AETC AIDS Education & Training Center Program Mountain West

2020 HIV Treatment Update: What's New & What's Coming Soon?

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November 17, 2020

Thank you Dr. Jehan Budak, Dr. David Hachey, and Dr. David Spach for slide contributions.

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Disclosures

No financial disclosures or conflicts of interest.

Will be discussing investigational antiretrovirals.

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Outline

- Initial ART recommendations and ARV safety during conception and pregnancy
- Optimizing ART, particularly considering weight change, metabolic syndrome, and cardiovascular risk
- Newest antiretrovirals for salvage therapy

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Resources

- National HIV Curriculum: http://hiv.uw.edu
- HHS Guidelines: https://clinicalinfo.hiv.gov/en/guidelines
- IAS-USA Guidelines: https://jamanetwork.com/journals/jama/fullarticle/2771873

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Case: Starting ART

- 30-year-old Latina woman referred after new HIV diagnosis
- CD4 count 447 cells/mm^3; HIV RNA 13,700 copies/mL; genotype pending
- Presents with her male partner; they use condoms sometimes; his HIV screen is negative
- She prefers not to start other contraception; hopes to have a baby within the next couple of years
- *Which ART regimen would you recommend for her?*

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POLL

Which ART regimen would you recommend for her?
(insurance will not cover bictegravir/FTC/TAF)

A) Dolutegravir + FTC/TAF

B) Dolutegravir + FTC/TDF

C) Dolutegravir/ABC/3TC (assuming HLA-B5701 neg)

D) Dolutegravir/3TC

E) Raltegravir + FTC/TAF

F) Raltegravir + FTC/TDF

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HIV Treatment as Prevention (TasP) and "U=U"
Integration into Clinical Practice

- Key message: consistent viral load <200 copies/mL <u>prevents</u> transmission of HIV to sexual partners
  - Inform persons with HIV about TasP/U=U, importance of ART adherence, and risk of transmission during periods off ART
  - Persons starting ART should use another form of prevention for ≥6 months and until HIV RNA <200 copies/mL

ART for Treatment-Naïve Individuals
When to Start

- **Start immediately or as soon as possible in order to:**
  - Increase the uptake of ART
  - Decrease time to virologic suppression
  - Reduce the risk of HIV transmission
  - Improve the rate of virologic suppression

- Panel supports same-day start “when possible”

- Emphasis on immediate ART for acute or early infection

ART for Treatment-Naïve Individuals
What to Start

DHHS (Dec. 2019)[1] Recommended for Most People With HIV	IAS-USA (Oct. 2020)[2] Recommended for Most People with HIV
Bictegravir/FTC/TAF	Bictegravir/FTC/TAF
Dolutegravir/ABC/3TC (if B*5701 neg) Dolutegravir + FTC/TAF or FTC/TDF	Dolutegravir/ABC/3TC (if B*5701 neg) Dolutegravir + FTC/TAF Dolutegravir + FTC/TDF
Raltegravir + FTC/TAF or FTC/TDF	
Dolutegravir/3TC (if HIV RNA <500k, no HBV, have baseline genotype results)	Dolutegravir/3TC (not for rapid start; option if HIV RNA <500k, no HBV, CD4 >200)

Abbreviations:
ABC – abacavir, 3TC – lamivudine, FTC – emtricitabine, TDF – tenofovir disoproxil fumarate, TAF – tenofovir alafenamide

Sources:
1. DHHS: clinicalinfo.hiv.gov/en/guidelines.
2. IAS-USA: https://jamanetwork.com/journals/jama/fullarticle/2771873

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How do you choose TDF vs TAF for adults? (My opinions mixed in here)

Strong indications for TAF

- Creatinine clearance <60 mL/min
- Osteopenia or osteoporosis

Moderate indications for TAF

- Risk factors for renal disease or osteopenia/osteoporosis
- Age >50 (due to higher risk of TDF-induced renal toxicity)
- Difficulty swallowing pills

Moderate indications for TDF

- Post-exposure prophylaxis (PEP)
- Trying to conceive or first trimester of pregnancy

Weak indications for TDF

- Elevated BMI, metabolic syndrome, dyslipidemia

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Dolutegravir & Neural Tube Defects: Update

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Tsepamo Study
Background

- Birth-outcomes observational surveillance study in Botswana
- Started in 2014 to evaluate neural tube defects (NTDs) associated with ART exposure at conception
- In infants born to women who started dolutegravir (DTG) prior to conception, increased prevalence of NTDs observed
  - May 2018: 4/426 (rate: DTG **0.94% vs 0.12%** non-DTG ART)[1]
  - April 2019: 5/1683 (rate: DTG **0.30%**)[2]

1 - Zash. NEJM. 2018; 79:979. 2 - Zash. IAS 2019. Abstr MOAX0105LB

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Tsepamo Study
Latest Update: Data Through April 2020

NTD Outcome by Analysis, % (95% CI)	Conception			Pregnancy	HIV Negative
	DTG	Non-DTG	EFV	DTG	
Results as of March 2019	n =1683	n = 14,792	n = 7959	n = 3840	n = 89,372
NTD prevalence	0.30 (0.13-0.69)	0.10 (0.06-0.17)	0.04 (0.01-0.11)	0.03 (0-0.15)	0.08 (0.06-0.10)
Prevalence difference	Ref	0.20 (0.01-0.59)	0.26 (0.07-0.66)	0.27 (0.06-0.67)	0.22 (0.05-0.62)
Results as of April 2020	n = 3591	n = 19,361	n = 10,958	n = 4581	n = 119,630
NTD prevalence	**0.19** (0.09-0.40)	**0.11** (0.07-0.17)	0.07 (0.03-0.17)	0.04 (0.01-0.16)	0.07 (0.06-0.09)
Prevalence difference	Ref	0.09 (-0.03-0.30)	0.12 (0-0.32)	0.15 (0-0.36)	0.12 (0.01-0.32)

Zash R et al. AIDS 2020. Abstract OAXLB0102.

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Tsepamo Study
Summary

Take-Home Points: reassuring that DTG use at conception not higher risk than other ARV's; engage in shared-decision making and prioritize folate supplementation pre-conception

Zash R et al. AIDS 2020. Abstract OAXLB0102.

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Perinatal Guidelines
Last updated April 2020

- **Dolutegravir (DTG):**
  - Preferred for pregnant women, irrespective of trimester
  - Alternative for women who are trying to conceive*

- **Tenofovir alafenamide (TAF)**:
  - Insufficient data**

*Not yet updated to incorporate most recent Tsepamo data

**Not yet updated to reflect IMPAACT 2010 (VESTED) data: TAF safe and potentially preferred over TDF when started after 14 weeks gestation (*Chinula L et al, CROI 2020*)

Case: Switching ART

- 52-year-old Black/African American man
- Diagnosed with HIV in 2010; started efavirenz/TDF/FTC
- Switched to dolutegravir + FTC/TAF in 2016
- Robust CD4 count; routinely suppressed viral loads
- Comorbidities: depression, chronic pain, HTN, type 2 DM (A1C's 7-9), OSA, BMI 34.5, GERD (takes famotidine)
- Excellent adherence; wishes to minimize pill burden
- *Would you recommend an ART change to reduce long-term cardiac or metabolic risks related to weight changes?*

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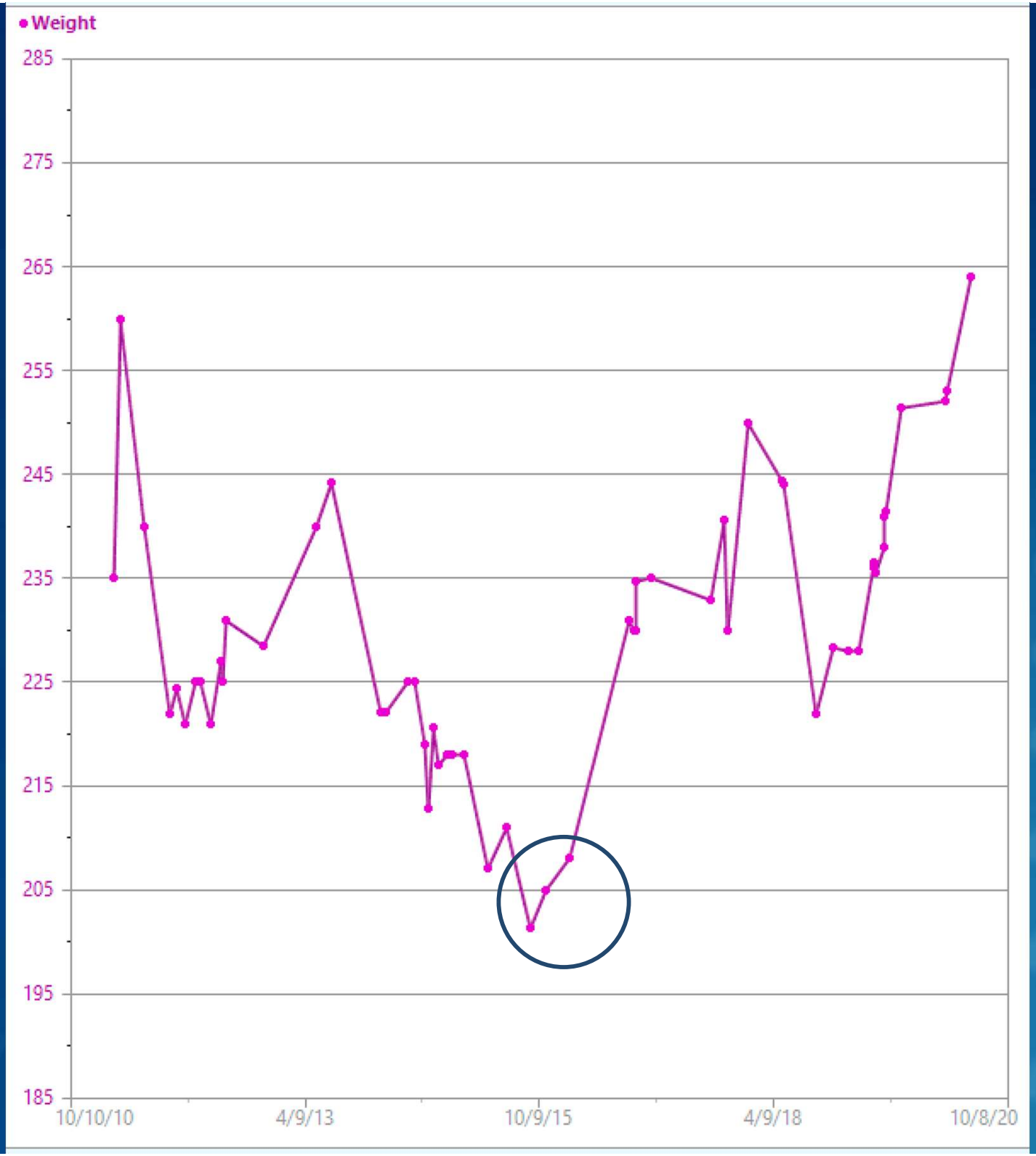
Weight
285
275
265
255
245
235
225
215
205
195
185
10/10/10
4/9/13
10/9/15
4/9/18
10/8/20

POLL

Would you recommend an ART change? (insurance will not cover bictegravir/FTC/TAF, dolutegravir/3TC, or dolutegravir/rilpivirine)

A) Yes, to raltegravir-HD + FTC/TAF

B) Yes, to dolutegravir + rilpivirine

C) Yes, to dolutegravir + 3TC

D) Yes, to dolutegravir + doravirine

E) Yes, to doravirine/3TC/TDF

F) No, hold course, wait for long-acting options

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New Language on Weight Gain with ART
IAS-USA Guidelines

- Initiation of ART often leads to weight gain; can lead to obesity among individuals with HIV who start treatment with a normal or elevated baseline weight
- Risk factors for excess weight gain: low CD4, high viral load, Black race, female sex, INSTI (especially DTG/BIC), TAF
- *Clinical consequences and mechanisms unknown and data insufficient to change recommendations for initial ART; PWH should be counseled about potential for weight gain*

IAS-USA Guidelines: https://jamanetwork.com/journals/jama/fullarticle/2771873

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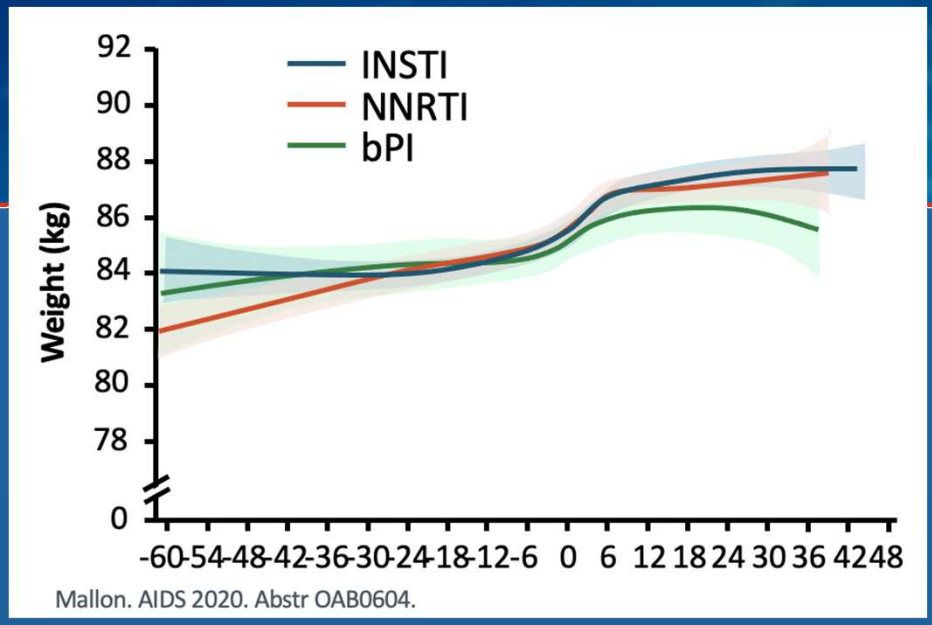
Weight Gain with ART
My Interpretation



- Most PWH who start ART gain some weight over the subsequent 12-24 months; median 2.0 kg [IQR -0.9 to 5.9][1]
- Small proportion gain excess weight, which likely increases risk of diabetes and metabolic syndrome; predictors include HIV/ART factors and social determinants of health
- Some PWH gain weight after switching to TAF or to an INSTI; mean with TDF to TAF: 2-3 kg (in first 9 months)[2]

1. Sax et al. CID 2019. 2. Mallon P et al. OPERA Cohort. AIDS 2020 Conference.

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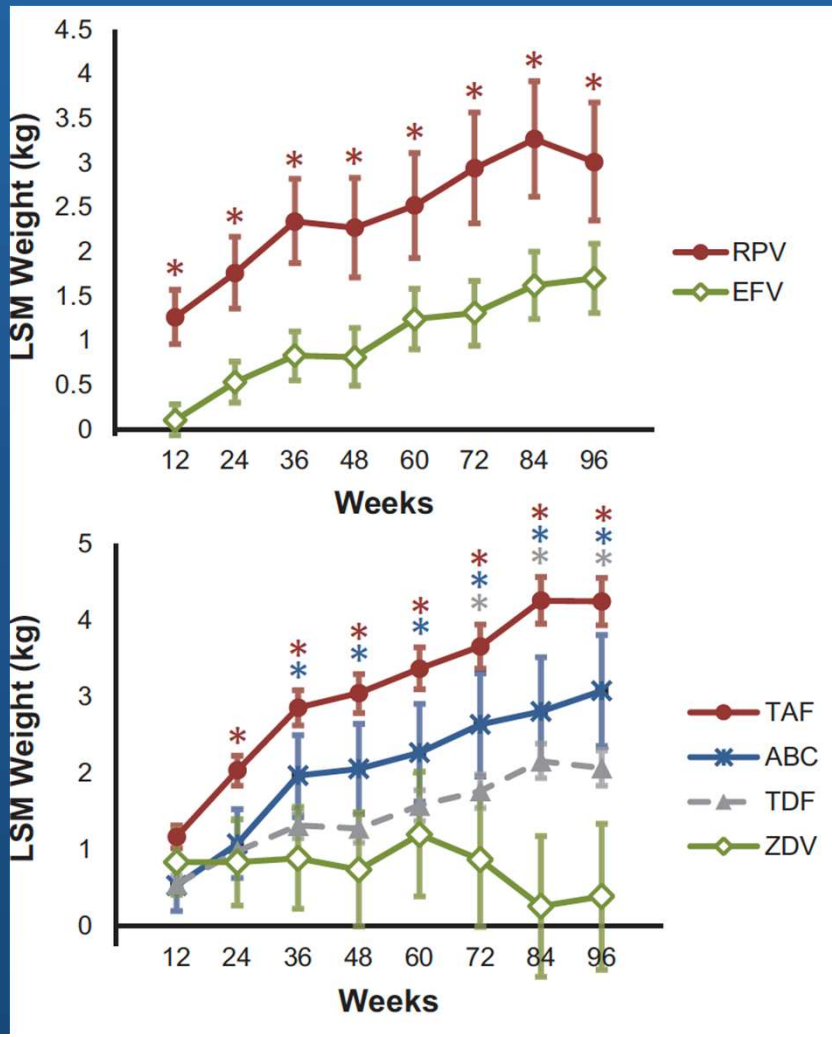
Weight Gain with ART
My Interpretation

- *Mechanism: likely secondary to previously unrecognized appetite suppression with TDF and older anchor drugs*

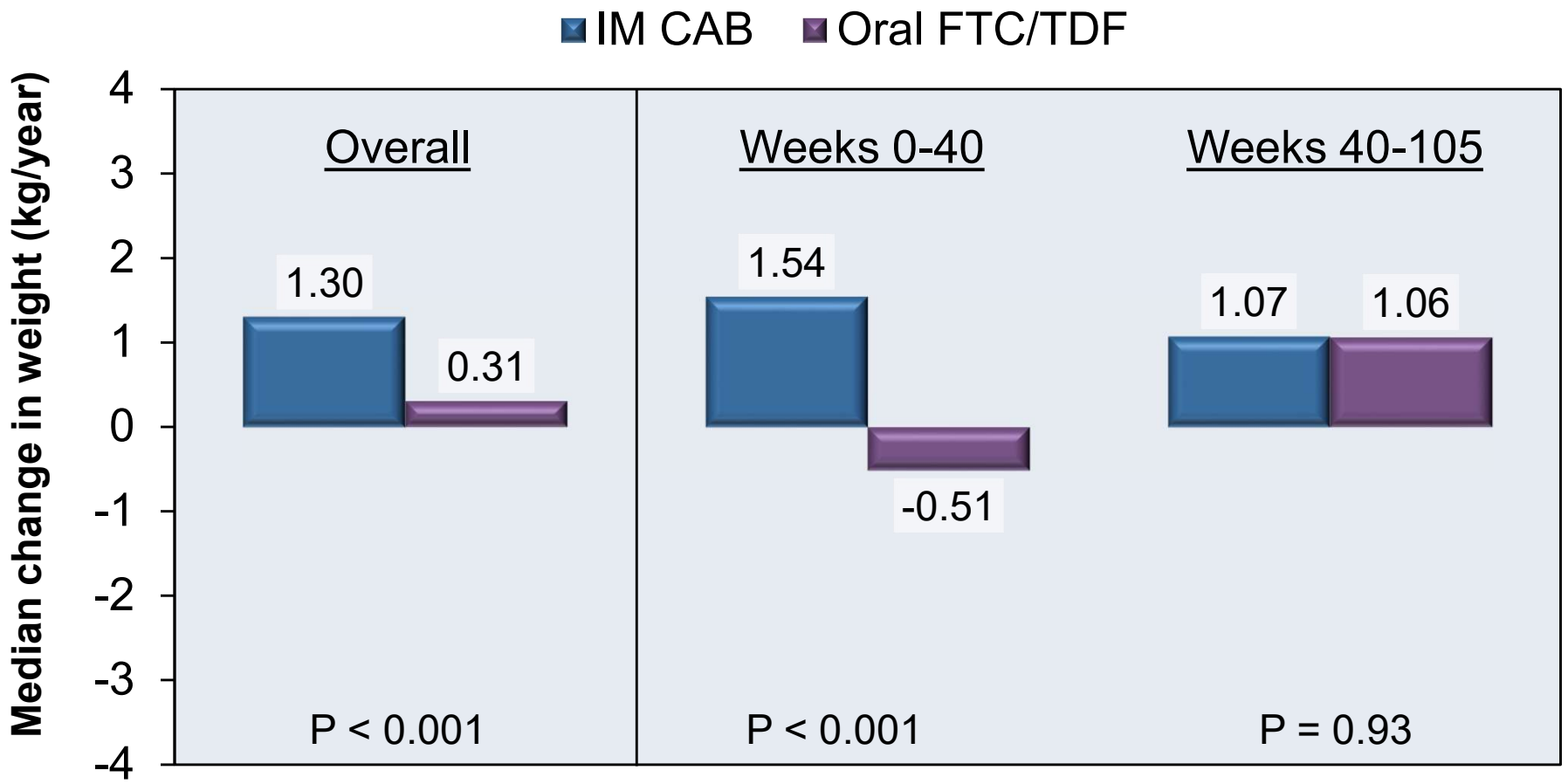
- ACTG ART initiation data (see figure)[1]
- ADVANCE: higher EFV levels → less weight gain on EFV and greater change after switch to INSTI[2]
- McComsey: switch TDF to TAF → more likely to gain than ABC to TAF[3]
- GEMINI: mean weight gain 3.7 kg with DTG/3TC, 2.4 kg with DTG + FTC/TDF[4]



1. Sax et al. CID 2019. 2. Griesel R et al. CID Sept 2020.
3. McComsey G et al. ID Week 2020. 4. Cahn. HIV Glasgow 2020.

IM CAB Every 2 Months vs Oral Daily FTC/TDF for HIV PrEP
HPTN 083 Pre-Exposure Prophylaxis Results

Annualized weight change



Source: Landovitz R et al. AIDS2020 Abstract OAXLB01.

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Switch to DTG/3TC vs Continued TAF-Based 3-Drug ART

TANGO

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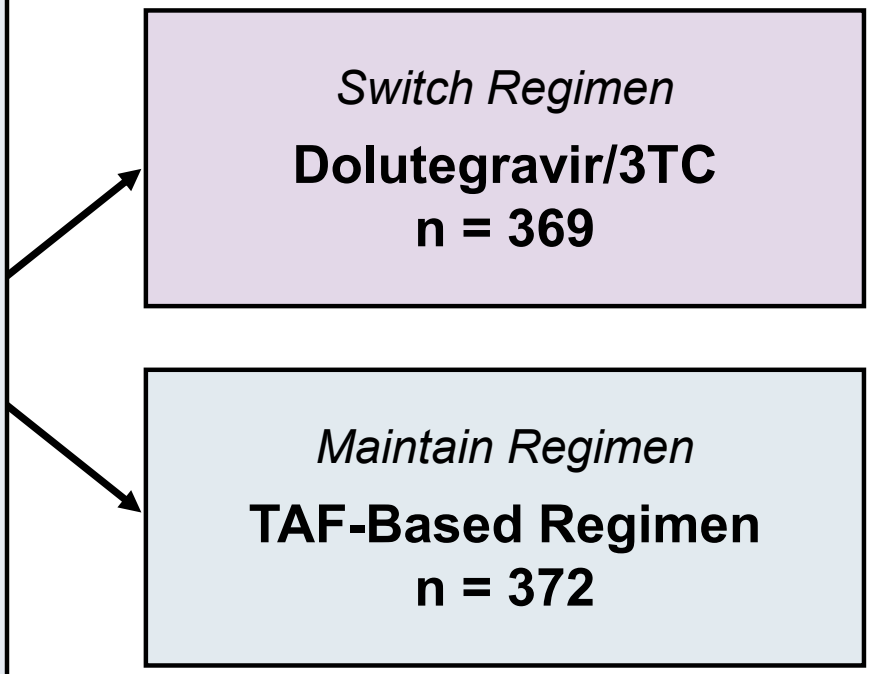
Switch to DTG/3TC vs Continued TAF-Based 3-Drug ART
TANGO: Background

Study Design: TANGO

- **Background**:
  - Ongoing, phase 3, randomized, open label, multicenter, non-inferiority trial comparing switching to 2-drug DTG-3TC versus remaining on 3- or 4-drug TAF-based regimen

- **Enrollment Criteria:**
  - Age ≥18 years
  - HIV RNA <50 copies/mL for >6 months
  - Taking 3- or 4-drug TAF-based ART
  - TDF to TAF switch allowed if ≥3 months before screening
  - No HBV or need for HCV treatment
  - No prior virologic failure
  - No prior NRTI or INSTI resistance



Primary endpoint: virologic response at 48 weeks by FDA snapshot

Source: van Wyk J, et al. Clin Infect Dis, Jan. 2020

Switch to DTG/3TC vs Continued TAF-Based 3-Drug ART
TANGO: Baseline Characteristics

Characteristic	DTG/3TC (n = 369)	TAF-Based ART (n = 372)
Age, years, median (range)	40 (20-74)	39 (18-73)
Female, n (%)	25 (7)	33 (9)
White, n (%)	297 (81)	289 (78)
African American/African, n (%)	50 (14)	58 (16)
CD4 cell count <500, n (%)	98 (27)	74 (20)
CD4 cell count ≥500, n (%)	271 (73)	298 (80)
Months on ART, median (range)	33.8 (7.1-201.2)	35.1 (7.0-160.8)
Baseline third agent class		
INSTI (mostly ELV/cobi)	**289 (78)**	**296 (80)**
NNRTI (mostly RPV)	51 (14)	48 (13)
Boosted PI (mostly DRV)	29 (8)	28 (8)

Source: van Wyk J, et al. Clin Infect Dis, Jan. 2020

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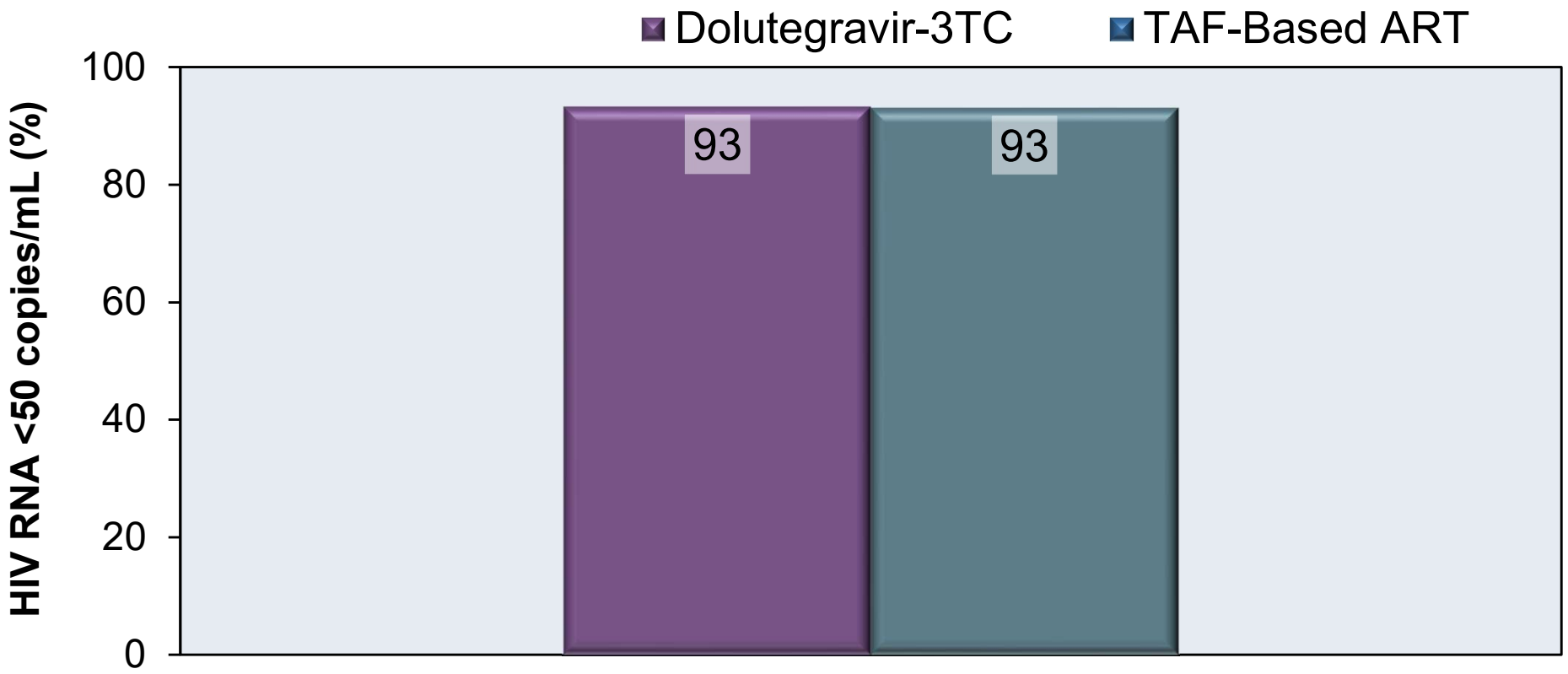
Switch to DTG/3TC vs Continued TAF-Based 3-Drug ART
TANGO: Results

Week 48 Virologic Response (Intention-to-Treat Analysis)



- Confirmed withdrawal for virologic failure: 0 in DTG/3TC arm, 1 in TAF-based ART arm
- No new resistance mutations occurred
- 4 with baseline M184V/I in DTG/3TC arm (by proviral genotype) suppressed at week 48

Source: van Wyk J, et al. Clin Infect Dis, Jan. 2020

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Switch to DTG/3TC vs Continued TAF-Based 3-Drug ART
TANGO: Metabolic Parameter Changes

- Weight change not significantly different: +0.81 kg with DTG/3TC vs +0.76 kg with continued TAF-based ART
- TC, LDL, TG, & TC:HDL ratio improved in the DTG/3TC group & worsened in the comparator group
- Risk of insulin resistance significantly lower in DTG/3TC
- **Improvements in lipids and insulin resistance driven by switch off a booster (EVG/cobi or boosted PI)**

Source: van Wyk J, et al. AIDS 2020. Abstract OAB0606.

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How about a switch to DOR/3TC/TDF?

Review of Doravirine (DOR)

- Most recently approved NNRTI
- Once-daily dosing with no food requirement
- Fewer drug-drug interactions than previous NNRTI's
- Better lipid effects compared to some previous NNRTI's
- In vitro activity against isolates with some common NNRTI mutations (K103N, Y181C, K103N/Y181C, G190A, E138K)

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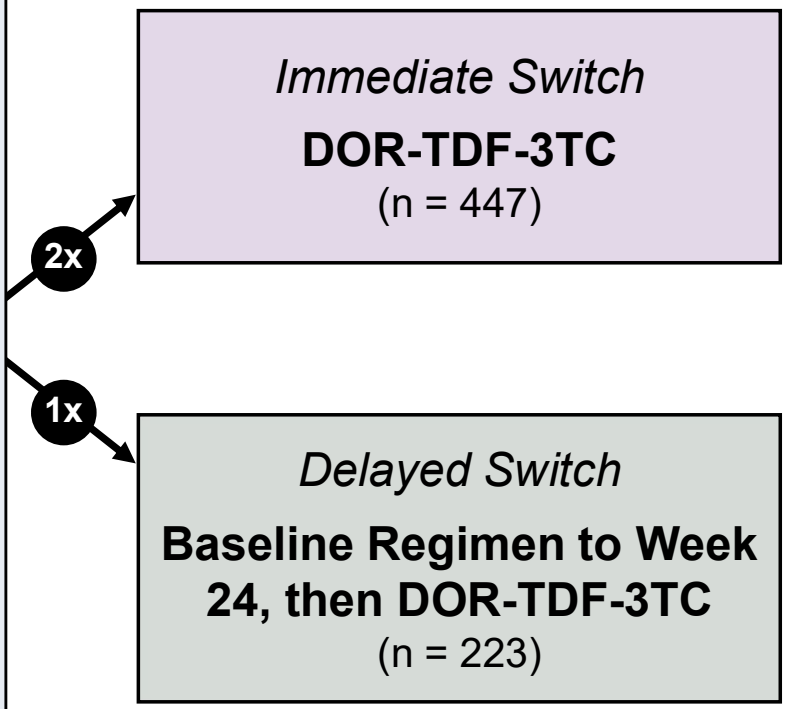
Switch to DOR-TDF-3TC vs. Continued Baseline Regimen
DRIVE SHIFT: Design

DRIVE SHIFT: Study Design

- **Background**: Open-label, active-controlled, non-inferiority trial that enrolled adults with suppressed HIV RNA on 2 NRTIs plus [a boosted PI, boosted elvitegravir, or an NNRTI], then randomized (2:1) to switch immediately to once-daily, single-tablet doravirine-tenofovir-DF-lamivudine (DOR/3TC/TDF) or continue baseline regimen until 24 weeks then switch.
- **Inclusion Criteria**
  - Age ≥18 years
  - Suppressed HIV RNA ≥6 months
  - No history of virologic failure
  - Creatinine clearance ≥50 mL/min
- **Baseline Regimen**
  - 2 NRTIs + boosted PI or EVG/cobi or NNRTI
  (*70% boosted PI, 25% NNRTI, 75% TDF)

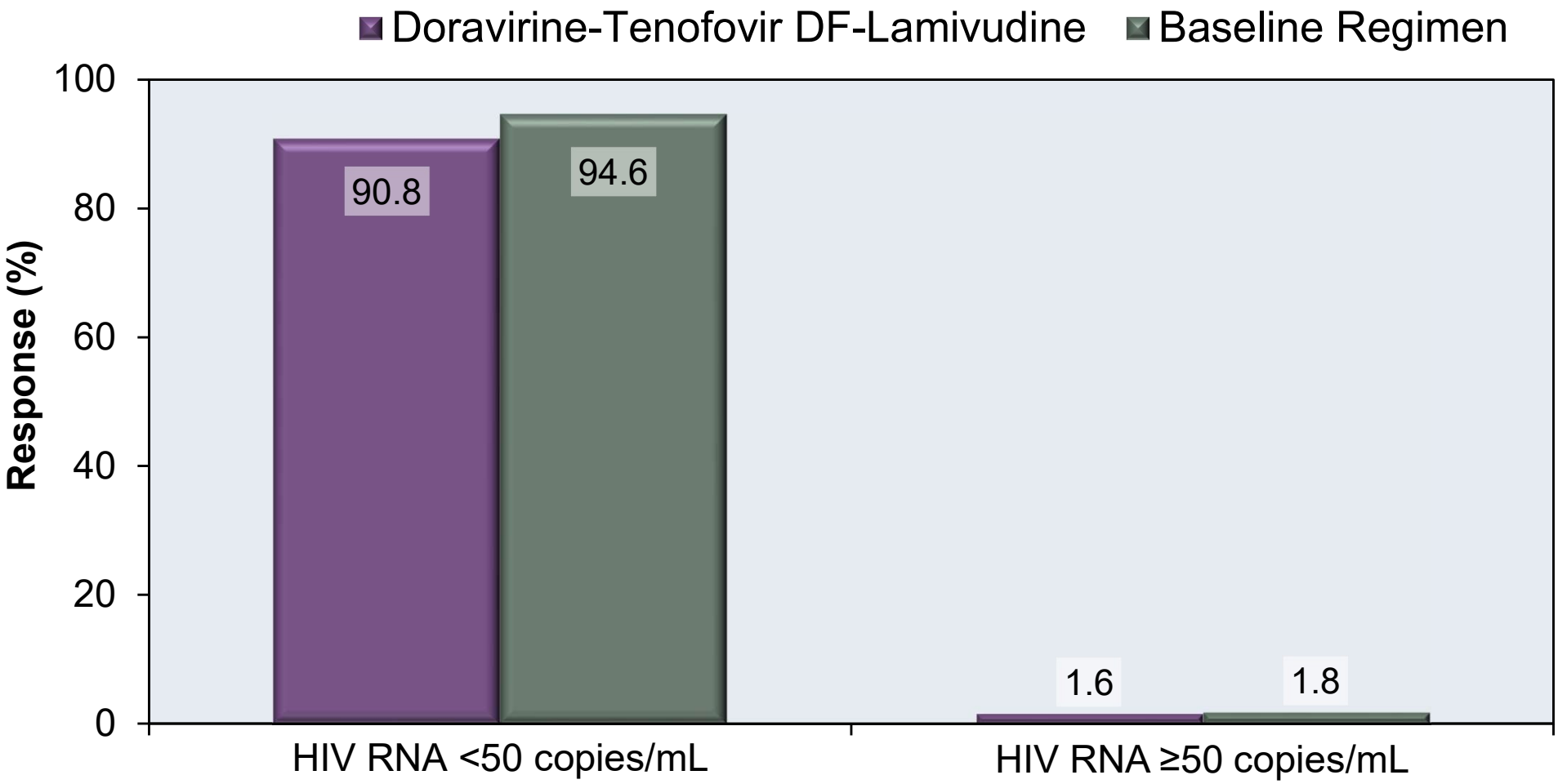


Source: Johnson M, et al. J Acquir Immun Defic Syndr. 2019;81:463-72.

National HIV Curriculum

Switch to DOR-TDF-3TC vs. Continued Baseline Regimen
DRIVE SHIFT: Results

Week 48 DOR-TDF-3TC vs Week 24 Baseline Regimen (FDA snapshot)



Source: Johnson M, et al. J Acquir Immun Defic Syndr. 2019;81:463-72.

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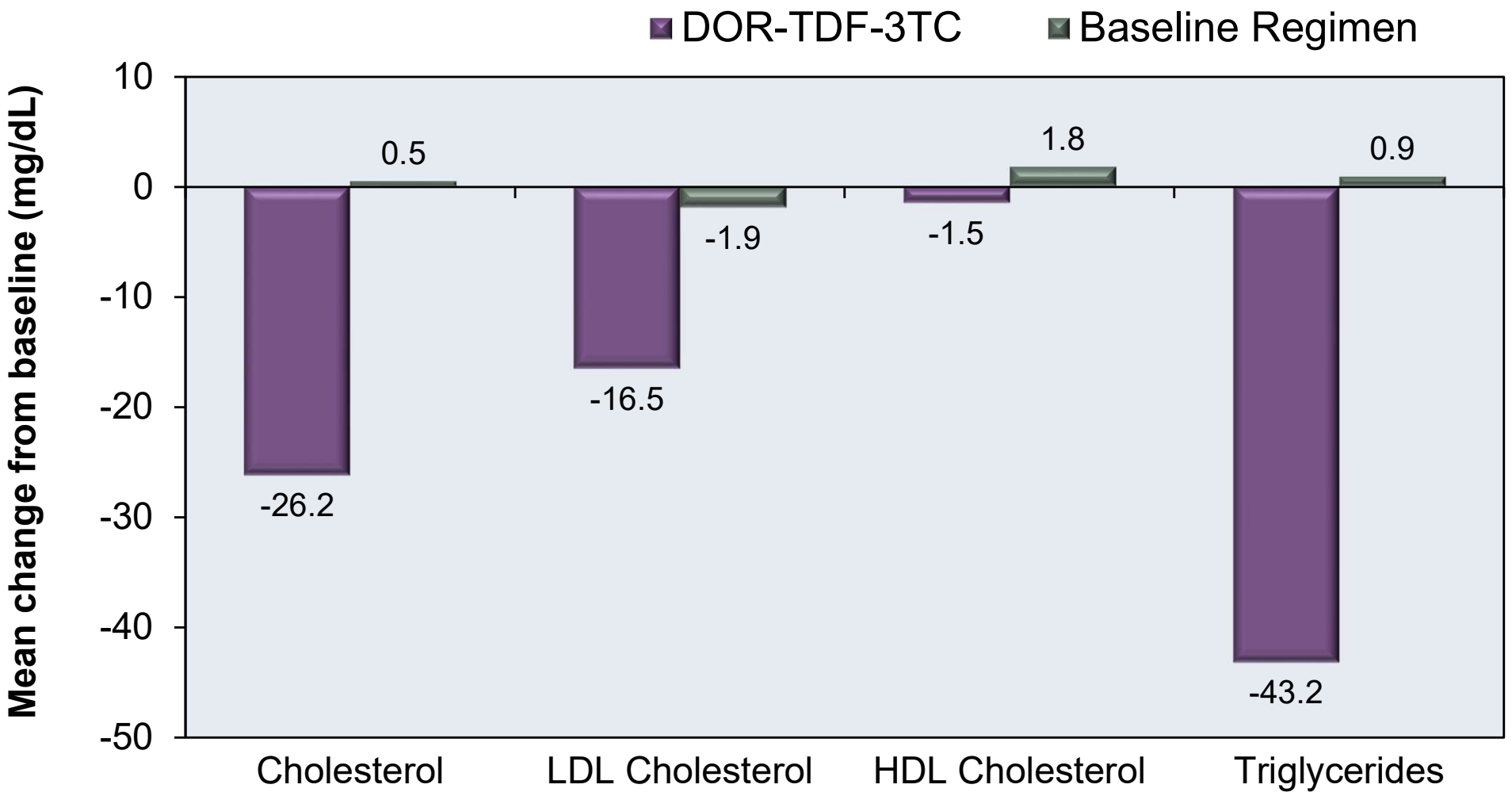
Switch to DOR-TDF-3TC vs. Continued Baseline Regimen
DRIVE SHIFT: Results

Change in Fasting Lipids in Participants Taking a Boosted PI at Baseline



Source: Johnson M, et al. J Acquir Immun Defic Syndr. 2019;81:463-72.

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What Data Would Help Inform These Decisions?

- *What's Missing?*
  - DTG/RPV compared to TAF-based 3-drug ART
  - Switch to DTG/3TC vs continue DTG + 2 NRTI's
  - Comparisons of DOR vs INSTI's
  - Switch to DTG + DOR

- *What's Coming?*
  - **ACTG 5391**: enroll individuals who have gained weight on a TAF-containing INSTI regimen (RAL, BIC, or DTG); randomize to switch to DOR + TDF/FTC, switch to DOR + TAF/FTC, or continue current regimen

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Or, Let's Wait for Long-Acting IM Cabotegravir + Rilpivirine…

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Summary of Key Studies
Cabotegravir-Rilpivirine

- Phase 2 Trials in Treatment Naïve
  - LATTE: Oral CAB-RPV daily versus EFV plus 2 NRTI's
  - LATTE-2: IM CAB-RPV q1 or 2 months vs. oral CAB + ABC-3TC
- Phase 3 Trials in Treatment Naïve
  - FLAIR: IM CAB-RPV every month versus oral DTG-ABC-3TC
- Phase 3 Trials in Treatment Experienced
  - ATLAS: Switch to monthly IM CAB-RPV or continue 3-drug ART
  - ATLAS-2M: switch to IM CAB-RPV every one or two months
  - LATITUDE: IM CAB-RPV for persons with detectable HIV RNA

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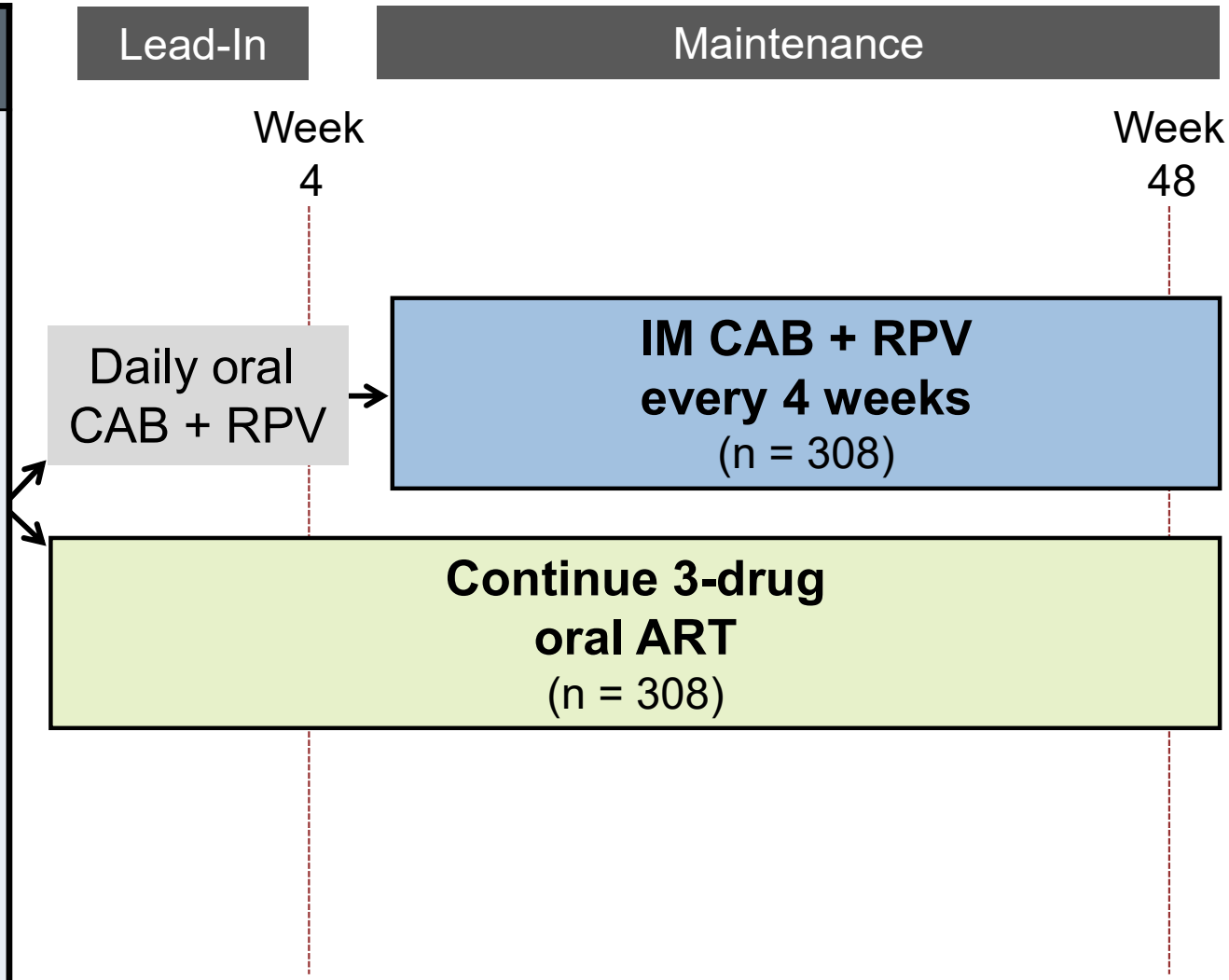
Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Design

Study Design:

- **Background**: Phase 3, randomized, open-label trial assessing IM CAB-RPV after oral induction for adults taking 3-drug oral ART
- **Inclusion Criteria**
  - Age ≥18 years
  - Taking an INSTI, NNRTI, boosted PI, or unboosted atazanavir, plus 2 NRTI's
  - Stable regimen & HIV RNA <50 copies/mL for ≥ 6 months
  - No history of virologic failure
  - No INSTI or NNRTI resistance (K103N allowed)
  - No chronic hepatitis B



Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

National HIV Curriculum

Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Baseline Characteristics

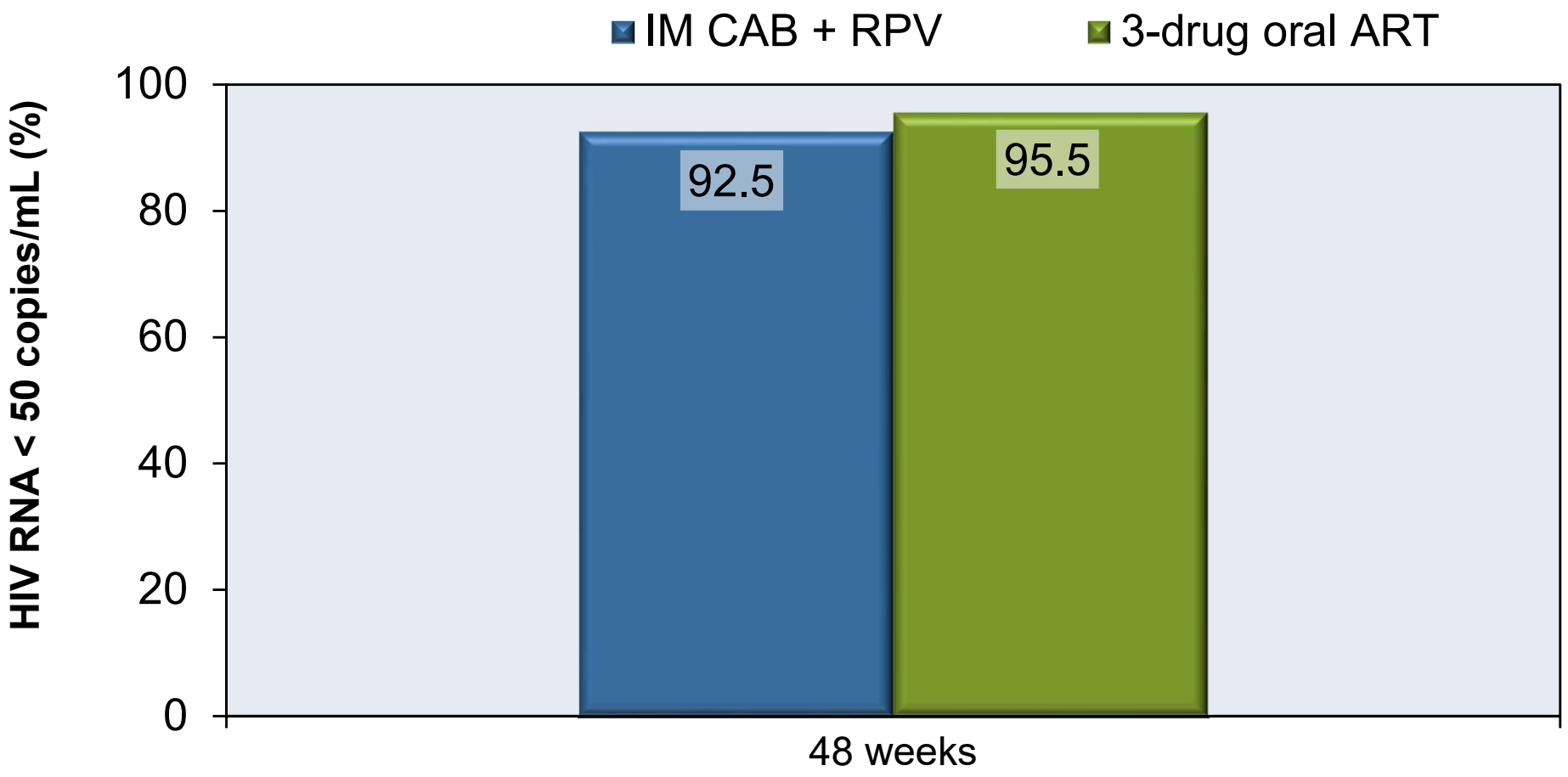
ATLAS: Baseline Characteristics			
Characteristic	**IM CAB + RPV** (n = 308)	**Oral ART** (n = 308)	**Overall** (n=616)
Age, years, median	40	43	42
Female, n, %	99 (32)	104 (34)	203 (33)
White, n, %	214 (69)	207 (67)	421 (68)
Black, n, %	62 (20)	77 (25)	139 (23)
Median body-mass index	26	26	26
CD4 count <350 cells/mm^3, n, %	23 (7)	27 (9)	50 (8)
Time since first ART (months), median, range	52 (7-222)	52 (7-257)	52 (7-257)
Third class agent, n, %	6	6	6
NNRTI (mostly EFV)	**155 (50)**	**155 (50)**	**310 (50)**
INSTI (mostly ELV/cobi)	**102 (33)**	**99 (32)**	**201 (33)**
PI	51 (17)	54 (18)	105 (17)

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

National HIV Curriculum

Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis



HIV RNA ≥ 50 copies/mL at 48 weeks: 1.6 % CAB-RPV, 1.0% 3-drug oral ART

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

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Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Adverse Events

Injection Site Reactions (ISRs)	
Reactions	**Baseline N = 308**
Participants who received injections, n	303
Any reaction, n (%)	250 (81)
Pain, n (%)	231 (75)
Grade 3 pain, n, (%)	10 (3)
Pain leading to withdrawal	4 (1)
Nodule, n (%)	37 (12)
Induration, n (%)	30 (10)
Swelling, n (%)	23 (7)
Median duration of reaction, days	3
The majority of ISRs (99%) were grade 1-2; 88% resolved within 7 days.	

At week 48, median weight gains were 1.8 kg (IQR, −0.3 to 4.9) in the long-acting–ART group and 0.3 kg (IQR, −1.6 to 2.5) in the oral ART group.

Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

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Reflections on Long-Acting CAB-RPV

- Excellent option for carefully selected individuals
  - No resistance, likely to adhere to regular injections, no hep B
  - Struggling with pill fatigue or stigma; care transitions
- Many operational & clinical questions
  - Burden on clinic staff
  - Every 1 vs 2 month dosing
  - Optimal oral lead-in, bridge for missed doses, oral tail
  - Role for persons with imperfect adherence/detectable VL
  - Injection site reaction fatigue over time
  - Metabolic/weight gain differences over standard oral ART
  - **Costs/access**

See also: Currier J. NEJM. March 2020;382(23)

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Recommended Cabenuva Dosing Schedule
From Canadian Package Insert

Table 1 Recommended Dosing Schedule in Adults

ORAL LEAD-IN	I.M. INITIATION INJECTIONS	I.M. CONTINUATION INJECTIONS
Month 1*	Month 2**	Month 3 onwards
VOCABRIA 30 mg cabotegravir tablet once daily	CABENUVA 3 mL (600 mg) cabotegravir injection and 3 mL (900 mg) rilpivirine injection	CABENUVA 2 mL (400 mg) cabotegravir injection once monthly and 2 mL (600 mg) rilpivirine injection once monthly
EDURANT 25 mg rilpivirine tablet once daily		

IM = Intramuscular injection
*At least 28 days
**Final oral doses of VOCABRIA and EDURANT should be taken on the same day as initiation injections are started.

gphandlahdpffmccakmbngmbjnjiiahp/https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_CA/cabenuva.pdf

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Time Since Last Injection	Recommendations for Oral Bridging
Less than 1 Month + 7 days	Continue with 2 mL (400 mg) cabotegravir and 2 mL (600 mg) rilpivirine injections.
Greater than 1 Month + 7 days	<u>Planned Missed Injections</u> If a patient plans to miss a scheduled injection visit by more than 7 days, the patient should be initiated on oral therapy (1 tablet each of VOCABRIA and EDURANT, once daily), with the first oral dose taken approximately 1 month after the last injection doses. Injections are to be resumed on the same day as the last day of oral therapy dosing. Oral therapy can be used to replace up to 2 consecutive monthly injection visits.
Greater than 1 Month + 7 days	<u>Unplanned Missed Injections</u> If a patient's monthly injection visit is missed or delayed for more than 7 days and oral therapy has not been taken, patients should be clinically reassessed to ensure resumption of injections remains appropriate (e.g. evaluate patient commitment to comply with the dosing schedule and consider HIV-1 RNA viral load retesting).
Time Since Last Injection	**Recommendation for Resumption of Injections**
≤2 months	If clinically appropriate, resume with 2 mL (400 mg) cabotegravir and 2 mL (600 mg) rilpivirine injections as soon as possible. If the patient was on oral therapy, injections are to be resumed on the same day as the last day of oral therapy dosing.
>2 months	If clinically appropriate, reinitiate the patient on 3 mL (600 mg) cabotegravir and 3 mL (900 mg) rilpivirine, and then continue to follow the monthly 2 mL (400 mg) cabotegravir and 2 mL (600 mg) rilpivirine injection schedule. If the patient was on oral therapy, injections are to be resumed on the same day as the last day of oral therapy dosing.

Or, We Could Wait for Oral Islatravir plus Doravirine…

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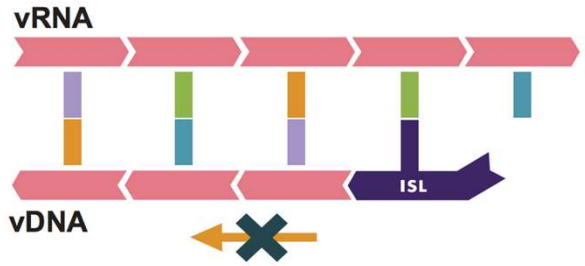
What is Islatravir (ISL)?

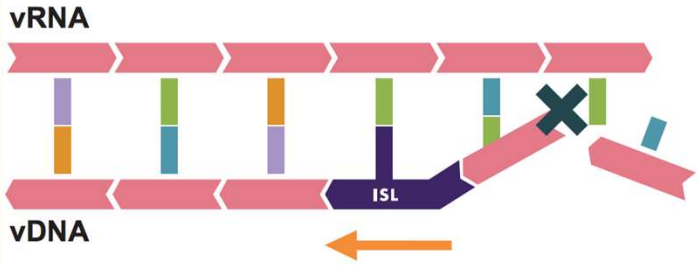
- NRTTI: nucleoside reverse transcriptase translocation inhibitor

Translocation Inhibition



- Translocation inhibition prevents opening of the RT nucleotide binding site
- Nucleotides cannot be incorporated into vDNA
- **Viral replication is inhibited**

Delayed Chain Termination



- ISL changes vDNA structure such that nucleotide incorporation is prevented
- As ISL is not in the RT active site, it is not susceptible to resistance-conferring mutations
- **Viral replication is inhibited**

Source: McComsey G, et al. CROI 2020. Abstract 686.

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Potential Advantages of Islatravir (ISL)

- Active against isolates with pre-existing NRTI resistance
- Potent viral load reduction plus high barrier to resistance
- Inhibitory quotient achieved with low doses
- Long intracellular half-life (190 hours with oral dosing)
- Potential for once-daily, once-weekly, or less frequent oral dosing; much less frequent for other formulations

Source: McComsey G, et al. CROI 2020. Abstract 686.

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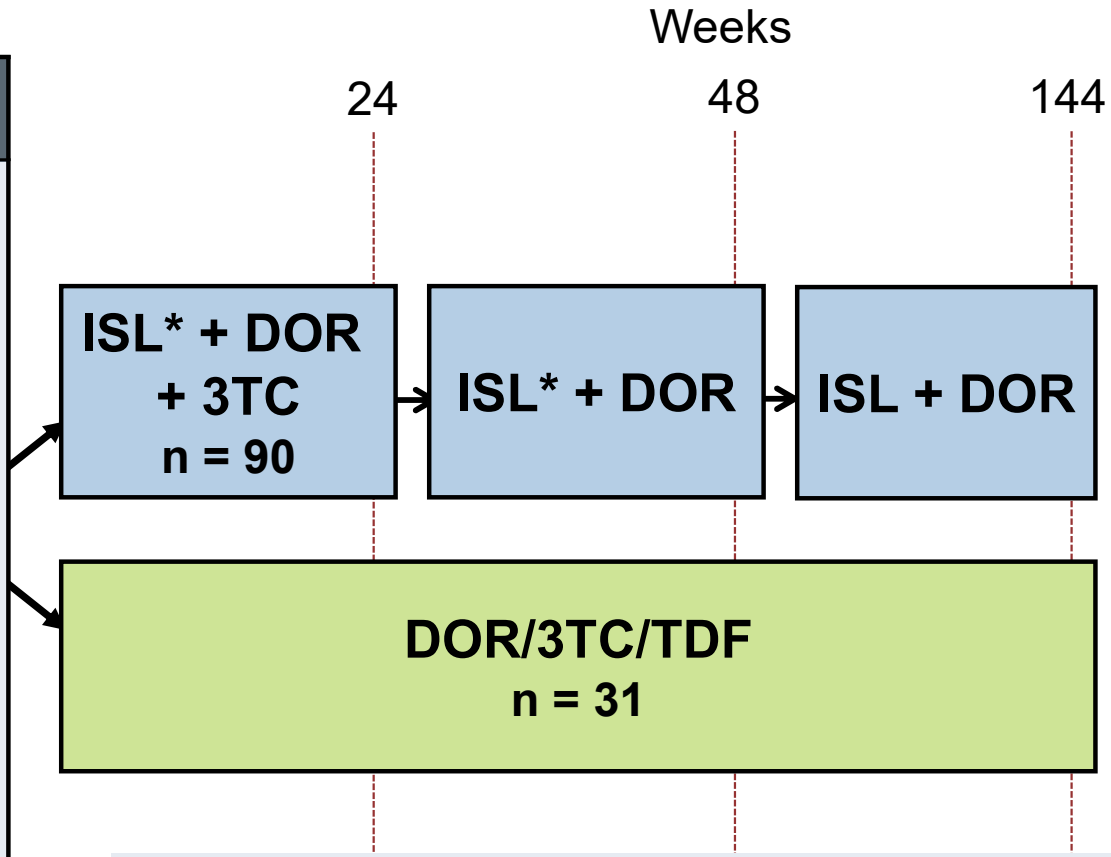
Oral ISL + DOR Dual ART Maintenance vs DOR/3TC/FTC
DRIVE2SIMPLIFY: Background

Study Design: DRIVE2SIMPLIFY

- **Background**:
  - International, randomized, double-blind phase IIb trial
- **Enrollment Criteria:**
  - Treatment-naïve adults
  - HIV RNA >1,000 copies/mL
  - CD4 T-cell count >200 cells/mL
  - No ARV drug resistance
  - No active HBV or HCV
- **Primary Endpoint**:
  - HIV RNA at 24 & 48 weeks; adverse events



*ISL dose: 0.25 mg, 0.75 mg, or 2.25 mg daily

Current analysis: weight; BMI; hip and spine BMD, peripheral & trunk fat by DXA; fasting plasma glucose; and lipid profile at 48 weeks

Source: McComsey G, et al. CROI 2020. Abstract 686.

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Oral ISL + DOR Dual ART Maintenance vs DOR/3TC/FTC
DRIVE2SIMPLIFY: Results

- Change in weight & BMI similar in ISL + DOR groups and DOR/3TC/TDF group, and consistent with average weight gain in general population (0.5-1.0 kg/year)
- ISL + DOR regimens had lower impact on hip BMD than DOR/3TC/TDF; spine BMD changes similar
- Changes in glucose and fasting lipids modest and similar
- Overall, minimal effects on body composition and metabolic parameters supports phase 3 trials of ISL + DOR

- *Limitations: short follow-up, no TAF or INSTI comparison*

Source: McComsey G, et al. CROI 2020. Abstract 686.

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Newest Options for Salvage ART

Case: New Drug for Salvage ART

- 57-year-old Caucasian man with 30-year history of HIV, complicated by neuropathy, lipodystrophy, chronic diarrhea
- Chronic reduced renal function; estimated CrCl 45 mL/min
- Significant NRTI, NNRTI, and INSTI resistance
- Tropism assay: dual/mixed
- Meds: atorvastatin, gabapentin, omeprazole, duloxetine
- *Would fostemsavir (FTR) be an option for this individual?*

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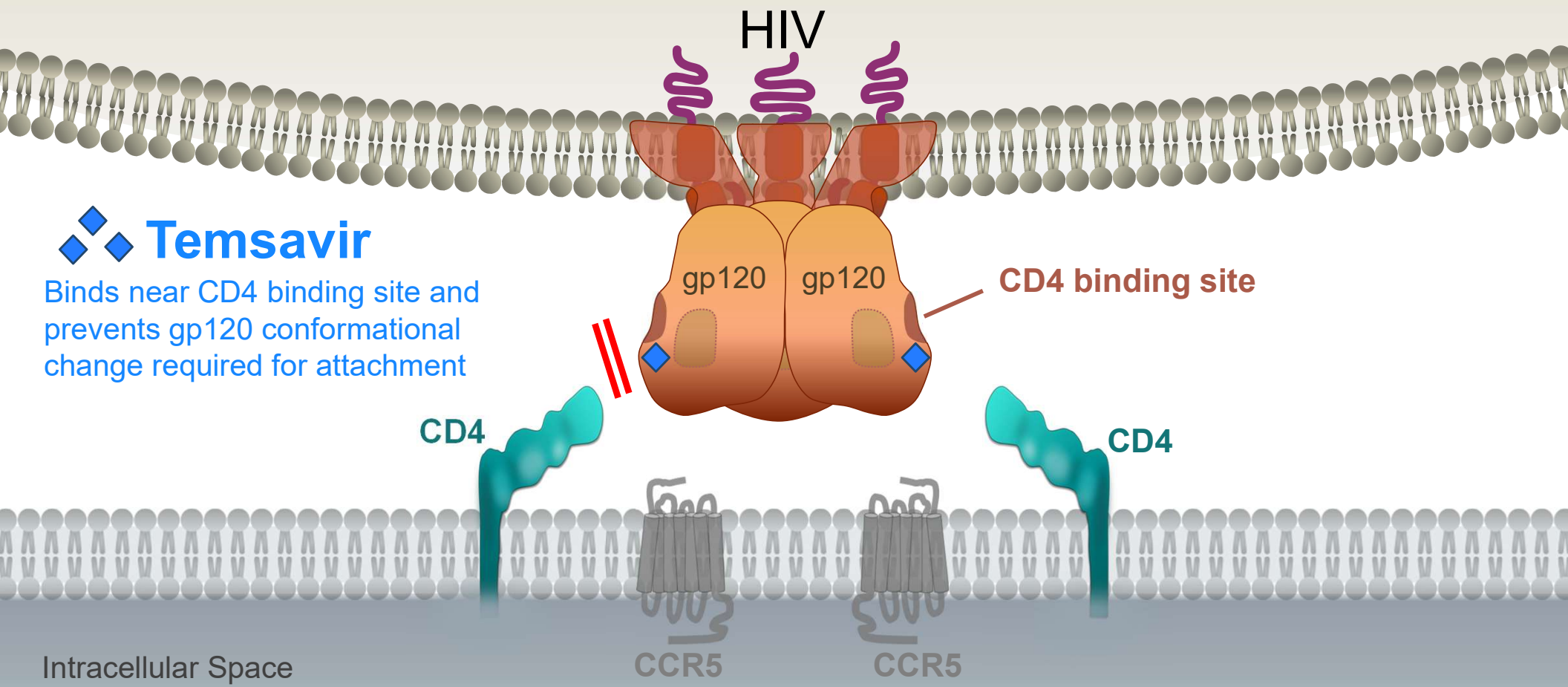
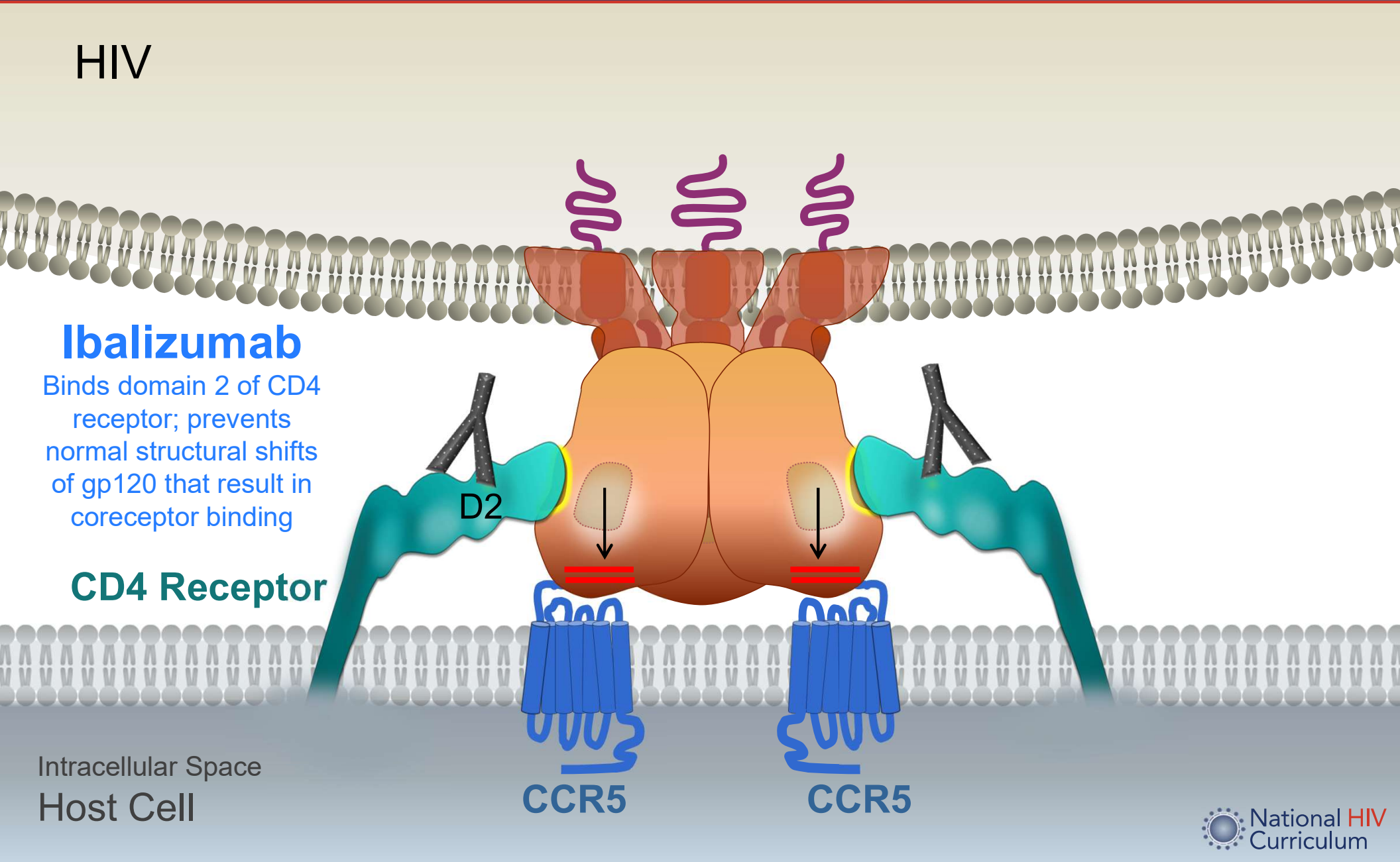
Fostemsavir (*Rukobia*)
Attachment Inhibitor

HIV



National HIV Curriculum

Ibalizumab (*Trogarzo*)
Post-Attachment Inhibitor



National HIV Curriculum

Fostemsavir Take-Home Points

- For heavily ART-experienced adults with few ARV options
- Blocks **attachment** of the virus to CD4 at gp120
  - **Works regardless of R5/X4 status**
- Oral tablet taken **twice daily** with or without food
- Few drug interactions overall, but avoid **CYP3A4 inducers**
  - Rifampin contraindicated
- Safe in renal impairment and hemodialysis; levels may increase with hepatic impairment
- ***Answer: yes, FTR would be an option for the patient***

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Thank You!

- Feel free to email questions or comments: bwood2@uw.edu

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Also in the Pipeline
Novel Delivery and Dosing Strategies

- Weekly oral elsufavirine (NNRTI)
- Implants: islatravir, TAF
- Subcutaneous injections: lenacapavir (capsid inhibitor), albuvirtide (entry inhibitor)

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New Language on Weight Gain with ART
HHS Guidelines

- "Data from studies showing increased weight gain with particular ARV medications, including some INSTIs and TAF, and especially in certain patient populations (i.e., women, Black people, and Hispanic people)…"
- "There are now data suggesting greater weight gain with certain INSTI-based regimens and TAF than with other ARV drugs. *The clinical significance of these findings is still unknown*."

HHS Adult and Adolescent Treatment Guidelines: https://clinicalinfo.hiv.gov/en/guidelines

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The More Distant Pipeline (Phase 2)

- Elsufavirine: once-weekly oral NNRTI
- GSK’232: oral maturation inhibitor
- Lencapavir: subcutaneous capsid inhibitor

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Oral 2-Drug Maintenance ART
Prospective RCT's

DUAL ART	MAINTENANCE ART STUDIES
Dolutegravir/rilpivirine[1]	SWORD (n=1,028, comparator: TDF-based 3-drug ART)
Dolutegravir/3TC[2]	TANGO (n=750, comparison: TAF-based 3-drug ART)
Dolutegravir + FTC[3]	SIMPL'HIV (n=188, comparison: TAF, TDF, ABC-based 3-drug ART)
Boosted darunavir + 3TC[4]	DUAL GESIDA (n=249, comparator: TDF-based 3-drug ART)
Boosted darunavir + dolutegravir[5]	DUALIS (n=263, comparison: TDF-based 3-drug ART)

1. 148 Week Data: van Wyck, BHIVA, April 2019.
2. 48 Week Data: van Wyck, IAS, July 2019.
3. 48 Week Data: Sculier, EACS, Nov 2019.
4. 48 Week Data: Pulido, CID, 2017.
5. 48 Week Data: Spinner C, IAS 2019.

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Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction
FLAIR Study: Results

Participants in the IM CAB + RPV arm with viral rebound meeting protocol-defined criteria for genotype resistance testing				
Sex, Country, HIV-1 Subtype, Viral Load (Baseline)	**Baseline INSTI RAMs**	**Baseline NNRTI RAMs**	**Viral Load at Confirmed Virologic Failure**	**INSTI RAMs at Virologic Failure**
F, Russia, A1, 54,000 copies/mL	L74I	None	456 copies/mL	L74I, Q148R
M, Russia, A1, 23,000 copies/mL	L74I	None	299 copies/mL	L74I, G140R
F, Russia, A1, 20,000 copies/mL	L74I	None	440 copies/mL	L74I, Q148R
There were also 3 virologic failures in the DTG-ABC/3TC arm; no new RAM's detected Abbreviations: RAMs = resistance associated mutations				

Source: Orkin C, et al. N Engl J Med. 2020;382:1124-35.

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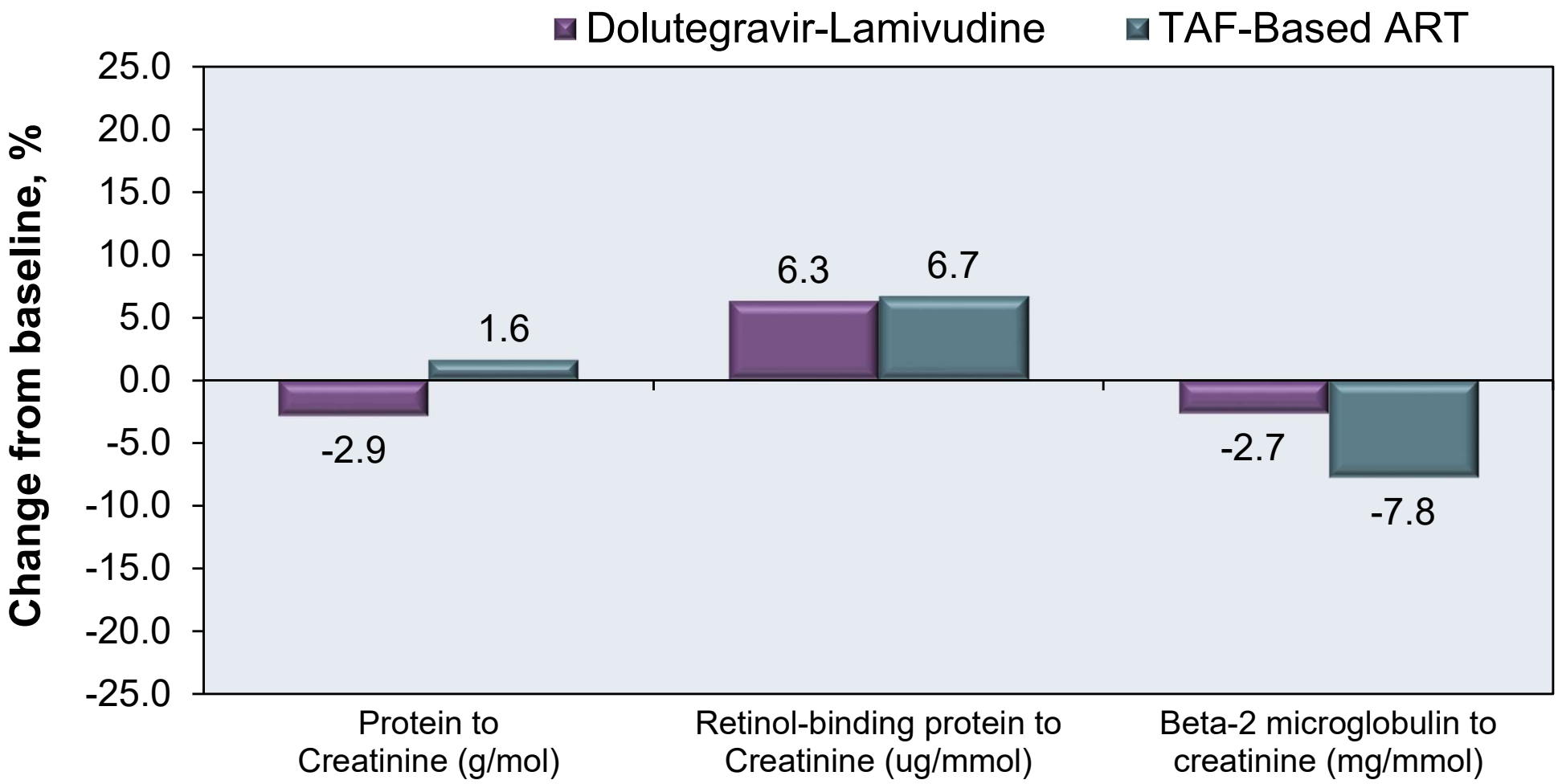
Switch to DTG/3TC vs Continued TAF-Based 3-Drug ART
TANGO: Results

Week 48 Changes in Markers of Proximal Tubulopathy (Urine Tests)



Source: van Wyk J, et al. Clin Infect Dis. 2020. Jan 6. [Epub ahead of print]

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Oral ISL + DOR Dual ART Maintenance vs DOR/3TC/FTC
DRIVE2SIMPLIFY: Results

DRIVE2SIMPLIFY: Metabolic Results at 48 Weeks

Characteristic	Combined ISL + DOR Groups (n = 90)	DOR/3TC/TDF (n = 31)
Mean % change in weight	3.8	3.0
Mean % change in hip BMD	-1.1*	-3.5
Mean % change in spine BMD	-1.3	-2.2
Mean % change in peripheral fat	10.2	9.6
Mean % change in trunk fat	15.0	12.9
Mean change in fasting markers (mg/dL)		
Glucose	2.3	-2.0
Total cholesterol	5.4	-6.5
HDL	4.3	0.8
LDL	-0.8	-4.7
Triglycerides	6.2	-10.9

Source: McComsey G, et al. CROI 2020. Abstract 686.

*p <0.05

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