AETC AIDS Education & Training Center Program Northeast/Caribbean

PrEP Guidelines 2021 Update

Alexandra Danforth, PharmD, BCACP, AAHIVP
Director, Infectious Disease & Clinical Pharmacy
Trillium Health
Rochester, NY

Disclosures

“This program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $3,845,677 with zero percent financed with nongovernmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS or the U.S. Government.”

Disclosures

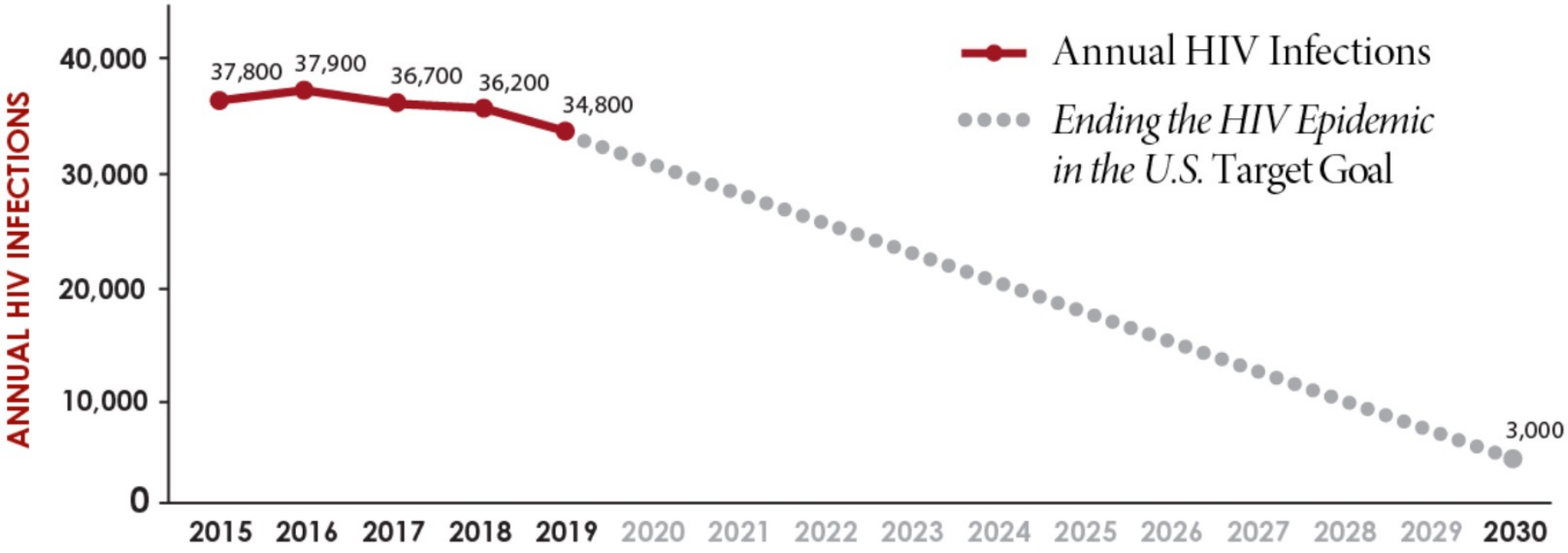
Gilead: Research Support

Learning Objectives

- Discuss new guidelines for PrEP
- Review the role of HIV RNA and Antigen/Antibody testing in evaluating HIV infection while on PrEP
- List 3 medications on the horizon for PrEP

NEW HIV INFECTIONS FELL 8% FROM 2015 TO 2019, AFTER A PERIOD OF GENERAL STABILITY

ANNUAL HIV INFECTIONS IN THE U.S., 2015-2019

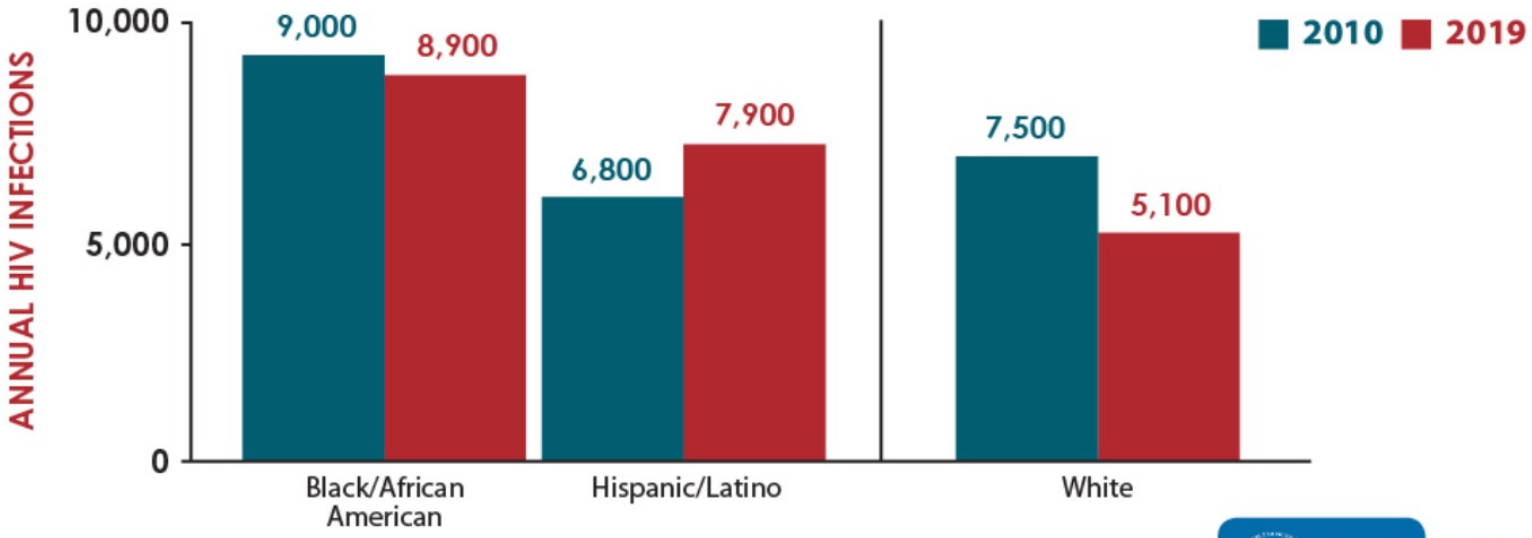


For more information, visit
cdc.gov/nchhstp/newsroom

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

FROM 2010 TO 2019, NEW HIV INFECTIONS REMAINED RELATIVELY STABLE AMONG BLACK AND HISPANIC/LATINO GAY AND BISEXUAL MEN, AND DECLINED AMONG WHITE GAY AND BISEXUAL MEN

NEW HIV INFECTIONS AMONG GAY AND BISEXUAL MEN IN THE U.S., BY RACE/ETHNICITY, 2010 VS. 2019

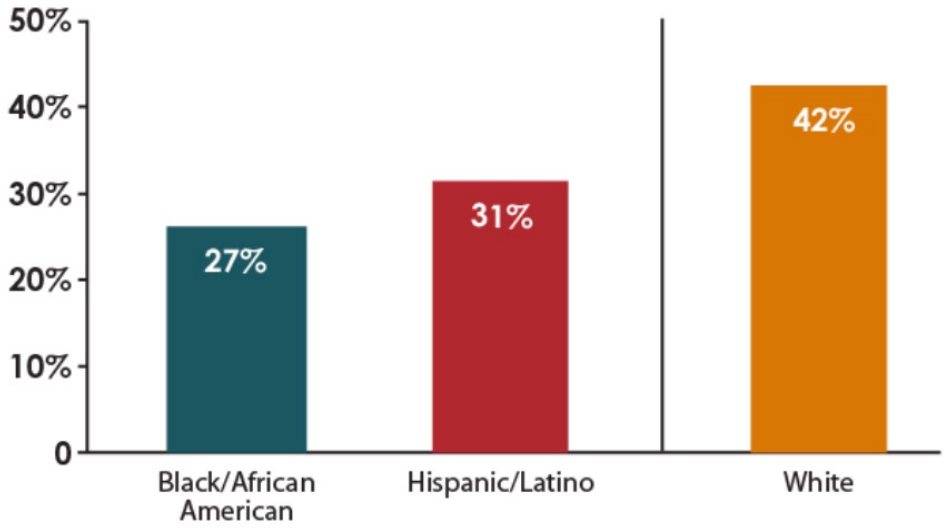


For more information, visit
cdc.gov/nchhstp/newsroom

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

HIV PREVENTION IN THE U.S. IS NOT REACHING GAY AND BISEXUAL MEN EQUITABLY

PERCENT OF GAY AND BISEXUAL MEN USING PREP IN THE U.S., BY RACE/ETHNICITY, 2017*



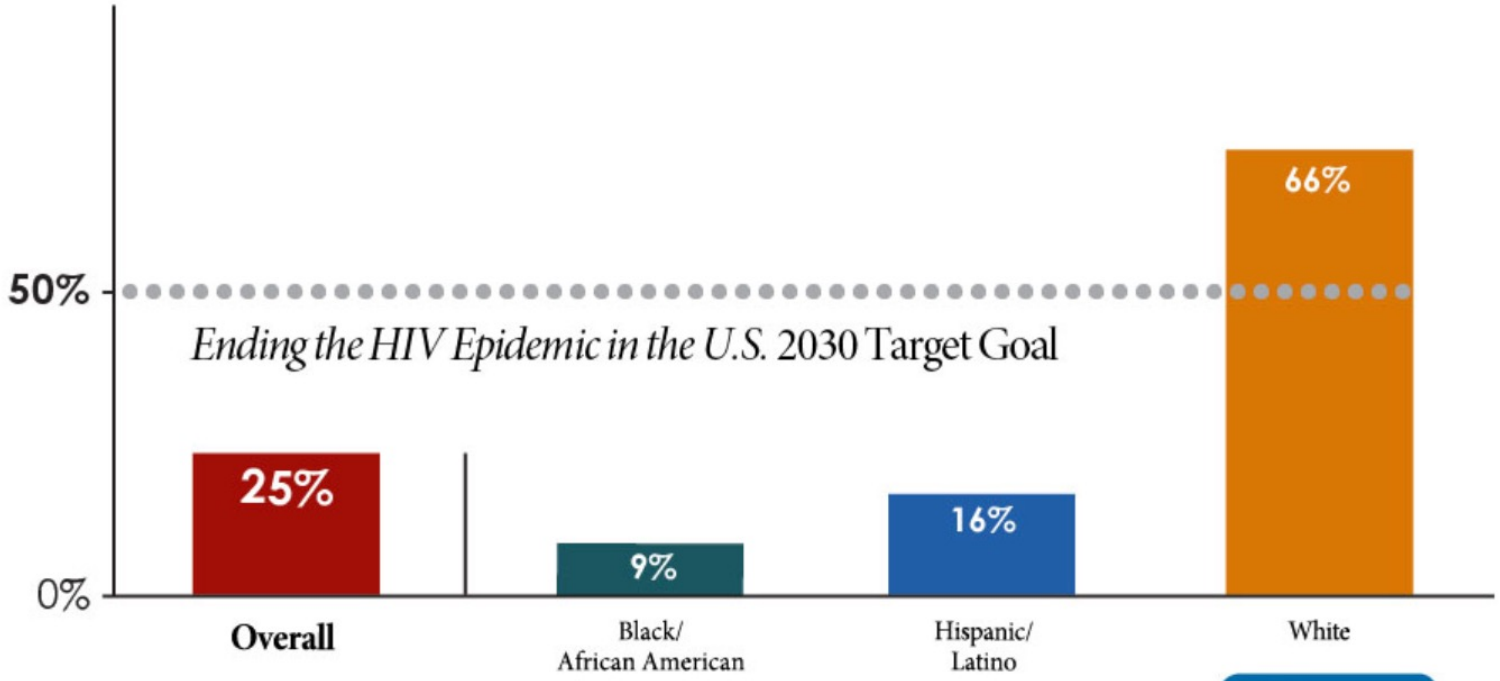
* While not nationally representative, the PrEP use data were collected from gay and bisexual men in 23 cities, where more than half of all people with HIV in large urban areas reside.

For more information, visit
cdc.gov/nchhstp/newsroom

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

WHILE 25% OF PEOPLE ELIGIBLE FOR PREP WERE PRESCRIBED IT IN 2020, COVERAGE IS NOT EQUAL

PREP COVERAGE IN THE U.S. BY RACE/ETHNICITY, 2020



For more information, visit
cdc.gov/nchhstp/newsroom

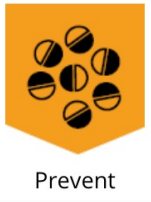
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CDC Select PrEP Data - 2020

Prevent

- For those whom PrEP is recommended
  - 16% of 38,454 for 16-24 years of age
  - 27% of 119,246 for 25-34 years of age
  - 30% of 72,146 for 35-44 years of age
- 3X as high among males
- 32% of HIV-negative transgender women reported using PrEP, even though 92% were aware of the medication

CDC PrEP Efforts

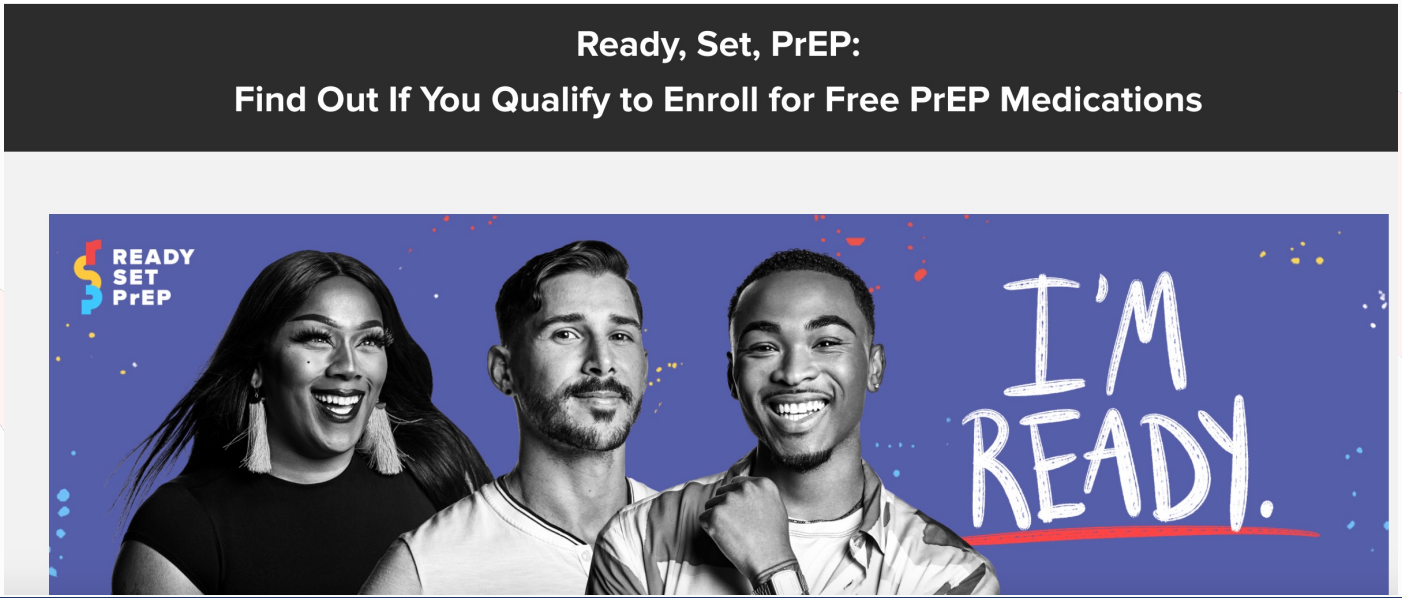


- Requires state/local health departments to incorporate PrEP into their local strategies
- Awarded $109 million in 2020 and $117 million in 2021 to strengthen HIV prevention strategies in 57 priority areas
- CDC funding to CBOs – $210 million over five years to nearly 100 CBOs
  - $55 million to approximately 30 additional CBOs in 2022
  - Focus on linking more young Black and Hispanic/Latino gay and bisexual men and also transgender women

Ready, Set, PrEP

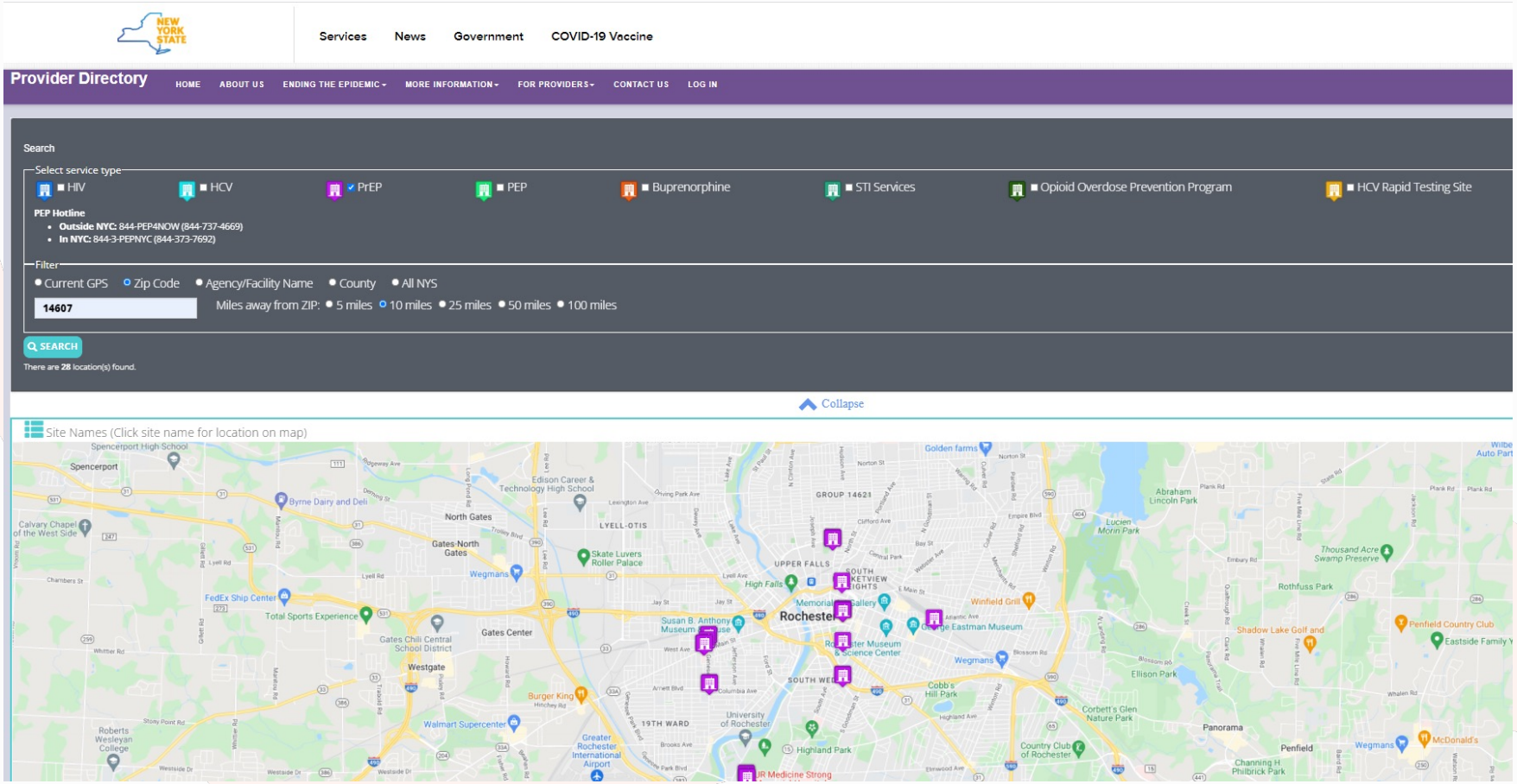
Prevent

- To be used for people who:
  - Don’t have health insurance coverage for prescription drugs
  - Have a prescription for PrEP
- People will not have to pay for medication
- Costs of your clinic visits and lab tests may vary depending on your income



providerdirectory.aidsinstituteny.org/

Prevent



www.preplocator.org

Prevent

PrEP Locator **Find Your Provider**

About Us | About PrEP | Locator Data | FAQ | Add Provider | Add Locator To Your Site | Contact

Zip code or full address

PrEP for uninsured

PrEP access assistance

Trillium Health
259 Monroe Ave Rochester, New York 14607
(585) 545-7200
Distance from your location: 0.45 miles

Highland Hospital
777 S Clinton Ave Rochester, New York 14620
(585) 279-4800
Distance from your location: 0.6 miles

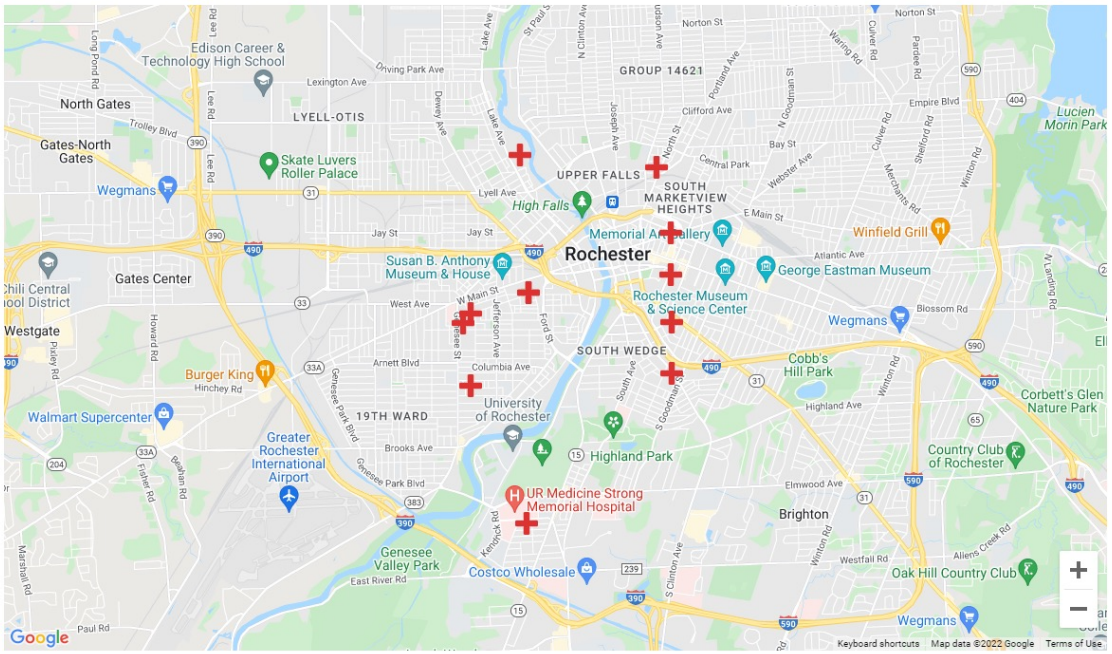
University of Rochester Medical Center
454 E Broad St Rochester, New York 14607
(585) 276-7640
Distance from your location: 0.67 miles

Planned Parenthood of Central and Western New York Incorporated
114 University Ave Rochester, New York 14605
(866) 600-6886
Distance from your location: 0.99 miles

Jordan Health
82 Holland St Rochester, New York 14605
(585) 423-5800
Distance from your location: 1.59 miles

Add PrEP Locator to Your Site

Suggest a provider for the directory



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

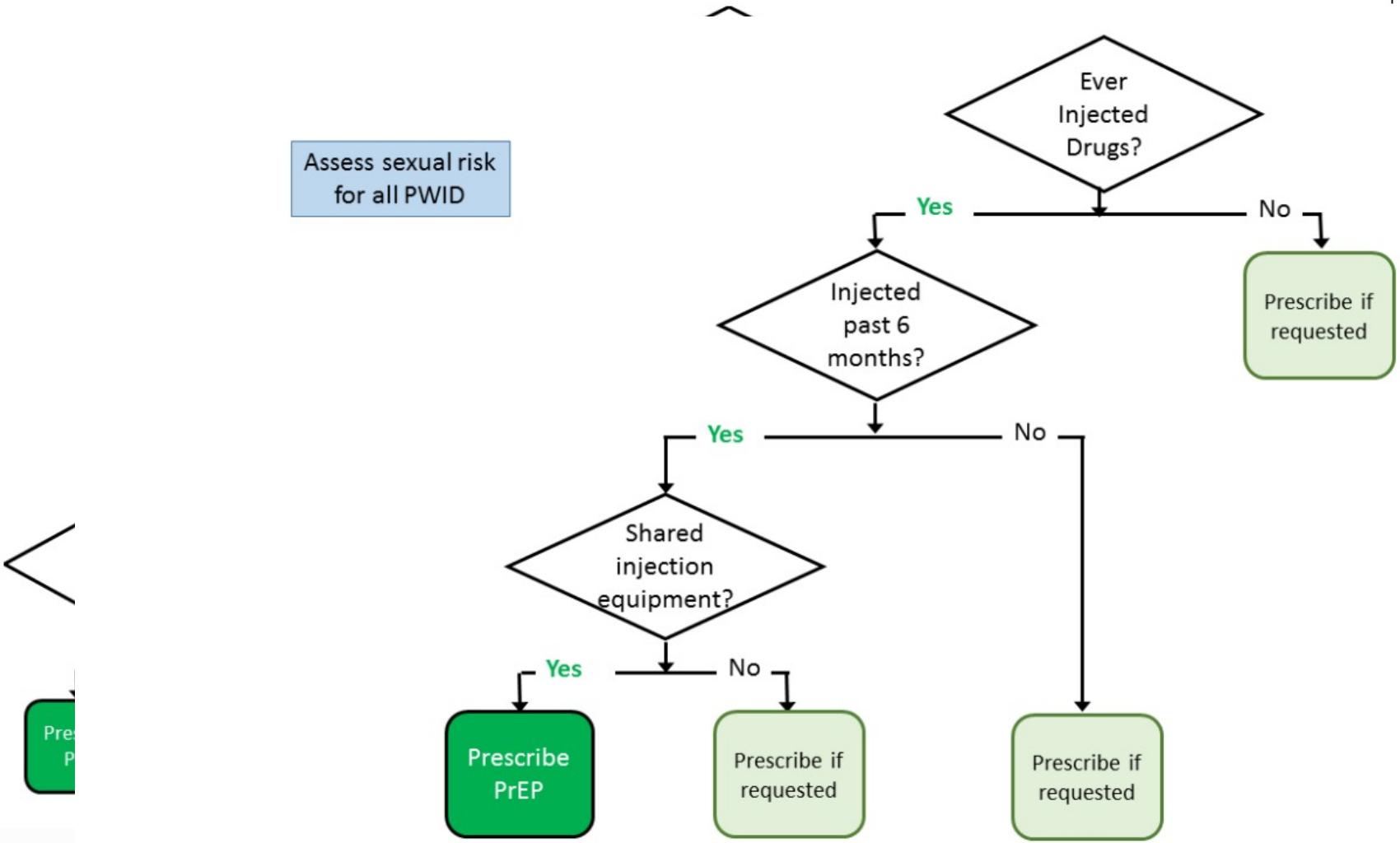
- **IA - Inform all sexually active adults and adolescents that PrEP can protect them from getting HIV**
  - Providers should offer PrEP to anyone who asks for it, including sexually active adults who do not report behaviors that put them at risk for getting HIV.
  - Telling all sexually active adults and adolescents about PrEP will increase the number of people who know about PrEP.
  - Talking about PrEP may also help patients overcome embarrassment or stigma that may prevent them from telling their health care provider about behaviors that put them at risk for getting HIV.

- **IIIB - Prescribe cabotegravir (CAB) injections for sexually active adults if the FDA approves using CAB for PrEP.*** CAB may be right for people:
  - Who had problems taking oral PrEP as prescribed
  - Who prefer getting a shot every 2 months instead of taking oral PrEP
  - Who have serious kidney disease that prevents use of other PrEP medications

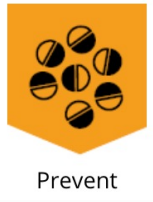
https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf

Assessing PrEP, Algorithms

Prevent



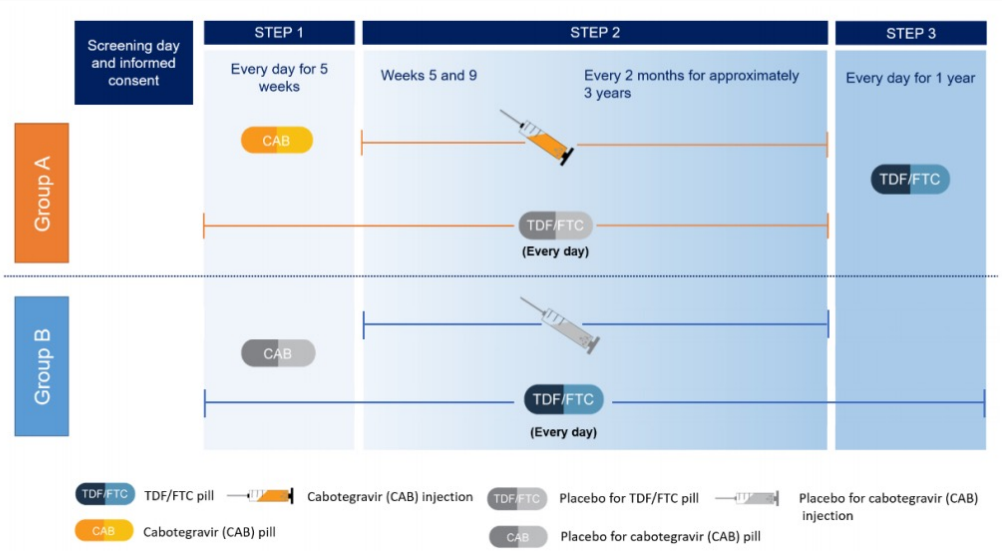
HPTN-083 – Injectable PrEP

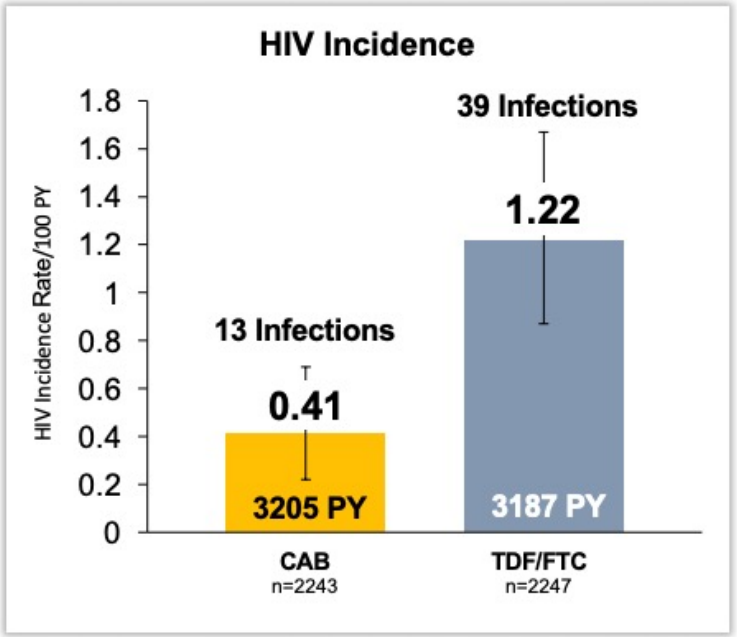


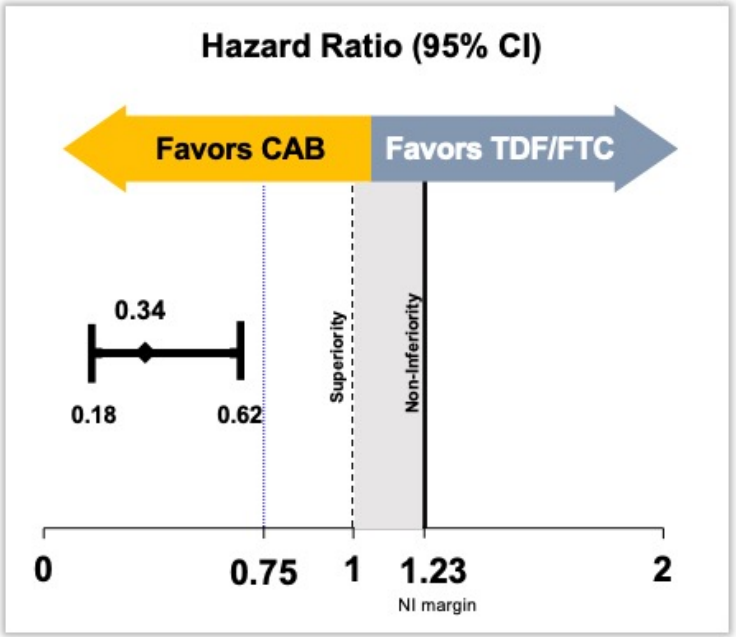
- PrEP study comparing long-acting cabotegravir injected once every 8 weeks to daily oral TDF/FTC
  - Cisgender men who have sex with men and transgender women
- Interim analysis from May 2020 includes data from 4,566 study participants
- 52 participants acquired HIV, 13 were in the cabotegravir and 39 were in the daily oral TDF/FTC
- **HIV incidence rate of 0.41% (95% confidence interval [CI] 0.22%-0.69%) in the cabotegravir group and 1.22% (95% CI 0.87%-1.67%) in the TDF/FTC group—indicating 66% lower incidence in the cabotegravir group. Data indicated that the superior efficacy of cabotegravir was statistically significant.**

Landovitz *et al*. 23rd International AIDS Conference
Grinsztejn *et al*. 23rd International AIDS Conference

HPTN-083 CAB q2 Months for PrEP







CI, confidence interval

Landovitz R, et al. CROI 2021, March 6-10, 2021. Abstract 153

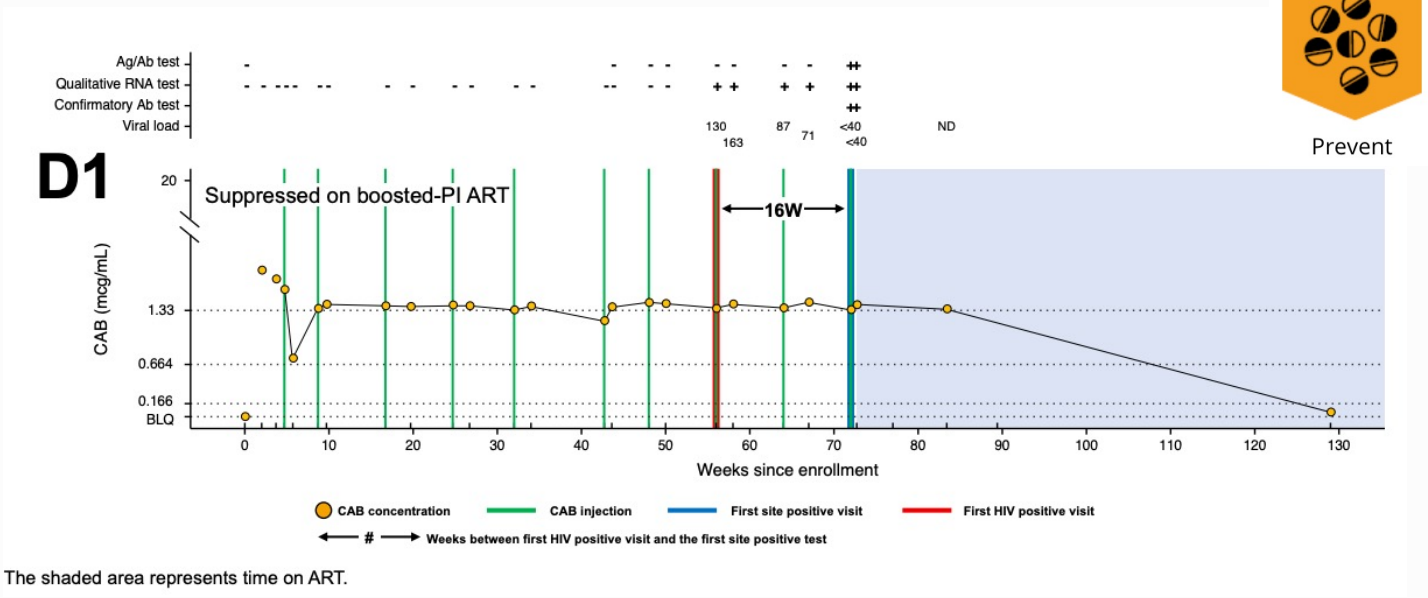
HPTN-083 Key Points

Prevent

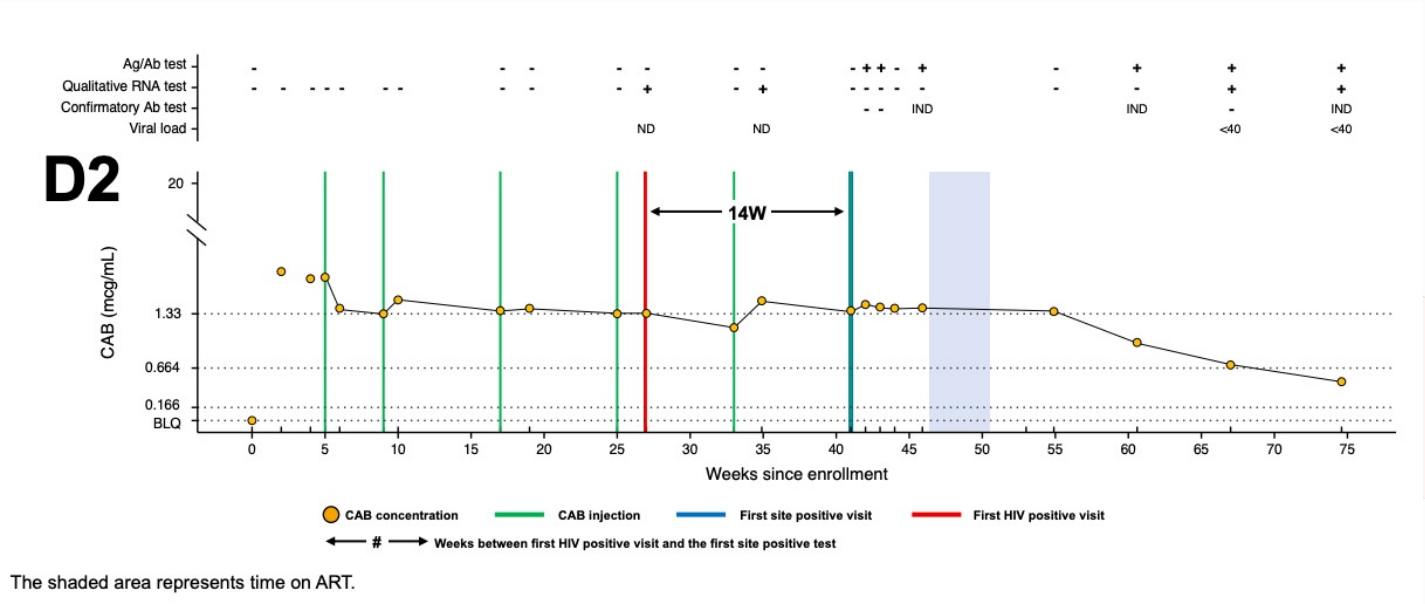
- 4 incident infections in CAB arm occurred despite target CAB plasma concentrations
- CAB-LA can delay detection of infection using standard diagnostic testing
- INSTI resistance was evident when viremic “escape” occurs at higher CAB concentrations
- 37/39 in the TDF/FTC arm with incident infection had suboptimal or non adherence
- Prompt HIV diagnosis and ART initiation needed to avoid resistance – use of VL testing as a primary screen for HIV infection being used in HPTN-083 OLE

Landovitz R, et al. CROI 2021, March 6-10, 2021. Abstract 153

Infected during on Time CAB Injections



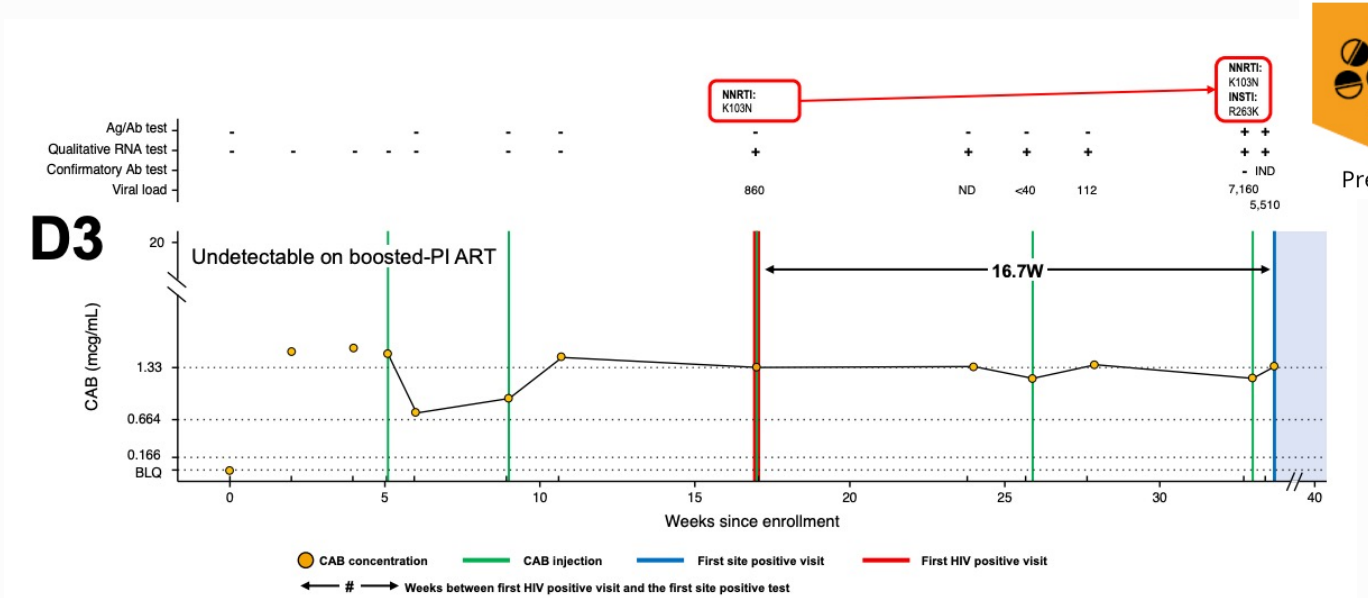
The shaded area represents time on ART.



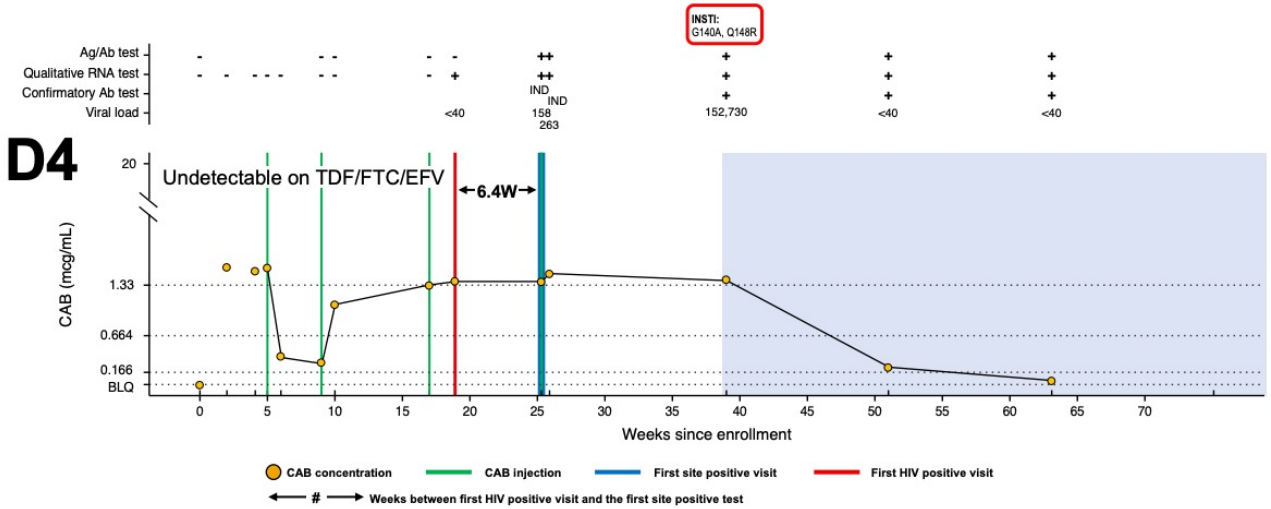
The shaded area represents time on ART.

Landovitz R, et al. CROI 2021, March 6-10, 2021. Abstract 153

Infected during on Time CAB Injections



The shaded area represents time on ART.



The shaded area represents time on ART.

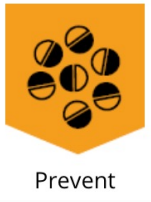
Landovitz R, et al. CROI 2021, March 6-10, 2021. Abstract 153

HPTN-084 – Injectable PrEP

Prevent

- Enrolled 3,223 cis-gender women aged 18-45 years old who were at risk for acquiring HIV infection in 20 sites across seven countries in sub-Saharan Africa (Botswana, Kenya, Malawi, South Africa, eSwatini, Uganda and Zimbabwe)
- Arm A – Cabotegravir LA (as an intramuscular injection every 8 weeks) and daily oral TDF/FTC placebo
- Arm B – Daily oral TDF/FTC and intramuscular cabotegravir LA placebo every 8 weeks
- 38 women in the trial acquired HIV in the trial; 4 who were randomized to the long-acting cabotegravir arm and 34 were randomized to the daily, oral FTC/TDF arm
- Overall the incidence rate of HIV was 0.21% in the cabotegravir group and 1.79% in the FTC/TDF group.
- Long-acting cabotegravir was 89% more effective than FTC/TDF

PrEP Guidelines 2021, Oral Options



- Prescribe emtricitabine/tenofovir disoproxil fumarate (Truvada®/generic equivalent) or consider the additional option of prescribing emtricitabine/tenofovir alafenamide (Descovy®) for sexually active men and transgender women
- Updated guideline adds emtricitabine/tenofovir alafenamide as a PrEP option for these groups
  - Not recommended for people assigned female sex at birth who could get HIV through receptive vaginal sex

TDF/FTC vs. TAF/FTC as PrEP

Prevent

	TDF/FTC	TAF/FTC
Effectiveness	All populations.	Cisgender men and transgender women.*
Renal safety	• Potential effect on renal tubular function. Meta-analysis shows good safety. • Discontinue if confirmed CrCl <50 mL/min.	• Improved renal biomarkers compared to TDF. • Can be used with stage 3 chronic kidney disease (CrCl 30-59 mL/min).
Bone safety	Potential decrease in bone mineral density. Meta-analysis shows good safety.	Favorable bone biomarkers compared with TDF.
Weight	Weight neutral.	Mild weight gain observed in studies.
LDL cholesterol	Small decreases.	Small increases.
Dosing	Daily dosing is preferred. On-demand dosing is an option in cisgender MSM.	Daily dosing only.
Cost	Off patent in 2020	Currently similar to TDF/FTC.

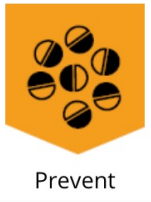
*Transgender women made up only 1% of the DISCOVER study population.

Characteristic	TDF/FTC (Truvada)	TAF/FTC (Descovy)
Dosing	One tablet daily with or without food	One tablet daily with or without food
Plasma tenofovir levels (potentially linked to higher rates of renal and bone adverse events)	Higher than Descovy	Up to 90% lower than with Truvada
Time to Onset and Duration Post Dose	Longer time to onset and shorter duration after dosing for Truvada	Shorter time to onset and longer duration after dosing for Descovy. Effective concentrations within 1–2 hrs of first dose compared to 3 days for Truvada. Descovy levels expected to remain above effective concentrations for 16 days vs 10 days for Truvada
Lymphocyte tenofovir levels	Lower than Descovy	TFV-DP levels in PBMCS were 6.3 fold higher with F/TAF vs F/TDF
Box Warning	HBV	HBV
MSM	YES	YES
Women at birth	YES	NO
Adolescents	YES	YES
Transgender women	YES	YES
Transgender men	YES	NO
Adverse events	Diarrhea, nausea, headache fatigue, abdominal pain, rare renal and bone adverse events	Diarrhea, nausea, headache fatigue, abdominal pain, rare renal and bone events possible, but may be less likely than Truvada
Renal dysfunction	Not recommended for creatinine clearance less than 60ml/min	Not recommended for creatinine clearance less than 30ml/min
Pill size	Larger than Descovy	Smaller than Truvada
Drug Interactions	Minimal- Monitor levels when dosed with hepatitis C antiretrovirals.	Avoid with potent PGP inducers such as: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St. John's Wort, tipranavir/ritonavir

Time to Protection

- Time to protection is based on pharmacokinetic modeling studies and has not been clinically determined.
- For rectal exposure, protection against HIV acquisition is achieved after 7 days of TDF/FTC daily dosing and possibly earlier.
- For genital and blood exposure, protection against HIV acquisition is likely achieved after 7 days of TDF/FTC daily dosing, but optimal drug levels are achieved after 20 days of daily dosing.
- Taking 2 pills of TDF/FTC as PrEP on the day of initiation will decrease the time needed to achieve protective drug levels for all sites of exposure.
- Data are insufficient to make an estimate regarding time to protection for TAF/FTC.

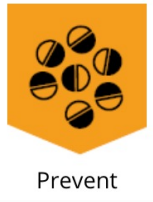
PrEP Guidelines 2021, Lab Testing



- Patients starting or restarting PrEP after a long stop, test using an HIV antigen/antibody test (lab-based preferred)
- Patients taking or recently taken PrEP (including patients who have taken oral PrEP in the last 3 months or patients who had a CAB injection in the last 12 months), **test using an HIV antibody/antigen assay AND a qualitative or quantitative HIV-1 RNA assay**
  - If positive antigen/antibody test and a detectable HIV-1 RNA test confirming the patient has HIV, link to HIV care.
  - If negative antigen/antibody test and undetectable HIV-1 RNA test, continue prescribing PrEP

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

PrEP Guidelines 2021, Ongoing Assessments



- **Oral PrEP**
  - CrCl once every 12 months for patients under 50 years old or patients with baseline CrCl greater than 90 mL/min
    - Everyone else CrCl every 6 months
  - If taking F/TAF, annual triglyceride, cholesterol, weight
  - Review medications for interactions
- **Injectable PrEP**
  - Kidney, triglyceride, cholesterol assessments are not needed
  - Recommended assessments is different for CAB users:
    - HIV testing every 2 months (at each injection visits)
    - STI testing every 4 months (at every other injection visit)

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

PrEP Guidelines 2021, Other Considerations

Prevent

- **Offer same-day PrEP to patients when appropriate**
  - Conducting baseline assessments and tests
  - Offering information on insurance or co-pay assistance
  - Scheduling follow-up tests and appointments
  - Giving or prescribing oral PrEP or CAB injections
- **Provide PrEP by telehealth when available**
  - Includes options for offering PrEP services by telehealth, such as having telephone or web-based visits, using laboratory or home testing, and prescribing a 90-day supply of PrEP medication
- **Learn about 2-1-1 dosing**
  - Provides information on how to correctly use off-label 2-1-1 dosing for oral PrEP
  - This information may benefit gay, bisexual, and other men who have sex with men who choose to use 2-1-1 dosing
  - **Not approved by FDA, not recommended by CDC**

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

PrEP - Previnir

HIV-negative high risk
Inconsistent condom use
eGFR >50ml/min
HbS Ag negative for on demand

TDF/FTC Daily

TDF/FTC On Demand

- Paris, France, open label, n=>3,000
- Participants opted for Daily or On Demand PrEP, allowed to switch regimens
- F/U q3 months, 4th generation HIV testing, Scr, STI screening at MD discretion
- Condoms, gels, risk reduction, adherence, sexual activity questions at each visit

*At last sexual intercourse: cocaine, GHB, MDMA, mephedrone

Baseline Characteristics	N=3067
Age (years)	36 (29-34)
Caucasian	2622 (85.6)
MSM	3022 (98.5)
Heterosexual men/women	31 (1.0)
Transgender	14 (0.5)
2 year college or more	2215 (85.8)
Employed	2206 (85.7)
History of PrEP use	1713 (55.8)
Use of ChemSex*	427 (13.9)
On demand dosing	1515 (49.5)
Number condomless sex in past 4 weeks	2 (0-5)
Number sexual partners in prior 3 months	10 (5-20)

Molina JM, et al. CROI 2021, March 6-10, 2021. Abstract 148.

PrEP - Previnir

TDF/FTC On Demand

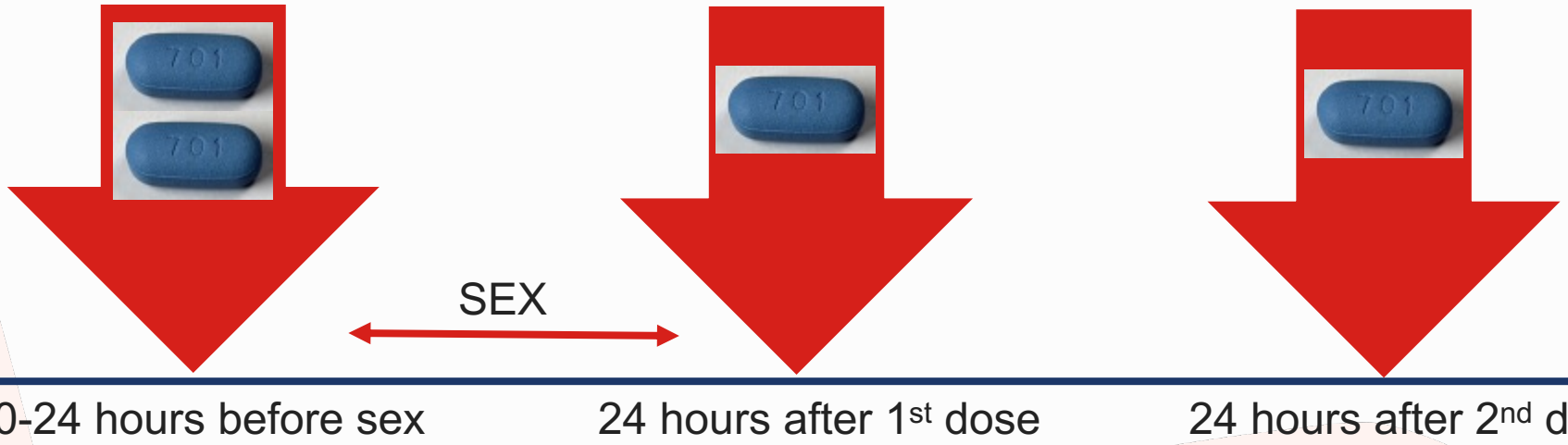
TDF/FTC Daily

HIV Incidence			
Global HIV Incidence; 0.11/100 PY (95% CI:0.04-0.23)			
Mean 22.1 months; 5633 Person-Years			
Treatment	F/U Patient Years	HIV Incidence per 100 patient Years	IRR (95%CI)
TDF/FTC Daily	2583.25	0.12 (0.02-0.34)	0.99 (0.13-7.38)
TDF/FTC On Demand	2553.68	0.12 (0.02-0.34)	

Assume 6.6/100 PY incidence (Ipergay placebo), 361 infections averted

Molina JM, et al. CROI 2021, March 6-10, 2021. Abstract 148.

On Demand PrEP, AKA 2-1-1 Regimen, IAS-USA Guidelines



- **2 tablet dose of PrEP should be taken closer to the 24-hour pre-sex time if sex is pre-planned**
- 2 doses with food 2 to 24 hours before sex, 1 dose 24 hours after the first (double) dose, and 1 dose 24 hours later ("2-1-1" dosing).
- **ONLY DATA IN MSM! NO DATA FOR TAF/FTC!!**

Saag M, et al. JAMA. 2018;320(4):379-396

Who Should Receive PrEP?

Sexually-Active Adults and Adolescents	Persons Who Inject Drugs
Anal or vaginal sex in the past 6 months; **and** HIV-positive sexual partner (especially if partner has unknown or detectable viral load); **or** Recent bacterial STI; **or** History of inconsistent or no condom use with sexual partner(s)	HIV-positive injecting partner; **or** Shares drug preparation or injection equipment
Documented negative HIV test result before prescribing PrEP; **and** No signs/symptoms of acute HIV infection; **and** Normal renal function; **and** No contraindicated medications	

- Sexually active gay and bisexual men without HIV
- Sexually active heterosexual men and women without HIV
- Sexually active transgender persons without HIV
- Persons without HIV who inject drugs
- Persons who have been prescribed non-occupational post-exposure prophylaxis (PEP) and report continued risk behavior, or who have used multiple courses of PEP

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

Figure 4b Clinician Determination of HIV Status for PrEP Provision to Persons with Recent or Ongoing Antiretroviral Prophylaxis Use

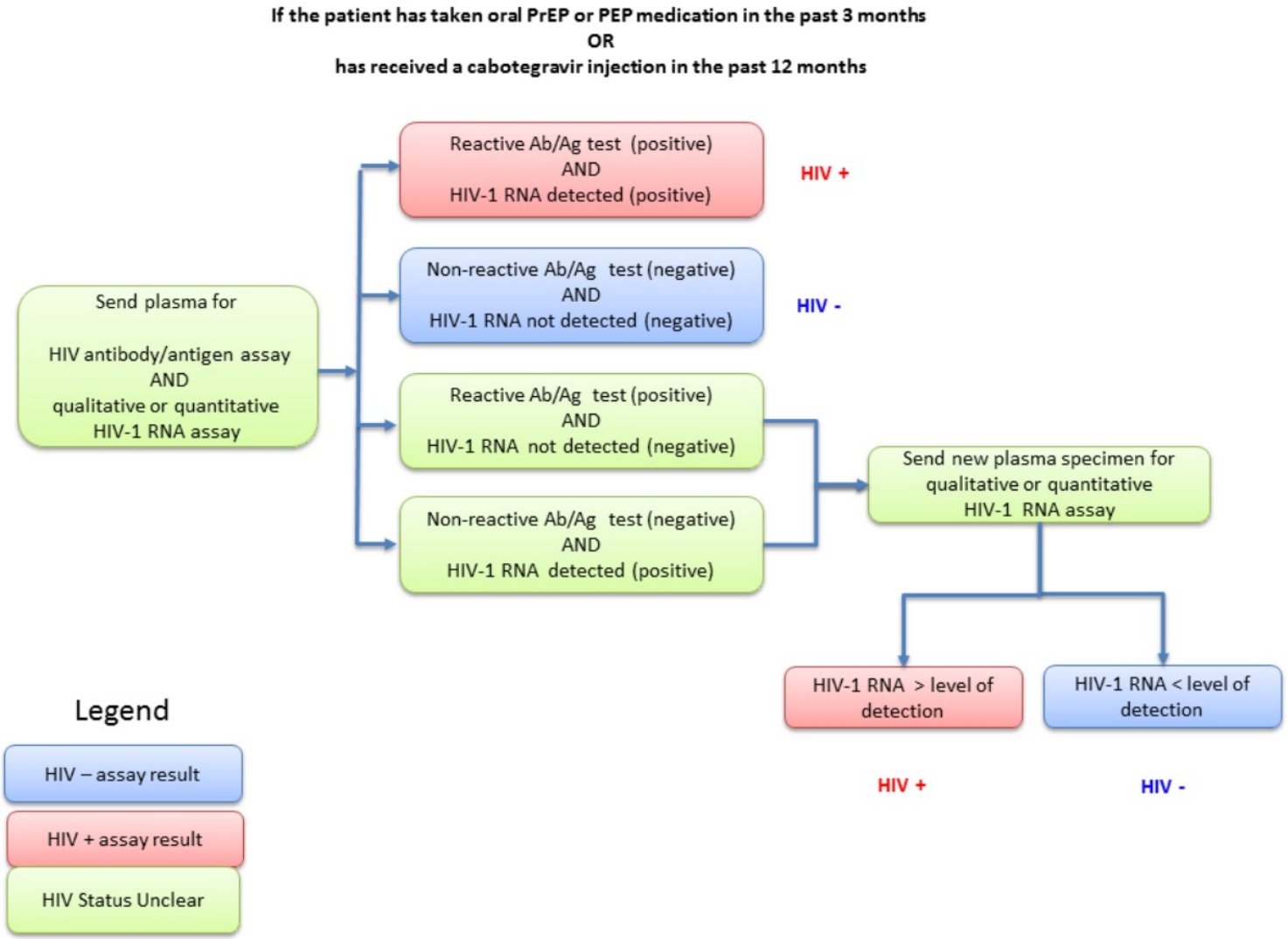


Table 1a: Summary of Clinician Guidance for Daily Oral PrEP Use

	Sexually-Active Adults and Adolescents[1]	Persons Who Inject
Identifying substantial risk of acquiring HIV infection	Anal or vaginal sex in past 6 months AND any of the following: • HIV-positive sexual partner (especially if partner has an unknown or detectable viral load) • Bacterial STI in past 6 months[3] • History of inconsistent or no condom use with sexual partner(s)	HIV-positive injecting OR Sharing injection equi
Clinically eligible	**ALL OF THE FOLLOWING CONDITIONS ARE MET:** • Documented negative HIV Ag/Ab test result within 1 week before initially prescribing PrEP • No signs/symptoms of acute HIV infection • Estimated creatinine clearance ≥30 ml/min[4] • No contraindicated medications	
Dosage	• Daily, continuing, oral doses of F/TDF (Truvada®), ≤90-day supply OR • For men and transgender women at risk for sexual acquisition of HIV; daily, continuing, oral doses of F/TAF (Descovy®), ≤90-day supply	
Follow-up care	**Follow-up visits at least every 3 months to provide the following:** • HIV Ag/Ab test and HIV-1 RNA assay, medication adherence and behavioral risk reduction support • Bacterial STI screening for MSM and transgender women who have sex with men[3] – oral, rectal, urine, blood • Access to clean needles/syringes and drug treatment services for PWID **Follow-up visits every 6 months to provide the following:** • Assess renal function for patients aged ≥50 years or who have an eCrCl <90 ml/min at PrEP initiation • Bacterial STI screening for all sexually-active patients[3] – [vaginal, oral, rectal, urine- as indicated], blood **Follow-up visits every 12 months to provide the following:** • Assess renal function for all patients • Chlamydia screening for heterosexually active women and men – vaginal, urine • For patients on F/TAF, assess weight, triglyceride and cholesterol levels	

[1] adolescents weighing at least 35 kg (77 lb)

[2] Because most PWID are also sexually active, they should be assessed for sexual risk and provided the option of CAB for PrEP when indicated

[3] Sexually transmitted infection (STI): Gonorrhea, chlamydia, and syphilis for MSM and transgender women who have sex with men including those who inject drugs; Gonorrhea and syphilis for heterosexual women and men including persons who inject drugs

[4] estimated creatine clearance (eCrCl) by Cockcroft Gault formula ≥60 ml/min for F/TDF use, ≥30 ml/min for F/TAF use

Table 5 Timing of Oral PrEP-associated Laboratory Tests

Test	Screening/Baseline Visit	Q 3 months	Q 6 months	Q 12 months	When st PrEP
HIV Test	X*	X			X*
eCrCl	X		If age ≥50 or eCrCL <90 ml/min at PrEP initiation	If age <50 and eCrCl ≥90 ml/min at PrEP initiation	X
Syphilis	X	MSM /TGW	X		MSM/TGW
Gonorrhea	X	MSM /TGW	X		MSM /TGW
Chlamydia	X	MSM /TGW	X		MSM /TGW
Lipid panel (F/TAF)	X			X	
Hep B serology	X				
Hep C serology	MSM, TGW, and PWID only			MSM,TGW, and PWID only	

* Assess for acute HIV infection (see Figure 4)

Table 1b: Summary of Clinician Guidance for Cabotegravir Injection PrEP Use

	Sexually-Active Adults	Persons Who Inject Dru
Identifying substantial risk of acquiring HIV infection	Anal or vaginal sex in past 6 months AND any of the following: • HIV-positive sexual partner (especially if partner has an unknown or detectable viral load) • Bacterial STI in past 6 months[2] • History of inconsistent or no condom use with sexual partner(s)	HIV-positive injecting part OR Sharing injection equipment
Clinically eligible	**ALL OF THE FOLLOWING CONDITIONS ARE MET:** • Documented negative HIV Ag/Ab test result within 1 week before initial cabotegravir injection • No signs/symptoms of acute HIV infection • No contraindicated medications or conditions	
Dosage	• 600 mg cabotegravir administered as one 3 ml intramuscular injection in the gluteal muscle o Initial dose o Second dose 4 weeks after first dose (month 1 follow-up visit) o Every 8 weeks thereafter (month 3,5,7, follow-up visits etc)	
Follow-up care	**At follow-up visit 1 month after first injection** • HIV Ag/Ab test and HIV-1 RNA assay **At follow-up visits every 2 months (beginning with the third injection – month 3) provide the following:** • HIV Ag/Ab test and HIV-1 RNA assay • Access to clean needles/syringes and drug treatment services for PWID **At follow-up visits every 4 months (beginning with the third injection- month 3) provide the following:** • Bacterial STI screening[2] for MSM and transgender women who have sex with men[2] – oral, rectal, urine, blood **At follow-up visits every 6 months (beginning with the fifth injection – month 7) provide the following:** • Bacterial STI screening[1] for all heterosexually-active women and men – [vaginal, rectal, urine - as indicated], blood **At follow-up visits at least every 12 months (after the first injection) provide the following:** • Assess desire to continue injections for PrEP • Chlamydia screening for heterosexually active women and men – vaginal, urine **At follow-up visits when discontinuing cabotegravir injections provide the following:**	

[1] Because most PWID are also sexually active, they should be assessed for sexual risk and provided the option of CAB for PrEP when indicated

[2] Sexually transmitted infection (STI): Gonorrhea, chlamydia, and syphilis for MSM and transgender women who have sex with men including those who inject drugs; Gonorrhea and syphilis for heterosexual women and men including persons who inject drugs

Prevent

Table 7 Timing of CAB PrEP-associated Laboratory Tests

Test	Initiation Visit	1 month visit	Q2 months	Q4 months	Q6 months	Q12 months	When Stopping CAB
HIV*	X	X	X	X	X	X	X
Syphilis	X			MSM^/TGW~ only	Heterosexually active women and men only	X	MSM/TGW only
Gonorrhea	X			MSM/TGW only	Heterosexually active women and men only	X	MSM/TGW only
Chlamydia	X			MSM/TGW only	MSM/TGW only	Heterosexually active women and men only	MSM/TGW only

* HIV-1 RNA assay

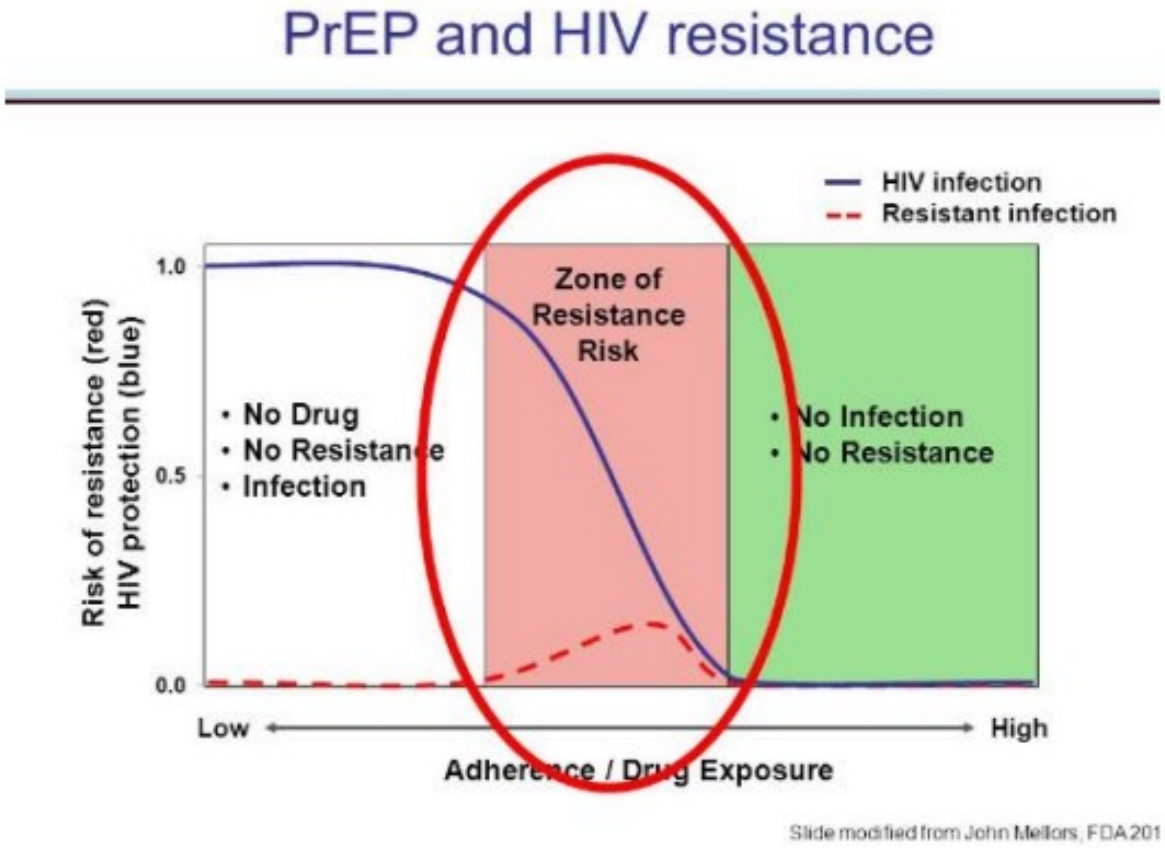
X all PrEP patients

^ men who have sex with men

~ persons assigned male sex at birth whose gender identification is female

Stopping PrEP-CAB

Prevent



Medications on the Horizon

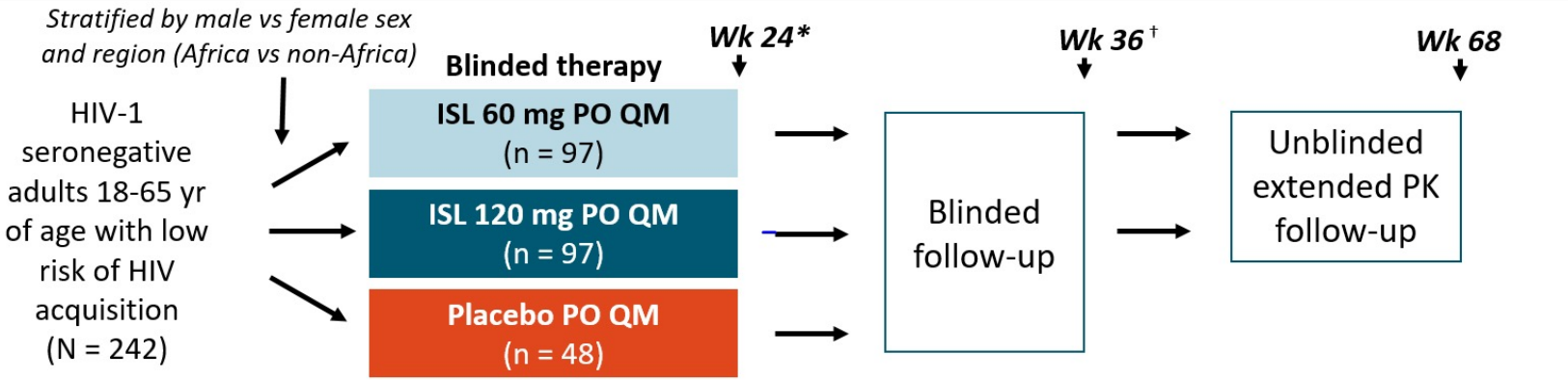
ISLATRAVIR

Islatravir (ISL, MK-8591)

- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
  - Chain terminator and translocation inhibitor
- Half-life is 50-60hrs in plasma
- Low doses orally and parenteral formulations
- Potent activity with broad coverage for HIV-1 and HIV-2

ISL for PrEP: Long acting oral

- Protocol 016: Multicenter, randomized, double-blind, placebo-controlled phase IIa trial: 67% female, 53% White, 42% Black, median age 31 yr



*Sponsor unblinded at Wk 24 to allow for interim evaluation of safety. Participants and investigators remain blinded to Wk 36.
†After Wk 36, participants in PBMC/PK Bridging Subset randomized to receive ISL have an additional 32-wk unblinded PK follow-up.

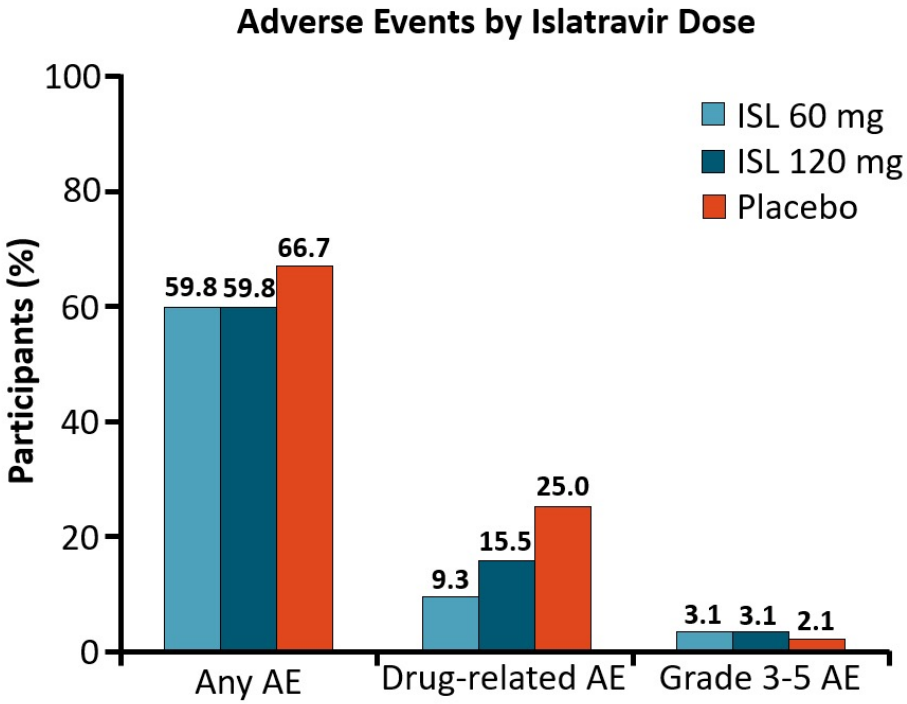
- Primary endpoints: safety/tolerability, pharmacokinetics of ISL-TP (active form of ISL)
- Exploratory endpoints: pharmacokinetics in PBMCs, pharmacokinetics in tissue, hormonal drug-drug interactions

Hillier. IAS 2021. Abstr OALC01LB03.

Slide credit: clinicaloptions.com

ISL for PrEP: Protocol 016

- 73.5% of AEs were mild
  - 2 discontinuations* due to AEs considered drug-related
    - Mild foreign body sensation in throat
    - Moderate rash and pruritis
  - 1 participant* had 2 serious AEs; neither considered drug-related



*Treatment assignment not identified to avoid unblinding individual participants.

Hillier. IAS 2021. Abstr OALC01LB03.

Slide credit: clinicaloptions.com

ISL for PrEP: Protocol 016

- Grade 3/4 laboratory abnormalities were rare and observed at similar rates in ISL and placebo groups
  - Decreased creatinine clearance in 14 participants (5.8%); 1 grade 4*
  - Elevated lipase in 5 participants (2.1%); 1 grade 4*

AEs with incidence ≥5% overall, n (%)	ISL 60 mg QM (n = 97)	ISL 120 mg QM (n = 97)	Placebo (n = 48)
Headache	10 (10.3)	9 (9.3)	2 (4.2)
▪ Grade 1	9 (9.3)	9 (9.3)	1 (2.1)
▪ Drug-related	2 (2.1)	0	1 (2.1)
Diarrhea	5 (5.2)	5 (5.2)	4 (8.3)
▪ Grade 1	4 (4.2)	5 (5.2)	4 (8.3)
▪ Drug-related	1 (1.0)	2 (2.1)	4 (8.3)
Nausea	5 (5.2)	7 (7.2)	2 (4.2)
▪ Grade 1	5 (5.2)	7 (7.2)	2 (4.2)
▪ Drug-related	0	2 (2.1)	2 (4.2)

*Treatment assignment not identified to avoid unblinding individual participants.

Hillier. IAS 2021. Abstr OALC01LB03.

Slide credit: clinicaloptions.com

ISL for PrEP: Protocol 016

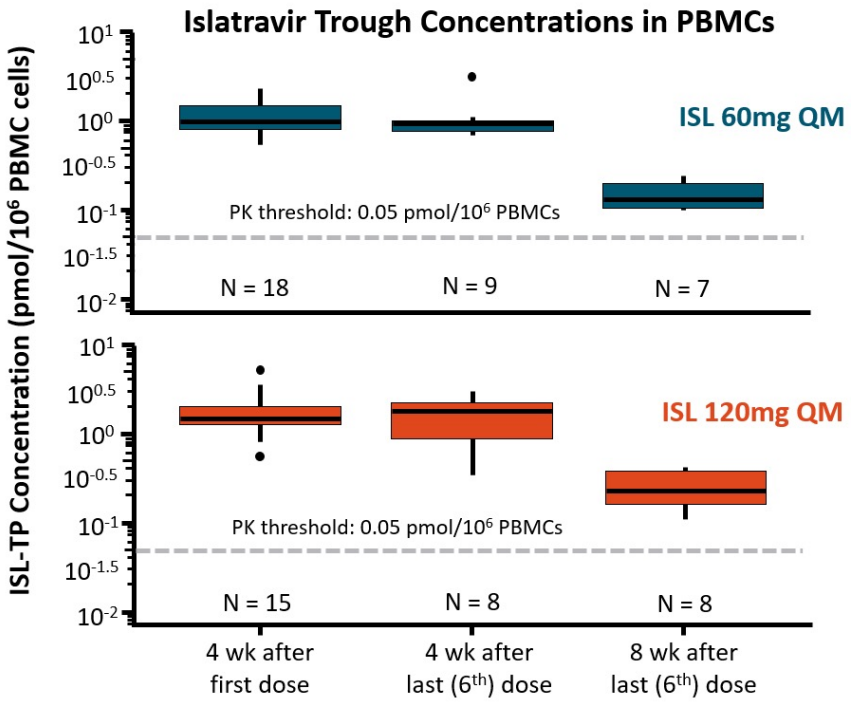
Median % Change From Baseline to Wk 24	ISL 60 mg QM (n = 97)	ISL 120 mg QM (n = 97)	Placebo QM (n = 48)
Weight, kg	+0.4	+1.8	+0.2
DXA parameters			
▪ Body fat			
— Peripheral fat	-0.35 (n = 83)	+2.50 (n = 89)	+0.77 (n = 41)
— Trunk fat	+0.95 (n = 83)	+3.42 (n = 89)	+0.25 (n = 41)
▪ BMD			
— Total hip	+0.22 (n = 83)	-0.09 (n = 87)	+0.10 (n = 42)
— Lumbar spine	+0.53 (n = 82)	0 (n = 89)	+0.63 (n = 42)
Renal parameters			
▪ Serum creatinine, mg/dL (IQR)	0 (-11.8 to +12.8)	0 (-5.8 to +11.1)	0 (0 to +14.3)
▪ eGFR, mL/min/1.73 m^2 (IQR)	0 (-12.9 to +15.6)	0 (-11.5 to +7.2)	0 (-14.3 to 0)

- At Wk 24, no clinically meaningful differences from placebo in metabolic and renal parameters with islatravir 60 mg or 120 mg after 6 QM doses
- Islatravir PrEP program placed on hold by FDA due to observed changes in lymphocytes in clinical trials

Macdonald. CROI 2022. Abstr 85.

Slide credit: clinicaloptions.com

ISL for PrEP: Protocol 016



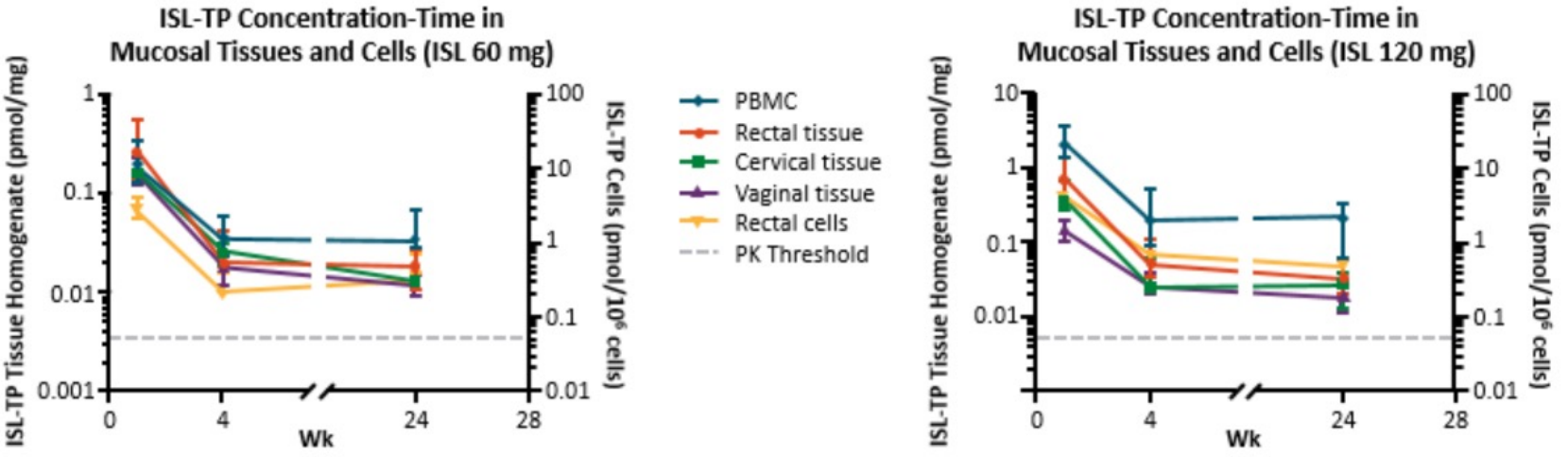
Hillier. IAS 2021. Abstr OALC01LB03.

- Trough concentrations of ISL-TP (active form of ISL) remained above prespecified PK threshold for HIV-1 prevention for at least 8 wk following last dose

Slide credit: clinicaloptions.com

ISL in blood and mucosal tissues

- Substudy of phase IIa trial of ISL for PrEP (n = 54, 41 female)
  - Plasma ISL highly correlated with ISL-TP in cervical, vaginal, rectal tissues (adjusted $R^2 \geq 0.7$; $P < .001$)



Hendrix. CROI 2022. Abstr 83.

Slide credit: clinicaloptions.com

ISL for PrEP: Long acting oral

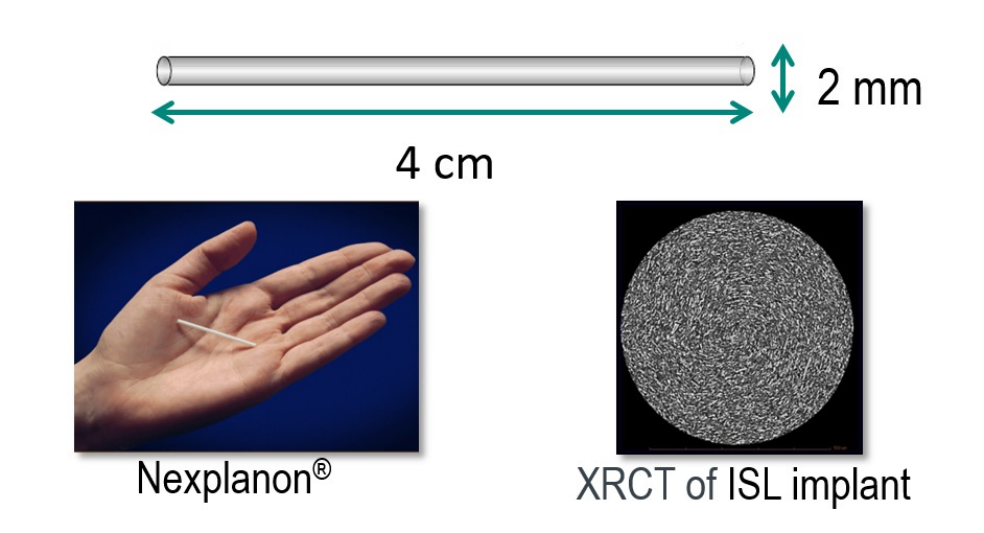
- Currently recruiting
- Phase III, randomized, double blind, placebo-controlled

- Impower-022: Oral ISL 60mg once monthly vs daily TDF/FTC in cisgender women

- Impower-024: Oral ISL 60mg once monthly vs daily TAF/FTC or TDF/FTC in MSM and transgender women

ISL for PrEP: Long acting implant

- ISL prototype design based on Nexplanon®/Implanon®
  - Uses same applicator and polymer
  - Removable



ISL for PrEP: Long acting implant

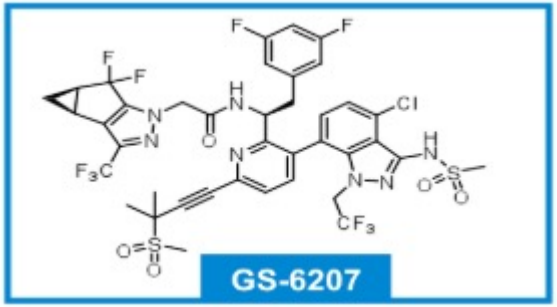
- **Protocol 008:** double-blind, placebo-controlled phase I clinical trial of next-generation ISL-eluting implant that uses the same applicator as currently approved etonogestrel implant
  - Subdermal implants containing 48 mg, 52 mg, or 56 mg ISL placed in upper arm of nondominant hand for 12 wk
  - 52-mg and 56-mg ISL implants maintained concentrations above PK threshold estimated to be suitable for HIV prophylaxis (0.05 pmol/10^6 cells) throughout 12-wk implant placement
  - 56-mg ISL implant projected to release sufficient drug to maintain ISL-triphosphate levels to above PK threshold for >52 wk
  - Well tolerated with most implantation site reactions self-resolving

Matthews. CROI 2021. Abstr 88.

LENACAPAVIR

Lenacapavir (LEN): Capsid Inhibitor

- First in-class inhibitor of HIV capsid inhibitor with picomolar potency
- Given as subcutaneous suspension
  - Also has oral formulation in trials



- In-vitro: active against HIV-1 variants and resistant strains
- Low clearance and low solubility→very long half life
- In clinical trials, for both treatment and PrEP

Sager et al. CROI 2019, #141

LEN for PrEP: Twice Yearly Subcutaneous Injections

- Currently recruiting

- PURPOSE-1
  - Regimen: oral LEN 600 mg on Days 1 and 2 and subcutaneous LEN 927 mg every 26 wk vs daily oral FTC/TAF vs daily oral FTC/TDF
  - Population: cisgender adolescent girls and young women (aged 16-25 yr)

- PURPOSE-2
  - Regimen: oral LEN 600 mg on Days 1 and 2 and subcutaneous LEN 927 mg every 26 wk vs daily oral FTC/TDF
  - Population: cisgender men, transgender women, transgender men, and gender nonbinary people who have sex with partners assigned male at birth

DAPIVIRINE

Dapivirine (DAP)

- NNRTI
- Used as a topical microbicide
- Currently being studied as vaginal ring
  - Flexible silicone
  - Future combo with contraception?
- Low systemic levels

Dapivirine Vaginal Ring

- Female-controlled method of HIV prevention that allows for dapivirine delivery over 1 mo

- **March 2021:** WHO released new clinical recommendations on HIV prevention that include detailed guidance for dapivirine ring as additional choice for women at substantial HIV risk as part of combination prevention package
- **Early 2021:** International Partnership for Microbicides submitted to FDA for regulatory review (withdrawn in Jan 2022)

PrEPWatch. www.prepwatch.org/nextgen-prep/dapivirine-vaginal-ring/.

Dapivirine Ring

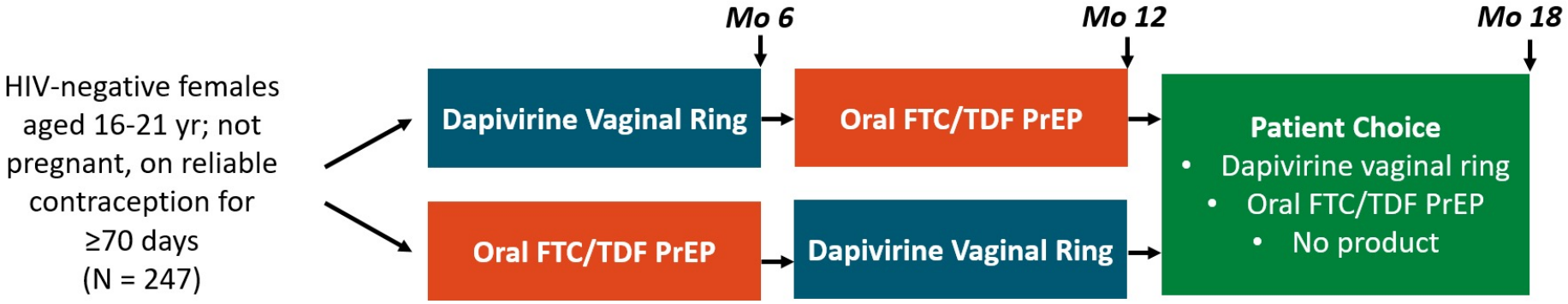
- In **phase III** MTN-020/ASPIRE and IPM 027/The Ring Study, **HIV incidence reduced by ≈30% vs placebo in African women**[1,2]
  - **ASPIRE:** 27% reduction (*P* = .046)
  - **The Ring Study:** 31% reduction (*P* = .04)
  - Dapivirine ring evaluated in nearly 4600 women aged 18-45 yr in Malawi, South Africa, Uganda, and Zimbabwe
- **No safety concerns** with long-term use based on open-label phase III extension, and >40 safety studies of different dapivirine formulations (oral, gel, film, ring)[3]
- IPM acceptability studies: Nearly all women found ring to be acceptable and expressed interest in using it if proven effective[3]

1. Baeten. NEJM. 2016;375:2121. 2. Nel. NEJM. 2016;375:2133.
3. www.ipmglobal.org/sites/default/files/attachments/publication/ipm_ring_backgrounder_mar_2021.pdf

Slide credit: clinicaloptions.com

REACH Study: Dapivirine Ring

- Randomized, open-label phase IIa crossover study conducted in Africa



Note: Adherence support and counseling included for all patients.

- Endpoints: safety (AEs ≥grade 2), adherence, acceptability, preference

Adherence	DPV (Measured by Drug Levels in Returned Rings)	FTC/TDF (Measured by Drug Levels in Dried Blood Spots)
High	≥0.1071 mg/day	≥4 doses/wk (>500 fmol/punch at Wk 4, >700 fmol/punch at Wk 8)
Medium	0.0321- <0.1071 mg/day	~1-3 doses/wk (16.6-499 fmol/punch at Wk 4, 16.6-699 fmol/punch at Wk 8)
Low	≤0.0321 mg/day	No drug detected (<16.6 fmol/punch)

Nair. IAS 2021. Abstr OALC01LB01.

Slide credit: clinicaloptions.com

REACH Study: Dapivirine Ring

Outcome, %	Dapivirine Vaginal Ring	Oral PrEP
Adherence		
▪ High	50.2	58.6
▪ Medium	45.4	39.9
▪ Low/none	4.4	1.5
Compliance, self-report*		
▪ Full compliance	50.2	22.4
▪ Below full compliance	49.8	77.6
Acceptable		
▪ Yes	88.5	63.9
▪ No	11.5	36.1

*Full compliance to ring defined as leaving the ring in place a full mo; full compliance to oral PrEP defined as 6+ doses per wk.

- HIV-1 incidence (overall population): 0.5/100 woman-yr (1/247)
- Pregnancy incidence (overall population): 1.8/100 woman-yr (4/247)

Nair. IAS 2021. Abstr OALC01LB01.

Slide credit: clinicaloptions.com

HIV - HCV - PrEP - PEP
Clinical Consultations
For Providers in Upstate NY

Call or E-mail for a consultation
Monday – Friday 8:00 am – 4:30 pm*

518-262-6864 or prokopw@amc.edu

*If you have experienced an occupational exposure such as a needle stick, please call **518-262-4043**. You will be given an opportunity on the telephone menu to speak to a physician 24 hours a day.

www.amc.edu/hiv

Questions/Contact

Alex Danforth, PharmD, BCACP, AAHIVP

adanforth@trilliumhealth.org

Thank you to John Faragon, PharmD for providing slide content!