

# HIV and Women



## HIV Health Services Planning Council February 22, 2016

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## Women Die Younger Than Men from HIV in U.S.

Long-running gap may, however, be getting narrower

By Christine Gorman | November 10, 2015

Medications are keeping people with HIV alive longer than ever before, but women with AIDS tend to die at a younger age in the U.S. than men with the illness (see chart below). This long-standing gap may in part reflect differences in race among men and women with HIV, particularly as concerns access to health care. Nearly one in four people living with HIV in the U.S. are women.

Among newly infected women in 2010, there were five times more blacks than whites. By comparison for that same year, there were almost equal numbers of black and white men who



November 10, 2015

# Outline

## *Is HIV a feminist?*

### ● **Epidemiology:**

- Global and U.S.

### ● **HIV prevention in women**

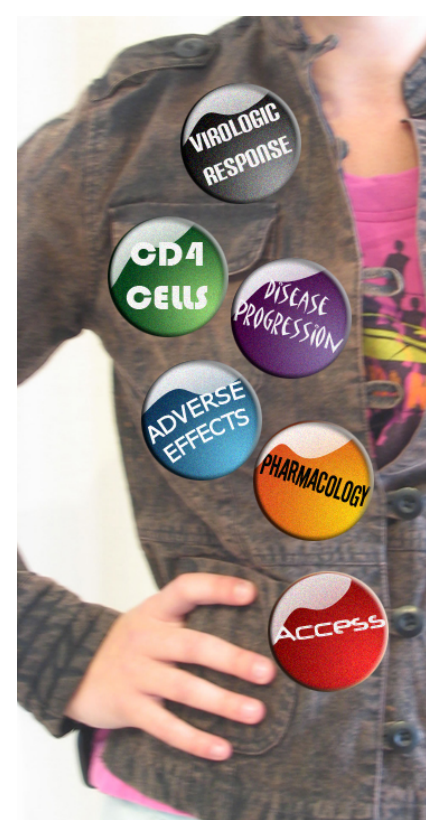
- Sex differences

### ● **HIV treatment in women**

- Sex differences in outcomes, toxicities, pharmacokinetics

### ● **Primary care for women**

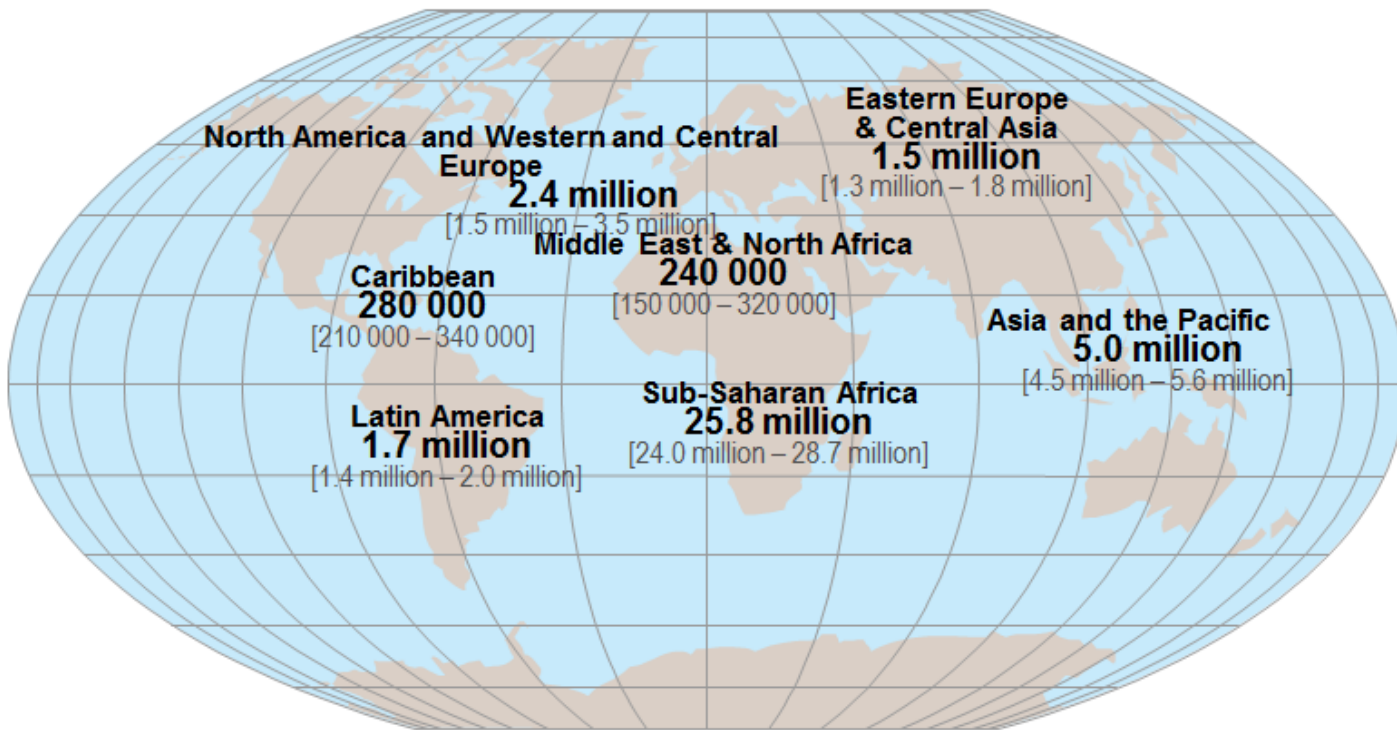
- Breast and cervical cancer screening



# When did prevalence of HIV in women worldwide become 50%?

1. 2000
2. 2008
3. 2012
4. 2014
5. Has not yet reached 50: 50 mark

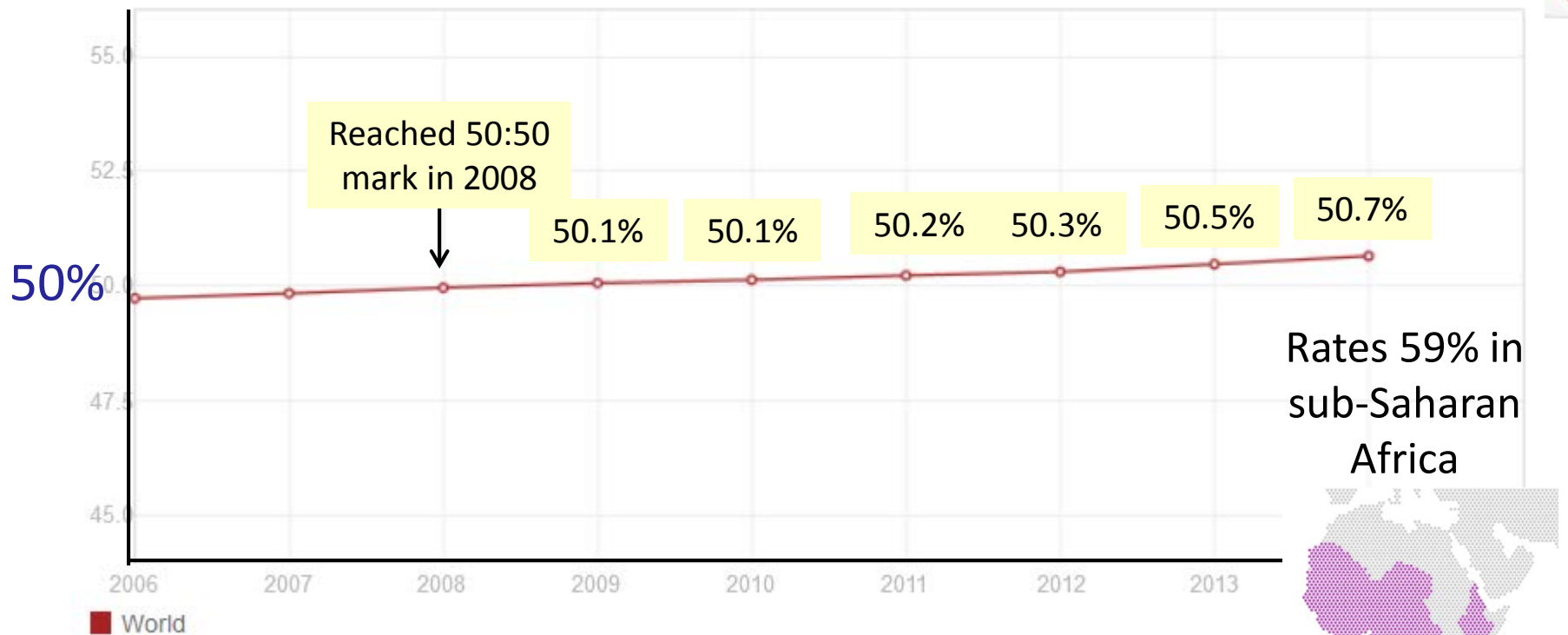
# Adults and children estimated to be living with HIV | 2014



**Total: 36.9 million** [34.3 million – 41.4 million]

Children (< 15 y)	2.6
<b>Women</b>	<b>17.4*</b>
Adults	34.3
Total	36.9

# Percentage of adults (15+ years) living with HIV worldwide who are female, 2006-2014



# WHY PEOPLE LIVING WITH HIV ARE BEING LEFT BEHIND

THE GAP  
REPORT

UNAIDS

## THE TOP 4 REASONS

- 01 Human rights violations, stigma and discrimination
- 02 Access to treatment and services
- 03 **Gender-based inequalities**
- 04 Criminalization and exclusion

# Gender-based inequalities

- Infection rates among young women are twice as high as among young men in sub-Saharan Africa. .
- In some settings, up to 45% of adolescent girls report that their first sexual experience was forced
- In sub-Saharan Africa, only 15% of young women aged 15–24 are aware of their HIV status.
- In low & middle income countries, average HIV prevalence among female sex workers is ~12% (in 27 countries HIV prevalence among male sex workers is 14%).

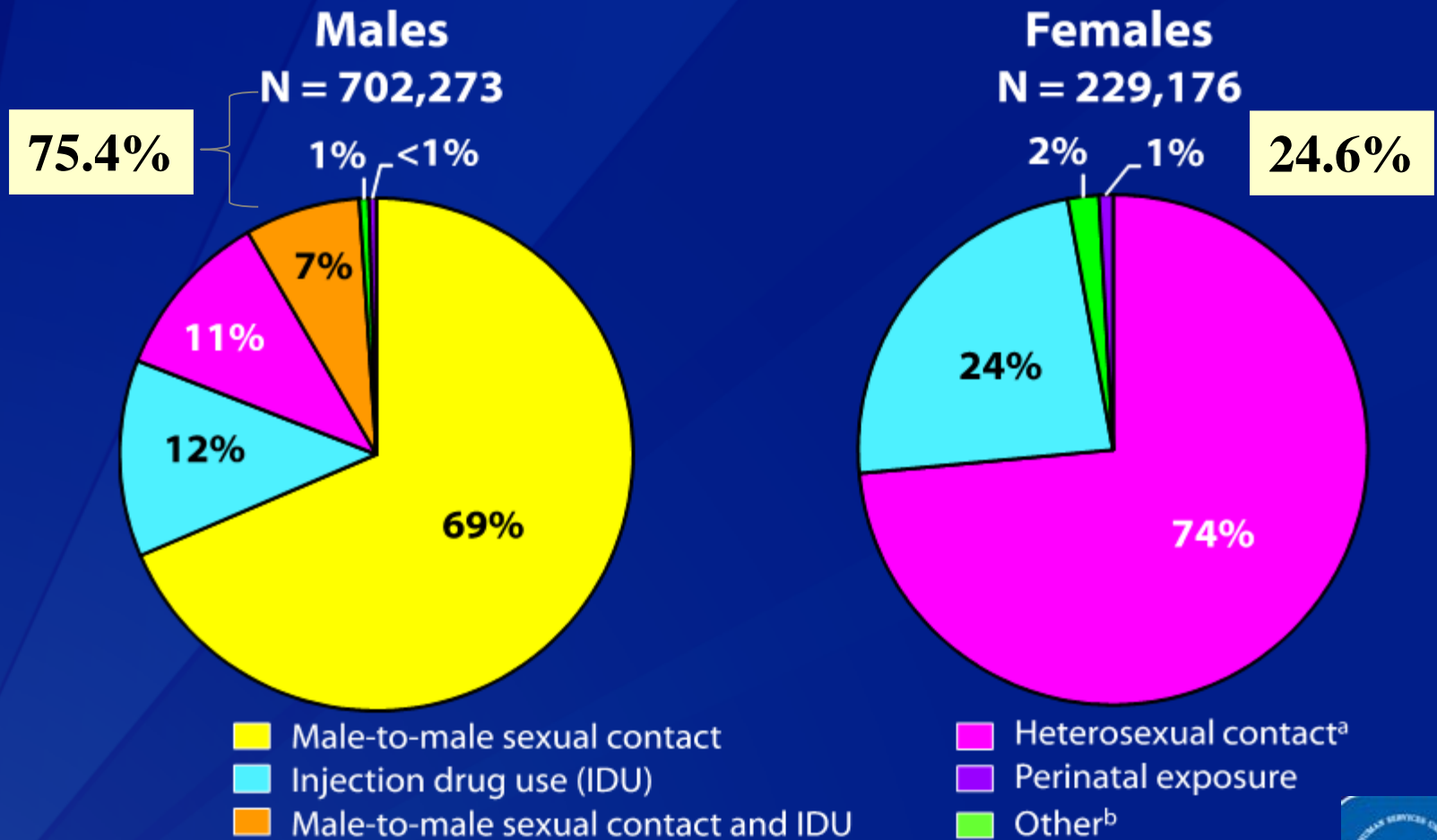




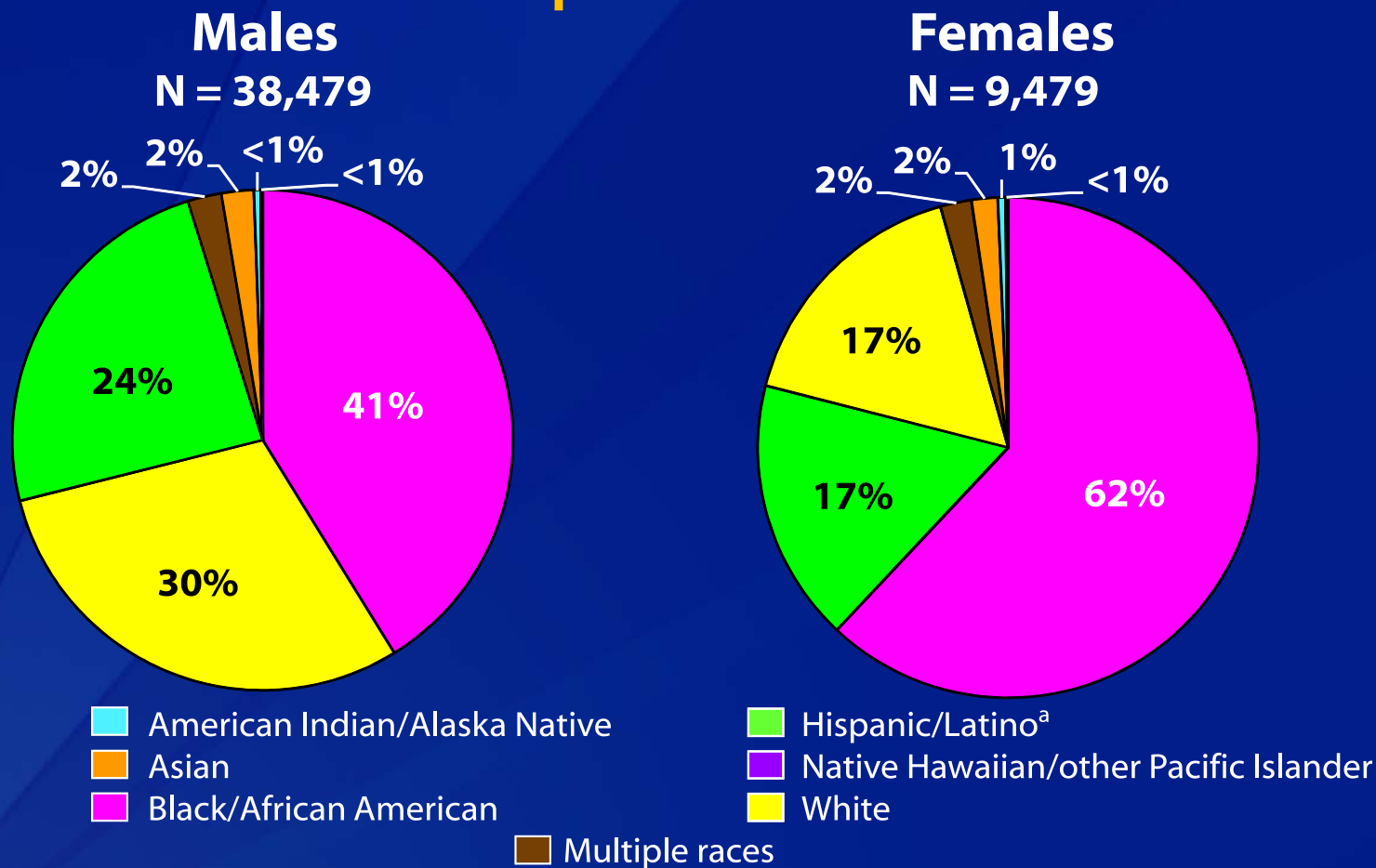
What about HIV infections among women in the U.S.?



# Adults and Adolescents Living with Diagnosed HIV Infection, by Sex and Transmission Category, Year-end 2012—United States and 6 Dependent Areas



# Diagnoses of HIV Infection among Adults and Adolescents, by Sex and Race/Ethnicity, 2013—United States and 6 Dependent Areas



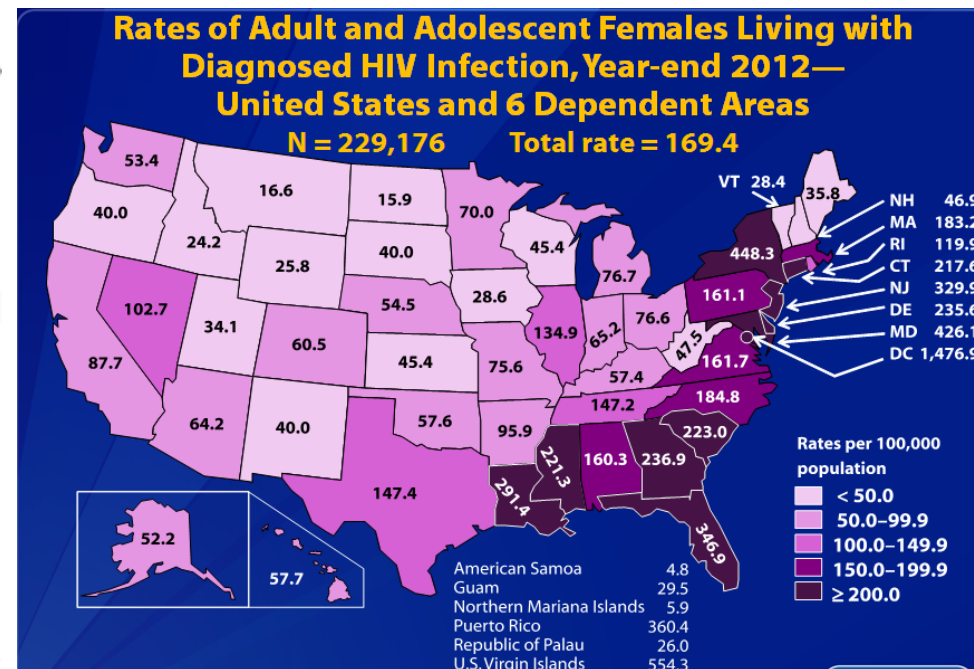
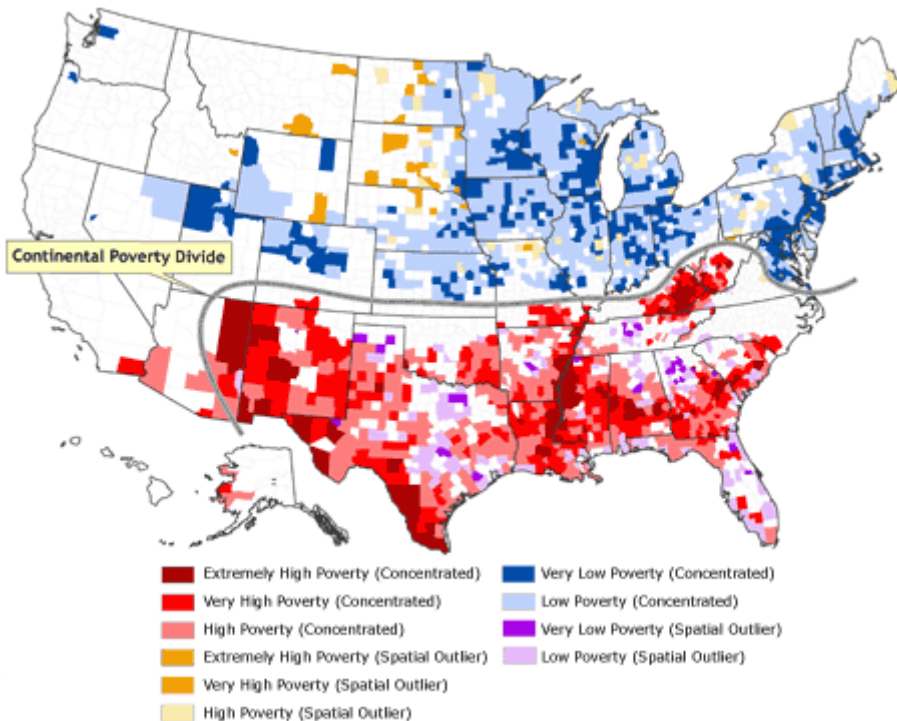
Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.

<sup>a</sup> Hispanics/Latinos can be of any race.



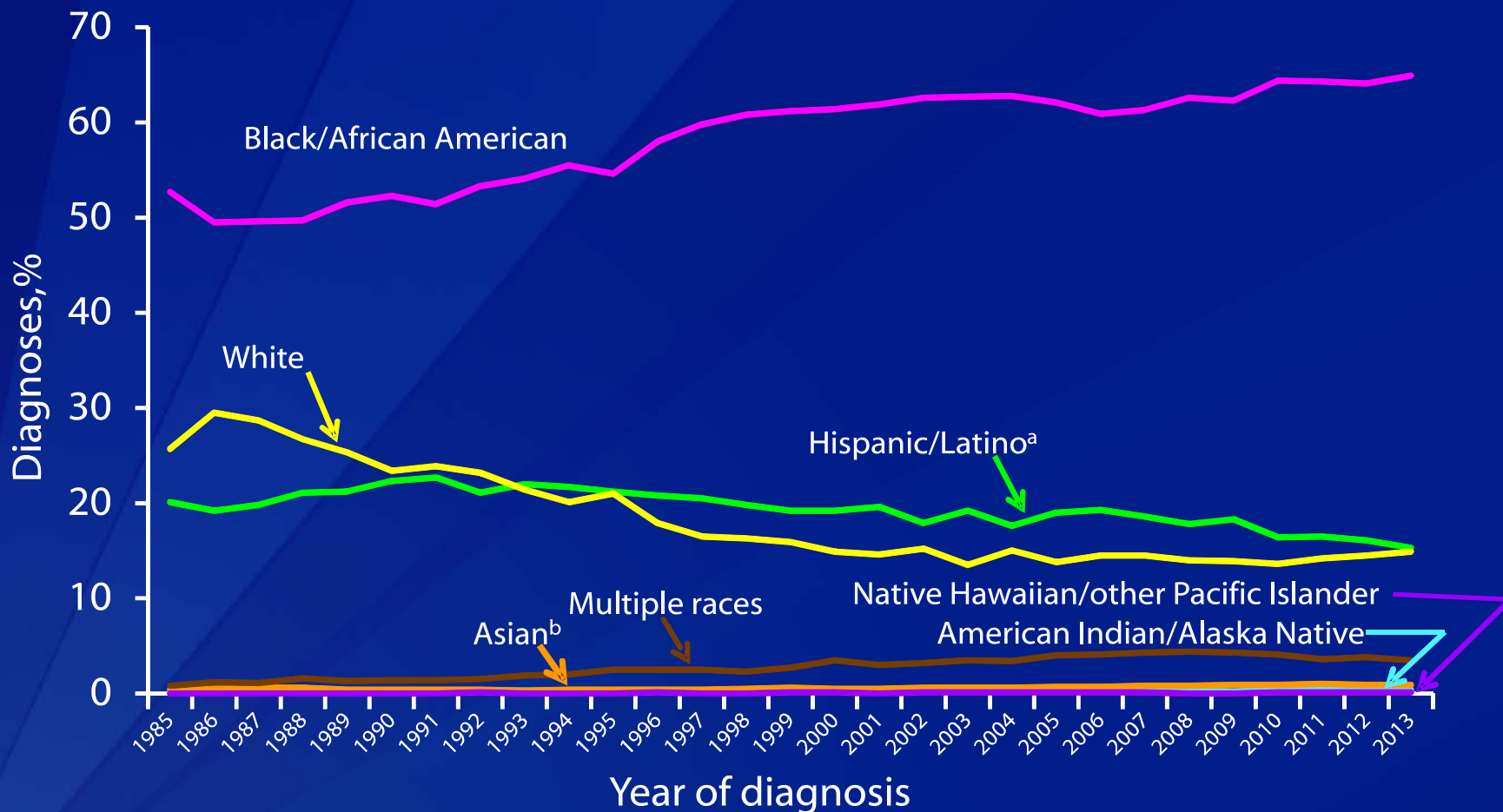
# Risks in U.S. women cluster with poverty, disempowerment

- HIV in women clusters with poverty<sup>1,2</sup>; interpersonal violence<sup>3</sup>; incarceration<sup>4-7</sup>; self-esteem, alcohol/drugs<sup>8</sup>



<sup>1</sup>Amidora. STDs 2006; <sup>2</sup>CDC Surveillance 2011; <sup>3</sup>Wyatt. Am J Public Health 2002; <sup>4</sup>Doherty. JAIDS 2009; <sup>5</sup>Doherty. Am J Public Health 2007; <sup>6</sup>Adimora. Am J Public Health 2007; <sup>7</sup>Khan. J Urban Health 2009; <sup>8</sup>Forna. J Natl Med Assoc. 2006

# Percentages of Stage 3 (AIDS) Classifications among Adult and Adolescent Females, by Race/Ethnicity and Year of Diagnosis 1985–2013—United States and 6 Dependent Areas



Note. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.

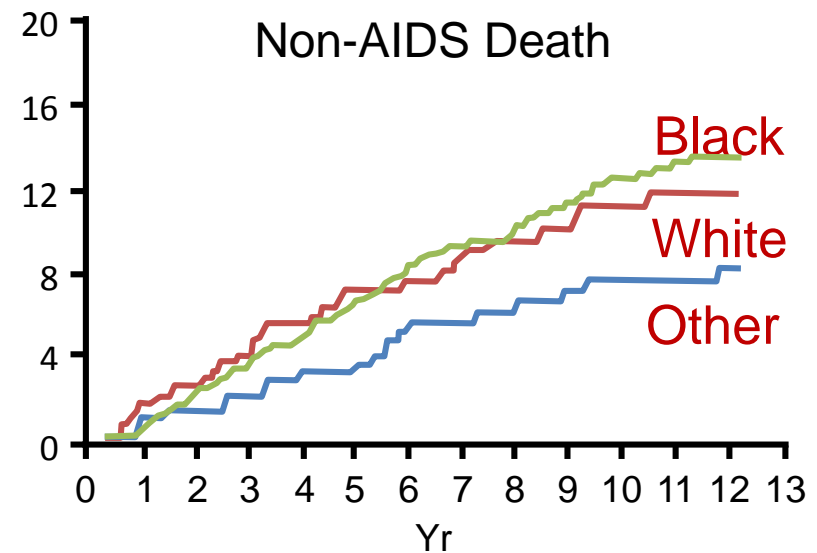
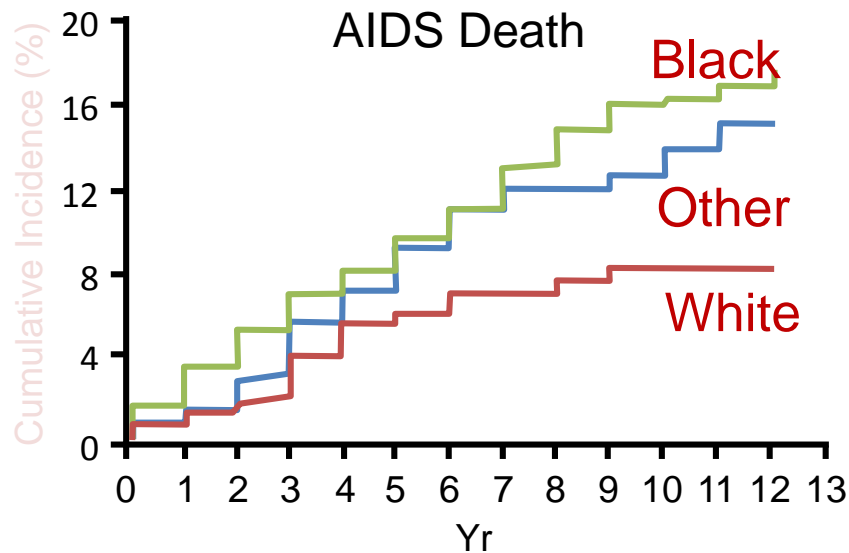
<sup>a</sup> Hispanics/Latinos can be of any race.

<sup>b</sup> Includes Asian/Pacific Islander legacy cases.



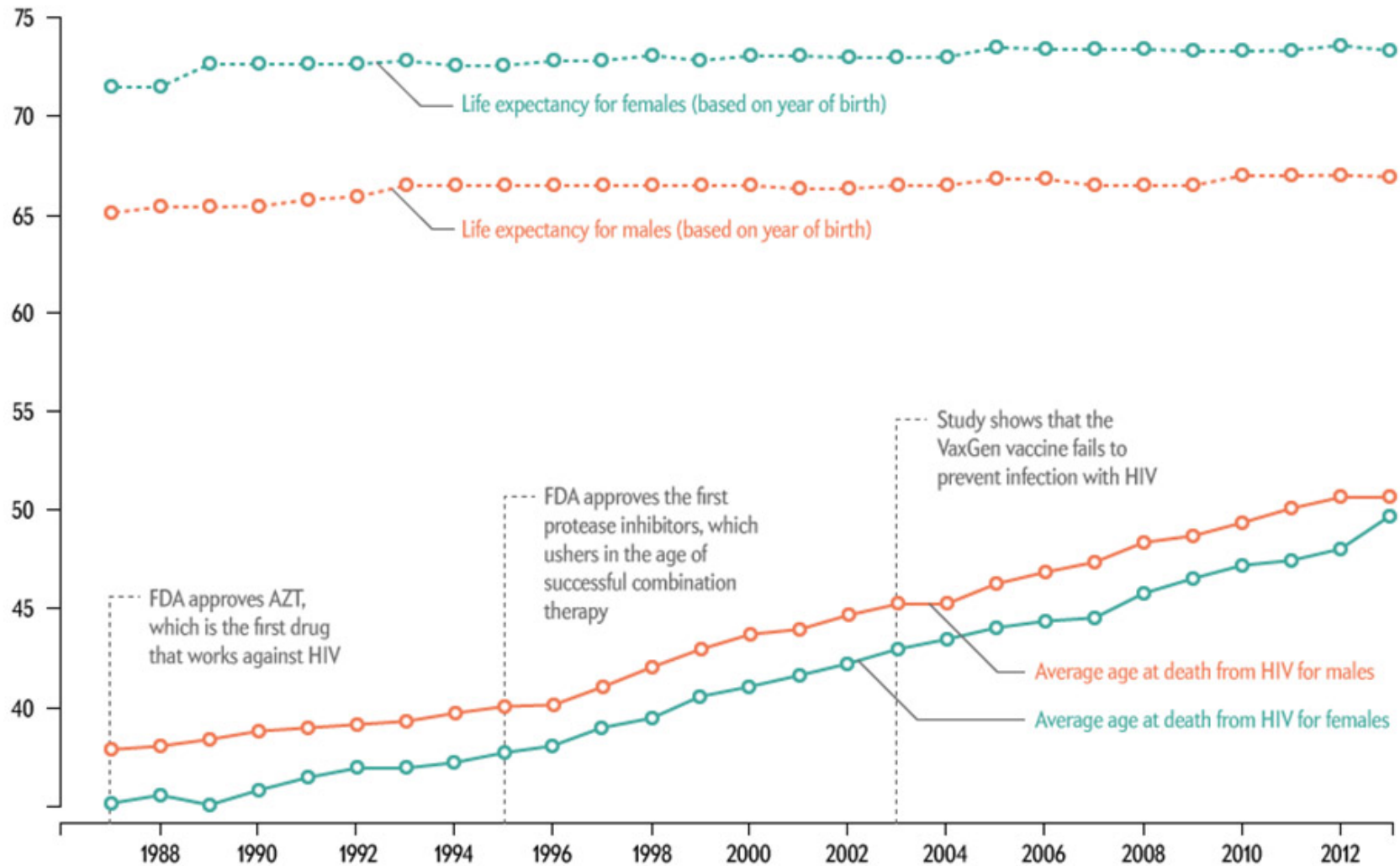
# WIHS: Black HIV+ Women Twice as Likely to Die of AIDS Than White HIV+ Women

- N = 1471 women on continuous HAART



- Other significant predictors of AIDS death: depression, peak HIV-1 RNA, nadir CD4+ cell count, HCV co-infection, substance use, < 95% adherence to ART
- Black race, depression predicted reduced adherence to ART, but black race remained associated with AIDS death after adjusting for adherence

Average Age at Death from HIV in the United States, 1987-2013



Graphic by Amanda Montañez, for SCIENTIFIC AMERICAN

Sources: National Vital Statistics System: U.S. mortality data files, 1987-2013; Aids.gov: A Timeline of AIDS; National Center for Health Statistics: life expectancy

What about HIV prevention in women?





**Of the following interventions, which has the best evidence of efficacy in preventing HIV transmission to women?**

1. Microbicides
2. Circumcision of the male partner
3. Male condoms
4. Giving the HIV-negative woman pre-exposure prophylaxis (PrEP)
5. Giving the HIV-positive male partner HIV treatment

# Prevention only works if you know you're at risk

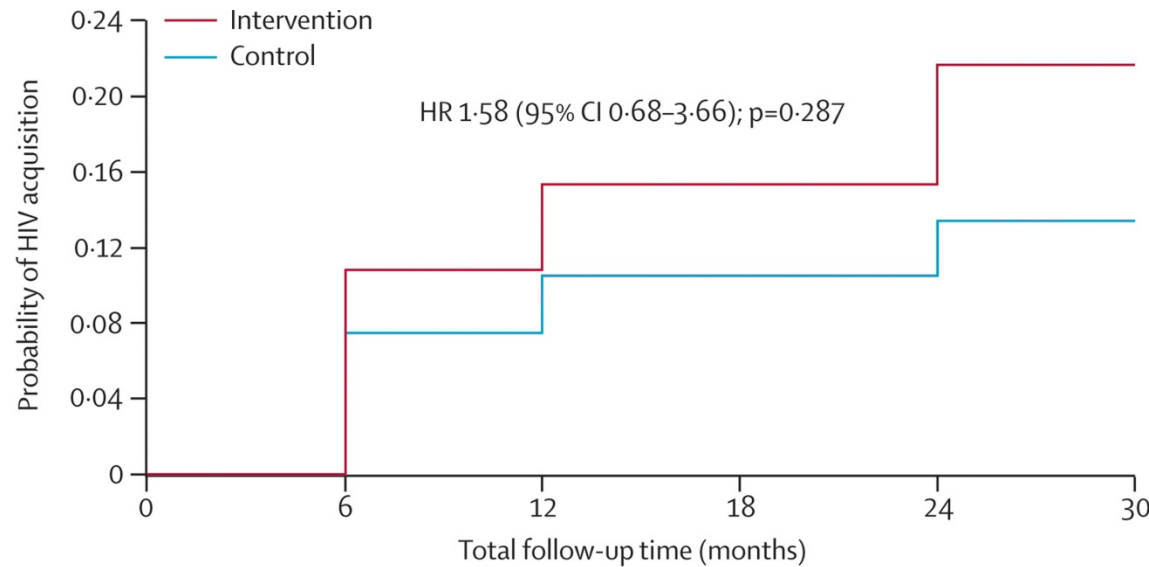
*“Women at risk for HIV acquisition frequently do not appreciate their risk. The HIV epidemic among US women is, in many ways, hidden from effective dialogue, both among the populations at risk and within the broader scientific community”<sup>1</sup>*

- In recent study (members of couple interviewed separately), 1 in 5 black women had a male partner at high risk (MSM or IVDU), but fewer than half knew<sup>2</sup>
- 74% heterosexual<sup>3</sup>
- Economic disempowerment – access to health care, condom negotiation
- 11% men concomitant relationships<sup>4</sup>
- Underestimate of bisexual behavior<sup>5</sup>
- 1 in 9 black men incarcerated<sup>6</sup>

<sup>1</sup>Hodder S. JAIDS 2010; <sup>2</sup>Denning P IAS 2015; <sup>3</sup>CDC Surveillance 2013; <sup>4</sup>Adimora. JAIDS 2003;;  
<sup>5</sup>Singh S. Am J Public Health 2014; <sup>6</sup>Adimora JAIDS 2014

# Circumcision- conflicting data for women

- Parallel study of serodiscordant female partners in Rakai circumcision trial (60% ↓ to men<sup>1</sup>)<sup>2</sup>
- Circumcision did not ↓ transmission to females over 24 mo (intercourse before wound healing?)
- Meta-analysis same findings<sup>3</sup>
- Prospective study in African males - 40% reduction of transmission to females but not quite statistically significant (95% CI 0.35-1.10, p 0.10)<sup>4</sup>



<sup>1</sup> Gray H. Lancet. 2007; <sup>2</sup>Wawer MJ. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda. Lancet. 2009; <sup>3</sup>Weiss HA. Lancet ID, Nov 2009; <sup>4</sup>Baeten J. AIDS 2010

# Major RCTs of microbicides

Trial location	Candidate microbicide	Efficacy	Reference
Thailand, South Africa (Female sex workers)	Nonoxynol-9	Increased transmission	<i>Van Damme. AIDS 2000</i>
South Africa	Carraguard gel	No protective effect	<i>Skoler-Karpoff. Lancet 2008.</i>
Africa, India	Cellulose sulfate	No protective effect	<i>Van Damme. NEJM 2008</i>
Africa	PRO2000 gel	No protective effect	<i>McCormack. Lancet 2010</i>
Africa, USA	BufferGel	No protective effect	<i>Abdool-Karim. AIDS 2011</i>
South Africa	1% tenofovir gel, coitally dependent, CAPRISA 004	39% reduction in HIV acquisition (54% in high gel adherers)	<i>Abdool-Karim. Science 2010</i>
South Africa	1% tenofovir gel, daily, VOICE	No overall protection, Some efficacy with PK detection	<i>Marrazzo. NEJM 2015; Dai JID 2015</i>
Africa	1% tenofovir gel, coitally dependent, FACTS 001	No protective effect, PK showed low adherence	<i>Rees. CROI 2015</i>

# Does PrEP work as well in women as men?

1. Yes
2. No
3. No one knows



8 major PrEP trials	Population/Setting	Intervention	Reduction in HIV Infection Rate, %
iPrEX <sup>[1]</sup> (N = 2499)	MSM, 11 sites in US, S. America, Africa, Thailand	<ul style="list-style-type: none"> <li>Daily oral TDF/FTC</li> </ul>	44% (95% CI 15-63, p 0.005), no cis-women
Partners PrEP <sup>[2]</sup> (N = 4747)	Serodiscordant couples in Africa	<ul style="list-style-type: none"> <li>Daily oral TDF</li> <li>Daily oral TDF/FTC</li> </ul>	<ul style="list-style-type: none"> <li>Women: 71%; men: 63%, p 0.79</li> <li>Women: 66%; men: 84%, p 0.06</li> </ul>
TDF2 <sup>[3]</sup> (N = 1219)	Heterosexual males and females in Botswana	<ul style="list-style-type: none"> <li>Daily oral TDF/FTC</li> </ul>	62%* (underpowered for sex differences)
Bangkok TFV Study <sup>[4]</sup> (N= 2413)	IDU (use in last year) in Bangkok, 20% female	<ul style="list-style-type: none"> <li>Daily oral TDF</li> </ul>	Women 78.6% (p 0.03); men 37.6% (p 0.15)
FEM-PrEP <sup>[5]</sup> (N = 2120)	High-risk women, Africa	<ul style="list-style-type: none"> <li>Daily oral TDF/FTC</li> </ul>	<ul style="list-style-type: none"> <li>Study stopped early, no significant efficacy</li> </ul>
VOICE <sup>[6]</sup> (N = 5029)	High-risk women, Africa	<ul style="list-style-type: none"> <li>Daily oral TDF</li> <li>Daily oral TDF/FTC</li> <li>1% TFV gel</li> </ul>	<ul style="list-style-type: none"> <li>1% TDF gel &amp; daily oral TDF arm both stopped early (HR 0.34 gel with detectable drug)</li> <li>Daily TDF/FTC arm. no significant efficacy</li> </ul>
IPERGAY and PROUD <sup>[7,8]</sup>	Both MSM, Ipergay (“on demand” PrEP) and PROUD (daily)	<ul style="list-style-type: none"> <li>Ipergay: 2 h before, 2-24h after, q24h</li> <li>PROUD: Daily</li> </ul>	<ul style="list-style-type: none"> <li>86% effective, no cis-women</li> </ul>

1. Grant RM. NEJM 2010; 2. Baeten JM, NEJM. 2012; 3. Thigpen MC. NEJM 2012. 4. Choopanya K Lancet 2013; 5. Van Damme L. NEJM. 2012; 6. Murrain J. NEJM 2015; 7. McCormack Lancet 2015; 8. Molina. NEJM 2015

# VOICE (MTN-003) trial

Halted 2011, futility

Oral tenofovir

Reported 2013, published 2015

Oral Truvada<sup>®</sup>

Halted 2011, futility

Vaginal tenofovir gel

Didn't work either

Placebo study product

- Vaginal and Oral Interventions to Control the Epidemic (VOICE) MTN-003 trial: 5-arm trial to compare DAILY oral tenofovir, oral tenofovir/emtricitabine (Truvada), vaginal TFV gel, 2 placebo groups (5000 women)

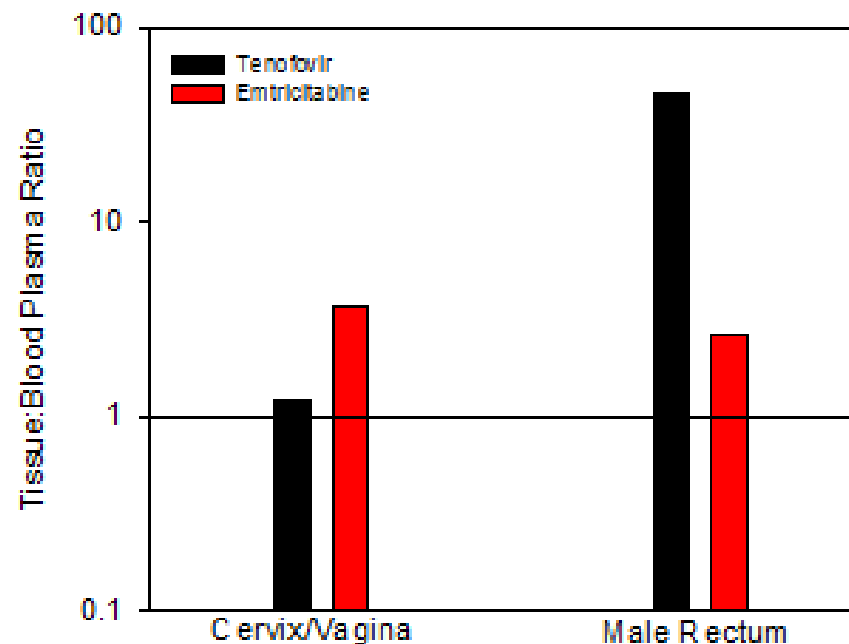
# VOICE: Adherence = Efficacy

Study Drug	Percentage of patients		
	TDF	FTC/TDF	TFV Gel
Returned Pill or Applicator Counts	87	92	86
Self Report (7 days)	90	91	90
Adherence based on plasma TFV detection	30	29	25



# Exposure/adherence may be particularly important in women

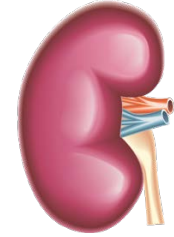
- Adherence may be more critical in women - tenofovir concentrations are higher in rectal than vaginal tissue<sup>1</sup>
- Cumulative exposure of rectal tissue to tenofovir and tenofovir-emtricitabine 30x and 120x higher, respectively, vs vaginal tissue in same women<sup>2</sup>



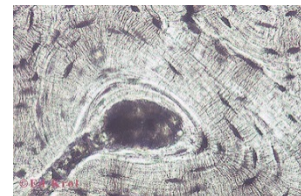
<sup>1</sup>Patterson KB. *Sci Transl Med* 2011;

<sup>2</sup>Louissaint NA *AIDS Res Hum Retroviruses*. 2013;

# Safety Issues of PrEP in women



- Effect on **renal** function
  - Partners PrEP study: risk of small, non-progressive, reversible decline in glomerular filtration rate shown
- Effect on **bone mineral density**
  - Women are at higher risk than men for bone toxicities
  - Rates of osteopenia and osteoporosis are higher in HIV-infected patients than the general population<sup>2</sup>



# PrEP in women: Practical considerations

- “PrEP-ception”: HIV- woman with HIV+ male partner taking PrEP before and during pregnancy
  - Likely safe (PROMISE trial\*)
  - Male partner should be on ART treatment
  - Ongoing PrEP-ception trial –HIV serodiscordant couples in 4 U.S. cities wishing to conceive- looking at adherence, condom use, teratogenicity
- Likely safe in breastfeeding; does not interfere with hormonal contraceptives<sup>1</sup>
- Along with usual screening in PrEP (HIV Ab, Hep B, renal function), pregnancy tests every 3 months.

\*when combined with a protease inhibitor, this combination lead to poorer newborn outcomes. Appears to be safe when used alone.

<sup>1</sup>Callahan R, JAIDS 2015

What about treatment outcomes in HIV for women?



# What is the percent of women being enrolled in publicly-funded ARV trials?

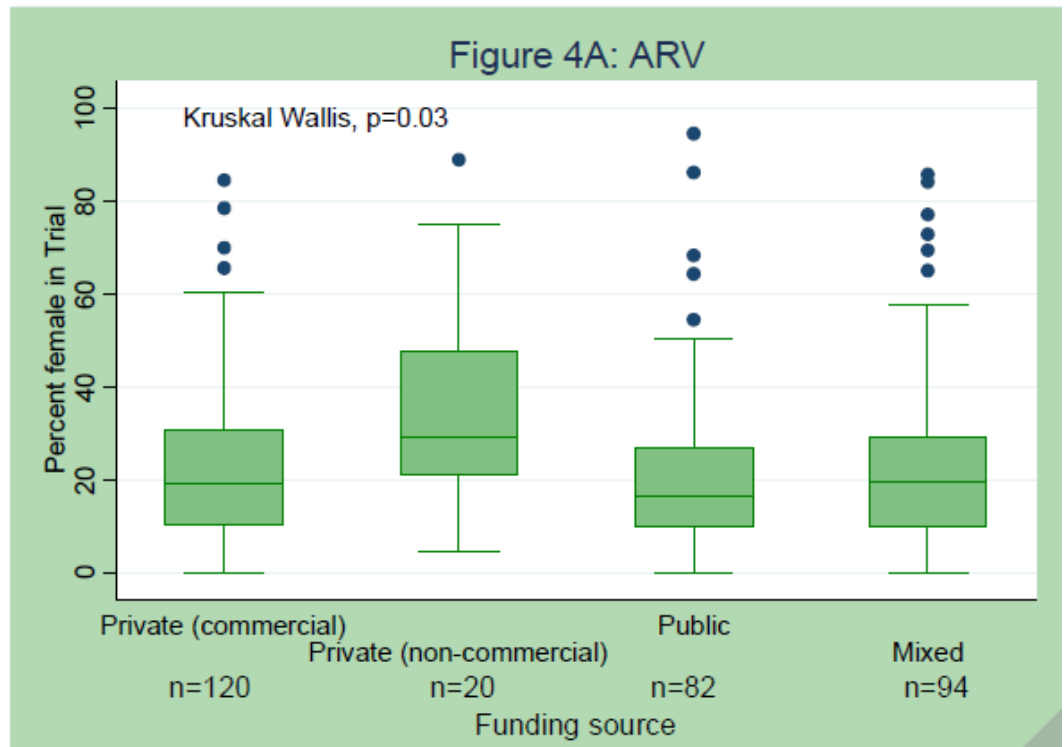
1. 12.5%
2. 16.7%
3. 22.5%
4. 33.7%
5. 50%

# Women underrepresented in clinical trials....STILL

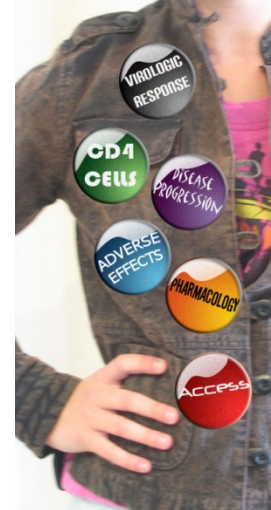
*Women represented a median of 19.2% participants in ARV studies (387), 38.1% in VAX studies 47 (53) and 11.1% in CURE studies (104).*



Curno M et al.  
JAIDS. 9/2015



# Treatment outcomes by sex



## ● Long story short:

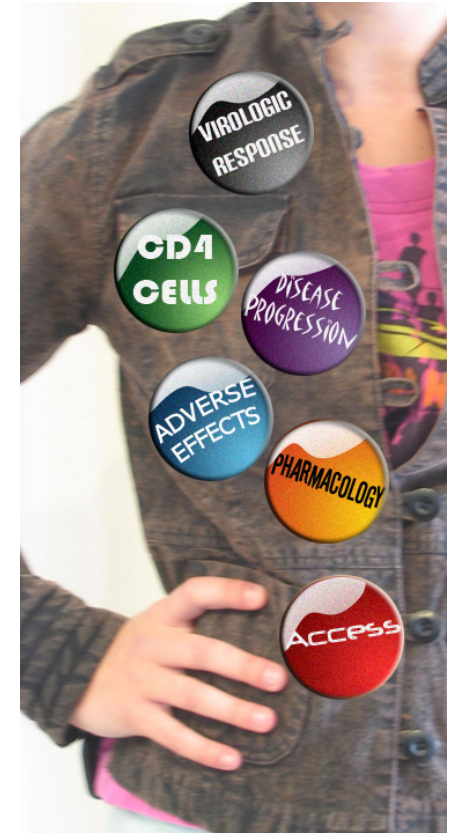


- Women do better than men on ARVs globally, mainly from coming earlier to care through antenatal setting, adherence, less attrition
- Women do worse than men in the U.S. (Canada, Europe), mainly due to social determinants of health



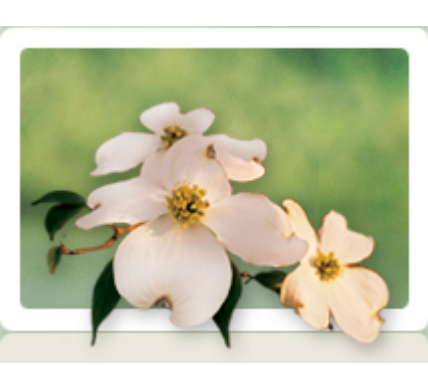
# In U.S., usual suspects in terms of social determinants of health

- Lower socioeconomic status<sup>1</sup>
- Lower education levels<sup>1, 2</sup>
- Lower rates of having health insurance
- More food insecurity<sup>3</sup>
- Competing priorities (childcare, etc.)<sup>7</sup>
- Depression<sup>4</sup>
- Substance use<sup>5,6</sup>
- Domestic violence<sup>8</sup>
- Distrust of the medical system<sup>9</sup>
- Knowledge base of HIV/AIDS poor<sup>10</sup>



<sup>1</sup>Sohler et al. AIDS Patient Care & STDs, 2009; <sup>2</sup>Braitstein. J Women's Health 2008; <sup>3</sup>Weiser. JAIDS 2009; <sup>4</sup>Ickovics. JAMA 2001; <sup>5</sup>Ghebremichael M AIDS Care 2009; <sup>6</sup>Cook et al. AIDS 2008; <sup>7</sup>Stein. J Gen Intern Med 1991; <sup>8</sup>Wyatt AJPH 2002; <sup>9</sup>Bogart LM AIDS 2005; <sup>10</sup>Fleming. STDs 2006





# GRACE (Gender, Race and Clinical Experience) Study – Higher side effects with many ARVS in women

- Landmark study: 67% women (84% black or Hispanic), comparing outcomes on Darunavir
- 32.8% of women (vs 23.2% men) discontinued ART
- Trend - worse virologic responses in women driven by higher d/c rates<sup>1,2</sup>
- Conclusion (many studies): Real world and even clinical studies in HIV lose HIV-infected women: discontinuation rates high, adverse effects higher<sup>3</sup>

<sup>1</sup>Currier J et al. Sex-based outcomes of darunavir-ritonavir: A single group trial. *Annals of Internal Medicine* September 21, 2010; 153(6): 349-358; <sup>2</sup>Squires K. *AIDS Patient Care and STDS* 2013; Smith K. *J Nat Med Assoc* 2012; <sup>3</sup>Loutfly MR. *J Intl AIDS Society* 2013\*

# Pharmacokinetics: The explanation of sex differences?



- If women have higher ARV levels than men, could explain
  - Increased risk of toxicities
  - Improved outcomes
  - Drug levels in treatment experienced patients may be particularly determinative of outcome

Gandhi M. Sex differences in PK and PD. *Annu Rev Pharm Tox* 2004; Hoffman. Evaluation of sex differences of fosamprenavir in HIV-infected men and women. *HIV Clin Trials* 2007; Ofotokun. Antiretroviral pharmacokinetic profile: A review of sex differences. *Gender Med.* 2007; Loutfly MR. *J Intl AIDS Society* 2013\*

# Primary care screening for HIV-infected women



# The rate of which two cancers is not typically elevated in HIV infection?

1. Kaposi's sarcoma and CNS lymphoma
2. Cervical cancer and anal cancer
3. B cell lymphoma and primary effusion lymphoma
4. Lung cancer and colorectal cancer
5. Prostate cancer and breast cancer

# Breast and prostate cancer rates not typically higher in HIV infection

**Table 2.** Crude Cancer Type-Specific Incidence Rates and All-Cause Death Rates, by HIV Infection Status, NA-ACCORD, 1996-2009

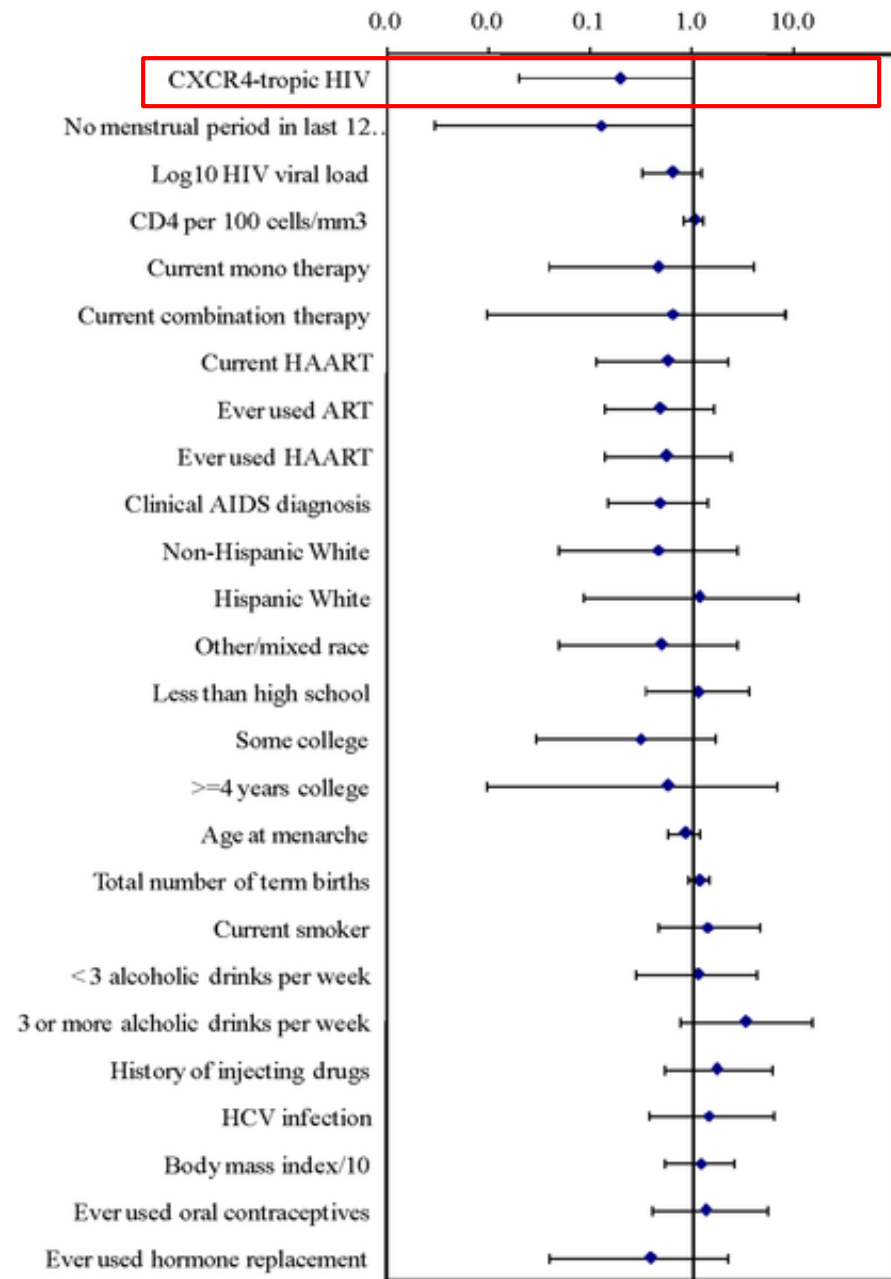
Event	Persons With HIV		Uninfected Persons	
	Persons, <i>n</i>	Incidence Rate per 100 000 Person-Years	Persons, <i>n</i>	Incidence Rate per 100 000 Person-Years
Kaposi sarcoma	612	130.4	3	0.2
Non-Hodgkin lymphoma	725	153.5	233	12.6
Lung cancer	614	129.3	839	45.4
Anal cancer	285	60.1	22	1.2
Colorectal cancer	173	36.4	510	27.7
Liver cancer	220	46.3	201	10.9
Hodgkin lymphoma	159	33.5	36	1.9
Melanoma	78	16.4	268	14.5
Oral cavity/pharyngeal cancer	163	34.3	340	18.4
Death	17 534	3686.0	15 400	833.0

NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.

NA-ACCORD Study: 86 620 persons with HIV and 196 987 uninfected adults

# Possible mechanism

- HIV binds to CD4 and to CCR5 or CXCR4 chemokine co-receptors
- Neoplastic breast cells commonly express CXCR4, but not CCR5
- In vitro, binding HIV protein to CXCR4 has been shown to induce self destruction of neoplastic breast cells
- Women with CXCR4-tropic HIV in large HIV+ women cohort had lower rates of breast CA



# Breast and cervical cancer screening in HIV+ women

Intervention	Recommendation	Comment(s)
Mammography	Perform annually in all women age 50 years or older	In women aged 40–49 years, providers should perform individualized assessment of risk for breast cancer and inform them of the potential benefits and risks of screening mammography
Cervical Pap smear	HIV-infected women should have a cervical Pap test performed upon initiation of care, and this test should be repeated at 6 months and annually thereafter if results are normal	Women with atypical squamous cells (both ASCUS and ASC-H [ASC, cannot rule out high-grade squamous intraepithelial lesion]), atypical glandular cells, low-grade or high-grade squamous intraepithelial lesion, or squamous carcinoma noted by Pap testing should undergo colposcopy and directed biopsy, with further treatment as indicated by results of evaluation

# Summary

- Women doing more poorly in U.S. than men, may be closing gap
- PrEP works, but adherence may be especially important in women due to mucosal pharmacokinetics
- Bone safety with tenofovir and pregnancy monitoring in PrEP special considerations
- Women may have higher drug levels (PK) than men, leading to higher toxicities
- Breast cancer screening same as HIV-negative, but cervical cancer screening more frequently





# Thank you

- + Dr. Monica Gandhi
- + Researchers studying all aspects of HIV in women
- + HIV infected women for continuing to teach us
- + The HIV Health Services Planning Council

