Long-acting Injectable Medications for HIV Treatment and Prevention

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I have no relevant financial disclosures.

Learning objectives

1. Summarize the evidence for long-acting injectable HIV treatment and prevention
2. Analyze the advantages and disadvantages of long-acting injectable antiretrovirals
3. Describe the implementation of long-acting injectable HIV treatment and prevention

Image from oceanographicmagazine.com

Two patients interested in long-acting HIV treatment

Patient A

- 52-year-old cisgender woman diagnosed with AIDS ~10 years ago (CD4 1, HIV RNA > 10,000,000)
- Treated with TDF/FTC/EFV, then TDF/FTC and DTG, and most recently 3TC/DTG
- Excellent medication adherence; no history of virologic failure or resistance
- Recent HIV RNA undetectable, CD4 915

Patient B

- 34-year-old cisgender man with HIV and injection methamphetamine use diagnosed with acute HIV ~5 years ago (CD4 556, HIV RNA > 10,000,000)
- Treated with TDF/FTC/EVG/COBI
- Virologic failure after 1 year with NRTI resistance; placed on TAF/FTC and DRV/r
- Often misses weeks of medications at a time; recent CD4 530 and HIV RNA 98

Which patient(s) would you switch to long-acting cabotegravir/rilpivirine?

- Patient A
- Patient B
- Both
- Neither

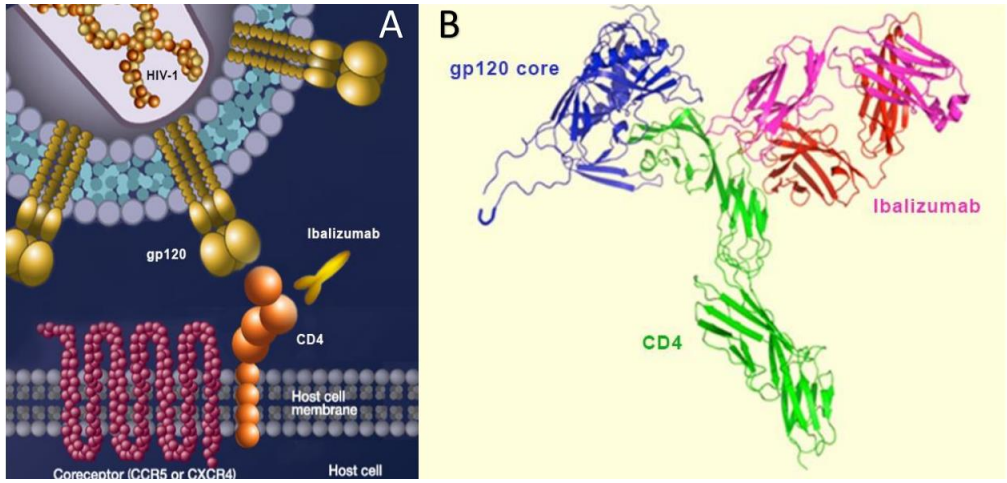
Potential advantages and disadvantages of long-acting injectable HIV treatment

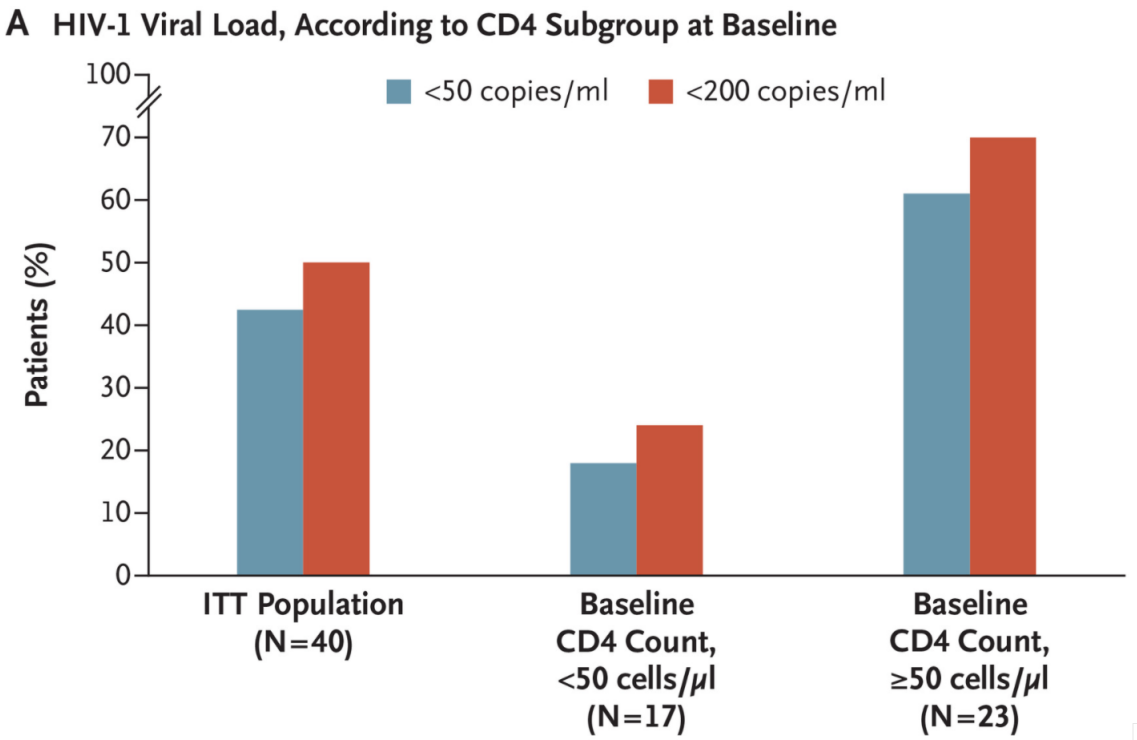
Advantages	Disadvantages
Choice	Cost?
Adherence	Schedule of care?
Confidentiality	Injection site reactions
Reduced stigma	Long subtherapeutic tails
Does not require GI absorption	

Kerrigan D, et al. PLoS One. 2018

Brief aside: Ibalizumab

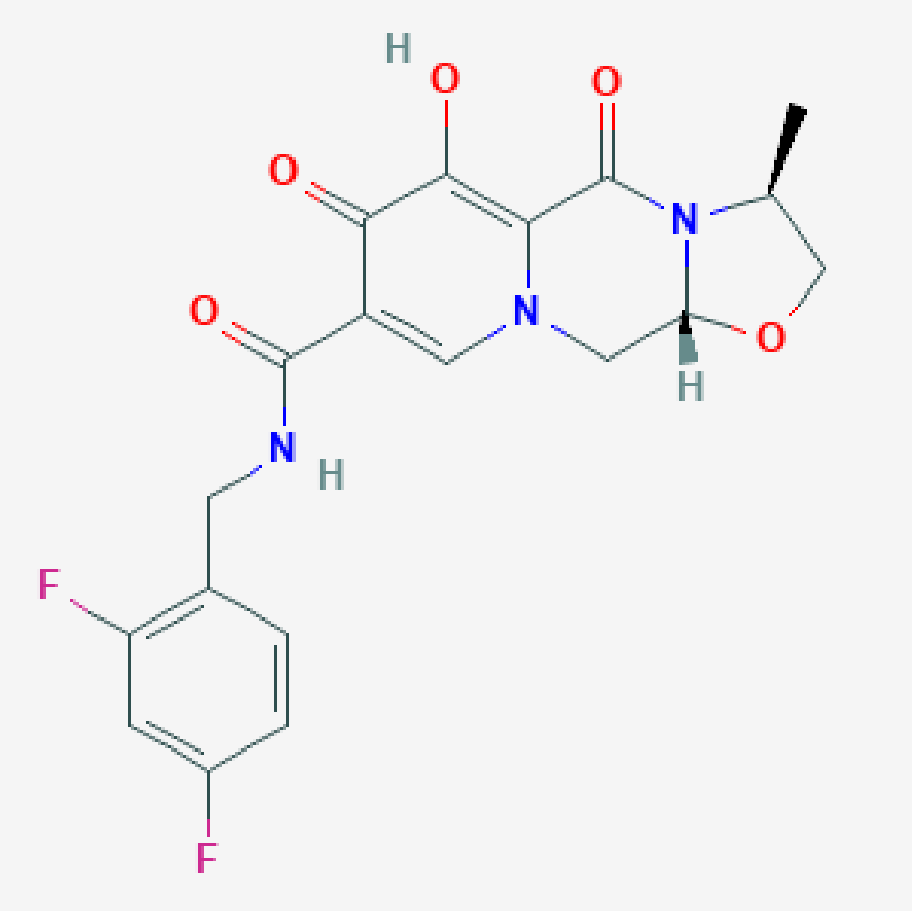
- Monoclonal antibody, post-attachment inhibitor
- An option for treatment of people with multi-class resistance, along with an optimized background regimen
- Administered as an IV infusion every 2 weeks



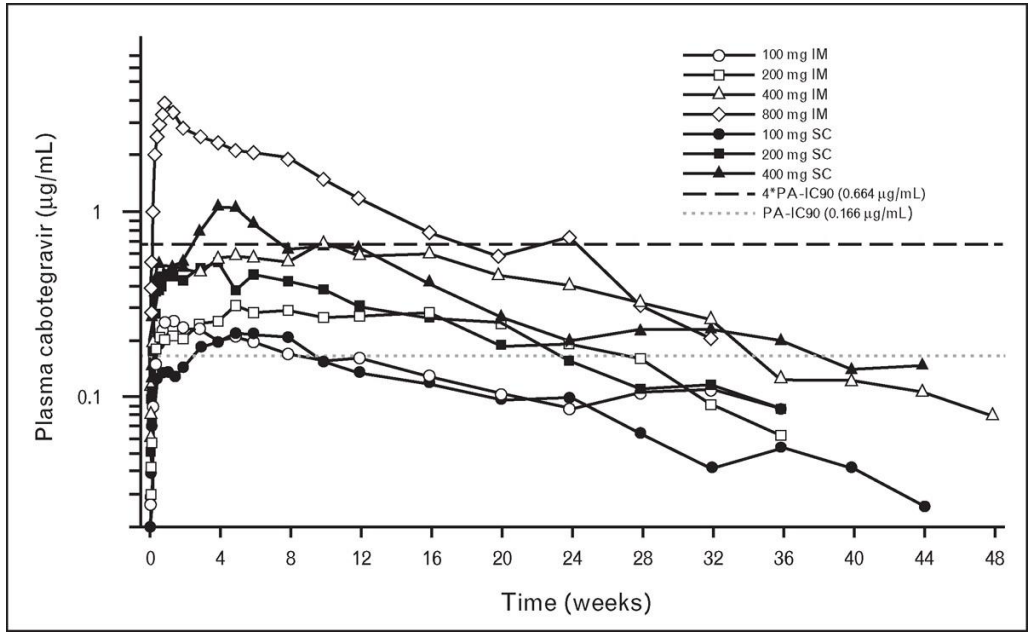


Emu B, et al. N Engl J Med. 2018.

Long-acting cabotegravir



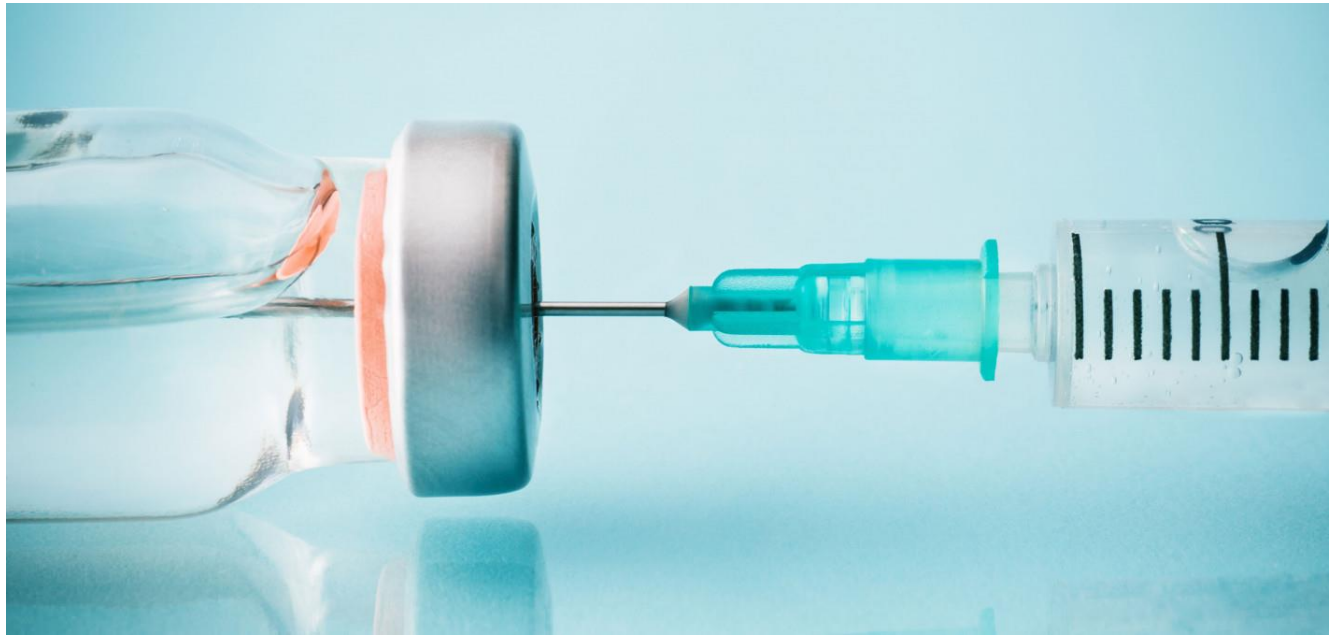
- Integrase inhibitor (structurally similar to dolutegravir)
- Elimination half-life = 40 days
- Prolonged subtherapeutic tail



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

Long-acting cabotegravir/rilpivirine for HIV treatment (CAB/RPV)

- Indicated for people with HIV-1 who “are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure or known or suspected resistance to either cabotegravir or rilpivirine”
- Monthly intramuscular injections after a 1-month oral lead-in phase with CAB and RPV



Cabenuva prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212888s000lbl.pdf
Image from https://www.poz.com/article/cabenuva-every-month-maintains-viral-suppression-two-years

ATLAS Study

The NEW ENGLAND JOURNAL of MEDICINE

Long-Acting Cabotegravir and Rilpivirine for HIV-1

PHASE 3, OPEN-LABEL, MULTICENTER, RANDOMIZED TRIAL

616

Participants receiving antiretroviral therapy without virologic failure

Long-acting therapy

(cabotegravir and rilpivirine intramuscular injections every 4 wk)

(N=308)

Current oral therapy

(N=308)

HIV-1 RNA ≥50 copies/ml at 48 wk

1.6%

1.0%

Adjusted difference, 0.6 percentage points; 95% CI, −1.2 to 2.5

83% of participants who received long-acting therapy reported injection-site reactions

S. Swindells et al. 10.1056/NEJMoa1904398

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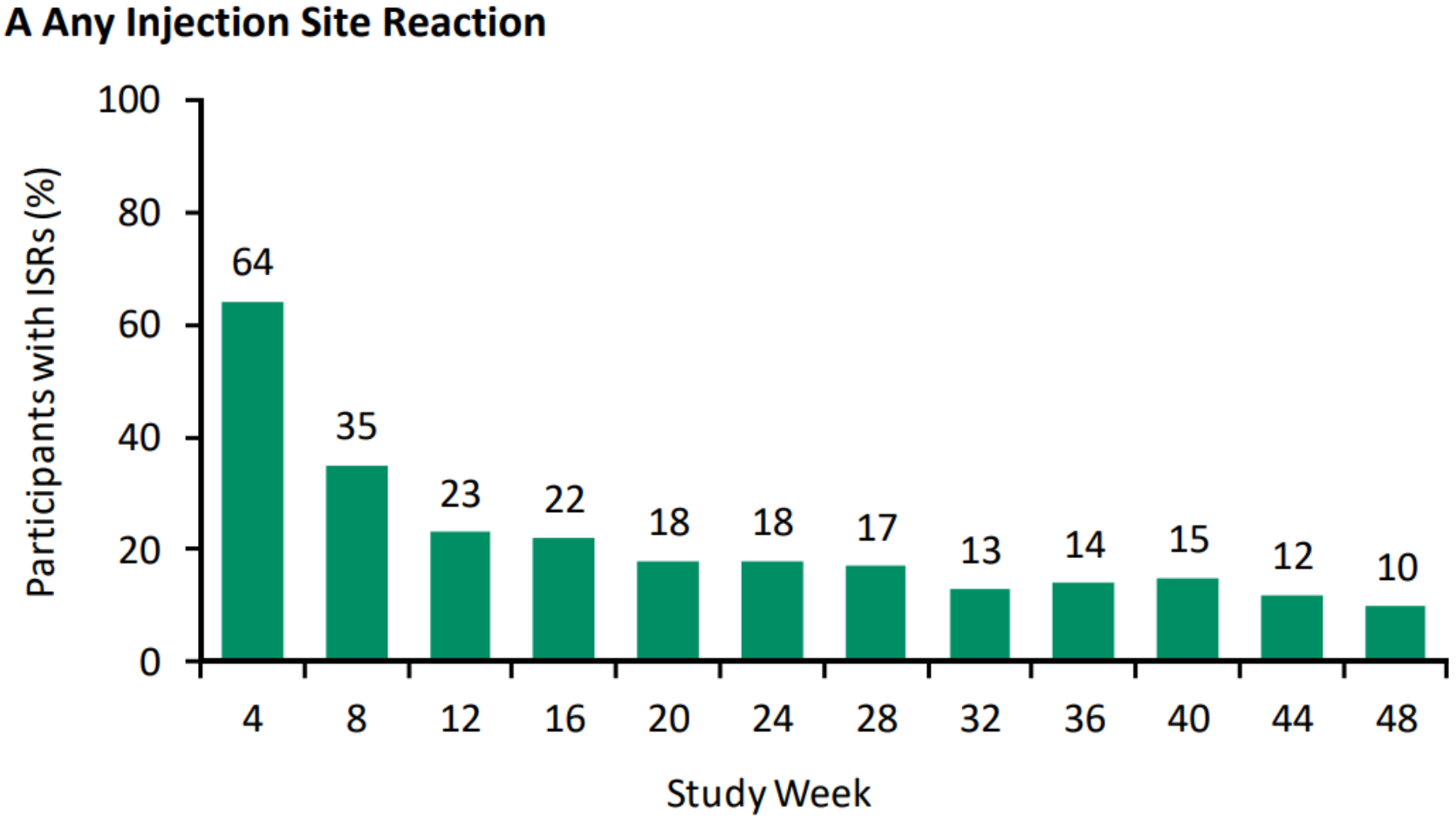
Figure S3. Incidence of Injection Site Reaction Adverse Events, LA Arm.



- 83% of participants in the long-acting therapy group reported an injection site reaction
- 99% of these were of mild or moderate severity
- Most resolved within 7 days (median = 3 days)

Swindells S, et al. N Engl J Med. 2020.

FLAIR Study

- **Design:** Open-label RCT of CAB/RPV versus continued oral therapy
- **Population:** 566 treatment-naïve people with HIV-1 who achieved virologic suppression after 16 weeks of ABC/3TC/DTG
- **Outcome:** HIV-1 RNA ≥ 50 copies/mL at 48 weeks
- **Results:**
  - HIV-1 RNA ≥ 50 in
    - 2.1% of CAB/RPV group
    - 2.5% of oral therapy group
  - Injection site reactions in 86% (mild or moderate in 99% of cases)
  - 91% preferred long-acting therapy

Orkin C, et al. N Engl J Med. 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

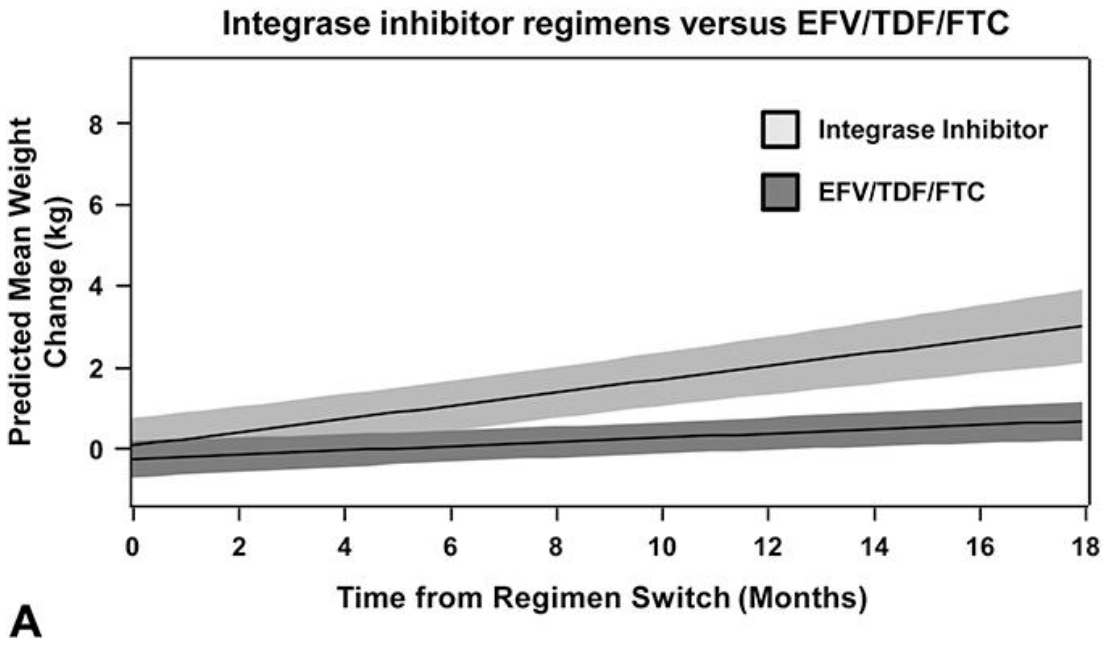
Table S1. Confirmed Virologic Failure (CVF) Through Week 48

	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

Cabotegravir and weight gain

- Pooled analysis of subjects in ATLAS, FLAIR, and ATLAS-2M
- Weight changes at 48 weeks were:
  - + 1.2 kg in the every-4-week CAB/RPV group
  - + 1.25 kg in the every-8-week CAB/RPV group
  - + 1.0 kg in the oral ART group



Patel P, et al. CROI 2021; Norwood, J AIDS, 2017

Managing missed doses

- If dose is ≤ 7 days overdue, give the next dose.
- If dose is > 7 days overdue, start oral CAB/RPV.
- For unplanned missed doses, re-assess the appropriateness of long-acting injectable ART.
- If resuming injectable ART after a missed dose,
  - Administer the maintenance dose (CAB 400 mg and RPV 600 mg) if the time since the last injection was ≤ 2 months.
  - Administer the loading dose (CAB 600 mg and RPV 900 mg) if the time since last injection was > 2 months.

Cabenuva prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212888s000lbl.pdf

Additional considerations

- Do not use CAB/RPV in people with hepatitis B (unless they are receiving separate treatment for HBV).
- Data in pregnancy are extremely limited; there is potential for fetal exposure even after the drug is discontinued.
- For administration:
  - Use a 23-guage, 1.5 inch needle or, if BMI is > 30, a 2 inch needle
  - Inject into the gluteus, ideally on opposite sides
  - Not an option for people with buttock implants or fillers
- Check HIV-1 RNA 4-8 weeks after switching to injectable ART and when there are unplanned missed visits and delayed doses

Department of Health and Human Services ART Guidelines; Cabenuva prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212888s000lbl.pdf

The ATLAS-2M study supports every 8 week dosing for CAB/RPV.

	Long-acting cabotegravir and rilpivirine every 8 weeks (n=522)	Long-acting cabotegravir and rilpivirine every 4 weeks (n=523)	Adjusted difference* (95% CI)
Intention-to-treat exposed population analysis			
HIV-1 RNA <50 copies per mL†	475 (91%)	472 (90%)	0·8 (–2·8 to 4·3)
HIV-1 RNA ≥50 copies per mL‡	11 (2%)	6 (1%)	1·0 (–0·6 to 2·5)

- This dosing strategy is not currently FDA approved.
- The every-8-week dose is higher than the every-4-week dose.

Jaeger H, et al. Lancet HIV. 2021

Two patients interested in long-acting HIV treatment

Patient A

- 52-year-old cisgender woman diagnosed with AIDS ~10 years ago (CD4 1, HIV RNA > 10,000,000)
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- Treated with TDF/FTC/EVG/COBI
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- Often misses weeks of medications at a time; recent CD4 530 and HIV RNA 98

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

Natap.org

Case

- A 27-year-old cisgender man presents in follow-up.
- He injects methamphetamine daily, often sharing injection equipment with others.
- He has insertive/receptive sex with cisgender men and does not use condoms.
- 2 months ago, he was diagnosed with early latent syphilis and was treated with long-acting benzathine penicillin.
- He is prescribed oral TDF/FTC for PrEP but struggles to take it, often missing weeks of pills at a time.
- Today, he is asymptomatic, and a routine HIV antibody/antigen test is negative.

If available, would you recommend long-acting cabotegravir for PrEP for him?

- Yes
- No
- I’m not sure.

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

GROUP	ESTIMATED NUMBER ELIGIBLE FOR PrEP	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

Which barriers will long-acting injectable 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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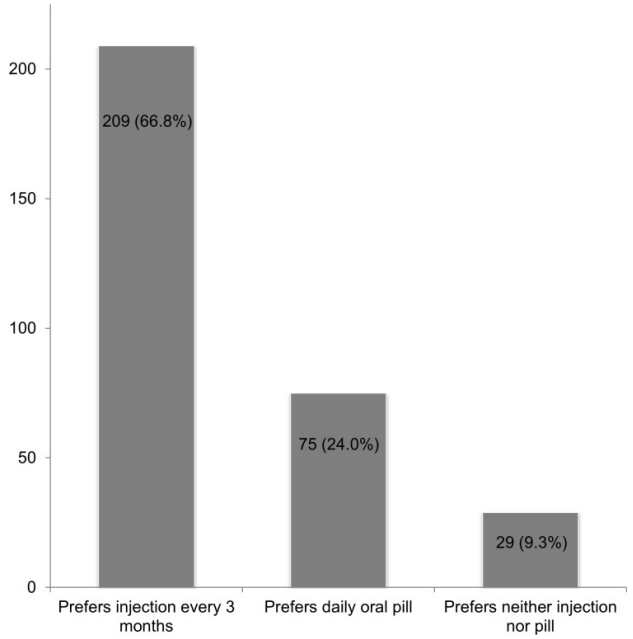
Confidentiality concerns		HIV-related stigma
Adherence		

Perceptions of long-acting injectable PrEP among MSM

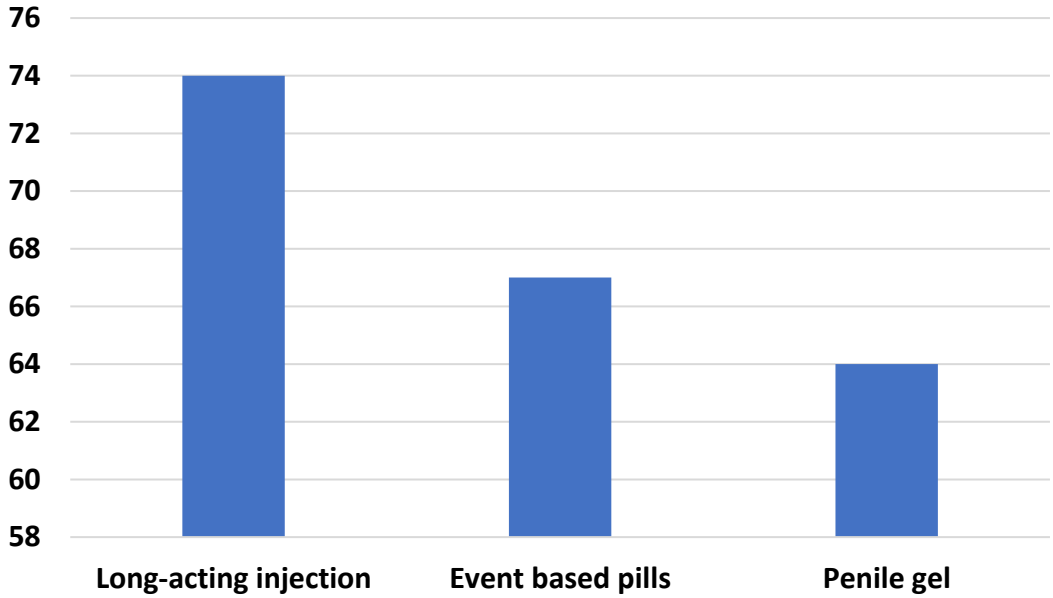
314 MSM in Washington, DC

- Median age 30, 41% non-Hispanic Black



M-cubed study

Proportion of MSM reporting likelihood of using PrEP formulations



Levy ME 2017

Perceptions of long-acting injectable PrEP among women

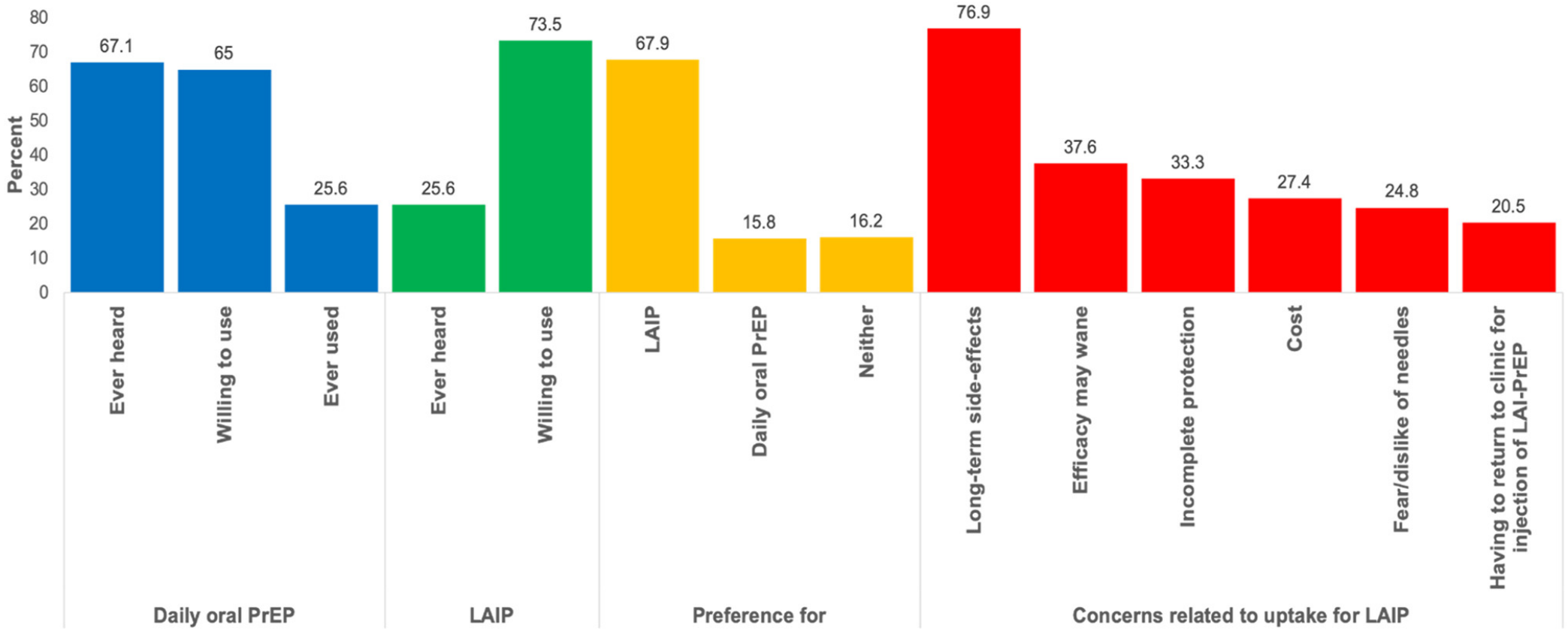
- 30 subjects in the Women's Interagency HIV Study
- Median age = 51 years
- 77% Black/African-American
- 60% no education beyond high school

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

Philbin MM 2020

Perceptions of long-acting injectable PrEP among people who inject drugs

Perceptions among 234 people with opioid use disorder in CT

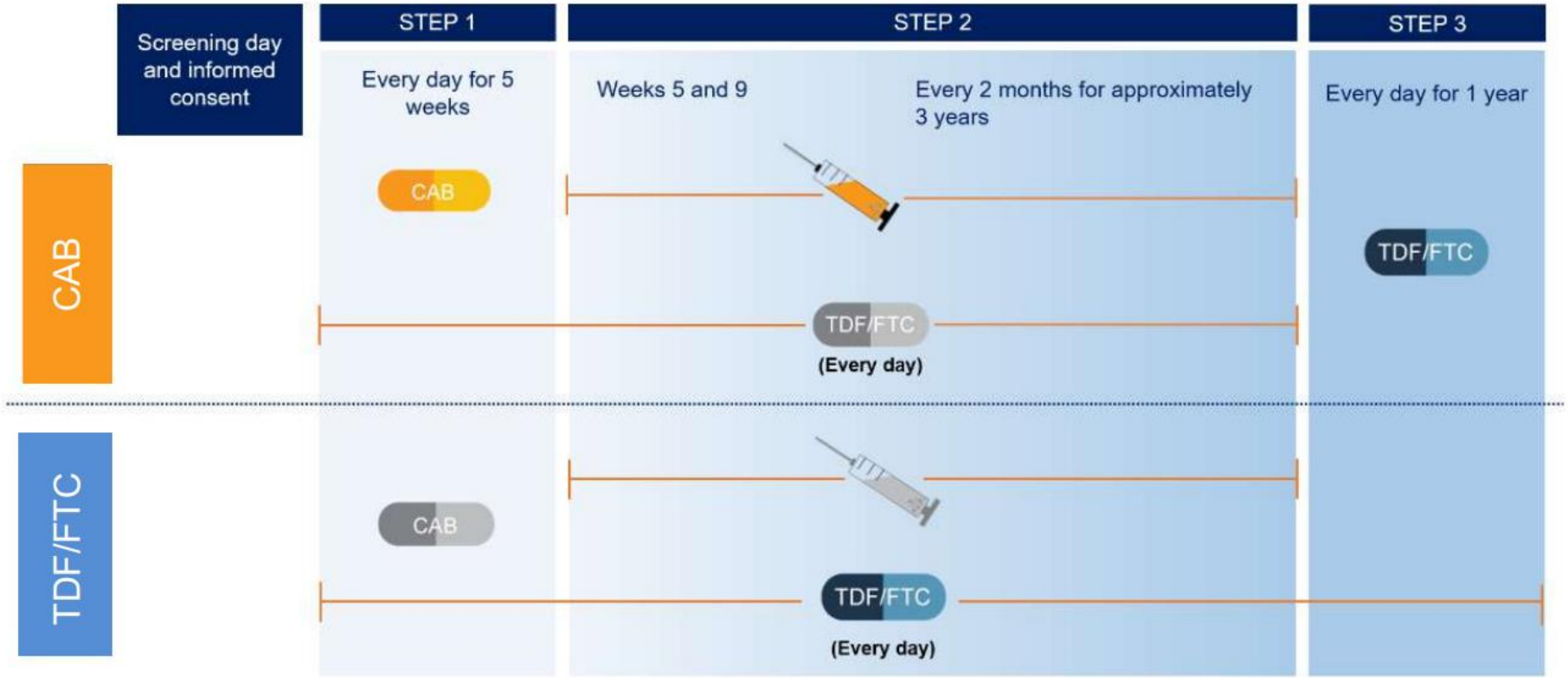


Shrestha R 2020

Conclusion from perception studies

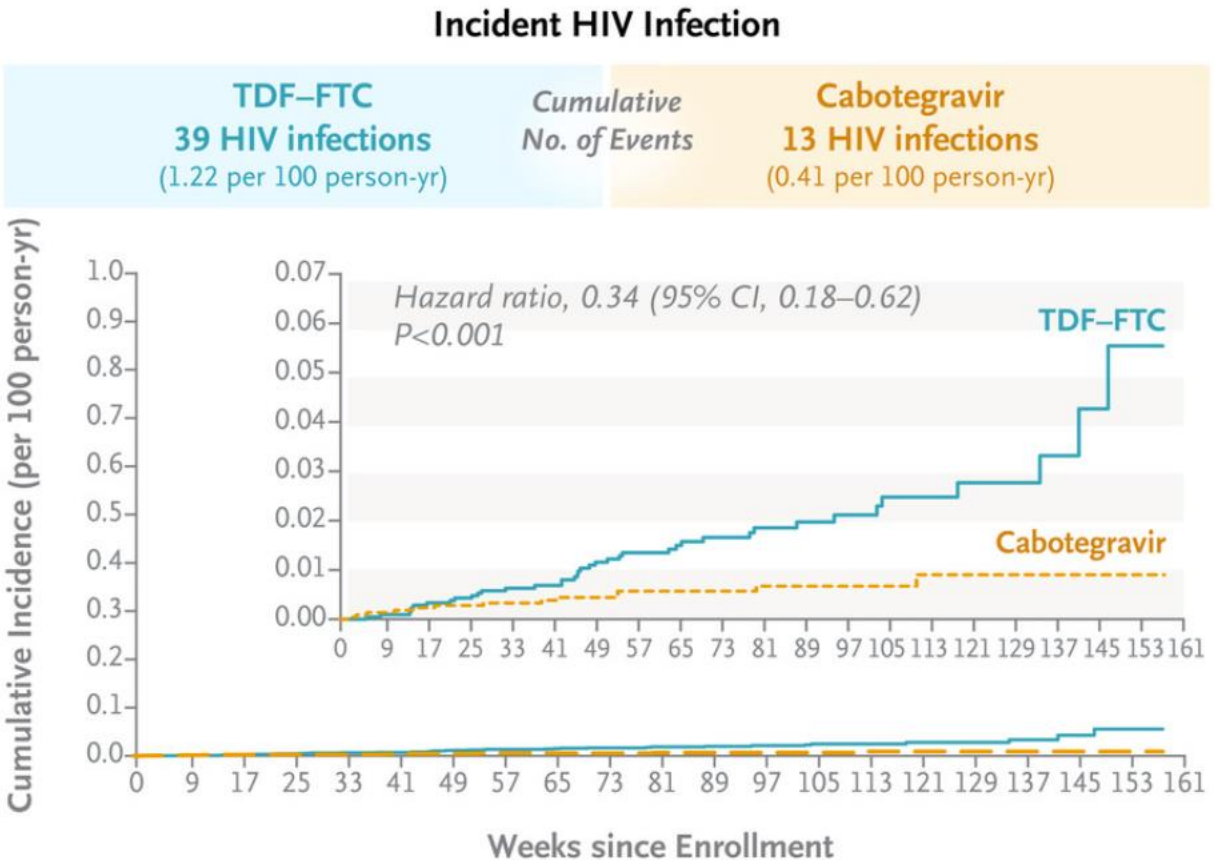
- Many people report being more likely to use long-acting injectable PrEP than other forms of PrEP.
- Enthusiasm is limited in some populations with low oral PrEP use.
- Prior use of oral PrEP predicts willingness to use long-acting injectable PrEP.
- Perceptions may be different once there are available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

HPTN 083 Study Design



Landovitz RJ et al. AIDS 2020, #OAXLB01

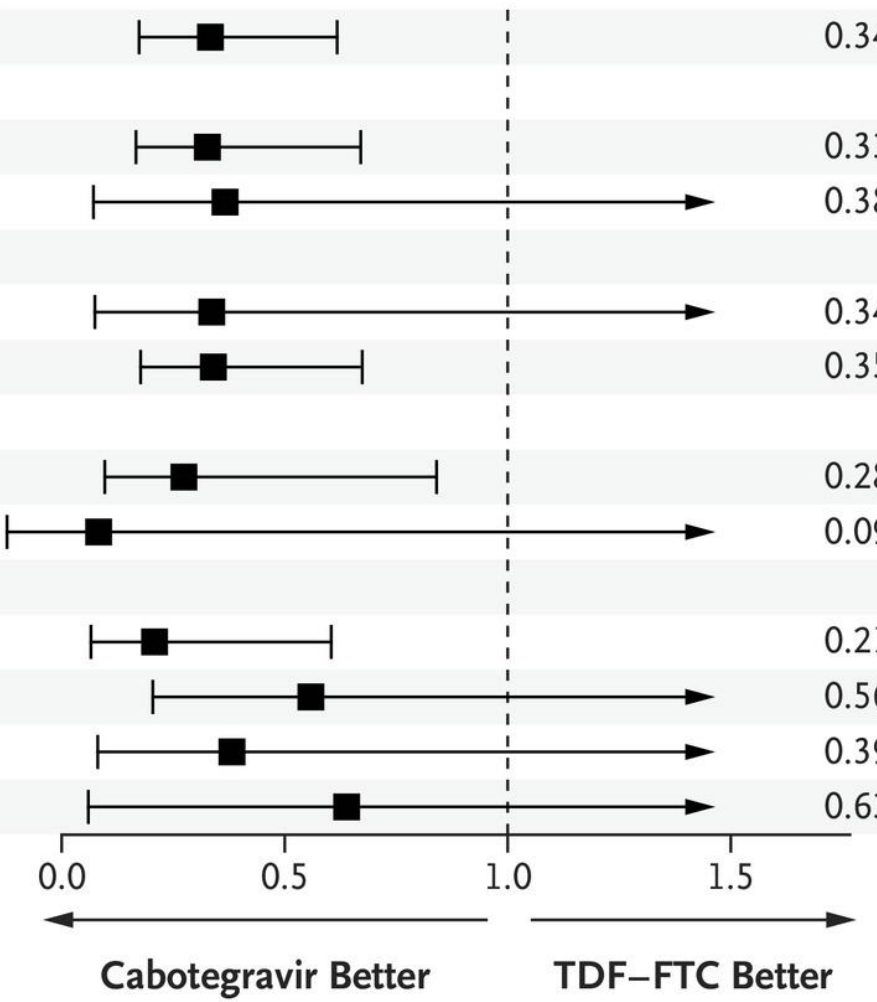
CAB is superior to TDF/FTC for PrEP among MSM and transgender women.



Landovitz RJ, N Engl J Med, 2021

B **Incident HIV Infection in Prespecified Subgroups**

Subgroup	Cabotegravir	TDF–FTC	Hazard Ratio (95% CI)
	no. of events/PY (incidence per 100 PY)		
Overall	13/3205 (0.41)	39/3187 (1.22)	0.34 (0.18–0.62)
Age			
≤30 yr	11/2189 (0.50)	33/2116 (1.56)	0.33 (0.17–0.65)
>30 yr	2/1016 (0.20)	6/1071 (0.56)	0.38 (0.08–1.77)
Cohort			
Transgender women	2/370 (0.54)	7/388 (1.80)	0.34 (0.08–1.56)
MSM	11/2831 (0.39)	32/2797 (1.14)	0.35 (0.18–0.68)
Race, United States			
Black	4/688 (0.58)	15/715 (2.10)	0.28 (0.10–0.84)
Non-Black	0/836	5/785 (0.64)	0.09 (0.00–2.05)
Geographic region			
United States	4/1525 (0.26)	20/1502 (1.33)	0.21 (0.07–0.60)
Latin America	6/1018 (0.59)	11/1009 (1.09)	0.56 (0.21–1.51)
Asia	2/569 (0.35)	6/580 (1.03)	0.39 (0.08–1.82)
Africa	1/92 (1.08)	2/96 (2.08)	0.63 (0.06–6.50)



Landovitz RJ, N Engl J Med, 2021

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 sexual 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%)

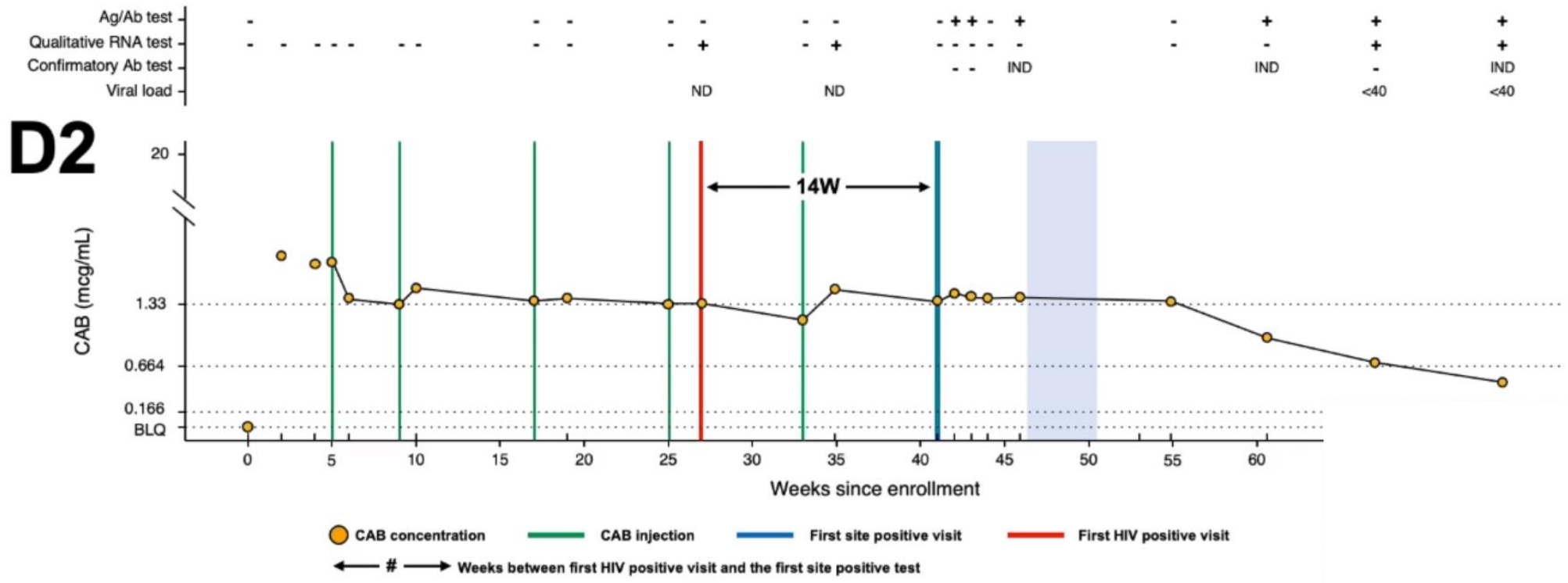
www.hptn.org/sites/default/files/inline-files/HPTN%20084%20DSMB%20FAQ_V1.0_8Nov2020_0.pdf

Antiretroviral resistance in HPTN 083

Context of infection	Integrase inhibitor mutations
Prior to CAB injection	Q148R in 2 of 3 subjects
Infection despite on-time CAB	R263K in 1 of 4 subjects Q148R in 1 of 4 subjects
Tail phase	None in 5 subjects

Landovitz RJ, et al. N Engl J Med. 2021.

In rare cases of HIV acquisition despite cabotegravir, seroconversion was delayed.



The shaded area represents time on ART.

Landovitz R, CROI 2021, abstract 153.

Questions about CAB for PrEP

- 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?

Possible programmatic implications of long-acting cabotegravir

- Rapid HIV testing if same-day administration
- Every-two-month visits
- Intensive support for an oral lead-in phase?
- Fewer opportunities for telehealth
- HIV RNA assays as part of laboratory monitoring
- Benefits navigation

Oral lead-in phase

- Noted in FDA approval of CAB/RPV; 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 CAB without oral lead-in

Landovitz R 2018, Markowitz M 2017, Swindells S 2020

Draft guidance on cabotegravir for PrEP includes HIV viral load assays.

Draft for Public Comment

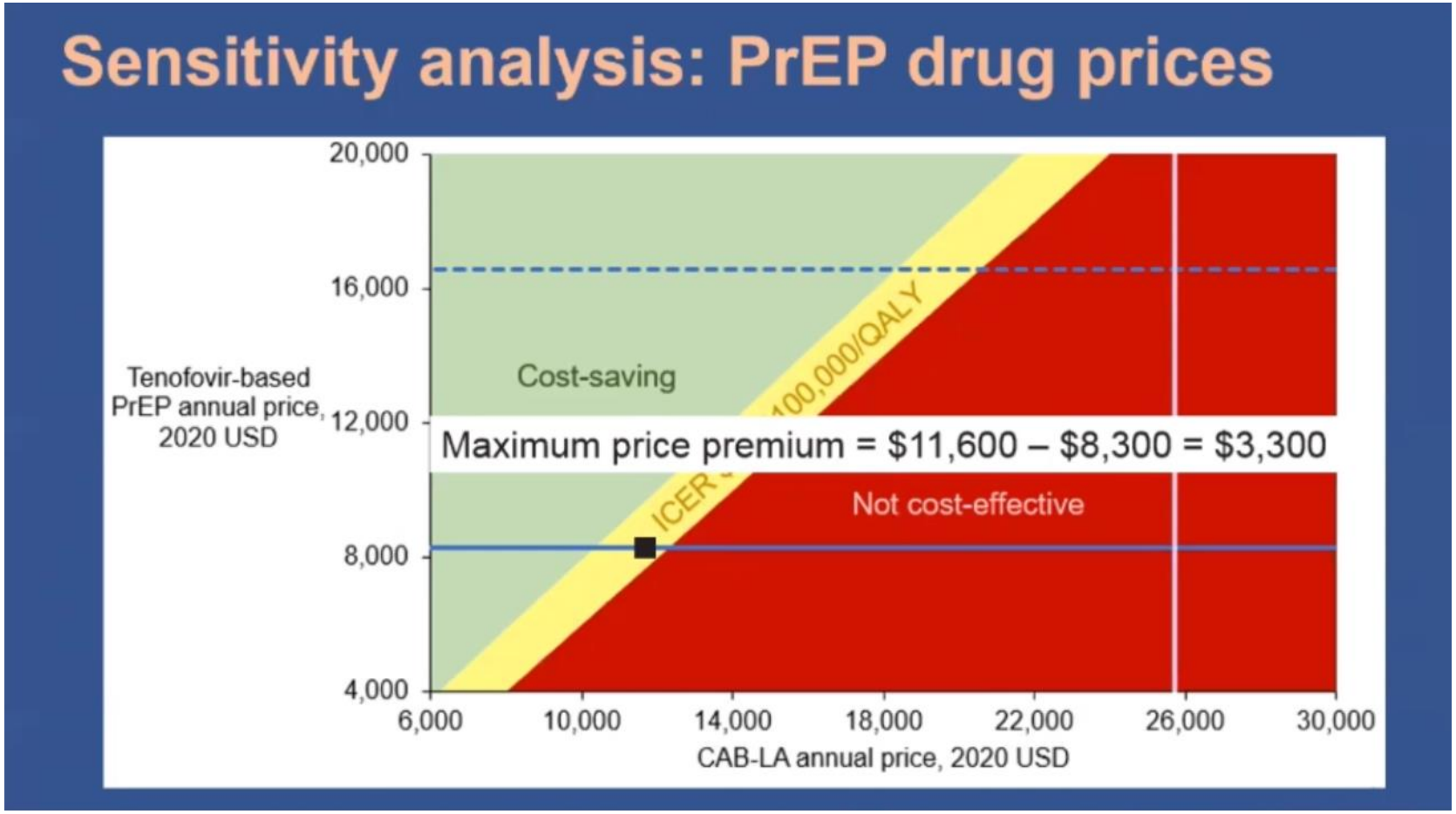
Table 7 Timing of CAB PrEP-associated Laboratory Tests

Test	Initiation Visit	1 month visit	Q2 months	Q4 months	Q6 months	When Stopping CAB
HIV*	X	X	X	X	X	X
Syphilis	X			MSM^/TGW~ only	Heterosexually active women and men only	MSM/TGW only
Gonorrhea	X			MSM/TGW only	Heterosexually active women and men only	MSM/TGW only
Chlamydia	X			MSM/TGW only	Heterosexually active women and men only	MSM/TGW only
Pregnancy	Persons with childbearing potential	Persons with childbearing potential	Persons with childbearing potential			Persons with childbearing potential

* HIV-1 viral load assay
X all PrEP patients
^ men who have sex with men
~ persons assigned male sex at birth whose gender identification is female

Draft Update for PrEP Clinical Practice Guidelines, CDC, 2021

Compared to oral PrEP, CAB is worth more, but not much more.



Neilan AM, CROI 2021, Abstract 150

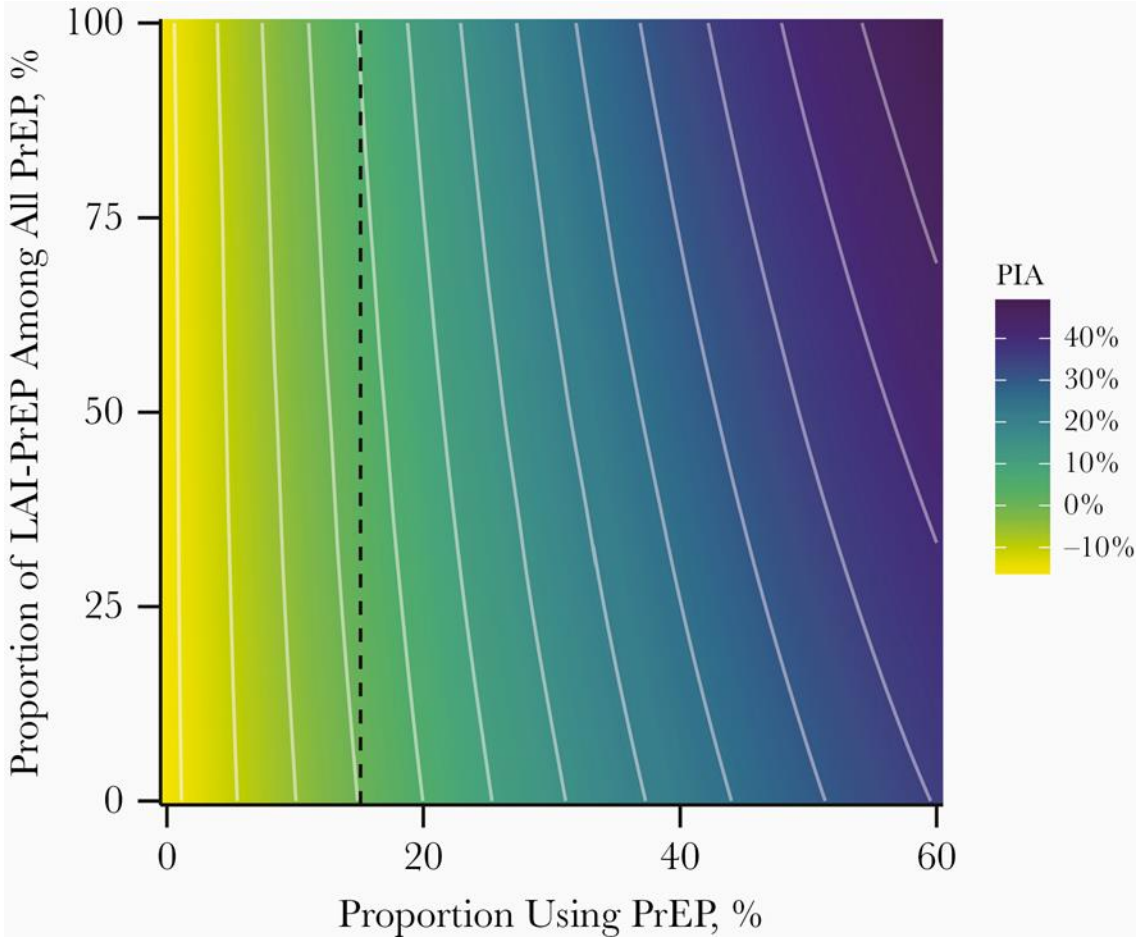
Scenario analyses

Scenario	Impact on CAB-LA price premium	Maximum price premium, 2020 USD
Resistance due to CAB-LA	—	$3,100
HIV diagnostic testing sensitivity and costs in CAB-LA	—	$3,300 - $3,400
Among a population of all potential MSM/TGW PrEP users at lower risk for HIV	↓	$1,000

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

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

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



Maloney KM 2021

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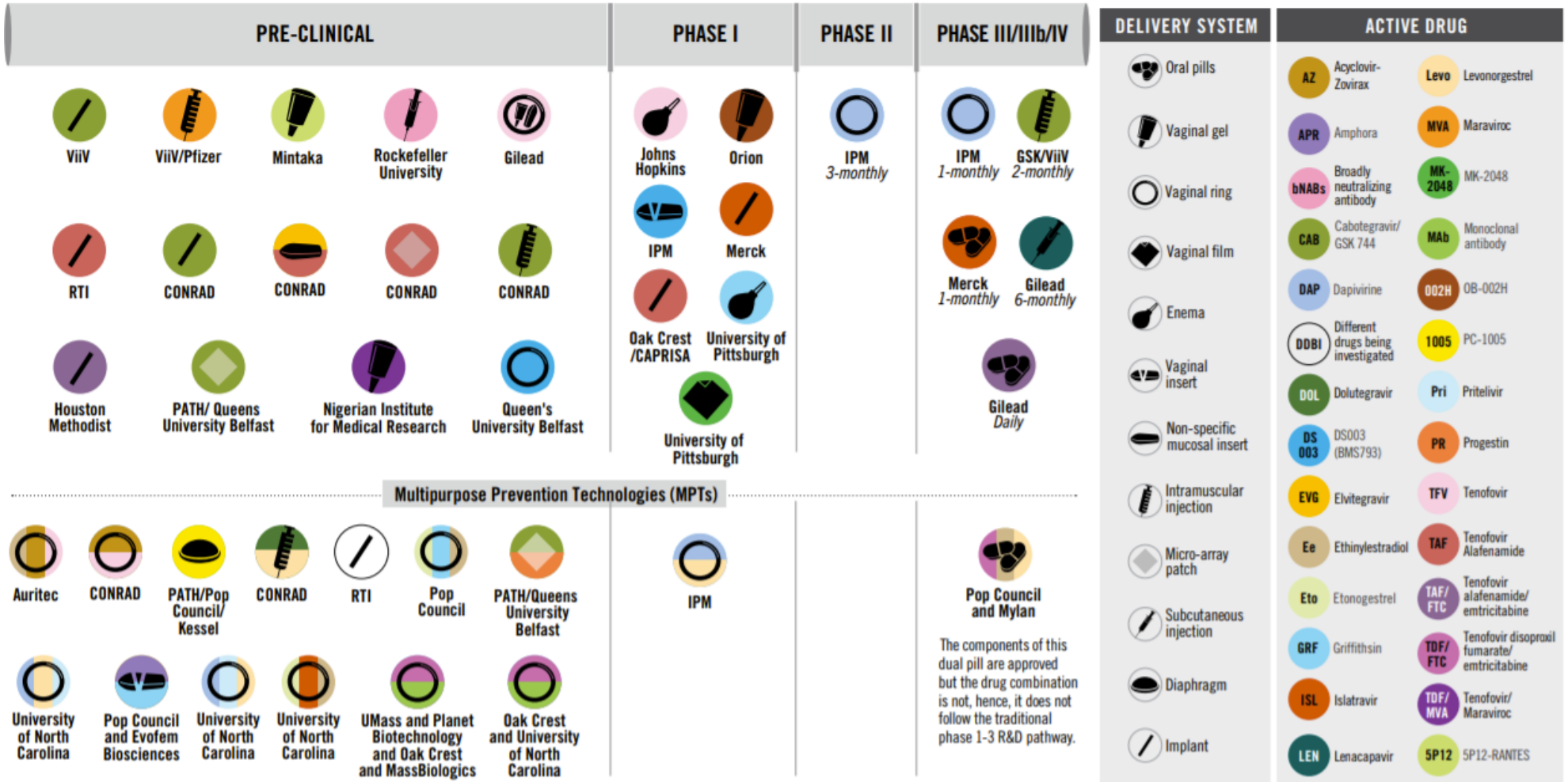
- He injects methamphetamine daily, often sharing injection equipment with others.
- He has insertive/receptive sex with cisgender men and does not use condoms.
- 2 months ago, he was diagnosed with early latent syphilis and was treated with long-acting benzathine penicillin.
- He is prescribed oral TDF/FTC for PrEP but struggles to take it, often missing weeks of pills at a time.
- Today, he is asymptomatic, and a routine HIV antibody/antigen test is negative.

AVAC
Global Advocacy for HIV Prevention

The Future of ARV-Based Prevention and More *(June 2021)*

The pipeline of non-vaccine HIV prevention products includes oral pills, vaginal rings, vaginal and rectal gels, vaginal films, long-acting injectable antiretrovirals and more. Also pictured are the range of multipurpose prevention technologies in development that aim to reduce the risk of HIV and STIs and/or provide effective contraception for women. (Visit *www.avac.org/hvad* for vaccine and broadly neutralizing antibody pipelines.)



AVAC www.avac.org June 2021

Summary

- The era of long-acting injectable HIV treatment and prevention has arrived.
- Monthly IM injections of CAB/RPV comprise a full treatment regimen for people with HIV who have been virologically suppressed on oral therapy.
- Every-8-week IM injections of CAB are superior to oral TDF/FTC for PrEP among MSM, transgender women, and cisgender women.
- New long-acting options for HIV treatment and prevention will require programmatic changes, especially for PrEP.

THANK YOU!

Please complete the post-event evaluation.
It will be emailed to you after the webinar.
It is required for CME credits.