Antiretroviral Fact vs. Fiction: New Data on ARV Controversies & the Future of ART

Brian R. Wood, MD
Professor of Medicine
University of Washington
Mountain West AIDS Education & Training Center

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Disclosures

No conflicts of interest or relationships to disclose.

Objectives

1. Review the latest data on several controversial aspects of ART management
2. Highlight recent changes to the adult & adolescent HIV treatment guidelines
3. Discuss data for newer ARV agents and the future ART pipeline

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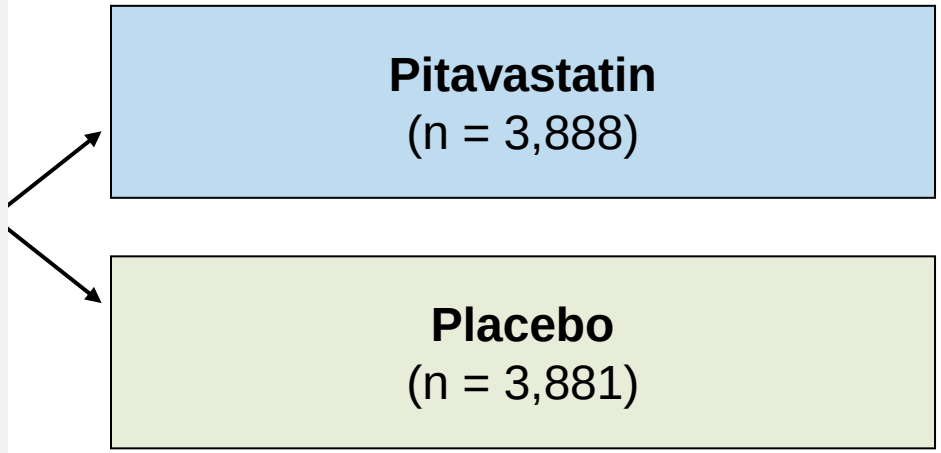
Poll #1

- Fact or fiction: abacavir increases risk of major adverse cardiovascular events
  - A) Fact
  - B) Fiction
  - C) We need more data

REPRIEVE: Abacavir Exposure Status and Risk of Major Adverse Cardiovascular Events (MACE)

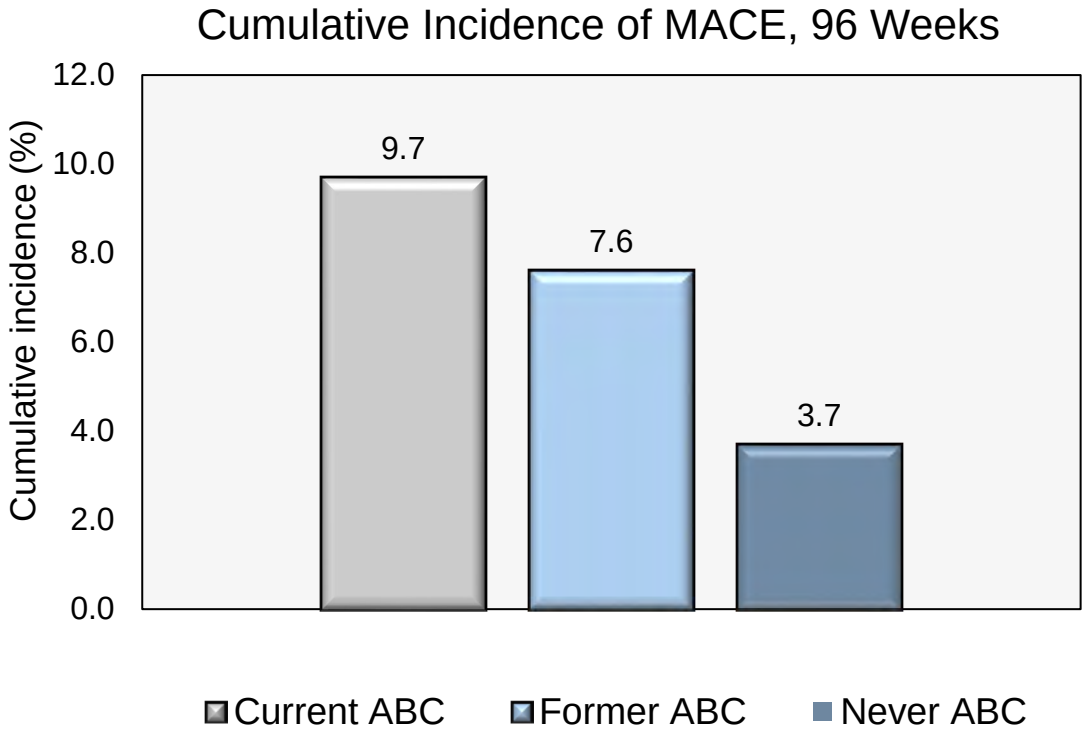
- **Design**
  - Phase 3, randomized controlled trial
- **Inclusion Criteria**
  - PWH taking stable ART
  - 40 to 75 years of age
  - Low-to-moderate risk of atherosclerotic CVD
- **New Analysis:**
  - Compare risk of MACE with current abacavir exposure, prior exposure, or no exposure
  - Abacavir exposure: 13% current (median 1.5 years), 9% former (median 3.0 years), 78% never



Source: Fichtenbaum CJ, et al. IAS 2024. Abstract OAB3406LB.

REPRIEVE: Abacavir Exposure Status and Risk of Major Adverse Cardiovascular Events (MACE)

- Principal result: abacavir exposure (versus none) associated with higher incidence of MACE
- Adjusted hazard ratio (95% CI):
  - Former use: **1.50** (1.04, 2.15)
  - Current use: **1.42** (1.00, 2.00)
- No association with current or former use of TDF, AZT, D4T, or PI



Source: Fichtenbaum CJ, et al. IAS 2024. Abstract OAB3406LB.

HHS Recommended Initial Regimens for Most People with HIV
For People Who Do Not Have a History of Cabotegravir PrEP

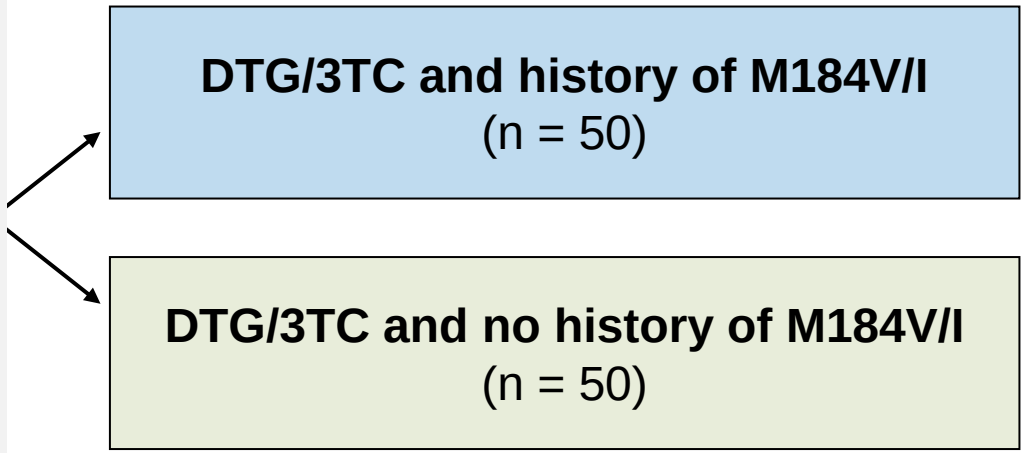
INSTI + 2 NRTIs	Abbreviation
Bictegravir/tenofovir alafenamide/emtricitabine	BIC/TAF/FTC
Dolutegravir + tenofovir alafenamide/emtricitabine	DTG + TAF/FTC
Dolutegravir + [tenofovir DF/emtricitabine *or* tenofovir DF/lamivudine]	DTG + [TDF/FTC *or* TDF/3TC]
INSTI + 1 NRTI	**Abbreviation**
Dolutegravir/lamivudine (only if HIV RNA <500k, no HBV, have genotype results)	DTG/3TC

HHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Updated Sept. 12, 2024. (http://www.clinicalinfo.hiv.gov)

Is this the end of the road for abacavir?
Are there clinical scenarios in which you would still recommend it?

SOLAR3D: Switch to DTG/3TC with Prior Virologic Failure and M184V/I Mutation

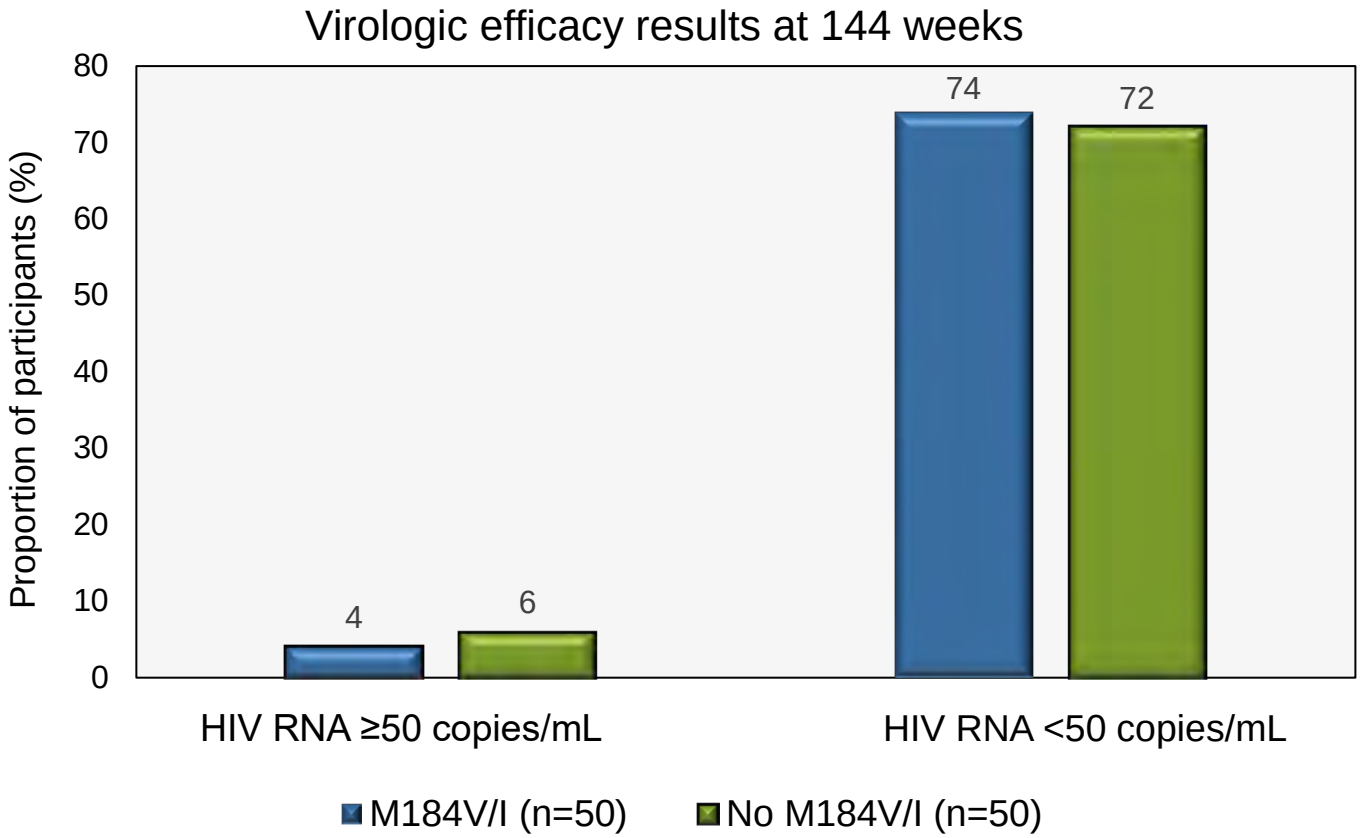
- **Design**
  - Prospective, open-label, comparative study
- **Eligibility Criteria**
  - Adults with HIV RNA <50 copies/mL for ≥6 months on any stable 2-/3-/4-drug ART
  - All with prior virologic failure and at least 2 prior ART regimens
  - No exclusion for CD4 count, INSTI experience, past NRTI resistance, M184V/I or K65R on baseline proviral genotype
- **Primary endpoint:**
  - Proportion of participants with HIV RNA >50 copies/mL at 144 weeks



At baseline: median ART duration 22.3 years, median 7 previous ART regimens, median duration viral suppression 11.8 years

Source: Blick G, et al. IAS 2024. Abstract SS0403LB.

SOLAR3D: Switch to DTG/3TC with Prior Virologic Failure and M184V/I Mutation



	M184V/I on Historical Genotype (n = 50)	No M184V/I on Historical Genotype (n = 50)
Proviral genotype	41 (82)	29 (58)
M184V/I present	15 (37)	0
M184V/I absent	26 (63)	29 (100)
All reported as: n (%)		

No difference in rate of virologic suppression, confirmed virologic failures (0 with M184V/I, 1 with no M184V/I due to missed doses), incidence of viral blips

Source: Blick G, et al. IAS 2024. Abstract SS0403LB.

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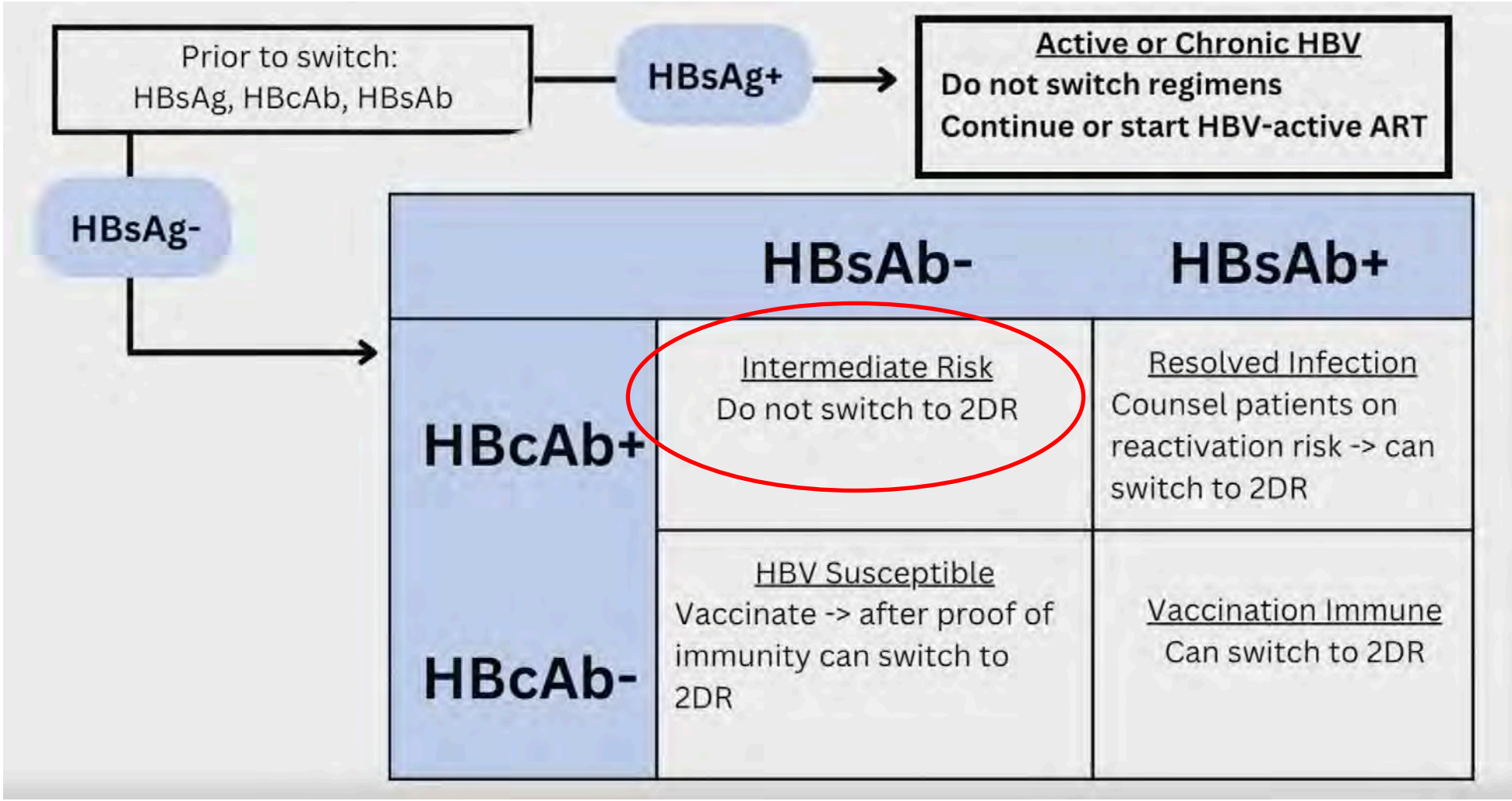
Poll #2

- Fact or fiction: isolated positive hepatitis B core antibody should be considered a contraindication to switching off TAF or TDF.
  - A) Fact
  - B) Fiction
  - C) We need more data

Positive Hepatitis B Virus (HBV) Core Antibody: Mt. Sinai QI Protocol



Source: Margolis M, et al. ID Week 2024. Abstract 156.

Switch off TDF or TAF to LAI CAB/RPV or DTG/RPV with +HBV CoreAb

- N = 41; 15 switch to DTG/RPV, 26 to LAI CAB/RPV
- 34 with +core Ab and + surface Ab: no reactivations
- 7 with isolated +core Ab: 1 (14.3%) switch to LA CAB/RPV developed HBV reactivation
- Conclusion: close monitoring of ALT and possibly HBV DNA mandatory with isolated +HBV core Ab after switch

Figure 2. Trend of transaminases in the participant with HBV reactivation

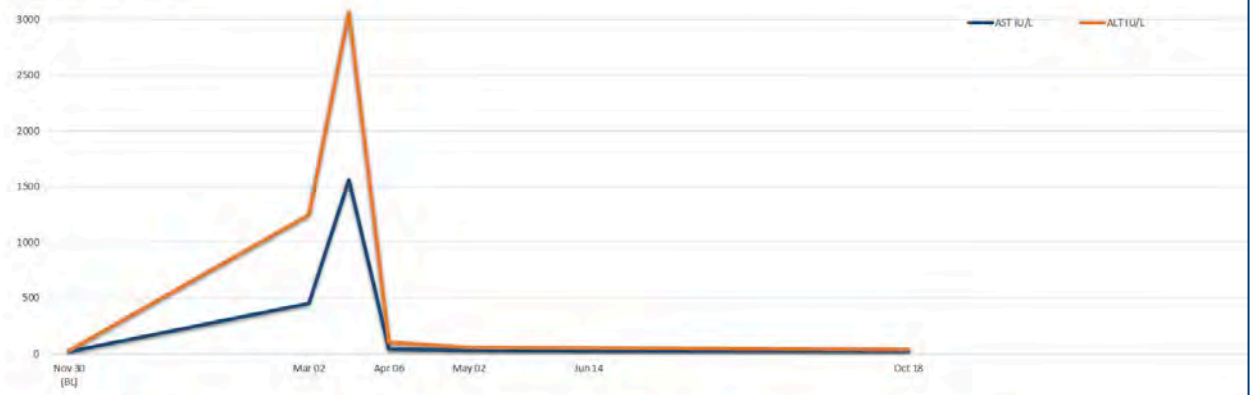
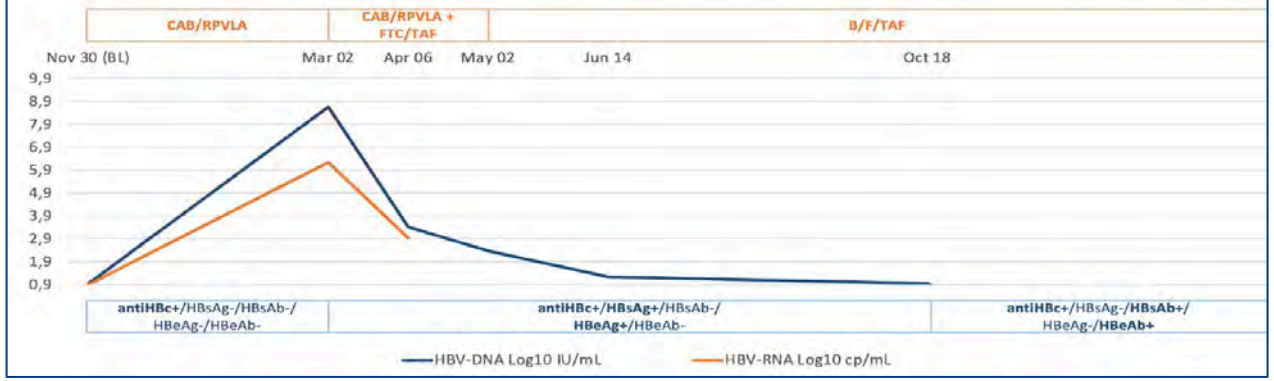


Figure 3. Trend of HBV-DNA, -RNA and serology in the participant with HBV reactivation. Alignment of the partial HBsAg before any ART and during HBV reactivation in the bottom



Source: Morsica, et al. CROI 2024. Abstract 737.

More on Hep B Reactivation after Switch Off Hep B-Active ARVs

- Veterans Aging Cohort Study
- PWH with +HBV core Ab who switched off active HBV ARVs (no TAF, TDF, FTC, or 3TC)
- 39 HBV reactivation cases (0.7%)
- Median time to reactivation: 292 days (IQR 164-816 days)

Serology prior to switch		Cases Amongst PWH who Continued on ART Without Hepatitis B Activity Prior to Reactivation		
		N	%	
Never sAg+, never sAb+	*n=1,345*	16	1.2	*p=0.0012*
Never sAg+, ever sAb+	*n=4,379*	18	0.4	
Ever sAg+, never sAb+	*n=66*	4	6.1	*p<0.0001*
Ever sAg+, ever sAb+	*n=164*	1	0.6	
Total	*n=5,954*	39	0.7	

Source: Denyer, et al. ID Week 2023. Abstract 1026.

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DTG/3TC in Adults with HIV and Isolated Reactive HBV Core Antibody

- Results from the phase 3/3b GEMINI-1/-2, STAT, TANGO, and SALSA:
  - n = 76 with isolated +HBV core Ab received DTG/3TC (51 initial ART, 25 switch)

Zero cases of HBV reactivation

Conclusion: DTG/3TC safe & effective in setting of isolated HBV core Ab positivity

Source: Fox D, et al. IAS 2024. Abstract OAB0106LB.

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HBV Reactivation Risk with ART Switch: My Interpretation

- Important to obtain HBV serologies, vaccinate if non-immune (including if isolated core Ab+), and consider HBV reactivation risk when switching ART
  - Ideal to vaccinate and document protective surface Ab before switch off TAF or TDF
- If positive core Ab and switching off TAF or TDF:
  - Risk of HBV reactivation is low but not zero
  - Risk lower if also surface Ab positive
  - Risk higher if also switch off FTC or 3TC (such as to DTG/RPV, CAB/RPV)
  - Risk higher with low CD4 count (see Mican et al, AIDS 2021)
  - Monitor ALT, check HBV DNA if ALT rises

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Poll #3

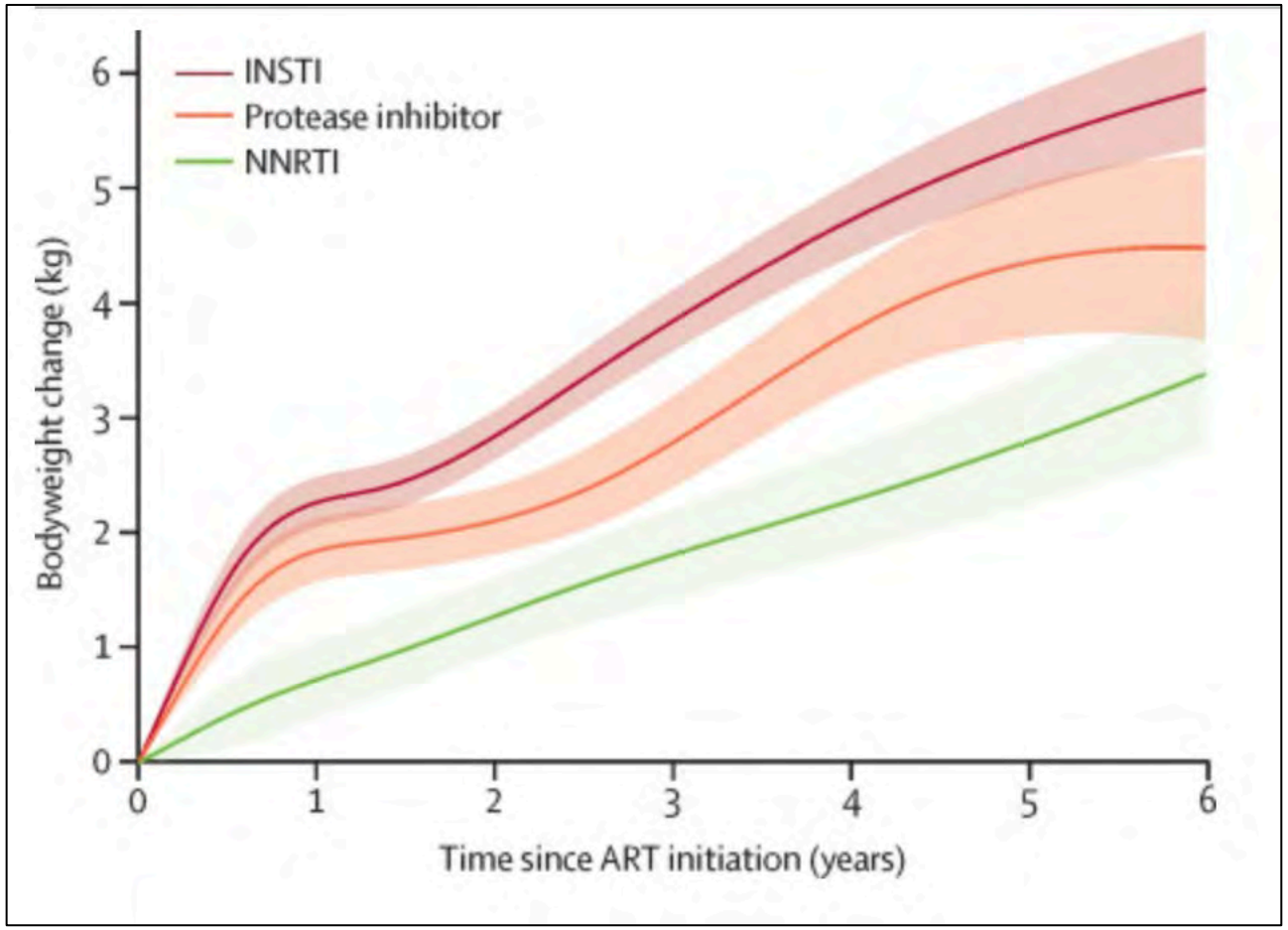
- Fact or fiction: integrase inhibitors *cause* weight gain
  - A) Fact
  - B) Fiction
  - C) We need more data to answer the question

Poll #4

- Fact or fiction: tenofovir alafenamide (TAF) *causes* weight gain
  - A) Fact
  - B) Fiction
  - C) We need more data to answer the question

CASCADE Collaboration: Changes in Bodyweight after ART Initiation Close to Seroconversion

- Retrospective data
- Europe & Canada
- Individuals who started first regimen within 1 year of HIV seroconversion
- More weight gain if: TAF, cisgender woman, from sub-Saharan Africa, baseline BMI <30



Source: Pantazis N, et al. Lancet HIV. 2024 Oct;11(10):e660-e669.
Accompanying editorial: Manne-Goehler J, Siedner MJ. 2024 Oct;11(10):e650-e651.

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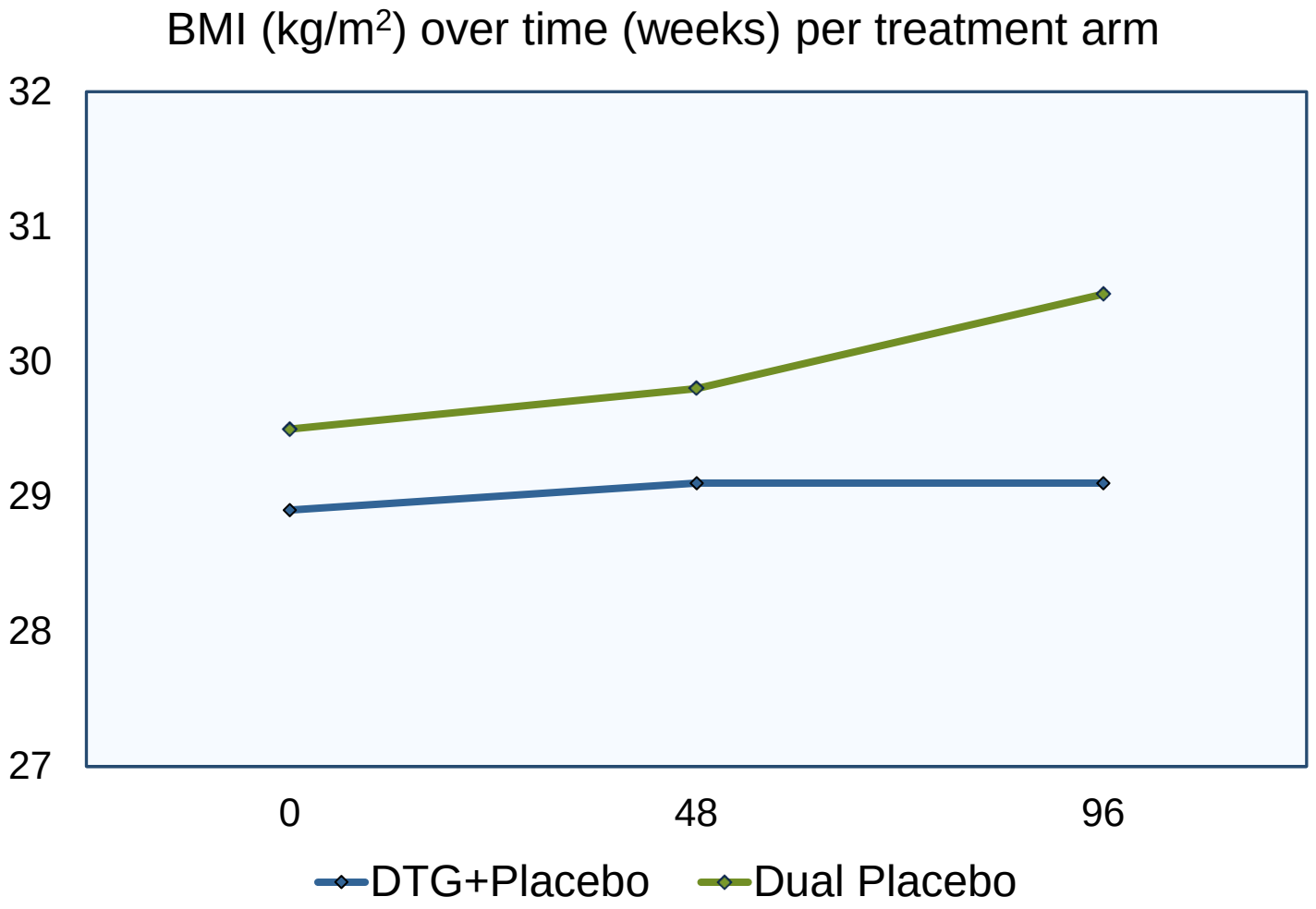
ACTG 5234:
ART Intensification with Dolutegravir vs. Placebo

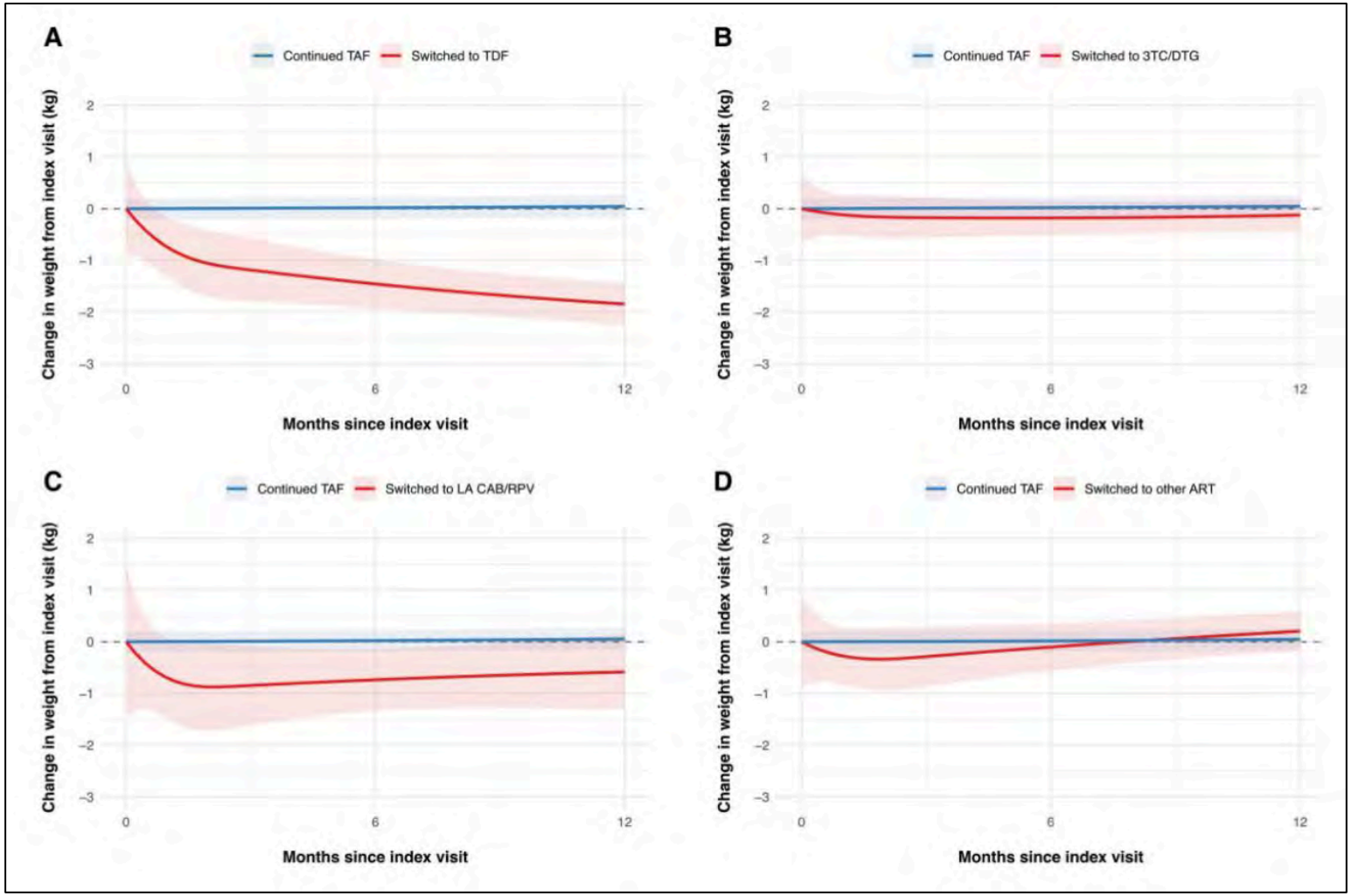
- Randomized, double blind, placebo-controlled, 96-week trial of ART intensification
- N = 191 enrolled; RNA <50
- Randomized to add either:
  - Dolutegravir + maraviroc, or
  - Dolutegravir + placebo, or
  - Dual placebo
- Weight increase did not differ between arms at week 96



Source: Letendre SL, et al. Clin Infect Dis. 2023;77(6):866-874.

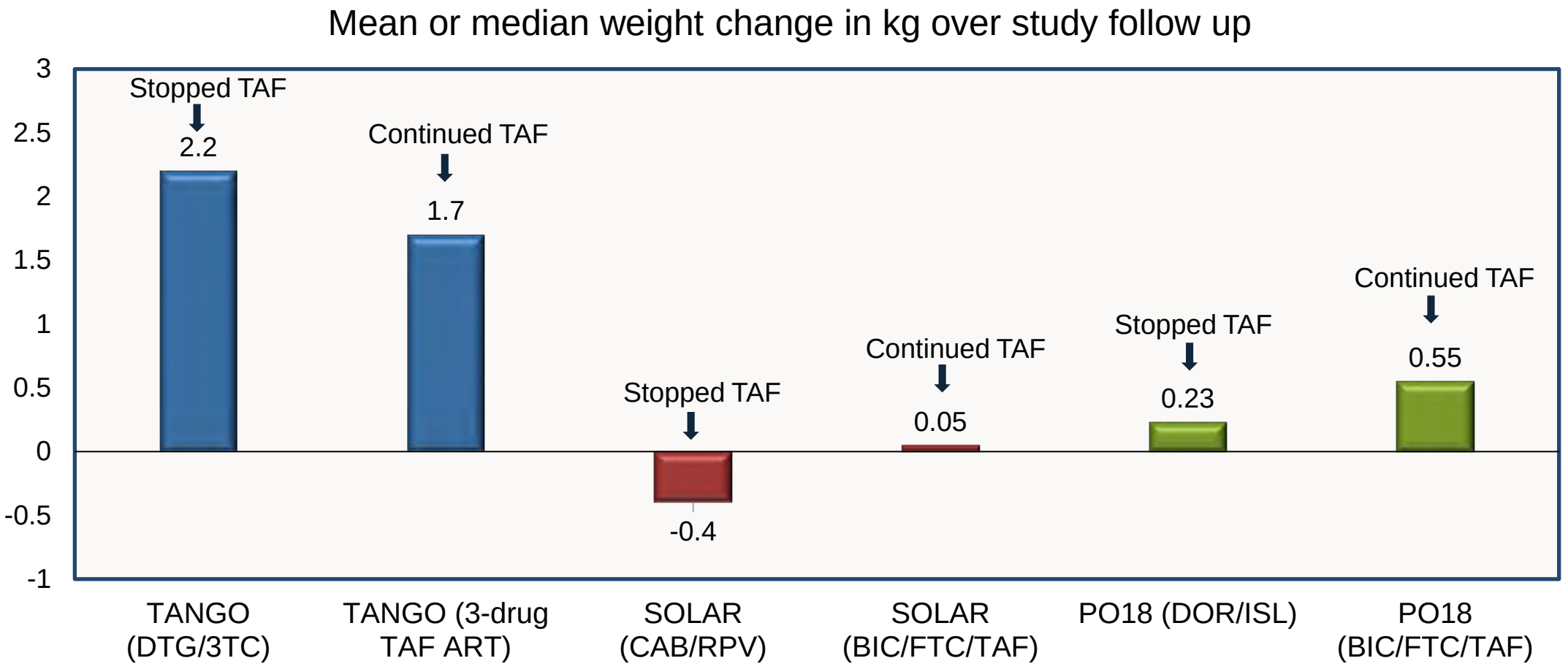
Swiss HIV Cohort Study: What Happens After Stopping TAF?

- 6,555 participants who received >6 months of TAF, then either continued or switched
- Replacing TAF with TDF led to decreased body weight and improved lipids at 1 year
- Weight changes not observed if switched to DTG/3TC or IM CAB/RPV



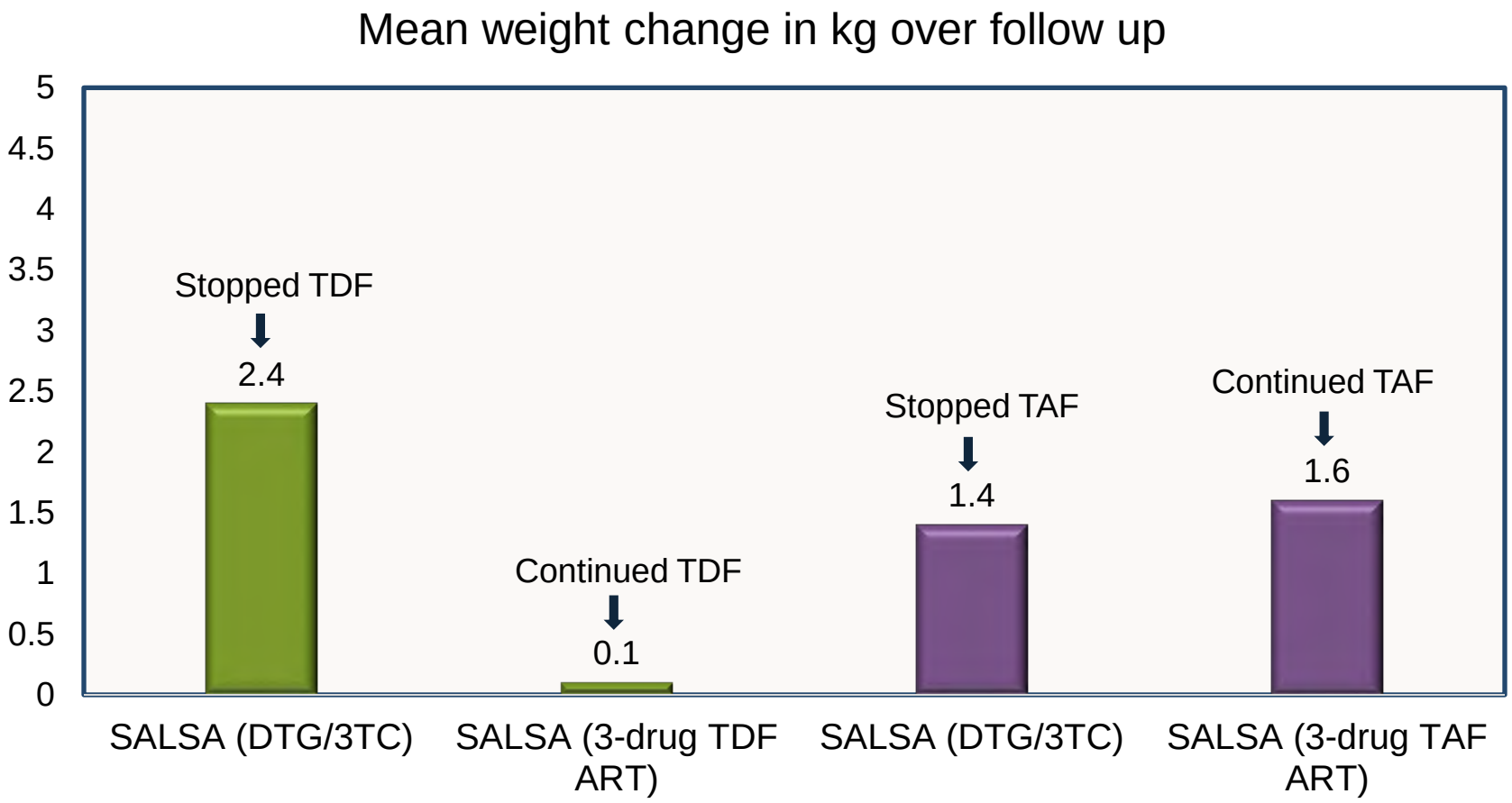
Source: Damas J, et al. Clin Infect Dis. 2024;79(4):990-998.

ART Switch:
Stopping TAF does not lead to weight loss



Recreated from: Wohl DA, et al. Clin Infect Dis. 2024 (Oct 15);79(4):999-1005.

ART Switch:
Stopping TDF leads to weight gain



Recreated from: Wohl DA, et al. Clin Infect Dis. 2024 (Oct 15);79(4):999-1005.

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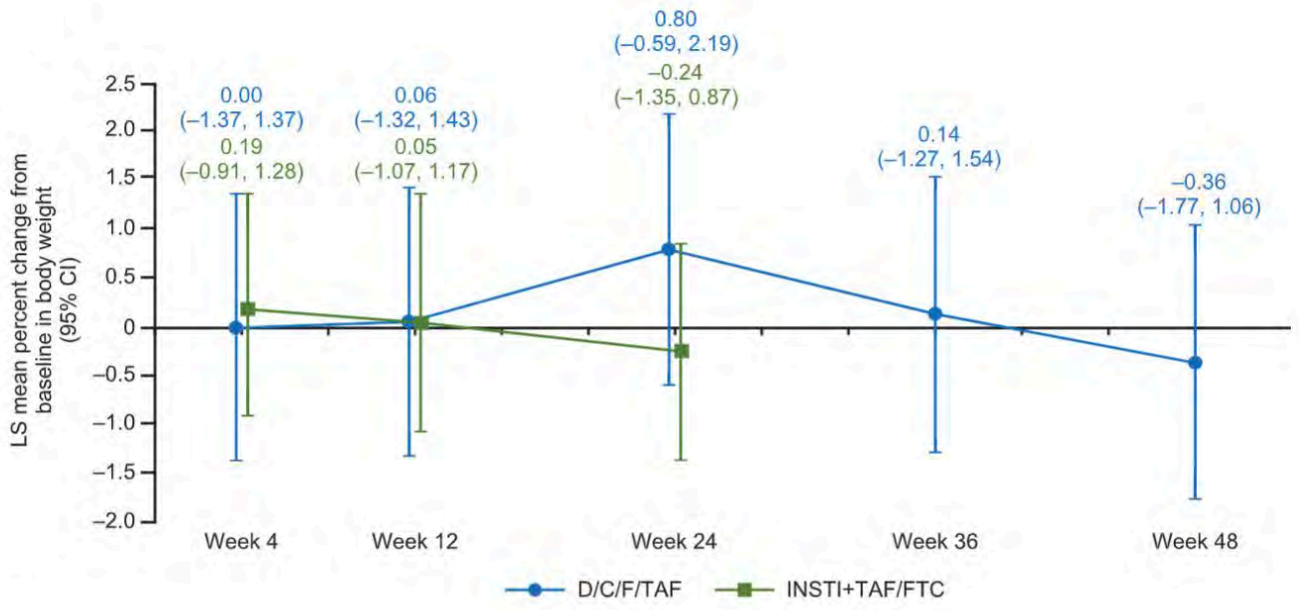
DEFINE Trial:
Switch to Boosted PI After INSTI-Associated Weight Gain

- Prospective, randomized, open-label, active-controlled phase 4 trial
- Virologically suppressed adults who experienced ≥10% increase in body weight on INSTI + TAF/FTC (n = 103)
- Switch to DRV/cobi/TAF/FTC immediately vs.
  switch after 24 weeks
- No difference at 24 weeks; trend towards weight loss after 24 weeks for those in immediate switch group



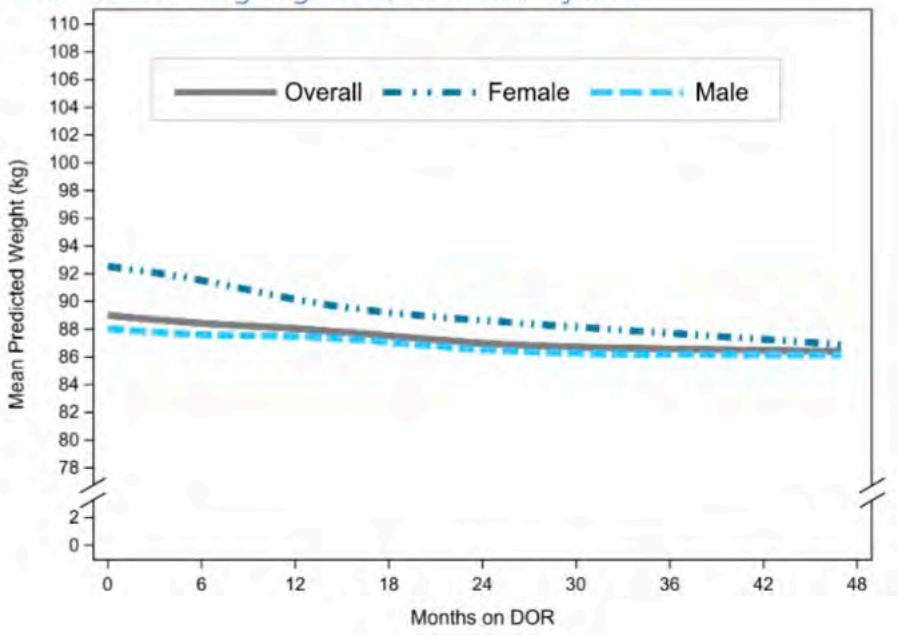
Source: Anderson D, et al. Clin Infect Dis. 2024 Sep 4:ciae449.

Does an INSTI to Doravirine (DOR) Switch Improve Weight? Maybe…

- OPERA Cohort:[1] observational study of individuals who switched to DOR-containing ART (n = 388)
  - 0.80 kg/year weight loss overall
  - 1.67 kg/year weight loss for cisgender women

- Kousari:[2] retrospective chart review of individuals who switched to DOR-containing ART (n = 49)
  - Mostly switched from BIC/TAF/FTC
  - Mean 2.6% weight decrease 1 year following switch

Figure 1. Changes in body weight after switching to a DOR-containing regimen, stratified by sex[a]

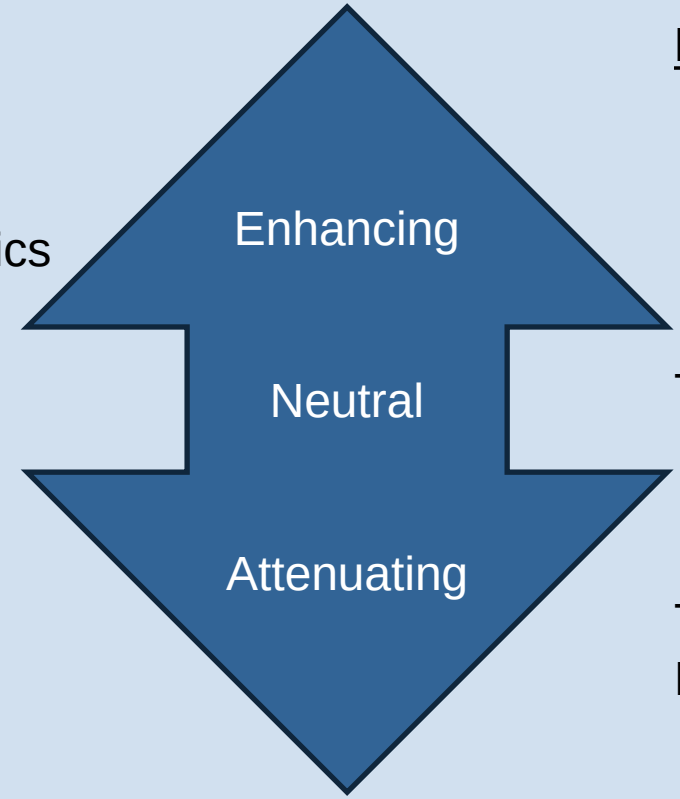


Sources: 1. Mounzer K, et al. CROI 2024. Poster 807. 2. Kousari AE, et al. HIV Res Clin Pract. 2024 Dec;25(1):2339576.

ART-Associated Weight Change: Proposed Model

Return to health weight gain

<u>Individual Factors:</u>
High pre-treatment VL
Low pre-treatment CD4
Underweight at ART initiation
Host genetics/pharmacogenetics
Social determinants of health



<u>HIV Treatment Factors:</u>

TAF, BIC, DTG, CAB

Opportunistic condition
Substance use

TDF
EFV (especially slow metabolizers)

Adapted from: Wohl DA, et al. Clin Infect Dis. 2024 (Oct 15);79(4):999-1005.

TDF Weight Suppression Mechanisms?
TDF vs. TAF & Duodenal Enterocytes: Hypothesis for Differing Effects on Weight

- PWH taking TDF (n=12) or TAF (n=12), 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

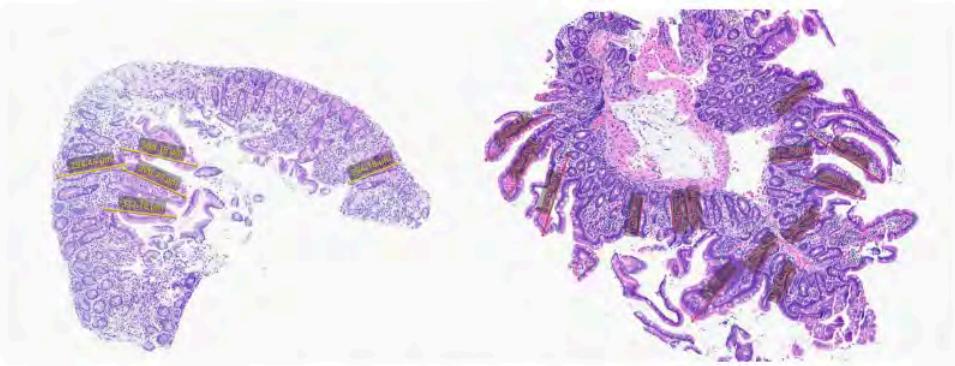


Figure 1. Histological sample of duodenal epithelium of patients receiving TDF (left) or TAF (right).

Source: Kauppinen K, et al. CROI 2024.

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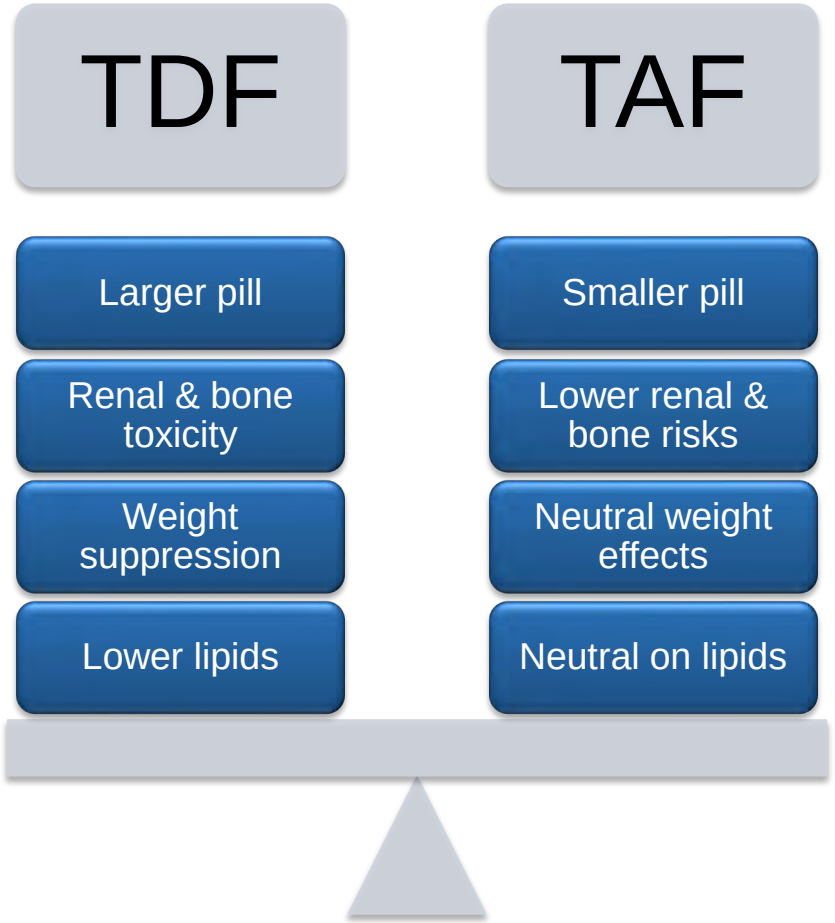
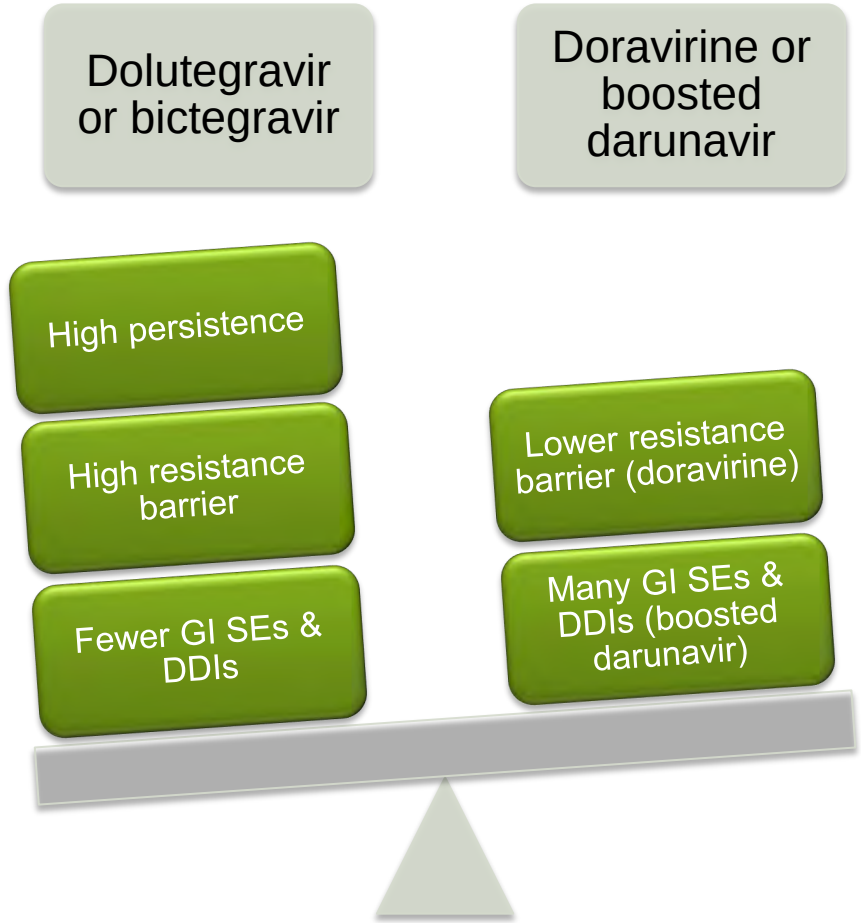
Summary of the ARV-Weight Considerations: My Interpretation





Stopping TAF does not help people lose weight (unless switch to TDF)
Does switching off an INSTI help? Need more data…

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Poll #5

- Fact or fiction: long-acting cabotegravir/rilpivirine is an effective HIV treatment option for individuals with detectable viral loads.
  - A) Fact
  - B) Fiction
  - C) We need more data

Summary of Data for LAI CAB/RPV with Viremia

Study	Setting/Design	Number of PWH	Clinical Outcomes	VF	Notes
ACTG 4939 (LATITUDE)	RCT	Step 2: 146 LAI CAB/RPV vs. 148 oral ART (median VL 42,900)	6 VF on LAI CAB/RPV vs. 28 VF on oral ART (7.2% vs. 25% probability)	2/6 with emergent RAMs	Economic incentives for VS prior to randomization
Ward 86 Clinic	Academic Ryan White Clinic	59 (32% VL >100k)	92% with VL <50 at 48 weeks	6 (5 with emergent RAMs)	VS estimate includes use of alternate ART
Univ. of Mississippi	Academic Ryan White Clinic	12 (mean VL 150k)	100% VL <50 (50% with 1 year follow up)	N/A	Half started with Q8 week dosing
SF Street Medicine	Public Health Program	14 with VL >30	93% VL <30 (mean follow up 11 months)	2 VF with emergent RAMs	2 also started LEN
OPERA Cohort	84 clinics across 18 US states	229 VL >50 (93 VL >200)	94% VL <200 (median f/u 6 months), 75% VL <50	7 (4%) VF	Median follow up only 6 months

Sources: Rana, CROI 2024. Hickey, CID 2024. Brock et al, CID 2023. Mehtani, JAIDS 2024. Hsu R, ID Week 2023.
Table adapted from a slide presented at ID Week 2024 by Dr. Susan Colestar.

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Updated Data from Ward 86: Persons Who Started LAI CAB/RPV with Viremia

- N = 59 (49% CD4 <200, median VL 42,900, IQR 5,272-139,038, 69% VL >10k)
  - 53% housing instability or unhoused, 63% using stimulants
- At 48 weeks, 47 had VL <50 and still receiving LAI CAB/RPV (80%)
  - 5 switched to oral ART
  - 5 virologic failures (3 with new RPV RAMs, 2 with new RPV & CAB RAMs)
    - All 5 had VL >10k when started CAB/RPV and most had CD4 <200
    - 1 changed to LEN + BIC/TAF/FTC, 1 to LEN + CAB, 2 to LEN + CAB/RPV, 1 died
  - 1 lost to follow up
  - 1 added LEN due to low-level viremia (98-614 copies/mL)
- If include those receiving alternate ART at 48 weeks, 54 had VL <50 (92%)

Source: Hickey MD, et al. Clin Infect Dis, Oct 2024.

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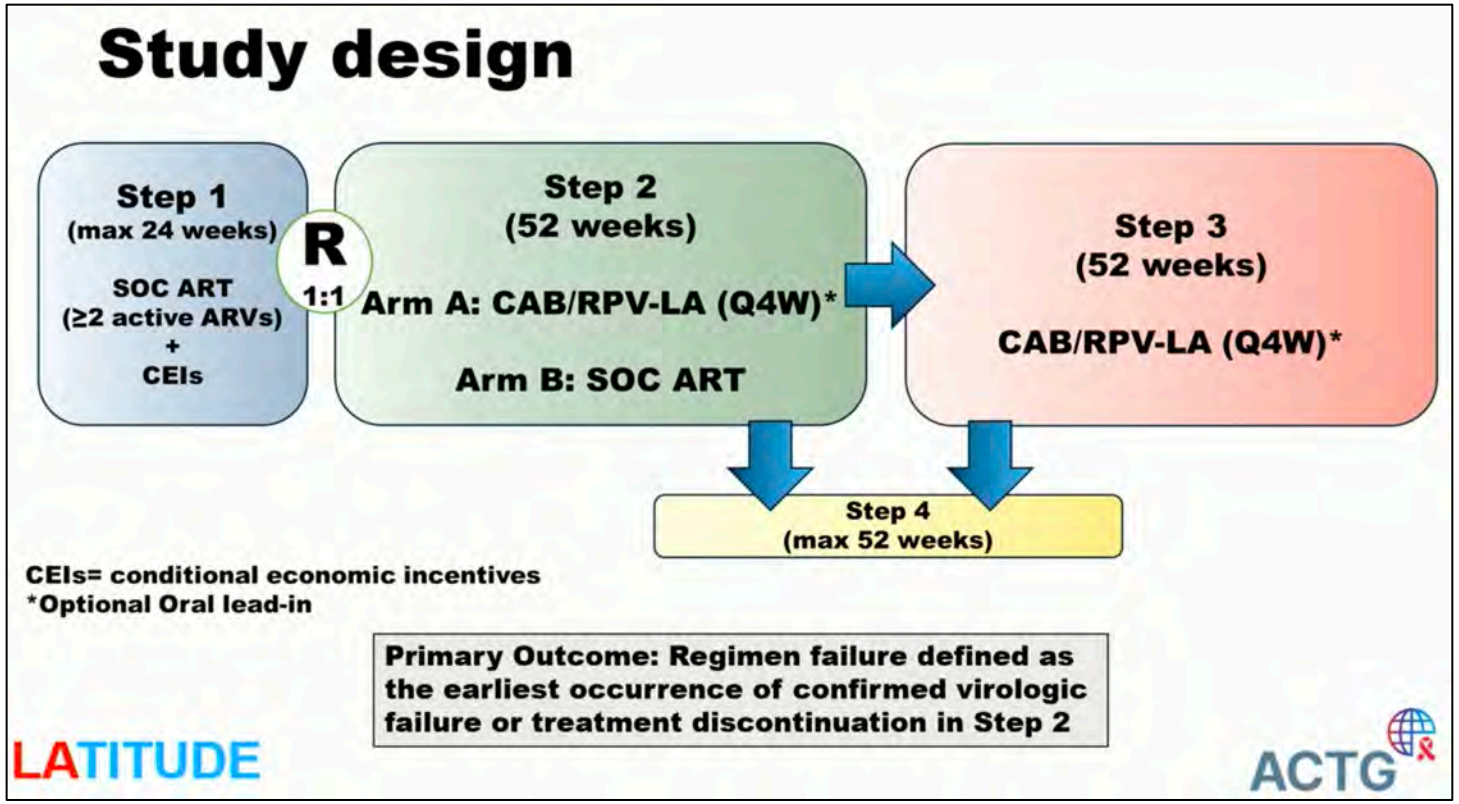
ACTG 5359 (LATITUDE): Long-Acting Therapy to Improve Treatment Success in Daily Life

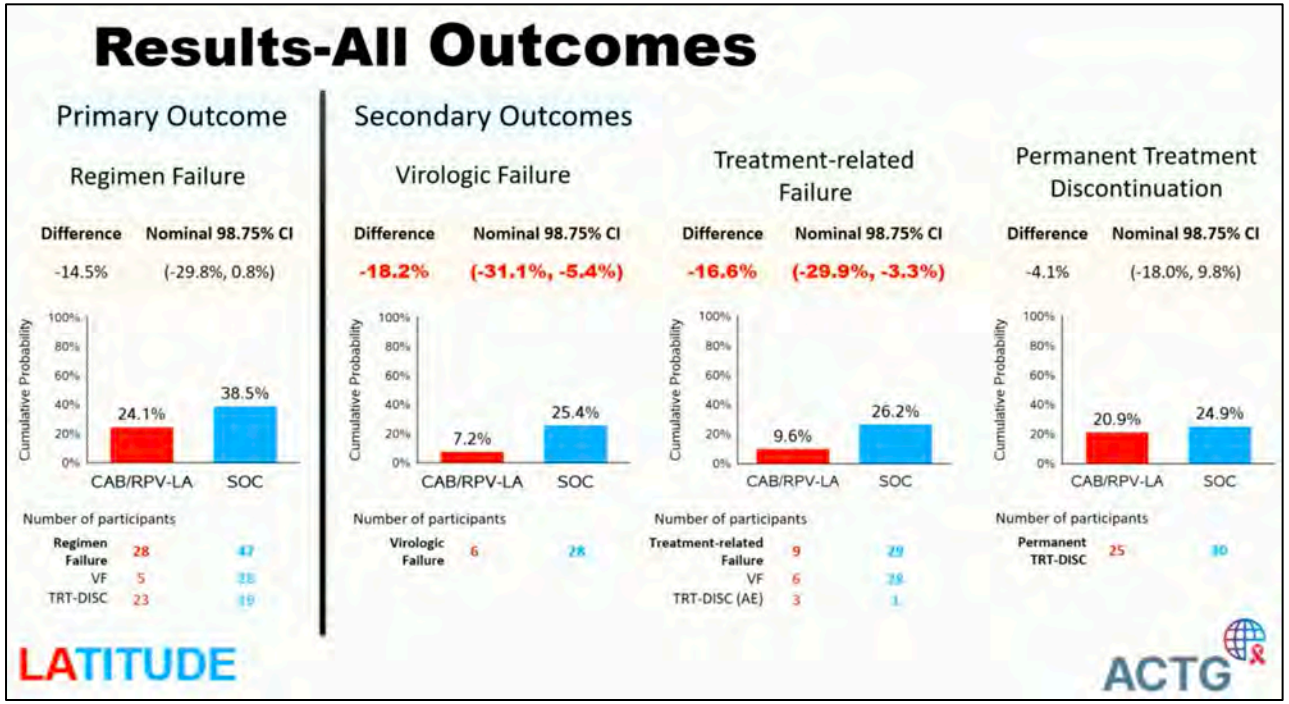
- Phase 3, prospective, randomized, open-label trial
- PWH with barriers to taking oral ART, no hep B, no INSTI or RPV RAMs; no exclusion based on CD4, VL, substance or alcohol use, or housing instability



Source: Rana AI, et al. CROI 2024.

ACTG 5359 (LATITUDE): Long-Acting Therapy to Improve Treatment Success in Daily Life

- N = 434 step 1; 294 step 2 (146 LAI CAB/RPV, vs. 148 SOC oral ART)
- Overall proportion who remained on LAI CAB/RPV with VL suppression: 80%
- VL >200 at randomization visit: 24 (17%) in CAB/RPV arm; 8 with VL >10k
  - 6 VF in CAB/RPV arm vs. 28 with oral ART (2 with emergent RAMs in each arm)



Source: Rana AI, et al. CROI 2024.

New Language in HHS Guidelines

- Some people with HIV cannot reach or maintain viral suppression on oral ART despite intensive adherence support. A complete regimen of LAI CAB/RPV has been used in this population with some success, although long-term efficacy data are limited
- **Panel recommends use on a case-by-case basis in select individuals with persistent virologic failure despite intensive adherence support on oral ART, who have no resistance to CAB or RPV, with shared decision-making (CIII)**
- The Panel notes that people with HIV and their providers must be aware of the significant risk of developing resistance to NNRTIs and INSTIs if virologic failure occurs; such resistance may limit future treatment options and may lead to HIV transmission

Source: HHS Guidelines for ART for Adults & Adolesecents, Updated Sept 12, 2024 (clinicalinfo.hiv.gov)

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More on Long-Acting ART in Setting of Viremia

- Long-acting IM CAB/RPV + subQ LEN in setting of long-term missed oral ART doses + INSTI or NNRTI RAMs
- University of Mississippi Medical Center, n = 9
- Mean baseline VL 36,251; all had RPV RAMs; one had CAB RAMs (N155H, T97A) – low CAB resistance
- Follow up ranged 24 to 36 weeks
- 100% maintained VL <200

Table 1. NNRTI Mutations by Patient

Patient	Y181C	K101E	E138K	G190A	A98G	E138K/Q/G	H221Y	RPV Mutation Score[a]
1	X			X				70
2					X			15
3		X		X		X		75
4		X	X		X			105
5						X		45
6	X			X				70
7							X	15
8	X							45
9		X				X		60

Source: Brock JB, et al. ID Week 2024. Abstract 558.

IM CAB/RPV + SubQ LEN: Case Series & Call for a Trial

- N = 34, 4 institutions
- LEN + CAB, +/-RPV
- 53% detectable viral load
- Reasons for combo:
  - 21 NNRTI resistance
  - 5 minor INSTI resistance
  - 6 high viral load
  - 4 viremia on CAB/RPV
  - 1 BMI >40 kg/m^2
  - 1 IM RPV adverse reaction
- 32/34 suppressed (<75 copies) at median 8 weeks (range 4-16)

Open Forum Infectious Diseases

MAJOR ARTICLE

Case Series of People With HIV on the Long-Acting Combination of Lenacapavir and Cabotegravir: Call for a Trial

Monica Gandhi,[1,6] Lucas Hill,[2] Janet Grochowski,[1] Alexander Nelson,[3] Catherine A. Koss,[1] Francis Mayorga-Munoz,[1] Jon Oskarsson,[1] Mary Shiels,[1] Ann Avery,[4] Laura Bamford,[2] Jillian Baron,[5,6] William R. Short,[5] and Corrilynn O. Hileman[4]

[1]Division of HIV, Infectious Diseases and Global Medicine, University of California, San Francisco (UCSF), San Francisco, California, USA, [2]Division of Infectious Diseases and Global Public Health, University of California San Diego (UCSD), San Diego, California, USA, [3]Department of Specialty Pharmacy, MetroHealth Medical Center, Cleveland, Ohio, USA, [4]Division of Infectious Diseases, MetroHealth Medical Center, and Case Western Reserve University (CWRU), Cleveland, Ohio, USA, and [5]Division of Infectious Diseases, Hospital of the University of Pennsylvania (UPenn), Philadelphia, Pennsylvania, USA

Background. Injectable cabotegravir (CAB)/rilpivirine (RPV) is the only combination long-acting (LA) antiretroviral regimen approved for HIV. RPV may not be effective among individuals with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance, which has >10% prevalence in many countries. Lenacapavir (LEN) is an LA capsid inhibitor given every 6 months, but has not been studied in combination with other LA agents.

Methods. We assembled a case series from 4 US academic medical centers where patients with adherence challenges were prescribed LEN subcutaneously every 26 weeks/CAB (+/− RPV) intramuscularly every 4 or 8 weeks. Descriptive statistics, including viral load (VL) outcomes, were summarized.

Results. All patients (n = 34: 76% male; 24% cis/trans female; 41% Black; 38% Latino/a; median age [range], 47 [28–75] years; 29% and 71% on CAB every 4 or 8 weeks) reported challenges adhering to oral ART. The reasons for using LEN/CAB with or without RPV were documented or suspected NNRTI mutations (n = 21, 59%), integrase mutations (n = 5, 15%), high VL (n = 6, 18%), or continued viremia on CAB/RPV alone (n = 4, 12%). Injection site reactions on LA LEN were reported in 44% (32% grade 1, 12% grade 2). All patients but 2 (32/34; 94%) were suppressed (VL <75 copies/mL) after starting LEN at a median (range) of 8 (4–16) weeks, with 16/34 (47%) suppressed at baseline.

Conclusions. In this case series of 34 patients on LEN/CAB, high rates of virologic suppression (94%) were observed. Reasons for using LEN/CAB included adherence challenges and underlying resistance, mostly to NNRTIs. These data support a clinical trial of LEN/CAB among persons with NNRTI resistance.

Keywords. cabotegravir; HIV; lenacapavir; long-acting antiretroviral therapy; NNRTI resistance.

Source: Gandhi M, et al. Open Forum Infect Dis. 2024 Apr 16;11(4):ofae125.

Poll #6

- Fact or fiction: new oral ARVs that are in the pipeline will make a major difference for people with HIV.
  - A) Fact
  - B) Fiction
  - C) To be determined

Oral Regimens in the ARV Pipeline

Novel Oral ARVs or ARV Combinations in the Development Pipeline		
Medication or Regimen	**Data to Date**	**Notes**
Daily doravirine (NNRTI) + islatravir (NRTTI)	Phase 3 initial ART & switch data published, but islatravir 0.75 mg affected CD4 & lymphocytes	New phase 3 study with lower islatravir dose (0.25 mg daily) ongoing, comparing to continued BIC/TAF/FTC or other ART
Daily bictegravir (INSTI) + lenacapavir (capsid inhibitor)	ARTISTRY-1: week 48 results of phase 2/3 study of switching from complex ART presented at IAS 2024	Proceeding to phase 3 switch studies from BIC/TAF/FTC or from other ART
Weekly lenacapavir + islatravir	Week 48 results from phase 2 study presented at ID Week 2024	No issue with CD4 or lymphocytes with weekly islatravir dose; phase 3 switch studies starting soon
Weekly GS-1720 (novel INSTI) + GS-4182 (lenacapavir pro-drug)	WONDERS-1: week 48 results of phase 2/3 switch study, compared to continued BIC/TAF/FTC	Phase 2/3 study launched in August 2024

Source: clinicaltrials.gov

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Two New Oral ARVs that May Change the Treatment Landscape

New Oral ARVs with Weekly Dosing	
GS-1720	**GS-4182**
Novel, oral, weekly INSTI	Novel, oral, weekly LEN prodrug
Potent, high in vitro barrier to resistance (similar to BIC, DTG), activity against strains with INSTI resistance, median ½ life 9.3 days	Greater intestinal absorption than oral LEN, improved systemic exposure, smaller tablet size, median ½ life 11 days
Favorable safety profile, well tolerated in phase 1 studies	Favorable safety profile, well tolerated in phase 1
Weekly oral combination now in phase 2/3 switch study	

Source: slide adapted from an ID Week 2024 presentation by Dr. Susan Koletar

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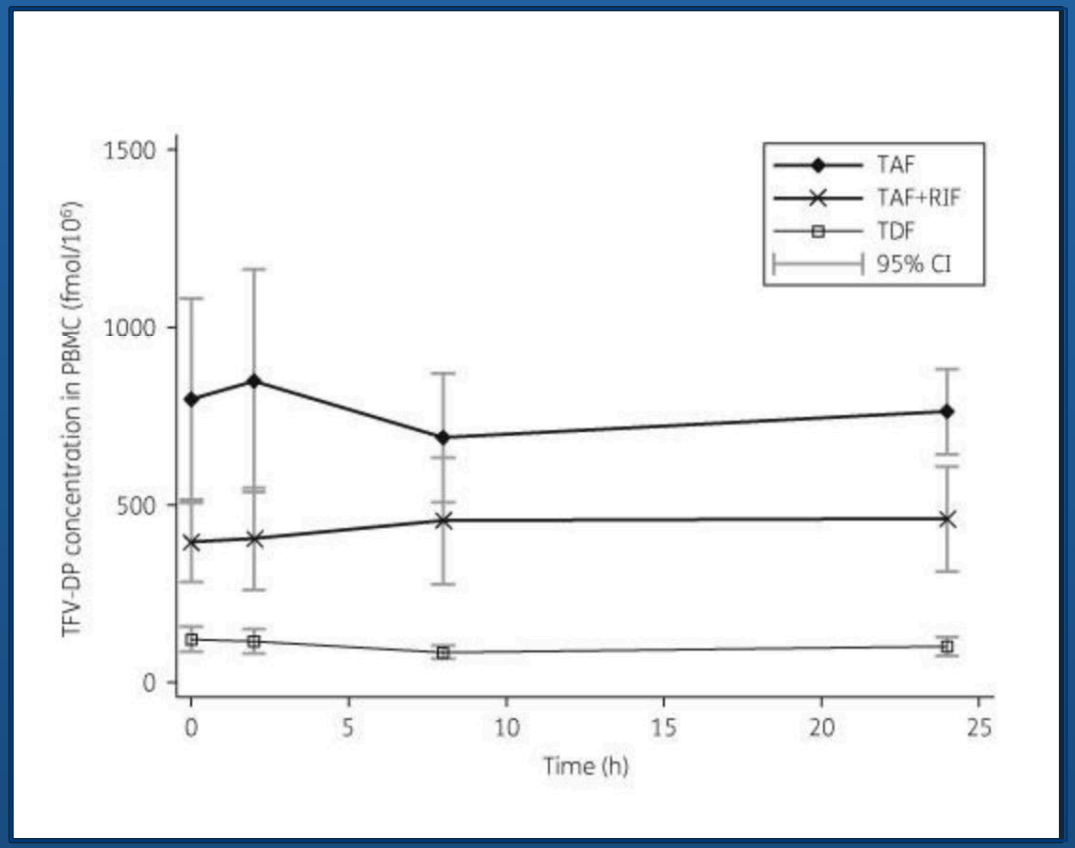
Poll #7

- Fact or fiction: rifamycins (e.g., rifampin, rifapentine) should always be avoided for a person taking TAF.
  - A) Fact
  - B) Fiction
  - C) We need more data to answer the question

Data for TAF-Rifamycin PBMC Levels

- Volunteers without HIV took TAF/FTC daily x 28 days, then TAF/FTC + rifampin daily x 28 days, then TDF daily x 28 days
- Plasma levels of tenofovir-DP decreased with rifampin
- *However*, concentrations in PBMCs remained higher than with TDF



Source: Cerrone M, et al. J Antimicrob Chemother. 2019;74(6):1670-1678.

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Latent Tuberculosis Treatment-Antiretroviral Options
Key Update: Dolutegravir BID Option with 1HP

PREFERRED Latent Tuberculosis Treatment-Antiretroviral Options (Per OI Guidelines)

Regimen	TB Med(s)	Duration, Dosing	Anchor Drug Options	NRTI Options
3HP	INH & rifaPentine	3 months, weekly	EFV 600 mg daily RAL 400 mg twice-daily DTG 50 mg daily	TDF/FTC TAF/FTC* ABC/3TC
3HR	INH & Rifampin	3 months, daily	EFV 600 mg daily RAL 800 mg twice-daily DTG 50 mg twice-daily	TDF/FTC TAF/FTC* ABC/3TC

*Rifapentine may lower concentrations of TAF; if used, monitor viral load carefully. TAF-rifampin: use with caution. If coadministered, monitor virologic response. Intracellular TFV-DP levels are higher when TAF is coadministered with rifampin than when TDF is administered alone, but clinical outcomes have not been studied.

HHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Updated Sept. 12, 2024.

Latent Tuberculosis Treatment-Antiretroviral Options
Key Update: Dolutegravir BID Option with 1HP

ALTERNATIVE Latent Tuberculosis Treatment-Antiretroviral Options (Per OI Guidelines)				
Regimen	**TB Med(s)**	**Duration, Dosing**	**Anchor Drug Options**	**NRTI Options**
9H or 6H	INH	9 or 6 months, daily	No change to ART	No change to ART
4R	Rifampin	4 months, daily	EFV 600 mg daily RAL 800 mg twice-daily DTG 50 mg twice-daily	TDF/FTC TAF/FTC* ABC/3TC
1HP	INH & rifaPentine	1 month, daily	EFV 600 mg daily DTG 50 mg twice-daily	TDF/FTC TAF/FTC* ABC/3TC

*Rifapentine may lower concentrations of TAF; if used, monitor viral load carefully. TAF-rifampin: use with caution. If coadministered, monitor virologic response. Intracellular TFV-DP levels are higher when TAF is coadministered with rifampin than when TDF is administered alone, but clinical outcomes have not been studied.

HHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Updated Sept. 12, 2024.

Poll #8

- Fact or fiction: emtricitabine (FTC) and lamivudine (3TC) require dose reduction if the estimated GFR (or creatinine clearance) is 30-49 mL/min
  - A) Fact
  - B) Fiction
  - C) We need more data to answer the question

Poll #9

- Fact or fiction: emtricitabine (FTC) and lamivudine (3TC) require dose reduction if the estimated GFR (or creatinine clearance) is <u>≤30 mL/min</u>
  - A) Fact
  - B) Fiction
  - C) We need more data to answer the question

“To Dose Adjust or Not to Dose Adjust: Lamivudine Dose in Kidney Impairment” (Data from OPERA Cohort)

Prevalence of Outcomes when eGFR Between 30 and 49 mL/min			
Outcome (# events/n)	**3TC 150 mg daily**	**3TC 300 mg daily**	**aIRR (95% CI)**
Composite outcome 1: severe lab abnormalities or specific diagnoses*	5/67	29/312	1.51 (0.59,3.92)
Composite outcome 2: moderate/severe lab abnormalities, specific diagnoses,* or GI symptoms**	6/24	26/85	3.07 (1.12,8.40)

*Diagnosis: lactic acidosis, paresthesias, peripheral neuropathy, pancreatitis, rhabdomyolysis, anemia, neutropenia, thrombocytopenia
**Hyperlactatemia, nausea, vomiting, abdominal pain

Source: Mounzer K, et al. AIDS. 2021;35(8):1201-1208.

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Which ART controversies did I miss?

Questions or comments?

bwood2@uw.edu

Key Revisions
What to Start: Initial Antiretroviral Regimens for People with HIV

Key Revision #1: Dolutegravir/abacavir/lamivudine moved from *Recommended Initial Regimens for Most People with HIV* to *Other Initial Antiretroviral Regimens for Certain Clinical Scenarios*

- Why? Need for HLA-B*5701 testing, increased risk of cardiovascular events, availability of other options

HHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Updated Sept. 12, 2024. (http://www.clinicalinfo.hiv.gov)

Key Revisions
What to Start: Initial Antiretroviral Regimens for People with HIV

Key Revision #2: Several regimens no longer recommended as initial therapy due to higher pill burden, more adverse effects, or lower barrier to resistance

- Includes: elvitegravir/cobicistat and raltegravir-based regimens, boosted atazanavir-based regimens, efavirenz-based regimens, rilpivirine/TDF/FTC

HHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Updated Sept. 12, 2024. (http://www.clinicalinfo.hiv.gov)

HHS Recommended Initial Regimens for Most People with HIV
For People Who Have a History of Using Cabotegravir PrEP

Boosted PI + 2 NRTIs	Abbreviation
Boosted darunavir + (tenofovir alafenamide or tenofovir DF) + (emtricitabine or lamivudine) (pending integrase genotype resistance result)	(DRV/COBI or DRV + RTV) + (TAF or TDF) + (FTC or 3TC)

HHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Updated Sept. 12, 2024. (http://www.clinicalinfo.hiv.gov)

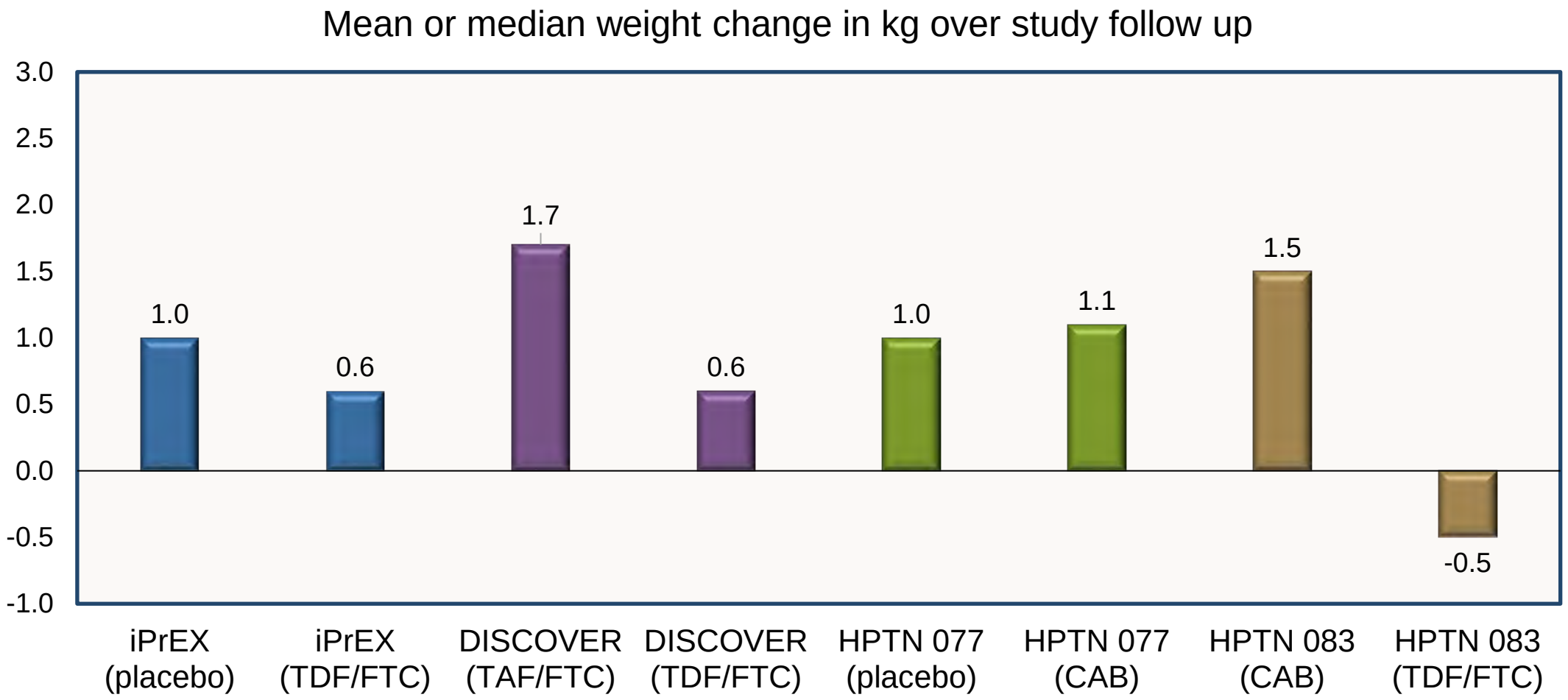
HHS Recommended Initial Regimens in Certain Clinical Situations
For People Who Do Not Have a History of Using Cabotegravir PrEP

INSTI + 2 NRTIs
Dolutegravir/ABC/3TC (if HLA-B*5701 negative and no hepatitis B coinfection)
Boosted PI + 2 NRTIs
(Darunavir/cobicistat or darunavir + ritonavir) + (TAF or TDF + FTC or 3TC) or + (ABC/3TC) (for ABC/3TC, only if HLA-B*5701 negative and no hepatitis B coinfection)
NNRTI + 2 NRTIs
Doravirine/TDF/3TC or doravirine + TAF/FTC
Rilpivirine/TAF/FTC (only if CD4 count >200 cells/mm^3 and HIV RNA <100,000 copies/mL)
Abbreviations: *ABC = abacavir, 3TC = lamivudine, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, FTC = emtricitabine*

HHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Updated Sept. 12, 2024. (http://www.clinicalinfo.hiv.gov)

PrEP Trials

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



Recreated from: Wohl DA, et al. CID 2024. DOI: 10.1093/cid/ciae191

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Summary of the ART-Weight Issue: My Interpretation

- Difference between weight gain when compare INSTIs to other classes? **Yes**
  - Do INSTIs directly *cause* weight gain? **Probably not**
  - What's the biggest issue? **Switch from EFV to DTG or BIC**
- 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**

STOPPING TAF DOES NOT HELP PEOPLE LOSE WEIGHT!
DOES SWITCHING OFF AN INSTI HELP? NEED MORE DATA

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Other New ARVs in the Pipeline

- VH4524184 (VH184):
  - 3rd gen INSTI, potency similar to DTG or BIC but distinct resistance profile
  - Phase 1, oral daily dosing in persons without HIV presented at IAS 2024
- MK-8527:
  - Novel oral NRTTI with few DDIs, potential for weekly or monthly dosing
  - Two phase 1, single dose, monotherapy studies completed in PWH; PrEP potential
- Ultra-long-acting injectable CAB (CAB-ULA):
  - Phase 1 data presented at CROI 2024; potential for every 4-month dosing
  - IM or subQ with rHuPH20 (recombinant human hyaluronidase)

Sources: Rogg L, et al. IAS 2024. Carstens R, et al. CROI 2024. Han H, et al. CROI 2024.

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LAI CAB/RPV in Setting of Viremia: UCSD Experience

- Retrospective, PWH with adherence challenges who started LAI CAB/RPV
- Demographics: 41% history of any IDU; 33% active meth use; 65% Medicaid
  - 7 participants VL >10,000 (all received an additional ARV with LAI CAB/RPV)

	24-Week (N = 63)	48-Week (N=54)
Years since HIV diagnosis median (IQR)	14.2	13.5 (8.7, 19.5)
Median CD4 at LAI-ART initiation (IQR) cells/μL	488 (306,728)	469 (334, 699)
VL ≥ 50 at LAI-ART initiation N (%)	27 (42.9)	24 (44.4)
VL > 10,000 at LAI-ART initiation N (%)	7 (11.1)	7 (13.0)

	24-Week (N = 63)	48-Week (N=54)
Oral lead in CAB/RPV, N (%)	9 (14.3)	8 (14.9)
CAB/RPV dosing regimen, N (%) Q2month only Q1month then Q2month	 60 (95.2) 3 (4.8)	 51 (94.4) 3 (5.6)
Number of participants with any late injection, N (%)	10 (15.9)	8 (14.8)
Other ART at LAI-initiation TAF/FTC Lenacapavir (sq injection) Fostemsavir	 3 (4.8) 9 (14.3) 1 (1.6)	 2 (3.7) 8 (14.8) 1 (1.9)

Source: Hastie, et al. ID Week 2024. Abstract 154.

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LAI CAB/RPV in Setting of Viremia: UCSD Experience

- 48-week outcomes: 10 individuals (18.5%) stopped
  - 5 virologic failure, 5 other reasons
  - 44 remained on LAI CAB/RPV and had VL suppression (81.5%)
- Similar outcomes to interim LATITUDE study results
- *Factors associated with virologic failure: low CD4, active substance use

Source: Hastie, et al. ID Week 2024. Abstract 154.

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