Long-acting injectable PrEP: Challenges and Opportunities

Kevin L. Ard, MD, MPH
Director, Sexual Health Clinic, Division of Infectious Diseases
Massachusetts General Hospital

I have no financial conflicts of interest.

Agenda

1. The dawn of LAI HIV treatment
2. Current state of PrEP
3. Patient perceptions of LAI-PrEP
4. LA-cabotegravir
5. Modeling the impact of LAI-PrEP
6. Discussion

FDA NEWS RELEASE

FDA Approves First Extended-Release, Injectable Drug Regimen for Adults Living with HIV

More Press Announcements

Press Announcements

For Immediate Release: January 21, 2021

The U.S. Food and Drug Administration today approved Cabenuva (cabotegravir and rilpivirine, injectable formulation) as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace a current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. This is the first FDA-approved injectable, complete regimen for HIV-infected adults that is administered once a month.

The FDA also approved Vocabria (cabotegravir, tablet formulation), which should be taken in combination with oral rilpivirine (Edurant) for one month prior to starting treatment with Cabenuva to ensure the medications are well-tolerated before switching to the

Content current as of:
01/21/2021

Regulated Product(s)
Drugs

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Follow @US_FDA
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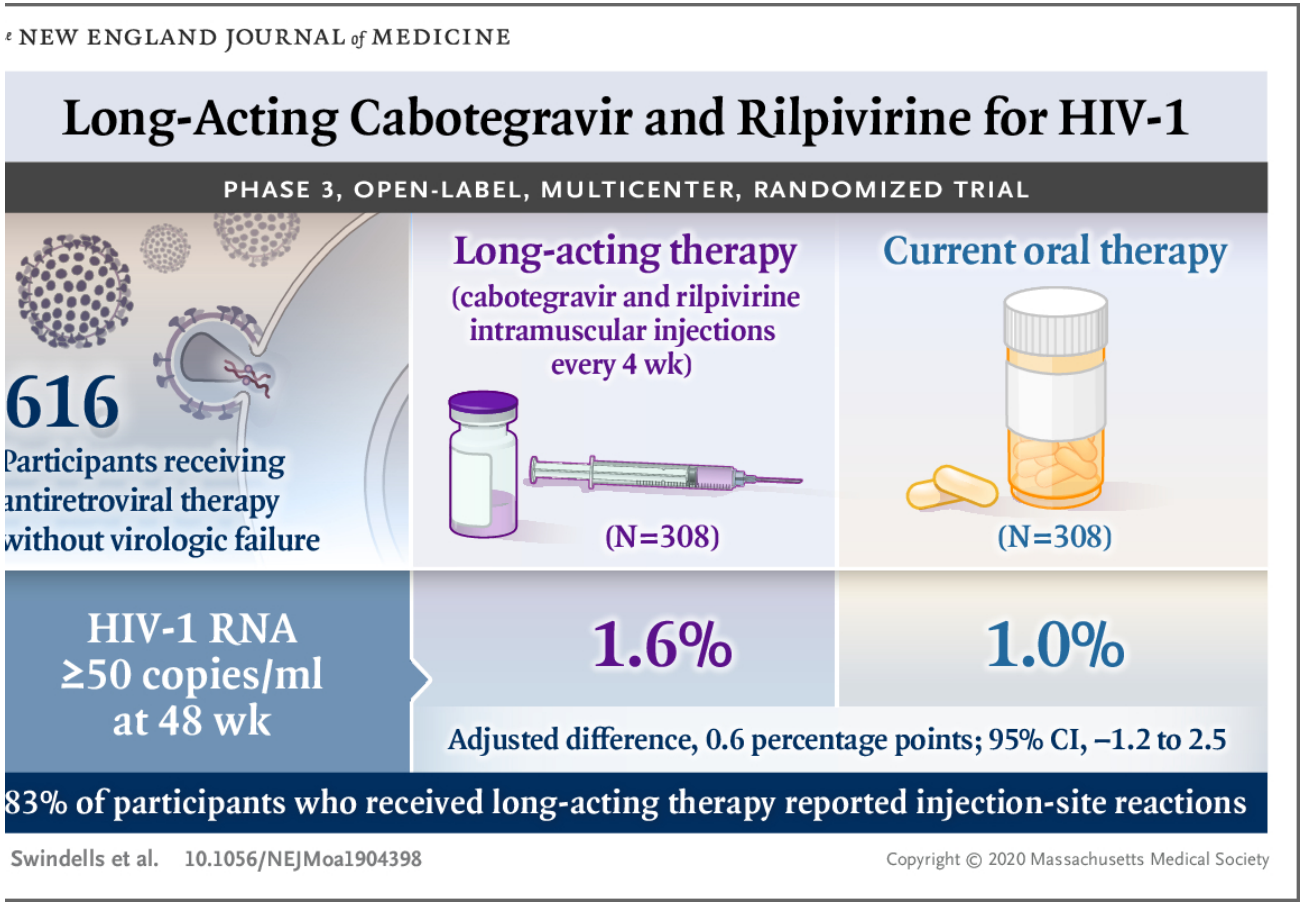
Follow @FDAmedia

ATLAS and FLAIR studies

- Approved for people who are already virologically suppressed on another regimen
- 1 month oral lead-in phase
- ~90% of trial participants preferred injectable over oral treatment
- Resistance to rilpivirine +/- cabotegravir common with virologic failure



Swindells S 2020, Orkin C 2020

Resistance at treatment failure in ATLAS

Table S4. Confirmed Virologic Failure.

	Treatment Arm	HIV-1 Subtype	On-Treatment RAMs (HIV-1 RNA) SVF Timepoint				Drug Sensitivity (Fold Change) at SVF Timepoint*			Baseline RAMs (PBMC/HIV-1 DNA on Day 1)	
			NRTI	NNRTI	PI	INSTI	NRTI	NNRTI	INSTI	RT	INSTI
1	**LA**	A/A1	none	E138A	none	none	none	RPV (2.4)	none	E138E/A	none
2	LA	A1/A	none	E138E/K	none	N155H	none	DLV (30) EFV (3.3) ETR (5.2) NVP (11) RPV (6.5)	RAL (16) EVG (33) CAB (2.7)	none	none
3	LA	AG	none	V108I E138K	N88N/S	none	none	DLV (15) EFV (4.2) ETR (5.8) NVP (16) RPV (3.7)	none	V108V/I E138K	none

Swindells S 2020

Resistance at treatment failure in FLAIR

Table S1. Confirmed Virologic Failure (CVF) Through Week 48

	Arm†	HIV-1 Subtype	On-Treatment RAMs (HIV-1 RNA) SVF Timepoint		Drug Sensitivity (Fold Change) at SVF Timepoint*		Baseline RAMs	
			NNRTI	INSTI	NNRTI	INSTI	NNRTI	INSTI
1	**LA**	A1	K101E	G140R	RPV (2.63)	CAB (6.7) DTG (2.2)	none	none
2	LA	A1	E138E/A/K/T	Q148R	RPV (7.1)	CAB (5.2) DTG (1.0)	none	none
3	LA	A1	E138K	Q148R	RPV (1.0)	CAB (9.4) DTG (1.1)	none	none

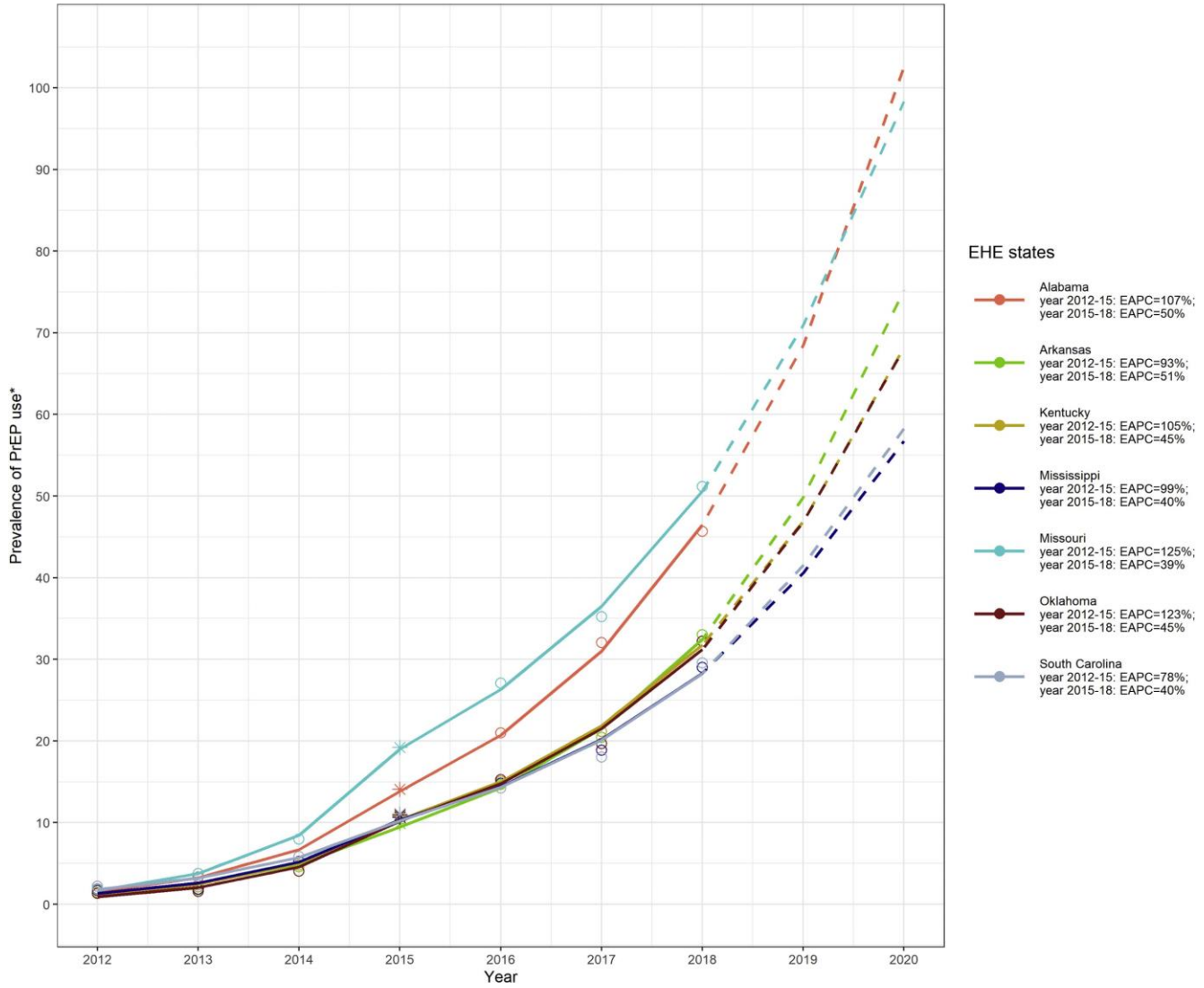
Orkin C 2020

Integrase resistance at treatment failure in ATLAS and FLAIR

Participant (Study)	Integrase mutation
1 (ATLAS)	None
2 (ATLAS)	N155H
3 (ATLAS)	None
4 (FLAIR)	G140R
5 (FLAIR)	Q148R
6 (FLAIR)	Q148R

Swindells S 2020; Orkin C 2020

PrEP use has increased since 2012.



*Number of PrEP users per 100,000 population aged 13 and above
Notes: Each county appears twice in legend describing rate of increase before and after Joinpoint i.e. inflection point in EAPC.
Joinpoint location is marked by a star (also indicated in legend).
Dashed lines mark projected rates based on most recent EAPC.

Sullivan PS, Ann Epidemiol, 2020

Most people who could benefit from PrEP are not taking it.

GROUP	ESTIMATED POPULATION SIZE IN THE U.S.	ESTIMATED PROPORTION OF ELIGIBLE POPULATION USING PrEP
Men who have sex with men (MSM)	814,000	35%
Heterosexual people	258,000	2.1% (women only)
People who inject drugs (PWID)	73,000	3%

CDC 2018, Finlayson T 2019, Huang YA 2018, Mistler CB 2020

PrEP use varies by race/ethnicity.

Reported PrEP use by MSM at risk for HIV in 20 urban areas, 2014 and 2017

Racial/ethnic group	2014	2017
Black	3.8%	26.2%
Hispanic/Latinx	3.8%	30.0%
White	8.3%	42.4%
Other	3.8%	39.8%

Finlayson T, MMWR, 2019

Which barriers will LAI-PrEP overcome?

Patient	Provider	Structural/environmental
Limited knowledge of PrEP	Knowledge of PrEP	Homophobia
Low HIV risk perception	Willingness to prescribe PrEP	Transphobia
Limited knowledge of partners' risks	"Purview paradox"	Sexism
Medical mistrust	Competing priorities	Racism
Financial concerns	Failure to elicit HIV risk information	Lack of health care access
Competing priorities	Billing/reimbursement concerns	Insurance climate
Confidentiality concerns		HIV-related stigma
Adherence		

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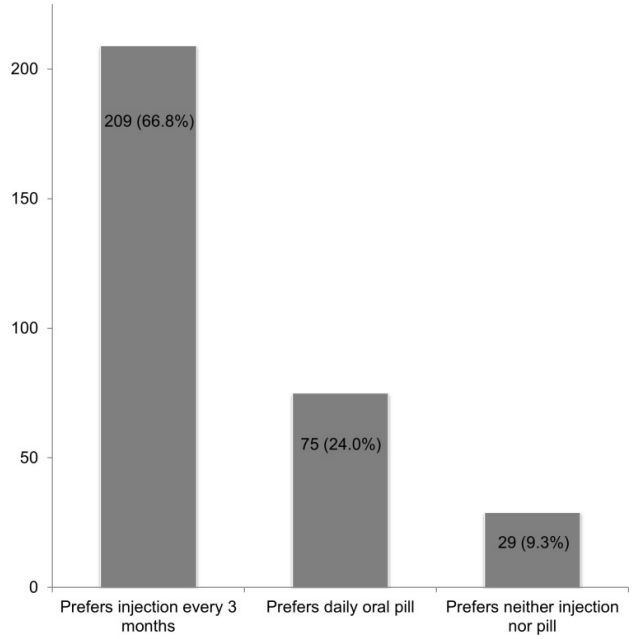
Perceptions of LAI PrEP among MSM

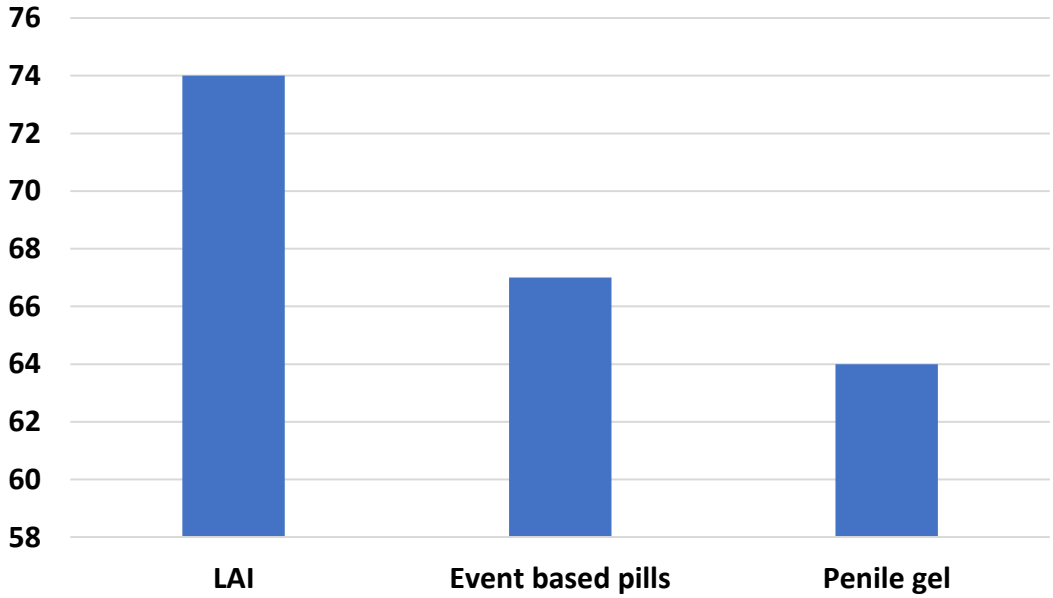
314 MSM in Washington, DC

- Median age 30, 41% non-Hispanic Black



M-cubed study

Proportion of MSM reporting likelihood of using PrEP formulations



Levy ME 2017

Perceptions of LAI PrEP among women

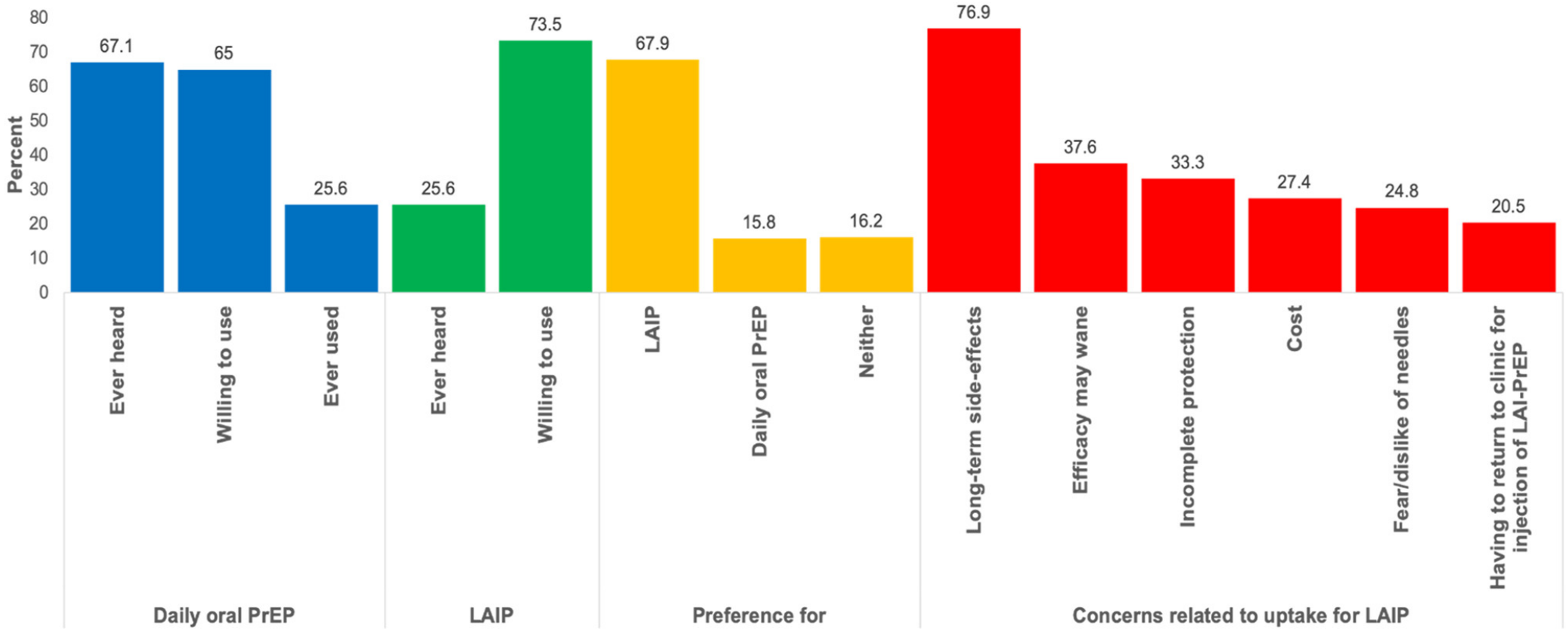
- 30 subjects in the Women's Interagency HIV Study
- Median age = 51 years
- 77% Black/African-American
- 60% no education beyond high school

- 57% knew of PrEP
- When asked to choose a formulation:
  - 55% preferred LAI PrEP
  - 10% preferred oral PrEP
  - 33% no PrEP

Philbin MM 2020

Perceptions of LAI PrEP among people who inject drugs

Perceptions among 234 people with opioid use disorder in CT



Shrestha R 2020

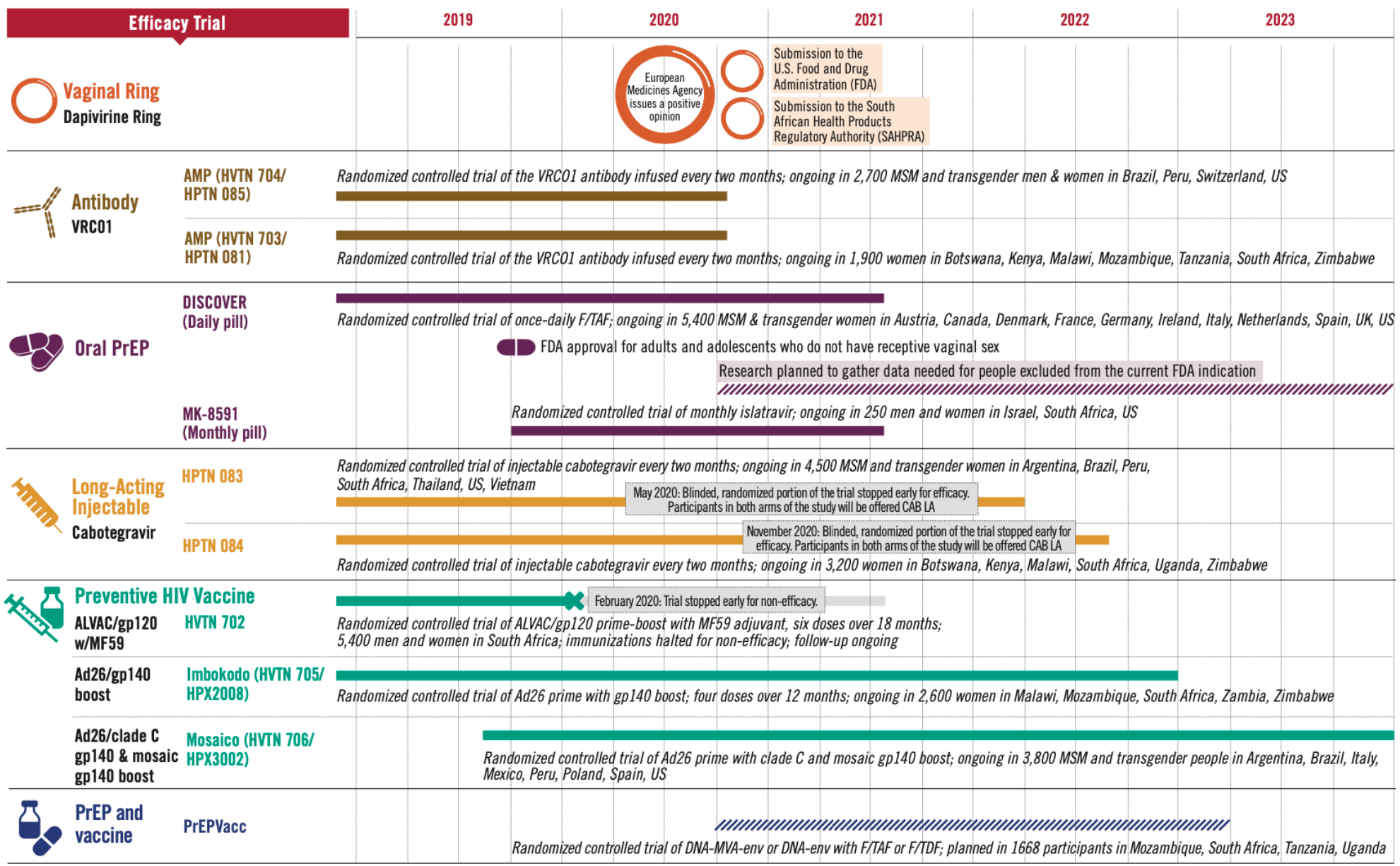
Conclusion from perception studies

- Many people report being more likely to use LAI PrEP than other forms of PrEP.
- Enthusiasm is limited in some populations with low oral PrEP use.
- Prior use of oral PrEP predicts willingness to use LAI PrEP.
- Perceptions may be different once there are proven, available therapies.

AVAC
Global Advocacy for HIV Prevention

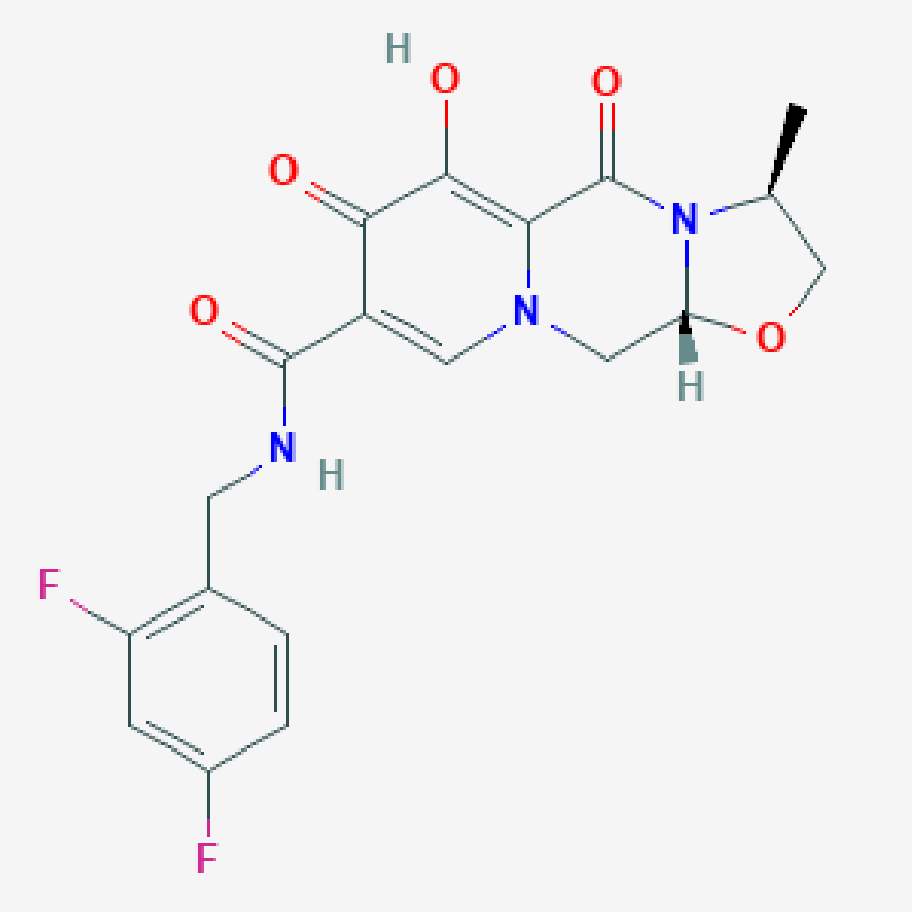
The Years Ahead in Biomedical HIV Prevention Research

Status of select biomedical HIV prevention clinical trials

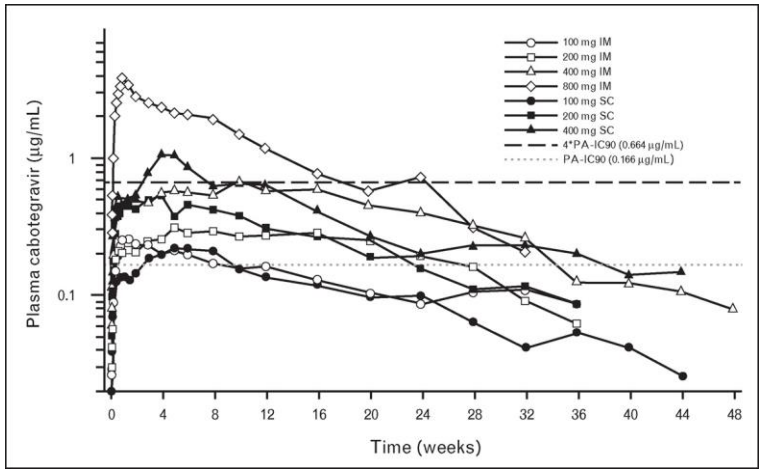


Ongoing //// Planned * Phase IIa trial

Cabotegravir

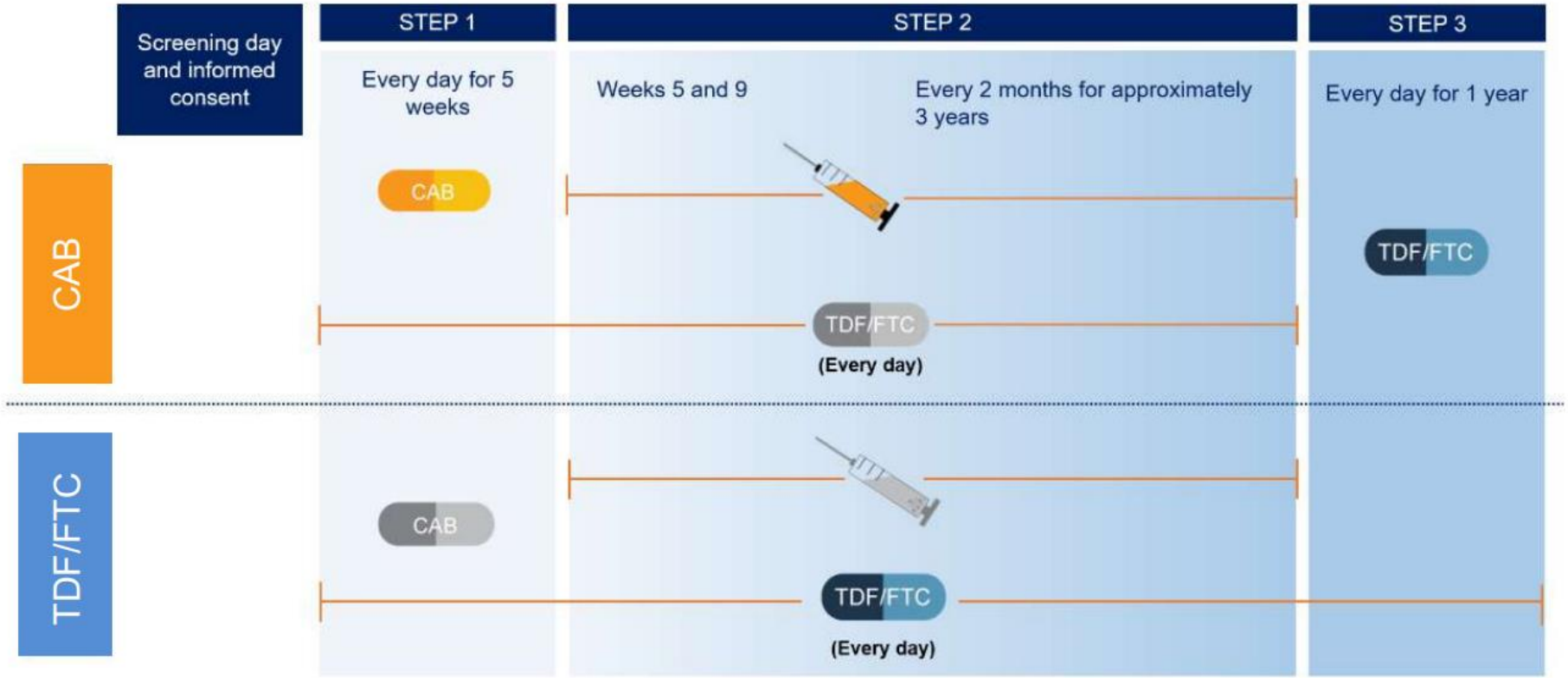


- Integrase inhibitor
- Elimination half-life = 40 days
- Not impacted by cytochrome P450 pathway
- Prolonged subtherapeutic tail



pubchem.ncbi.nlm.nih.gov/compound/Cabotegravir#section=2D-Structure, Trezza C 2015

HPTN 083 Study Design



Landovitz RJ et al. AIDS 2020, #OAXLB01

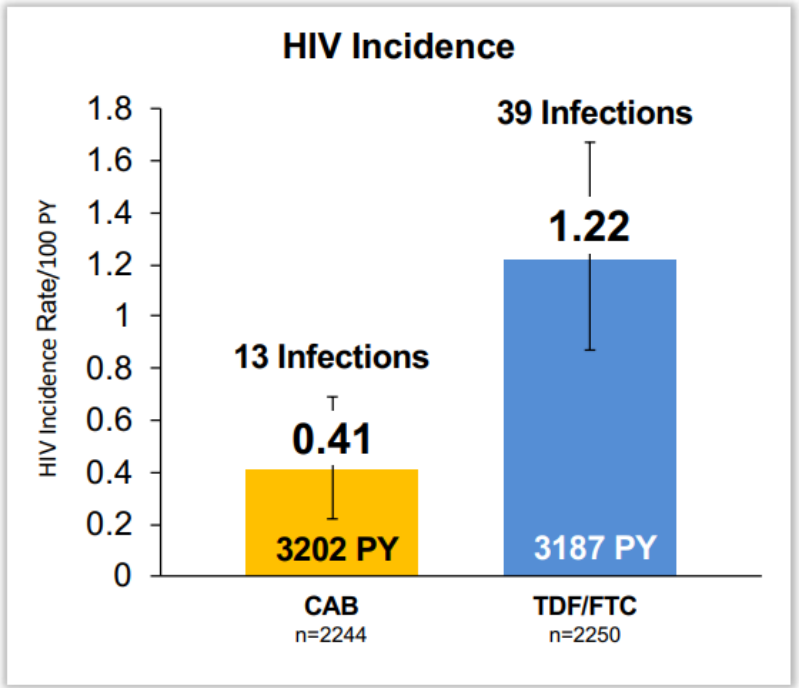
Study Population

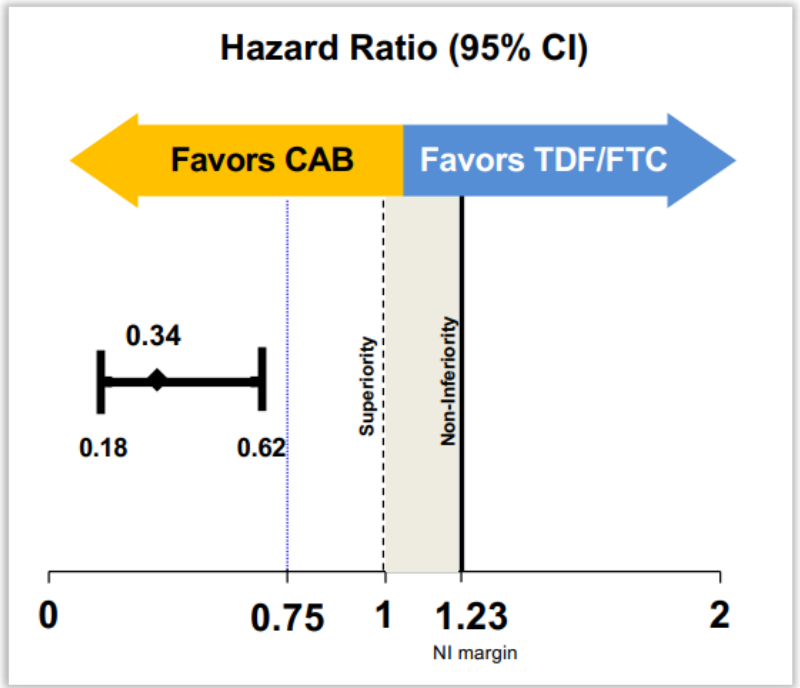
	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)
Gender Identity, n (%)			
MSM	3995 (87.5)	1981 (86.7)	2014 (88.3)
TGW	567 (12.4)	302 (13.2)	265 (11.6)
Age, median (IQR)	26 (22, 32)	26 (22, 32)	26 (22, 32)
Age, n (%)			
18-29	3079 (67.4)	1508 (66.0)	1571 (68.8)
30-39	1049 (23)	550 (24.1)	499 (21.9)
40-49	315 (6.9)	170 (7.4)	145 (6.4)
50-59	110 (2.4)	50 (2.2)	60 (2.6)
≥60	13 (0.3)	6 (0.3)	7 (0.3)
Region, n (%)			
United States	1698 (37.2%)	849 (37.2%)	849 (37.2%)
Latin America	1964 (43.0%)	984 (43.2%)	980 (42.9%)
Asia	752 (16.5%)	377 (16.5%)	375 (16.5%)
Africa	152 (3.3%)	74 (3.2%)	78 (3.4%)
Education, n (%)			
Post-Secondary (YES)	3477 (76.1)	1715 (75.1)	1762 (77.2)
Relationship Status, n (%)			
Single (YES)	3750 (82.1)	1863 (81.6)	1887 (82.7)

Landovitz RJ et al. AIDS 2020, #OAXLB01

HIV Incidence
CAB vs. TDF/FTC

52 HIV infections in 6389 PY of follow-up
1.4 (IQR 0.8-1.9) years median per-participant follow-up
Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY



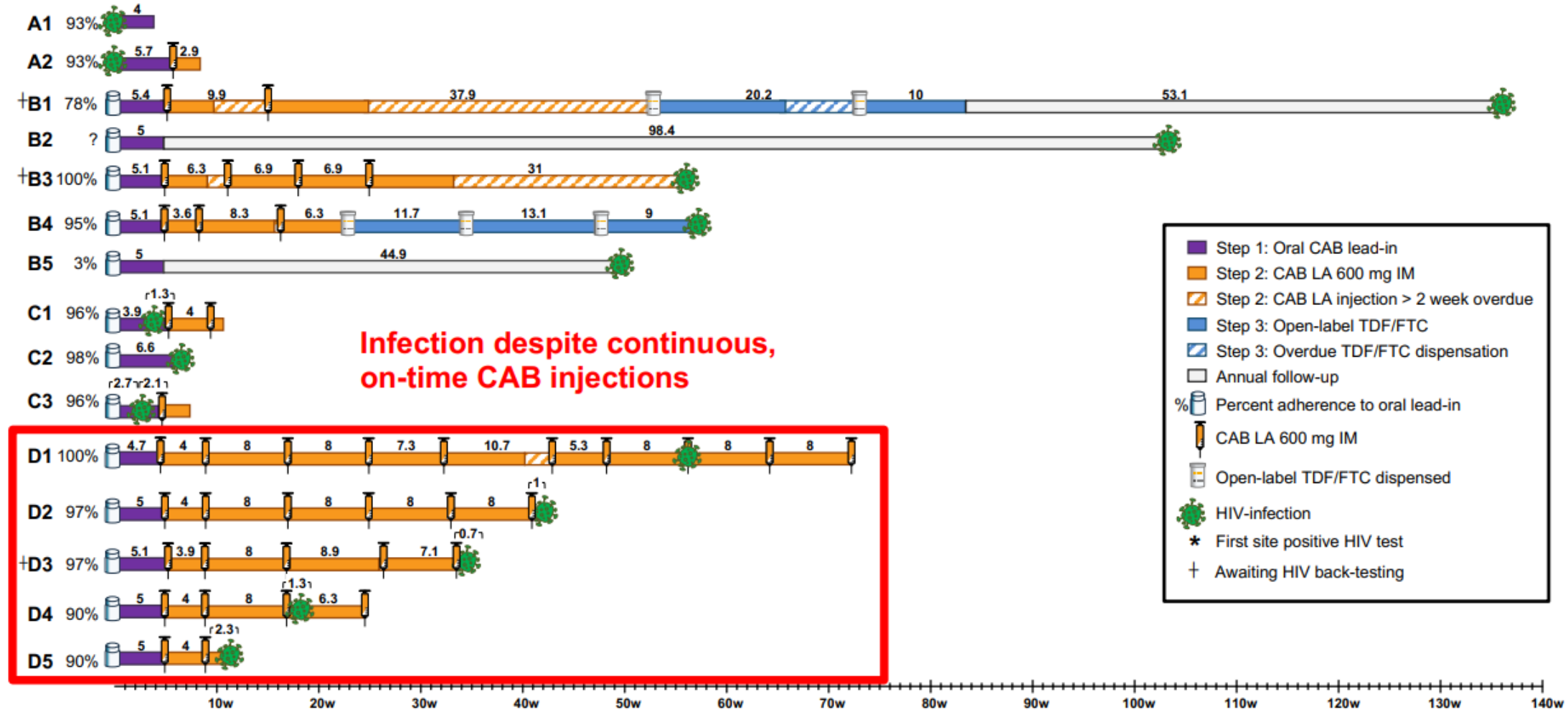


CI, confidence interval

Landovitz RJ et al. AIDS 2020, #OAXLB01

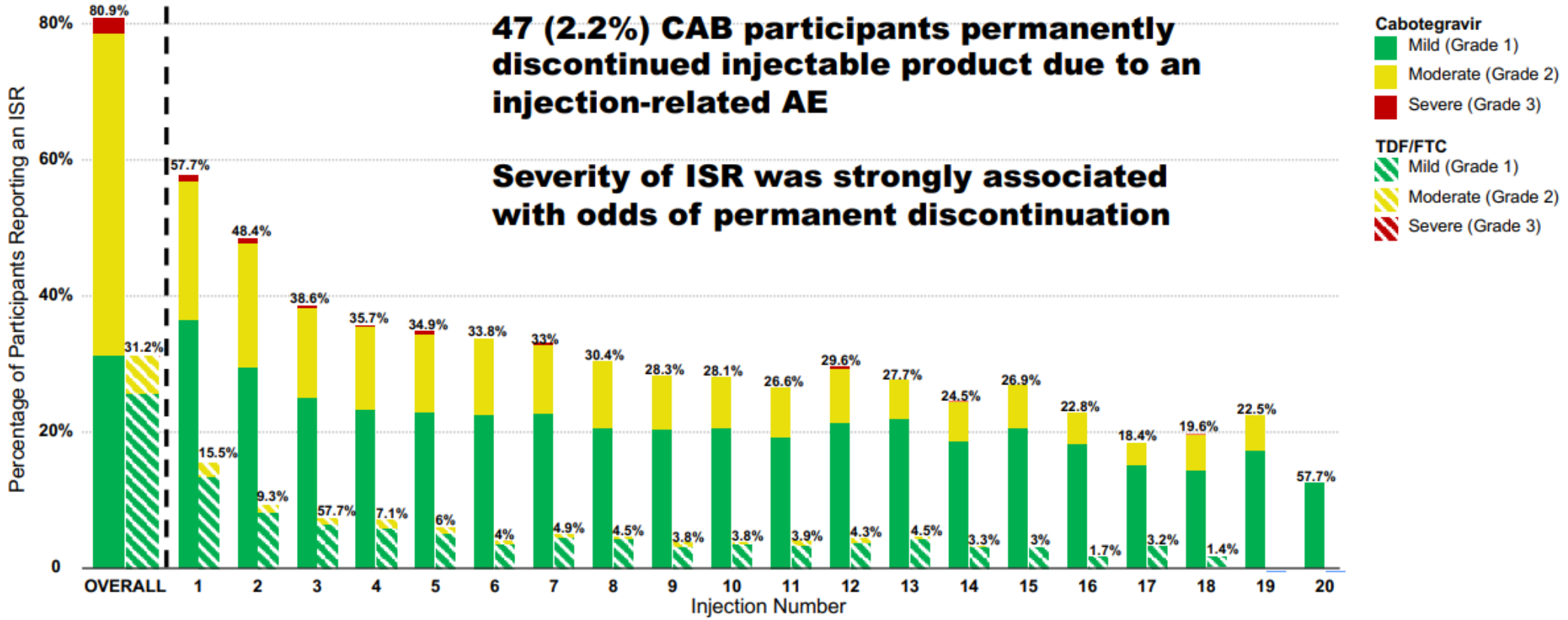
13 Incident HIV Infections

Cabotegravir



Landovitz RJ et al. AIDS 2020, #OAXLB01

Injection Site Reactions



Landovitz RJ et al. AIDS 2020, #OAXLB01

HPTN 084

- Enrolled 3,223 cisgender women in Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zimbabwe
- Design similar to HPTN 083
- Average age 26 years, 55% ≥ 2 partners in the past month, 34% with partners who have HIV or are of unknown HIV status
- Pregnant and breastfeeding women excluded
- DSMB recommended blinded phase be stopped in 11/2020
  - 38 HIV infections in the study
  - 4 in LA CAB arm (incidence 0.21%)
  - 34 in TDF/FTC arm (incidence 1.79%)

www.hptn.org/sites/default/files/inline-files/HPTN%20084%20DSMB%20FAQ_V1.0_8Nov2020_0.pdf

Questions about LA-cabotegravir

- Why is it superior to TDF/FTC?
- Will it reduce HIV risk from injection drug use?
- What will it cost?
- Will an oral lead-in phase be necessary?
- How should the drug be stopped, particularly in someone who remains at risk for HIV?

Oral lead-in phase

- Noted in FDA approval of LA-cabotegravir/rilpivirine; stated rationale is to ensure the medication is well-tolerated
- What do we know from the studies so far?
  - **HPTN 077:** 4 of 151 (2.6%) withdrew due to clinical AEs/lab abnormalities during oral phase
  - **ECLAIR:** 11 of 105 (10%) withdrew during the oral phase
  - **ATLAS:** 3 withdrew during oral phase
- In HPTN 084, unblinded subjects can switch to open label LA-cabotegravir without oral lead-in

Landovitz R 2018, Markowitz M 2017, Swindells S 2020

LA-cabotegravir versus oral tenofovir/emtricitabine for PrEP

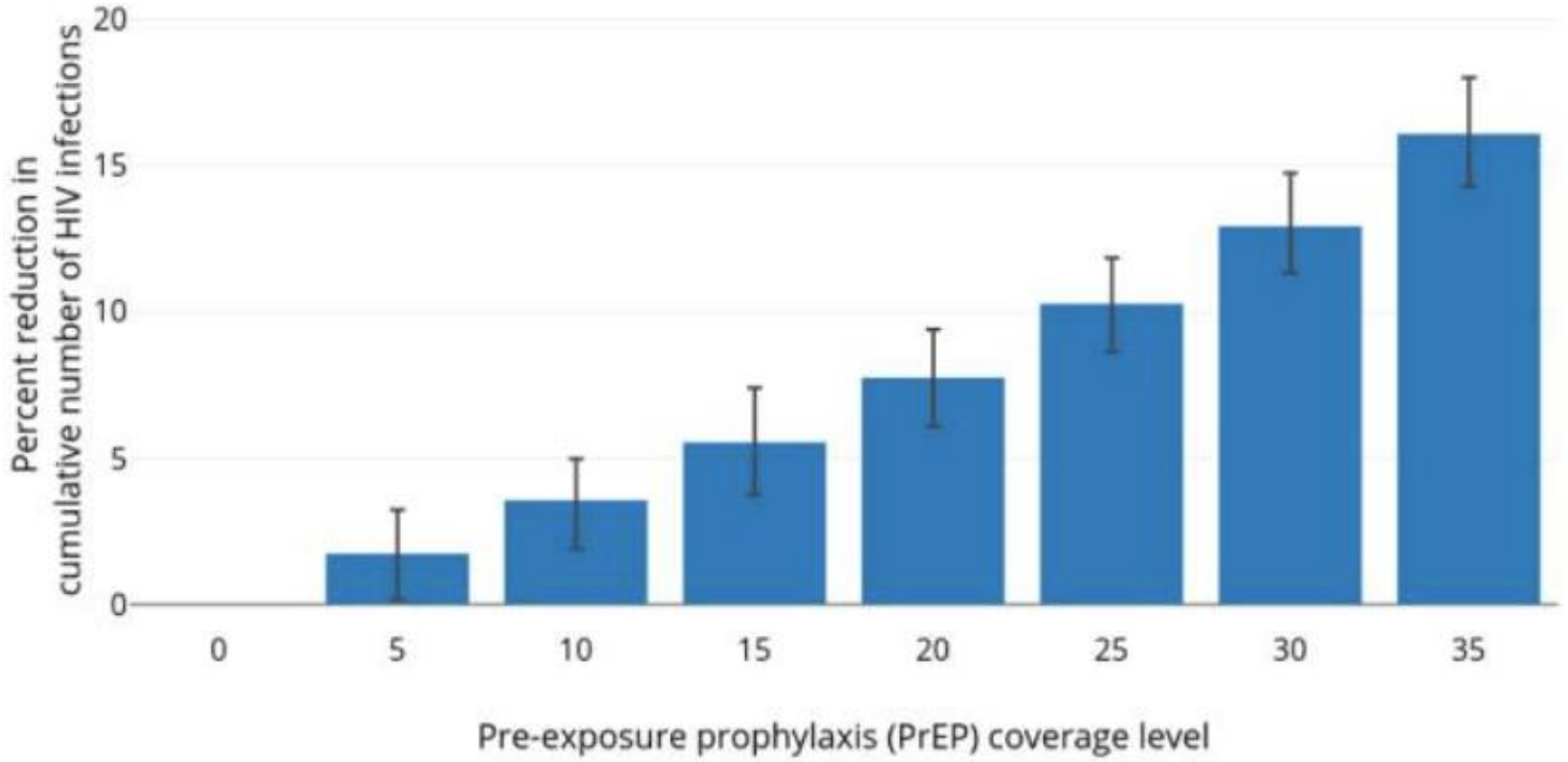
PROS

- Superior to TDF/FTC
- Does not require taking a pill daily
- Another option
- More discretion for patients?

CONS

- Still requires adherence
- Injection site reactions
- More frequent healthcare contact
- Resistance?
- Need for oral lead-in phase?

In comparison to oral PrEP, LAI-PrEP reduces HIV infections.

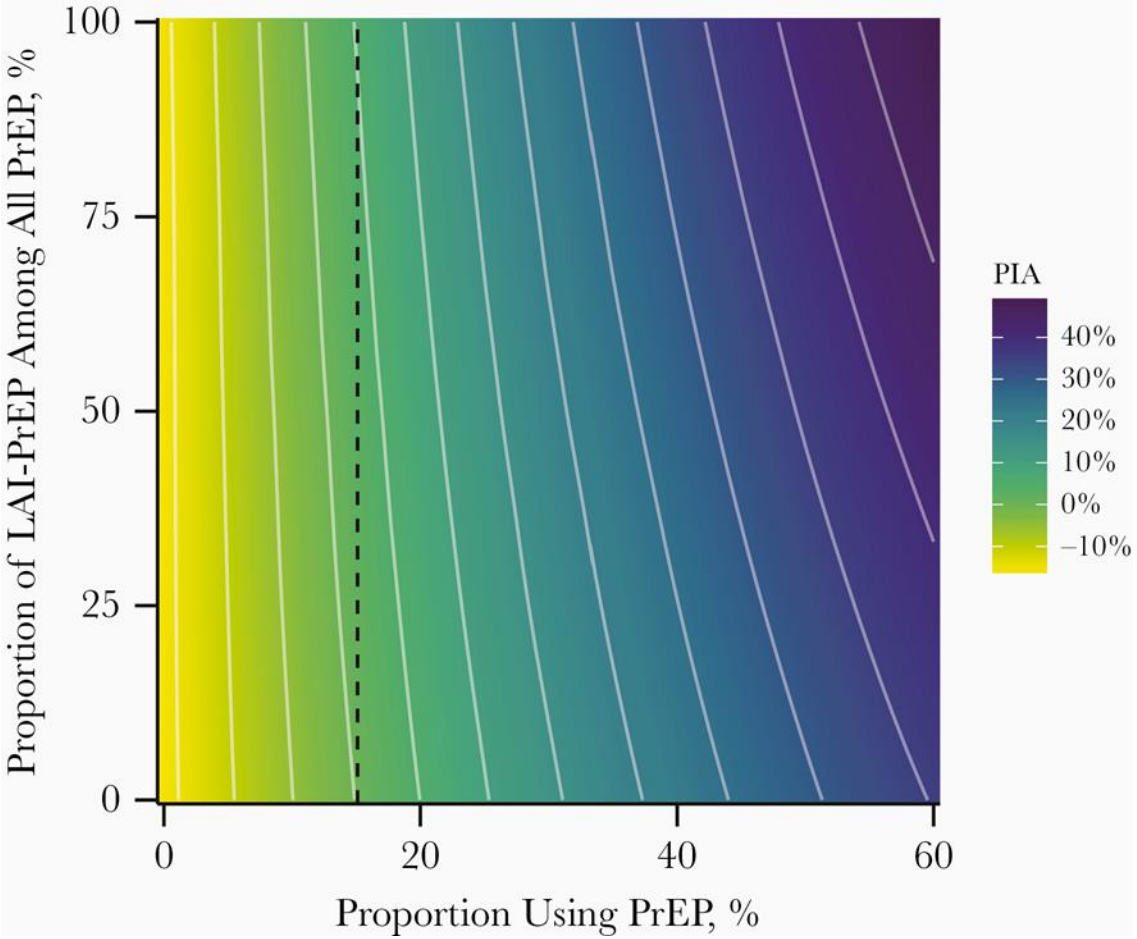


Marshall BD 2018

Modelled impact of LAI-PrEP among MSM in the southeastern U.S.

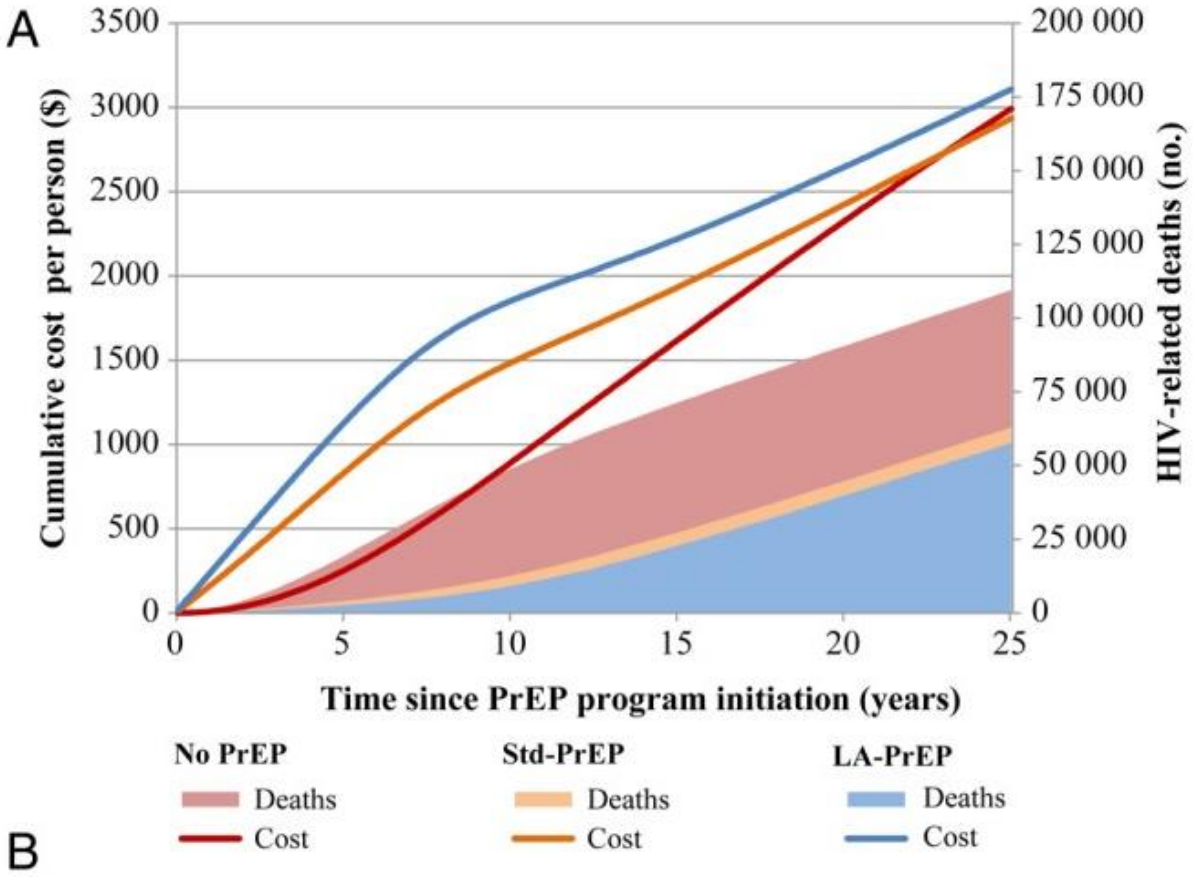
- **Comparison:** 15% of eligible MSM using daily oral PrEP

- If 50% of PrEP users opt for LAI-PrEP, 4% of infections averted over 10 years



Maloney KM 2021

LAI-PrEP is likely cost-effective in comparison to oral PrEP among South African women.



Walensky RP 2016

Discussion

1. What frequency of integrase resistance among those who acquire HIV despite LA-cabotegravir would make you less likely to use this drug? *(Paul Sax)*

2. What barriers to LA-cabotegravir do you see in your setting?

Health Care Provider Fact Sheet

ACTG Protocol 5359

The LATITUDE Study

Long-Acting Therapy to Improve Treatment SUccess in Daily LifE

STUDY PURPOSE: To compare the "regimen success"* of Long-Acting (LA) ART (using Rilpivirine (RPV)-LA and Cabotegravir (CAB)-LA) to Standard of Care (SOC) in persons living with HIV (PLWH) who have had barriers for adherence by 48 weeks of follow-up after an incentivized oral induction period.

KEY INCLUSION CRITERIA:

- PLWH ≥ 18 years of age; prescribed ART for at least 6 months with a screening HIV RNA > 200 copies/mL
- Evidence of non-adherence to HIV medications - Defined as having one of the criteria below:
  - Poor virologic response within the last 18 months in PLWH who have been prescribed ART for at least 6 consecutive months
  - Lost to clinical follow-up within the last 18 months with ART non-adherence for ≥ 6 consecutive months

Summary

- LAI-PrEP obviates the need for daily pill taking and thus may improve adherence and quality of life for people at risk for HIV.
- Enthusiasm for LAI-PrEP is high among people with experience taking oral PrEP.
- LAI-PrEP will not overcome many of the current barriers to PrEP.
- LA-cabotegravir is superior to TDF/FTC for PrEP among MSM, transgender women, and cisgender women.
- Modelling study suggest that HIV incidence declines as more people use PrEP and more of those using PrEP use LAI-PrEP.