

Jean M Keller, PAC
Assistant Professor
Johns Hopkins University
Co-Director, HIV Women's Program



PrEP and Serodiscordant Couples

PrEP:
*HIV PREVENTION
WITH JUST
1 PILL A DAY*



FDA approved emtricitabine/tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (PrEP) in 2012

HIV Prevention

PrEP



92%

Efficiency

Condom Use



80%

Efficiency

One Patient's Story...

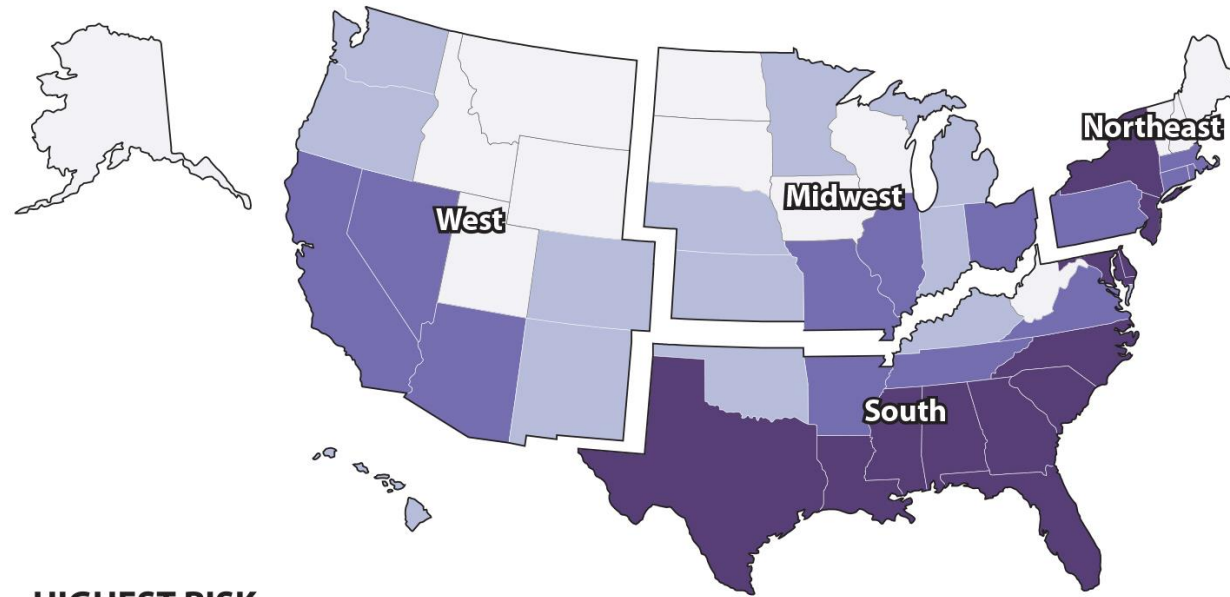
28yo G2P1001 presented for initial prenatal care visit at 22wks. She was seen in various EDs and OB triage x several visits.

- She did not have any notable medical illnesses
- FOB was not present
- She screened positive for IPV but was not ready to leave FOB
- NOB screening tests: (-)HIV, (+)syphilis (-)gc/ct
- Prenatal course uneventful – 28wk labs normal, (-)repeat gc/ct
- Delivered a healthy BB at 38wks
- Infant feeding method was breastfeeding upon discharge from hospital

One Patient's Story (continued)

- BB hospitalized for failure to thrive and diffuse LAD
- Diagnosed with HIV infection at 7 mos old
- FOB disclosed he was living with HIV
 - For quite some time
 - Not prescribed HAART because of active alcoholism
- This happened in 2007

Lifetime Risk of HIV by State



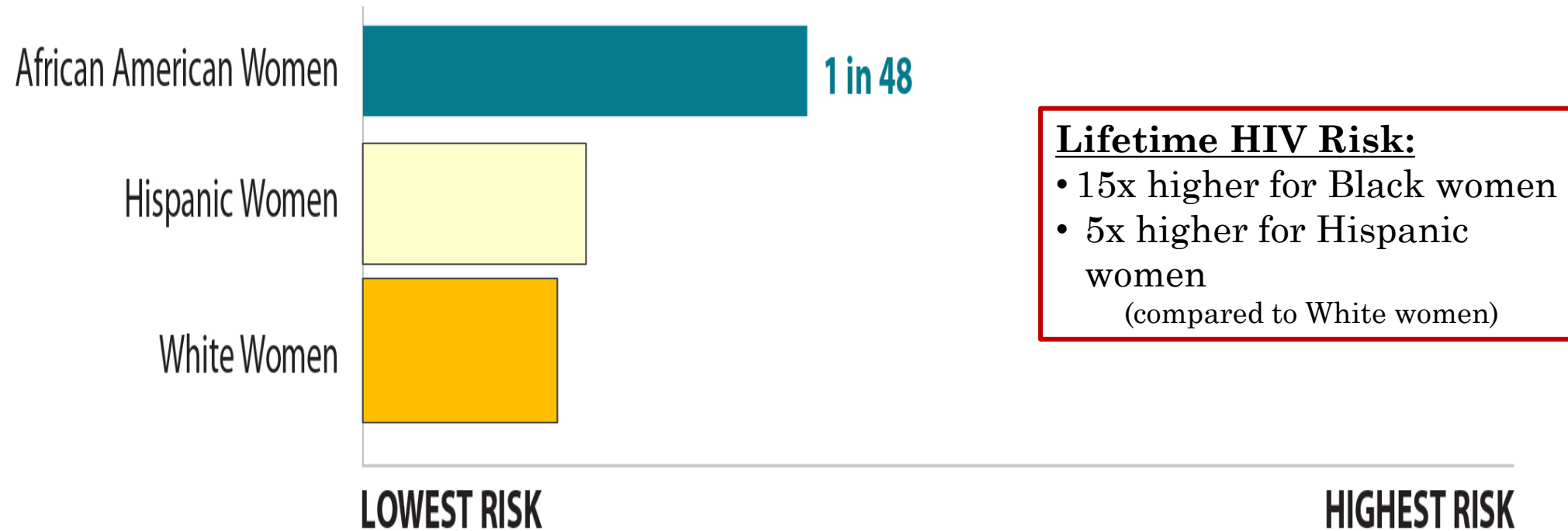
HIGHEST RISK

LOWEST RISK

State	One in "n"	State	One in "n"	State	One in "n"	State	One in "n"
District of Columbia	13	Nevada	98	Michigan	167	West Virginia	302
Maryland	49	Illinois	101	Oklahoma	168	Wisconsin	307
Georgia	51	California	102	Kentucky	173	Iowa	342
Florida	54	Tennessee	103	Indiana	183	Utah	366
Louisiana	56	Pennsylvania	115	Washington	185	Maine	373
New York	69	Virginia	115	Colorado	191	Alaska	384
Texas	81	Massachusetts	121	New Mexico	196	South Dakota	402
New Jersey	84	Arizona	138	Hawaii	202	New Hampshire	411
Mississippi	85	Connecticut	139	Oregon	214	Wyoming	481
South Carolina	86	Rhode Island	143	Minnesota	216	Vermont	527
North Carolina	93	Ohio	150	Kansas	262	Idaho	547
Delaware	96	Missouri	155	Nebraska	264	Montana	578
Alabama	97	Arkansas	159			North Dakota	670

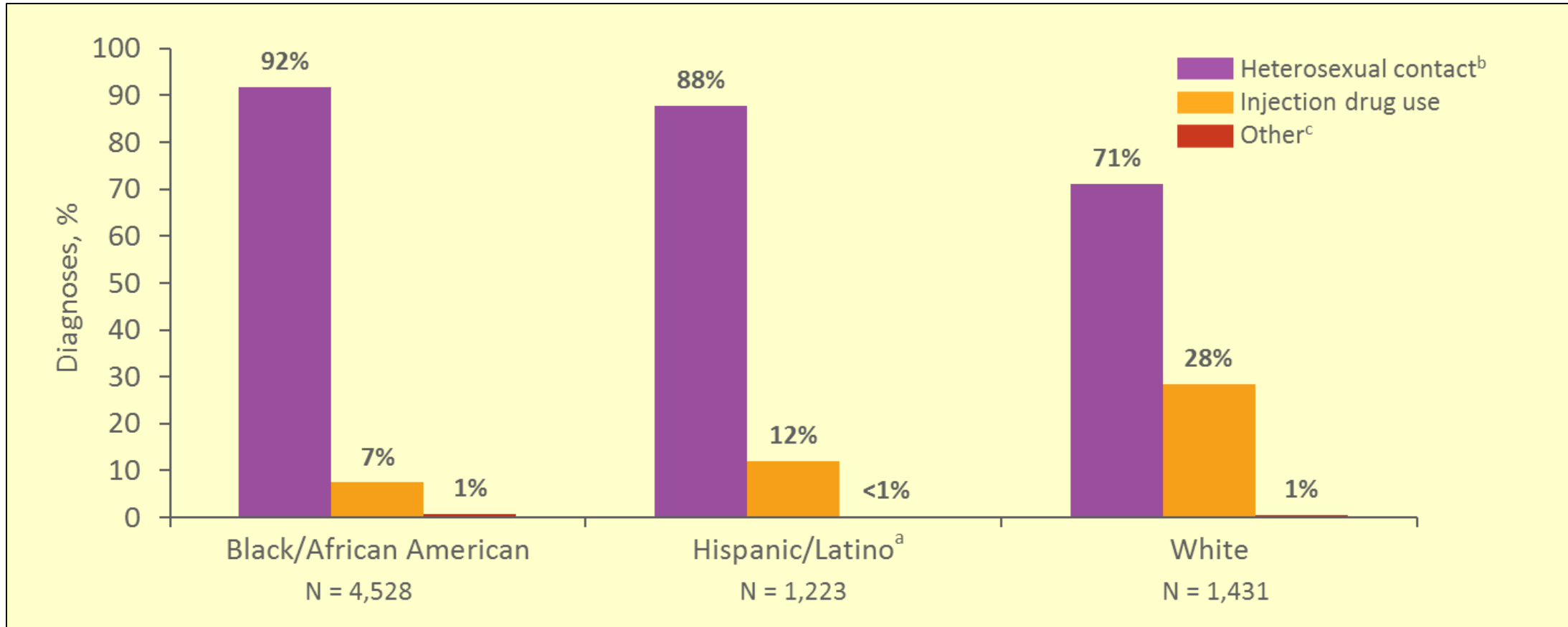


Racial Disparities in HIV Risk



New HIV diagnosis: in 2016, Black women accounted for over **61%** of the new HIV diagnoses among women

HIV Transmission Category in Women: by Race



Majority of cases are secondary to heterosexual sex

Some racial difference in IDU

CDC- 2016 Diagnosis of HIV in female adults and adolescents in U.S.

Oral PrEP Clinical Trials

Clinical trial	Participants	N	Drug	% reduction in acquisition of HIV infection ^a	
				%	(95% CI)
iPrEx	MSM	2499	TDF/FTC	42	(18-60)
<i>Partners PrEP</i>	<i>Heterosexual serodiscordant couples</i>	4747	TDF	67	(44-81)
			<i>TDF/FTC</i>	<i>75</i>	<i>(55-87)</i>
TDF 2	Heterosexually active men and women	1200	TDF/FTC	62	(22-83)
Bangkok Tenofovir Study	IV Drug Users	2413	TDF	49	(10-72)
Fem-PrEP	Heterosexually active women	1951	TDF/FTC	6 ^e	.59-1.52
VOICE	Heterosexually active women	5029	TDF/FTC	- 4 ^e	0.97-2.3

PrEP Effectiveness in Women

- Adherence

- If it isn't taken, it will not work!
- Self-report, pill counts underestimates true adherence
- In clinical trial: did not know if taking placebo or not

- Perception of risk

- VOICE trial (9%/yr HIV incidence in women <25)
 - <30% had detectable drug levels
- FEM-PrEP trial (5%/yr HIV incidence)
 - 70% of women reported feeling at little risk for HIV

- Stigma, risk, and vulnerability (e.g. economic, power differentials)

PrEP Effectiveness in Women

- Poor drug penetration into vaginal tissue compared with rectal tissue
 - **Missed pills less forgiving in women**
- Genital inflammation or breaks in mucosa
 - Related to menopause (i.e. lack of estrogen), STIs
- Greater susceptibility in women vs hetero men
 - Greater surface area, longer contact with seminal fluid

PrEP in Women: Effectiveness

- Meta-analysis of 5 RCTs of oral PrEP among women
 - 3 reported evidence of effectiveness and 2 did not
 - **Estimates by adherence** (based on plasma drug levels)
 - 25% adherence: *no protection* (RR 1.19 95% CI: 0.89 – 1.61)
 - 50% adherence: *32% protective* (RR 0.68 95% CI: 0.53 – 0.88)
 - 75% adherence: *61% protective* (RR 0.39 95% CI: 0.25 – 0.60)
- “90%” effective for women
 - ***Partners* PrEP (HIV serodiscordant couples) subgroup analysis**
 - ~20% HIV(+) partners initiated ARV (higher among men)
 - Condomless sex decreased (27% at start → 9% at month 24)
 - Less exposure to persons with acute HIV infection
 - Higher viral loads assoc with higher transmission risk

Challenges

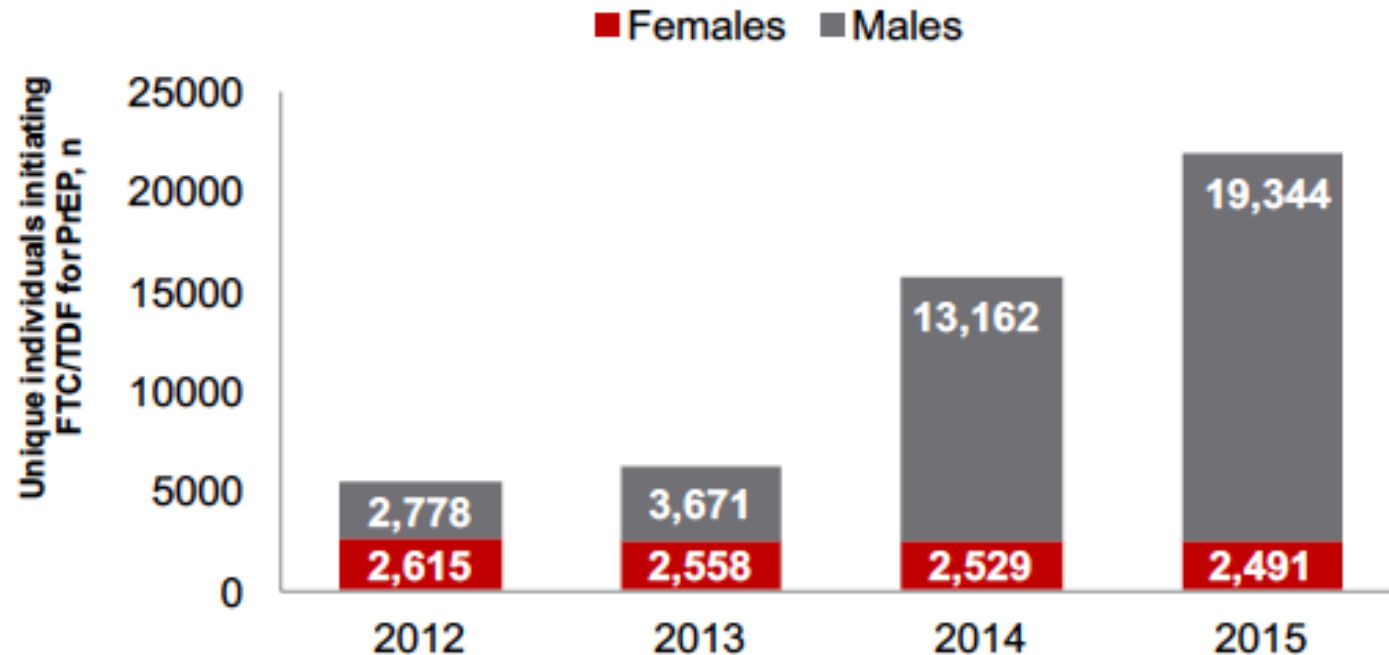
- **Provider-level**
 - Identifying women who are at-risk
 - Which provider best suited to prescribe
 - OBG, family planning, ID
- **Patient-level**
 - Awareness of PrEP (<10%)
 - Recognizing and understanding risk
 - Medication adherence in the face of daily life

ACOG PB: PrEP Use in Heterosexual Women

- HIV-negative and at substantial risk for HIV acquisition
 - Sexually active with a partner living with HIV
 - Living in a high HIV prevalence area or social network *AND*
 - Does not regularly use condoms during sex with partner of unknown HIV status
 - Recent sexually transmitted infection
 - Exchange sex for drugs, housing, money, etc
 - Incarceration
 - Use injection drugs
 - Abuse alcohol
 - Partner of unknown status with any of the above factors

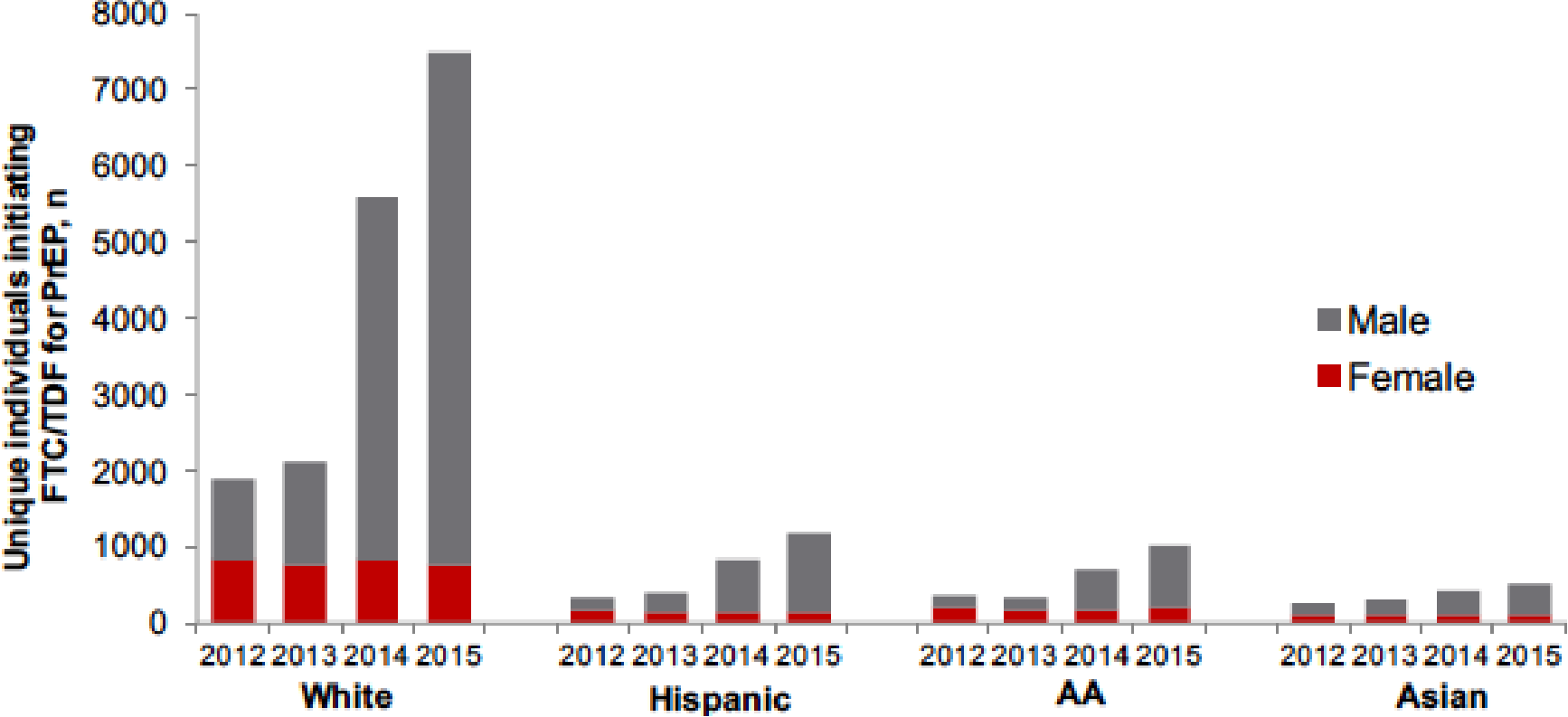
PrEP Utilization by Sex

-U.S. retail pharmacy data 2012-2015



- PrEP use among female patients << male patients
- Highlights the difficulty in identifying women at risk

Racial and Gender Disparity in PrEP Utilization



- In 2015, of the 13% of prescriptions filled by women, only 17% of those were among AA women

GYN/OB PrEP Study



- Retrospective cohort
 - Pregnant patients who had PNC and delivered at JHH in 2012
 - >1600 women
- Eligibility for PrEP defined as:
 - Prior or current sexually transmitted infection
 - Sexual partner living with HIV
- Over **10% of our patients** were eligible for PrEP

PrEP Safety during Pregnancy and Breastfeeding

- No randomized trials
 - Demonstration project (n=30): no difference in birth outcomes or infant growth
- Safety data are from women living with HIV or hepatitis B
 - No increased risk of birth defects, stillbirth, PTD, LBW
- WHO systematic review: safe during pregnancy/lactation
- Tenofovir serum levels was undetectable in 94% breastfed babies
 - Tenofovir is mostly not bioavailable: must be given as prodrug TDF

U.S. Women with Indications for PrEP

# U.S. people at-risk for HIV	Total	1.2 million	[661,000 – 1.8
	Heterosexual Adults	million]	
	Women	624,000	[404,000 – 846,000]
	MSM	468,000	[274,000 – 662,000]
		492,000	[212,000 – 772,000]

- CDC definition of substantial risk among heterosexual adults
 - 18-59 yo, not known to be HIV-positive, sex with 2 or more opposite sex partners in past 12 months AND 1 of the following:
 - Condomless sex in last 4 weeks AND sex with a partner who is IVDU
 - For women: sex with a bisexual male sex partner in past 12 months

Heterosexual Adults

1 in 200

Women

1 in 167

Heterosexual Men

1 in 500

MSM

1 in 4

Introduction

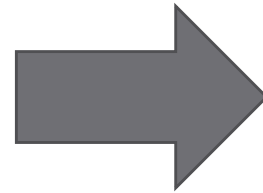
Universal Prenatal HIV
Counseling and Testing

Preconception
Care

ARV Prophylaxis

Scheduled C-section
(when indicated)

Avoidance of Breast
Feeding



U.S HIV
Perinatal
Transmission
is now <1%

A focus on appropriate overall medical care for HIV-infected couples is the best way to prevent HIV infection of infants.

Every HIV-infected infant is a sentinel event representing missed opportunities for prevention.

Who Desires Children?

- Partner who desires child (3/4 of HIV+ men and women desiring children)
- Fewer children (almost 40% desiring children had no previous children)
- Younger age
- Higher self-ratings of health
 - not related to CD4/viral load



Reasons HIV+ Men and Women Desire Children

- Leave a legacy
- Cope with loss (including replacing child HIV)
- To be loved and accepted
- To be taken care of
- Pregnancy has social/cultural
- Want to live “normal” life



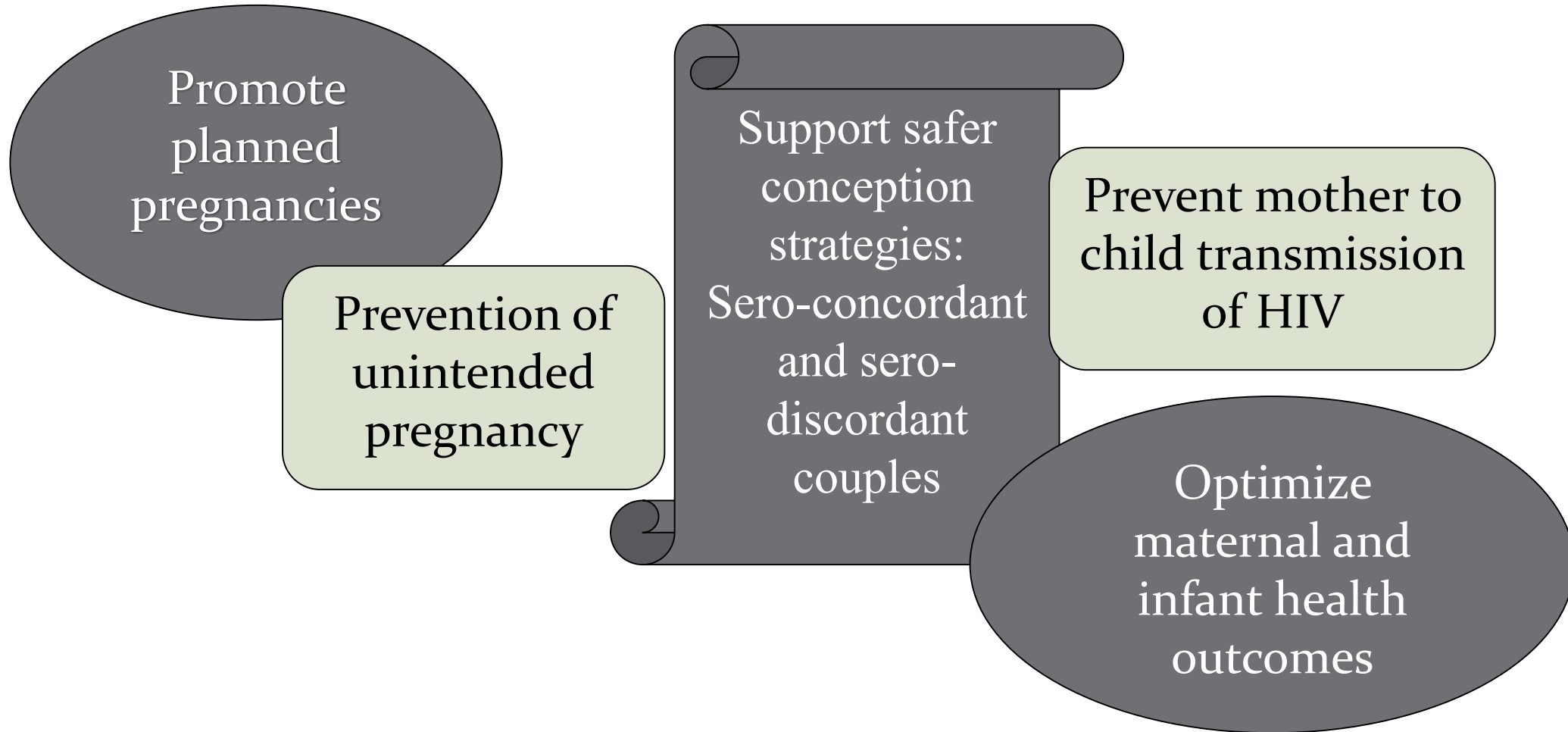
Reproductive Options for HIV Broader Family Planning Landscape

- Preconception care (PCC) for people living with HIV (PLWH) historically understudied
- Important dimension of FP/HIV
- PCC encompasses not only pregnancy prevention but also safe childbearing

Family Planning and Planning for a Family: Why is This Important?

- **High rates of unintended pregnancy:** of 382 women in the Medical Monitoring Project, 85% had one or more unplanned pregnancy after knowing their HIV status (JAIDS 2014;65:350)
- **High rates of HIV serodiscordance (SDC) among sexual partnerships:** more than half of HIV+ individuals have HIV- partners
- **HIV has an adverse effect on fertility and there is potential improvement in fertility with ART**
- **High rates of comorbidities potentially affecting maternal or fetal health: depression, interpersonal violence**
- **Fertility desires and intentions among HIV+ women:** Most studies show that pregnancy desires and reproductive decision-making are similar between HIV-infected and HIV-uninfected women

Goals of Preconception counseling for PLWH



Preconception Care: what can women's health providers do?

- **Recommend HIV testing of both partners**
 - For serodiscordant couples: discuss **Treatment as prevention (TasP) or Pre-exposure prophylaxis (PrEP)**
 - Discuss safer sexual practices

- **Assess childbearing plans/desires of HIV+ women on regular basis**
 - If desires children, ask about timing
 - If does not desire pregnancy currently, ensure access to effective contraception
 - Perform or refer for preconception counseling/care if desires to conceive

What is PCC for PLWH?

Assessment

Screening

Counseling

Prevention and
Treatment Services

Preconception Counseling and Care

- **Comprehensive family planning and preconception care is part of routine primary care and is recommended by CDC, ACOG, and other national organizations.**
- ***Purpose:***
 - Prevention of unintended pregnancies.
 - Optimization of maternal health prior to pregnancy.
 - Prevention of perinatal transmission.
 - Prevention of HIV transmission to an uninfected partner while trying to conceive including the use of PrEP

Case #1

33yo healthy woman presented to Ob/Gyn clinic with her husband for preconception counseling. They wanted to have a biological child together.

- Her husband was living with HIV
 - He was taking antiretroviral therapy and had an undetectable viral load for several years
- She had never been pregnant and had never tried to get pregnant
- Negative intimate partner violence screen

Would you offer her PrEP?

PrEP Use in Heterosexual Women

- HIV-negative and *at substantial risk* for HIV acquisition
 - Sexually active with a partner living with HIV
 - Living in a high HIV prevalence area or social network *AND*
 - Does not regularly use condoms during sex with partner of unknown HIV status
 - Recent sexually transmitted infection
 - Exchange sex for drugs, housing, money, etc
 - Incarceration
 - Use injection drugs
 - Abuse alcohol
 - Partner of unknown status with any of the above factors

Conception Options for HIV Serodiscordant Couples

- *Antiretroviral therapy is the most important intervention*
 - ARV for HIV+ partner as prevention (HPTN 052)
 - Pre-exposure prophylaxis (PrEP) for HIV- partner as well?
- Screen and treat sexually transmitted infections
- Undetectable viral load for HIV+ partner
- HIV+ woman: timed condomless sex, artificial insemination
- HIV+ man: timed condomless sex; assisted reproductive technology, i.e. semen washing with intrauterine insemination, IVF/ICSI

Reproductive Options for HIV Concordant and Serodiscordant Couples.

- PrEP is recommended with conception via sexual intercourse without a condom (counsel first) when VL is unknown or viral suppression is not attained to reduce risk of HIV transmission
 - Counsel couples to limit sex (sans condoms) to peak fertility times
- PrEP- may be used to minimize risk of transmission of HIV with discordant couples.
 - Unclear if PrEP with viral suppression further reduces the risk of Sexual transmission
 - Studies are currently evaluating the efficacy of PrEP in conception
 - Only TDF and Emtricitabine is currently approved for use as PrEP

PrEP

- Peri-conception PrEP
 - Very few data to date on periconception PrEP; studies under way.
 - Infected partner should be on ART with fully suppressed HIV viral load.
 - Once daily tenofovir/emtricitabine is currently FDA approved for PrEP; CDC recommends 1 month before and 1 month after conception attempted.
 - No reported increase in congenital anomalies for children whose mothers were exposed to tenofovir or emtricitabine during first trimester.

PrEP

- If used in serodiscordant couples counseling should include
 - Potential risks and benefits
 - Alternatives for safer conception
 - Start PrEP in the un-infected partner one month prior to conception
 - Continue PrEP one month after conception is attempted.
 - Follow Recommended Laboratory testing
 - Including HIV testing at baseline and every 3 months
 - Educate about symptoms of acute HIV infection
 - If HIV infection is documented discontinue PrEP ARV agents.

Case #2

28yo woman presented for prenatal care at 24 weeks of gestation. This was her 2nd pregnancy. Her male partner was not present.

- She did not have any chronic medical illnesses
- She tested negative for HIV but positive for syphilis at the initial prenatal visit
- Male partner with unknown HIV status
- She reported he can be physically abusive at times and abuses alcohol

Would you offer her PrEP?

HIV and Pregnancy

- Pregnancy may be time of enhanced risk of HIV acquisition
 - Unclear if biologic and/or behavioral
- Greater risk of mother-to-child transmission (MTCT) if seroconversion happens during pregnancy or breastfeeding
- 2144 pregnant WLHIV in NY (2002-2004)
 - ***Only 1.4% were seroconversions, but these accounted for 23.4% of all MTCT cases***
- CDC analysis of 10 states
 - 1.4% seroconversions among 4006 pregnant WLHIV
 - ***MTCT: 29.3% in acute HIV vs. 4.8% in chronic HIV***

Case #3

36yo healthy woman presented to Ob/Gyn for her routine annual examination

- Had 2 male sexual partners
 - One was a long-term casual partner and the other was a main partner
 - Unknown HIV status of partners but patient thought they were negative
- Tested positive for both trichomonas and gonorrhea
- HIV test was negative

Would you offer her PrEP?

PrEP Use in Heterosexual Women

- HIV-negative and *at substantial risk* for HIV acquisition
 - Sexually active with a partner living with HIV
 - Living in a high HIV prevalence area or social network *AND*
 - Does not regularly use condoms during sex with partner of unknown HIV status
 - **Recent sexually transmitted infection**
 - Exchange sex for drugs, housing, money, etc
 - Incarceration
 - Use injection drugs
 - Abuse alcohol
 - **Partner of unknown status with any of the above factors**

On the Horizon

- Studies of alternatives to daily dosing
- Studies of alternative antiretrovirals (MVC, RPV)
- Studies of alternative formulations: intravaginal rings, films, injectables
- Multipurpose technology (antiretroviral combined with contraceptive)
- Qualitative projects involving women at-risk

Conclusion

- PrEP is another tool for HIV prevention, but should be part of a comprehensive risk reduction package
- Good adherence is critical to PrEP effectiveness-need better measures, better support and more forgiving regimens
- Use of PrEP must take into account risk, risk perception, and fertility plans and desires

Case Follow-up

- **Case #1 (attempting pregnancy): offered PrEP but declined**
 - Conceived after 1st unprotected intercourse
 - Remained HIV-uninfected
 - Delivered last year
- **Case #2 (pregnant): PrEP not available yet (2010)**
 - Seroconverted during breastfeeding
 - Male partner was living with HIV but did not disclose
 - Infant tested positive
- **Case #3 (annual exam): offered PrEP but declined**
 - Did not think she was at risk
 - Remains HIV-uninfected

Percolating Pipeline in PrEP Era

Strategy	Trial	#	Population	Status	Location	PrEP Status
Oral PrEP: Daily oral F/TAF	Discover	5,400	MSM & transgender	Fully enrolled	Austria, Canada, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, UK, US	Oral TDF/FTC as part of active control in double-dummy, double-blind design
bNAb: VRC01 infused every 2 months	HVTN 704/ HPTN 085	2,700	MSM & transgender	Enrolling	Brazil, Peru, Switzerland, US	Access to oral FTC/TDF PrEP offered at no drug cost to every participant
	HVTN 703/ HPTN 081	1,500	Sexually active women	Enrolling	Botswana, Kenya, Malawi, Mozambique, Tanzania, South Africa, Zimbabwe	Oral TDF/FTC discussed in IC, risk reduction counseling sessions, and referral systems
Vax: ALVAC/gp120 MF59 adjuvant boost, 5 doses in 12 months	HVTN 702	5,400	Sexually active women & men	Enrolling	South Africa	
Long-acting injectable: cabotegravir every two months	HPTN 083	4,500	MSM & transgender	Enrolling	Argentina, Brazil, Peru, South Africa, Thailand, US, Vietnam	Oral TDF/FTC as part of active control in double-dummy, double-blind design
	HPTN 084	3,200	Sexually active women	Enrolling	Botswana, Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe	
HC/HIV: evaluating 3 contraceptives for possible increased risk	ECHO	7,800	Sexually active women	Fully enrolled	Kenya, South Africa, Swaziland, Zambia	Participants interested in oral TDF/FTC referred as programs become available in each study community
Vax: Ad26/Mosaic + gp140 boost, 4 doses in 12 months	HPX2008/ HVTN705	2,600	Sexually active women	Enrolling	Malawi, Mozambique, South Africa, Zambia, Zimbabwe	TBD
Ring/PrEP: dapivirine ring and oral TDF/FTC	MTN 034/IPM 045/REACH	300	Sexually active women	Planned 2018	Kenya, South Africa, Uganda, Zimbabwe	Open-label cross-over; all will try both ring and oral, then choose



90%

Daily PrEP can reduce the risk of sexually acquired HIV by more than 90%.



70%

Daily PrEP can reduce the risk of HIV infection among people who inject drugs by more than 70%.



1 in 3

1 in 3 primary care doctors and nurses haven't heard about PrEP.

UNAIDS - CDC Visual Signs, Oct. 2015