HIV PREVENTION: PREP, NPEP, U = U

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OBJECTIVES

1. Overview of disparities in HIV and PrEP
2. Overview of Oral PrEP
3. Overview of Event Driven PrEP
4. Overview of Injectable PrEP (Cabotegravir)
5. Overview of Injectable PrEP (Lenacapavir)
6. Overview of nPeP
7. Overview of U = U and Treatment as Prevention (TasP)

WHAT IS PREP?

- HIV Pre-Exposure Prophylaxis (PrEP) is **a medication taken daily to prevent HIV infection.**

- **2012:** The FDA approved **Truvada®**
  - A combination of two HIV medicines (tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine 200 mg) one tablet daily for PrEP use in individuals 18 years of age and older.

- **2019:** The FDA approved **Descovy®**
  - A combination of two HIV medicines (tenofovir alafenamide (TAF) 25 mg and emtricitabine 200 mg) one tablet daily for PrEP use in individuals 18 years of age and older **excluding individuals at-risk from receptive vaginal sex.**

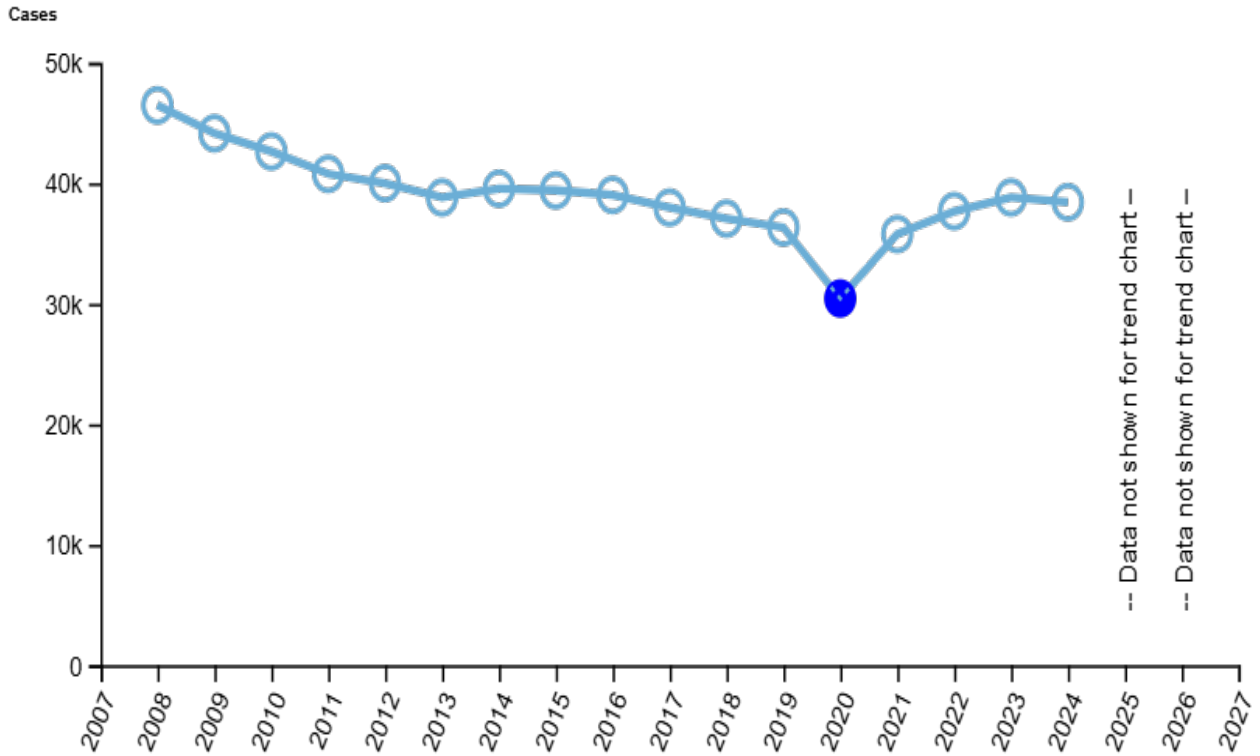
- **2021:** FDA approved **injectable intramuscular (IM) Cabotegravir**
  - Cabotegravir is an integrase inhibitor (HIV medicine) administered via intramuscular injection for PrEP use every 2 months in individuals 18 years of age and older

- **June 2025:** FDA approved **injectable subcutaneous (subq) Lenacapavir**
  - Lenacapavir is a capsid inhibitor (HIV medicine) administered via subcutaneous injection for PrEP use every 6 months in individuals 18 years of age and older

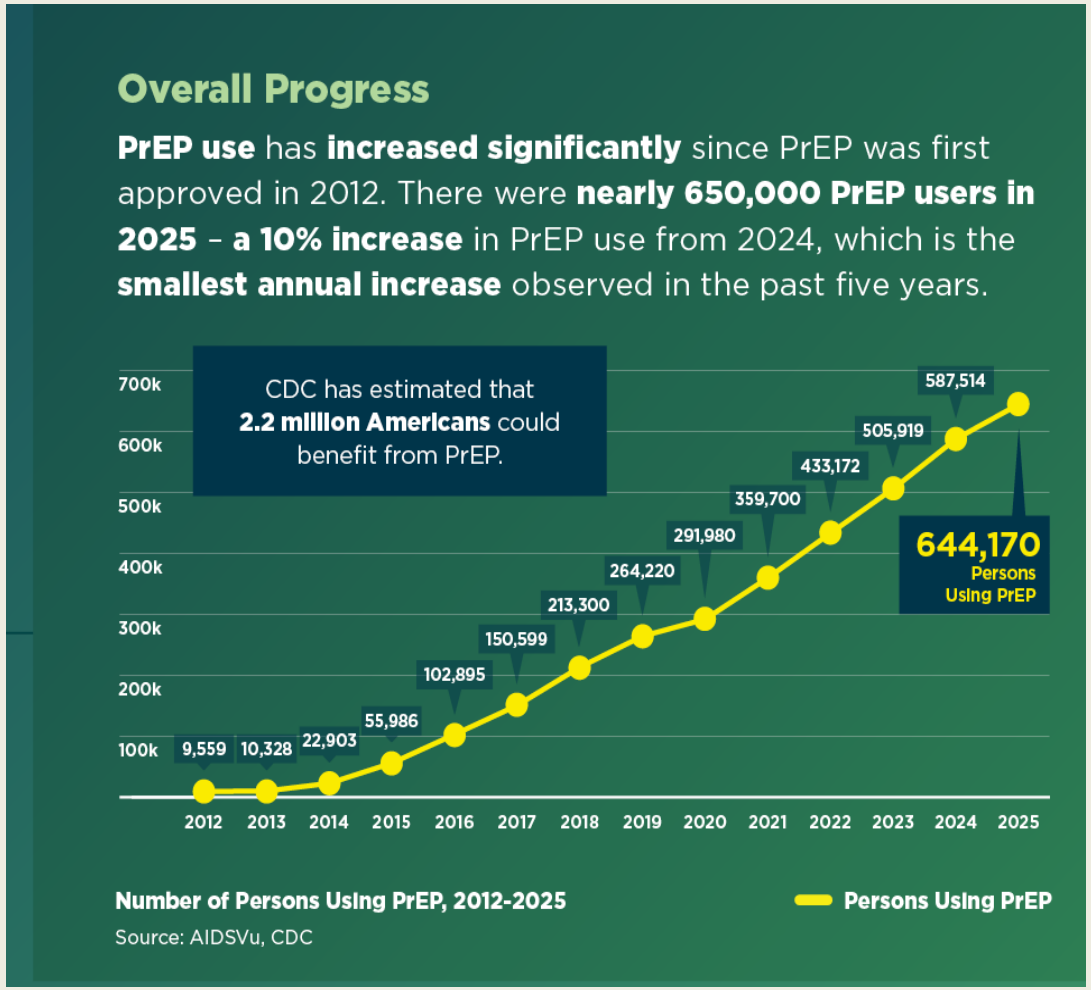
DISPARITIES IN HIV AND PREP

OVERALL TREND:
NEW HIV DIAGNOSIS AND PREP USE

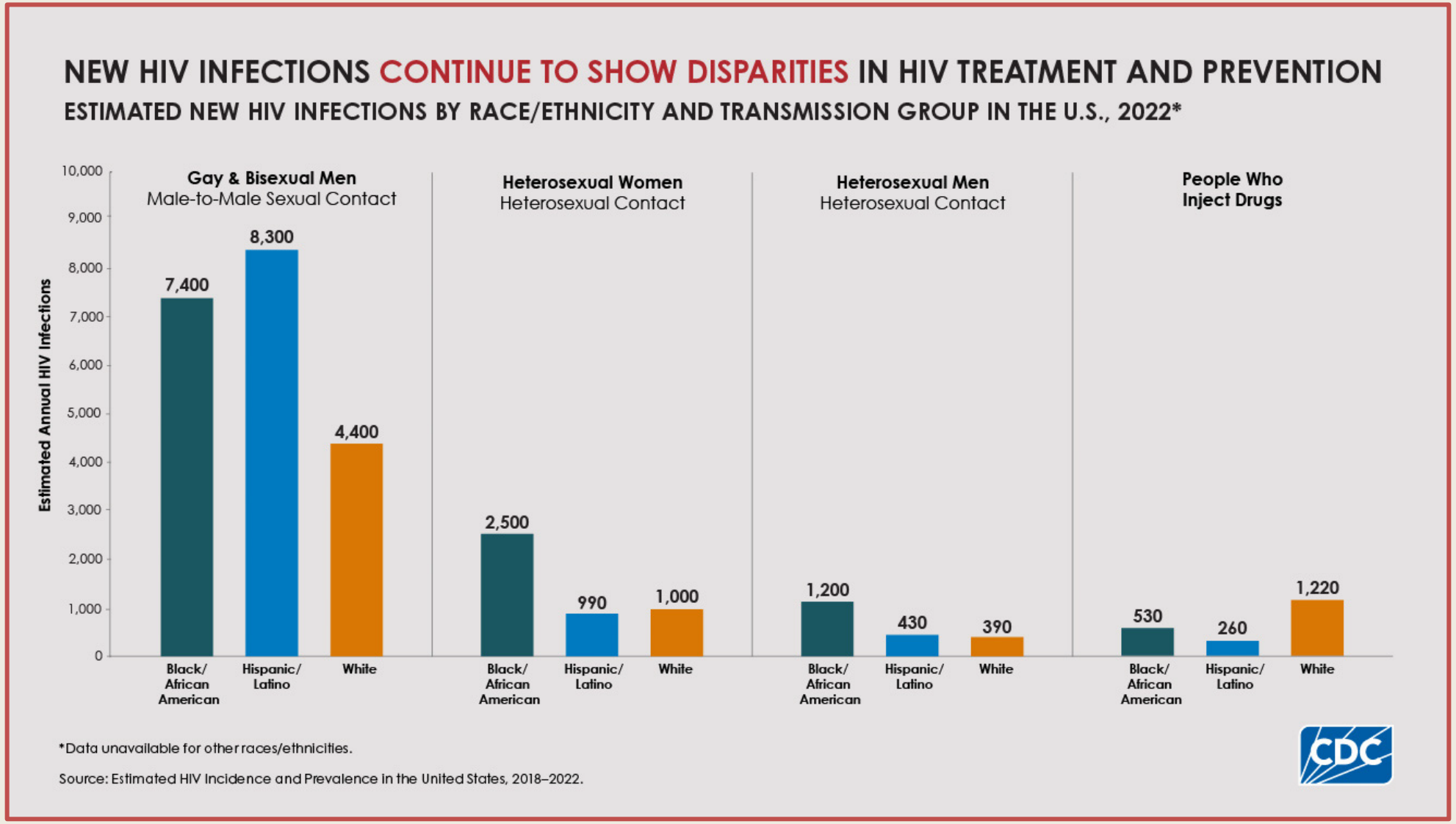
HIV Diagnosis
U.S, 207-2024



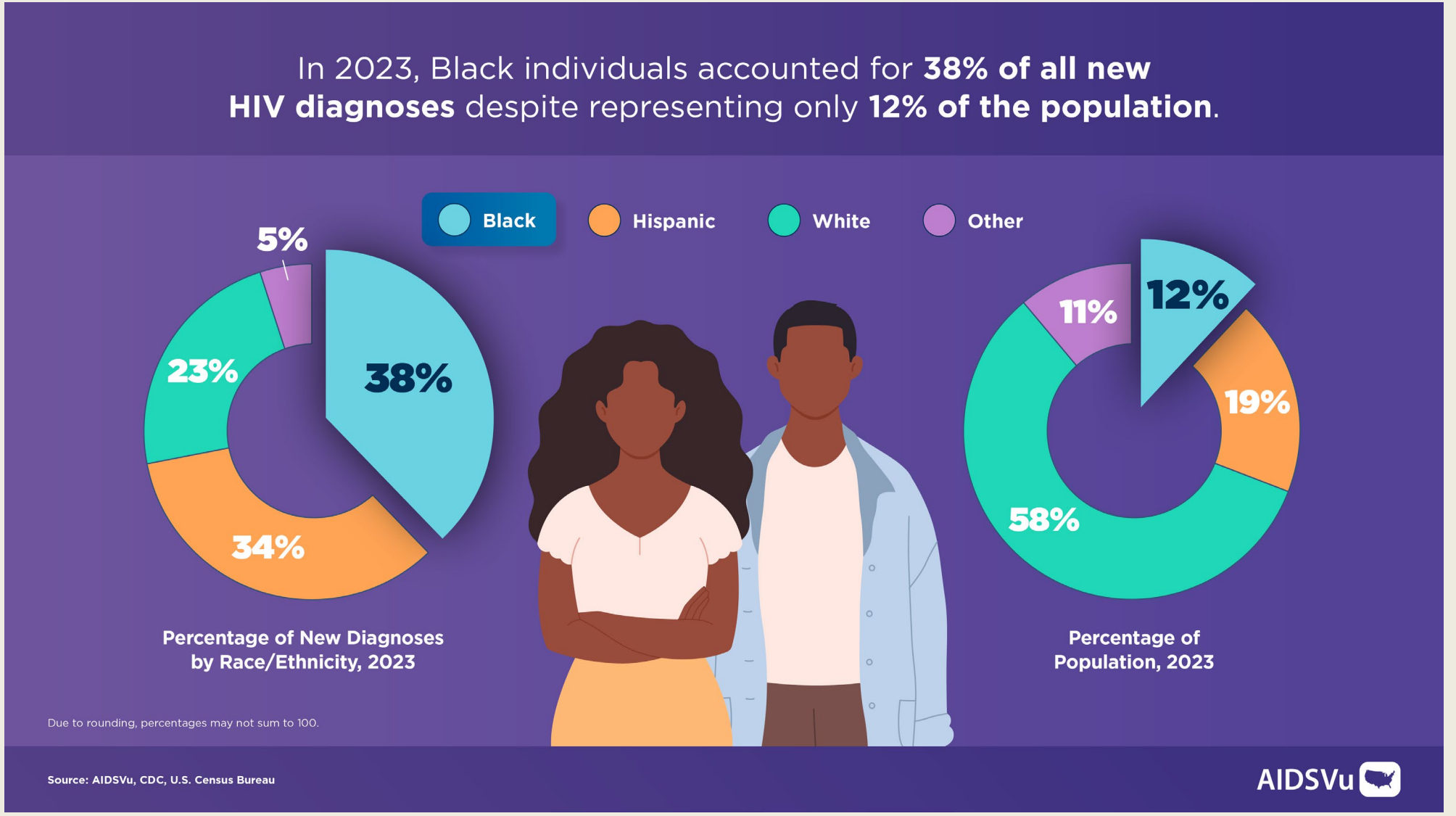
Atlas Plus, CDC Data



DISPARITIES IN HIV



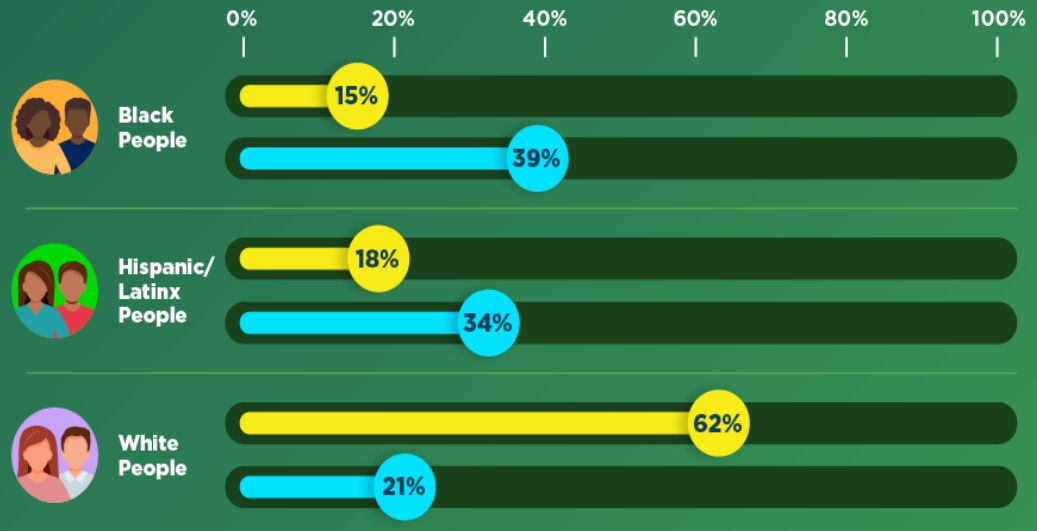
RACIAL DISPARITIES IN HIV



DISPARITIES IN PREP USE

PrEP Use by Race/Ethnicity

In 2024, **Black communities** represented **39% of all new HIV diagnoses**, the highest among all racial/ethnic groups, but only accounted for **15% of PrEP users in 2025**. Similarly, **Hispanic/Latinx communities** represented **34% of new HIV diagnoses** in 2024 but only accounted for **18% of PrEP users in 2025**.



Source: AIDSVu, CDC

Disparities in PrEP Use Relative to Need

In 2024, for **every new HIV diagnosis** among **Black individuals**, there were about **6 people using PrEP**. There were about **8 Hispanic/Latinx people using PrEP** per new HIV diagnosis.

In contrast, **42 White individuals used PrEP** for every new HIV diagnosis among their group.

A lower PnR (lighter shading on maps) indicates more unmet need for PrEP.



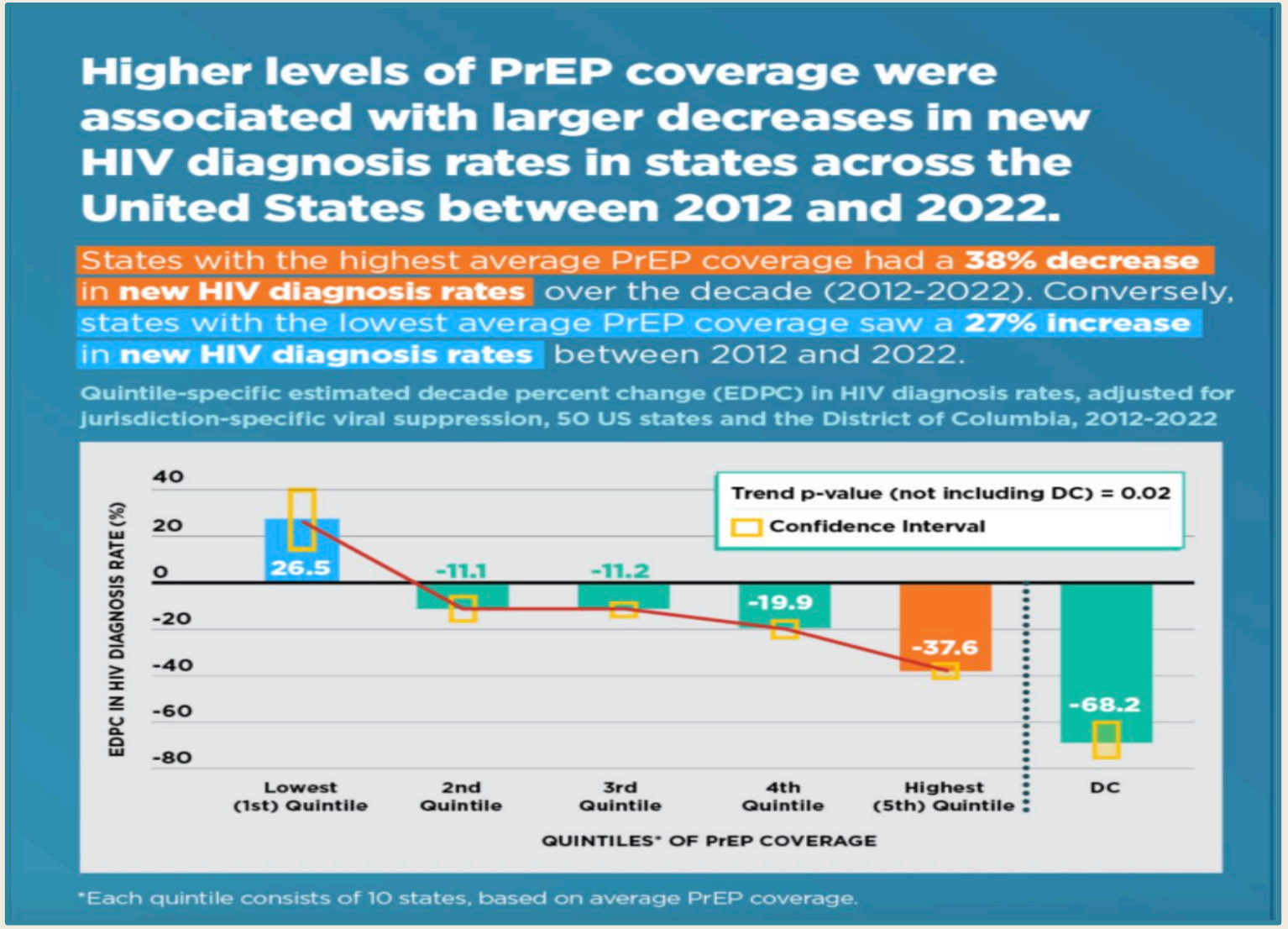
PrEP-to-Need Ratio (PnR), by Race/Ethnicity, 2024

0.44	11.0	24.7	39.8	62.2

0 Data not available

Source: AIDSVu, CDC

POPULATION LEVEL IMPACT OF PREP ON NEW HIV DIAGNOSIS



ORAL PREP

ORAL PREP

- **Truvada**
  - A combination of two HIV medicines (tenofovir disoproxil fumarate (**TDF**) 300 mg and emtricitabine 200 mg) one tablet daily for PrEP use in **individuals 18 years of age** and **adolescents weighing at least 35 kg**

- **Descovy**
  - A combination of two HIV medicines (tenofovir alafenamide (**TAF**) 25 mg and emtricitabine 200 mg) one tablet daily for PrEP use in individuals 18 years of age and older **excluding individuals at-risk from receptive vaginal sex.**

ORAL PREP: SUMMARY OF MAJOR EFFICACY TRIALS

Study	Population	Overall efficacy	Efficacy with high adherence
iPrEx[1]	MSM/Transgender women who have sex with men	44%	92%
Partners PrEP Trial[2]	Heterosexual discordant couples	75%	90%
TDF2 Trial[3]	Heterosexual discordant couples	63%	78%
Bangkok Tenofovir Study[4]	Intravenous drug users	49%	74%
DISCOVER Trial	5,000 cisgender men and transgender women	* Descovy has Non-inferior efficacy to Truvada	

1. Grant et al. *N Engl J Med* 2010
2. Baeten et al. *N Engl J Med* 2012
3. Thigpen et al. *N Engl J Med 2012*
4. Choopanya et al. *Lancet 2013*

CLINICAL INDICATIONS FOR PREP

PrEP for ALL

- Prescribe PrEP to **anyone who asks for it,** including sexually active people who do not report HIV risk factors.

- **Inform all Patients about PrEP**

Clinical Indicators for Strongly Recommending PrEP

- **Have had anal or vaginal sex in the past 6 months**, and you:
  - have a sexual partner with HIV (especially if the partner has an unknown or detectable viral load), or
  - have not consistently used a condom, or
  - have been diagnosed with an STD in the past 6 months.

OR

- **Inject drugs** and
  - have an injection partner with HIV, or
  - share needles, syringes, or other injection equipment.

OR

- **Been prescribed PEP** and
  - Report continued risk behavior or
  - Have used multiple courses of PEP

CONTRAINDICATIONS TO ORAL PREP

- Signs and Symptoms of Acute HIV
- Documented HIV infection

- **Truvada** - Creatinine clearance < 60 mL/min
- **Descovy** - Creatinine clearance < 30 mL/min

SIDE EFFECTS AND TOXICITY TO ORAL PREP

Side Effects

- Nausea
- Flatulence
- Diaarhea
- Rash
- Headache

Toxicity

- Decrease in bone mineral density
- Decrease renal function

ORAL PREP: TIME TO PROTECTION

- PrEP reaches maximum protection from HIV for **receptive anal sex** at about **7 days** of daily use.
- For **receptive vaginal sex and Iv drug use**, PrEP reaches maximum protection at about **21 days** of daily use
- **No data** on time to protection for **insertive vaginal sex and insertive anal sex**
- **The efficacy of the drug is dependent on adherence**

LABS AND CLINIC FOLLOW-UP

Table based on 2021 CDC Clinical Practice Guidelines for HIV PrEP

Laboratory Evaluation in Persons Taking Tenofovir Alafenamide-Emtricitabine (TAF-FTC) HIV PrEP

Test	Q 3 months	Q 6 months	Q 12 months	When stopping
HIV-1 RNA	ALL			ALL
HIV Antigen/ Antibody	ALL¶			ALL¶
Renal Function (eCrCl)		Age ≥50 years OR baseline eCrCl <90 mL/min	Age <50 years AND baseline eCrCl ≥90 mL/min	ALL
Syphilis Serology	MSM	MSW/WSM		MSM
Gonorrhea	MSM	MSW/WSM		MSM
Chlamydia	MSM	MSW/WSM		MSM
Hepatitis C Serology			MSM and/or PWID	
Lipid Panel			ALL	
Pregnancy Test	ALL^			

University of Washington: National HIV PrEP Curriculum

SPECIAL CONSIDERATIONS FOR ORAL PREP

- Acute HIV infection
- HBV Infection
- Pregnancy

ACUTE HIV

Symptoms

- Fever
- Chills
- Rash
- Night sweats
- Muscle aches
- Sore throat
- Fatigue
- Swollen lymph nodes
- Mouth ulcers

- Some people have flu-like symptoms within **2-4 weeks after infection** (called acute HIV infection).
- These symptoms may last for a few days or several weeks.
- Some patients are **asymptomatic** during acute HIV Infection

** HIV Ag/Ab testing may be falsely negative in Acute HIV**

** **HIV RNA** is test of choice for diagnosis of HIV in Acute HIV**

**** Drug-resistant virus can develop in persons on PrEP with unrecognized acute HIV infection****

M184V mutation (associated w/ emtricitabine resistance)

- Most common mutation to occur
- Minimal clinical effect on ARVs that can be used

K65R mutation (associated w/ tenofovir resistance)

- Rare mutation to emerge in PreP clinical trials
- Significant clinical impact on ARVs that can be used

CHRONIC HEP. B INFECTION

- TDF/TAF and FTC are each active against both HIV and HBV infection
- All patients screened for PrEP should order Hepatitis B Serology
  - **If Hepatitis B Surface Ag positive**, follow up with HBV DNA PCR to determine level of HBV replication

Reactivation of Hep. B

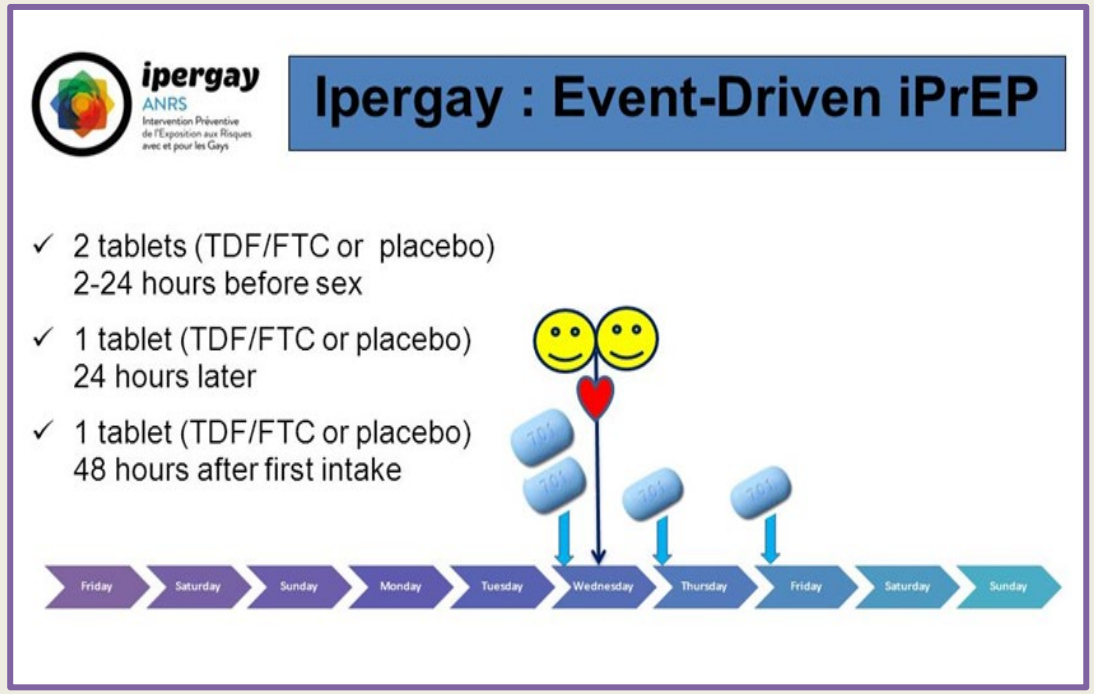
- TDF has high barrier to HBV resistance, but **intermittent use could lead to** TDF-resistance HBV has lead to reactivation of Hep. B/HBV acute flares
- Consistent adherence to TDF/FTC in patients with chronic Hep. B to prevent possibility of the reactivation of HBV infection

SAFETY OF PREP IN PREGNANCY AND BREASTFEEDING

- **Truvada (TDF/FTC)** is a FDA-approved PrEP option in pregnancy and breastfeeding with known safety and efficacy data
  - No evidence of human teratogenicity
  - High placental transfer to fetus
  - Minimal infant drug exposure during breastfeeding
- People who become pregnant while using Truvada as PrEP can continue PrEP throughout their pregnancy and PrEP can be started during pregnancy

EVENT-DRIVEN PREP
ON-DEMAND PREP
2-1-1

EVIDENCE: EVENT DRIVEN PREP



HIV Incidence		
Treatment	**Follow-up Pt Years**	**HIV Incidence per 100 Pt Years (95% CI)**
Placebo (double-blinded)	212	6.60 (3.60-11.1)
TDF/FTC (double-blinded)	219	0.91 (0.11-3.30)
TDF/FTC (open-label)	515	0.19 (0.01-1.08)

- 86% efficacy vs. Placebo (among 400 MSM)
- Median of 15 pills/month (among
- Only 1 HIV infection detected in 18-month follow-up (among 361 MSM)

2-1-1 VS. DAILY TDF/FTC PREP

	2-1-1 PReP	Daily PrEP
Which Oral Formulation?	Only TDF (Truvada)	TDF and TAF (Truvada and Descovy)
Who Can Use It?	Only Studied in MSM	Anyone
Chronic HBV	Can Trigger a Flair	Can Be Safely Used
Planning	Need to Plan Sex at Least 2 Hrs in Advance	No Planning Meded
"Forgiveness"	Not Forgiving of Missed Doses	Forgiving of Missed Doses During the Week

INJECTABLE PREP: IM CABOTEGRAVIR

CLINICAL TRIALS: CABOTEGRAVIR FOR HIV PREVENTION (PREP)

- **HPTN 083** Clinical Trial: Cabotegravir for HIV Prevention in **Cisgender men and Transgender**
- **HPTN 084** Clinical Trial: Cabotegravir for HIV prevention in **Cisgender women in sub-Saharan Africa**

Study Design

- Randomized, double-blinded, double-dummy, non-inferiority trial
- Comparing long-acting injectable cabotegravir (CAB-LA) at a dose of 600 mg, given intramuscularly every 8 weeks, with daily oral TDF-FTC for the prevention of HIV infection

CAB-LA was SUPERIOR to daily oral TDF-FTC in prevention of HIV infection
among MSM and transgender women (HPTN 083)
and in cisgender women (HPTN 084)

**Both trials were stopped early due to successfully meeting its specified objectives **

CABOTEGRAVIR FOR PREP

- **Apretude (Cabotegravir extended-release injectable suspension)** approved for use in adults and adolescents weight at least 35 kg (77 lbs) for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV

- **600 mg** (3 mL) of cabotegravir **injected** into **gluteal muscle** (gluteus medius or gluteus maximus)

- Given first as **2 initiation injections administered 1 month apart**, and then **every 2 months there after**
  - 2-inch needle for IM injections for patients with BMI of 30 or greater
  - 1.5-inch needle for IM injections for patients with a BMI < 30

- 30 mg daily oral cabotegravir is *optional* for a 4-week lead-in prior to injections

- **No data** yet available from clinical trials in men or women to **estimate the time from initiation of CAB injections to maximal protection** against HIV acquisition

ADVANTAGES TO CABOTEGRAVIR PREP

- Can be used in patients with renal disease

- For patients who difficulty with adherence to oral PrEP and prefer injections every 2 months

WHAT **NOT** TO DO

- Do NOT administer or prescribe other antiretroviral medical in combination with CAB for PrEP

- Do NOT administer CAB injections at any site *other than gluteal muscle* because the pharmacokinetics of drug absorption with injection at pother sites is unknown
  - **However, there is data to suggest that the ***thigh*** **may be an alternative site for injection**

- Do NOT dispense CAB injections for use by patients for *home administration* (unless and until self-administration is FDA approved)

- Do NOT prescribe ongoing daily oral CAB (other than for lead-in prior initiating or restarting injections)

CABOTEGRAVIR - DRUG INTERACTIONS

Table 6 Cabotegravir PrEP Drug Interactions (https://www.hiv-druginteractions.org/)

Rifampicin, rifapentin	**Do not co-administer with CAB** Rifampicin and rifapentine increase metabolism of CAB and may result in significantly reduced exposure to protective levels of CAB [142, 143]
Rifabutin	**Co-administer with caution** Rifabutin moderately increases metabolism of CAB and may result in somewhat reduced exposure to protective levels of CAB[144]
Hormonal contraceptives	No significant effect[145]
Feminizing hormones (Spironolactone, estrogens)	No data yet available[146]
Carbamazepine, oxcarbazepine, phenytoin, phenobarbital	**Do not co-administer with CAB** Concern that these anticonvulsants may result in significantly reduced exposure to protective levels of CAB but strength of evidence is weak

CABOTEGRAVIR: INITIAL PREP VISIT

- **Must ensure that patient DOES NOT have acute or chronic HIV infection**
  - Because of the long duration of drug exposure or **"long tail"** following injection of CAB, exclusion of acute HIV is necessary with the most sensitive test, an **HIV-1 RNA Assay**
  - If you wish to provide injection at the first PrEP evaluation visit based on rapid HIV Ag/Ab test, blood should always be drawn for laboratory confirmatory testing that includes HIV RNA assay
- Patients who have been taking daily oral PrEP can initiate CAB injections as soon as HIV-1 RNA results confirm they remain HIV negative

All CAB PrEP patients should have **baseline STI testing**

Labs NOT Indicated

- Creatinine, estimated creatinine clearance
- Hepatitis B serology
- Lipid panels
- Liver Functions Tests

CABOTEGRAVIR: CLINICAL FOLLOW-UP AND MONITORING

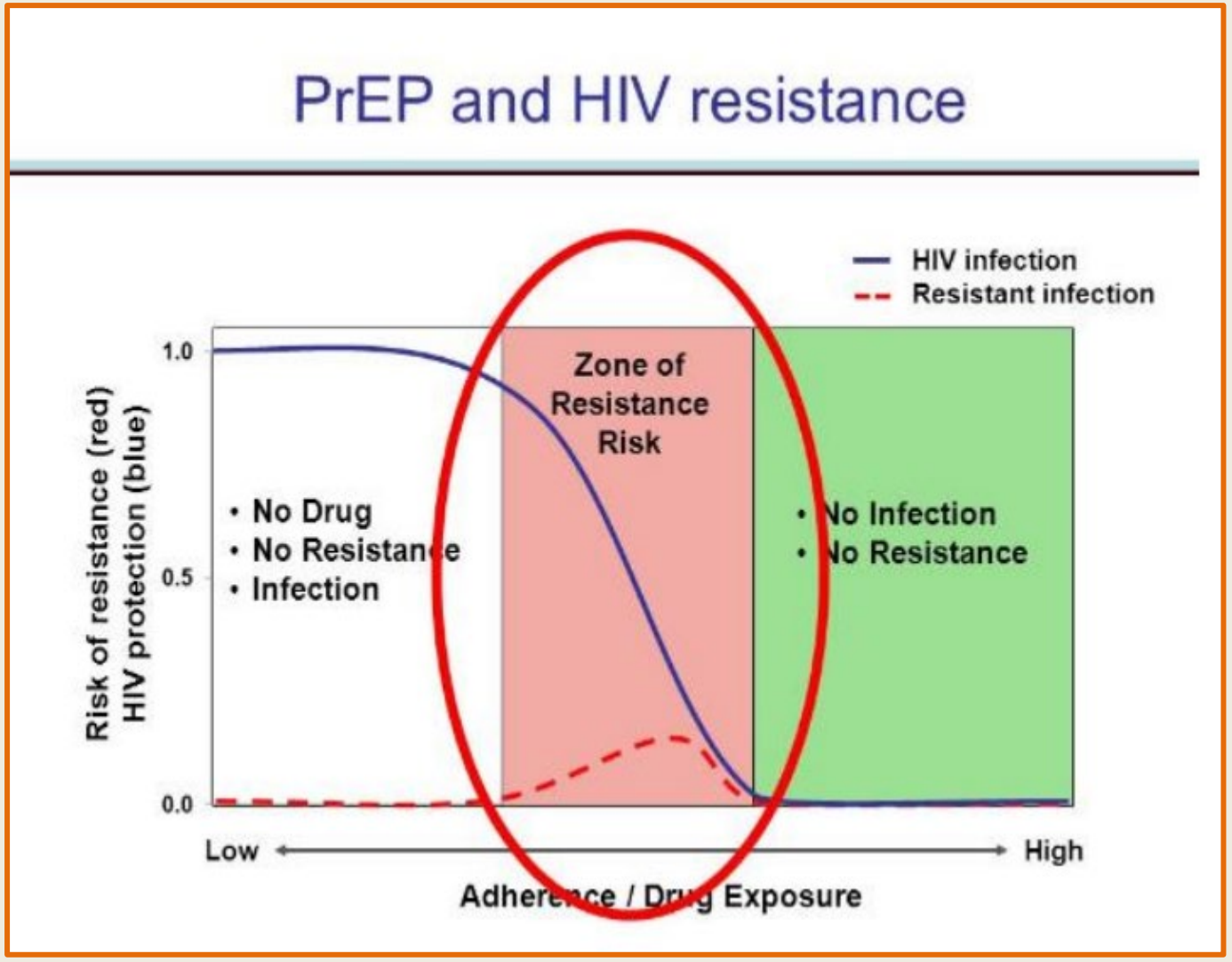
Table 7 Timing of CAB PrEP-associated Laboratory Tests

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

DISCONTINUING OR RESTARTING CAB PREP

- CAB level **slowly wane** over many months after injections are discontinued
- At some point during this **"tail" phase**,
  - CAB levels will fall bellow a protective threshold and persist for some time at non-protective levels, exposing the patient to the risk of HIV acquisition
  - These lower level of CAB may be sufficient to apply selective pressure that selects for viral strains with mutations that **confer resistance** to CAB or other INSTI medications
- CAB injections can be restarted at any point after determining HIV status with HIV-1 RNA testing



DISCONTINUING OR RESTARTING CAB PREP

When helping patients discontinue CAN PrEP safely, clinicians should:

- Re-educate patients about the "tail" and the risks during declining CAB levels
- Assess ongoing risk/indications
- Educate about nPeP
- Continue follow up visit quarterly for 12 months
- Conduct HIV-1 RNA tests at each quarterly follow-up visits after discontinuing CAB injections

CABOTEGRAVIR AND PREGNANCY

- In a study of 367 pregnancies has shown that overall, CAB-LA was safe and well tolerated

- **CAB-LA is safe prior to and during pregnancy.**

INJECTABLE PREP: LENACAPAVIR (LEN)/ YEZTUGO

EFFICACY OF LENACAPAVIR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons

Authors: Colleen F. Kelley, M.D., M.P.H. , Maribel Acevedo-Quiñones, M.D., Allison L. Agwu, M.D., Anchalee Avihingsanon, M.D., Ph.D., Paul Benson, D.O., Jill Blumenthal, M.D., Cynthia Brinson, M.D., +48 , for the PURPOSE 2 Study Team* Author Info & Affiliations

Published November 27, 2024 | N Engl J Med 2025;392:1261-1276 | DOI: 10.1056/NEJMoa2411858
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PURPOSE 1 Trial: Cisgender Women in Sub-Saharan Africa

PURPOSE 2 Trial: Cisgender Men, Transgender Men, Transgender Women, Gender Non-Binary individuals who have sex with partners whoa re assigned male at birth

- 96% reduction in the risk of acquiring HIV among study participants
- 99.9% of individuals using LEN did not acquire HIV
- 96% reduction in HIV incidence compared to background HIV incidence
- 89% more effective than daily oral TDF/FTC in preventing HIV acquisition.
- Lenacapavir was well tolerated, with no safety concerns identified

OVERVIEW OF LENACAPAVIR FOR PREP

- Antiretroviral medication
- **Mechanism:** Capsid Inhibitor

Protocol:

- Given **every 6 months**
- 2 **subcutaneous** injections given on the same visit in the abdomen.
- The **first visit:**
  - Taking 2 pills with the first set of injections
  - Followed by 2 more pills the following day.

Side Effects

- **Injection site reactions:**
  - Swelling, pain, redness, itching
  - Skin hardening, small mass or lump
    - Hardened skin or lumps at the injection site usually can be felt but not seen.
- Headaches
- Nausea

YEZTUGO: LAB AND CLINIC FOLLOW UP

Initiation Visit:

- HIV Ag/Ab Test
- HIV Viral RNA-PCR to rule out acute HIV Infection
- Hep. B Serology
- STI Screening
- ** Review oral-loading dose (day 0, day 1)**

Follow-Up Visits:

- Every 6 months for subq injections
- HIV Ag/Ab test
- *Consider every 3 months for STI screening

U = U

UNDETECTABLE = UNTRANSMITTABLE

Treatment as Prevention

PRINCIPLES OF U = U

- **Antiretroviral medication (ART)** can control HIV very effectively. They do not cure HIV or remove the virus form the body
- But, if ART is taken every day, as prescribed, HIV medicine reduces the amount of HIV in the body (**viral load**) to a very low level, which keeps the immune system working and prevents illness.
- This is called **viral suppression**—defined as having less than 200 copies of HIV per milliliter of blood. HIV medicine can even make the viral load so low that a test can't detect it.
- This is called an **undetectable viral load**.
- Getting and keeping an undetectable viral load is the best thing people with HIV can do to stay healthy.
- Another benefit of reducing the amount of virus in the body is that it prevents transmission to others through sex or syringe sharing, and from mother to child during pregnancy, birth, and breastfeeding. This is sometimes referred to as **Treatment as Prevention**.

U = U: EVIDENCE

Observational Data: 3 Discordant Couple Studies

	Partner 1	Partner 2	Opposites Attract
Number Of Couples	888	783	343
Risk	Heterosexual, MSM	MSM	MSM
# Condomless Sex Acts	58,000	77,000	17,000
# Unlinked Infections	11	15	3
# Linked Infections	**0**	**0**	**0**

Rodger et al, JAMA 2016;316:171-181
Bavinton et al, Lancet HIV 2018; 5(8) e438-e447
Rodger et al, IAS 2018; WEAX0104LB

CDC STATEMENT ON U = U

September 27, 2017

The US CDC sent out a “Dear Colleague” letter stating:

“…. people who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively NO RISK of sexually transmitting the virus to an HIV-negative partner.”

PEP: HIV POST-EXPOSURE PROPHYLAXIS

OPEP (OCCUPATIONAL) VS. NPEP (NON-OCCUPATIONAL)

oPeP

- Post exposure prophylaxis (**PEP**) for HIV was first studied in **occupational** settings (e.g. needlesticks)

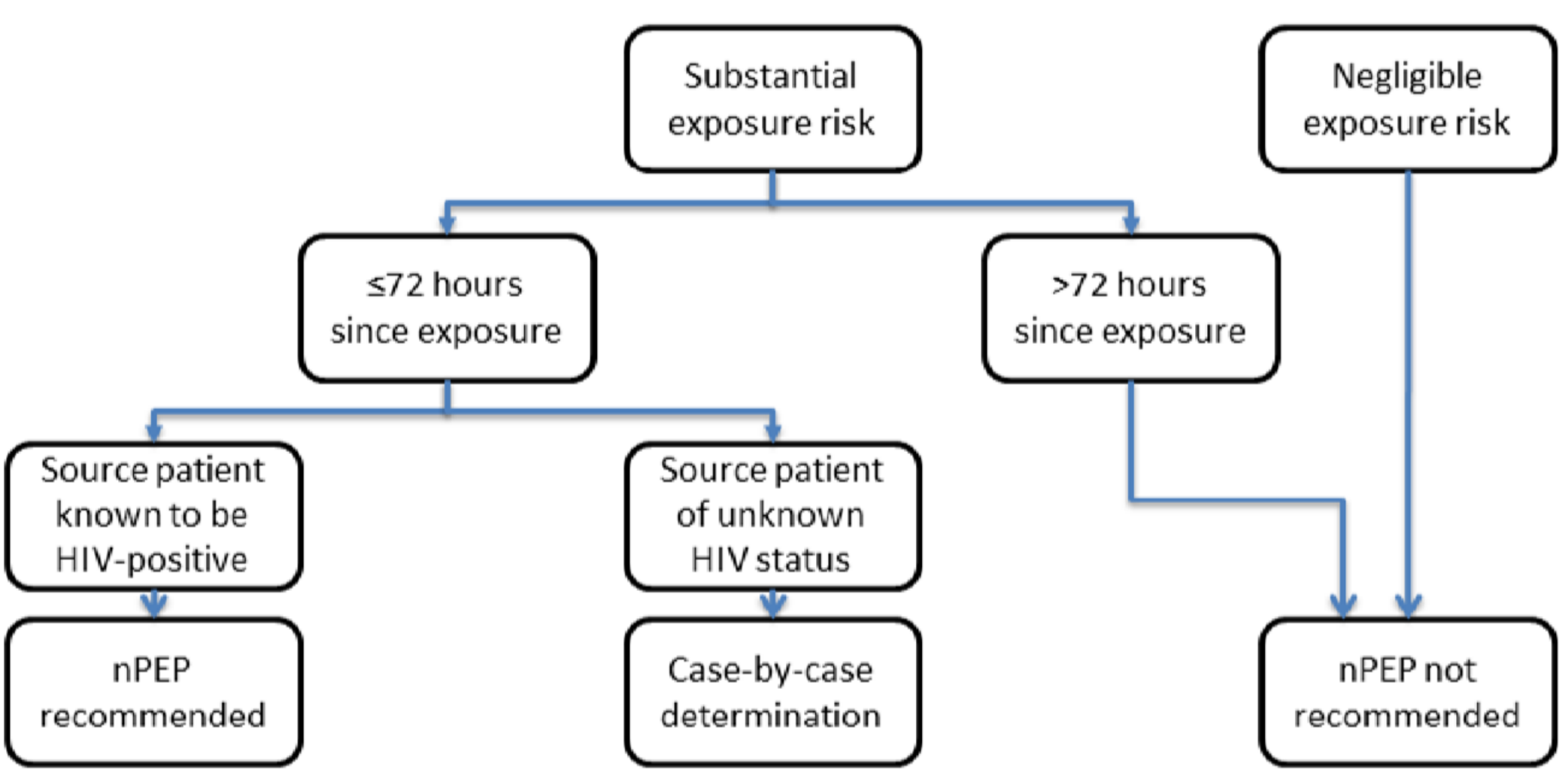
nPeP

- When a person is given PEP after a *non-occupational exposure*, such as through sexual or needle-sharing exposures, this is called **non-occupational PEP (nPEP)**

NPEP EFFICACY

- No randomized, placebo-controlled clinical trial of nPEP has been conducted
- Observational research suggests that PEP can **reduce the risk of getting HIV by more than 80%**, which means some people in the studies acquired HIV despite taking PEP.
- **PeP does not prevent 100%** of HIV infections but it is very effective at preventing HIV if used consistently and correctly.

INDICATIONS FOR NPEP



CDC *Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States 2016*

SUBSTANTIAL AND NEGLGIBILE RISK FOR HIV ACQUISITION

Substantial Risk

Substantial Risk for HIV Acquisition

Exposure of
vagina, rectum, eye, mouth,
or other mucous membrane,
nonintact skin, or percutaneous contact

With
blood, semen, vaginal secretions, rectal
secretions, breast milk, or any body fluid
that is visibly contaminated with blood

When
the source is known to be HIV-positive

Negligible Risk

Negligible Risk for HIV Acquisition

Exposure of
vagina, rectum, eye, mouth,
or other mucous membrane,
intact or nonintact skin,
or percutaneous contact

With
urine, nasal secretions, saliva, sweat,
or tears if not visibly contaminated
with blood

Regardless
of the known or suspected HIV status
of the source

CDC: *Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States ;2016*

HIV ACQUISITION RISK FROM THE EXPOSURE

Exposure type	Rate for HIV acquisition per 10,000 exposures
Parenteral	
Blood transfusion	9,250
Needle sharing during injection drug use	63
Percutaneous (needlestick)	23
Sexual	
Receptive anal intercourse	138
Receptive penile-vaginal intercourse	8
Insertive anal intercourse	11
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	Low
Insertive oral intercourse	Low
Other[b]	
Biting	Negligible
Spitting	Negligible
Throwing body fluids (including semen or saliva)	Negligible
Sharing sex toys	Negligible

http://www.cdc.gov/hiv/policies/law/risk.html

REGIMENS USED FOR NPEP

- 3 drug regimen for **28 day**
- Must be given **within 72 hours** of exposure

Preferred Regimen (adults and adolescent >12):
Integrase strand transfer inhibitors PLUS two nucleoside reverse transcriptase inhibitors:

- Bictegravir/emtricitabine/tenofovir alafenamide OR
- Dolutegravir PLUS (tenofovir alafenamide OR tenofovir disoproxil fumarate) PLUS (emtricitabine OR lamivudine)

Additional alternative regimens available for children <13 & persons with renal impairment

NPEP: SCHEDULE OF LABS AND FOLLOW-UP

Time Point	HIV Testing	Other Labs
Initial Visit	HIV Ag/Ab	• Kidney Function (serum creatinine) • Hep. B Serology • Hep. C Ab • STI Screening • Pregnancy Test
4-6 weeks follow-up Visit ** Transition to PrEP**	HIV Ag/Ab	
12-week follow- up Visit	HIV Ag/Ab	

THANK YOU!