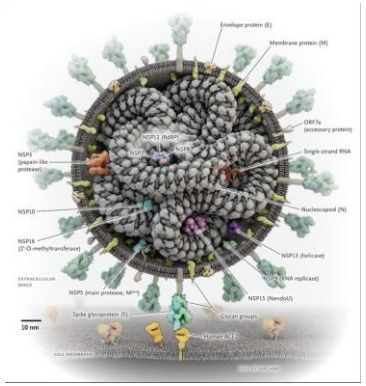
FAMILY HEALTH CENTERS OF SAN DIEGO



Update in HIV Medicine

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5/21/22

Disclosures

Research Grants: Gilead Sciences

Scientific Advisory Board: Gilead Sciences, AbbVie, Viiv Healthcare, Theratechnologies

Speakers Bureau: Gilead Sciences, Abbvie, Viiv Healthcare

FAMILY HEALTH CENTERS
OF SAN DIEGO

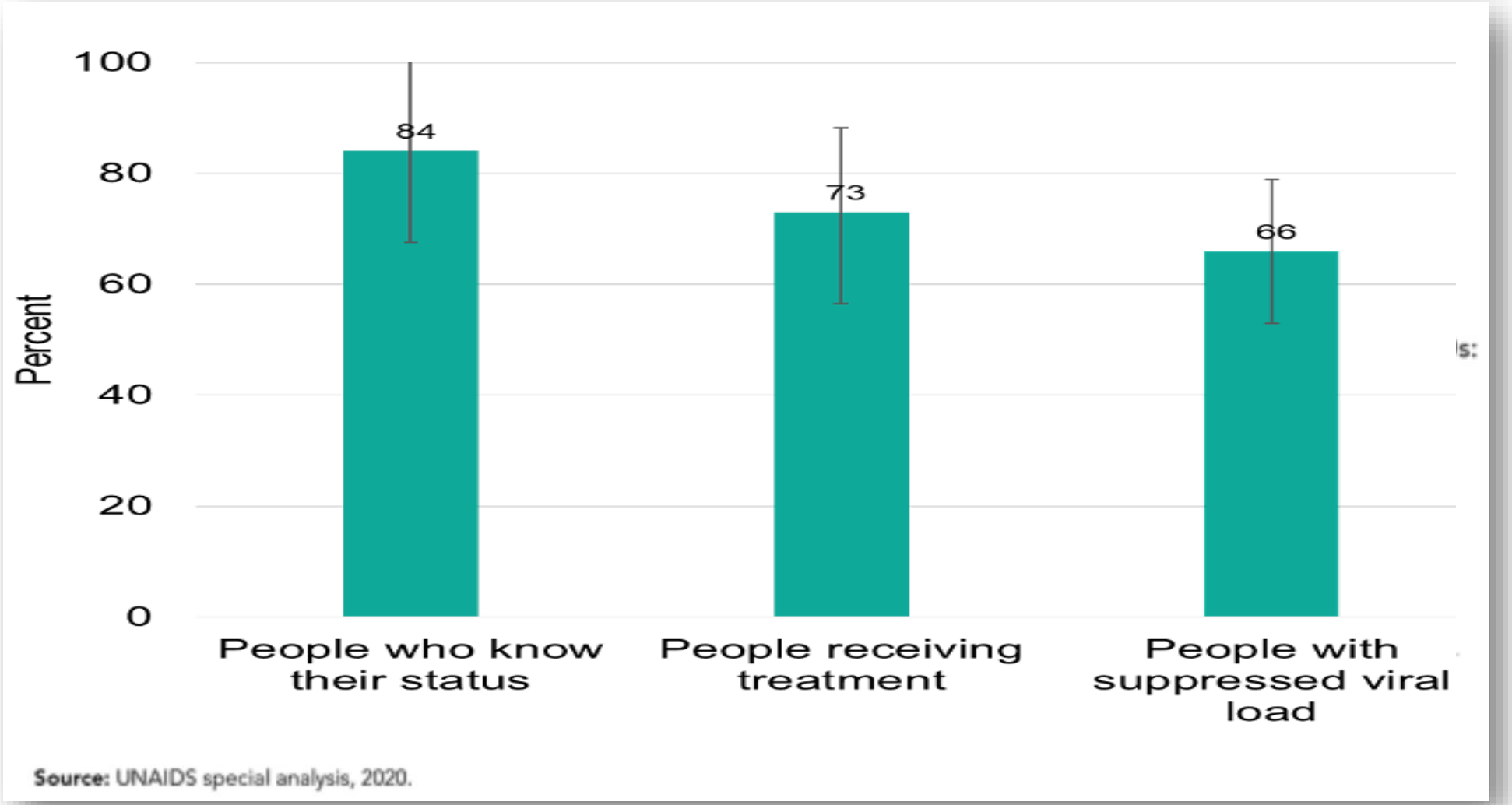
Outline

- **HIV Epidemiology**
- **HIV Treatment**
  - Guidelines
  - Rise of INSTI
  - Long-Acting Injectables
- **HIV Prevention**
  - PrEP
  - Vaccines

Epidemiology: When do we ‘get to zero’?

By 2020:

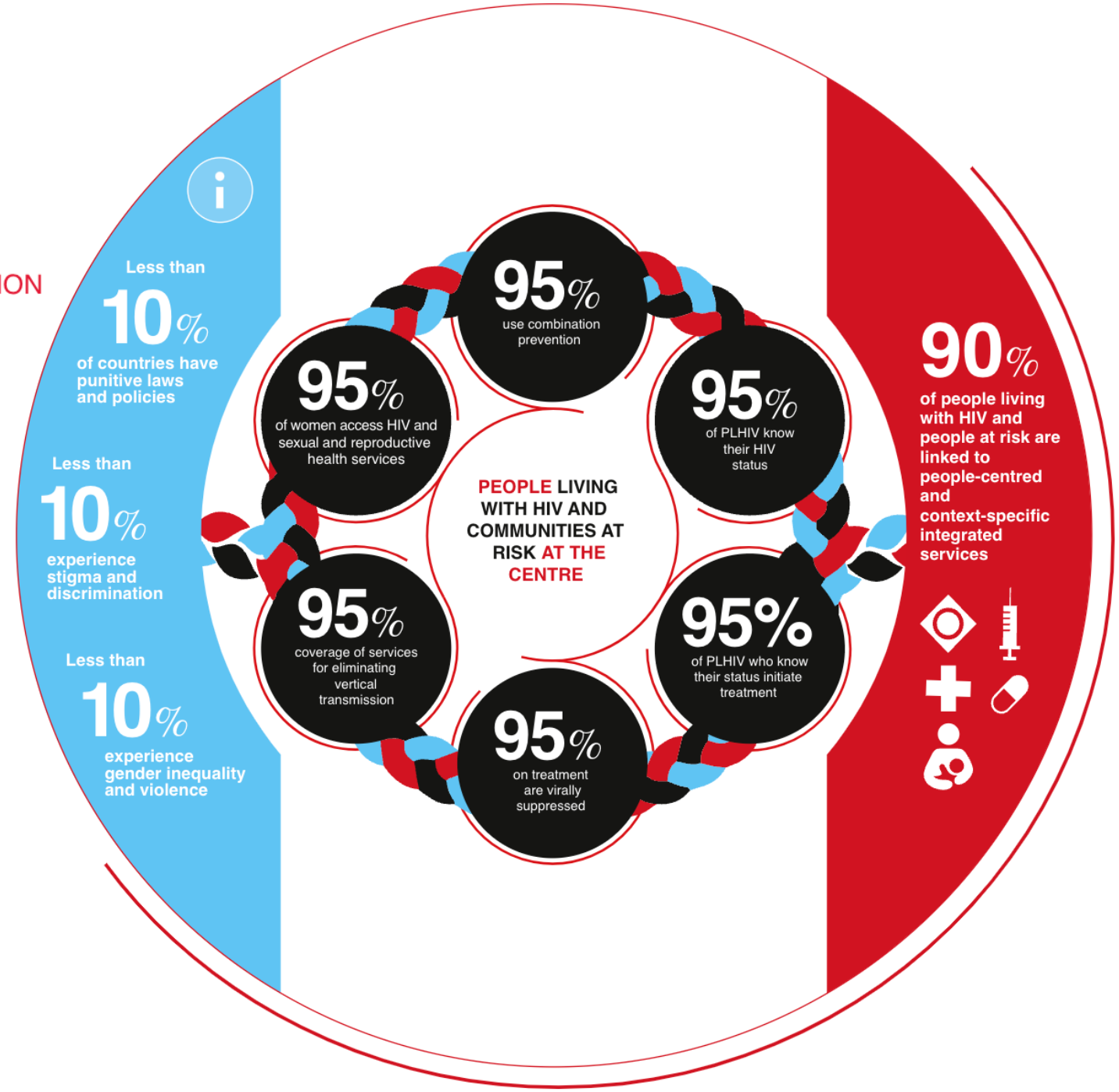
- **90%** of all people living with HIV will know their status
- **90%** of all people with diagnosed HIV infection will receive sustained antiretroviral therapy
- **90%** of all people receiving antiretroviral therapy will have viral suppression



https://www.unaids.org/en/resources/909090

2025 AIDS TARGETS

THE 10s THE 95s THE INTEGRATION



https://aidstargets2025.unaids.org/

End the HIV Epidemic (EHE)

Diagnose all people with HIV as early as possible.

Treat people with HIV rapidly and effectively to reach sustained viral suppression.

Prevent new HIV transmissions by using proven interventions, including pre-exposure prophylaxis (PrEP) and syringe services programs (SSPs).

Respond quickly to potential HIV outbreaks to get needed prevention and treatment services to people who need them.

INITIATIVE'S GOAL

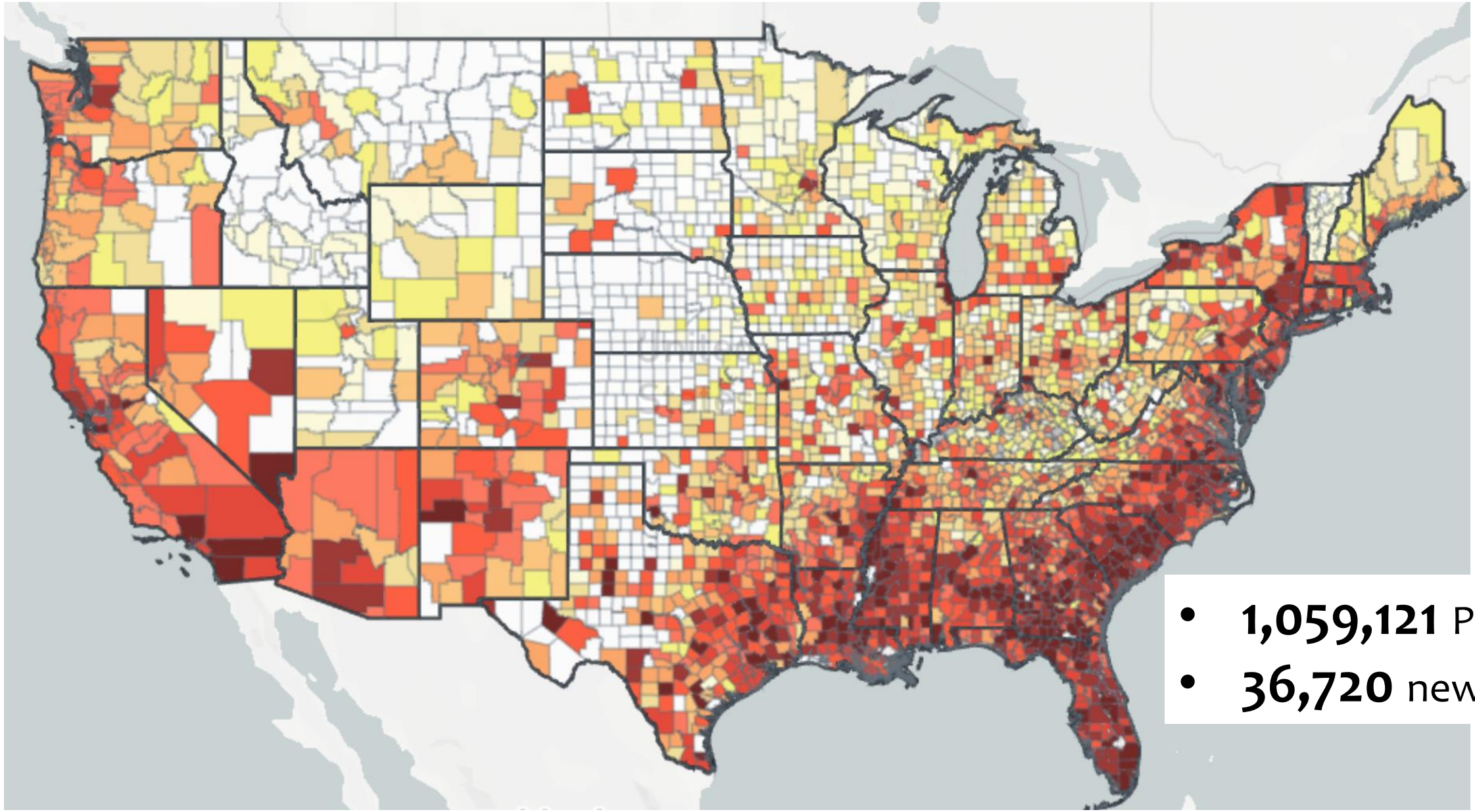
Reduce number of new HIV infections by

75% IN 2025

90% IN 2030

https://ahead.hiv.gov/about-ehe

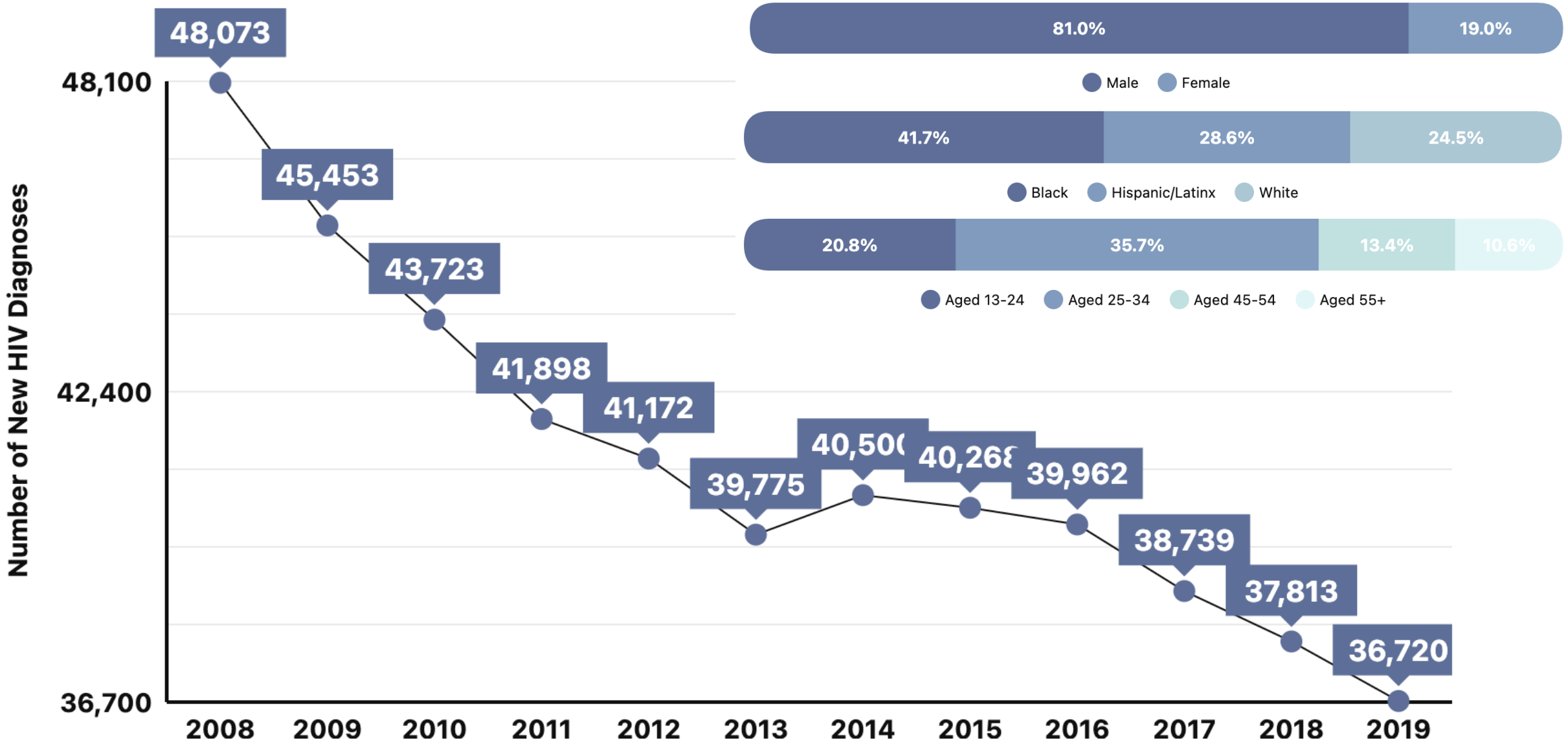
HIV Prevalence, 2019



- **1,059,121** PLHIV
- **36,720** new infections

https://aidsvu.org/local-data/united-states/#new-hiv-diagnoses

New HIV Diagnoses, United States (2008-2019)



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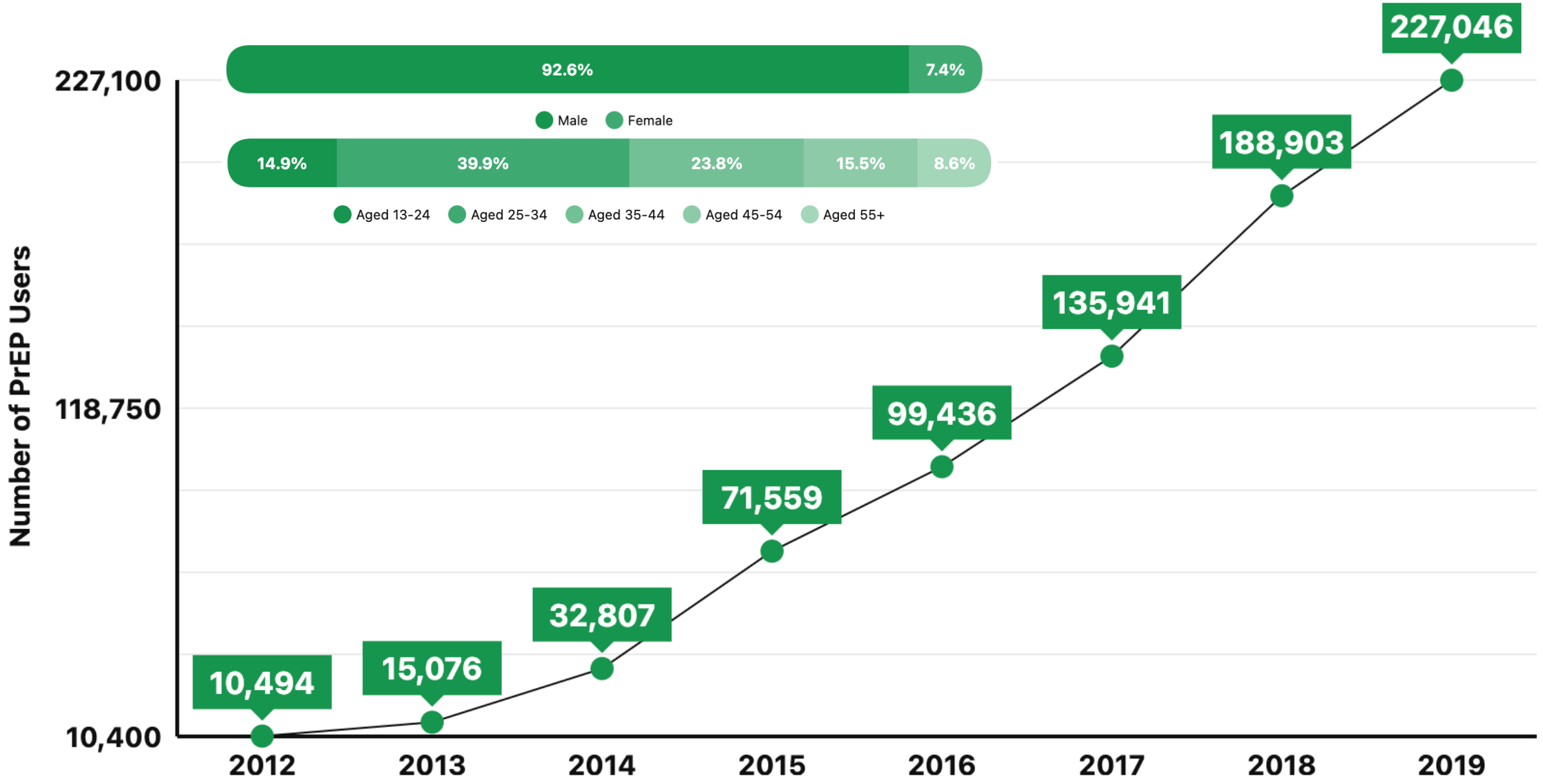
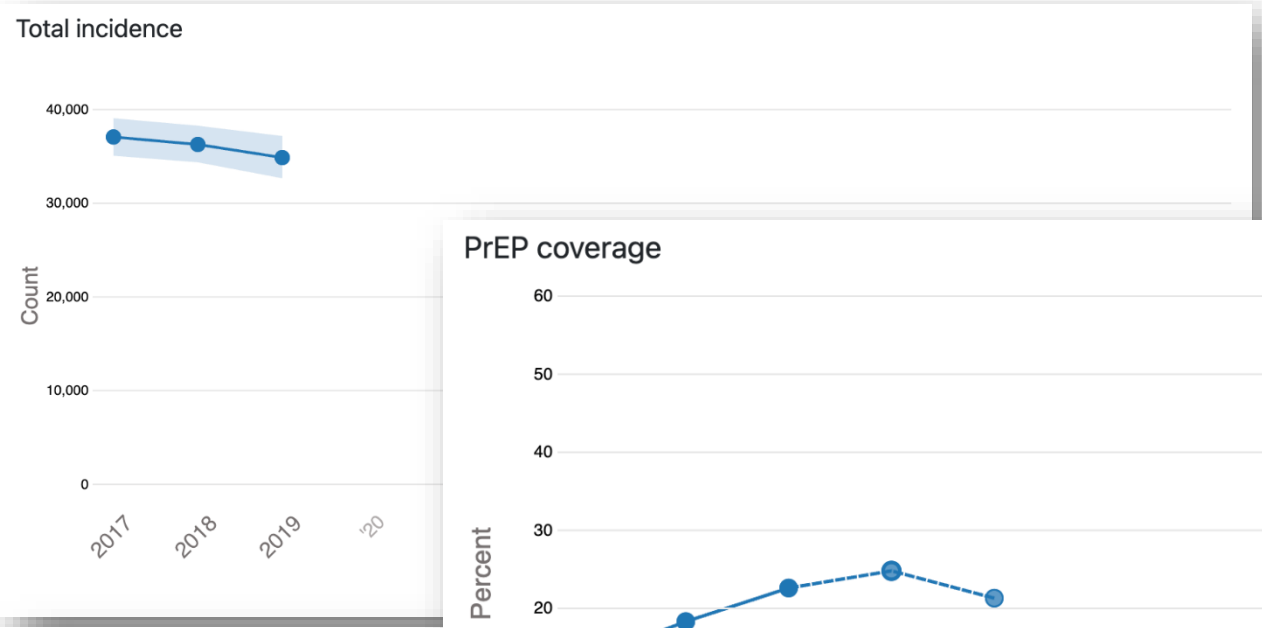
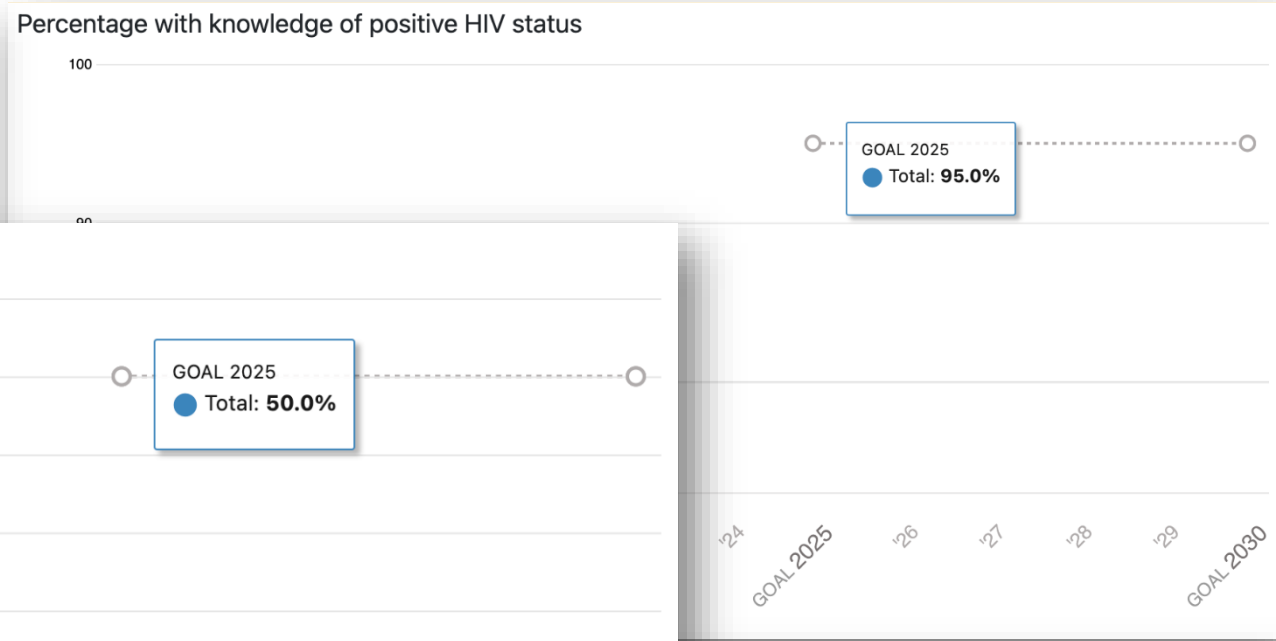
PrEP Users, United States (2012-2019)

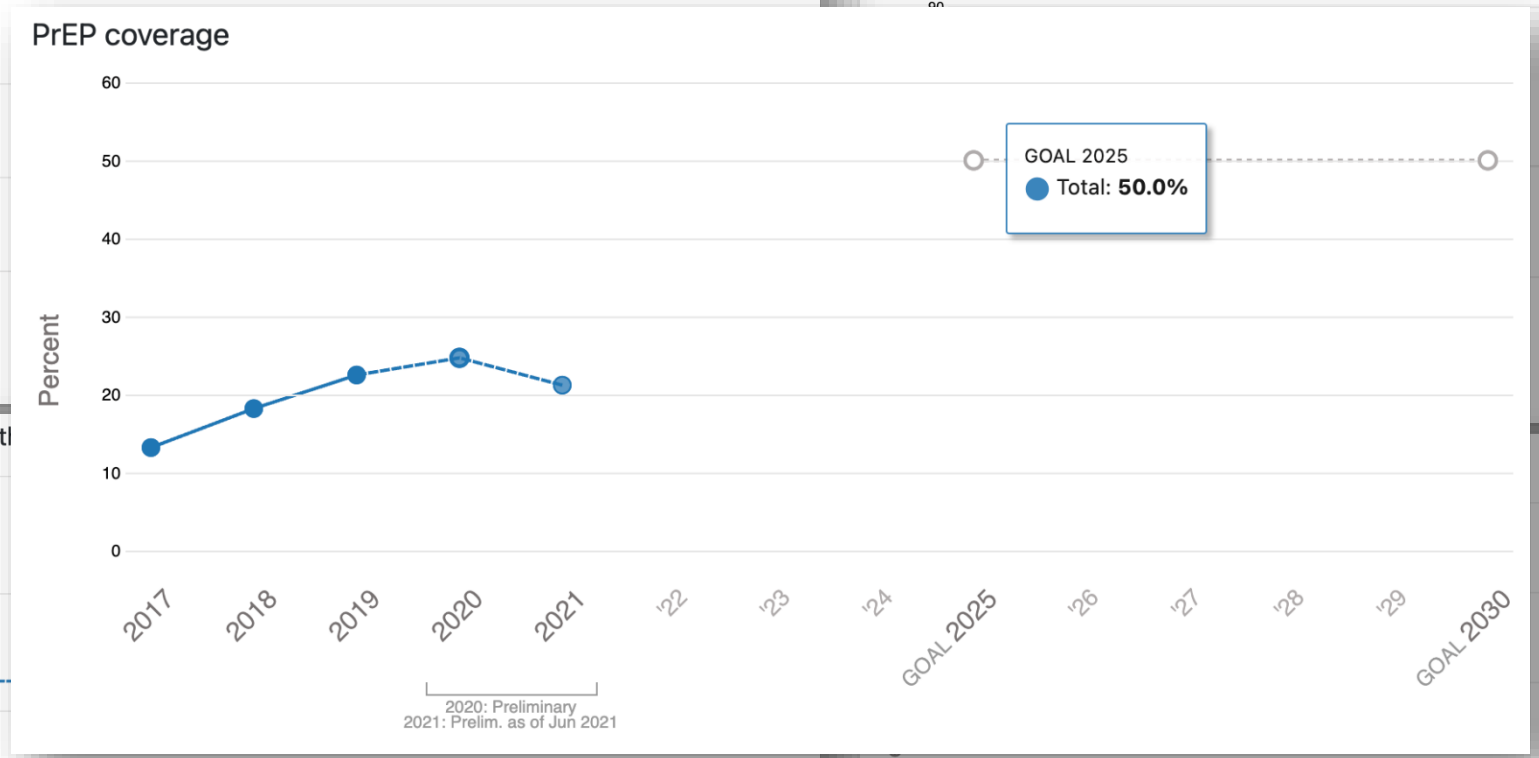


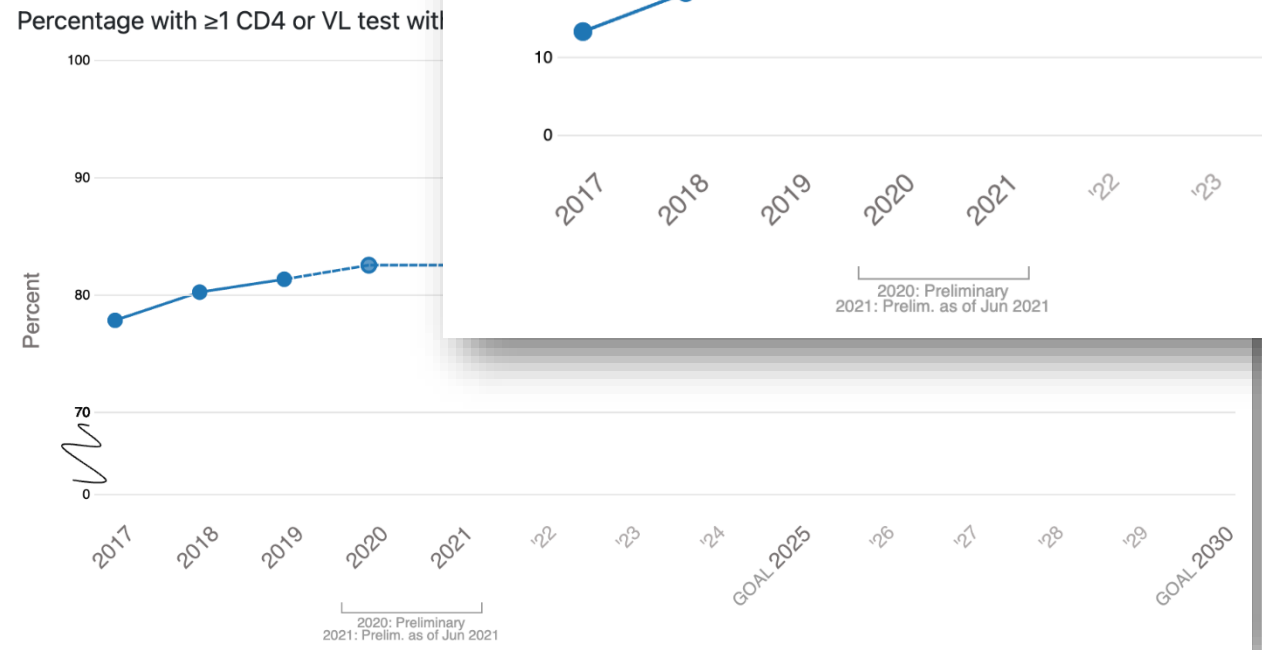
https://aidsvu.org/local-data/united-states/#new-hiv-diagnoses

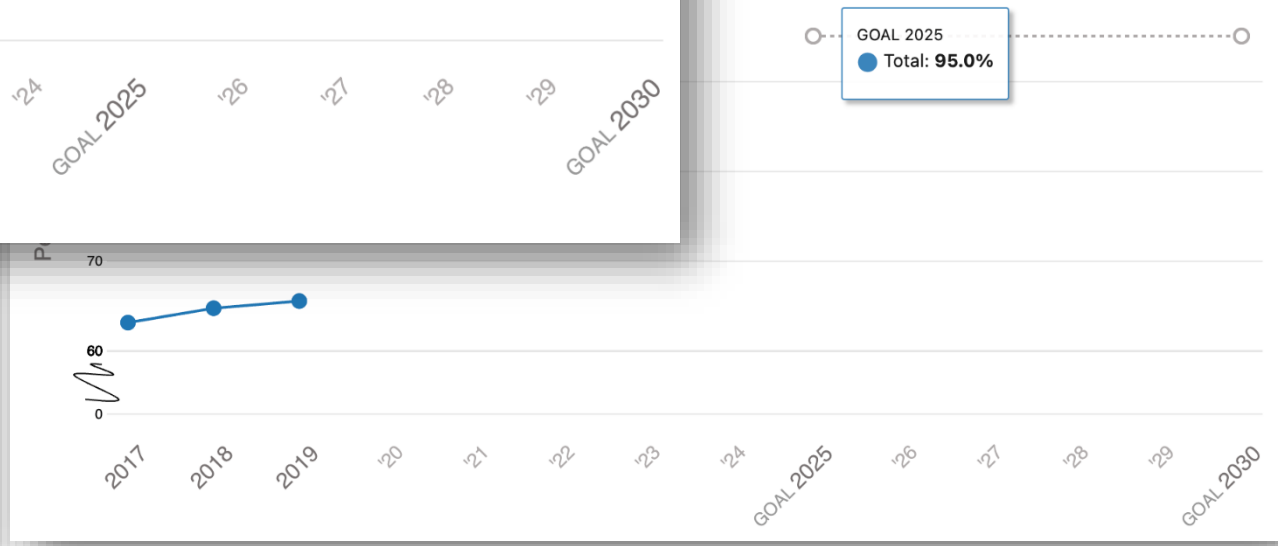
EHE Indicators











https://aidsvu.org/local-data/united-states/#new-hiv-diagnoses

Epidemiology - Summary

Good News

- Near-normal life expectancy if on ART
- Less toxic, more potent ART
- Undetectable = Untransmittable
- Increasing access to PrEP and falling declining incidence in US

Bad News

- 37.7 million PLHIV in the world
- 1.1 million PLHIV in the US
- Still around 35,000 incident infections in US
- Not on track to meet 2025 or 2030 targets

HIV Treatment

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

What's New in the Guidelines?

Updated: Jan. 20, 2022
Reviewed: Jan. 20, 2022

June 3, 2021

What to Start

- Since the release of the last guidelines, updated data from the Botswana Tsepamo study have shown that the prevalence of neural tube defects (NTD) associated with dolutegravir (DTG) use during conception is much lower than previously reported. Based on these new data, the Panel now recommends that a DTG-based regimen can be prescribed for most people with HIV who are of childbearing potential. Before initiating a DTG-based regimen, clinicians should discuss the risks and benefits of using DTG with persons of childbearing potential, to allow them to make an informed decision. Table 6b has been removed from this section.
- Raltegravir (RAL)-based regimens as initial antiretroviral therapy (ART) have been moved from the category of "Recommended Initial Regimens for Most People with HIV" to "Recommended Initial Regimen in Certain Clinical Situations" **(BI)**. The reasons for this change are as follows:
  - Updated Tsepamo data show a lower prevalence of NTD associated with DTG use during conception, which means choosing RAL over DTG is no longer necessary.
  - RAL has a lower barrier to resistance than DTG and bictegravir (BIC).
  - RAL-based regimens have a higher pill burden than other integrase strand transfer inhibitor (INSTI)–based regimens and are not available as part of a single-tablet regimen.

Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

- The update to this section primarily focuses on the role of the new long-acting injectable (LAI) regimen of intramuscular cabotegravir (CAB) plus rilpivirine (RPV) in this setting. The section describes the clinical trial data to date on long-acting CAB plus RPV, practical considerations when using these agents, and management recommendations in the event of missed doses.

Virologic Failure

- For patients with virologic failure, the Panel's recommendation of "A new regimen should include at least two, and preferably three, fully active agents **(AI)**" has been changed to "A new regimen can include two fully active drugs if at least one with a high resistance barrier is included (e.g., DTG or boosted darunavir) **(AI)**." This change is prompted by accumulating clinical trial data showing that in these patients, a new regimen containing two fully antiretroviral (ARV) drugs can effectively achieve viral suppression, provided that one of the two drugs has a high barrier to resistance.
- Clinical trial data on the use of fostemsavir for patients with multidrug-resistant HIV has been added.

What to Start: Initial Combination Regimens for the ART-naïve patient

>30 FDA-approved ARV's in 8 classes

Bictegravir/Tenofovir Alafenamide/Emtricitabine (AI)
Dolutegravir/Abacavir/Lamivudine (AI) (except if HLA-B*5701 positive)
Dolutegravir + 3TC/FTC + TAF/TDF (AI)
Dolutegravir/Lamivudine (AI) (except if VL >500,000, HBV, or genotype not available)

Patients without prior ART who wish to begin long-acting IM **cabotegravir (CAB)** and **rilpivirine (RPV)** should first achieve viral suppression on another regimen before switching to oral, and then injectable CAB + RPV

Initial Recommendations in Certain Clinical Situations

INSTI plus 2 NRTIs:

- EVG/c/(TAF or TDF)[c]/FTC **(BI)**[b]
- RAL plus (TAF or TDF)[a] plus (FTC or 3TC) **(BI for TDF/[FTC or 3TC], BII for TAF/FTC)**

Boosted PI plus 2 NRTIs:

- In general, boosted DRV is preferred over boosted ATV
- (DRV/c[b] or DRV/r) plus (TAF or TDF)[c] plus (FTC or 3TC) **(AI)**
- (ATV/c[b] or ATV/r) plus (TAF or TDF)[c] plus (FTC or 3TC) **(BI)**
- (DRV/c[b] or DRV/r) plus ABC/3TC —**if HLA-B*5701 negative (BII)**

NNRTI plus 2 NRTIs:

- DOR/TDF[c]/3TC **(BI)** or DOR plus TAF[c]/FTC **(BIII)**
- EFV plus (TAF or TDF)[c] plus (FTC or 3TC)
  - EFV 600 mg plus TDF plus (FTC or 3TC) **(BI)**
  - EFV 400 mg/TDF/3TC **(BI)**
  - EFV 600 mg plus TAF/FTC **(BII)**
- RPV/(TAF or TDF)[c]/FTC (**BII for TAF and BI for TDF)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**

Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available
- DRV/r plus RAL twice a day **(CI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**
- DRV/r once daily plus 3TC **(CI)**

Management of the Treatment-Experienced Patient

"A new regimen can include **two fully active ARV drugs** if at least one with a high resistance barrier is included (e.g., dolutegravir or boosted darunavir) (AI). If no fully active drug with a high resistance barrier is available, then every effort should be made to include three fully active drugs (AI)."

Fully active drugs may be in same class: **ETR, DOR, DRV, DTG, BIC** or may have a novel mechanism of action: **MVC, IBA, FTR**, and investigational agents are under study: **Lenicapavir, leronimab, islatravir**

Optimizing ART in the Setting of Viral Suppression

- The fundamental principle of regimen optimization is to maintain viral suppression without jeopardizing future treatment options

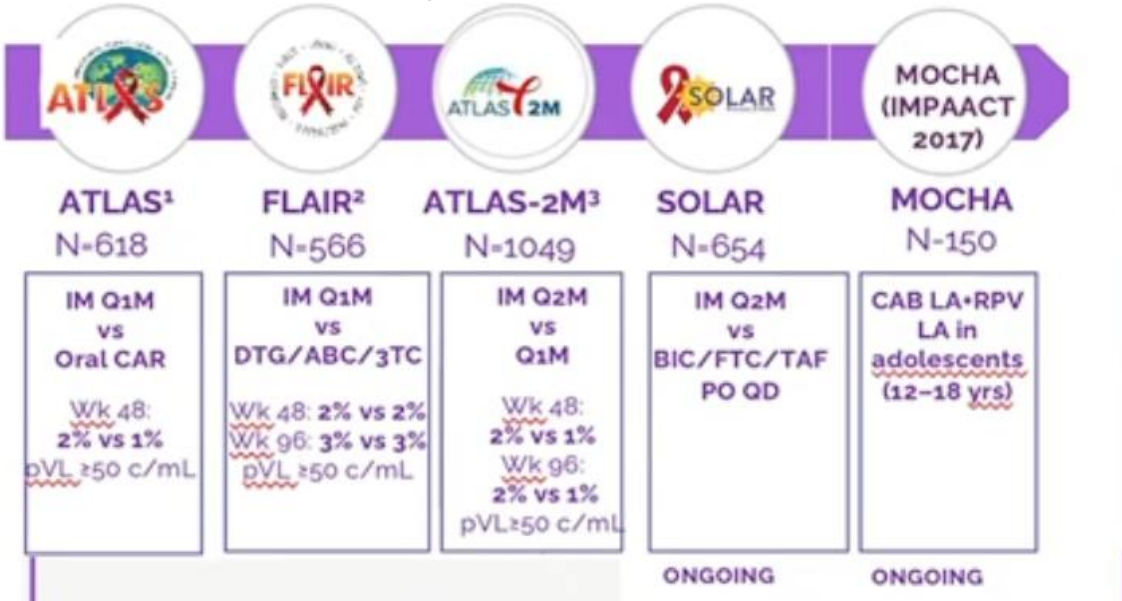
- Adverse events, drug-drug interactions, pill burden, pregnancy, cost, or the desire to simplify a regimen may prompt a regimen switch

- A long-acting ARV regimen, such as the combination of injectable **cabotegravir** and **rilpivirine**, is an optimization option for patients who are engaged with their health care, virologically suppressed on oral therapy for 3 to 6 months, and who agree to make the frequent clinic visits needed to receive the injectable drugs (AI)

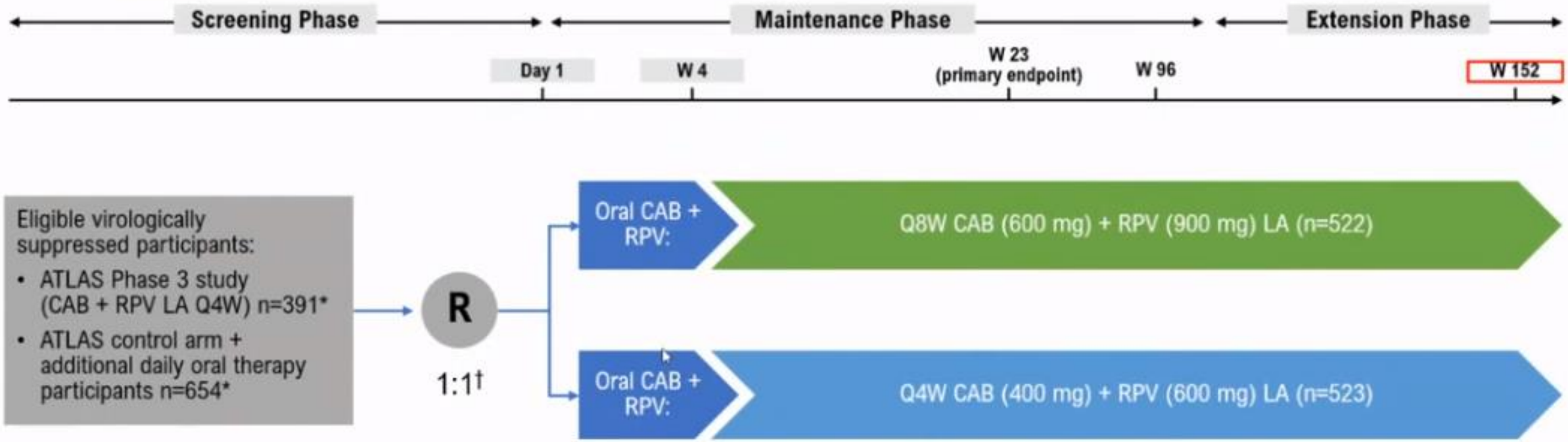
Long Acting cabotegravir + rilpivirine

- **Efficacy**: non-inferior to oral therapy at 48, 96, 124, 152 weeks
  - Q2M dosing non-inferior to Q1M dosing
- **Adverse Events:** 2% AE-related withdrawal, mild/mod, ISR's reduced over time
- **Virological Failure:** 1-1.5% (5in FLAIR, 13 in ATLAS-2M, 11/13 in Q8 wk arm)
- **Resistance:** Usually to two classes, mostly in 1st year
- **Oral Lead-in:** can be used with/without
- **Patient preference:** 9 of 10 patients in trial chose to stay on

EACS (Oct 2021)	US DHHS (Feb 2022)	IAS (Oct 2020)
CAB + RPV LA Q8W	CAB + RPV LA Q4W FDA Q8	CAB + RPV LA Q8W and Q4W

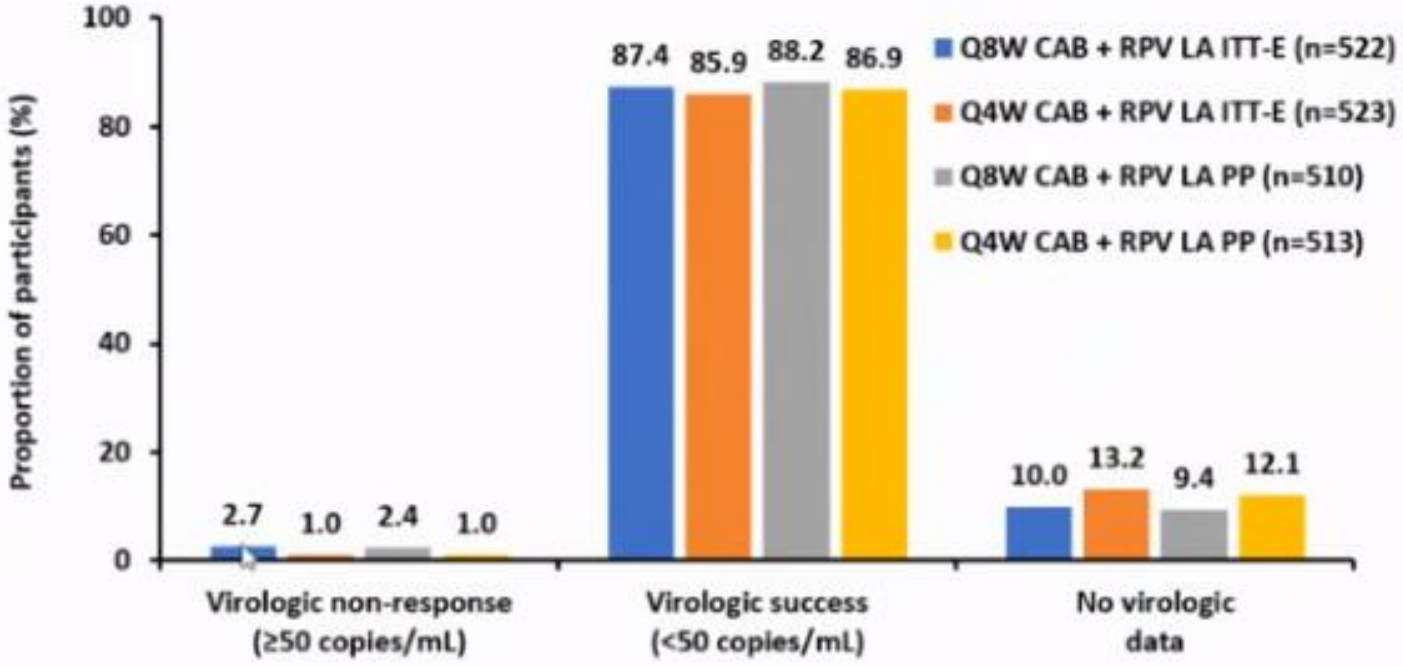


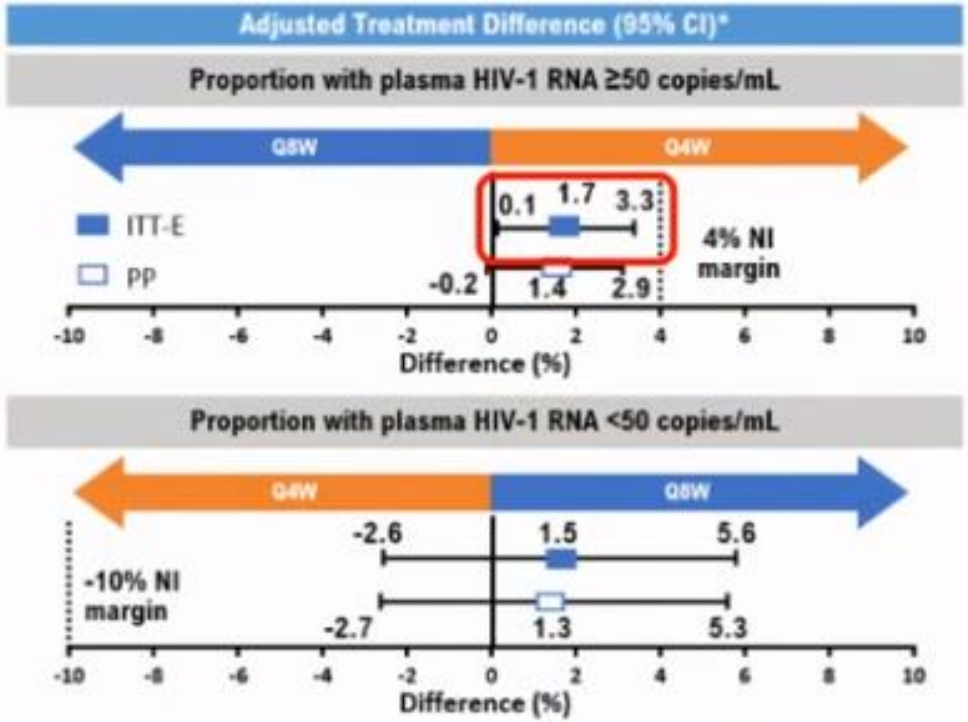
ATLAS 2M: CAB/RPV every 1 vs 2 months



Overton E, et al. Virtual CROI 2022; February 12-16, 2022. Abst. 479.

ATLAS 2M: Every 2 months is non-inferior to 1 month …





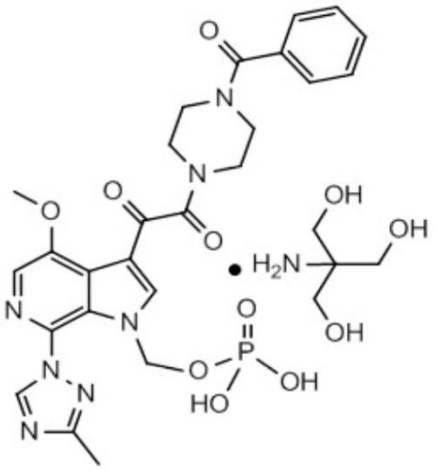
Overton E, et al. Virtual CROI 2022; February 12-16, 2022. Abst. 479.

ATLAS 2M: More details on confirmed virologic failures (CVF)

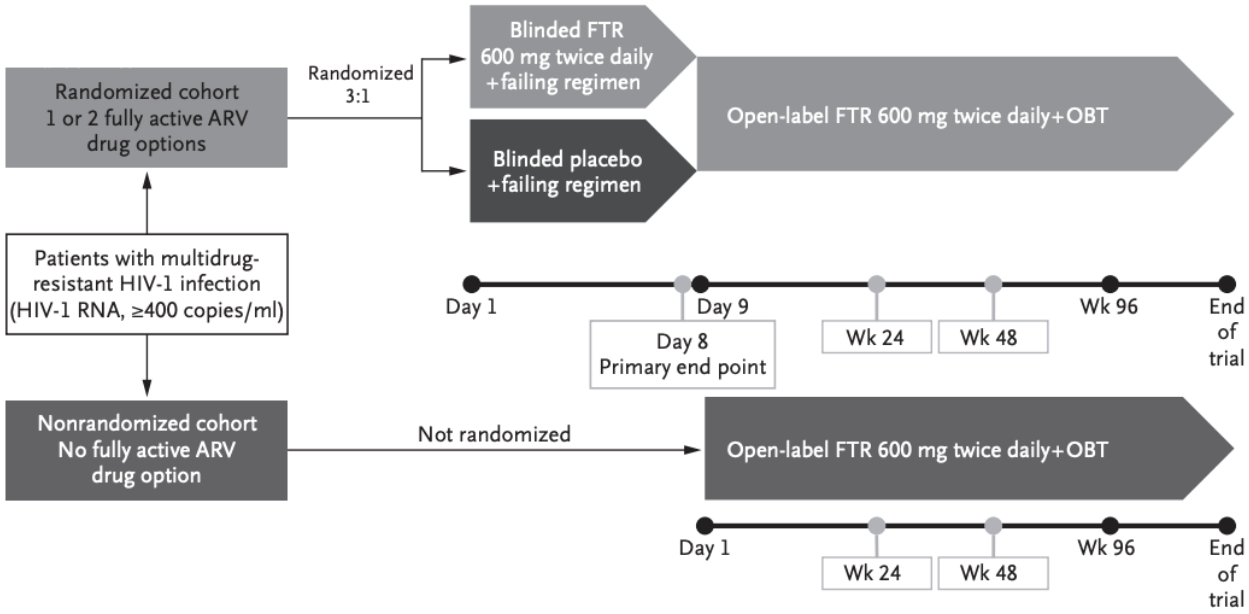
- At week 152, 13 participants had confirmed virologic failure (Q8W, n =11 [2%]; Q4W, n =2 [1%])
  - A non-protocol-defined virologic failure also developed at wk 48 (Q8W). Subtype A1, E138K and S230S/R (no RAMS at baseline)
- Out of the 13, 6 had ≥ 2 baseline factors (proviral RPV RAMSs, A6/A1, BMI ≥ 30)
- No participants with CVF through week 152 had injection visits > 7 days later than the scheduled visit date

Participants with CVF Since Week 96					
#, arm	Sex at birth, BMI (kg/m^2), country	HIV-1 subtype at baseline	Viral load at failure (copies/mL)	RPV RAMs observed at failure	INI RAMs observed at failure
1, Q8W	Male, <30, Germany	B	24,221	E138A+M230M/L	Q148R
2, Q8W	Male, <30, Russia	A6*	59,467	E138A+Y181Y/C	Q148R

Fostemsavir



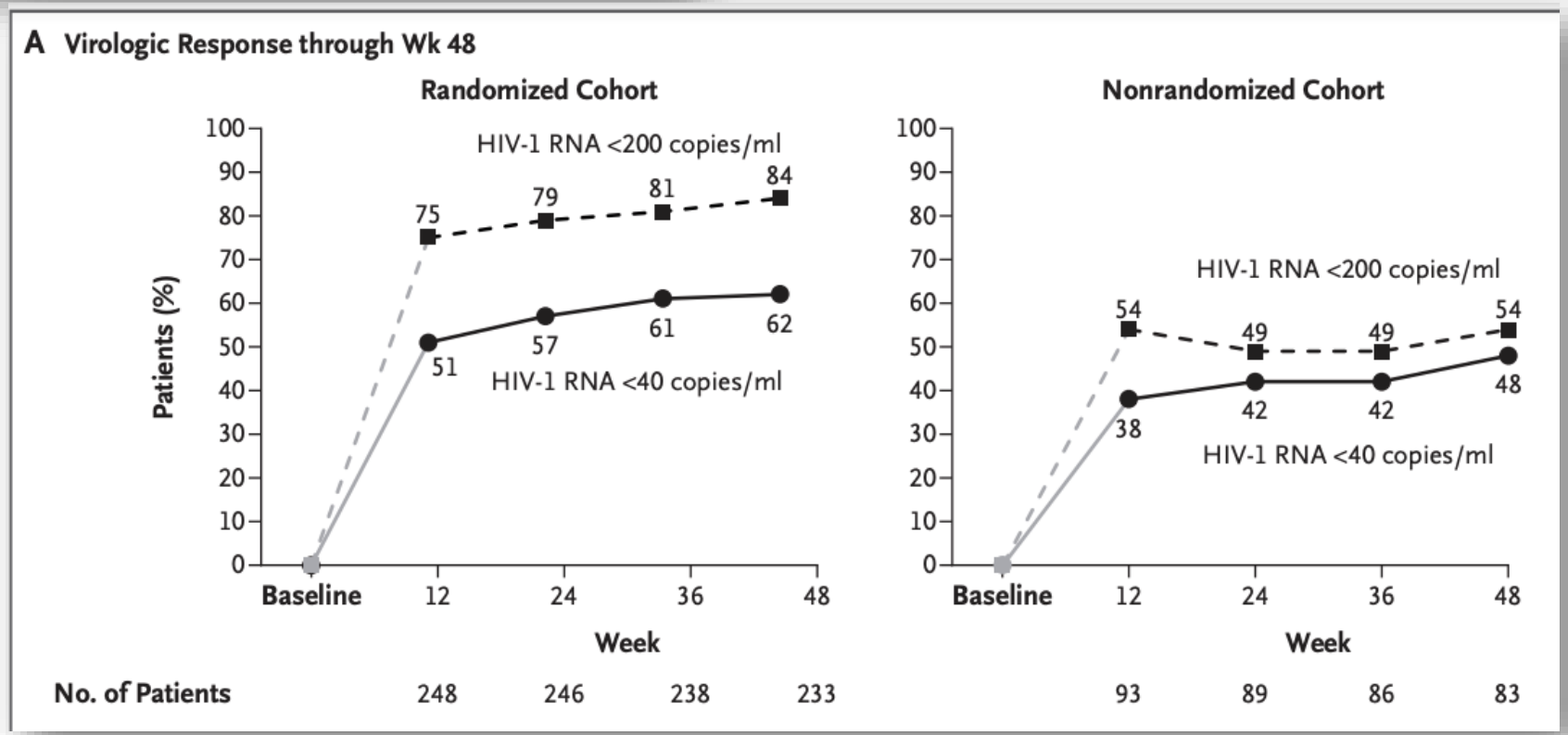
- gp120-directed attachment inhibitor
- Indicated in combination with other anti-retrovirals in heavily treatment-experienced adults with multi-drug resistant HIV-1 infection failing current regimen due to resistance intolerance, or safety concerns.
- One 600 mg ER tab PO BID
- BRIGHTE Study: 96 week Phase III trial of 371 heavily treatment experienced adults. Randomized cohort (N = 203), non-randomized cohort (N = 99, open label)



https://www.nejm.org/doi/pdf/10.1056/NEJMoa1902493?articleTools=true

Fostemsavir – BRIGHTE study

Characteristic	Randomized Cohort			Nonrandomized Cohort
	Placebo (N=69)	Fostemsavir (N=203)	Total (N=272)	Fostemsavir (N=99)
No. of fully active antiretroviral drugs in initial OBT — no. (%)‖				
0	1 (1)	15 (7)	16 (6)**	80 (81)
1	34 (49)	108 (53)	142 (52)	19 (19)††
2	34 (49)	80 (39)	114 (42)	0



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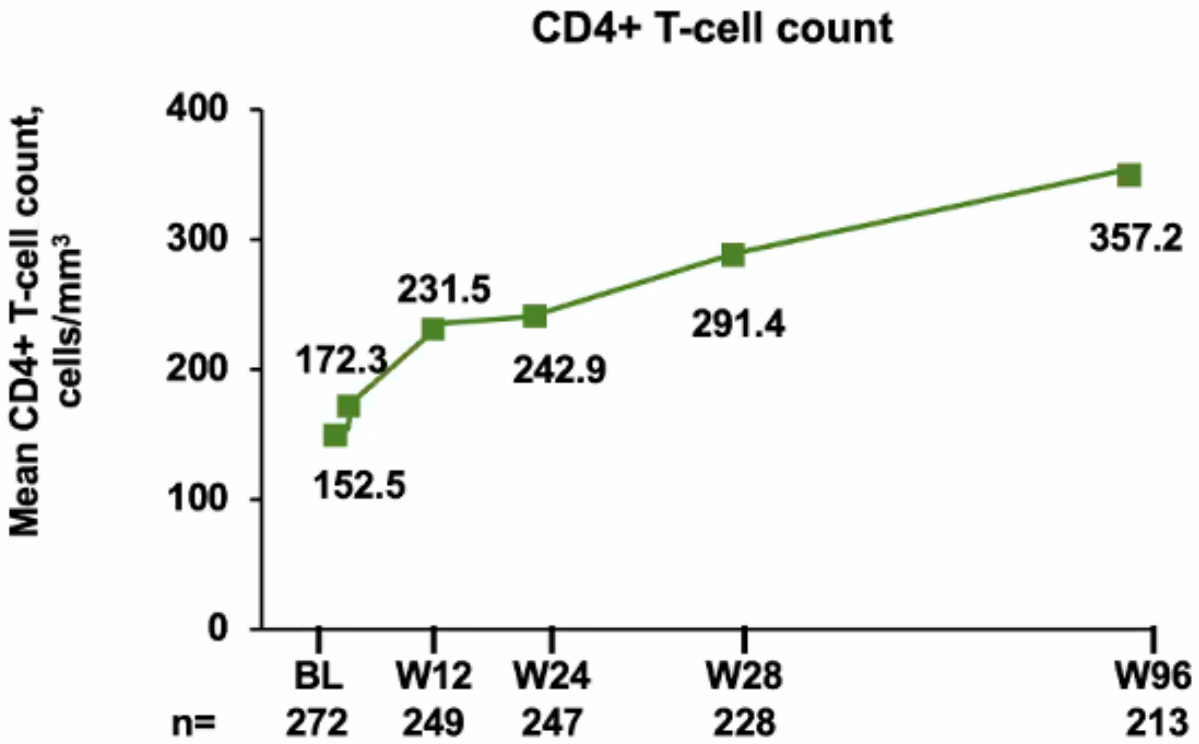
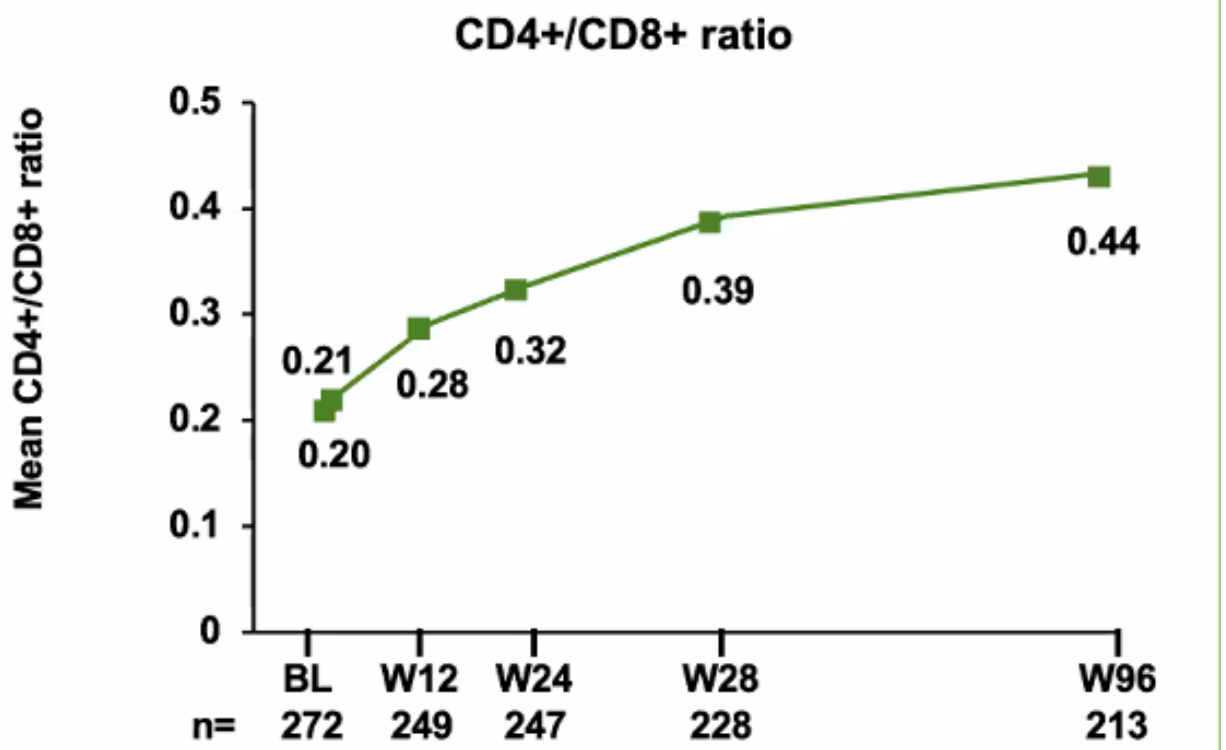
Fostemsavir – BRIGHTE study





- Sustained increases in CD4+ T-cells through week 96
- Mean CD4/CD8 ratios low at baseline (0.20), increased over time (0.44 at week 96)

Clark et al EACS 2021; Virtual and London, UK Poster PE2/73

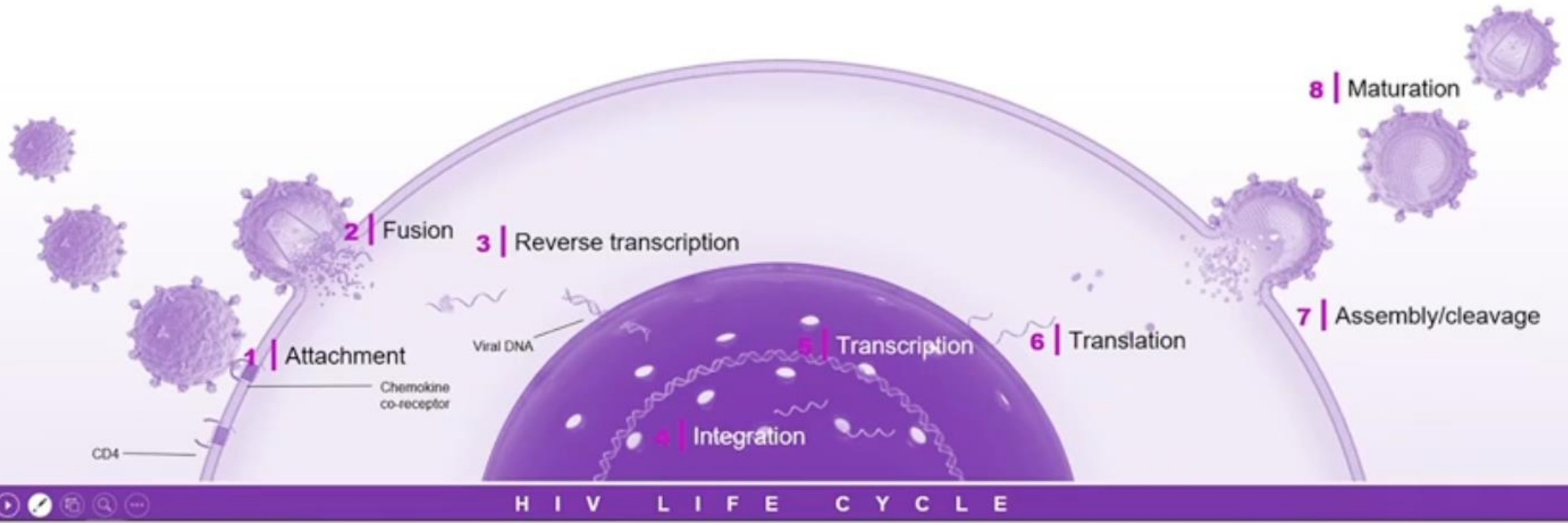
HIV Treatment - Summary

- 4 highly effective oral regimens for Treatment Naïve patients
- More consideration to ‘optimizing’ therapy for those currently on treatment
- Many options, even for heavily treatment experienced patients
- Long-Acting Injectable therapy has arrived with Cabotegravir + Rilpivirine as first available regimen in Q2 month dosing

Investigational HIV treatments

Classes in clinical development for treatment and prevention

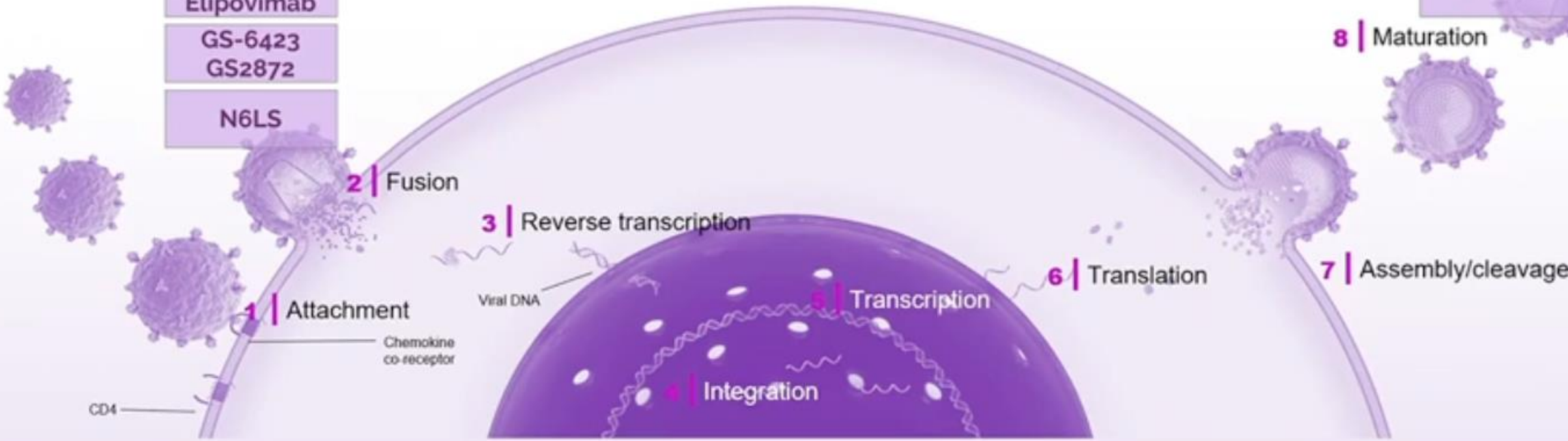
Entry inhibitors | bNAb | NRTI NRTTI | NNRTI | Integrase inhibitor | Protease inhibitor | Capsid inhibitor | Maturation inhibitor | Topical IVR /MPT



Courtesy of Chloe Orkin – CROI 2022

Compounds in clinical development for treatment and prevention

Entry inhibitor	bNAb	NRTI NRTTI	NNRTI	Integrase inhibitor	Protease inhibitor	Capsid inhibitor	Maturation inhibitor	Topical IVR /MPT
Albuvirtide	UB-421	Islatravir	Elsulfavirine	Bictegravir	GS-1156	Lenacapavir	GSK254	Dapivirine
	Leronlimab (PRO-140)	TAF implant	ACC007	S-365598			GSK937	MIV 150 PC1005 gel
	VRC 01/LS VRC 07/LS							EVO-100 gel
	PG121 + Elipovimab							MB66 film
	GS-6423 GS2872							
	N6LS							



HIV LIFE CYCLE

Courtesy of Chloe Orkin – CROI 2022

Compounds by modality and indication

Treatment

- Islatravir
- Lenacapavir
- MI 254

ORAL

INJECTABLE
IM, SC, IV

- Albuvirtide
- bNabs
- Lenacapavir
- Elsulfavirine
- Islatravir
- MI 934

Prevention

IVR/TOPICAL/ MPT

- Dapivirine IVR
- TAF/EVG insert
- EVO-100 gel
- MB66 film
- MIV 150 PC1005
- Tenofovir IVR
- Dapivirine + C
- Dual prevention pill

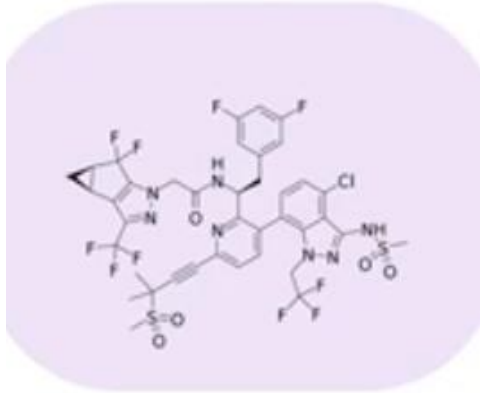
IMPLANTS PATCHES/IM

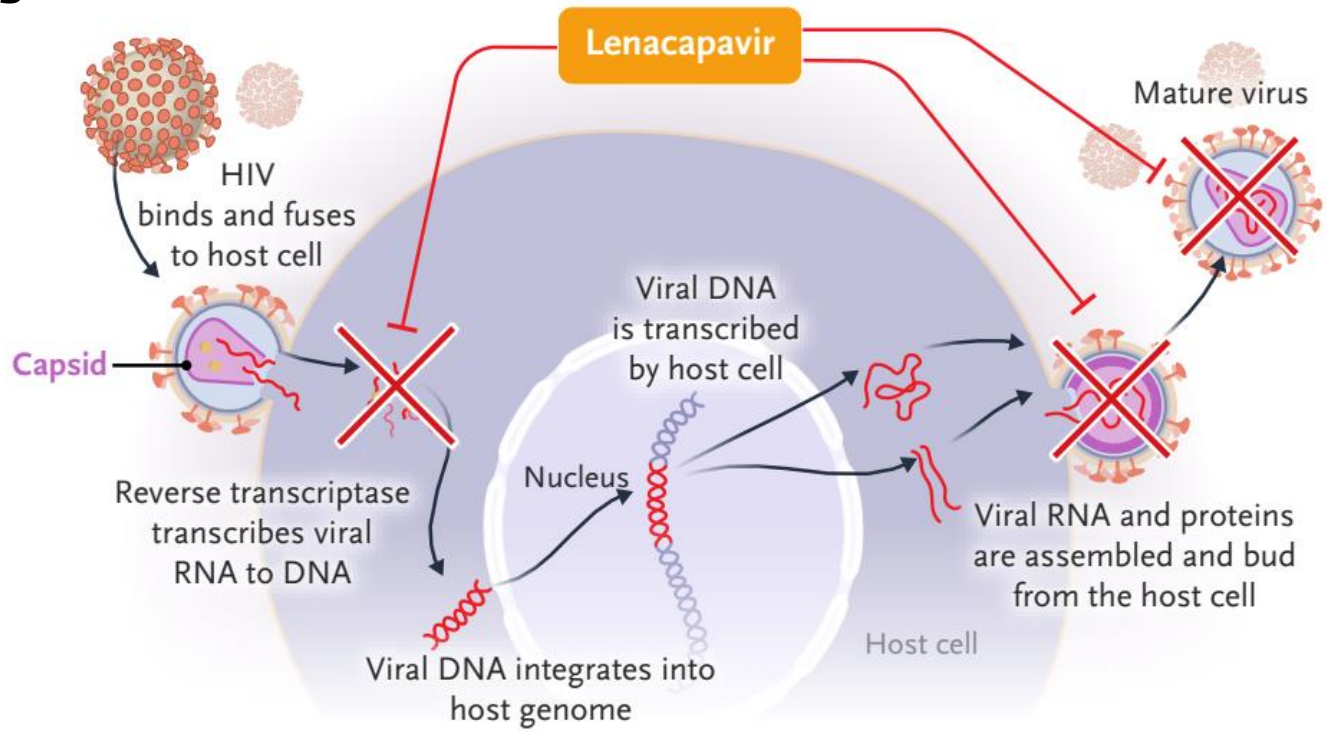
- Lenacapavir
- Islatravir implant
- INSTI MAP
- TAF implant
- RPV IM

Courtesy of Chloe Orkin – CROI 2022

Lenicapavir

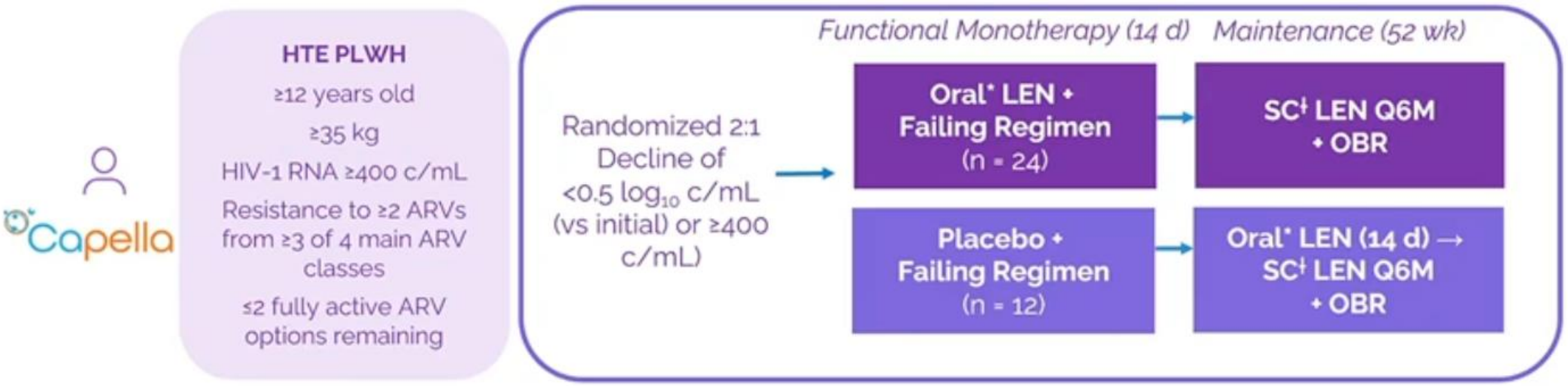
- First-in-class capsid inhibitor
- Oral or SubQ bioavailability
- Q6 month dosing is possible
- Multi-stage activity in early and late life cycle
- Small-molecule active at picomolar doses
- SHIV model supports use for PrEP
- **All studies on partial FDA hold
  - Changing away from glass vials
  - All patients remain on oral LEN





https://www.nejm.org/doi/suppl/10.1056/NEJMoa2115542/suppl_file/nejmoa2115542_research-summary.pdf

Lenicapavir – Phase II/III in heavily treatment experienced



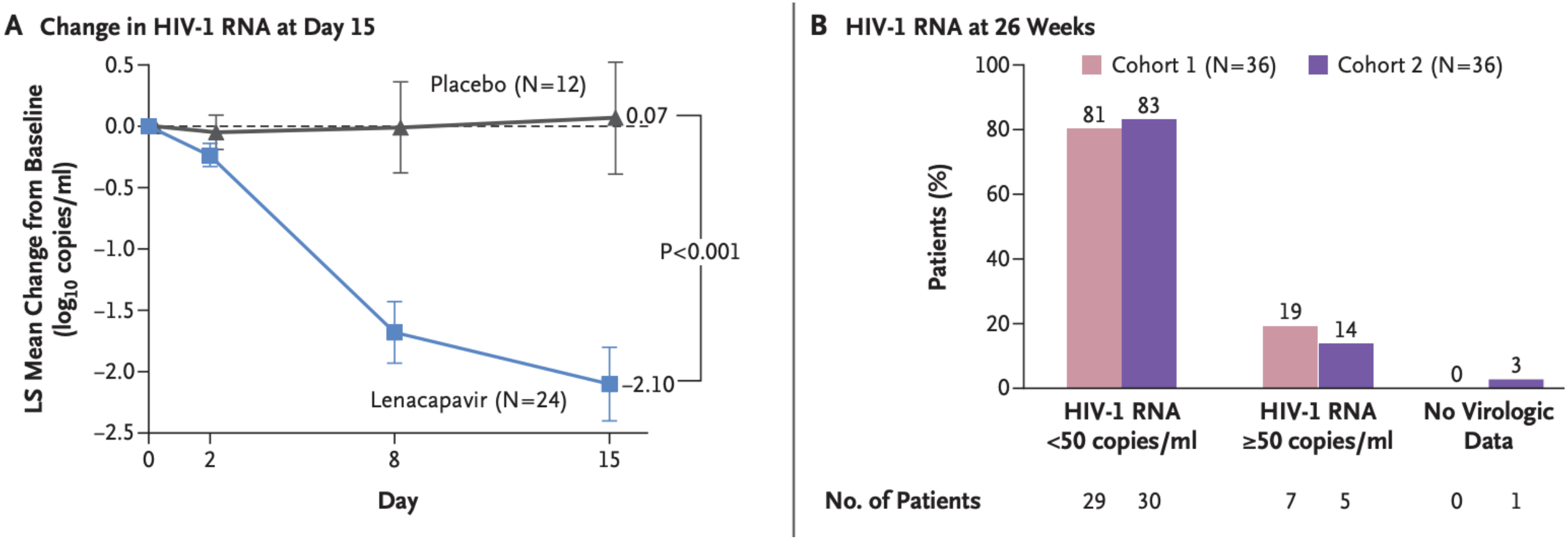
Primary endpoint achieved in prior analysis: ≥0.5-log decline in HIV-1 RNA with oral LEN 88% vs placebo 17% at Day 14 in randomized cohort (P <.0001)[1]

Secondary endpoints: HIV-1 RNA <50 c/mL, <200 c/mL at Week 26 in randomized cohort[2]

*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8.
†SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15.

Segal-Maurer, et al CROI 2021
Molina IAS 2021 Abstract OALX01LB02

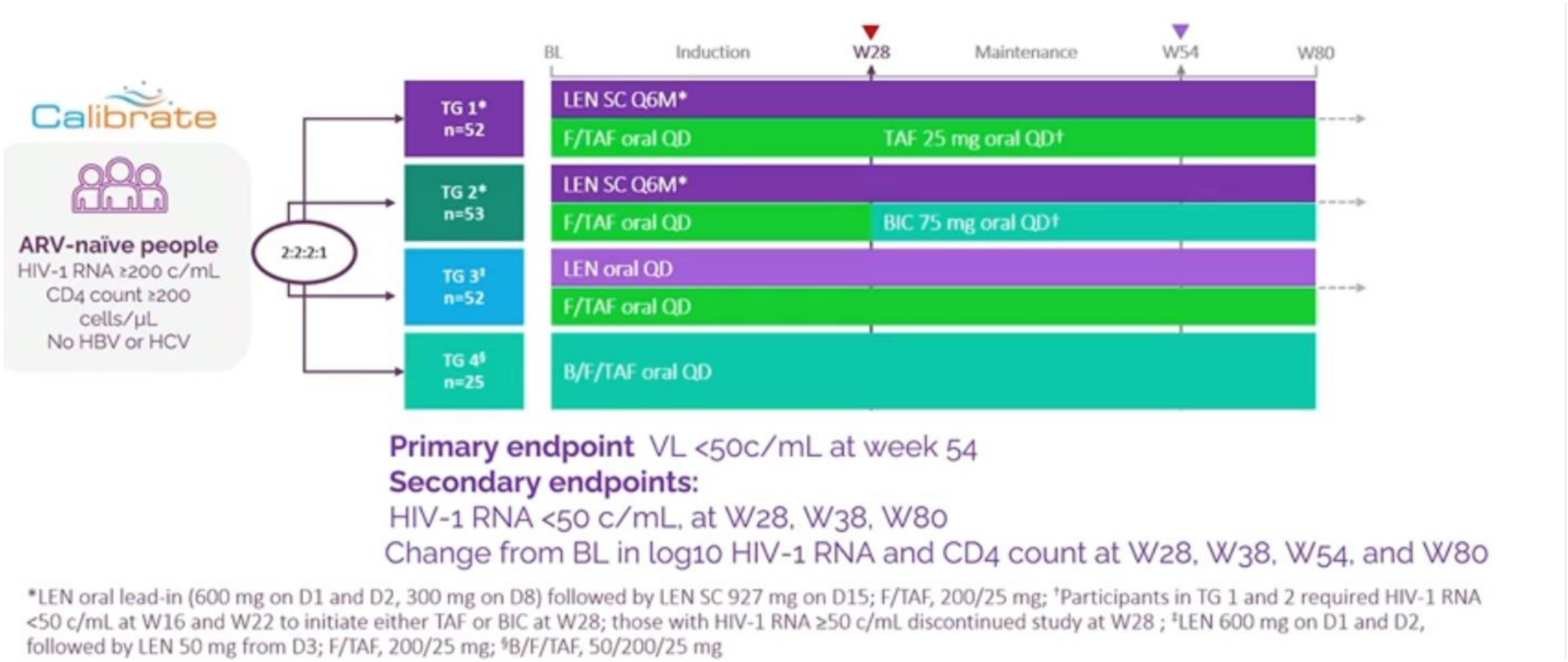
Lenicapavir – Phase II/III in heavily treatment experienced



- 4 pts developed LEN resistance (M66I); 2 functional monotherapy, 2 non-adherent
- ISR's in 56% of participants, 70% grade 1, resolved within days
- No AE's that led to discontinuations

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2115542?articleTools=true.

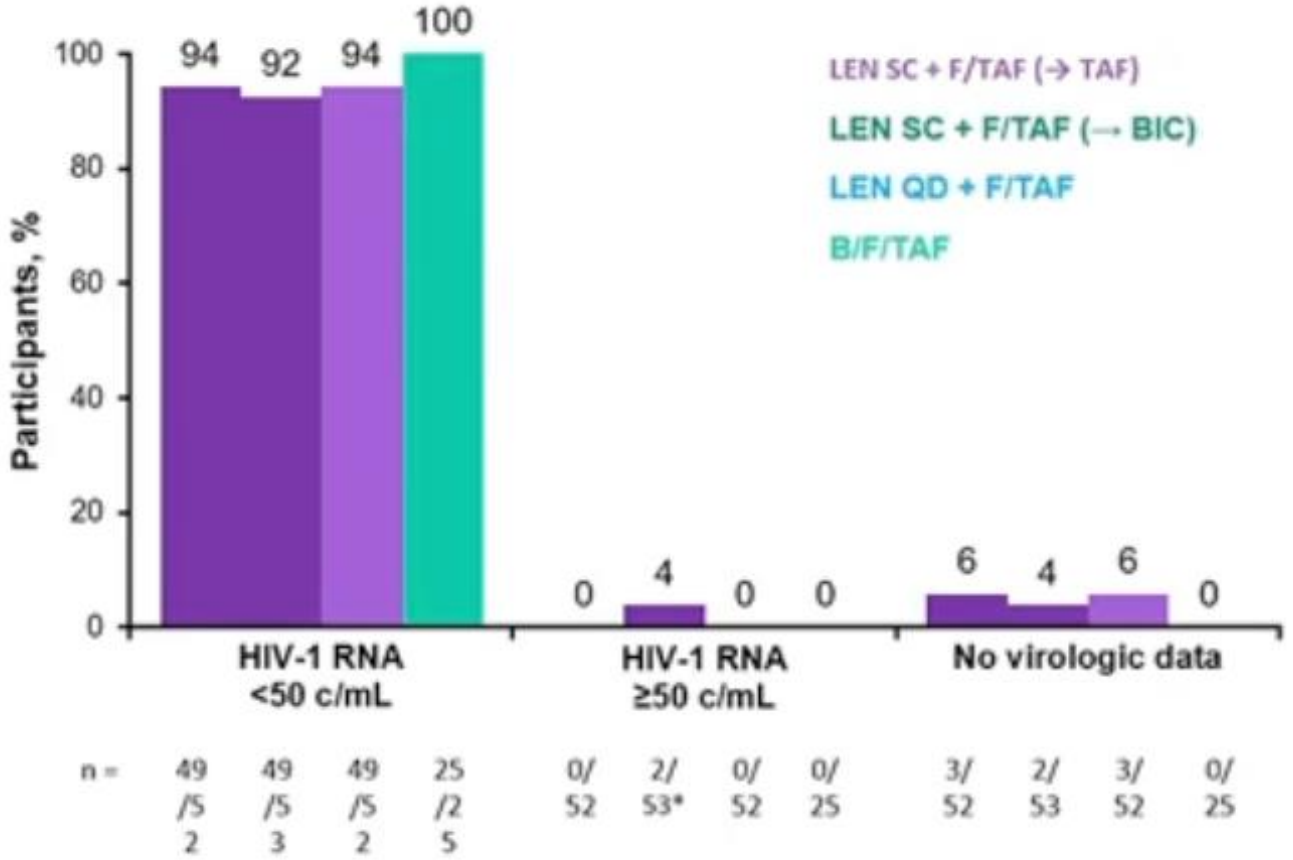
Lenicapavir – Treatment naïve



- Randomized, open-label, active controlled LEN for ART-naive

Gupta S, et al vIAS 2021. OALB0302

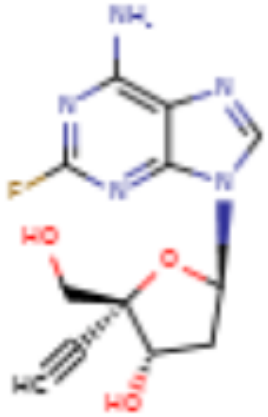
Lenicapavir – Treatment naïve, week #28 results



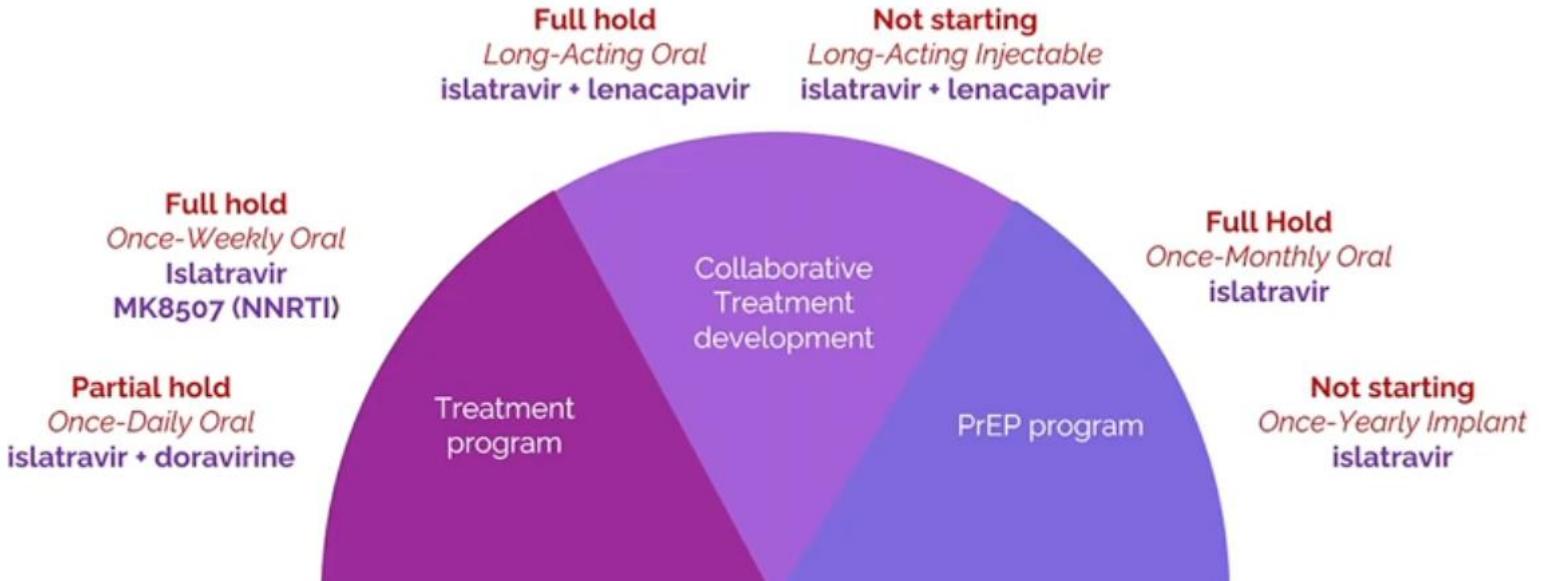
- Rapid viral suppression when combined with F/TAF in SQ and Oral form
- One case LEN resistance at week #10 (plasma concentrations in target range)
- ISR's in 49% of participants; 83% grade 1, resolved within days; 2 discontinuations
- Most common AE's: headache, nausea; no SAE's or grade 4 AEs

Gupta S. etl al vIAS 2021, OALB0302; Gupta S. et al Abstract 138 CROI 2022

Islatravir



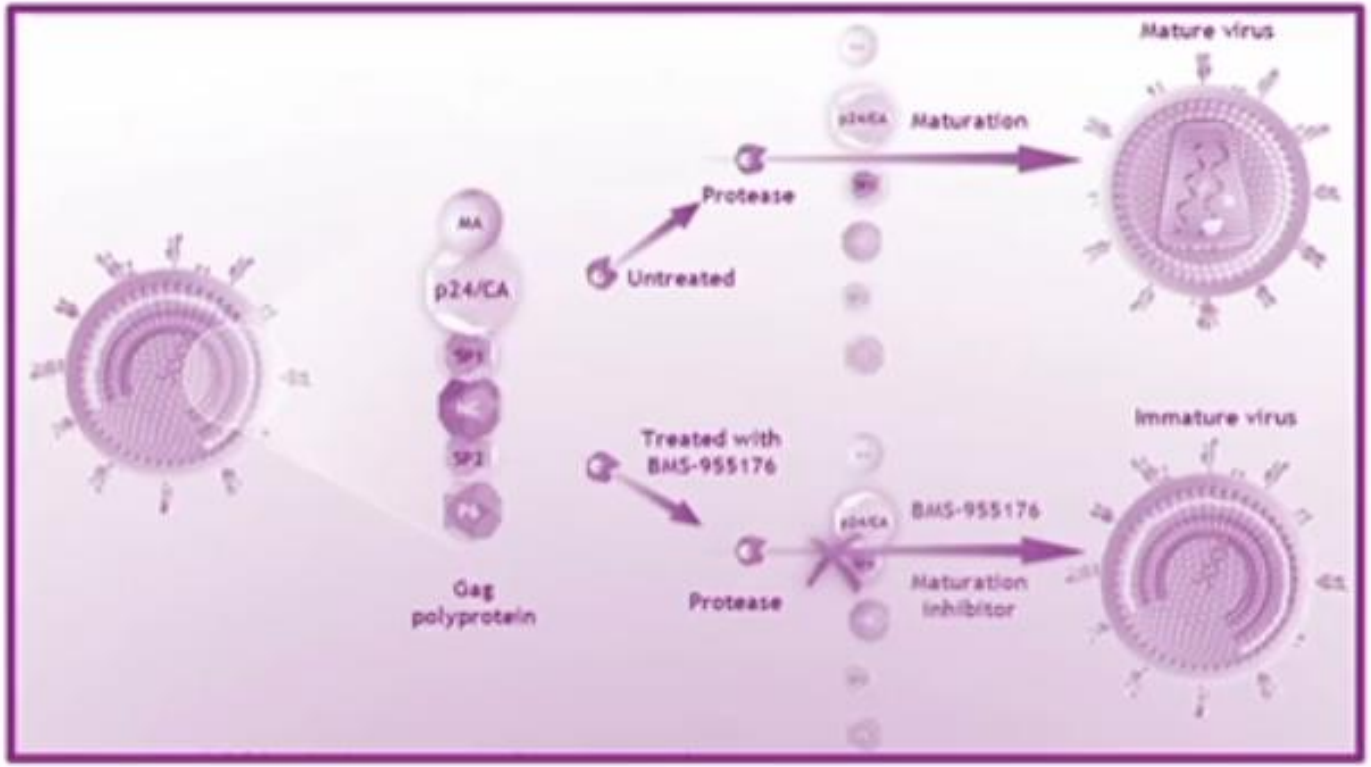
- Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI)
- Oral SubQ and implant bioavailability
- Potent activity against HIV-1/2 and highly resistant strains
- Dosing schemes being investigated: PO QD, Qweek, Qmonth, LAI, implant
- **12/13/21: All studies on partial FDA hold
  - Decreases in total lymphocytes and CD4+ cells in some participants
  - Some trials will continue study drug (DOR/ISL), but many will stop enrolling new patients
  - Prevention trials stopped



https://clinicalinfo.hiv.gov/en/drugs/islatravir/health-professional

Maturation Inhibitors

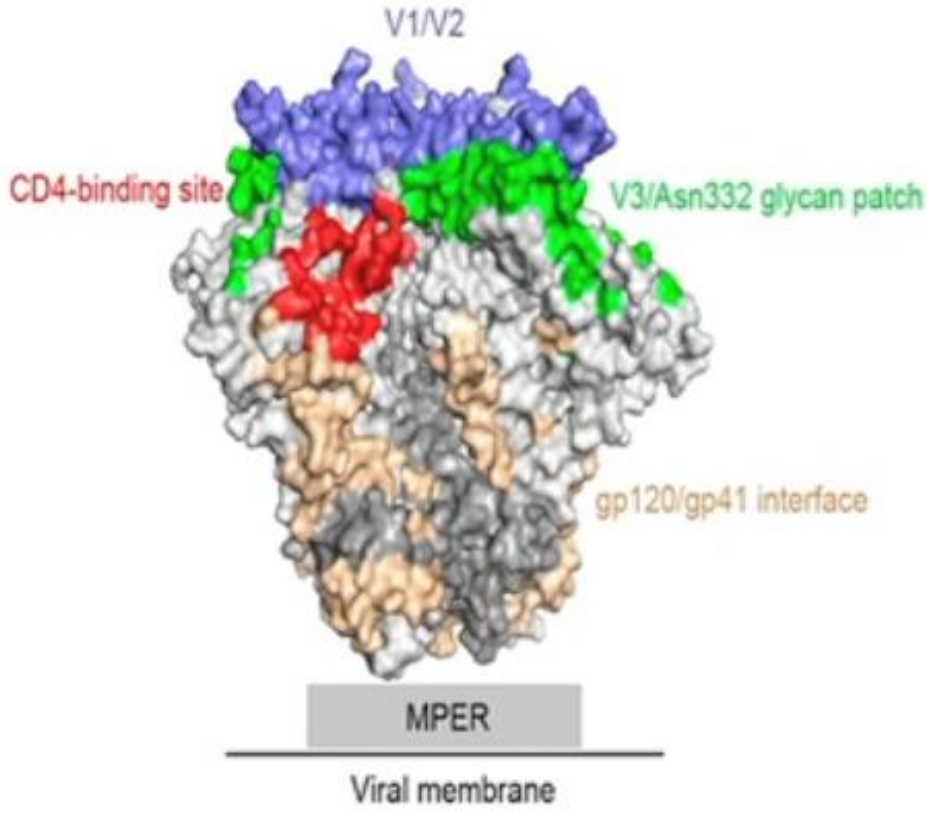
- **GSK 3640254, GSK 937, BMS-955176**
- Interrupt protein processing of Gag polyprotein late in life cycle
- Oral and long acting injectable formulations being studied
- **GSK 254** in oral phase II trials, alone and with DTG as FDC
- **GSK 937** in phase I as SQ and IM long-acting injectable
- Q2 month dosing going forward



https://clinicalinfo.hiv.gov/en/drugs/islatravir/health-professional

Broadly Neutralizing Antibodies (bNAbs)

- **GS-5423/2872, VRC01/07, UB-421, N6LS, Leronlimab (PRO-140), PG-121 (Elipovimab)**
- Delivered as long-acting Q6 month infusions
- Potential utility in treatment, prevention, and to reduce size of latent reservoir
- Investigated in combination with other classes of long acting small molecules:
  - Lenacapavir + GS-5423 + GS-2872 Q6 months
  - CAB-LA + N6LS
- Initial PrEP trials did not prevent HIV acquisition



https://clinicalinfo.hiv.gov/en/drugs/vrc01/patient
https://clinicalinfo.hiv.gov/en/drugs/10-1074/patient
https://clinicalinfo.hiv.gov/en/drugs/3bnc117/patient

Dapivirine

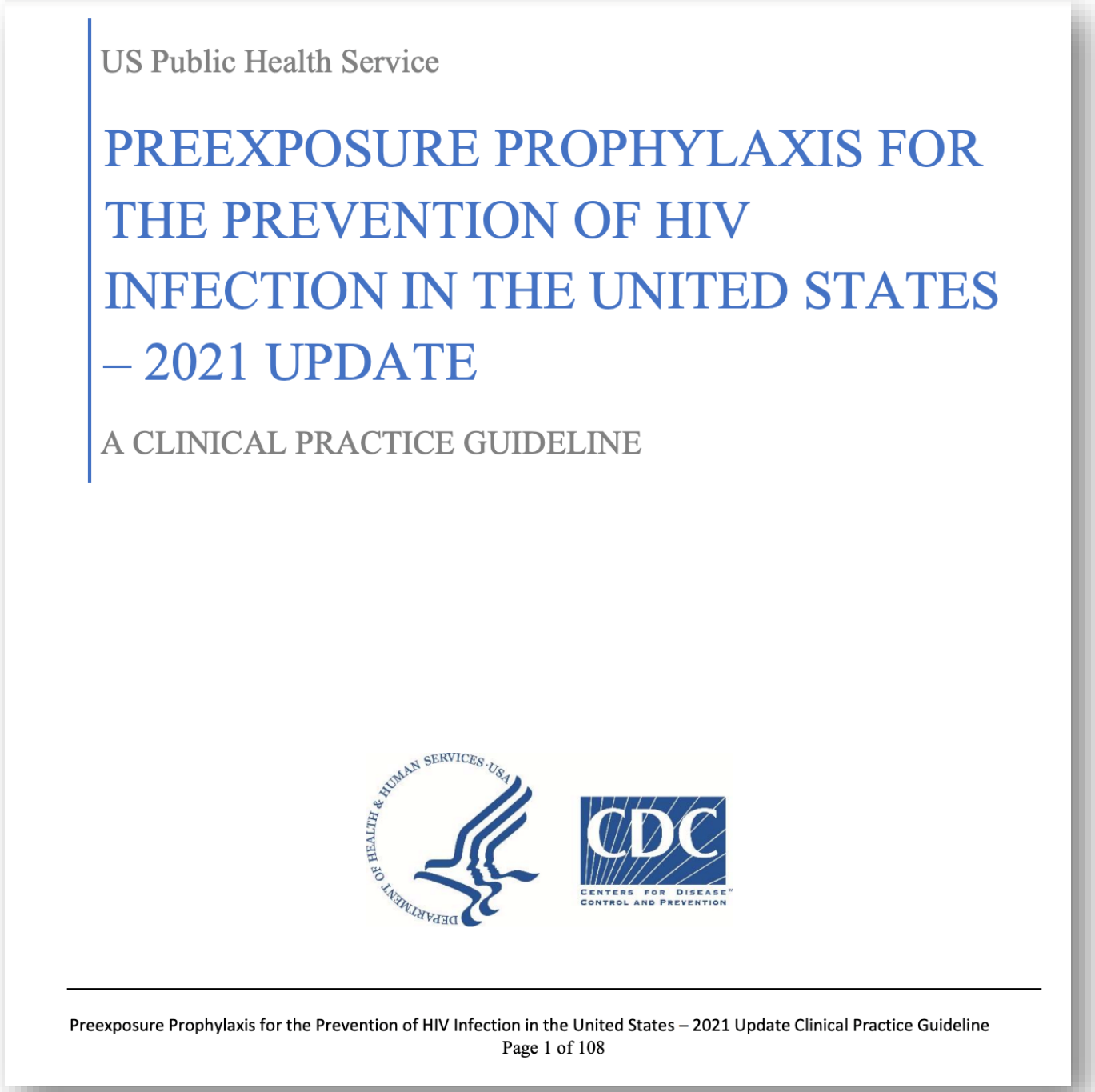
- **Silicone Intravaginal ring (IVR),** also investigated as gel, film, oral
- Female-controlled PrEP inserted QOMonth
- Highly acceptable form of PrEP as reported by participants
- Investigated for 'multi-purpose prevention' technology (contraception)
- WHO Guidance: may be used as additional choice for women at substantial risk as part of a combination prevention package
- ASPIRE and RING studies: RRR of 30%
- DREAM study: RRR 62%

Baeten J, et al NEJM 2016; 375: 2121
Nel, et al NEJM 2016; 375:2133
https://www.ipmglobal.org/content/adolescent-girls-and-young-women-can-and-will-use-hiv-prevention-products-results-croi-2022

Investigational HIV Treatment - Summary

- Additional options for LAI therapy are on the horizon
- Islatravir research currently on hold
- Increasing options for patients based on preference

HIV Prevention


US Public Health Service

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE

A CLINICAL PRACTICE GUIDELINE

Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2021 Update Clinical Practice Guideline
Page 1 of 108

What's New?

- CAB-LA Q2 months for men, women, transgender persons
- Recommendation to inform ALL sexually active persons about PrEP
- Revised HIV testing algorithm
  - No h/o PrEP
  - Ongoing PrEP
- Added F/TAF recommendations
- Same-day PrEP
- Tele-PrEP
- Off-label on-demand '2-1-1' PrEP

https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf

What to Start?

Table 3: Recommended Oral PrEP Medications

Generic Name	Trade Name	Dose	Frequency	Most Common Side Effects[109,110]
F/TDF	Truvada	200 mg/300 mg	Once a day	Headache, abdominal pain, weight loss
F/TAF	Descovy	200 mg/25 mg	Once a day	Diarrhea

- F/TAF only approved for Men and TGW
- "For most patients, there is no need to switch from F/TDF to F/TAF"
- F/TAF indicated for eCrCl > 30 ml/min; F/TDF for eCrCl > 60 ml/min

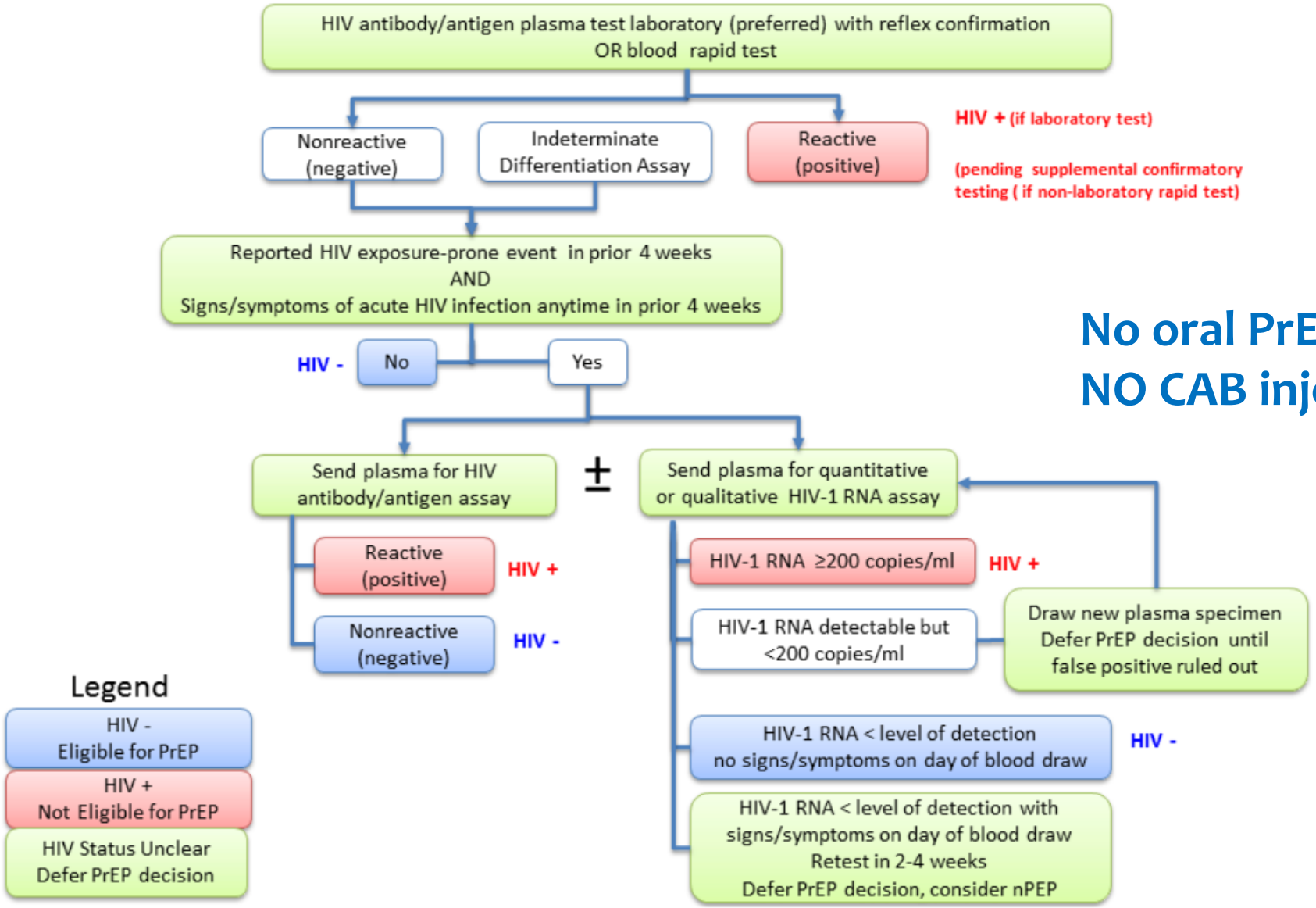
RECOMMENDED MEDICATION

- 600 mg of cabotegravir injected into gluteal muscle every 2 months is recommended (conditional on FDA approval) for PrEP in adults at risk of acquiring HIV.
- 30 mg daily oral cabotegravir is optional for a 4-week lead-in prior to injections.

- Not to be used in combination with other ARVs for PrEP
- Gluteal IM, health-care administered use only
- Do not use ongoing oral CAB outside of lead-in

https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf

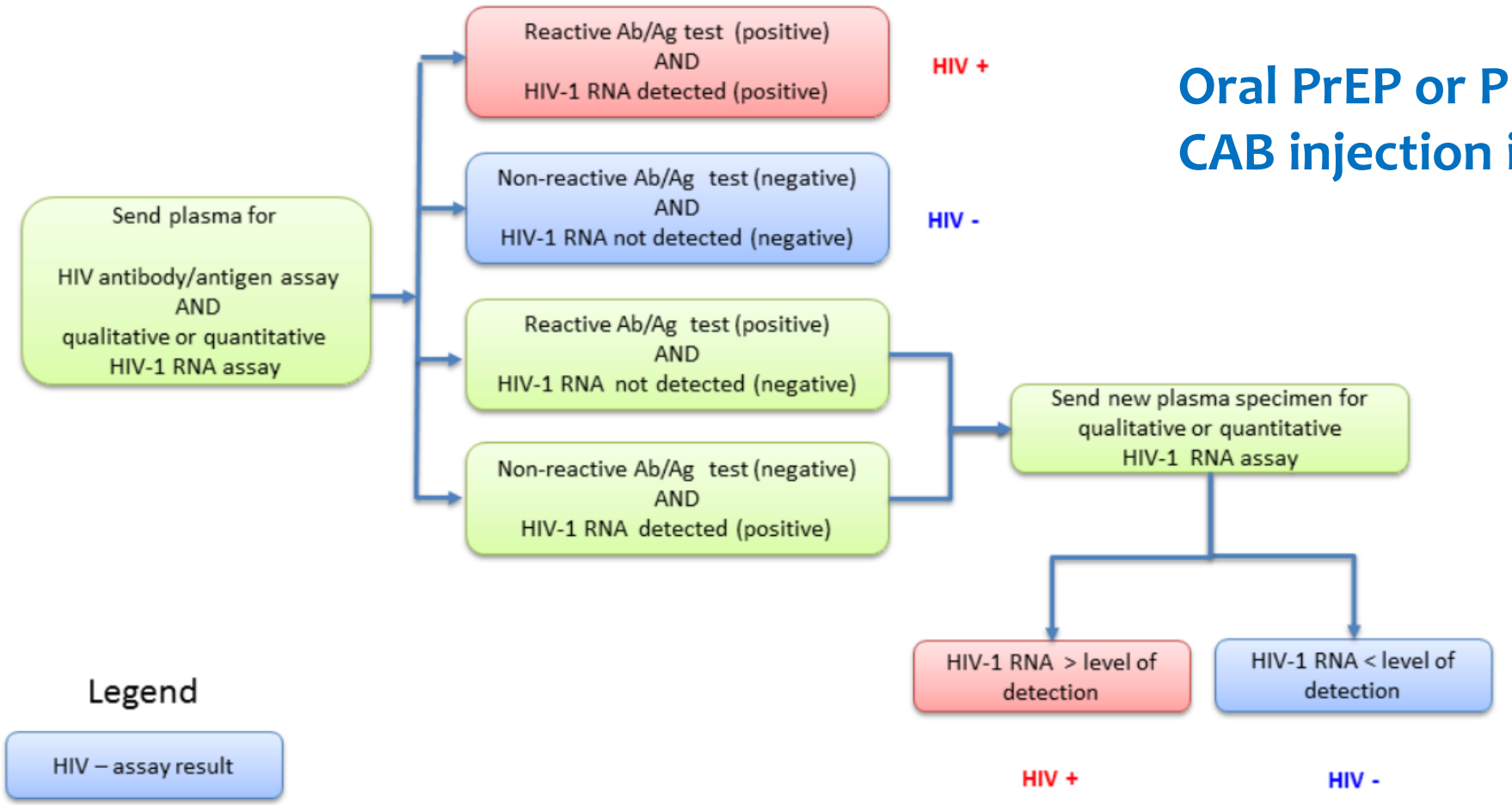
Testing Algorithm – NO recent PrEP



No oral PrEP or PEP in last 3 months,
NO CAB injection in past 12 months

https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf

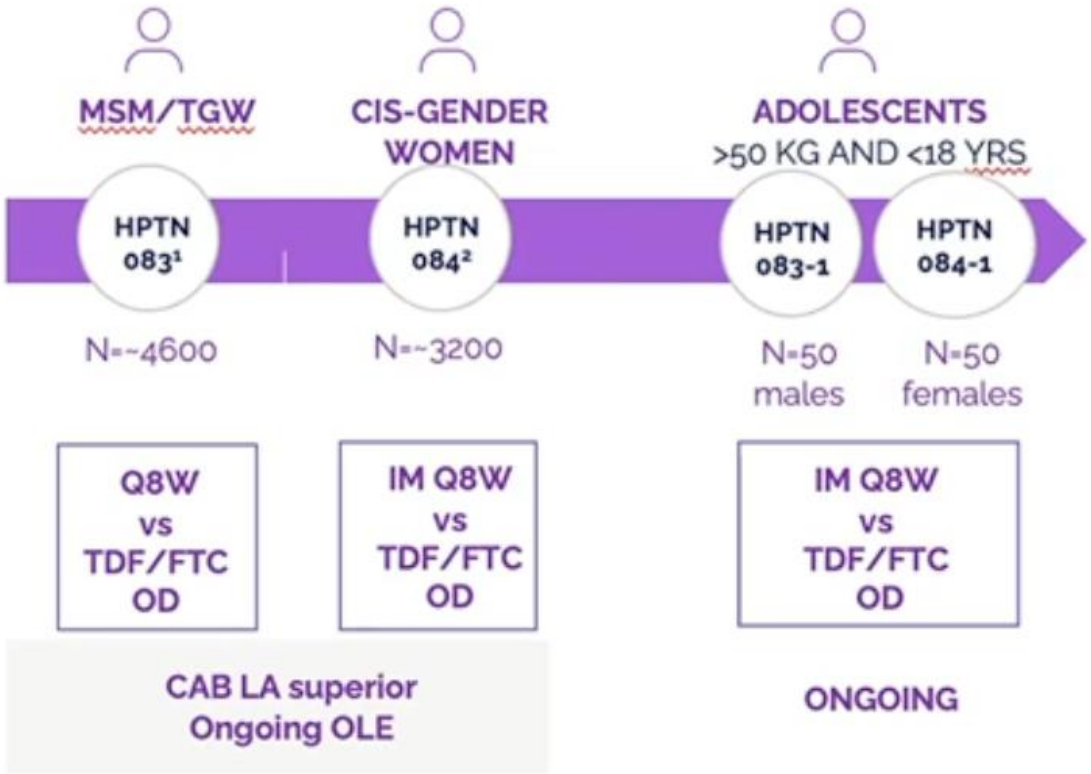
Testing Algorithm – Recent/Ongoing PrEP



Oral PrEP or PEP in last 3 months, or CAB injection in past 12 months

https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf

Long Acting Cabotegravir for PrEP

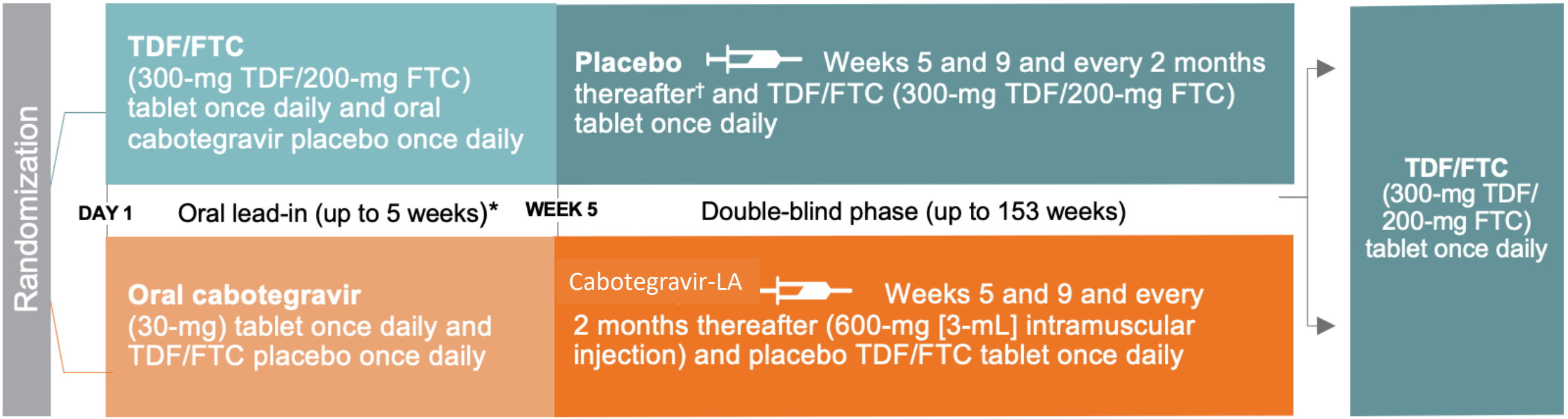


- CAB-LA superior to F/TDF in prevention of HIV acquisition
  - MSM/TGW: 68% RRR; Women: 89% RRR
- ISRs mostly grade 1-2; few discontinuations (none in women)
- Similar AEs to oral daily PrEP
- Preference for Q2 month dosing

Landowitz, R. NEJM 2021: 385:595-608
Delaney-Moretiwe S, LB1479 R4P virtual conference

Long Acting Cabotegravir for PrEP

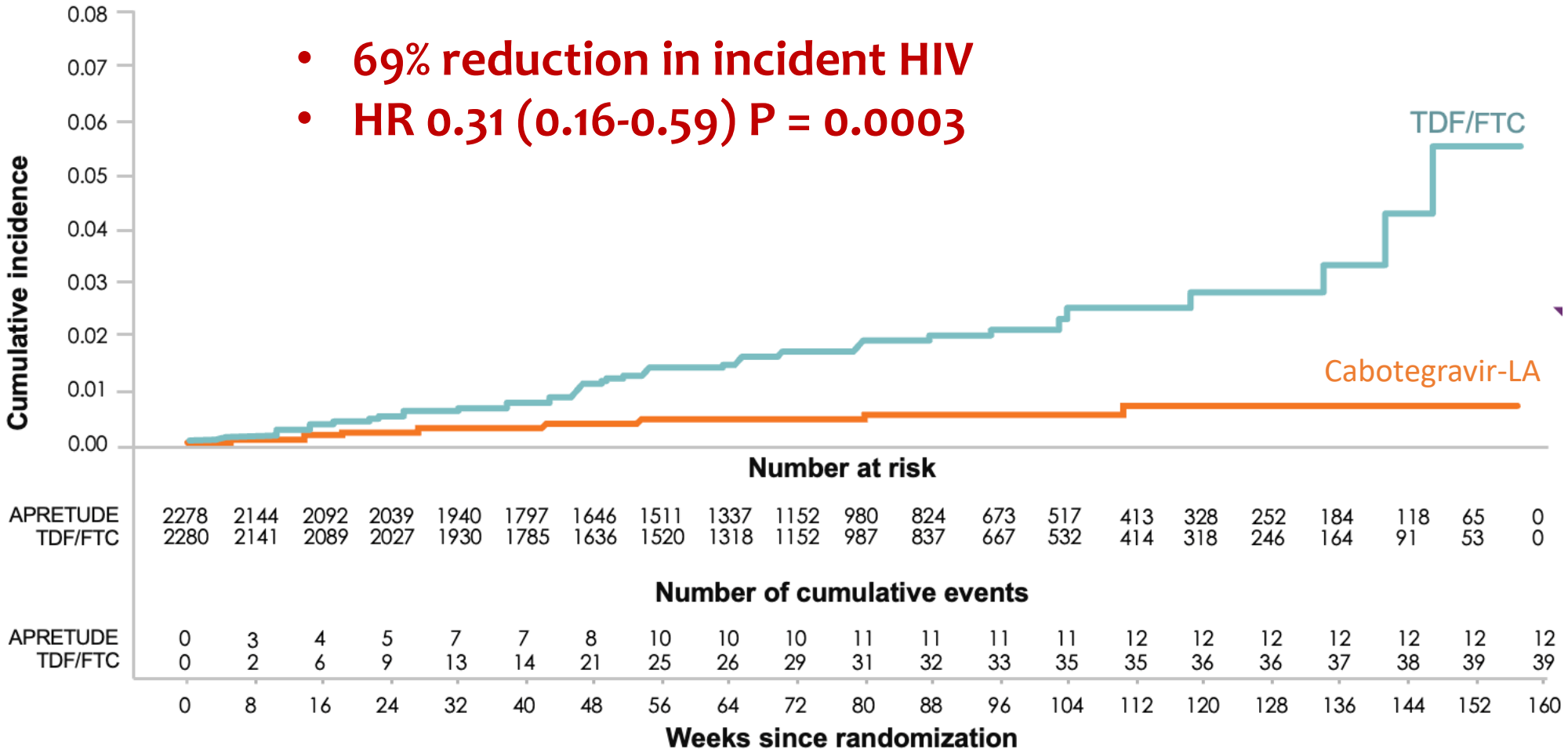
- **HPTN 083** – Uninfected cisgender men and transgender women who have sex with men at risk of sexually acquired HIV - 43 global sites (N = 4566)
- **HPTN 084** – Uninfected cisgender women at risk of acquiring HIV – 20 sub-Saharan African sites (N = 3224)



Landowitz, R. NEJM 2021: 385:595-608
Delaney-Moretiwe S, LB1479 R4P virtual conference

Long Acting Cabotegravir for PrEP – HPTN 083

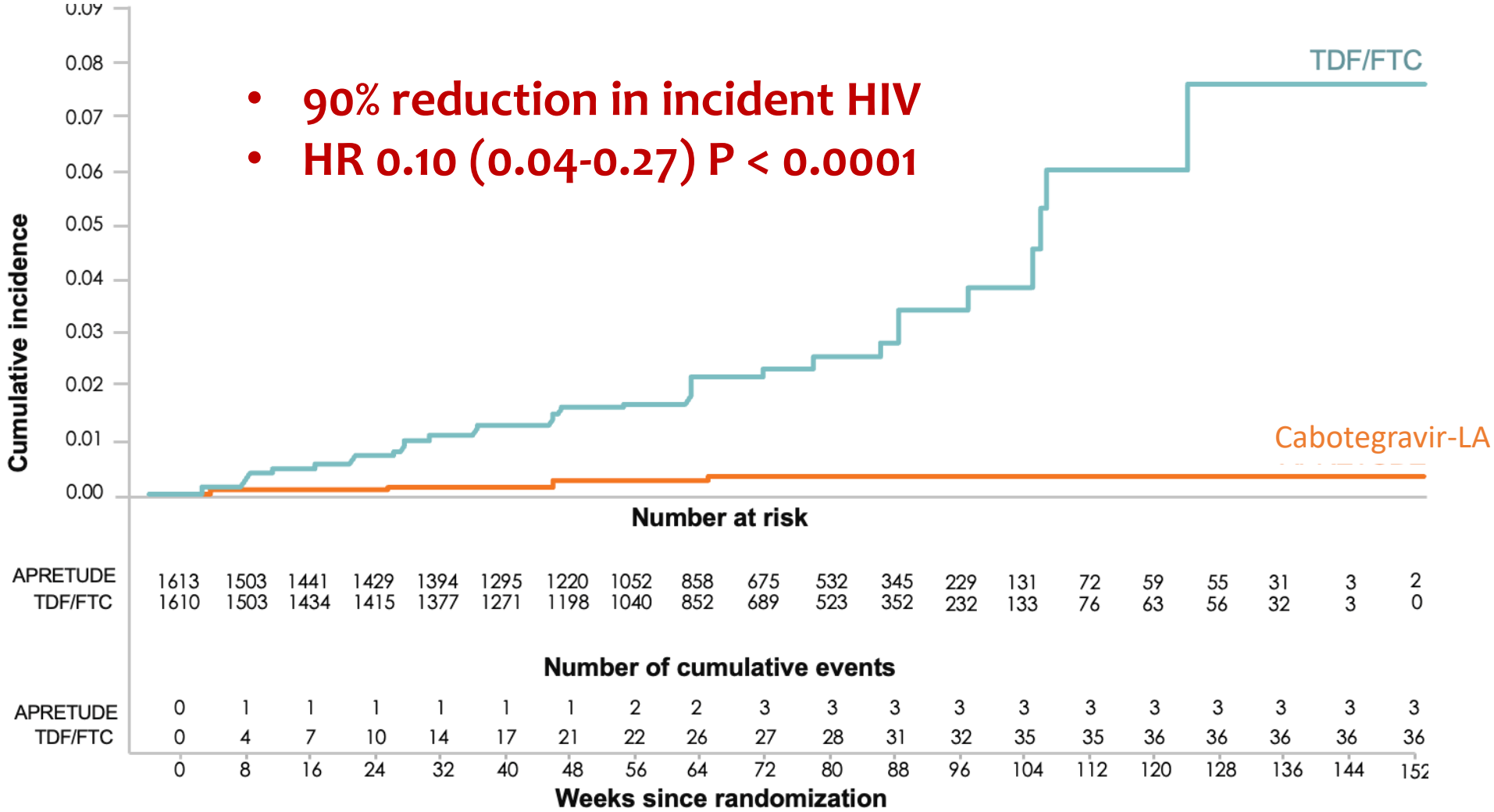
- 69% reduction in incident HIV
- HR 0.31 (0.16-0.59) P = 0.0003



- CAB-LA (N = 2282) vs. F/TDF (N = 2284) with active placebo
- 87% MSM, 13% TGW; 50% African-American; 68% < 30 yrs old

Landowitz, R. NEJM 2021: 385:595-608
Delaney-Moretiwe S, LB1479 R4P virtual conference

Long Acting Cabotegravir for PrEP – HPTN 084



- CAB-LA (N = 1614) vs. F/TDF (N = 1610) with active placebo
- 57% <25 yrs, 54% > 2 sex partners

Landowitz, R. NEJM 2021: 385:595-608
Delaney-Moretiwe S, LB1479 R4P virtual conference

Investigational Lenacapavir PrEP Q6 month injection

	Trial name (protocol number)	Population	Active comparator	Study design	Primary Endpoint
Phase 3	PURPOSE 1	Adolescent girls and young women at high risk	FTC/TDF or FTC/TAF	Randomized, double blind, placebo-controlled	LEN vs bHIV F/TAF vs bHIV
	PURPOSE 2	Men, TGM and non-binary people who have sex with men; transgender women at high risk	FTC/TDF	Randomized, double blind, placebo-controlled	LEN vs bHIV

Study design: counterfactual analysis

Use of recency assays to identify incident infections in screening population as a comparator

PURPOSE 1:
- **External control**: bHIV in those not on PrEP based on recency assay in screened population, historical data from ECHO, HVTN, PrEPVACC
- Dosing: Day 1 - LEN 927mg SC + 600mg oral, Day 2 - 600mg oral, followed by 927mg SC q26weeks; F/TAF 200/25mg oral daily, F/TDF 200/300mg oral daily
- **Internal Active Control**: F/TDF
- Locations: South Africa and Uganda

PURPOSE 2
- **External controls**: bHIV in those not on PrEP based on recency assay in screened population, rectal gonorrhea surrogate (Mullick & Murray 2018); CDC data background HIV incidence estimation (only for the US)
- Dosing: Day 1 - LEN 927mg SC + 600mg oral, Day 2 - 600mg oral, followed by 927mg SC q26weeks; F/TDF 200/300mg oral daily
- **Internal Active Control:** F/TDF and bHIV placebo-estimation (Glidden, et al IDWeek 2020)
- Locations: US, Peru, Brazil, South Africa

- Novel Study Design: bHIV control group is a counterfactual analysis of 'background in general population'

PURPOSE 1 NCT 04994509; PURPOSE 2 NCT04925752

HIV Prevention - Summary

- Major change in HIV testing algorithm for PrEP
- Much heavier reliance on HIV RNA
- Increasing options including now LAI Cabotegravir
- More options coming, including even longer-acting and potentially implantable therapies

Remaining Questions

- Who is ‘ideal patient’ for LAI therapy or prevention?
  - Patient choice? Easiest or Hardest to suppress?
- Where to best provide? Currently still in select clinics
  - Pharmacies? Primary Care? Self-administered?
- How best to monitor for breakthrough infections?
  - More complex picture of breakthrough infections on current testing algorithms
- Transitions on/off oral PrEP more complex
- Impact of long ‘tail’ of anti-retroviral
- Coverage, Cost-effectiveness

Conclusions

- Global and US progress on ending HIV is improving, but not yet on pace to meet lofty UNAIDS and EHE goals
- In the US, new infections stubbornly stuck at ~35,000 per year
- ART pipeline continues to yield novel mechanisms of action and novel delivery approaches with enthusiasms towards long-acting injectable medications
- PrEP options and access improving, but with stark racial/ethnic disparities
- Efforts will fall flat without ongoing funding (global and US) and recruitment of next generation of HIV treaters