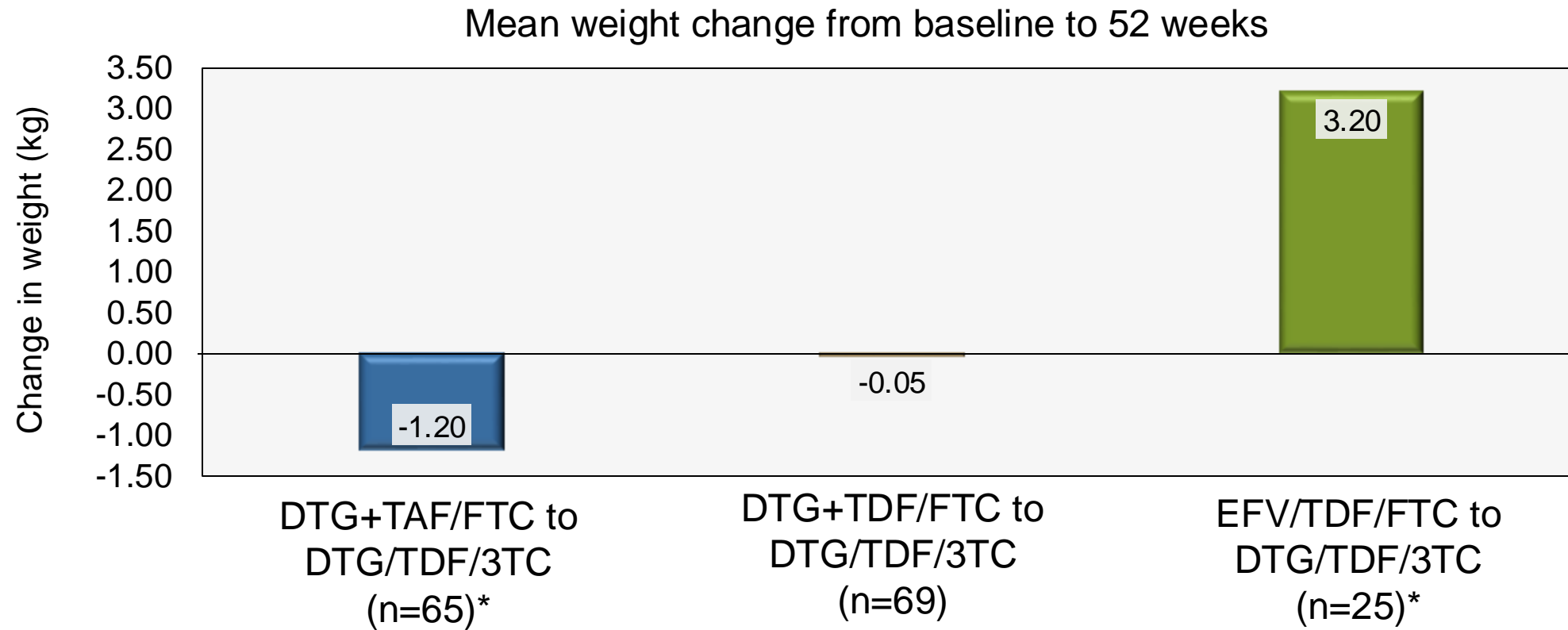
- Phase 3 RCT in South Africa
- Initial ART: DTG + FTC/TDF, DTG + FTC/TAF, EFV/FTC/TDF
- Virologic suppression outcome: DTG arms non-inferior with fewer discontinuations



CHARACTERISE

Open-Label Switch to TDF/3TC/DTG After ADVANCED Trial

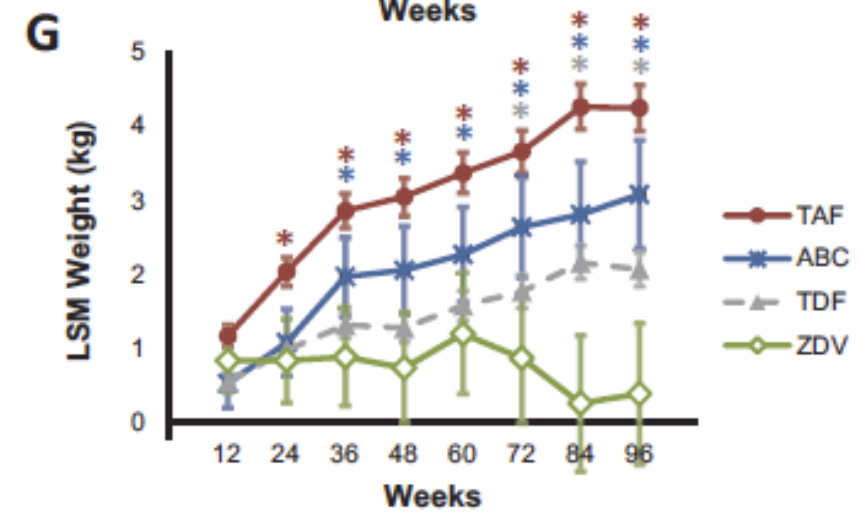
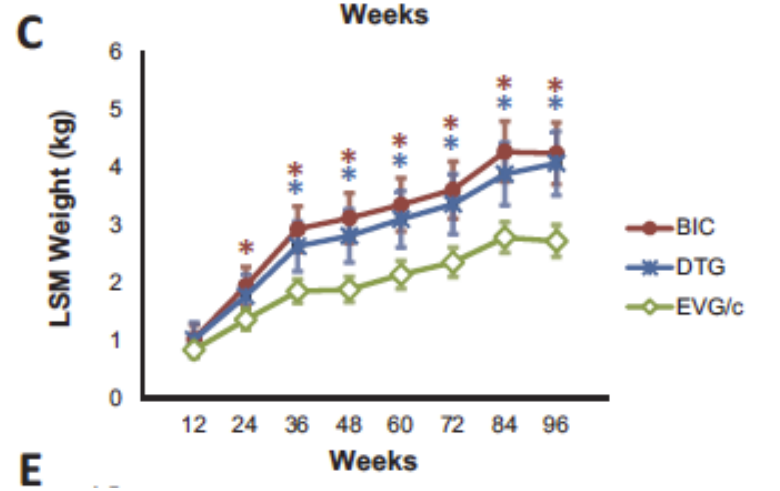
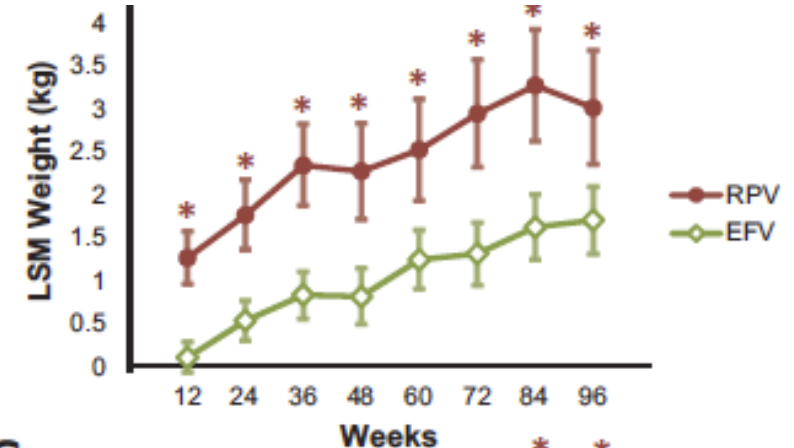
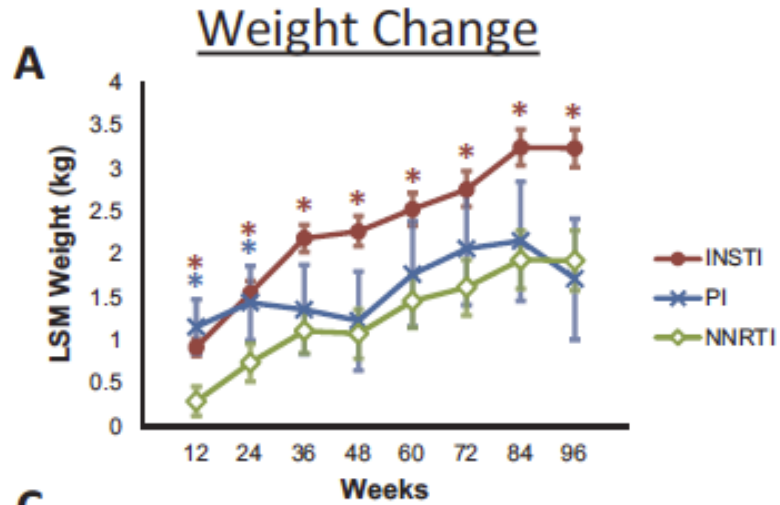
After 192 weeks in ADVANCE, volunteers switched to open-label DTG/TDF/3TC



* = statistically significant

ART Initiation

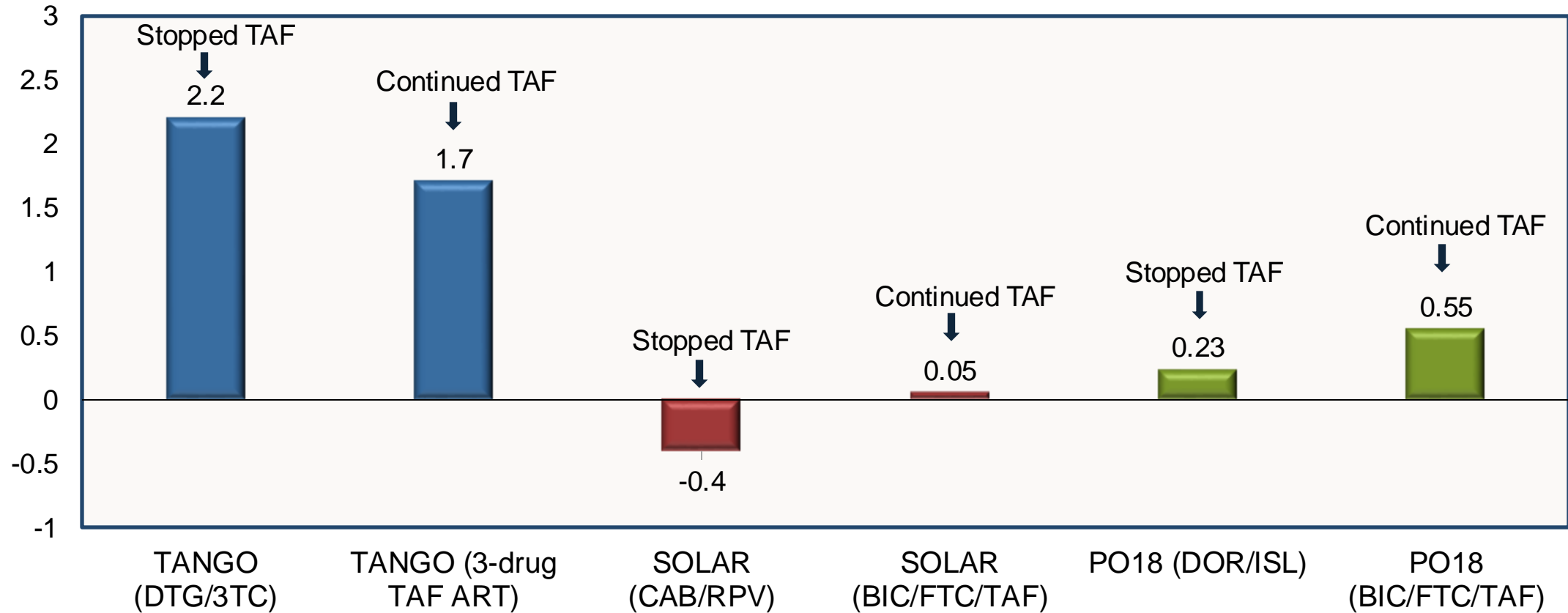
Pooled Analysis of 8 RCTs



ART Switch

Stopping TAF does not lead to weight loss

Mean or median weight change in kg over study follow up

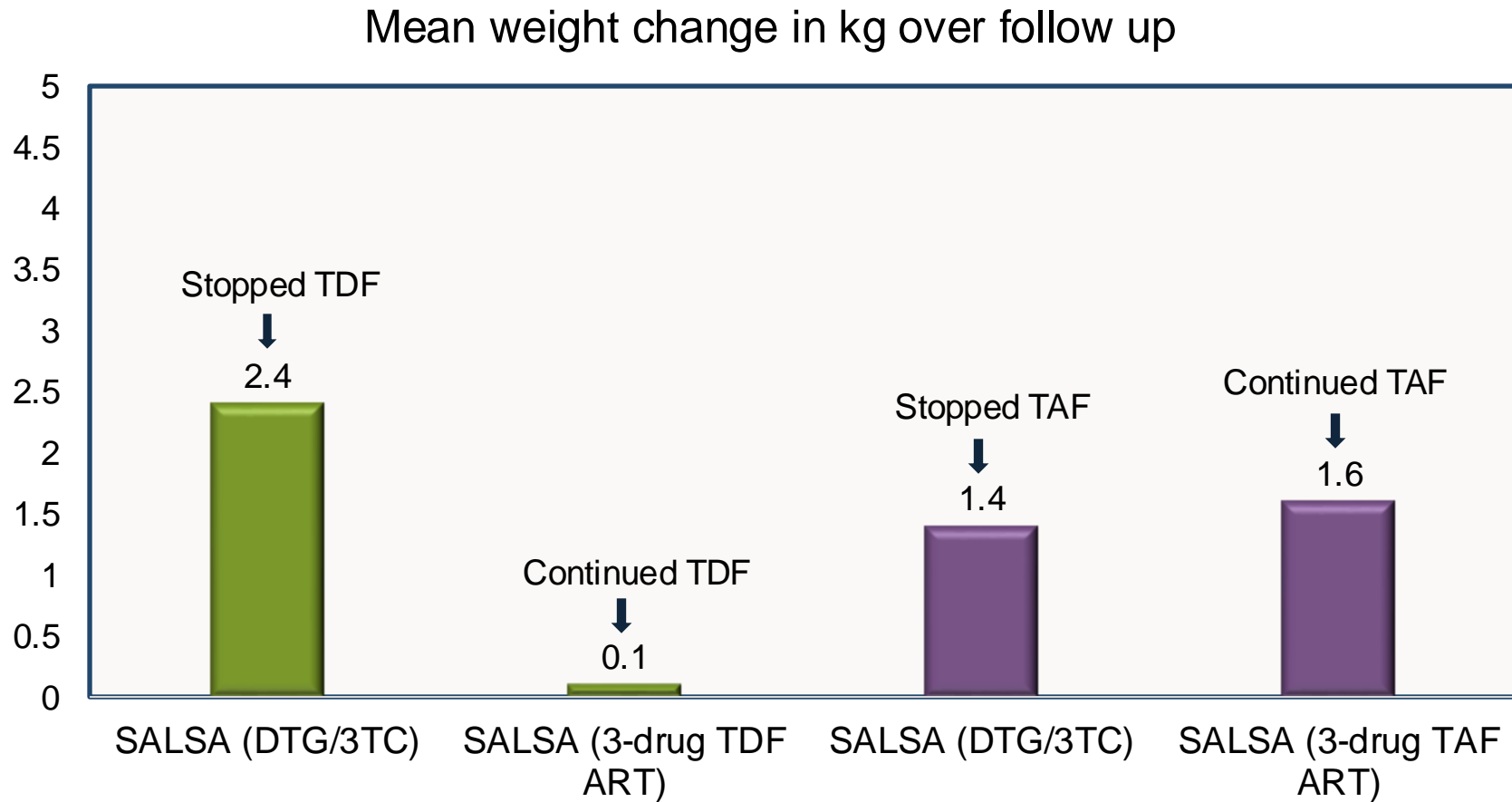


ART Switch

Stopping TDF leads to weight gain

Summary:

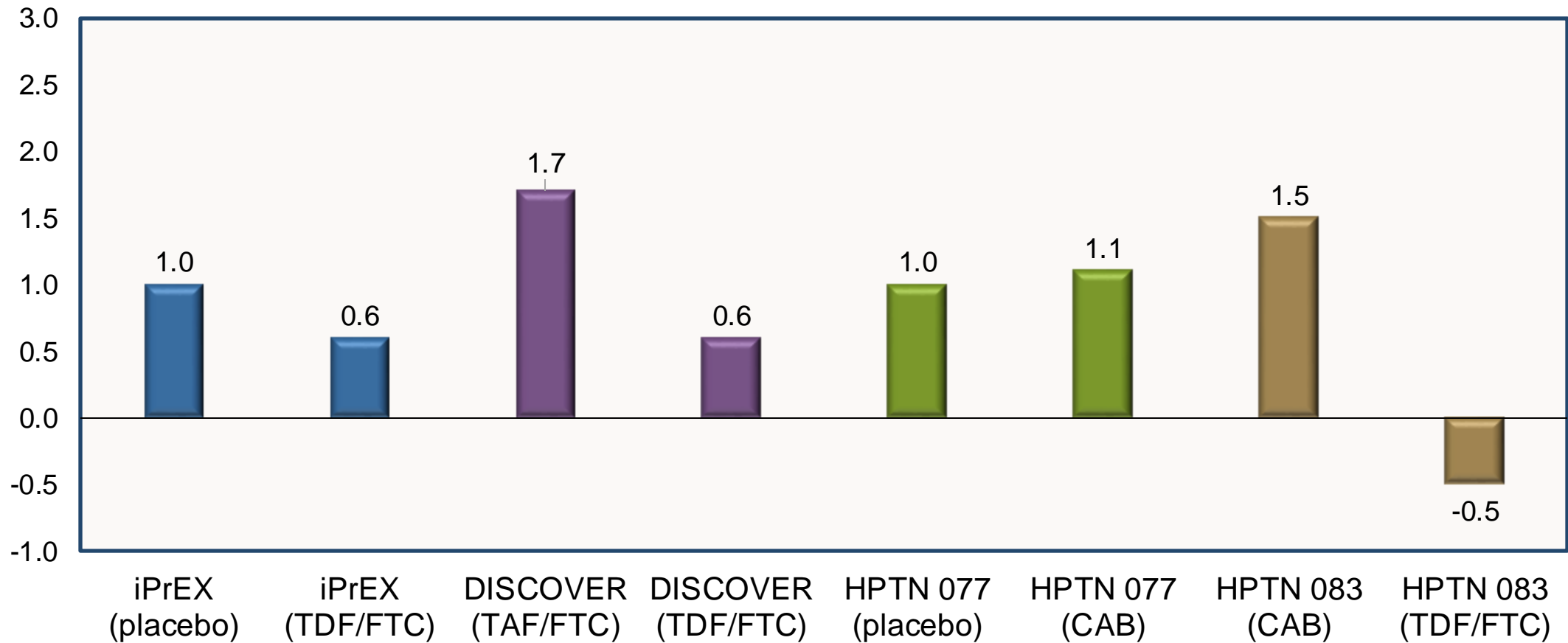
Stopping TAF does not lead to weight loss
Switching TAF to TDF leads to weight loss
Stopping TDF leads to weight gain



PrEP Trials

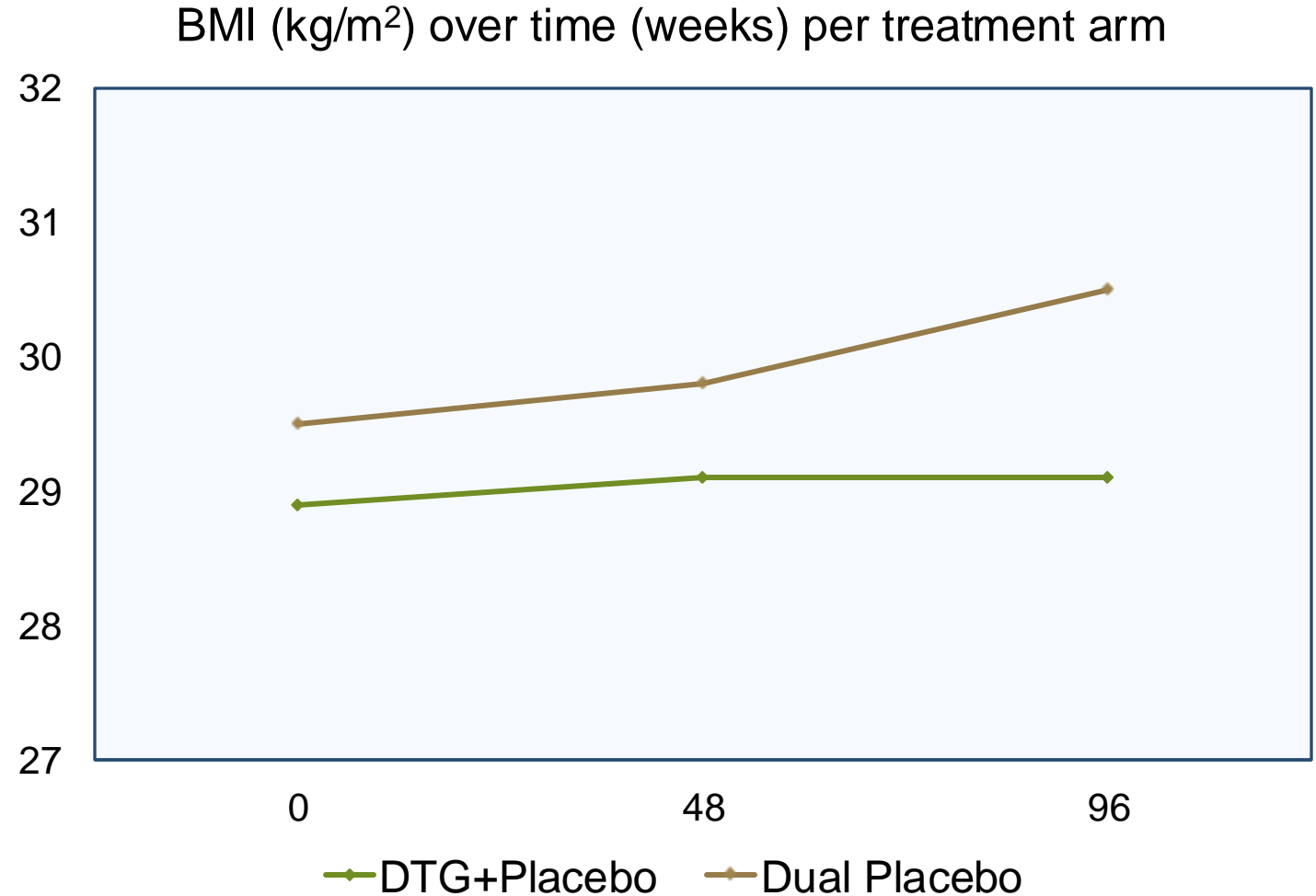
See also: meta-analysis of PrEP trials
- Total sample size 19,359 participants
- TDF associated with weight loss
(Shah S, et al. AIDS 2021)

Mean or median weight change in kg over study follow up



ACTG 5234: DTG vs. Placebo

- Randomized, double blind, placebo-controlled, 96-week trial of ART intensification
- N = 191 enrolled
- Randomized to add either:
 - Dolutegravir + maraviroc, or
 - Dolutegravir + placebo, or
 - Dual placebo
- Weight increase did not differ between arms at week 96



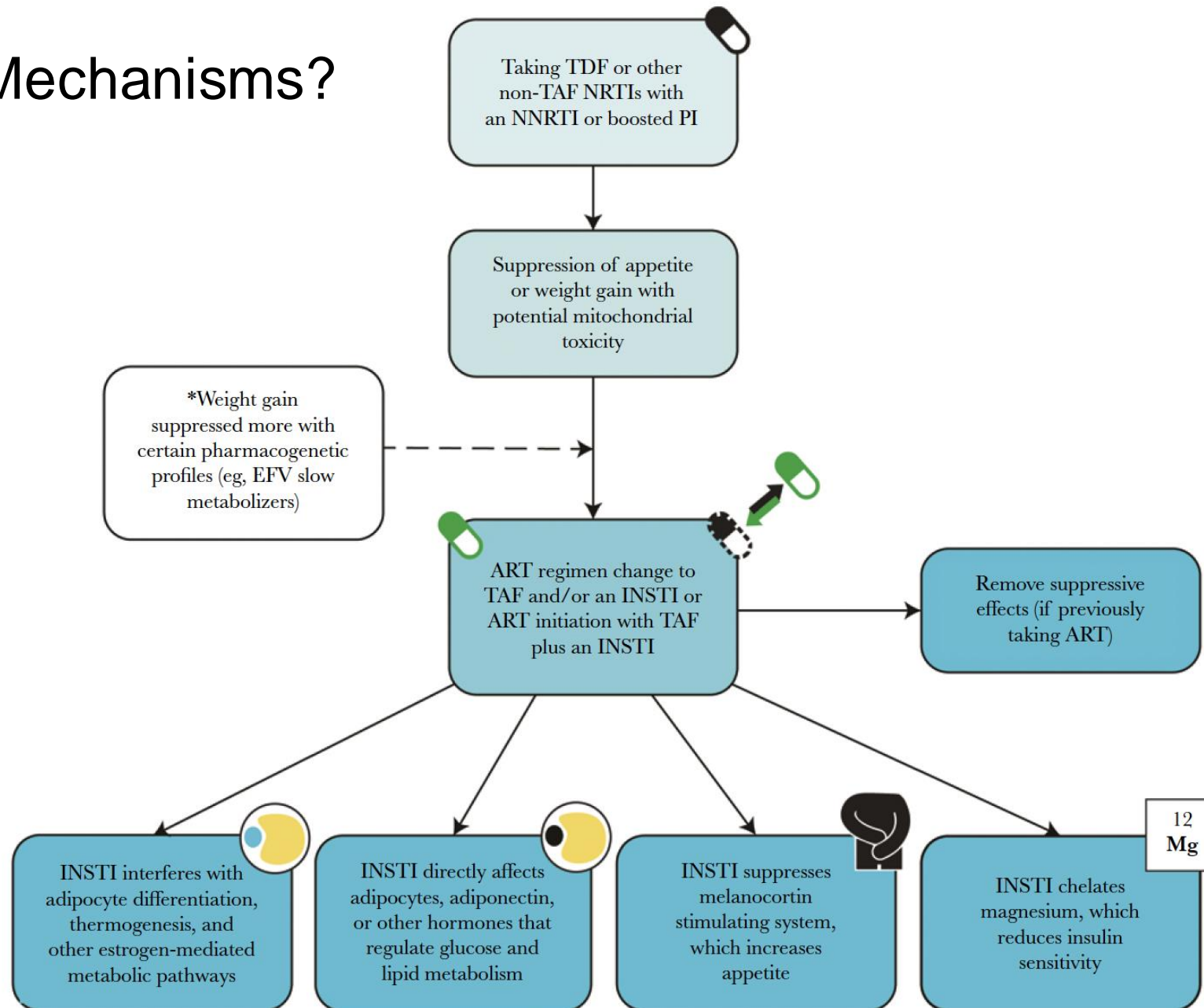
DEFINE Trial

Switch to Boosted PI after INSTI-Associated Weight Gain

- Prospective, randomized, open-label, active-controlled phase 4 trial
- Virologically suppressed adults who experienced $\geq 10\%$ increase in body weight on INSTI + TAF/FTC (n = 103)
- Switch to DRV/cobi/FTC/TAF vs. continue INSTI + FTC/TAF
- No significant difference in weight change between arms comparing baseline to week 24

% Change in Body Weight Over Time (ITT)	
DRV/cobi/TAF/FTC (n = 53)	INSTI + TAF/FTC (n = 50)
0.63	-0.24

Mechanisms?



TDF Weight Suppression Mechanisms?

Effect of TDF vs. TAF on Duodenal Enterocytes: A Hypothesis for Different Effects on Body Weight

- PWH taking TDF (n=12) or TAF (n=12) underwent gastroscopy with biopsies of proximal & distal duodenum
- TDF group:
 - More villous damage, especially in proximal duodenum
 - Increased intestinal fatty acid-binding protein, a marker of enterocyte damage
 - No difference in signs of mitochondrial damage
- Lower body weight and plasma lipids with TDF may be secondary to damage to duodenal villi and enterocytes

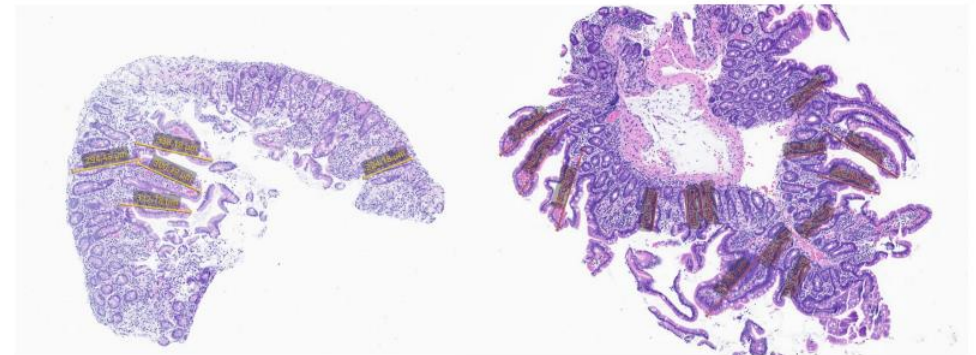


Figure 1. Histological sample of duodenal epithelium of patients receiving TDF (left) or TAF (right).

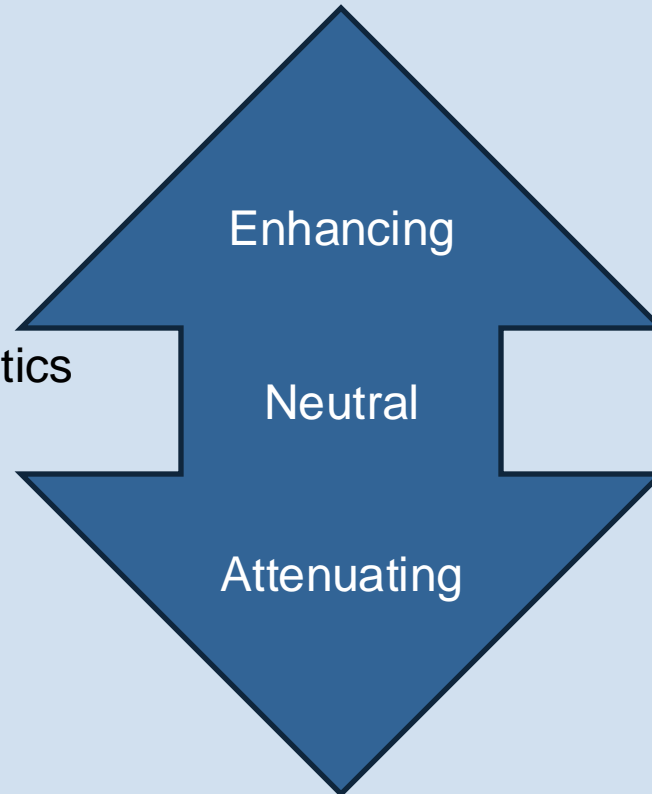
ART-Associated Weight Change: Proposed Model

Return to health weight gain

Individual Factors:

High pre-treatment VL
Low pre-treatment CD4
Female sex
Black race
Underweight at ART initiation
Host genetics/pharmacogenetics

Opportunistic condition
Substance use



HIV Treatment Factors:

TAF, BIC, DTG, CAB

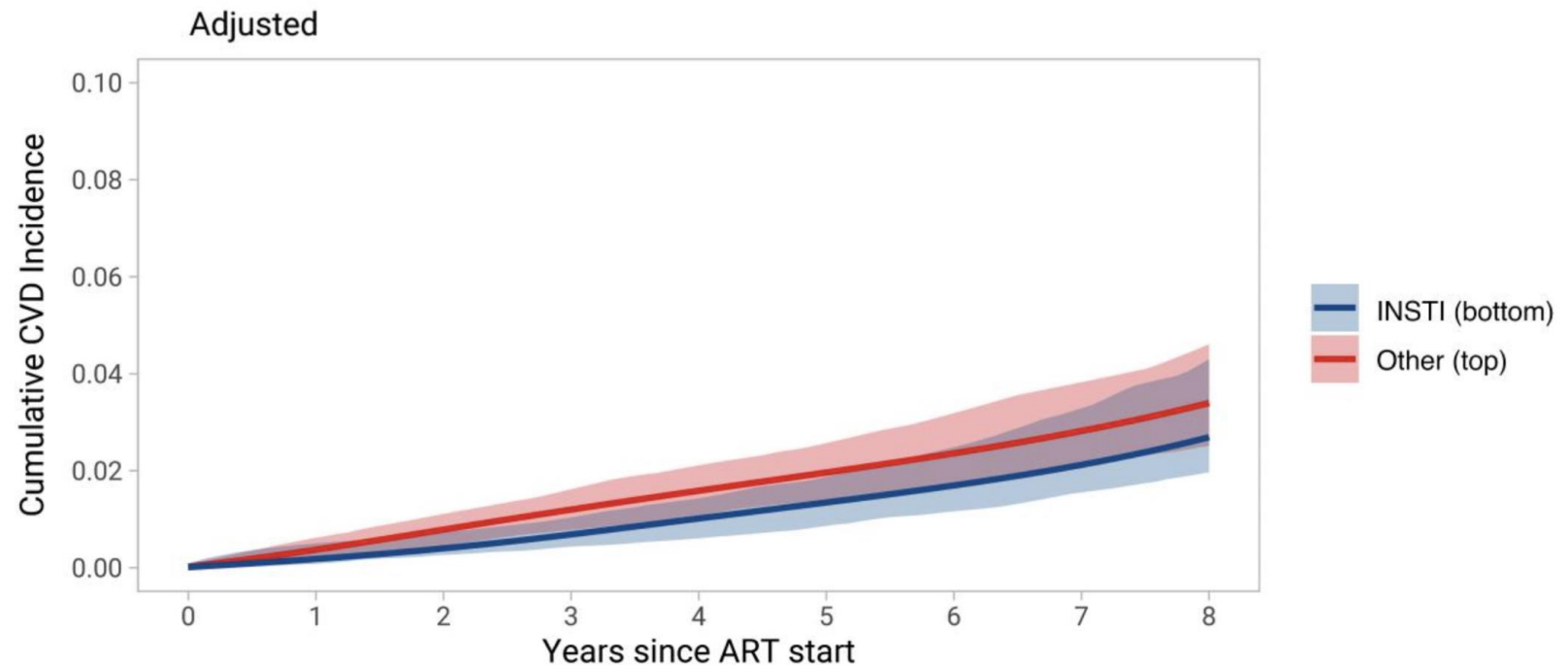
TDF
EFV (especially slow metabolizers)

The other complicated question...

Do INSTIs raise risk of cardiovascular events?

Swiss HIV Cohort Study:

- Adults who started INSTI vs. other regimen, followed until CV event
- 5,362 participants
- Median 4.9 years f/u, 116 CV events
- No difference in risk of CV events, adjusted for many potential confounders



Summary of the ART-Weight Issue: My Interpretation

- Is there a difference between expected weight gain between INSTIs and other ARV classes? **Yes**
 - Do INSTIs directly cause weight gain? **Probably not**
 - What's the biggest issue? **Switch from EFV to DTG or BIC**
- Is there a difference between expected weight gain comparing TAF to other NRTIs? **Yes**
 - Does TAF directly cause weight gain? **No**
 - What's the biggest issue? **Switch from older NRTI to TAF**

So how can we help address ART-associated weight gain?

- Early counseling, lifestyle changes, referral to Nutrition, exercise programs, gyms with sliding scale, free online options, exercise partner
- Review other meds that contribute to weight gain
- Try an ART regimen change? I don't do this routinely
- Start a med to stimulate weight loss?
 - Metformin? Try to get a GLP-1 RA or GLP-1/GIP agent approved?
 - Phentermine/topiramate, naltrexone/bupropion, orlistat, other?
- Other strategies?

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