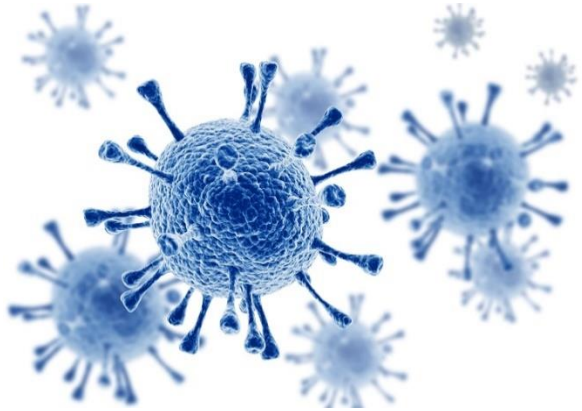

WHAT'S NEW IN HIV? HIGHLIGHTS & NEW DATA ON HIV TREATMENT

A PRESENTATION FOR HEALTHTRUST MEMBERS
JUNE 18, 2021

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CONFLICT OF INTEREST DISCLOSURE

- There are no relevant financial interest to disclose for myself or my spouse/partner within the last 12 months.
- The preceptor has a financial interest/arrangement, affiliation or relationship with Astellas and Merck that could be perceived as a real or apparent conflict of interest in the context of the subject of this activity.
- Note: This program may contain the mention of suppliers, brand products, services, or drugs presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes only and should not be perceived as an endorsement of any particular supplier, brand, product, service or drug.

LEARNING OBJECTIVES

1. Identify new antiretroviral agents and their role in the management of HIV/AIDS
2. Describe a two-drug regimen for treatment-naïve individuals and factors to consider when selecting an initial regimen for an individual.
3. Outline key counseling points to a patient receiving new antiretroviral agents related to drug administration, potential side effects, and drug-drug interactions

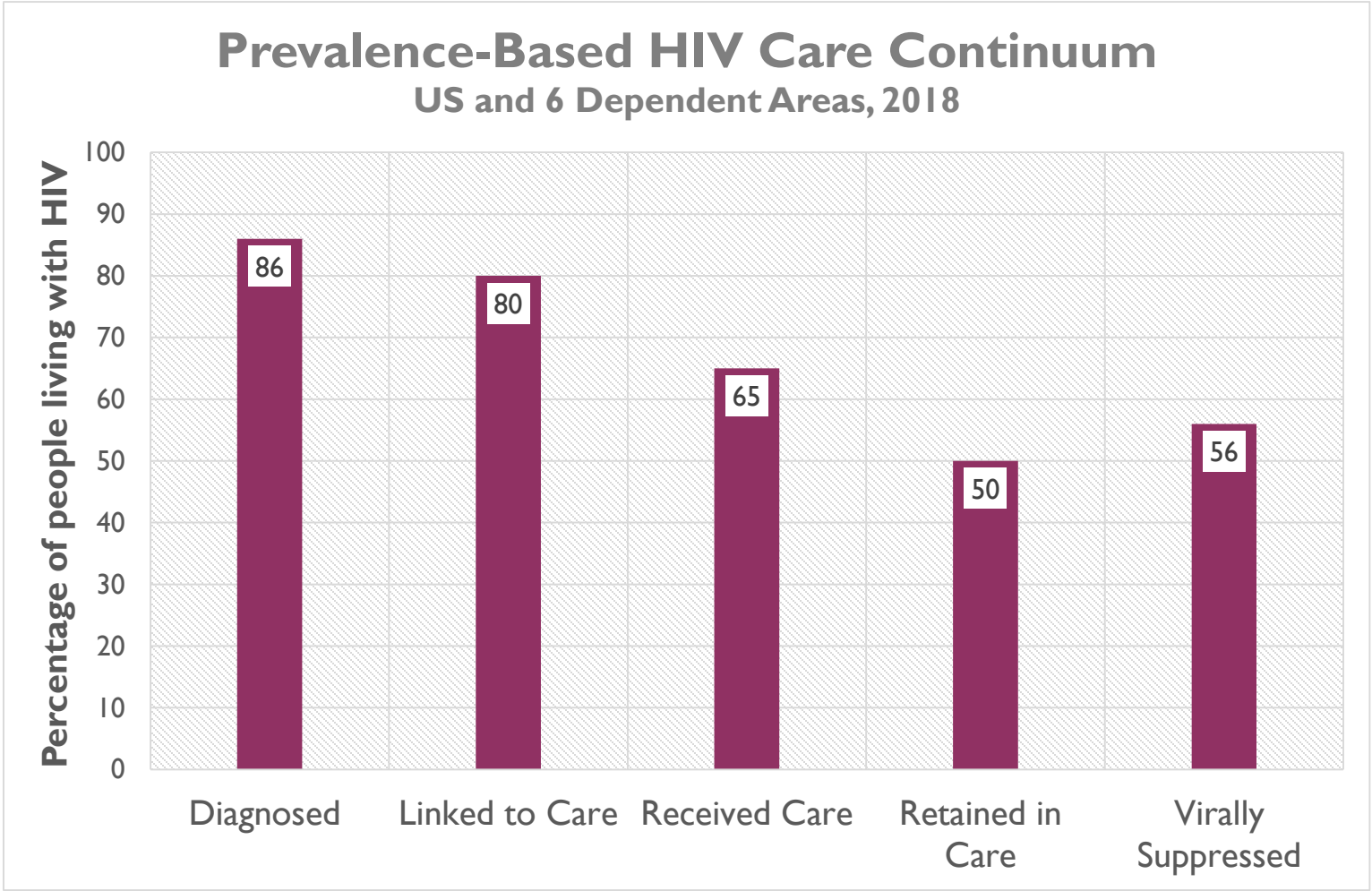
DRUG NAME ABBREVIATIONS

Abbreviation	Full Name	Abbreviation	Full Name	Abbreviation	Full Name
3TC	Lamivudine	DTG	Dolutegravir	NFV	Nelfinavir
ABC	Abacavir	EFV	Efavirenz	NVP	Nevirapine
ATV	Atazanavir	ETR	Etravirine	R5	CCR5-utilizing virus
ATV/c	Atazanavir/cobicistat	EVG	Elvitegravir	RAL	Raltegravir
ATV/r	Atazanavir/ritonavir	FPV	Fosamprenavir	RPV	Rilpivirine
BIC	Bictegravir	FTC	Emtricitabine	RTV or r	Ritonavir
CAB	Cabotegravir	FTR	Fostemsavir	T-20	Enfuvirtide
COBI or /c	Cobicistat	IBA	Ibalizumab	TAF	Tenofovir alafenamide
d4T	Stavudine	IDV	Indinavir	TDF	Tenofovir disoproxil fumarate
ddI	Didanosine	ISL	Islatravir	TMR	Temasvir
DLV	Delavirdine	LEN	Lenacapavir	TFV-DP	Tenofovir-diphosphate
DOR	Doravirine	LPV	Lopinavir	TPV	Tipranavir
DRV	Darunavir	MVC	Maraviroc	ZDV	Zidovudine

Source: DHHS: clinicalinfo.hiv.gov/en/guidelines.

EPIDEMIOLOGY

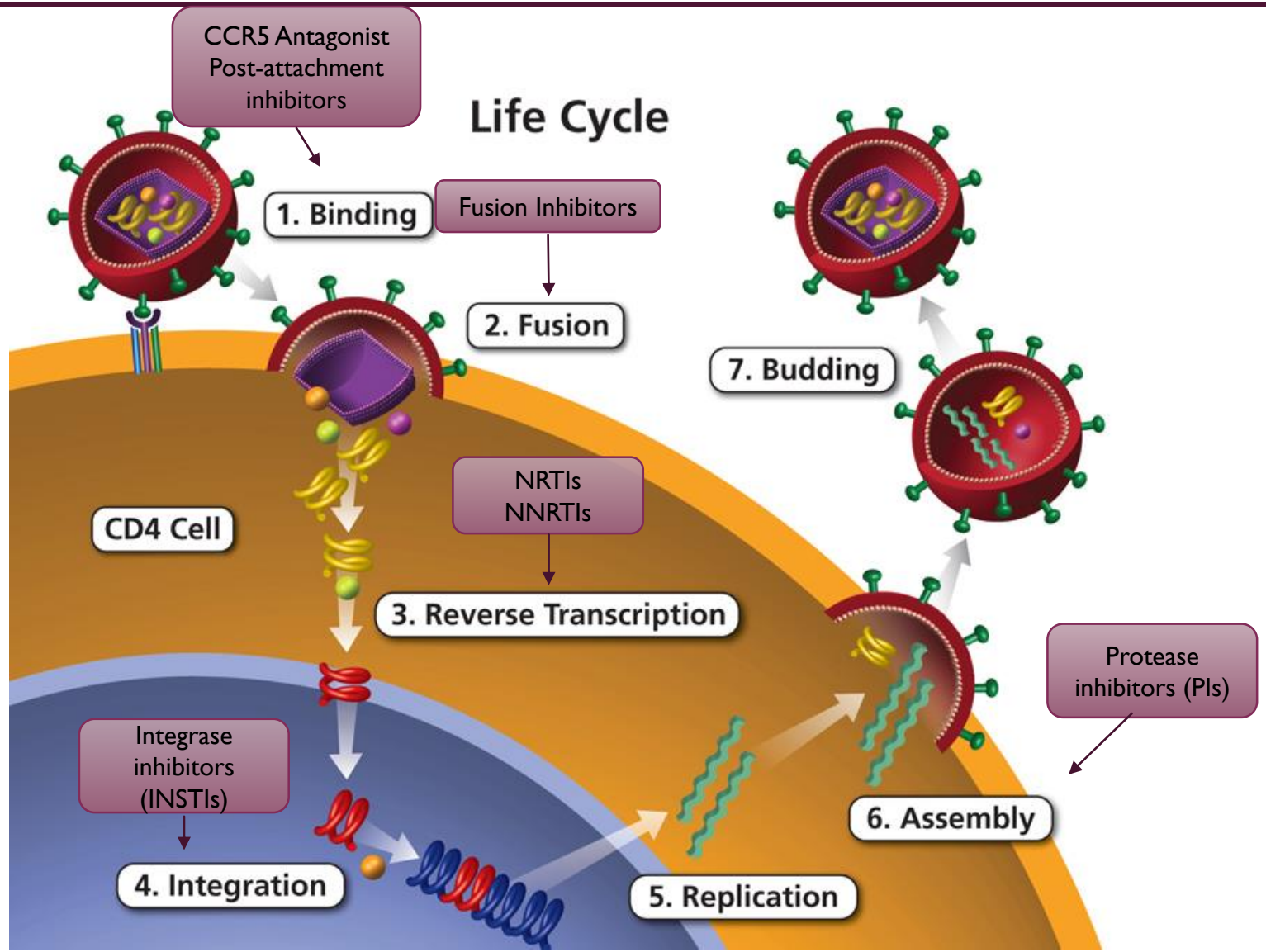
- About 1.2 million people in the U.S. are living with HIV[1]
- An estimated 36,400 new HIV infections occurred in the United States in 2018[1]
- HIV diagnoses overall declined in 2009–18, however HIV diagnoses among individuals aged 25–34 years increased during the same period[2]



Sources:

1. CDC. HIV Surveillance Report 2020; 31.
2. HIV.gov. Policies & Issues: HIV Care Continuum. May 2020.
3. Sullivan et,al. *Lancet*. 2021;397(10279):1095-1106.

HIV VIRAL REPLICATION CYCLE



Source: The HIV Life Cycle. National Institutes of Health. https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-life-cycle.

WHAT'S NEW IN THE GUIDELINES?

Sources:
DHHS: clinicalinfo.hiv.gov/en/guidelines.
IAS-USA: Saag. *JAMA*. 2020;324(16):1651-1669

TREATMENT AS PREVENTION

- Using ART to consistently suppress HIV RNA < 200 copies/ml **prevents transmission** of HIV to sexual partners
  - Patient should use another form of prevention for ≥6 months and until an HIV RNA <200 copies/mL
  - High level of adherence is necessary
  - Does not prevent transmission of STIs

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

WHEN IS THE RIGHT TIME TO START ART?

- Start ART **immediately or as soon as possible** after diagnosis
- Panel supports same-day start "when possible"
- Exceptions to immediate starts:
  - Tuberculous meningitis
  - Cryptococcal meningitis

Increase the uptake of ART

Improve the rate of virological suppression

Decrease the time to virologic suppression

Reduce the risk of HIV transmission

Sources:
1. HHS Adult and Adolescent Treatment Guidelines: https://clinicalinfo.hiv.gov/en/guidelines
2. Saag et al, *JAMA*. 2020;324(16):1651-1669.

INITIAL ART FOR TREATMENT-NAÏVE INDIVIDUALS WHAT TO START?

DHHS Recommendation (Dec 2019)[1]

- 2 – drug regimen
  - Dolutegravir (DTG)/lamivudine (3TC)
    (if HIV RNA < 500,000 copies/ml, no HBV co-infection, or if results of HIV genotypic resistance testing not available)
- 3 – drug regimens
  - Bictegravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC)
  - **Dolutagrevir/Abacavir (ABC)/ lamivudine (If HLA-B*5701 negative)**
  - Dolutegravir or **raltegravir** plus
    - Tenofovir alafenamide/emtricitabine
    - Tenofovir disoproxil fumarate (TDF)/emtricitabine
    - Tenofovir disoproxil fumarate/lamivudine

Source: 1. DHHS: clinicalinfo.hiv.gov/en/guidelines

IAS-USA Recommendation (Oct 2020)[2]

- 2 – drug regimen
  - Dolutegravir (DTG)/lamivudine (3TC)
    (if HIV RNA < 500,000 copies/ml, no HBV co-infection, or if results of HIV genotypic resistance testing not available)
- 3 – drug regimens
  - Bictegravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC)
  - Dolutegravir plus
    - Tenofovir alafenamide/emtricitabine
    - Tenofovir disoproxil fumarate (TDF)/emtricitabine
    - Tenofovir disoproxil fumarate/lamivudine

Sources: 2. IAS-USA: https://jamanetwork.com/journals/jama/fullarticle/2771873

RECOMMENDED INITIAL REGIMENS FOR MOST PEOPLE WITH HIV

INSTI + 2 NRTIs

- BIC/FTC/TAF (Biktarvy)
- DTG/ABC/3TC (Triumeq) If HLA-B*5701(-)
- DTG + FTC/TAF or TDF (Tivicay with Descovy or Truvada)
- RAL/FTC/TAF or TDF (Isentress HD or Isentress with Descovy or Truvada)

INSTI + NRTI

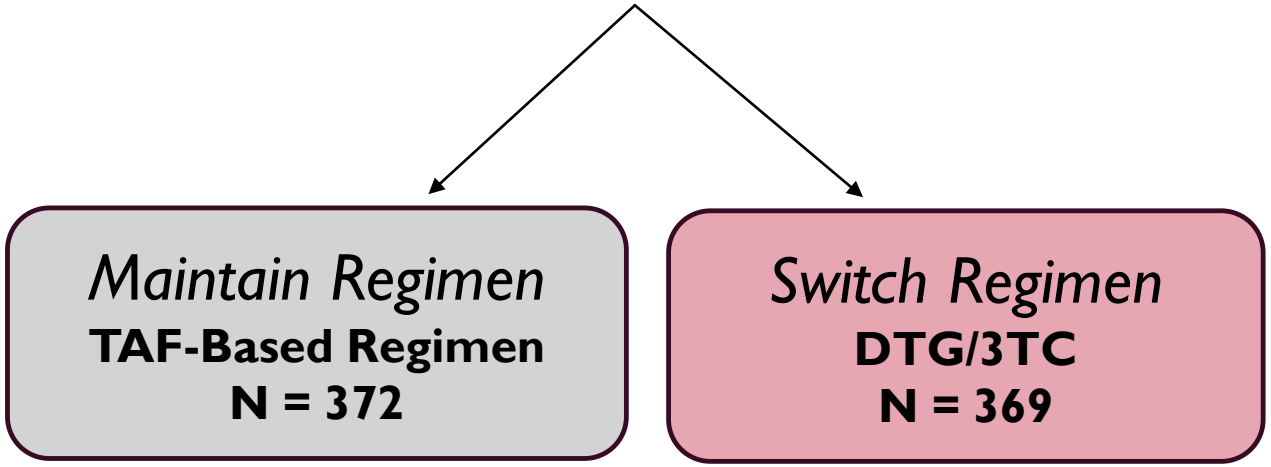
DTG/3TC (Dovato)

SWITCH TO 2 DRUG VS. CONTINUE 3 DRUGS ART? TANGO TRIAL

Source: Van, et al TANGO Study. *Clin Infect Dis*. 2020;71(8):1920-1929.

TANGO: BACKGROUND

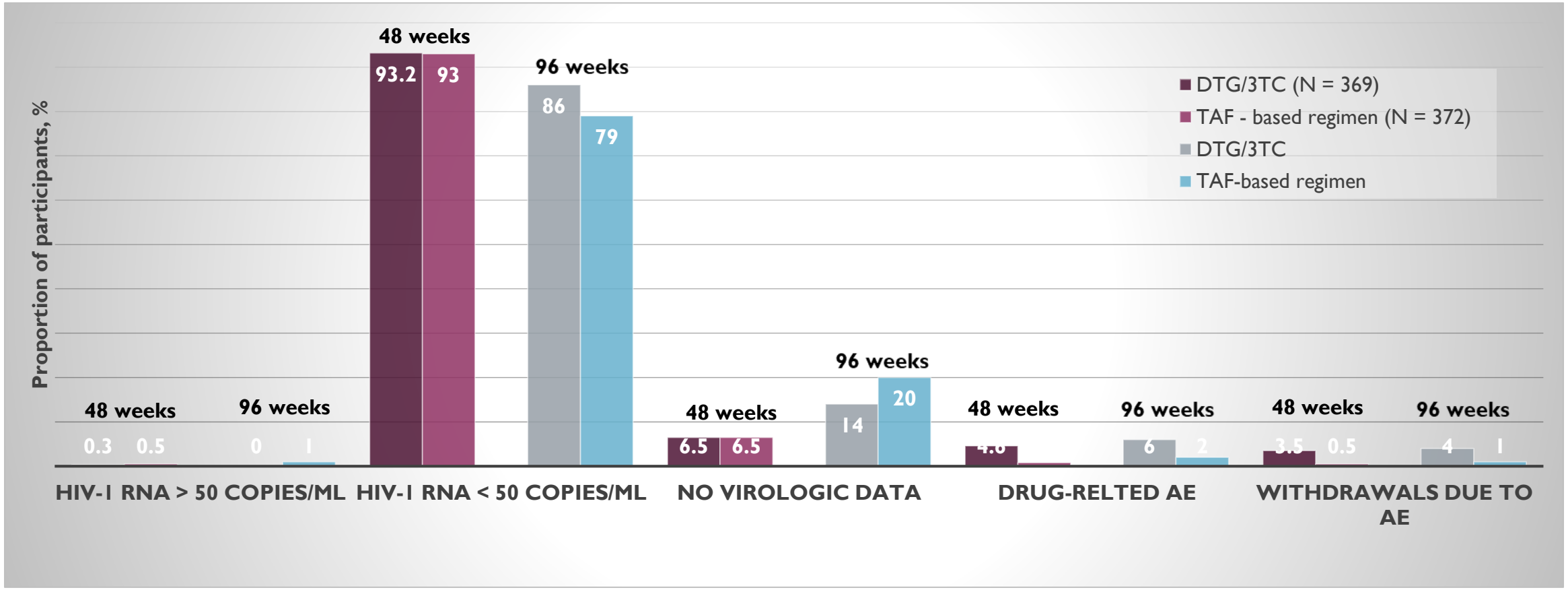
Background: ongoing, open-label, multicenter, phase 3, non-inferiority trial comparing switching to DTG/3TC versus remaining on 3-4 TAF based regimen



Primary endpoint: :Virologic response at 48 weeks

Source: Van, et al TANGO Study. *Clin Infect Dis*. 2020;71(8):1920-1929.

TANGO: VIROLOGIC OUTCOMES AT WEEK 48 & WEEK 96



Source: Van, et al TANGO Study. *Clin Infect Dis*. 2020;71(8):1920-1929.

SWITCH TO DTG/3TC VS. CONTINUED TAF-BASED 3-DRUG ART TANGO: SUMMARY

- DTG/3TC was non-inferior in maintaining virologic suppression when compared to a TAF-based regimen at week 48 and even at week 96
- No cases of treatment emergent resistance in virologically suppressed patients
- Weight change not significantly different: +0.81 kg with DTG/3TC vs +0.76 kg with continued TAF-based ART
- Lipid panel improved in the patient taking DTG/3TC, while it worsened in the TAF-based group
- Insulin resistance improved significantly after switching to DTG/3TC

Take home point: GEMINI and TANGO trials have provided strong evidence that the two-drug regimen (DTG/3TC) is non-inferior to 3-4 drug regimen therefore the DTG/3TC has been recommended for initial treatment for most people with HIV

Source: Van, et al TANGO Study. *Clin Infect Dis*. 2020;71(8):1920-1929.

ASSESSMENT QUESTION # 1

Which of the following is a two-drug regimen approved for a treatment naïve individual living with HIV?

A. Dolutegravir - rilpivirine
B. Dolutegravir - lamivudine
C. Emtricitabine - tenofovir alafenamide
D. Abacavir - lamivudine

ASSESSMENT QUESTION # 1 - RESPONSE

Which one of the following is a two-drug regimen approved for a treatment naïve individual living with HIV?

A. Dolutegravir - rilpivirine

B. Dolutegravir - lamivudine

C. Emtricitabine - tenofovir alafenamide

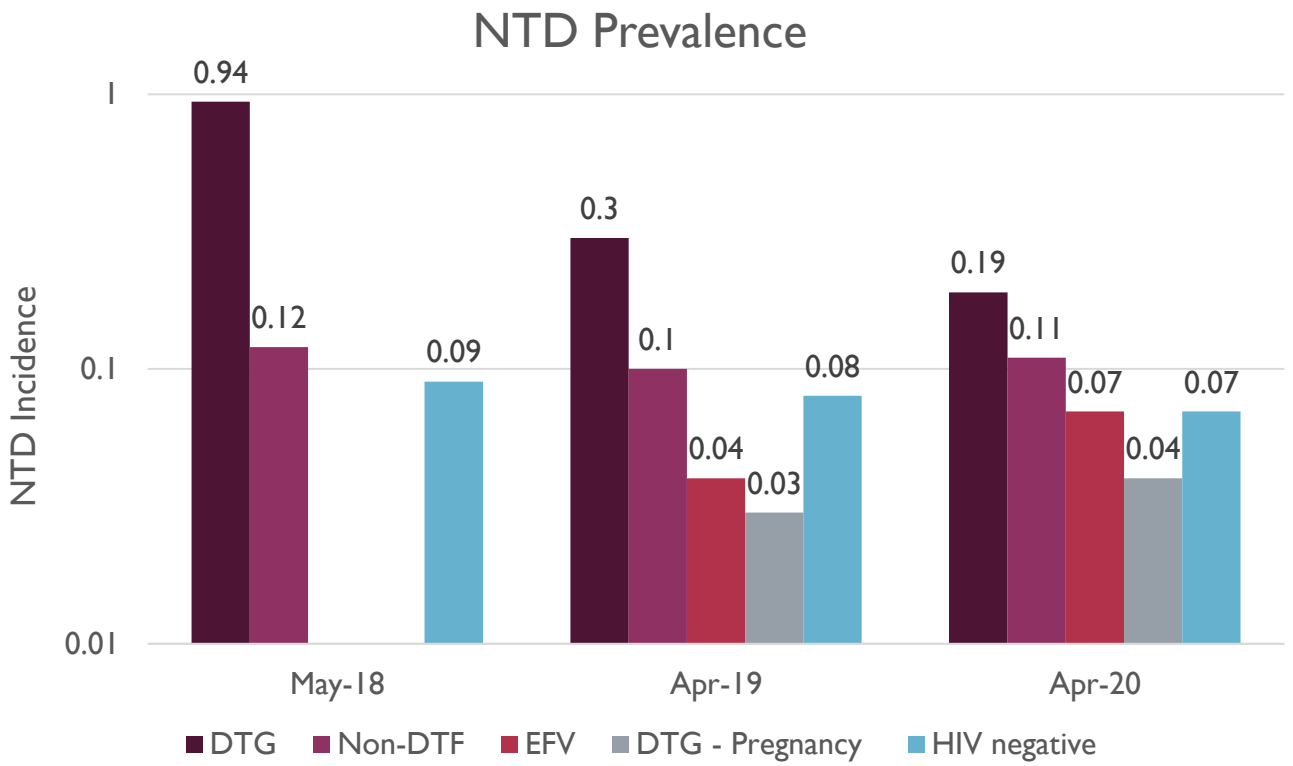
D. Abacavir - lamivudine

DOLUTEGRAVIR & NEURAL TUBE DEFECTS: UPDATE

TSEPAMO & IMPAACT 2010

TSEPAMO STUDY – APRIL 2020 UPDATE

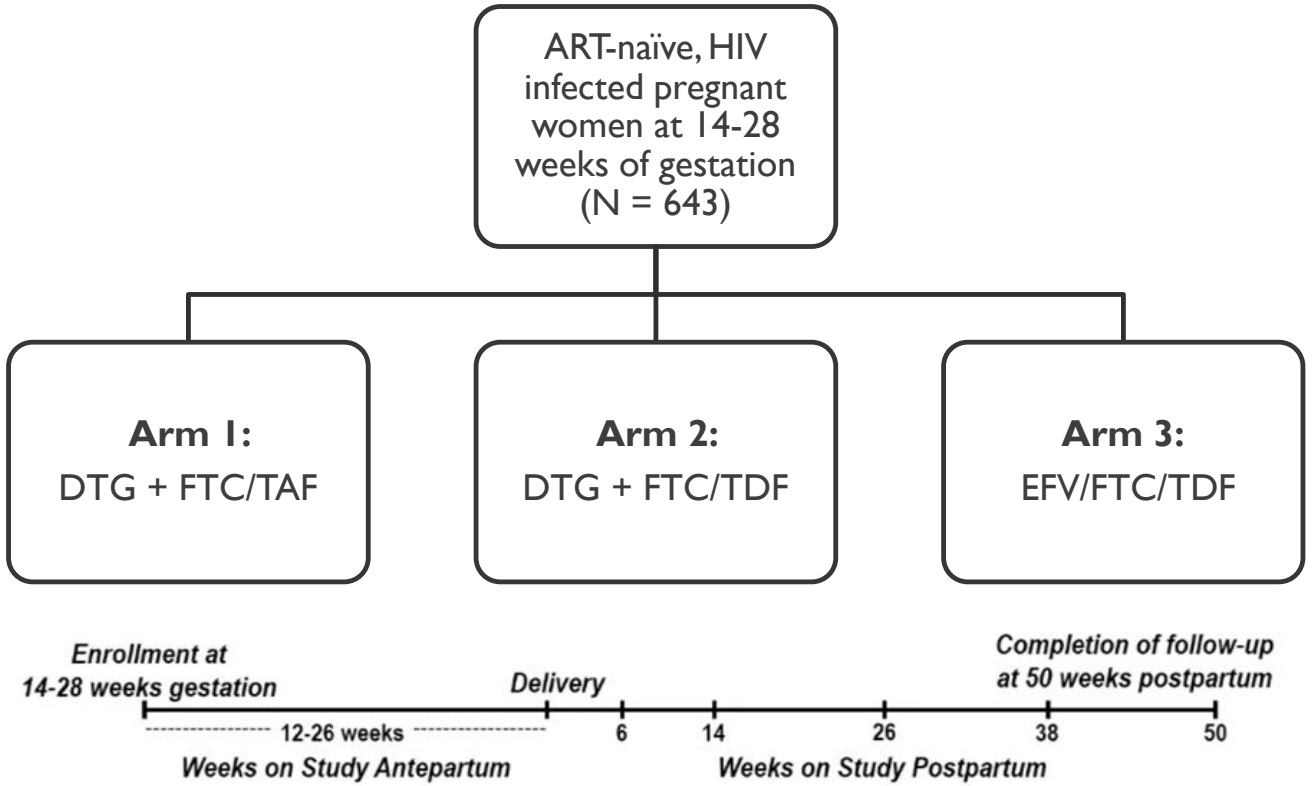
- This is a surveillance study performed at government maternity sites in Botswana since August 2014, with primary aim of evaluating neuronal tube defects (NTDs) prevalence associated with ARV exposure at conception
- In May 2018, an unplanned analysis of TSEMPO study reported increase in prevalence of NTDs after exposure to dolutegravir at conception



Sources:
1. Zash et al, *N Engl J Med*. 2018;379(10):979-981.
2. Zash et al,. *N Engl J Med*. 2019;381(9):827-840.

IMPAACT 2010 "VESTED STUDY"

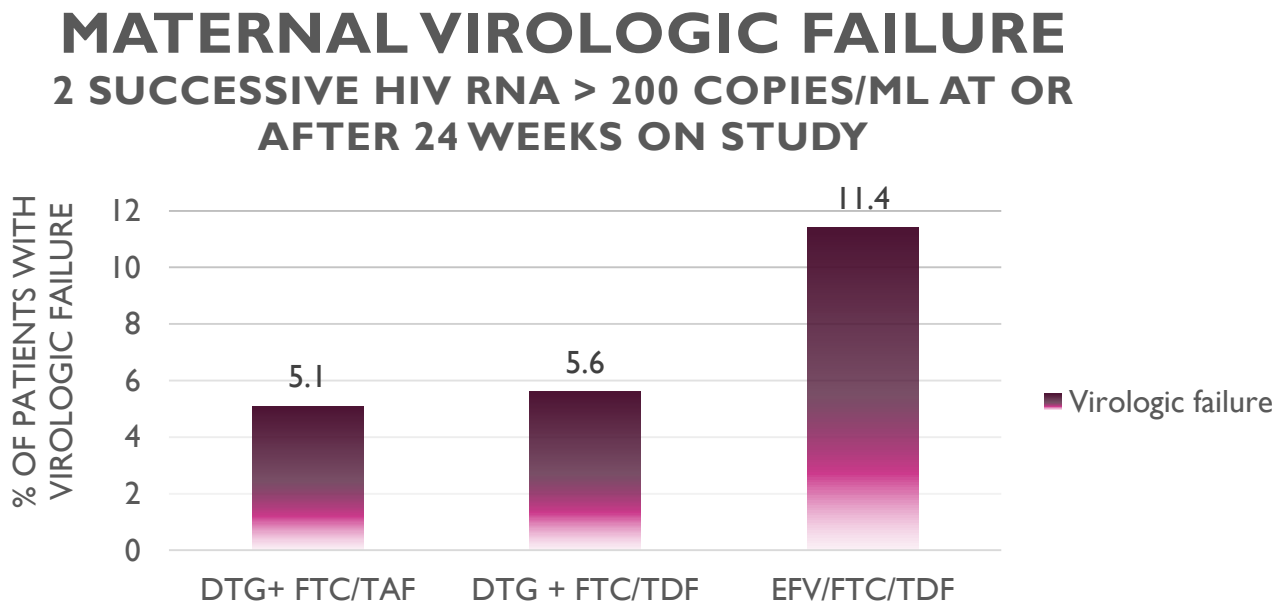
- IMPAACT 2010 is a phase III, multicenter, three-arm, randomized, open-label, non-inferiority study comparing the efficacy and safety of a DTG based ART to an EFV-containing ART in HIV infected pregnant women
  - **Primary efficacy endpoint**: maternal HIV-1 RNA < 200 copies/mL at delivery
  - **Primary safety endpoints**: adverse pregnancy composite outcome and mother and infant AEs



Sources: Chinula L et al, Virtual CROI 2021, Abstract #177

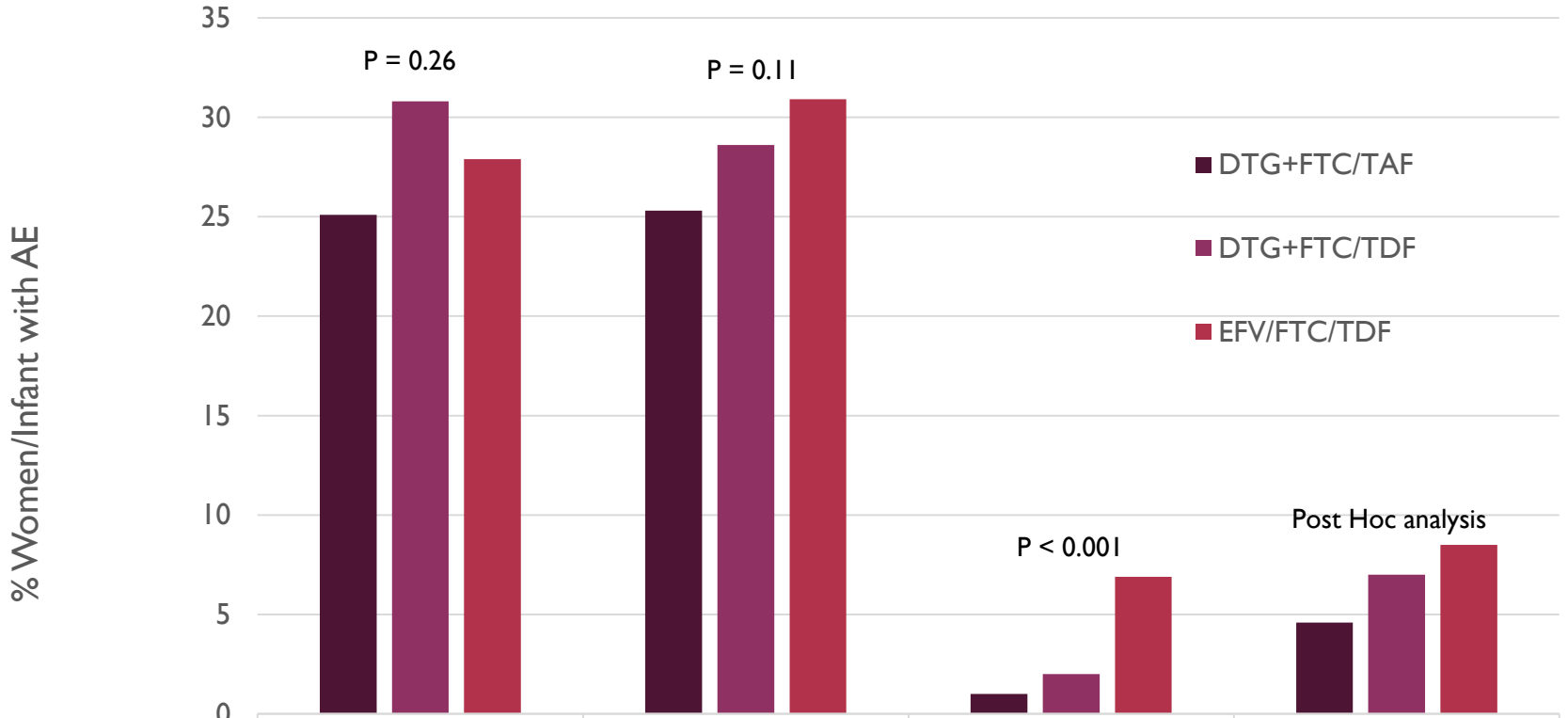
IMPAACT 2010: VIROLOGIC SUPPRESSION AT DELIVERY

Women With HIV-1 RNA < 200 c/mL at Delivery, %	Combined DTG-Based ART	EFV/FTC/TDF	P Value
ITT population	96.3	96.4	0.97



Sources: Chinula, L., et al, Virtual CROI 2021, Abstract #177

IMPAACT 2010 – GRADE 3 ≥ MATERNAL & INFANT ADVERSE EVENTS



	Materal Grade > 3 AE (%)	Infant Grade > 3 AE (%)	Infant Deaths (%)	Stillbirth or Infant Deaths (%)
DTG+FTC/TAF	25.1	25.3	1	4.6
DTG+FTC/TDF	30.8	28.6	2	7
EFV/FTC/TDF	27.9	30.9	6.9	8.5

Sources: Chinula, L., et al, Virtual CROI 2021, Abstract #177

SUMMARY DOLUTEGRAVIR BASED REGIMEN DURING PREGNANCY

- IMPAACT 2010 showed that the DTG-containing regimens and EFV-containing regimen were highly effective for viral suppression through 50 weeks postpartum
  - Infant mortality was higher in EFV/FTC/TDF arm
  - More women had virologic failure in the EFV arm

Take home point: Tsepamo and IMPAACT 2010 have shown that the DTG-containing ART are safe and provides similar virologic efficacy compared with EFV/FTC/TDF regimen.

Sources:
1. Chinula L et al, Virtual CROI 2021, Abstract #177
2. Zash et al. *N Engl J Med*. 2019;381(9):827-840

ASSESSMENT QUESTION # 2

True or False: Dolutegravir causes neuronal birth defect therefore it is contraindicated to be used in patients who are pregnant or have the potential to become pregnant.

True

False

ASSESSMENT QUESTION # 2 - RESPONSE

True or False: Dolutegravir causes neuronal birth defect therefore it is contraindicated to be used in patients who are pregnant or have the potential to become pregnant.

False

Take home point: Tsepamo and IMPAACT 2010 have shown that the DTG-containing ART are safe and provides similar virologic efficacy compared with EFV/FTC/TDF regimen. Engage in a shared-decision making and prioritize folate supplementation pre-conception.

WEIGHT GAIN WITH ART

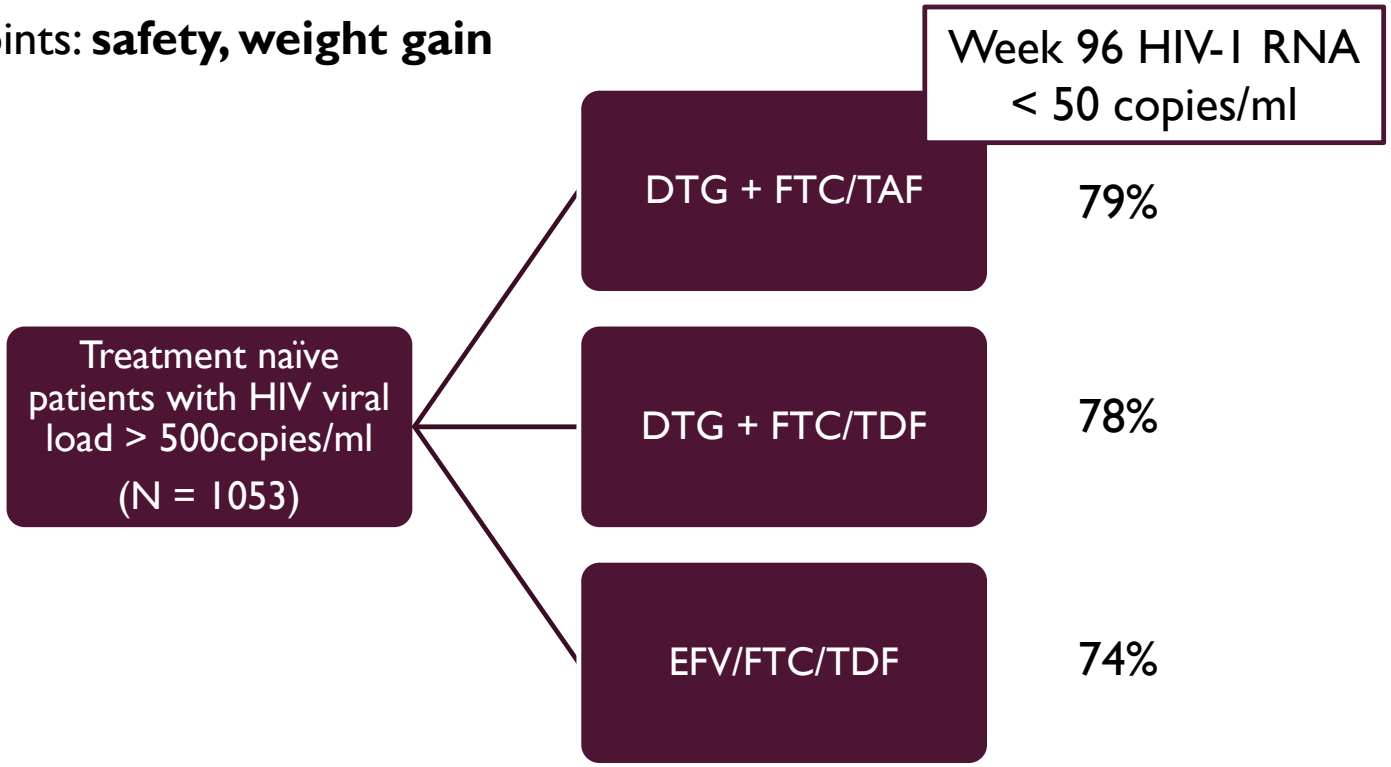
WEIGHT GAIN WITH ART

- Initiation of ART often leads to weight gain due to HIV-associated inflammation, accelerated catabolism, and alleviation of disease-related anorexia initially
- Studies suggest that patients taking INSTI and PI based ART are more likely to experience weight gain than those on NNRTI based treatment
- Patient risk factors for excess weight gain includes low CD4 count and high viral load, black race, female sex
- Regimens associated with weight gain are:
  - DTG and or BIC are associated with greater weight gain than regimens that include EVG/c and EFV
  - Among NRTIs, TAF is associated with greater weight gain than TDF or ABC
  - Among NNRTIs, RPV cause more weight gain than EFV

Sources:
1. Sax. Clin Infect Dis. 2019;[Epub].
2. Venter et al, N Engl J Med 2019; 381:803-815.
3. Van, et al TANGO Study. *Clin Infect Dis*. 2020;71(8):1920-1929.

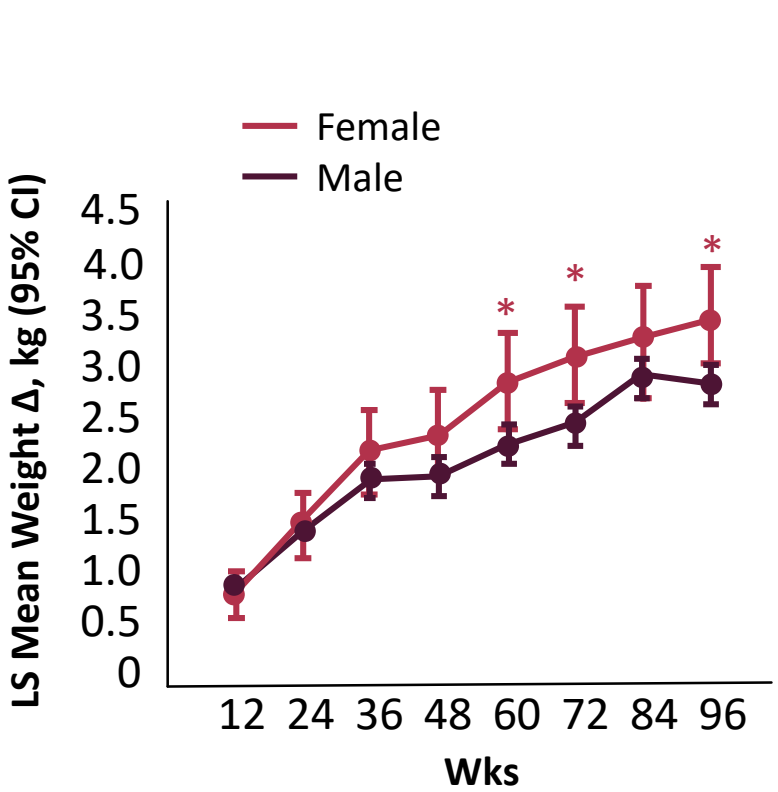
ADVANCE: DOLUTEGRAVIR PLUS TWO DIFFERENT PRODRUGS OF TENOFOVIR TO TREAT HIV

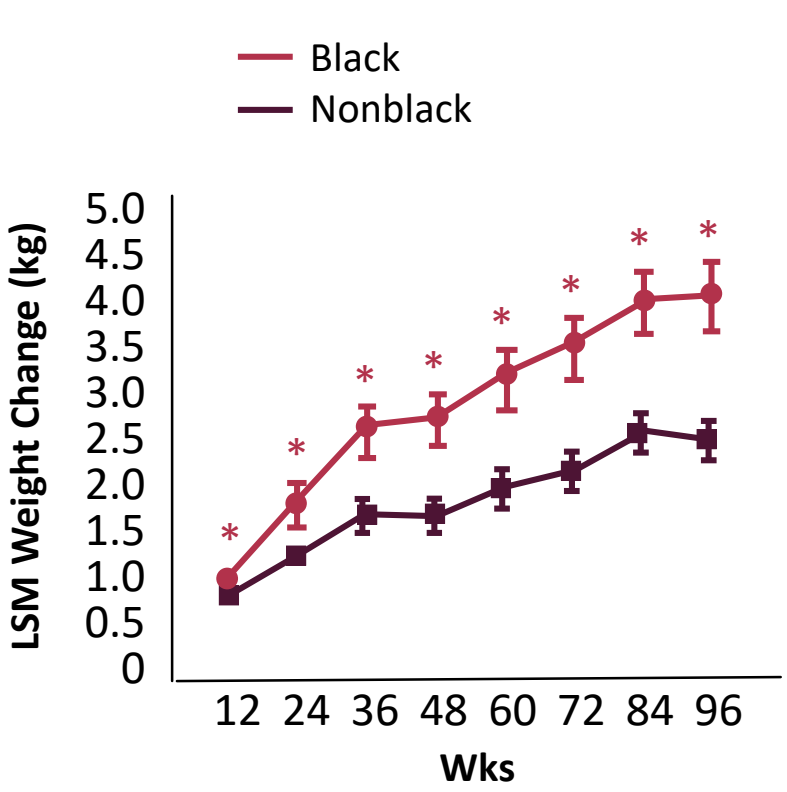
- 96-week, phase 3, investigator-led, open-label, randomized trial in South Africa
- Primary efficacy endpoint: HIV-1 RNA < 50 copies/mL at week 48
- Secondary endpoints: **safety, weight gain**

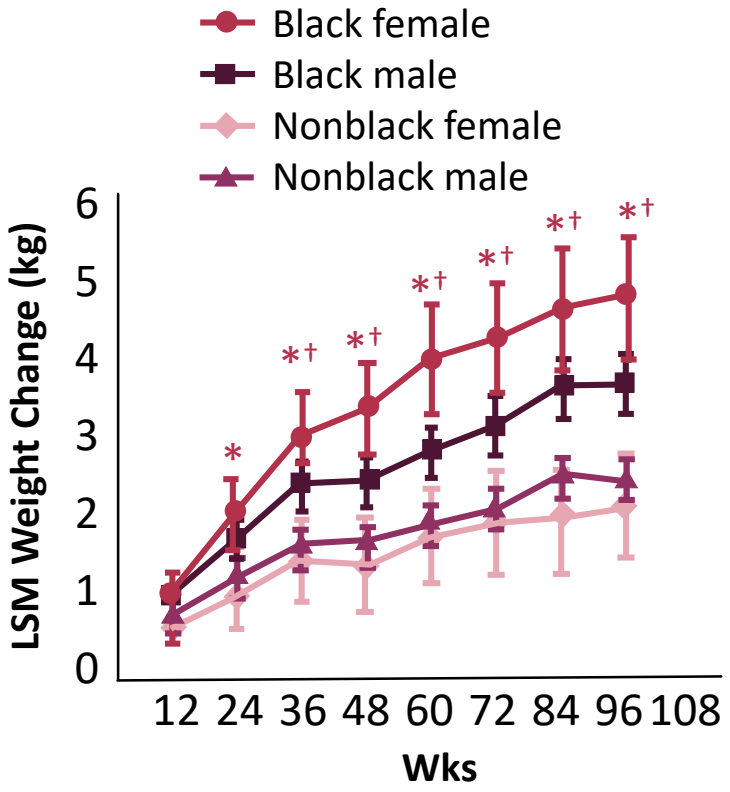


Source: Venter et al, the lancet HIV 2020; 7(10).

WEIGHT GAIN FOLLOWING INITIATION OF ANTIRETROVIRAL THERAPY





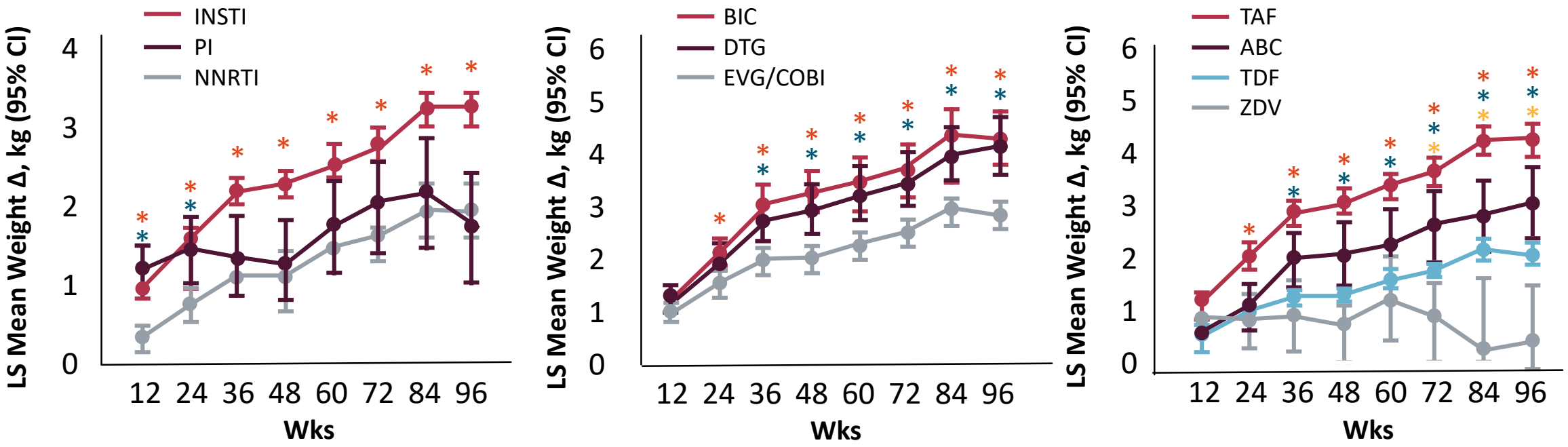


*Color-coded to match respective comparators, denoting $P < .05$ vs male (first panel), nonblack (second panel), or nonblack females (last panel).

Sources:

1. Hill. IAS 2019. Abstr MOAX0102LB.
2. Venter et al, N Engl J Med 2019; 381:803-815
3. Venter et al, the lancet HIV 2020; 7(10).

WEIGHT GAIN FOLLOWING INITIATION OF ART BY ARV CLASS/DRUG



*Color-coded to match respective comparators, denoting $P \leq .05$ vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (last panel).

Sources:
1. Hill. IAS 2019. Abstr MOAX0102LB.
2. Venter et al, N Engl J Med 2019; 381:803-815
3. Venter et al, the lancet HIV 2020; 7(10).

TAKE HOME POINTS

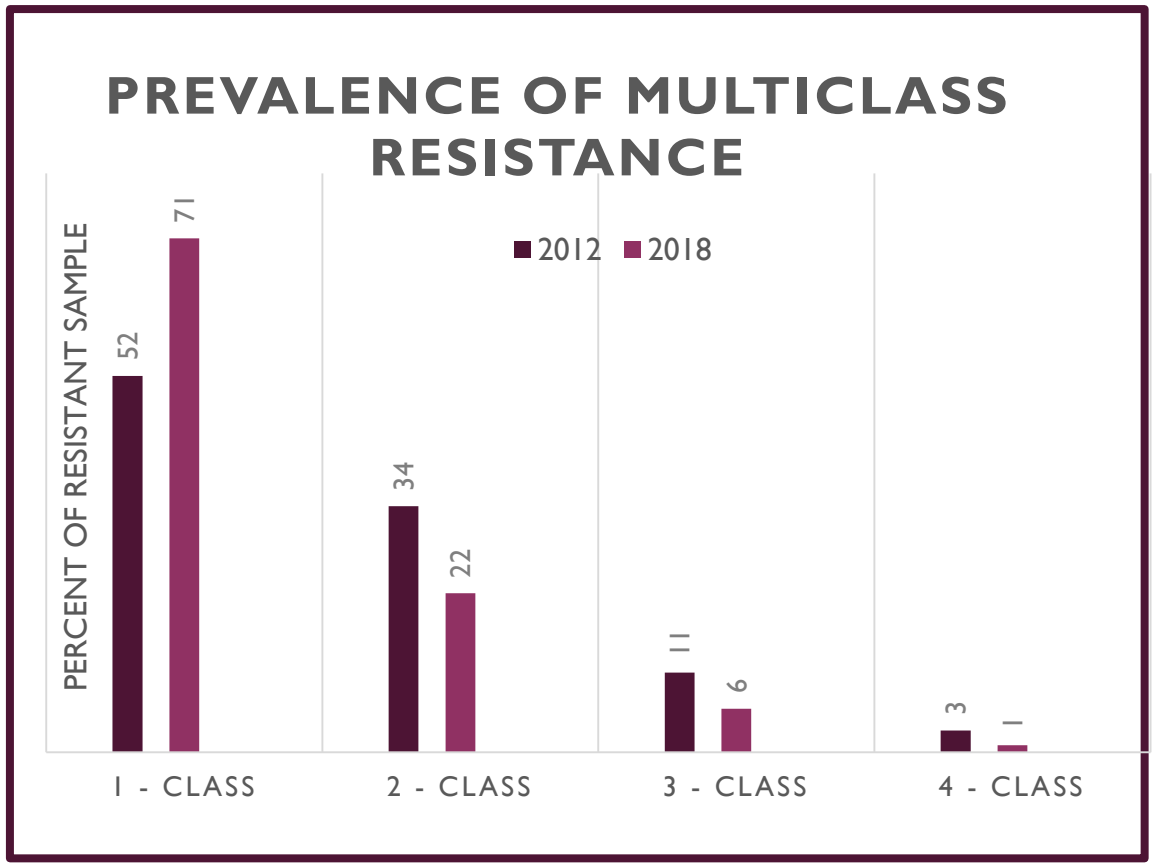
- In the ADVANCE study, patients in DTG and TAF group had a significantly greater weight increase than patient in EFV and TDF group
  - Switching from TDF to TAF based regimens also led to rapid weight gain, regardless of the other HIV drugs in the regimen
- According to the TANGO trial, DTG/3TC appears to be associated with decreased risk of insulin resistance and improvement in lipid profile compared to TAF based regimen

> The weight gain appears higher with INSTIs than other drug class. Also, greater weight increase has also been reported with TAF than with TDF.

- DHHS guideline recognizes the weight gain associated with ART but there are no current recommendation to avoid INSTIs or TAF due to potential for weight gain

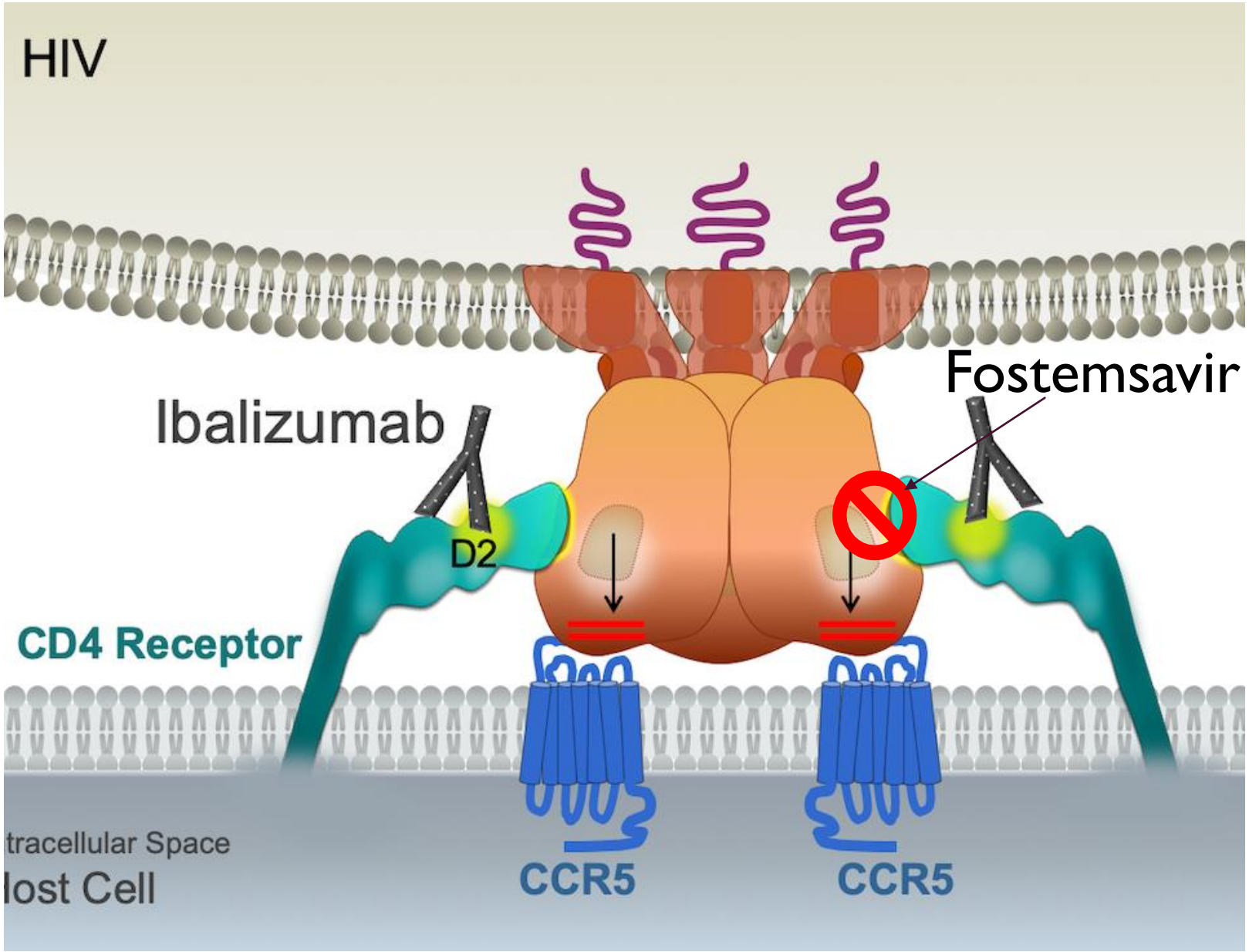
DO WE NEED NEW ART AGENTS?

TRENDS OF HIV-1 DRUG RESISTANCE IN THE U.S. (2012-2018)



- 84,611 samples evaluated, 27,911 (33.0%) demonstrated reduced susceptibility to at least one ARV
- The decline in the resistance trend was due to availability of newer treatment options with favorable cross-resistance profiles, improved efficacy, and more convenient formulations leading to better adherence

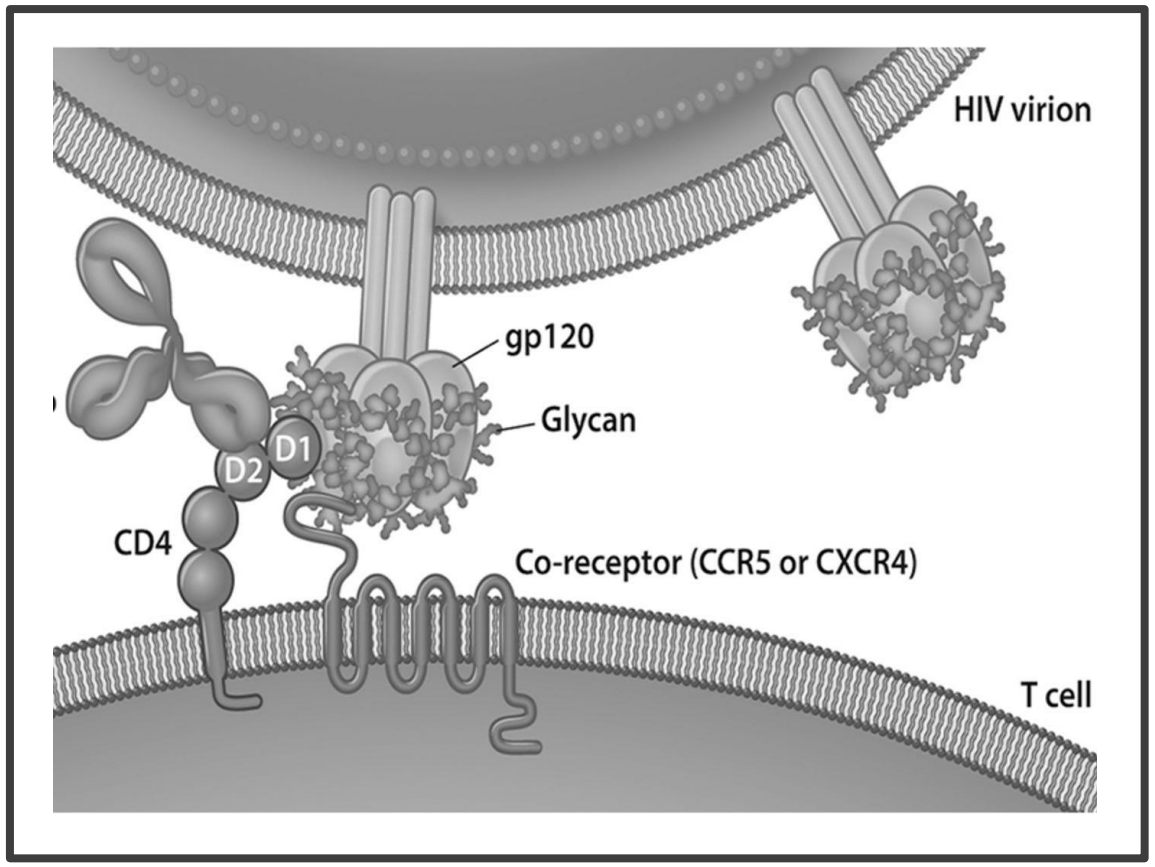
Source: Heneger CE et al. CROI 2020; Abstr. 521



Original illustration: David Spach, MD; https://www.hiv.uw.edu/

ENTRY INHIBITORS

IBALIZUMAB (TROGARZO®)



- FDA approved in March 2018 for heavily treatment experienced adults with MDR HIV-1
- **Class:** CD4-directed post-attachment inhibitor
  - Binds to CD4 and prevents HIV entry into the cell
  - Also blocks HIV from binding to CCR5 & CXCR4
- **IV infusion every 2 weeks**
  - Loading dose of 2 gm; maintenance dose of 800 mg
  - Observe patient for 1 hour post loading dose, if no reaction can be 15 min for maintenance doses
- Common side-effects: skin rash, diarrhea, dizziness, nausea

Source: Trogarzo (ibalizumab-uiyk) [package insert]. Montreal, Quebec, Canada: Theratechnologies Inc; March 2020.

TRIAL TMB 301 & 311: IBALIZUMAB FOR MULTIDRUG-RESISTANT HIV-1

- Single arm, open-label, multicenter Phase III study conducted in 40 heavily treatment experience with MDR
- Ibalizumab with optimized background regimen with at least 1 fully active agent
- 55% of patients had viral load <50 copies/mL at week 25 and at week 48, that increased to 67%

Day 14
7 days following loading dose of Ibalizumab

	Day 7 Control period	Day 14 Functional monotherapy Period	P – value
Decrease in viral load of > 0.5 log copies/ml (%)	3%	83%	< 0.001
Decrease in viral load of > 1.0 log copies/ml (%)	0%	60%	N/A
Mean change in viral load after baseline	0 log_{10}	-1.1 log_{10}	< 0.001

Sources:
1. Trogarzo (ibalizumab-uiyk) [prescribing information]. Montreal, Quebec, Canada: Theratechnologies Inc; May 2021.
2. Emu et al,. *N Engl J Med*. 2018;379(7):645-654.

FOSTEMSAVIR (*RUKOBIA*®)

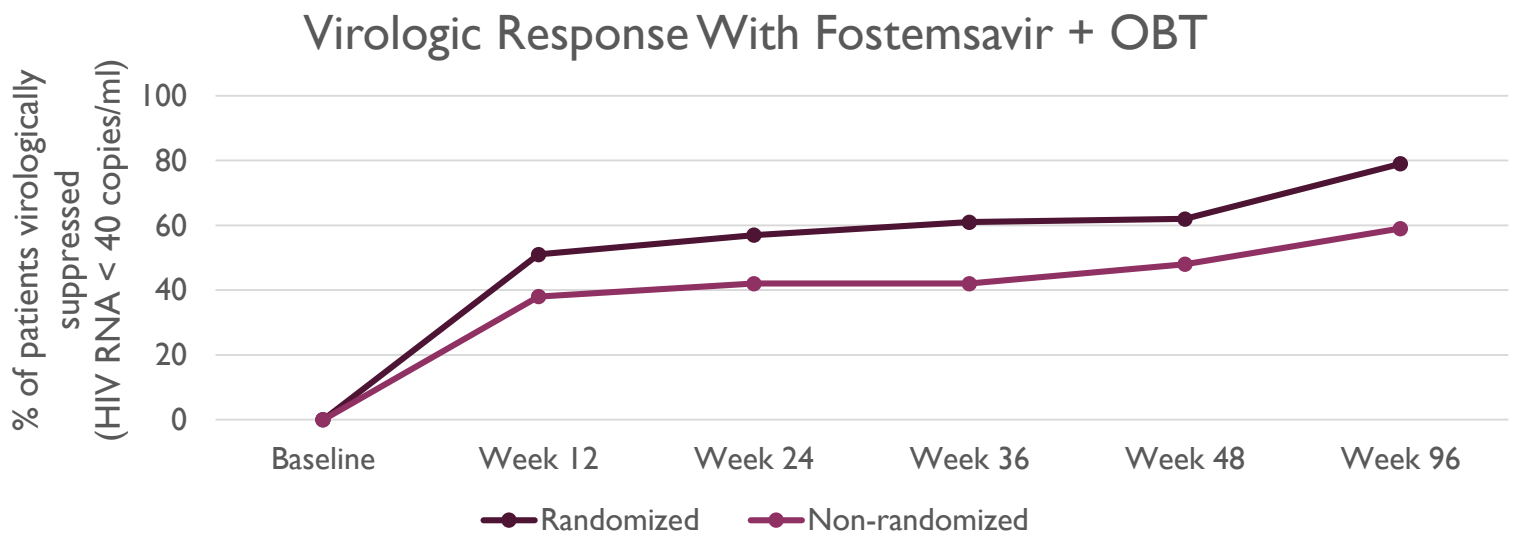
- **Class:** CD4 attachment inhibitor
- Temsavir, an active moiety attaches directly to gp120 on the surface of HIV-1 virions
- FDA approved in July 2020 for heavily treatment-experienced adults with MDR failing their current ART regimen
- **Dose:** 600mg tablet orally twice a day with or without food
- **Adverse reactions**: Immune reconstitution syndrome, QTc prolongation, elevations in hepatic transaminase

Sources: Rukobia (Fostemsavir) [package insert]. Research Triangle Park, NC: ViiV Healthcare; July 2020

BRIGHTE STUDY

SAFETY & EFFICACY OF FOSTEMSAVIR IN HEAVILY TREATMENT-EXPERIENCED INDIVIDUALS

- Phase 3, international, double blinded, placebo-controlled trial compared the addition of fostemsavir 600 mg twice daily or placebo to a failing ART regimen in a heavily treatment experienced adults with multiclass drug resistance
- On day 8, 65% of patients receiving fostemsavir demonstrated a viral load reduction > 0.5 log10 copies/mL
- Significant reduction in viral RNA level compared to placebo during first 8 days and this efficacy was sustained through week 96 weeks



Source: Kozal et al, *N Engl J Med*. 2020;382(13):1232-1243.

ASSESSMENT QUESTION # 3

Which one of the following statement is true about fostemsavir?

A. It is an entry/attachment inhibitor
B. It is designed to be used in HIV treatment experience patients
C. The tropism of HIV is unimportant
D. All of the above

ASSESSMENT QUESTION # 3 – RESPONSE

Which one of the following statements is true about fostemsavir?

A. It is an entry/attachment inhibitor
B. It is designed to be used in HIV treatment experience patients
C. The tropism of HIV is unimportant
D. **All of the above**

LONG-ACTING ART

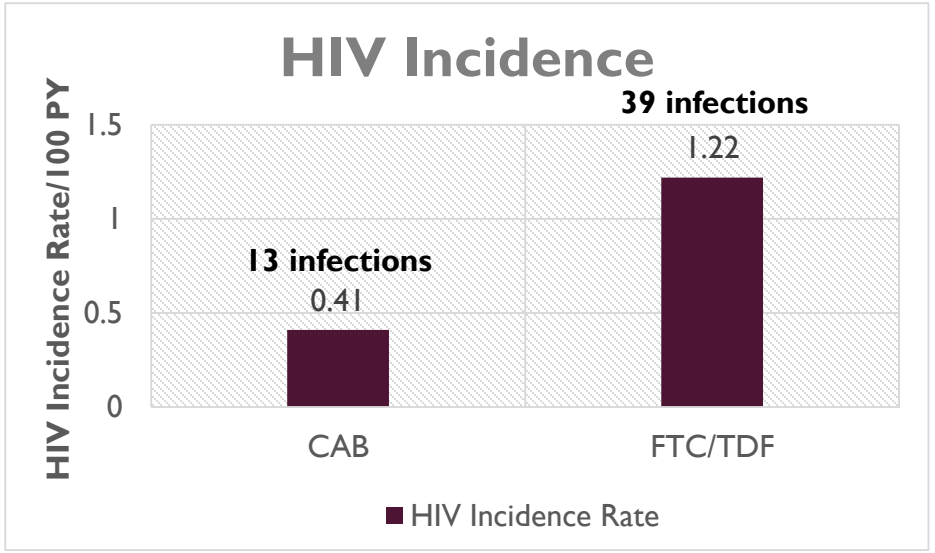
CABOTEGRAVIR (CAB) (VOCABRIA®)

- New Integrase strand transfer inhibitor (INSTIs) approved in January 2021
- Approved to be use with rilpivirine for short-term HIV treatment and in phase 3 trial for HIV prevention
  - Oral lead-in to assess tolerability prior to initiating cabotegravir with rilpivirine combination
  - Oral bridging therapy for missed cabotegravir with rilpivirine injection
- Active against some INSTI resistant strains
- Half-life: 5.6 to 11.5 weeks (ER injectable) and 41 hours (oral)
- Common side effects: mild injection site reactions, nodules with SC

Sources: Vocabria (cabotegravir)) [package insert]. Laval, Quebec, Canada: ViiV Healthcare ULC; March 2020

CABOTEGRAVIR FOR PRE-EXPOSURE PROPHYLAXIS

- **HPTN 083** is an ongoing randomized phase 2b/3 study evaluating long-acting CAB given **every 2 months** compared to daily FTC/TDF for HIV PrEP
  - 4566 men and transgender women who have sex with men received CAB for up to 3 years
  - 66% reduction in HIV infection demonstrated superiority of injectable CAB as PrEP
  - 2% of participants discontinue CAB because of an injection-related adverse event.
- **HPTN 084** in cis-women has recently reported superiority to oral PrEP, with an 89% reduction in HIV infections compared to the oral regimen



Source: Landovitz RJ et al. AIDS 2020, #OAXLB01

CABOTEGRAVIR + RILPIVIRINE (CABENUVA)

- First and only once-monthly, long-acting IM injectable containing combination of INSTI and NNRTI for the treatment of HIV approved in January 2021
- Indicated to replace current ART in virologically suppressed individual who are also on a current stable ART with no history of treatment failure or resistance
- ADRs: injection site reactions, fatigue, fever, headache, nausea, musculoskeletal pain

Oral Daily Lead In x 1 month

- Cabotegravir 30 mg daily + Rilpivirine 25 mg daily

Loading (injectable) x 1

- IM Cabotegravir 600 mg + Rilpivirine 900 mg

Maintenance (Monthly)

- IM Cabotegravir 400 mg + Rilpivirine 600 mg

<u>3 major studies</u>
ATLAS
ATLAS – 2M
FLAIR

Source: CABENUVA [package insert]. Research Triangle Park, NC: ViiV Healthcare; 2021.

CABOTEGRAVIR + RILPIVIRINE (CABENUVA) – SPECIAL CONSIDERATION

- Gluteal IM injection
- **Storage:** Refrigerator (vial may remain at room temperature for ≤6 hours)

Missed doses:

- Up to 7 days before or after the date of the scheduled monthly injection
- Planned missed injections:
  - Administer oral therapy to replace up to 2 consecutive monthly injections
- Unplanned missed injections:
  - ≤2 months since last injection: Continue with maintenance dose
  - >2 months since last injection: Reinitiate with leading injection then maintenance

Source: CABENUVA [package insert]. Research Triangle Park, NC: ViiV Healthcare; 2021.

ASSESSMENT QUESTION # 4

Which one of the following statements are true about administration of cabotegravir + rilpivirine? (Select all that apply)

A. Patient have to receive the injection on the same day every month
B. Patient can receive the injection up to 7 days before or after the date of the scheduled monthly injection
C. Patient can receive the injection up to 3 days before or after the date of the scheduled monthly injection
D. This is a Subcutaneous injection
E. This is intramuscular injection

ASSESSMENT QUESTION # 4 – RESPONSE

Which one of the following statement is true about administration of cabotegravir + rilpivirine? (Select all that apply)

A. Patient have to receive the injection on the same day every month

B. Patient can receive the injection up to 7 days before or after the date of the scheduled monthly injection

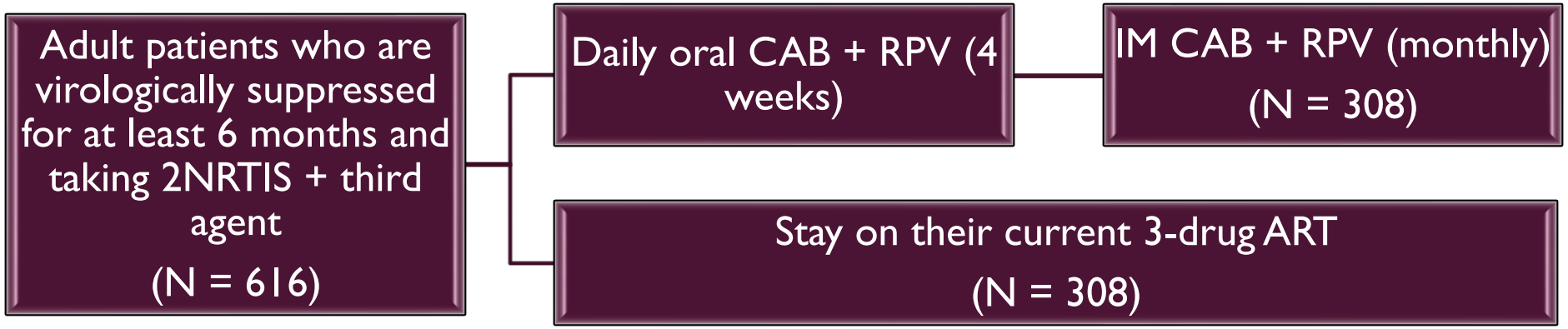
C. Patient can receive the injection up to 3 days before or after the date of the scheduled monthly injection

D. This is a Subcutaneous injection

E. This is intramuscular injection

ATLAS STUDY: LONG-ACTING IM CAB & RPV FOR HIV MAINTENANCE

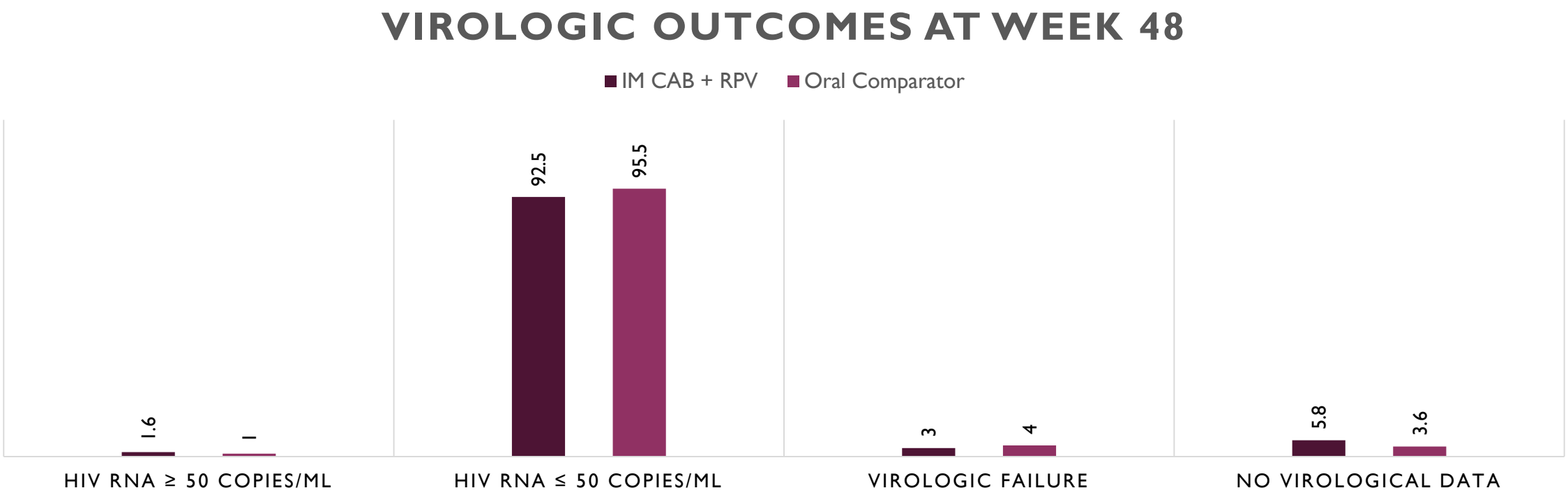
- Phase 3, randomized, open label trial assessing long-acting IM cabotegravir plus rilpivirine after oral induction for adults taking a 3-drug oral antiretroviral therapy regimen



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

ATLAS STUDY: LONG-ACTING IM CAB & RPV FOR HIV MAINTENANCE

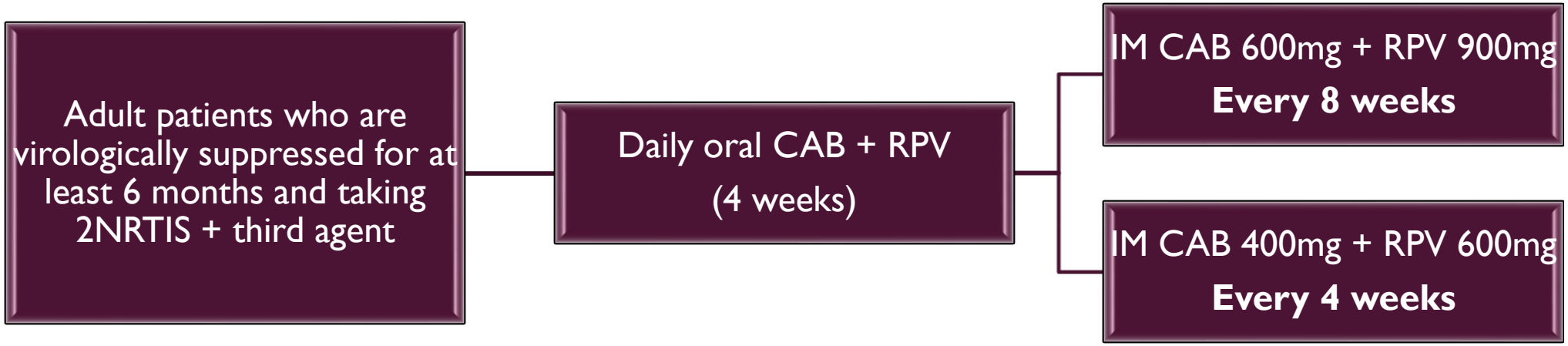
- Injectable site reactions were the common adverse events reported by patients receiving injectable ART



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

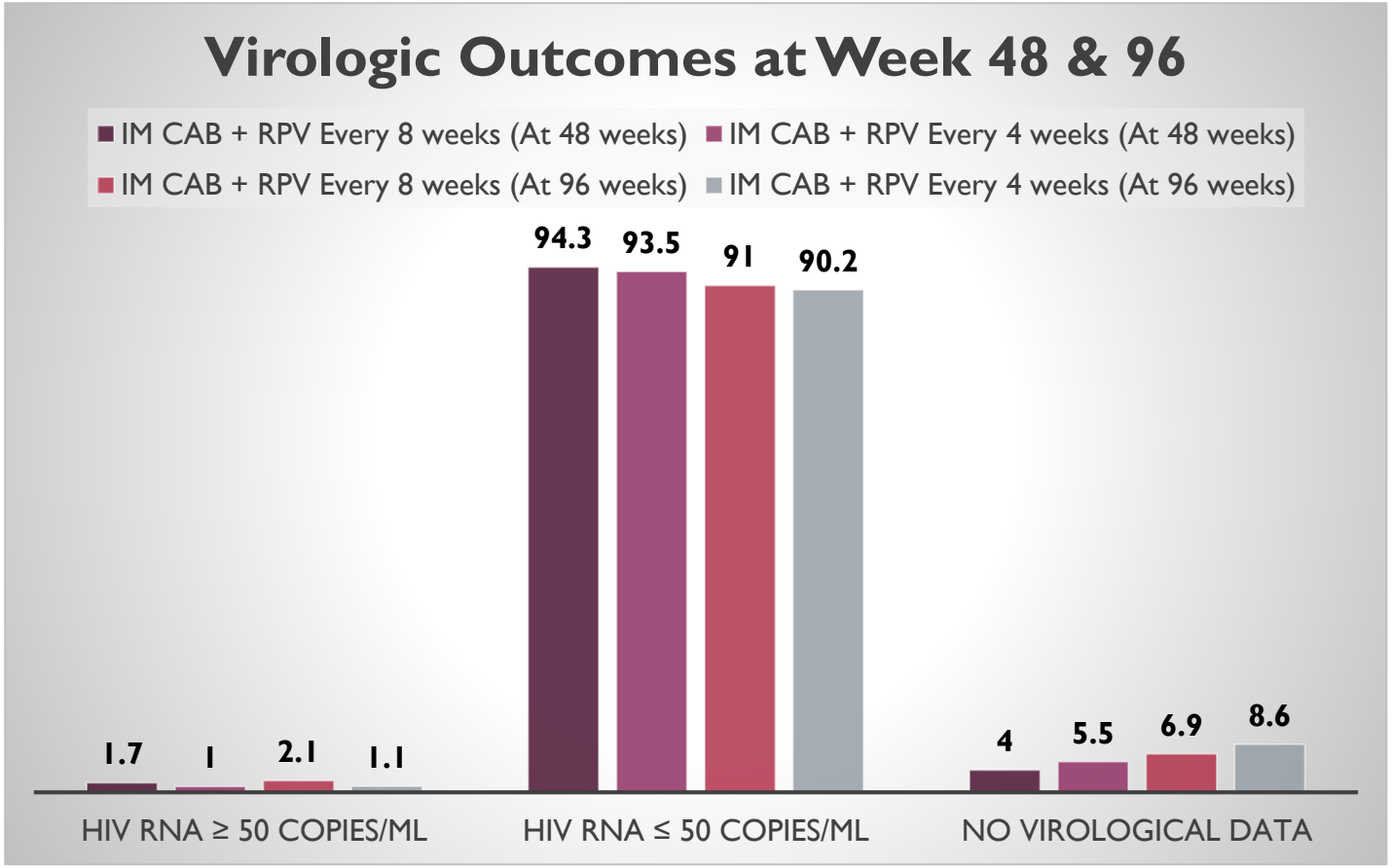
ATLAS 2M STUDY: LONG-ACTING IM CAB & RPV EVERY 2 MONTHS FOR HIV MAINTENANCE

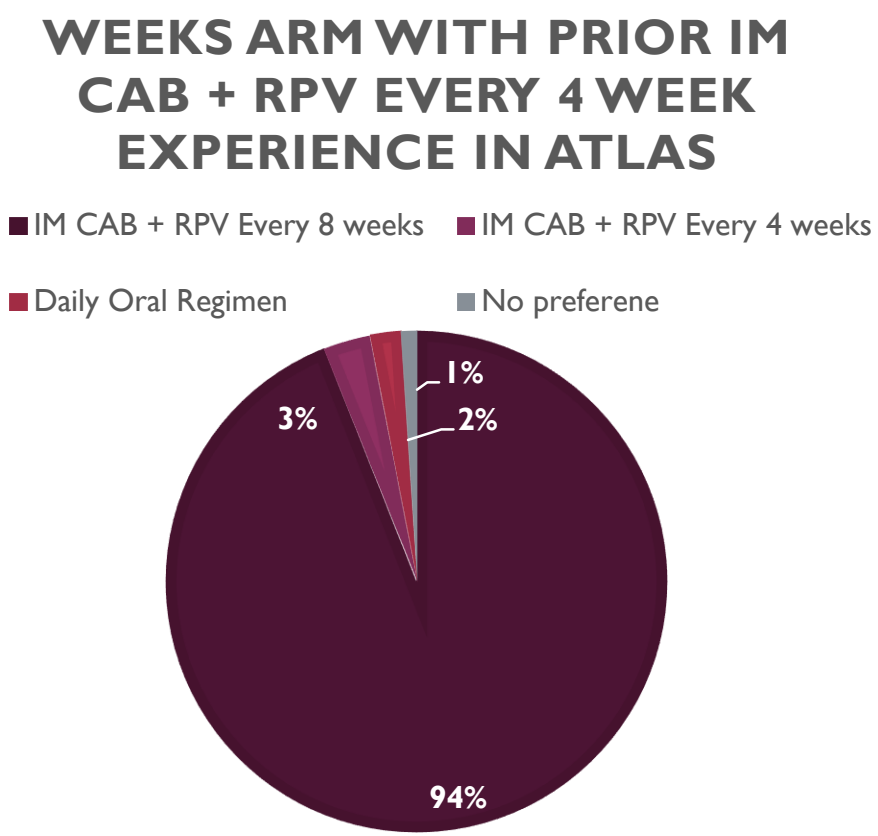
- A multicenter, open-label, Phase 3b noninferiority study of CAB+RPV LA maintenance therapy administered every 8 weeks versus every 4 weeks in the treatment-experienced, HIV-infected adults



Sources:
1. Overton et al, Lancet. 2021 Dec 19;396(10267):1994-2005
2. Jaeger H et al, Virtual CROI 2021, Abstract #401

ATLAS 2M STUDY: LONG-ACTING IM CAB & RPV EVERY 2 MONTHS FOR HIV MAINTENANCE



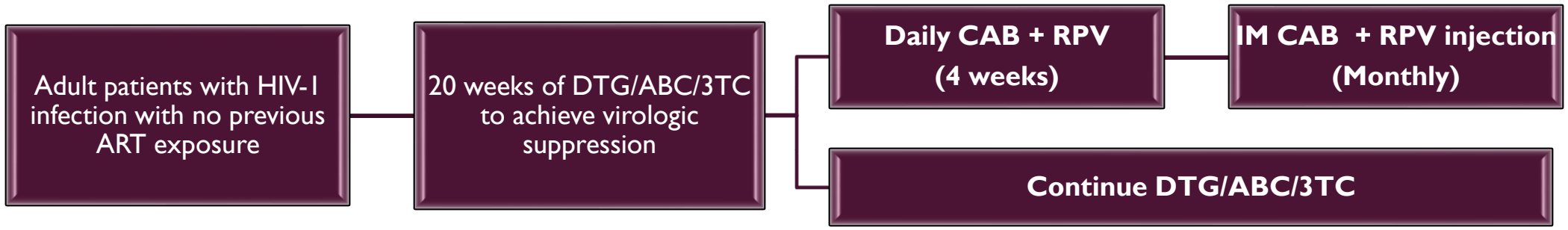


Sources:

1. Overton et al, Lancet. 2021 Dec 19;396(10267):1994-2005
2. Jaeger H et al, Virtual CROI 2021, Abstract #401

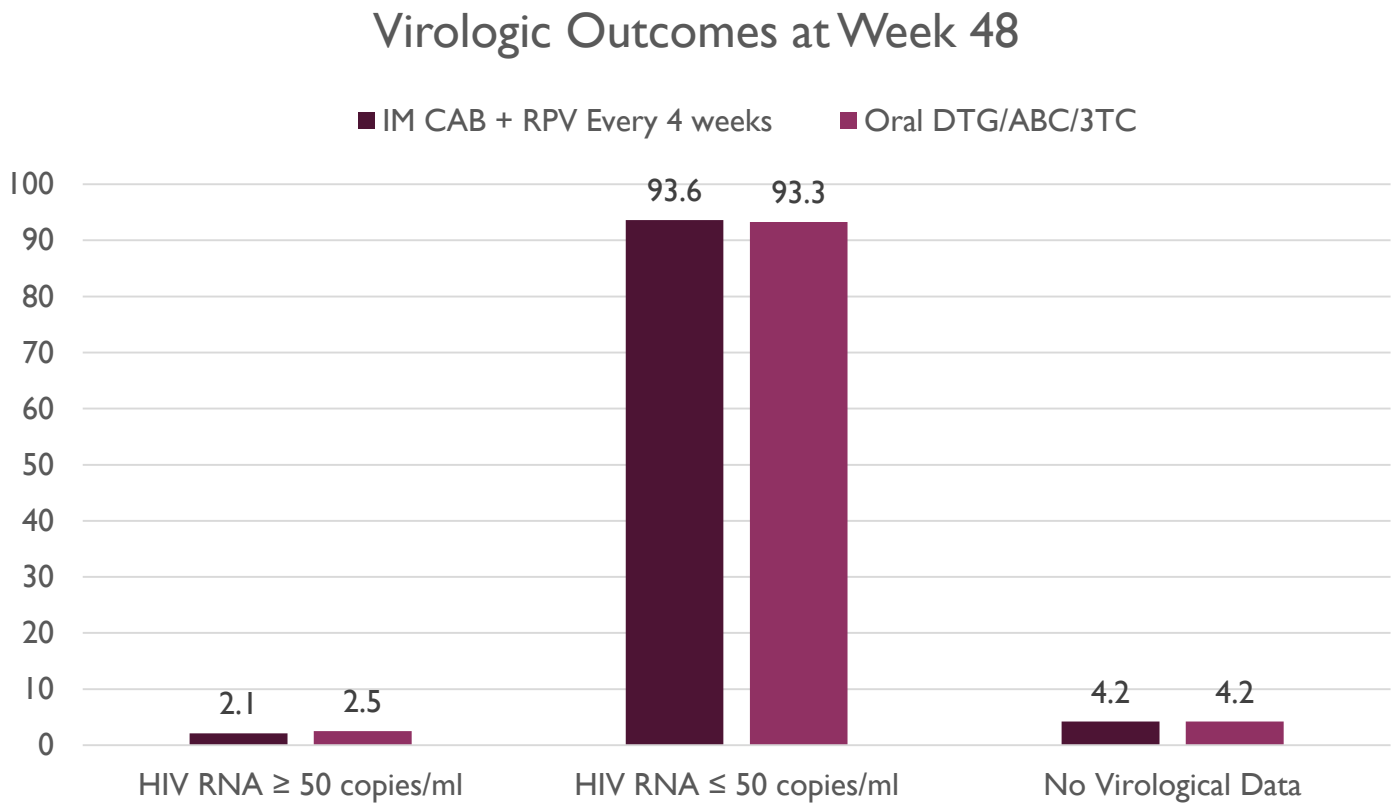
FLAIR STUDY: LONG-ACTING IM CAB & AFTER ORAL INDUCTION

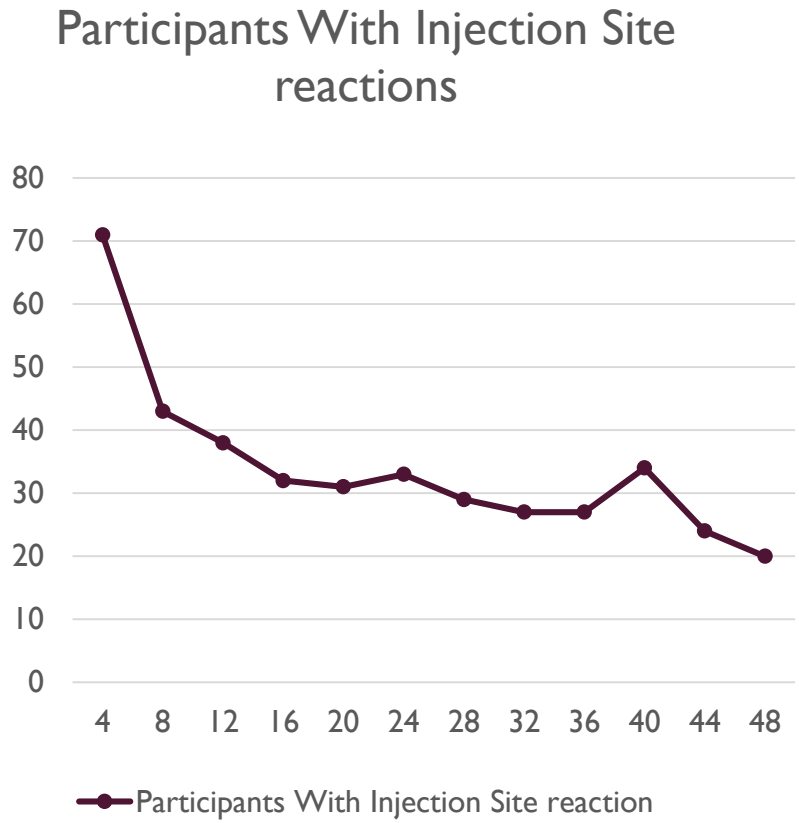
- Phase 3, randomized, open label, trial assessing IM CAB + RPV after oral induction for **treatment naïve** adults



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

FLAIR STUDY: LONG-ACTING IM CAB & AFTER ORAL INDUCTION





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

LONG-ACTING IM CABOTEGRAVIR + RILPIVIRINE

- **ATLAS:** IM injections of CAB + RPV every 4 weeks was non-inferior to daily oral ART at week 48
- **ATLAS 2M**: Every 8 weeks dosing of IM CAB+RPV was non-inferior to every 4 weeks dosing and well tolerated
- **FLAIR**: IM injections of CAB + RPV every 4 weeks was non-inferior to daily oral DTG/ABC/3TC at week 48
- Low rate of virologic failure in each arm
- No emergence of resistance
- Injection site reactions in the LA arm were common but mainly grade 1 or 2, with few associated discontinuations

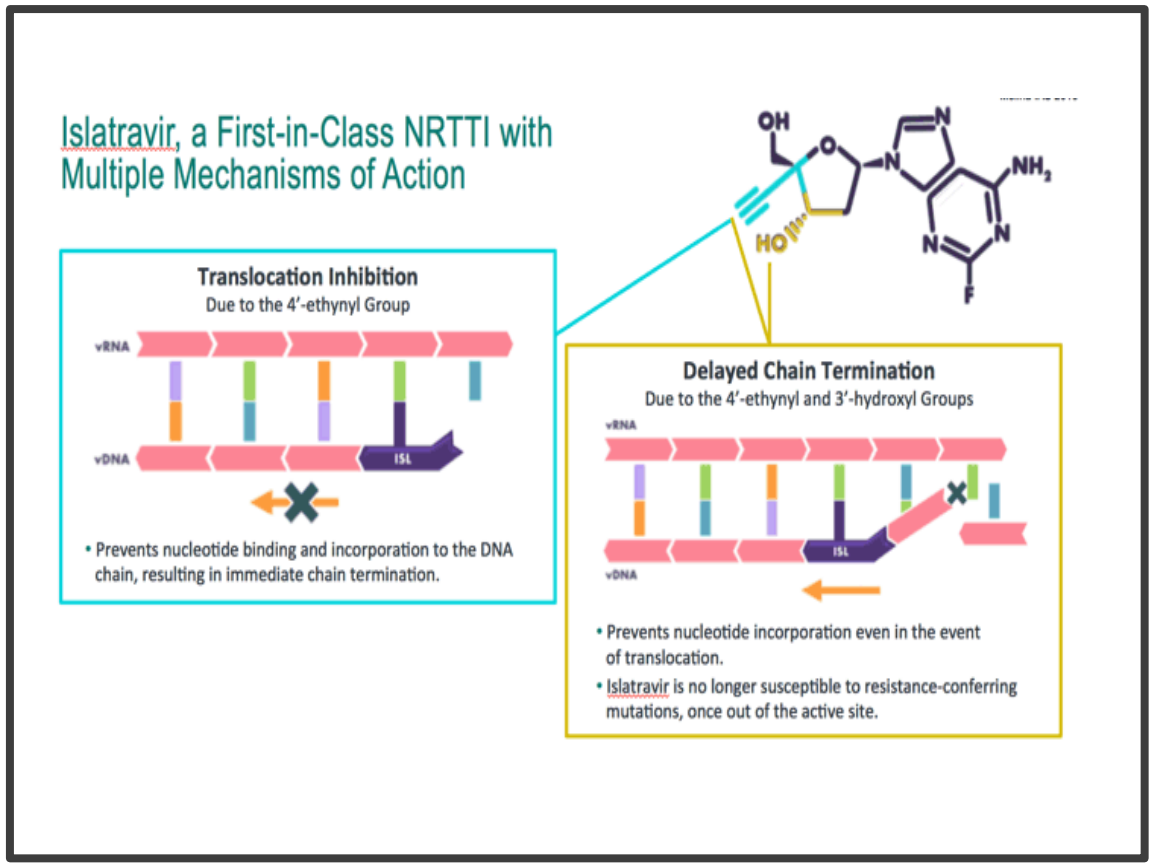
Take Home Point: Monthly injectable CAB and RPV is non-inferior to continuing oral ART. In both studies, adult patients expressed a high degree of treatment satisfaction and preference for the LAI ART. The Panel at HHS recommends this agent as an optimization strategy for people with HIV currently on oral ART with documented viral suppression for at least 3 months.

ART WITH NEW MECHANISM OF ACTION

TRANSLOCATION INHIBITOR

CAPSID INHIBITOR

ISLATRAVIR (ISL)

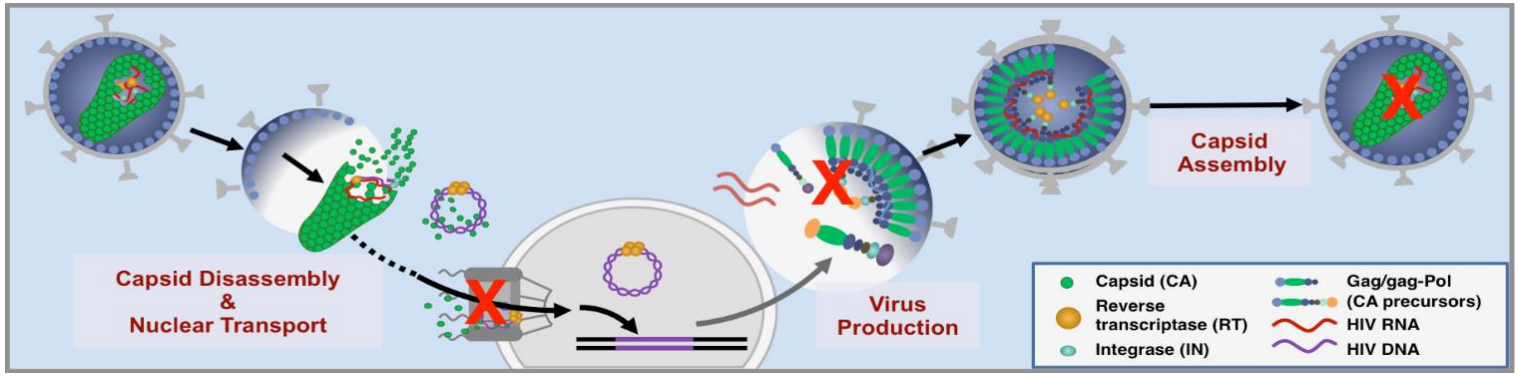


- First Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- **Potential advantages:**
  - Active against isolates with pre-existing NRTI resistance
  - Potent viral load reduction plus high barrier to resistance
  - Long half-life (190 hours with oral dosing)
  - Potential for once-daily, once-weekly, or less frequent oral dosing; much less frequent for other formulations
    - Potent at low doses: single 0.5mg suppressed HIV RNA for > 7 days
  - Ongoing phase 2 trial

Source: Schurmann et al, Lancet HIV, 2020.

LENACAPAVIR (LEN)

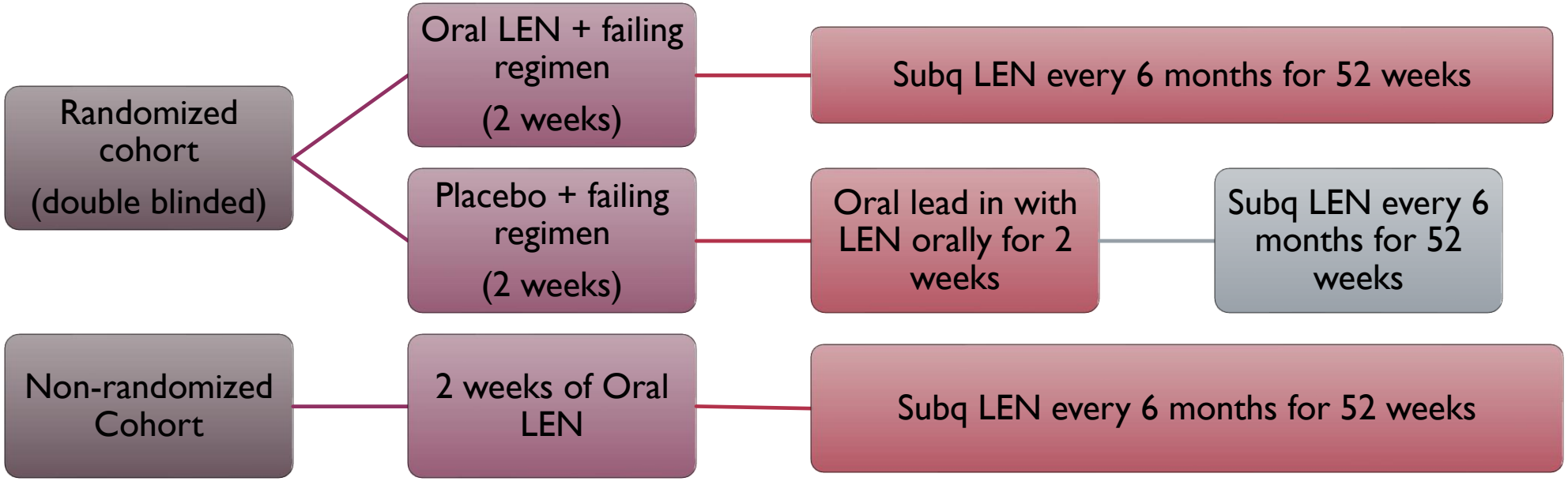
- HIV capsid inhibitor
- An option for heavily treatment experience patients with MDR HIV
- In-vitro: active against HIV-1 variants and resistant strains
- Low clearance resulting in a very long half life
- Ongoing clinical trials for both treatment and PrEP



Sources:
1. Segal-Maurer S et al, Virtual CROI 2021, Abstract # 127
2. Sager et al. CROI 2019, #141

CAPELLA STUDY – LENACAPAVIR IN MDR HIV INFECTION

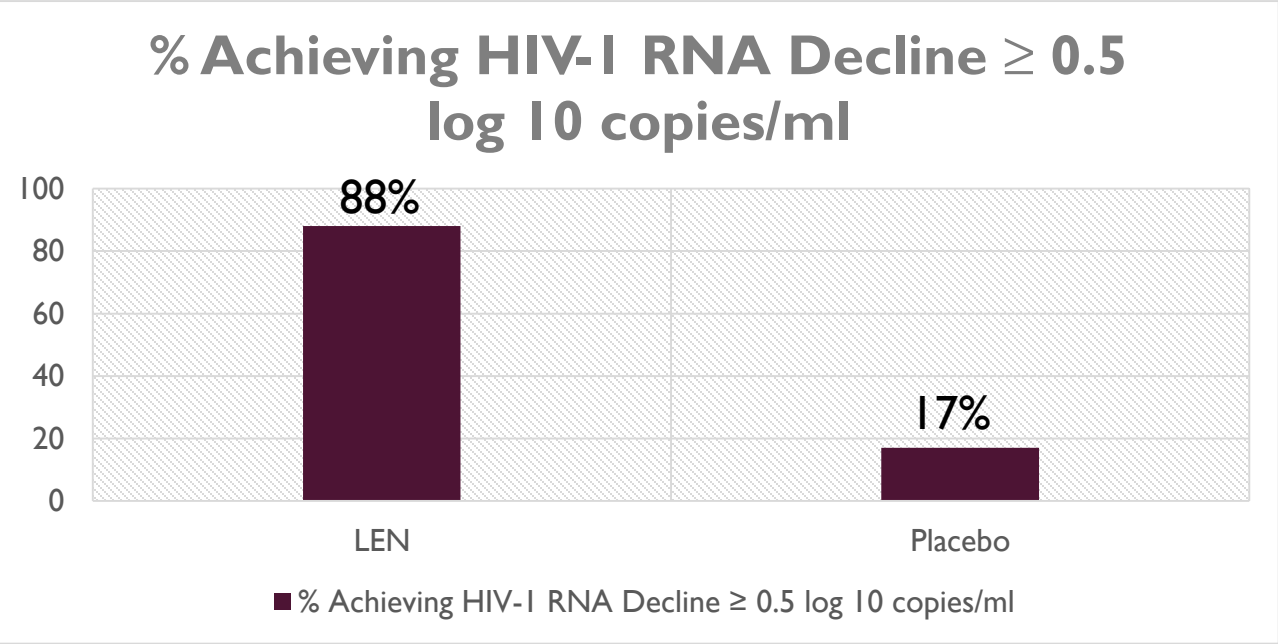
- Phase 2/3, randomized, double-blind, placebo-controlled study in heavily treatment-experienced people with HIV failing their current regimen with HIV-1 RNA (VL) > 400 copies/mL and documented resistance to > 2 agents from 3 of the 4 major ARV classes



Source: Segal-Maurer S et al, Virtual CROI 2021, Abstract # 127

CAPELLA STUDY – LENACAPAVIR IN MDR HIV INFECTION

- The early data from this study indicates that use of lenacapavir leads to a rapid and clinically relevant decline in viral load when added to a failing regimen. LEN was generally safe and well-tolerated.

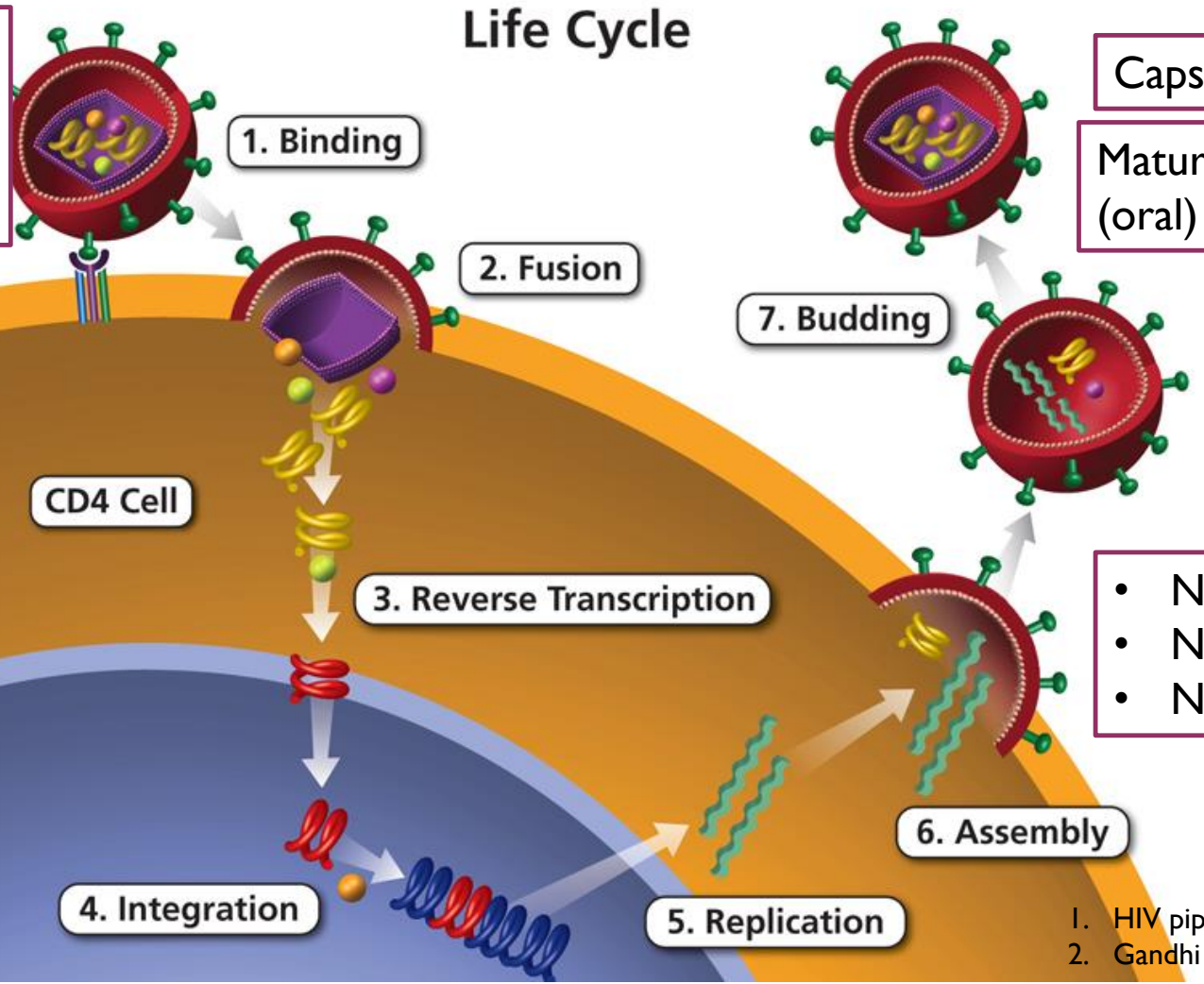


Source: Segal-Maurer S et al, Virtual CROI 2021, Abstract # 127

NEW DRUGS IN DEVELOPMENT

- Entry Inhibitors: Combinectin (GSK3732394)
- CCR5 Antagonist: Leronlimab
- Fusion inhibitor: Albuvirtide

mAb: UB-421 (CD4 receptor) VRC01/LS and VRC07/LS 3BNC117/LS and 10-1074/LS PGDM1400, 10E8.4/iMab PGT121 and elipovimab (GS-9722) N6LS (gp120)



Capsid inhibitor: Lenacapavir

Maturation inhibitor: GSK'254 (oral) GSK '937 (LA)

- NNRTIs: Elsulfavirine
- NRTTIs: Islatravir
- NRTIs: MK-8504, MK-8583

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THANK YOU FOR ATTENDING!

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