Update on Progress in HIV Pre-Exposure Prophylaxis

Challenges and opportunities on how to address women in PreP trials

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HELPING THE PHARMACEUTICAL INDUSTRY
SUPPORT A GLOBAL RESEARCH AGENDA FOR WOMEN
IAS INDUSTRY LIAISON FORUM

XVII International AIDS Conference (AIDS 2008)
Hall 10, AIDS2008, Mexico City
Monday 4 August 2008

PrEP Goes Back to Basics

- HIV Infection is The Cause of AIDS
  - Not Sex, Not Drugs
  - Antiretroviral Agents Target HIV Directly
- People Like Sex
  - For Pleasure, Intimacy, Company, Livelihood,
  - and Pregnancy....
  - Prevention is less used if it alters sex
    - Abstinence Programs, Condoms, Diaphragm
    - Microbicides? Male circumcision?
- Condom use, the main barrier method, is mainly male-controlled

Why Chemoprophylaxis?

- Anti-HIV Drugs
  - Inhibit HIV directly
  - Are already formulated and mass produced
  - Prevent mother to child transmission
- A pill is at least as female-controlled as a topical microbicide
- Chemoprophylaxis is a proven concept
  - EG: Malaria, TB pneumonia, meningitis

Why Pre-exposure?

- Pre-exposure dosing increases efficacy
  - SHIV exposed nonhuman primates (Garcia Lerma 2008)
- People have difficulty recognizing exposure
  - Denial (Schechter *JAIDS* 2004)
  - Substance use
  - Imperfect communication with partners
- For those at highest risk
  - Pre- and post-exposure periods overlap

Rationale for Pre Exposure Prophylaxis

- Used Daily
- Concept is proven for prevention of
  - Malaria (80 to 90% effective)
  - Tuberculosis Pneumonia (90% effective)
  - Unwanted Pregnancy (99% effective)
- Drug Is Initiated Before Large Infections Occur
- Can Be Initiated By Women
- Coordination with Risk Behavior Is Not Needed
- Requires Identification of High Risk Groups
  - But Not Specific High-Risk Acts

PrEP: The Key Points

- PrEP is a potential new HIV prevention intervention that could have an important impact on HIV prevention globally
- Only tenofovir (TDF) and a combination of TDF and emtricitabine (FTC) are currently being tested in clinical trials for use as PrEP
- Although exists enough confidence that either TDF or TDF/FTC would work for PrEP, this should not preclude the evaluation of other antiretrovirals for PrEP

Ongoing and Planned PrEP Trials as of August 2008

Location	Sponsor/ Funder	Population (mode of exposure)	Intervention arms	PrEP strategy(ies) being tested	Status / Expected completion
United States	CDC	400 gay men and other men who have sex with men (penile/rectal)	1	TDF	Fully enrolled – Ongoing / 2009
Thailand	CDC	2,400 injecting drug users (parenteral)	1	TDF	Enrolling / 2009
Botswana	CDC	1,200 heterosexual men and women penile and vaginal)	1	TDF/FTC (switched from TDF Q1 2007)	Enrolling / 2010
Brazil, Ecuador, Peru, US, additional sites TBD (iPrEX Study)	NIH, BMGF	3,000 gay men and other men who have sex with men (penile/rectal)	1	TDF/FTC	Enrolling / 2010
Kenya, Uganda (Partners PrEP Study)	BMGF	3,900 serodiscordant heterosexual couples (penile and vaginal)	2	TDF; TDF/FTC	Enrolling / 2012
Kenya, Malawi, South Africa, Tanzania (FEMPrEP)	FHI, USAID	3,900 high-risk women (vaginal)	1	TDF/FTC	Planning / 2012 Anticipated start Q3/2008
Southern Africa; specific sites TBD (VOICE Study)	MTN, NIH	4,200 sexually active women (vaginal)	3	TDF; TDF/FTC; TDF gel	Planning / 2012 Anticipated start Q1/2009

BMGF – Bill & Melinda Gates Foundation; CDC – US Centers for Disease Control; FHI – Family Health International; MTN – Microbicide Trials Network; NIH – US National Institutes of Health; USAID – United States Agency for International Development

Anticipating the Results of PrEP Trials. AIDS Vaccine Advocacy Coalition. August 2008

The iPrEx Study

Safety, Efficacy, Behavior, and Biology

Gladstone Institute of Virology and Immunology

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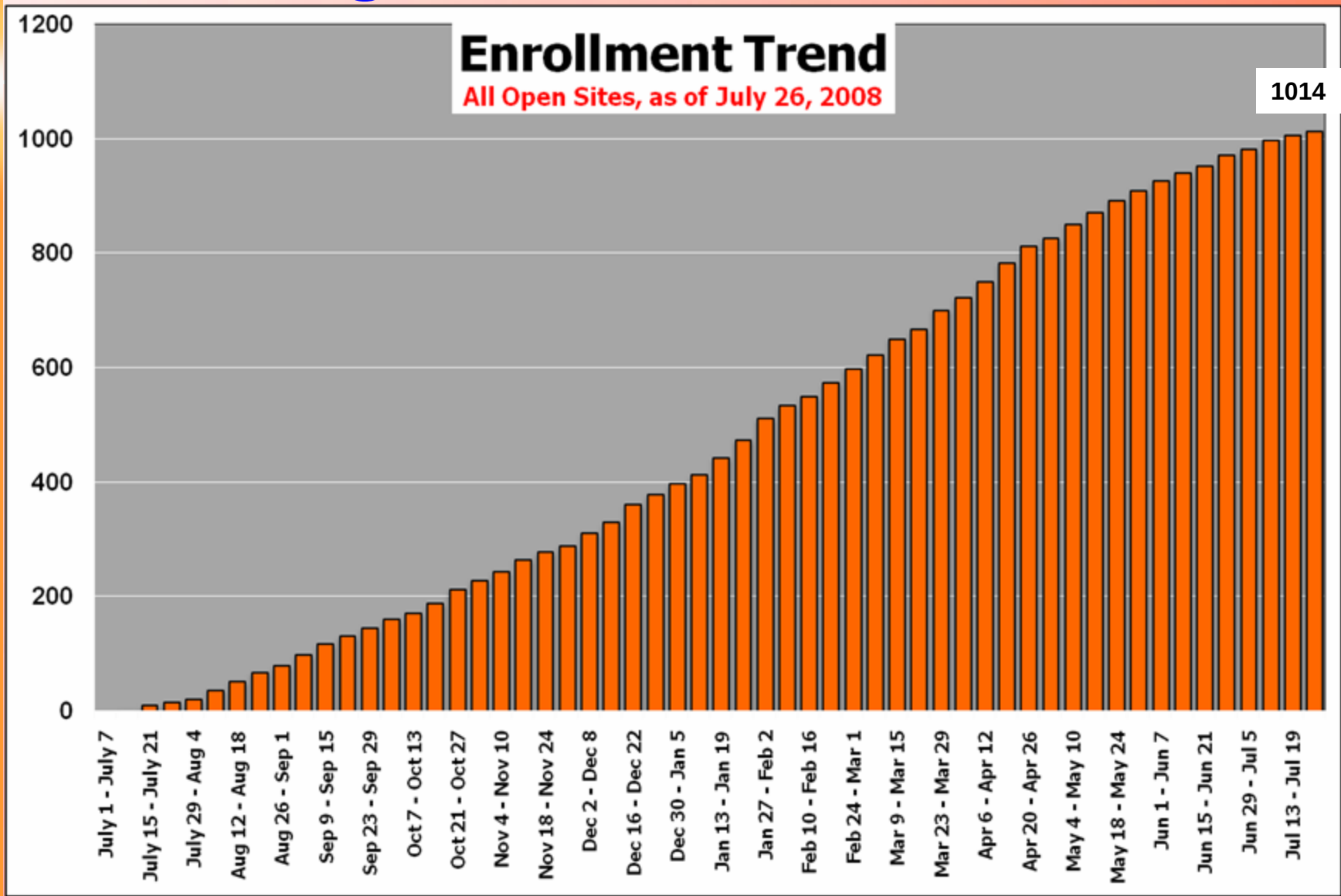
iPrEx Study Successfully Enrolling

Enrollment Status (Started Operations)	IMPACTA, Lima (June 2007)	INMENSA, Lima (July 2007)	ACSA, Iquitos (July 2007)	EQUIDAD, Guayaquil (November 2007)	SFDPH, San Francisco (June 2008)	FENWAY, Boston (June 2008)	Total
Screened	**853**	**626**	**447**	**180**	**15**	**8**	**2129**
Eligible	494	448	336	114	12	6	1410
Ineligible	359	178	111	66	3	2	719
Enrolled	**300**	**299**	**300**	**84**	**10**	**6**	**999**
Eligible but no enrolled	194	149	36	30	2	0	411

Screening: Enrollment ratio: 2.13

Lama JR, et al. XVII International AIDS Conference. 3-8 August 2008, Mexico City. Abstract No. WEPE0256

iPrEx Study: Successfully Enrolling



PrEP and Women

- Low-risk persons can become high-risk persons, and vice versa
- HIV transmission can occur:
  - In sexual contacts between female sex workers and their clients
  - Through marriage-like relationships
  - “Leakage” from infected individuals reflecting all non-paid casual sex
- HIV transmission through marriage and “leakage” only occurs in low risk groups

PrEP and Women:
What Would Affect PrEP Efficacy and/or Safety?

- Differences in body composition and size
- Differences in pharmacokinetics
- Differences in woman-specific concomitant medication use
  - E.g.: Contraception
- Differences in modes of exposure
- Differences in transmission rates

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PLOS CLINICAL TRIALS

2007

Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial

Leigh Peterson[1*], Doug Taylor[1], Ronald Roddy[2], Ghiorghis Belai[1], Pamela Phillips[1], Kavita Nanda[1], Robert Grant[3,4], Edith Essie Kekawo Clarke[5], Anderson Sama Doh[6], Renee Ridzon[7], Howard S. Jaffe[8], Willard Cates[1]

- Conducted between June 2004 and March 2006
- West Africa
- Daily dose of 300 mg oral Tenofovir DF vs. placebo
- All participants received testing, condoms, and counseling.
- Safety evaluated in N=936 including 428 person years

Sexual Behavior Among Women During PrEP Trial in West Africa

	Screening	Follow-up
Number of partners (30 days)	21	14
Number of new partners (30 days)	11	6
Number of sex acts (7 days)	12	15
Condom use (last act)	52%	94%

Peterson, *Plos Clinical Trials*, 2007

Findings From the West African PrEP Study

Safety in seronegatives confirmed

- No increase in grade 1 renal abnormalities
- No grade 2 or greater renal toxicity
- No flares among 23 known to be HBsAg+

A trend toward efficacy

- 8 seroconversions (2 TDF: 6 Placebo; P=0.34)
- 2 seroconversions after 1 and 2 months of TDF
  - No specimens to Rule Out Pre-PREP infection
  - No *bona fide* case of PREP failure yet documented

Peterson, *Plos Clinical Trials*, 2007

Pre-exposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child

P. Vernazza[1] I. Brenner[1] , I. Graf[2]

[1]Division of Infectious Diseases and [2]Social Services, Cantonal Hospital St. Gallen,

Vernazza P., et al. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention. 22-25 July 2007, Sydney. Abstract No. MOPDC01.

License to Love

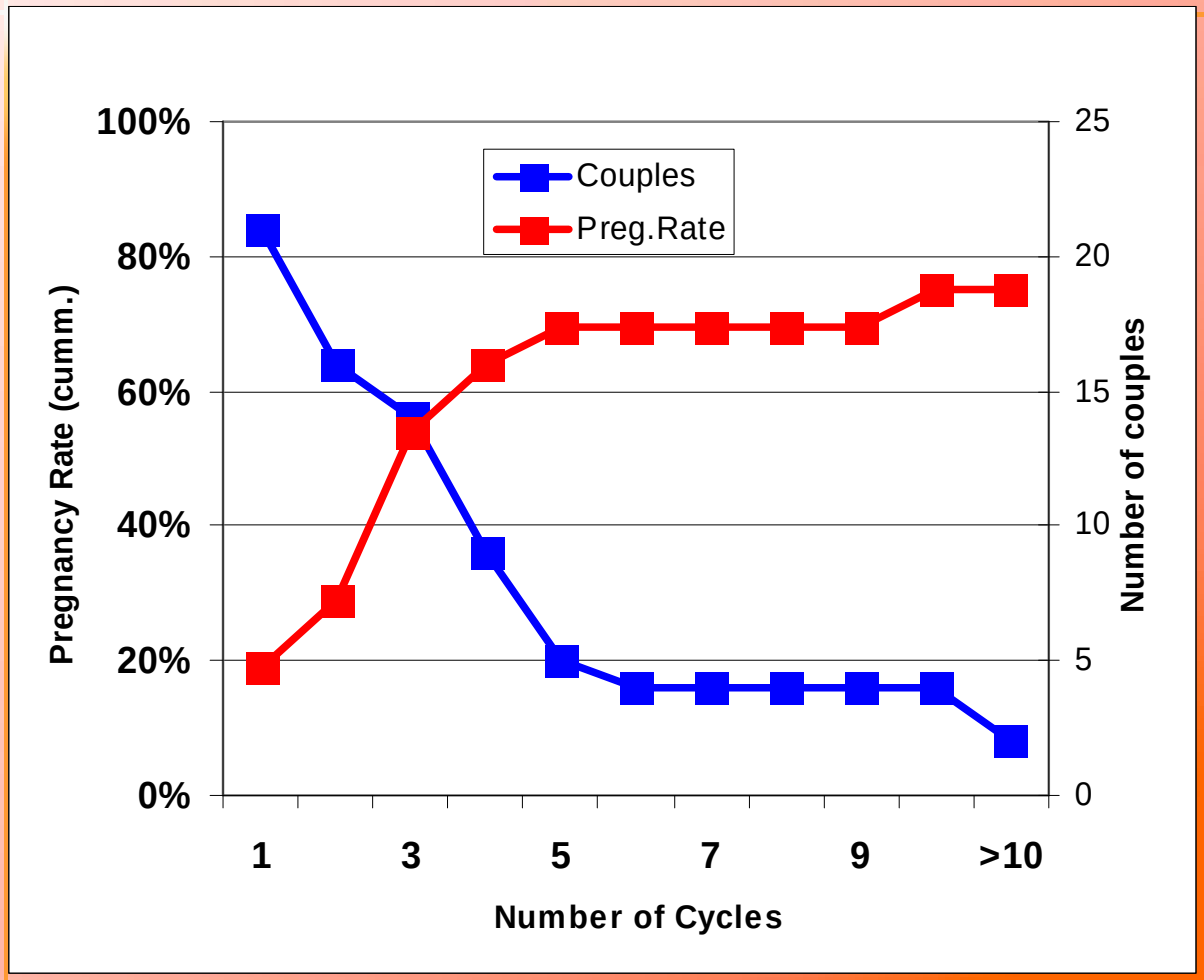
Counselling of HIV Discordant Couples

1. Discordant couples: Male HIV+/Female HIV-
2. Information to both partners about transmission risks
3. Rule out asymptomatic STDs
4. Maintain fully suppressive HAART
5. Timing of unprotected intercourse
   → 36 h after LH-peak (urine)
6. HIV-Pre-Exposure Prophylaxis (TDF)
   → 2 doses 0 and 24 hafter LH-peak

Vernazza P., et al. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention. 22-25 July 2007, Sydney. Abstract No. MOPDC01.

License to Love

Pregnancy-Rates in First 22 Couples



Vernazza P., et al. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention. 22-25 July 2007, Sydney. Abstract No. MOPDC01.

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PLoS one

Potential Impact of Antiretroviral Chemoprophylaxis on HIV-1 Transmission in Resource-Limited Settings

2007

Ume L. Abbas[1]*, Roy M. Anderson[2], John W. Mellors[1]

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Table 5. Potential Impact of PrEP Introduced in 2007 on HIV-1 Infections in Southern Sub-Saharan Africa[‡¶]

Region/Country	Baseline Adult HIV Prevalence %	Baseline Adult HIV Incidence %	Baseline Adult Population people	Population Growth Rate %	Cumulative New HIV Infections Averted after 10 Years	
					Optimistic Scenario & Targeted by Sexual Activity	
					No Disinhibition	100% Disinhibition
Lesotho	23.2	4.8	865 000	0.1	92 710	56 942
Botswana	24.1	6.7	909 000	0.1	132 870	81 608
Zambia	17.0	2.6	5 281 000	1.7	361 132	221 803
South Africa	18.8	2.4	25 204 000	0.8	1 477 691	907 581
Southern Sub-Saharan Africa[§]	19.6[†]		54 886 000		2 713 746–3 166 037	1 666 752–1 944 544

[‡]These are conservative projections based on estimates of the size of adult population [47,71] and assuming constant incidence [73–75,89], prevalence [47] and growth rate [47].

[¶]For southern sub-Saharan Africa overall, projections are based on the UNAIDS/WHO statement that the total number of infections in this region were 1.1 million for three consecutive years including 2005 [75]. With this estimate as a constant, low projection assumes 86% of these infections occur in adults, while the high projection assumes the full estimate.

[§]Excludes Angola, Madagascar, Mauritius and Seychelles.

[†]Refers to median country-prevalence.

doi:10.1371/journal.pone.0000875.t005

Abbas, *Plos*

The Impact of Pre-Exposure Prophylaxis (PrEP) on HIV Epidemics in Africa and India: A Simulation Study

Vissers DCJ et al. (2008) The Impact of Pre-Exposure Prophylaxis (PrEP) on HIV Epidemics in Africa and India: A Simulation Study. PLoS ONE 3(5): e2077. doi:10.1371/journal.pone.0002077

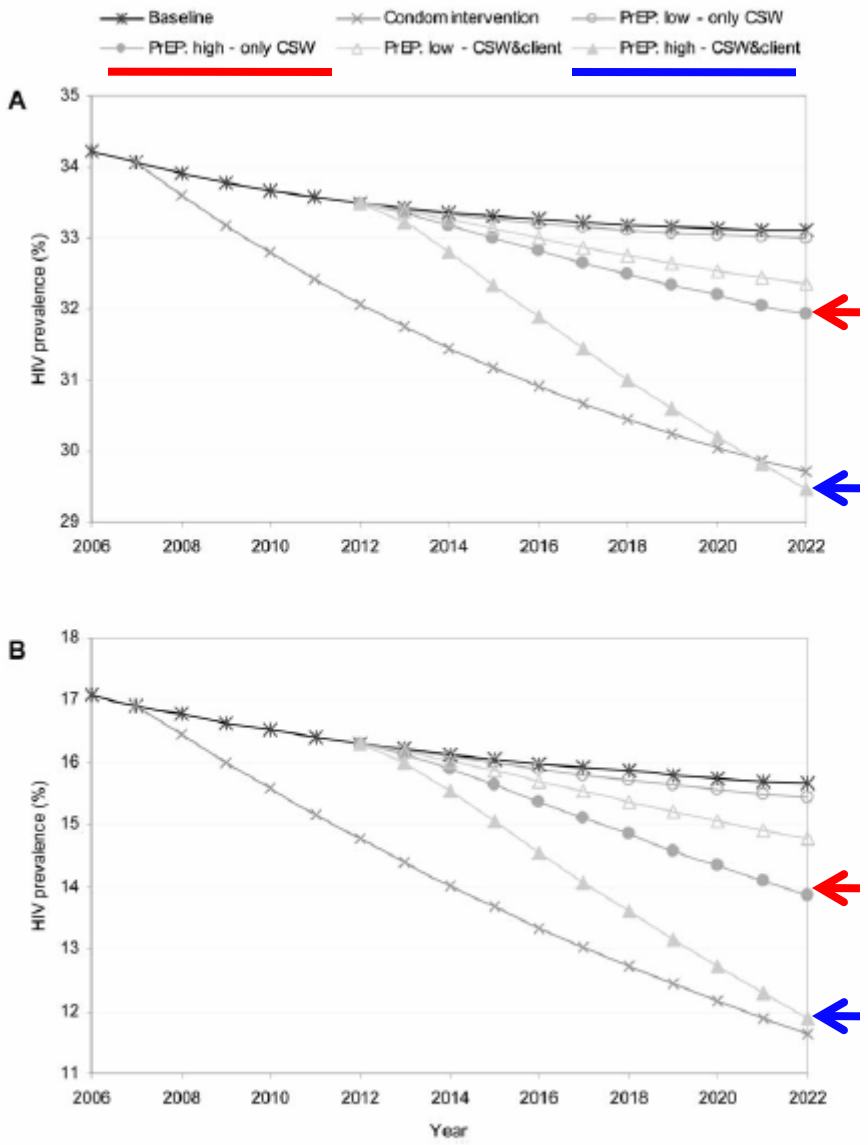

Figure 1. Effect of different PrEP scenarios and condom use on HIV prevalence. A: Botswana, B: Nyanza province, Kenya. 'PrEP low' means 25% coverage and 50% effectiveness; 'PrEP high' means 75% coverage and 90% effectiveness; 'Only CSW' means target group is sex workers; 'CSW&client' means target group is sex workers and clients.
doi:10.1371/journal.pone.0002077.g001

PrEP in Women: Recommendations

- Women are included in the PrEP research agenda
  - PrEP efficacy study results are expected in MSM and/or IDU before than in female populations
    - Careful interpretation and extrapolation to women
- Intervening women in settings where HIV is mainly “heterosexually” transmitted would have an important impact in the epidemic
- Social stigma/discrimination and access to PrEP are barriers to be addressed once PrEP programs are implemented
  - Coupling PrEP to other female-targeted intervention (e.g.: contraception) would have a higher impact in preventing HIV