Scientific Story for Women and PrEP

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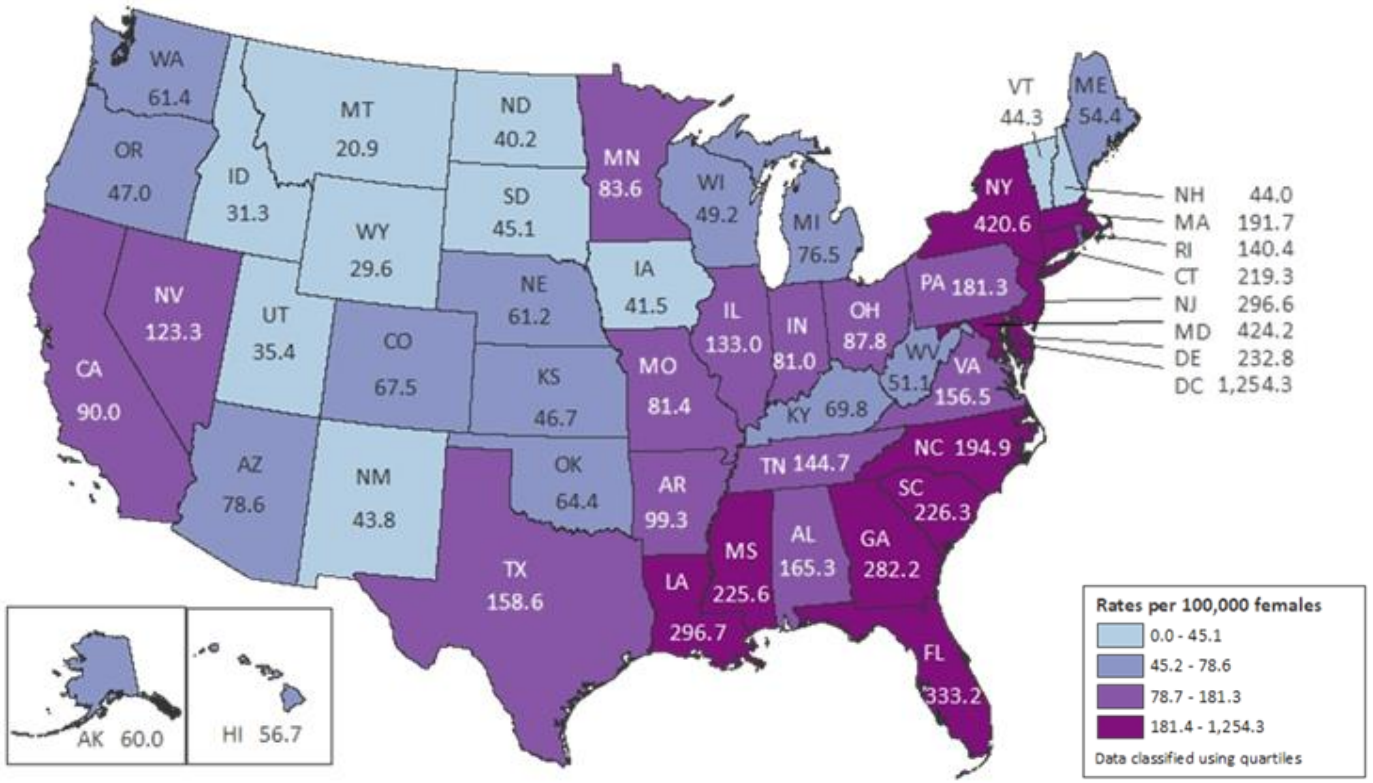
Case Study:
US Women and PrEP Epidemiology

Rates of **Female** Adults and Adolescents Living with HIV (Prevalence)

N = 240,306
Total Rate = 171.6



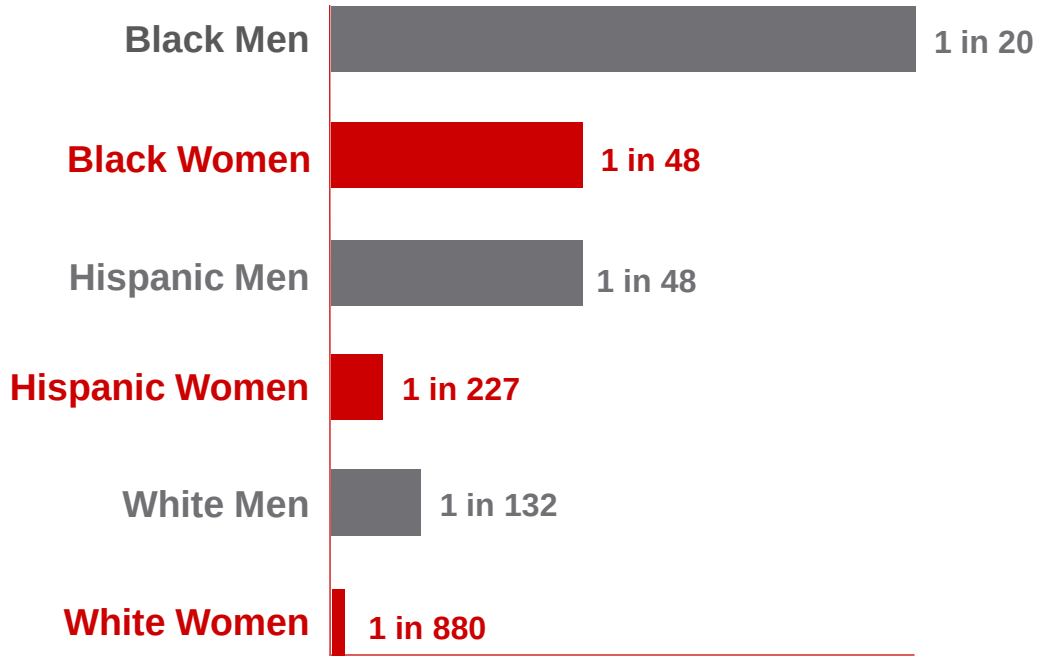
Rates per Jurisdiction, 2017

Location	Prevalence Overall (CDC)	Highest Prevalence ZIP Code within Jurisdiction (AIDSVU)
National	**171.6**	**---**
DC	1254.3	3312.0
MD	424.2	2,515.0
NY	420.6	2,784.0
FL	333.2	3,906.0
PR	324	3,614
LA	296.7	2,344.0
NJ	296.6	2,901.0
GA	282.2	2,129.2
SC	226.3	1,159.0

https://map.aidsvu.org/ Accessed May 2019

Lifetime Risk of HIV Diagnosis in the US

Lifetime risk of HIV diagnosis projections based on diagnoses and death rates from 2009-2013

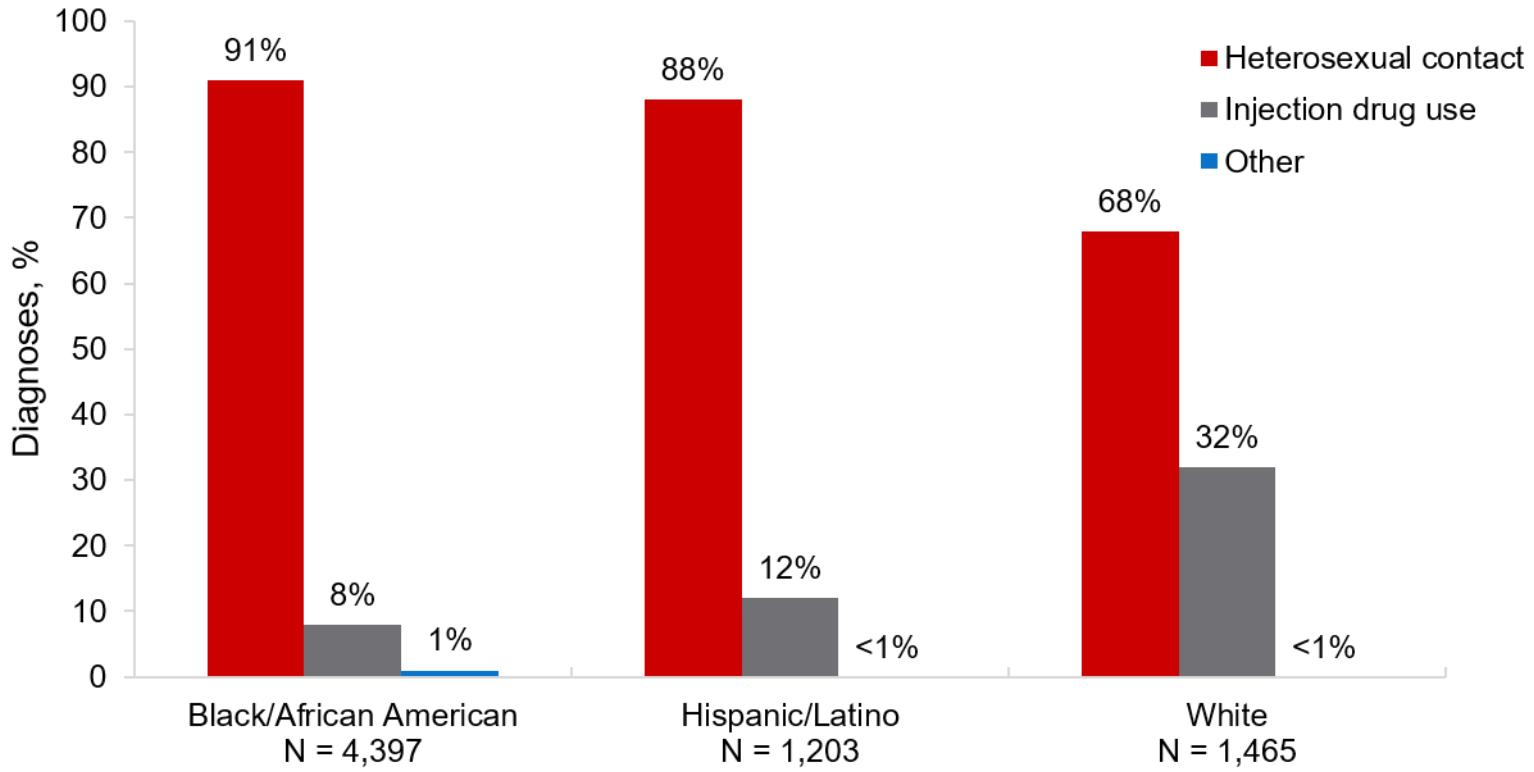


While lifetime risk of an HIV diagnosis in the US is 1 in 99 overall, African Americans have a much higher lifetime risk than Whites.

http://www.cdc.gov/nchhstp/newsroom/2016/croi-2016.html#Graphics. Accessed April 2018.

Diagnoses in **Females** Varies by Race/Ethnicity and Transmission Category

Diagnoses of HIV Infection among Female Adults and Adolescents, by Race/Ethnicity and Transmission Category, 2017—United States and 6 Dependent Areas



Note. Data for the year 2017 are considered preliminary and based on 6 months reporting delay. Data have been statistically adjusted to account for missing transmission category.

[a] Hispanics/Latinos can be of any race.

[b] Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

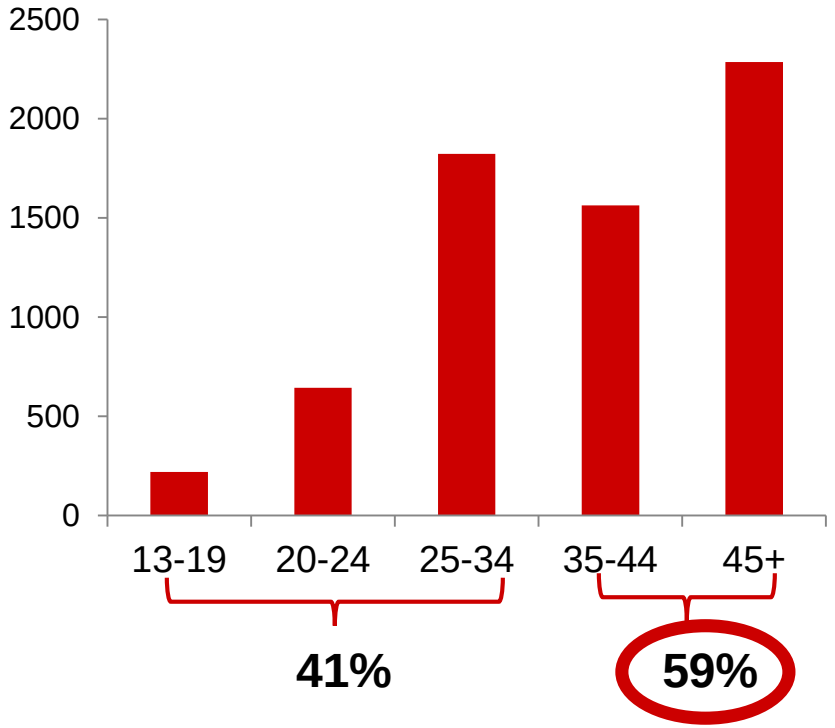
[c] Includes blood transfusion, perinatal exposure, and risk factor not reported or not identified.

Adapted from CDC HIV Surveillance Data - 2017

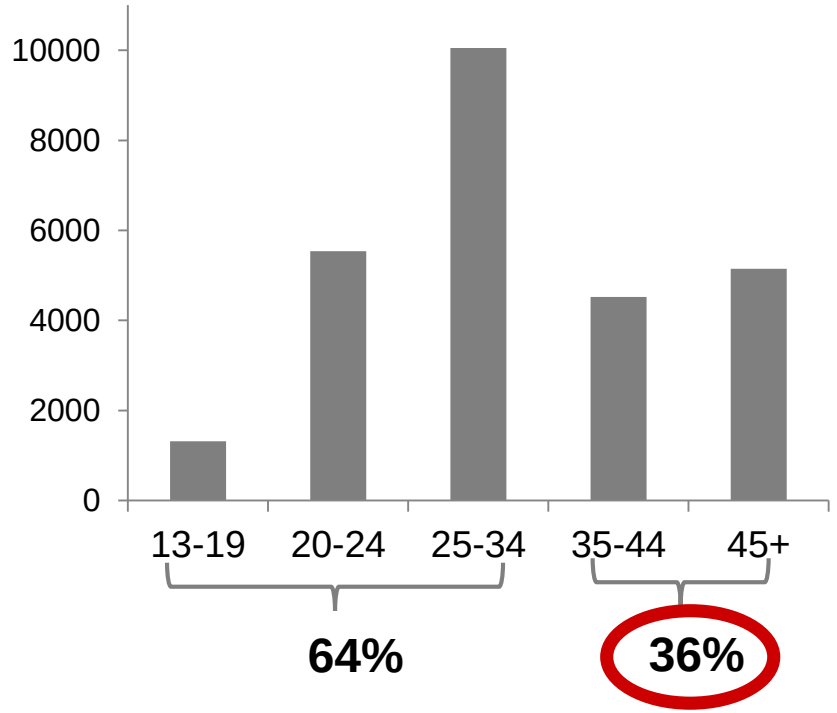
Age at Diagnosis Varies by Gender

Age of diagnoses of HIV infection among female and male adults and adolescents in the United States based on CDC HIV surveillance data, 2016

Diagnoses of HIV infection Attributed to Heterosexual contact[a] in Women, by Age, 2016 – United States



Diagnoses of HIV infection Among MSM, by Age, 2016 – United States



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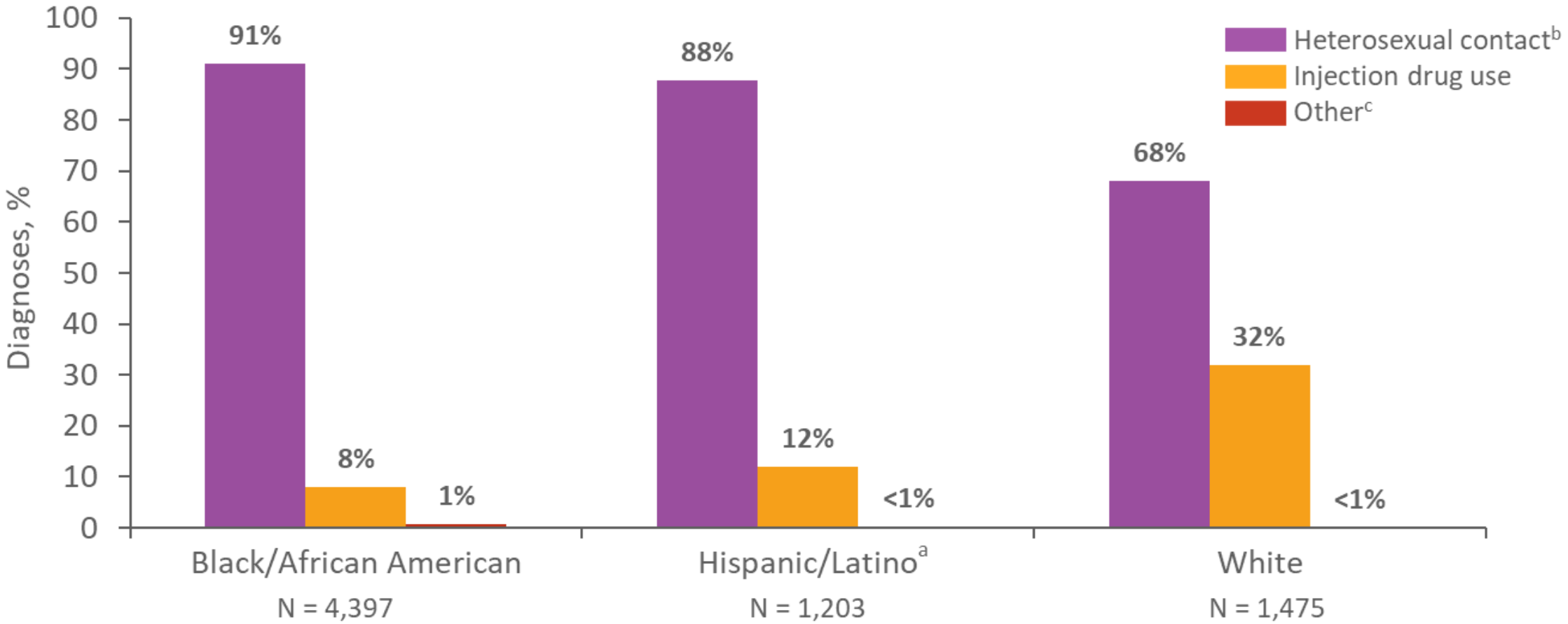
Centers for Disease Control and Prevention (CDC)

Diagnoses of HIV Infection among Female Adults and Adolescents, by Race/Ethnicity and Transmission Category, 2017—United States and 6 Dependent Areas



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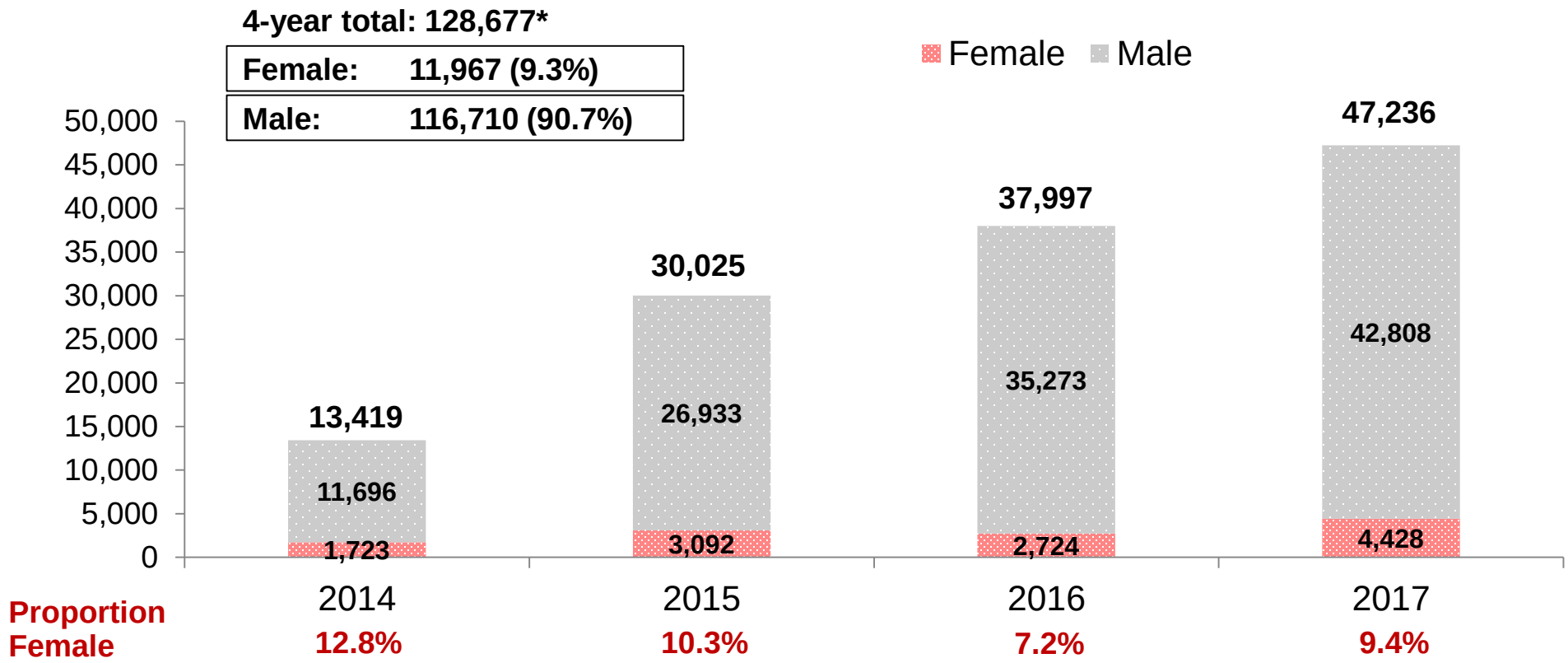
New PrEP Starts per Year, by Gender Marker

Analysis of pharmacy claims data to assess FTC/TDF for PrEP uptake trends in the U.S. between 2014-2017 (N=158,183)



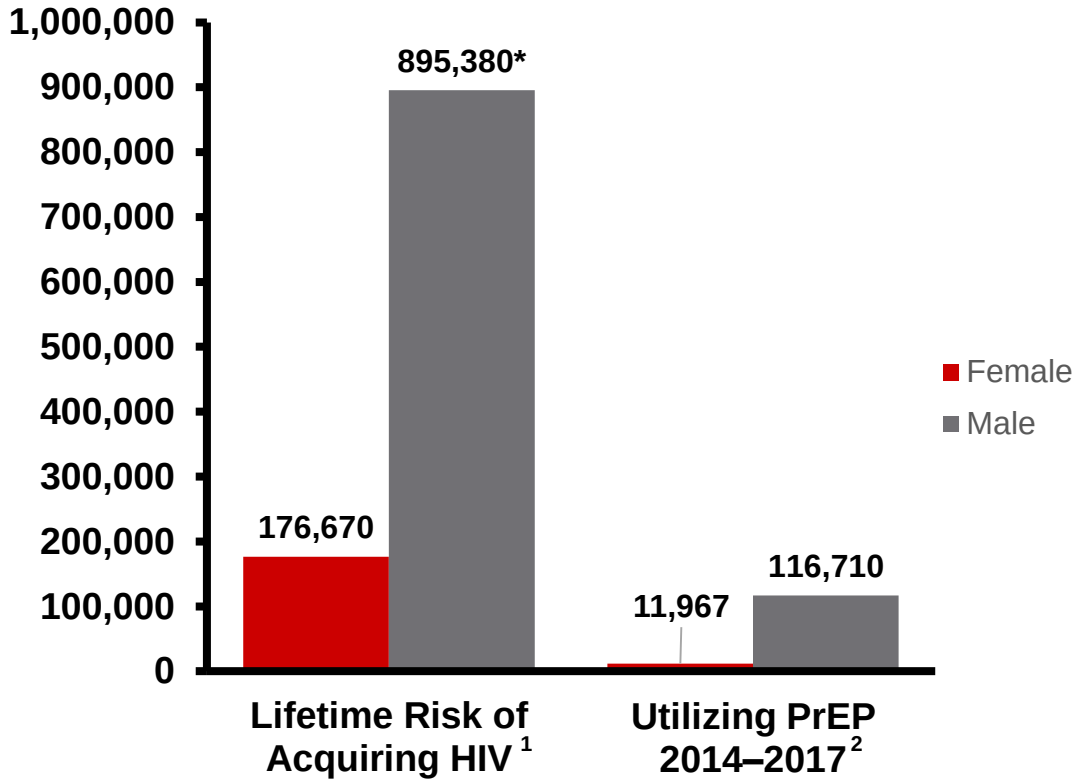
Between 2014-2017, the number of new PrEP starts among females increased 2.6 fold, however the proportion of females starting PrEP remained low

*Gender data were only available for 128,677 individuals

Nguyen C, et al. IAS 2019. Mexico City, Mexico. Poster #TUPEC405

Women and PrEP

- 93% of HIV-negative women reported having vaginal sex without a condom in the previous year
- 26% reported having anal sex without a condom
- Of the >170,000 women at risk, only 0.07% have started F/TDF for PrEP



Women make up an important part of the population for controlling HIV infections and are under represented in their low use of PrEP

[1]Smith D, et al. MMWR Morb Mortal Wkly Rep 2015;64:1-6;
[2]Nguyen C, et al. IAS 2019. Mexico City, Mexico. Poster #TUPEC405
Huang YA et al. MMWR October 19, 2018 / 67(41);1147–1150. Mera, R. et al. AIDS 2016. Durban, South Africa. Oral #TUAX0105LB
*Data includes MSM and HET men

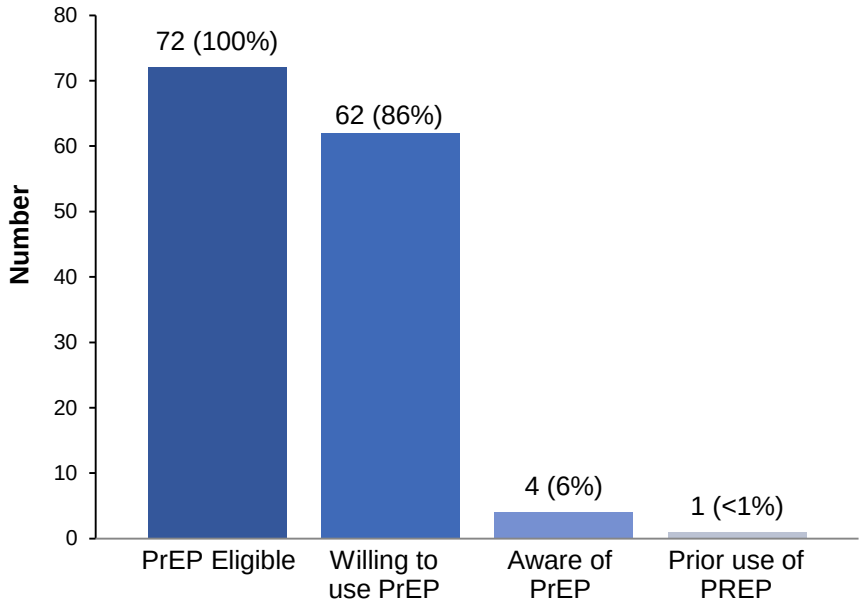
Predictors of PrEP Eligibility Among At-Risk Women

Longitudinal cohort using HIV-negative women eligible for enrollment in the 5 WIHS sites in the Southern U.S. (N=225)

- WIHS sites: Miami, FL; Chapel Hill, NC; Birmingham, AL; Atlanta, GA; Jackson, MS
- Nearly 1/3 of participants were eligible for PrEP based on adapted 2014 CDC PrEP clinical practice guidelines
- Factors associated with PrEP eligibility:

Education ≤ high school	AOR 2.56 (95% CI: 1.22-5.37)
Experienced **sexual violence** since last semiannual visit	AOR 4.52 (95% CI: 1.52-17.76)
Medium to high self-perception of HIV risk	AOR 6.76 (95% CI 3.26-14.05)

Continuum of PrEP willingness, awareness and use among PrEP eligible WIHS participants in the Southern US

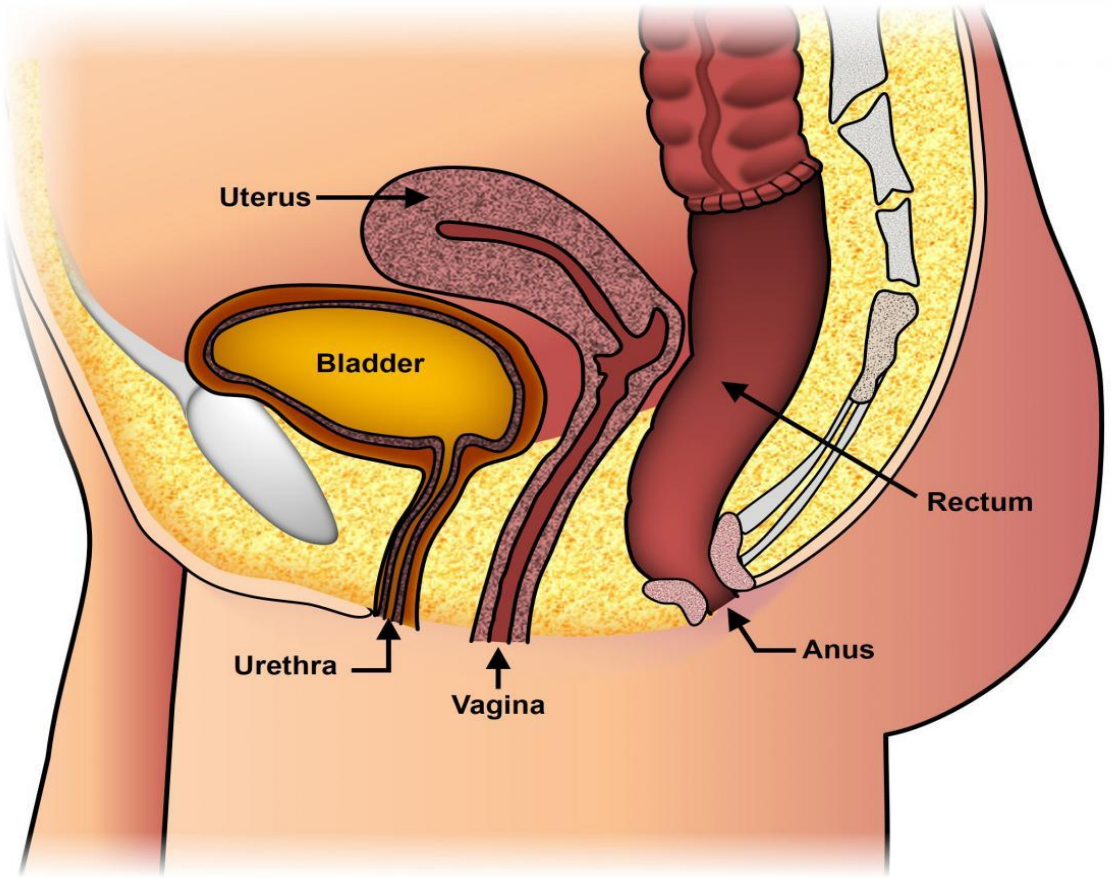


Extremely low awareness of PrEP despite high acceptability signifies a critical need to enhance PrEP education, screening, and uptake for at-risk women in the Southern U.S.

Patel A, et al. CROI 2018, Boston, MA. Poster #1048.

HIV Risk Factors

Female Genital Tract Anatomy May Contribute to HIV risk in Cis-Women

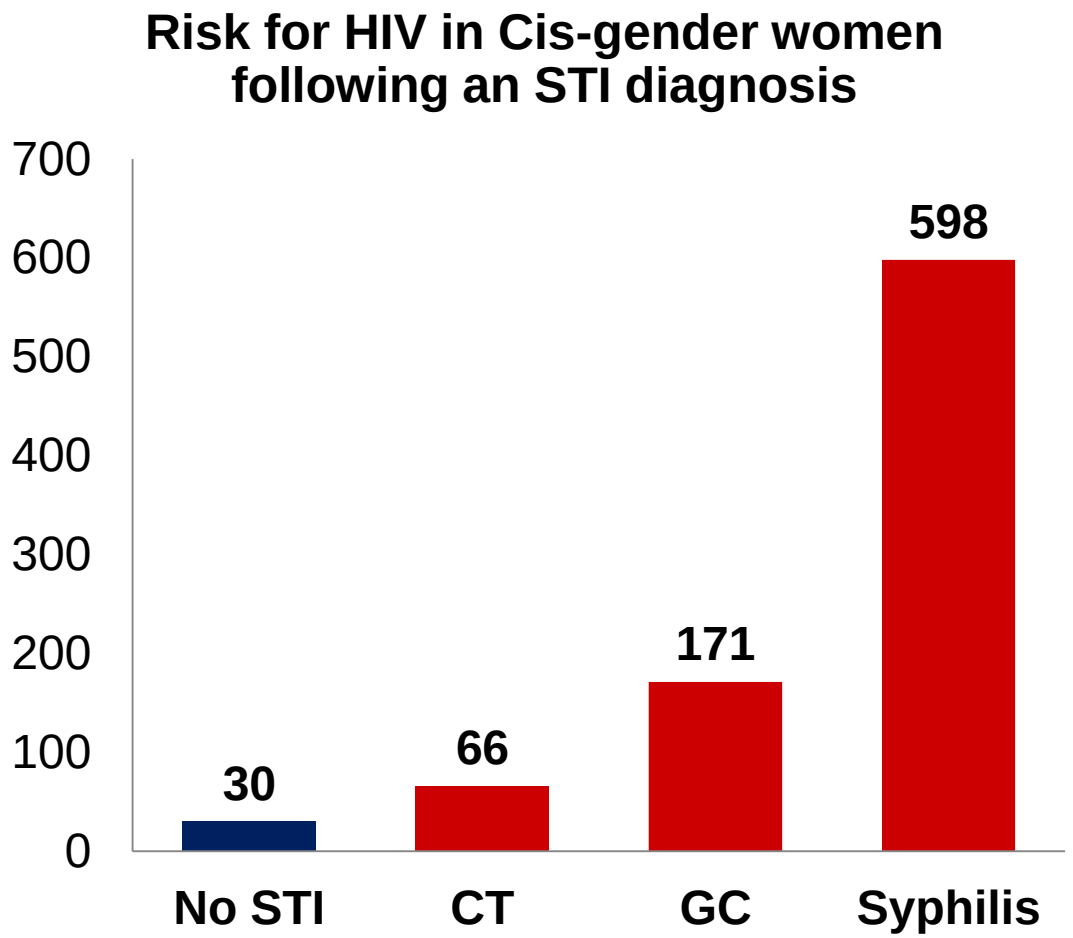


Florida

Risk for HIV in Cis Women Following a Diagnosis of Syphilis, Gonorrhea or Chlamydia

N=328,456 cis-women in Florida, 2000–2011

- **After having an STI, the rate of being diagnosed with HIV infection was 95/100,000 py**
  - 3.2 X the rate for other women in the same age range in Florida
  - 10 X the rate for women of all ages in the United States
- **Rates were highest for:**
  - Black women
  - Women with syphilis or gonorrhea
  - Older women
- **Black women aged 30–59 years living in high-risk areas and had syphilis HIV diagnosis rate- 1625.3/100,000 py**



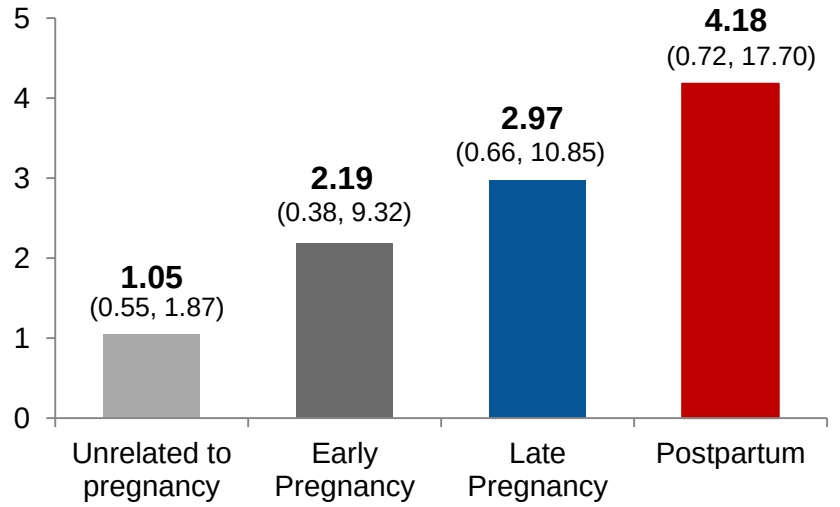
Peterman, T et al. International Journal of STD & AIDS 2015, Vol. 26(2) 113–119
Solomon, CID 2014

Female HIV Acquisition per Sex Act in Late Pregnancy and Post-Partum

Retrospective analysis of two studies* of African, HIV-uninfected women with male partners living with HIV and not on ARVs (N=2751)

Reproductive Stage	HIV incidence per 100 person years (95% CI, n = 78 new HIV infections)
Overall	1.62 (1.29, 2.01)
During non-pregnant/non-postpartum time	**1.25** (0.95, 1.62)
During early pregnancy through postpartum	5.37 (3.44, 7.99)
During early pregnancy	3.75 (1.22, 8.75)
During late pregnancy	**7.02** (3.74, 12.01)
During postpartum	4.68 (1.72. 10.18)

Modeled HIV infectivity per 1,000 sex acts (95% CI)*



*Calculated using a reference case of a 25-year old woman not pregnant, not using PrEP, with a partner with viral load of 10,000 copies/mL

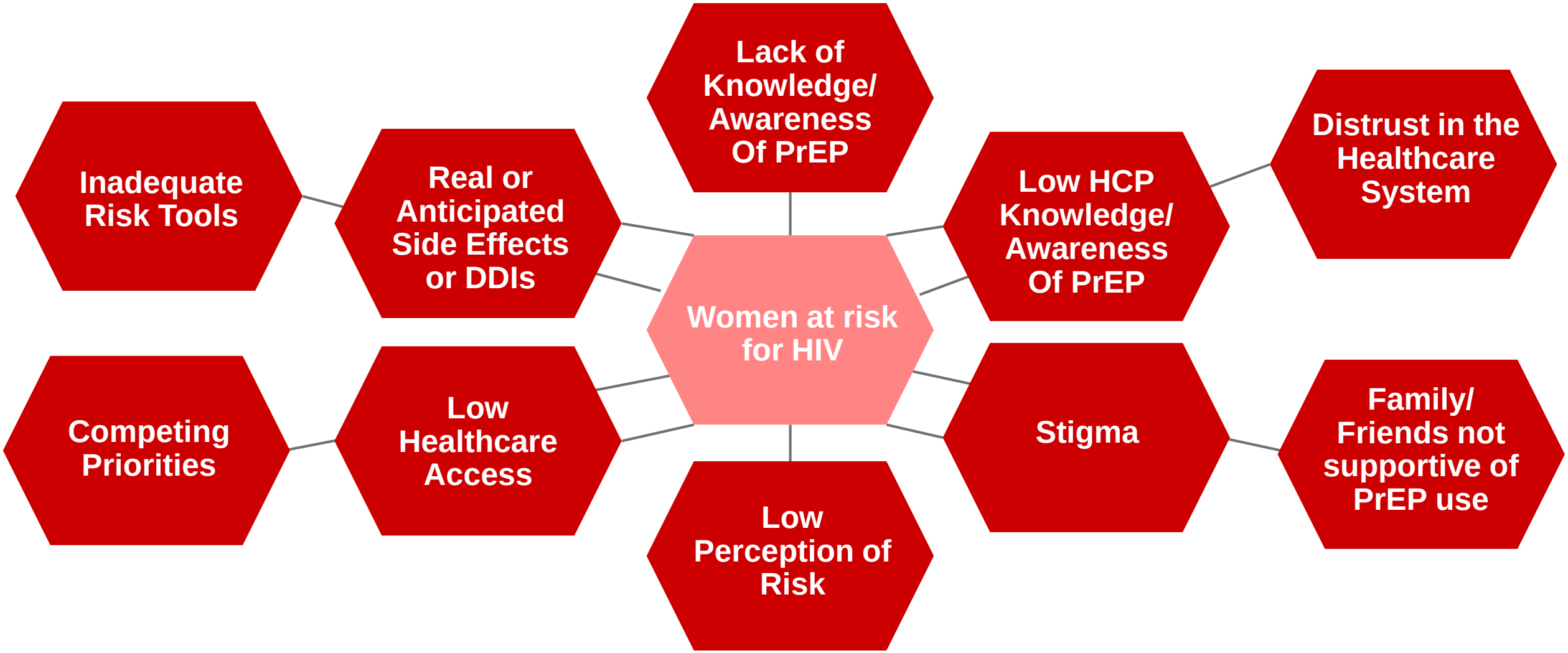
HIV risk is increased in pregnant women for later phases of pregnancy, even when adjusted for condom use, reproductive stage, age, PrEP use, and partner viral load

*Partners in Prevention HIV/HSV Transmission Study, (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia), 2004-2007; and Partners PrEP Study (Kenya, Uganda), 2008-2012

Thomson K, et al. CROI 2018. Boston, MA. Oral #45

Barriers to PrEP

Barriers to PrEP that Particularly Affect Cisgender Women?



Current CDC PrEP Guidelines Disqualify Many At-Risk and PrEP-Motivated Women

Online survey of cis- and transgender women ≥18 y.o. to determine the proportions with HIV risk factors and subjective motivation to use PrEP who would be deemed eligible according to current CDC criteria (N=679)

Summary of Guidance for PrEP Use

Heterosexual Women and Men
HIV-positive sexual partners
Recent bacterial STI
High number of sex partners
History of inconsistent or no condom use
Commercial sex work
In high HIV prevalence area or network

Recommended Indications for PrEP Use by Heterosexually Active Men and Women

- Adult person
- Without acute or established HIV infection
- Any sex with opposite sex partners in past 6 months
- Not in a monogamous partnership with a recently tested HIV-negative partner

AND at least one of the following

- Is a man who has sex with both women and men (behaviorally bisexual)
- **Infrequently uses condoms during sex with 1 or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (PWID or bisexual male partner)**
- **Is in an ongoing sexual relationship with an HIV-positive partner**
- **A bacterial STI (syphilis, gonorrhea in women or men) diagnosed or reported in past 6 months**

To qualify, women need to know their own sexual behavior and health as well as her partner's HIV risk behavior, know his HIV status, or recognize an STI

STI: Sexually Transmitted Infections

Calabrese SK, et al. IAPAC Adherence 2018. Oral abstract #23.

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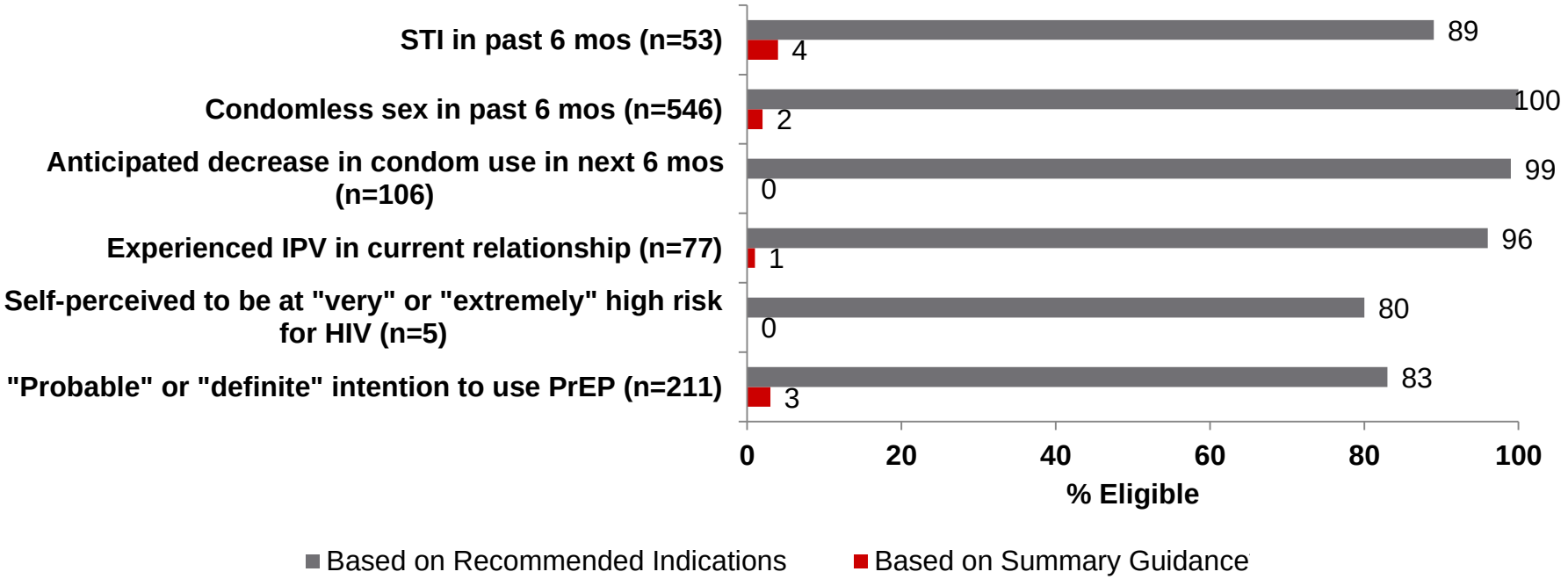


Current CDC PrEP eligibility criteria disqualify many women who are at risk for HIV, motivated to use PrEP, or both, and may deter providers from prescribing or discussing PrEP with their patients.

STI: Sexually Transmitted Infections, IPV: Intimate partner violence

Calabrese SK, et al. IAPAC Adherence 2018. Oral abstract #23.

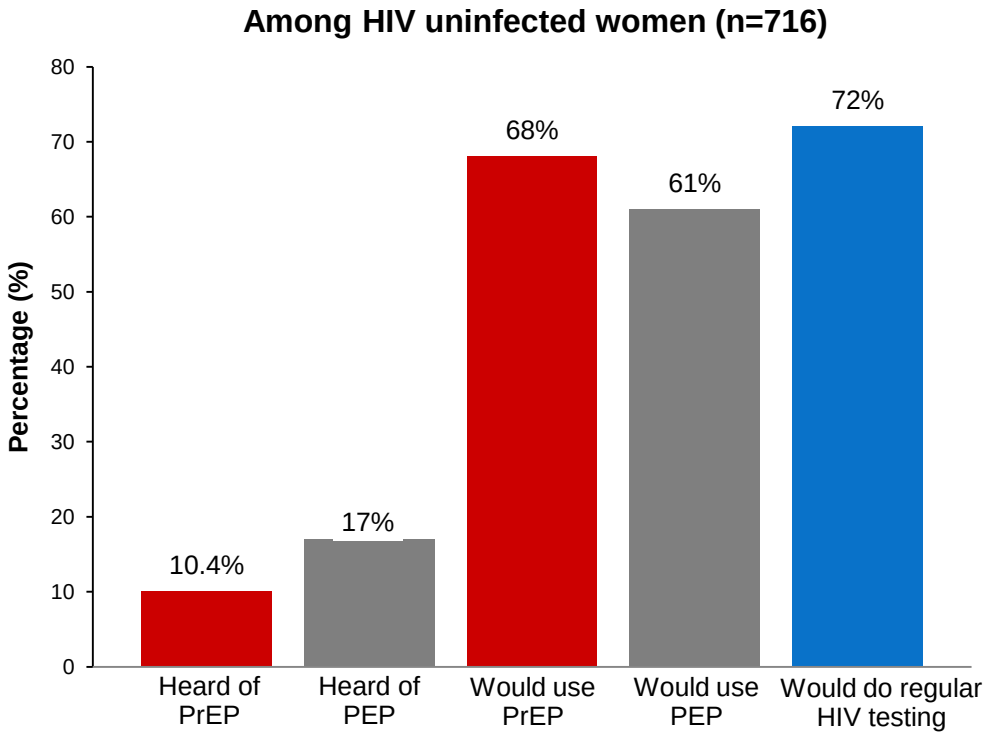
Women's Interagency HIV Study (WIHS)

HIV Biomedical Prevention Knowledge, Attitudes, and Behavior Among U.S. Women

Cross sectional survey among women enrolled in WIHS (HIV-infected and HIV-uninfected) to assess PEP, PrEP, and TasP knowledge, attitudes, and behavior, 2014-2015, (N=2406)

Reasons for taking daily PrEP	%
"Protecting myself"	83
Distrust of partners	46
Having a casual partner	40
Recommended by HCP	30
Having an HIV+ partner	26

Factors associated with willingness to use PrEP	Odds Ratio (95% CI)	P-value
Younger age	0.95 (0.92-0.98)	0.001
Believes PrEP will prevent HIV	**7.53 (2.02-28.13)**	0.0027
Willingness to recommend PrEP to others	**40 (21.28-76.92)**	<0.001

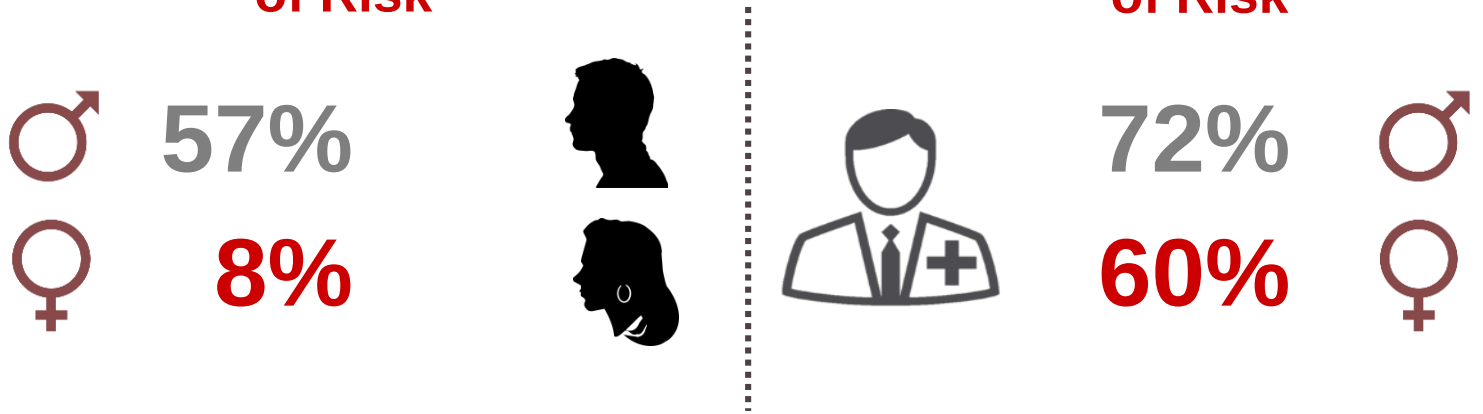


Active engagement of HCPs, policy makers, and multimedia mass campaigns will be needed for successful implementation of PrEP for women.

Kassaye S, et al. CROI 2018, Boston, MA. Poster #1050.

Self Perception of HIV Risk Is Low in At-Risk Populations

Persons undergoing HIV rapid testing in Philadelphia surveyed between May 2012 and December 2014 (N=5606; >90% African American)



A large proportion of patients at moderate or high risk for HIV infection, especially women, do not perceive themselves to be at high risk.

a. Perceived high/moderate risk of HIV infection.

Kwakwa, H. et al. *AIDS Behav.* 2016;20:1443-1450.

Considerations for PrEP Trials

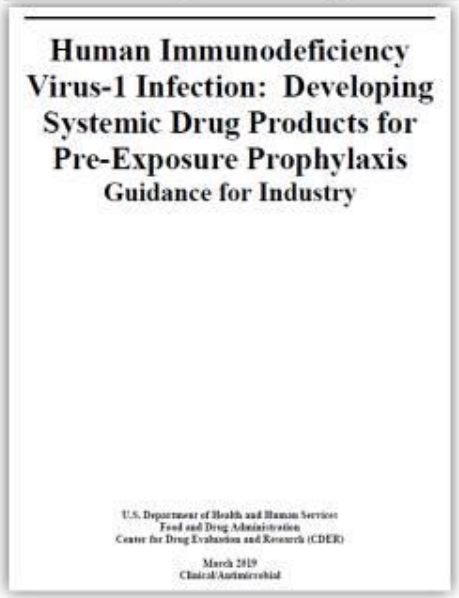
Designing a Prevention Study with the FDA

	MSM and TGW	Ciswomen	Comments
1. **Calculation of Efficacy**			
• Versus Placebo	UNETHICAL		
• Calculated rate from F/TDF for PrEP trials	noninferiority (NI) margin <1.62	Inability to achieve consensus on TVD for PrEP treatment effect in women	Unlike DISCOVER which pooled treatment effects from 3 RCTs with similar efficacy in MSMs, the 5 RCTs in women lacked a consistent treatment effect from which an appropriate non-inferiority margin could be constructed.

FDA and GS worked together to try to create a women's trial for D4P, but non-inferiority margin calculation and study design presented challenges.

FDA PrEP Trial Guidance

Trial Design for High-Risk Women



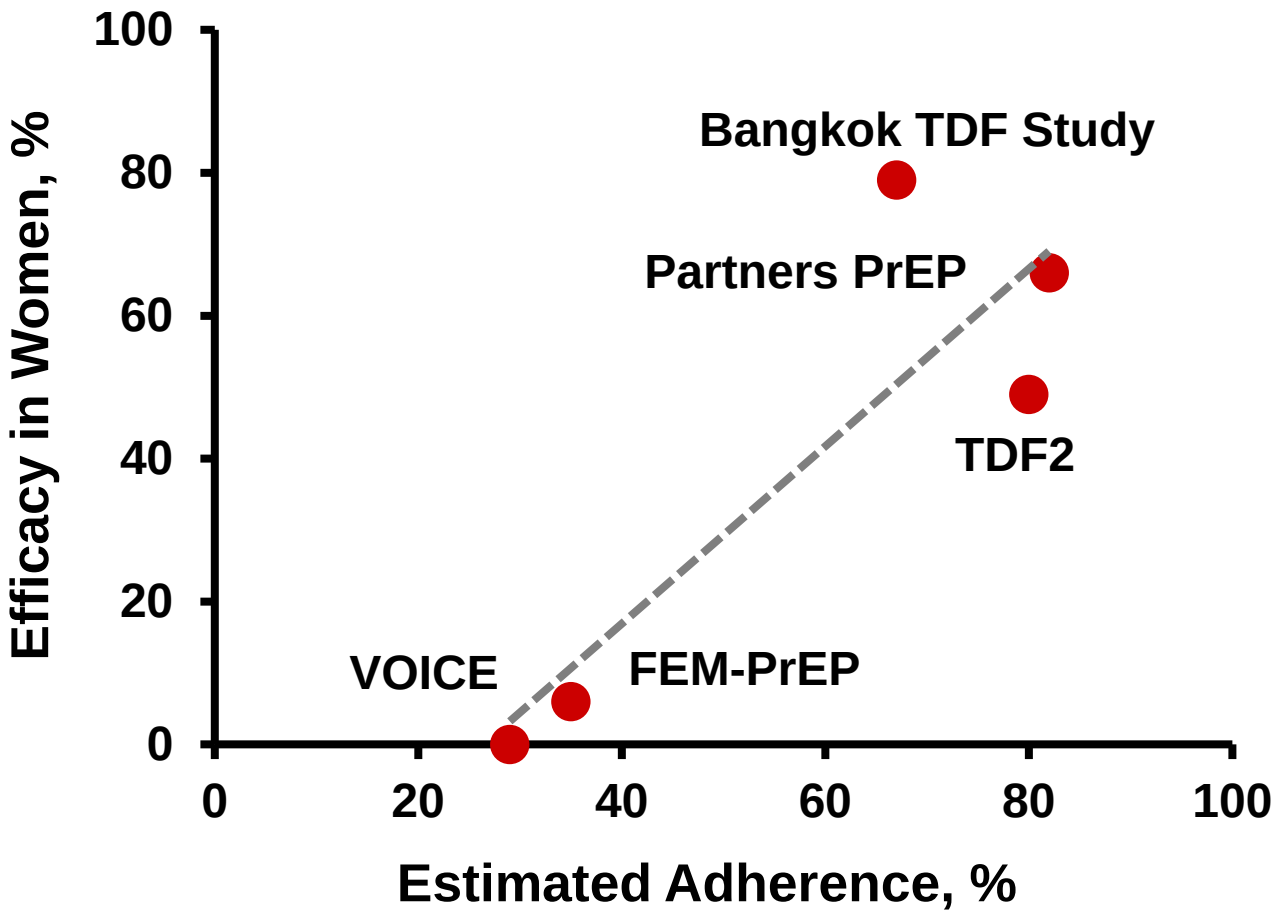
"Trials in high-risk women. FDA recommends superiority designs because determination of an NI margin is difficult or impossible in this population because of the variable historical evidence of HIV prevention efficacy in at-risk women."

1. U.S. Food and Drug Administration, March 2019. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-immunodeficiency-virus-1-infection-developing-systemic-drug-products-pre-exposure-prophylaxis

BU-1304

Gilead is currently working with the FDA to create a novel trial design and to identify sites in Africa that can enroll women at risk of HIV infection (with quantifying background incidence of at least 3-4/100 PY

Efficacy of F/TDF for PrEP in Women



- Partners PrEP and TDF2 reflected efficacy in women when adherence was comparable to other studies
- VOICE and FEM-PrEP showed poor efficacy when adherence was equally deficient

- Baeten J et al. HIV Research for Prevention Conference, Madrid, October 2018.

Efficacy Results From Pre-Approval PrEP Clinical Trials in Women Showed Mixed Efficacy Based on Adherence

Study	Population	Number	Drug	mITT [a] efficacy of % reduction in acquisition of HIV infection [a]	Adherence-adjusted efficacy based on TDF detection in blood [b]
				%	%
Partners PrEP	Heterosexual serodiscordant couples	4747	TDF	67	**86**
			TVD[c]	75	**90**
TDF 2	Heterosexually active men and women	1200	TVD[c]	62	**84**
Bangkok Tenofovir Study	IV Drug Users	2413	TDF	49	**74**
Fem-PrEP	Heterosexually active women	1951	TVD[c]	6[d]	**< 40%**
VOICE	Heterosexually active women	5029	TVD[c]	- 4[d]	**<30%**

Low Adherence = Low efficacy

a. Modified Intent to Treat
b. Excluded only those enrolled patients later found to be infected at randomization and those with no follow-up visit or HIV test
c. TVD = FTC/TDF
d. Not statistically significant

US Public Health Services. Preexposure Prophylaxis For The Prevention of HIV Infection In The United States, 2017. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

Designing a Prevention Study with the FDA

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• Calculated rate from F/TDF for PrEP trials	noninferiority (NI) margin <1.62	Inability to achieve consensus on TVD PrEP treatment effect in women	Unlike DISCOVER which pooled treatment effects from 3 RCTs with similar efficacy in MSMs, the 5 RCTs in women lacked a consistent treatment effect from which an appropriate non-inferiority margin could be constructed.
2. Even if non-inferiority margin was calculated**, Size of Trial** was an obstacle	~5,000 MSM and TGW	Very large	• In serodiscordant couples, TasP required • HIV incidence is 13-fold lower for US women compared with MSM at high risk for HIV • In the US : over 500,000 women would be required • Outside the US: over 20,000-30,000 would be required • It would take 8–10 years to conduct

Considerations for use of PrEP in Pregnancy

Prevention Considerations

- Increased risk of HIV-1 infection in women during pregnancy
- Increased risk of MTCT during acute HIV-1 infection

Risks and Benefits to Mother and Child[1]

- Developmental and health benefits of breastfeeding
- Maternal HIV risk and need for HIV-1 PrEP
- Potential adverse effects on the breastfed child
- Risk of HIV-1 acquisition due to nonadherence and subsequent MTCT

In women at risk of acquiring HIV-1, considerations should be given to methods to prevent acquisition of HIV, including continuing or initiating PrEP, during pregnancy.

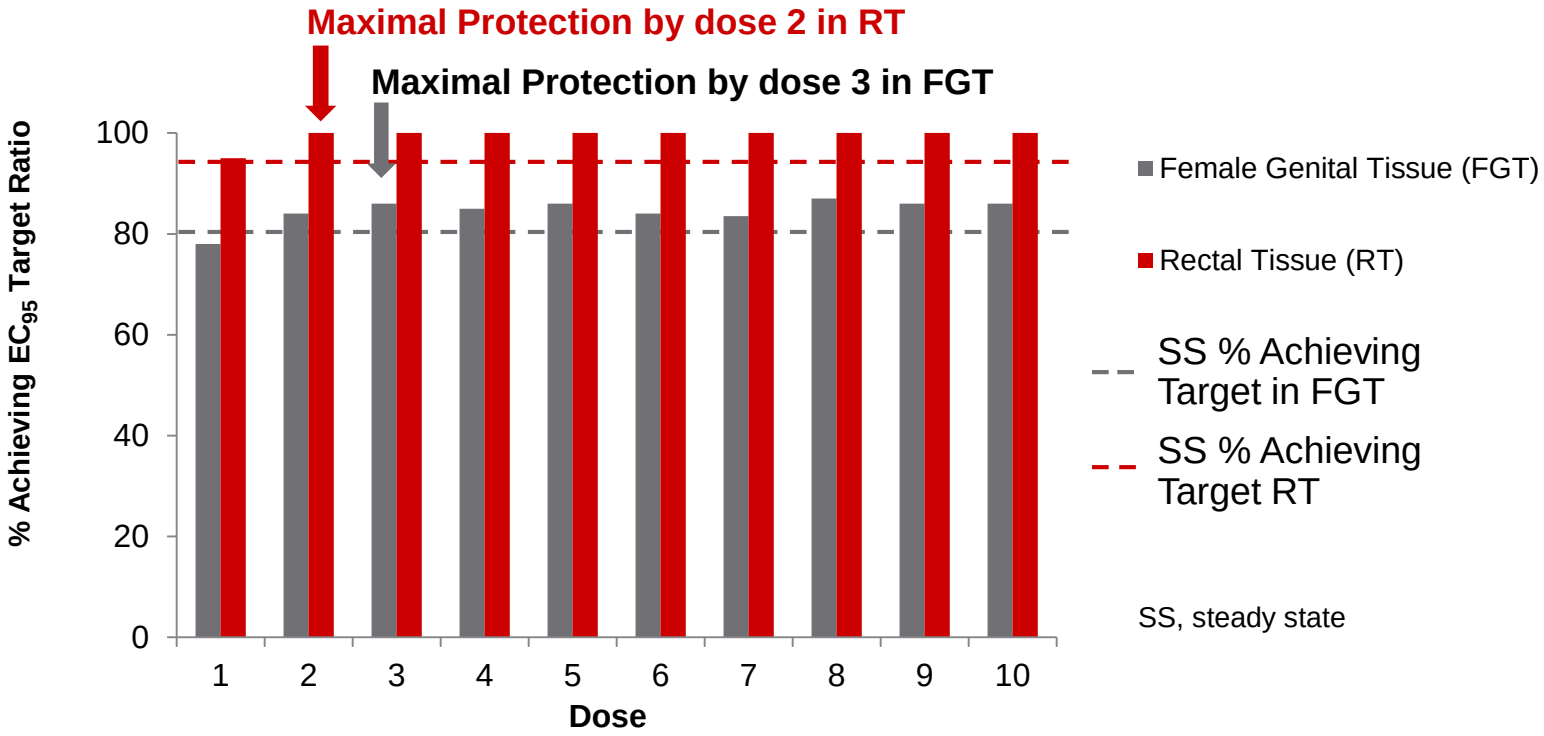
Providers should discuss current evidence about the potential risks and benefits of beginning or continuing PrEP during breastfeeding so that an informed decision can be made[2]

USPHS. PrEP for the prevention of HIV infection in the United States–2017. https://www.cdc.gov/hiv/pdf/guidelines/cdc-hiv-PrEPguidelines-2017.pdf

Next Steps

Time to Protection with Daily Dosing of FTC/TDF

WHO recommends additional HIV prevention measures should be used for 7 days after starting daily PrEP[1]



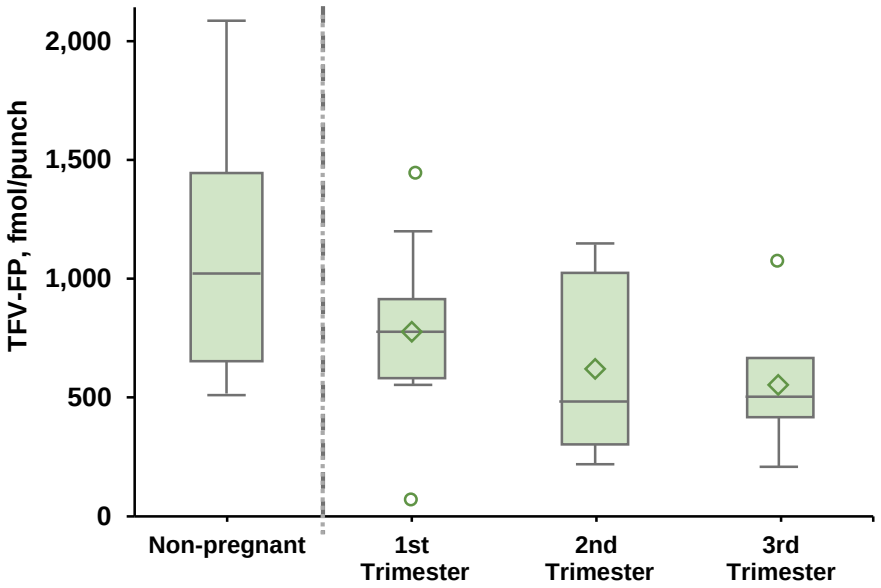
Target ratios have been defined for TFV and FTC for adequate cellular protection in genital tissue[2]

Time to maximal protection is achieved by 3rd dose in FGT and by 2nd dose in RT[3], well within the WHO recommendation of 7 days post-PrEP initiation

1. WHO Implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. Module 1: Clinical.Geneva: World Health Organization; 2017 (WHO/HIV/2017.17)
2. Cottrell M, et al J Infect Dis. 2016 Jul 1;214(1):55
3. Kashuba A, IAS 2017, France, Paris. Symposium #MOSY0803

Concentrations of TFV-DP During Pregnancy Among Women Using PrEP

Analysis of TFV and TFV-DP levels in HIV-uninfected Kenyan and Ugandan women on PrEP



- TFV n=33 pregnant/83 non-pregnant; TFV-DP n=31 pregnant/32 non-pregnant; mean age = 29 y/o
- After controlling for adherence, TFV and TFV-DP were 45-58% lower during pregnancy, with larger differences in later pregnancy
  - Evaluating adherence during pregnancy may require different cut-offs
- Changes in TDF metabolite levels were consistent with those seen in HIV-infected women using ART during pregnancy

Levels of TDF and TFV-DP are lower during pregnancy, especially later pregnancy. Additional studies are needed to determine protective levels of PrEP during pregnancy.

TDF: tenofovir disoproxil fumarate, TFV: tenofovir, TFV-DP: tenofovir diphosphate
Pyra M, et al. CROI 2018. Boston, MA. Poster #809

CONRAD 137 Clinical Study

HIV Prevention in Healthy Women: Safety and PK of a Potential New TAF-based Oral PrEP Regimen

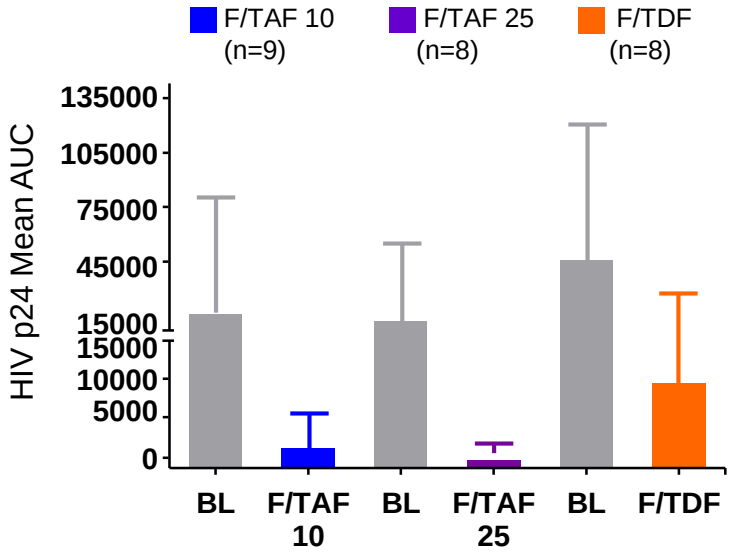
Phase I, prospective, randomized study to assess local and systematic PK, PD, and safety of daily oral FTC/TAF in healthy women over 8 months (N=75)

- FTC/TAF 10 mg and 25 mg had lower plasma TFV than FTC/TDF (C_{max}=2.4, 6, and 314 ng/mL, respectively)
- FTC/TAF 10 mg and 25 mg had higher TFV-DP in PBMCs (C_{max}=74.4, 189, and 23.4 fmol/10^6 cells)
- In the women assigned to a biopsy 4 hours after 14 daily doses, FTC/TAF 25 mg had higher CV tissue TFV-DP levels than FTC/TDF

	F/TAF (200/10) N=26	F/TAF (200/25) N=24	F/TDF (200/300) N=25
Number (%) of women reporting at least one TEAE	**13 (50)**	**18 (75)**	**20 (80)**
Not product related	9 (70)	12 (67)	9 (45)
Product related	4 (30)	6 (33)	11 (55)
Number (%) of women reporting at least one Gastrointestinal TEAE*	**3 (12)**	**3 (13)**	**11 (44)**

- FTC/TAF 25 mg was shown to protect against HIV infection in an ex vivo tissue infection model

Cervical Tissue Infectivity Ex Vivo



These results show that FTC/TAF has fewer TEAE and is more potent ex vivo in cervical tissue compared to FTC/TDF, providing a foundation for future studies in women for PrEP.

CV, cervical and vaginal; PD, pharmacodynamics; PK pharmacokinetics; TEAE, treatment-emergent adverse events.
* Nausea, diarrhea, vomiting, abdominal pain.
Schwartz J, et al. HIVR4P 2018, Madrid, Spain. OA15.04