HIV and Women

Optimizing Care – AAHM

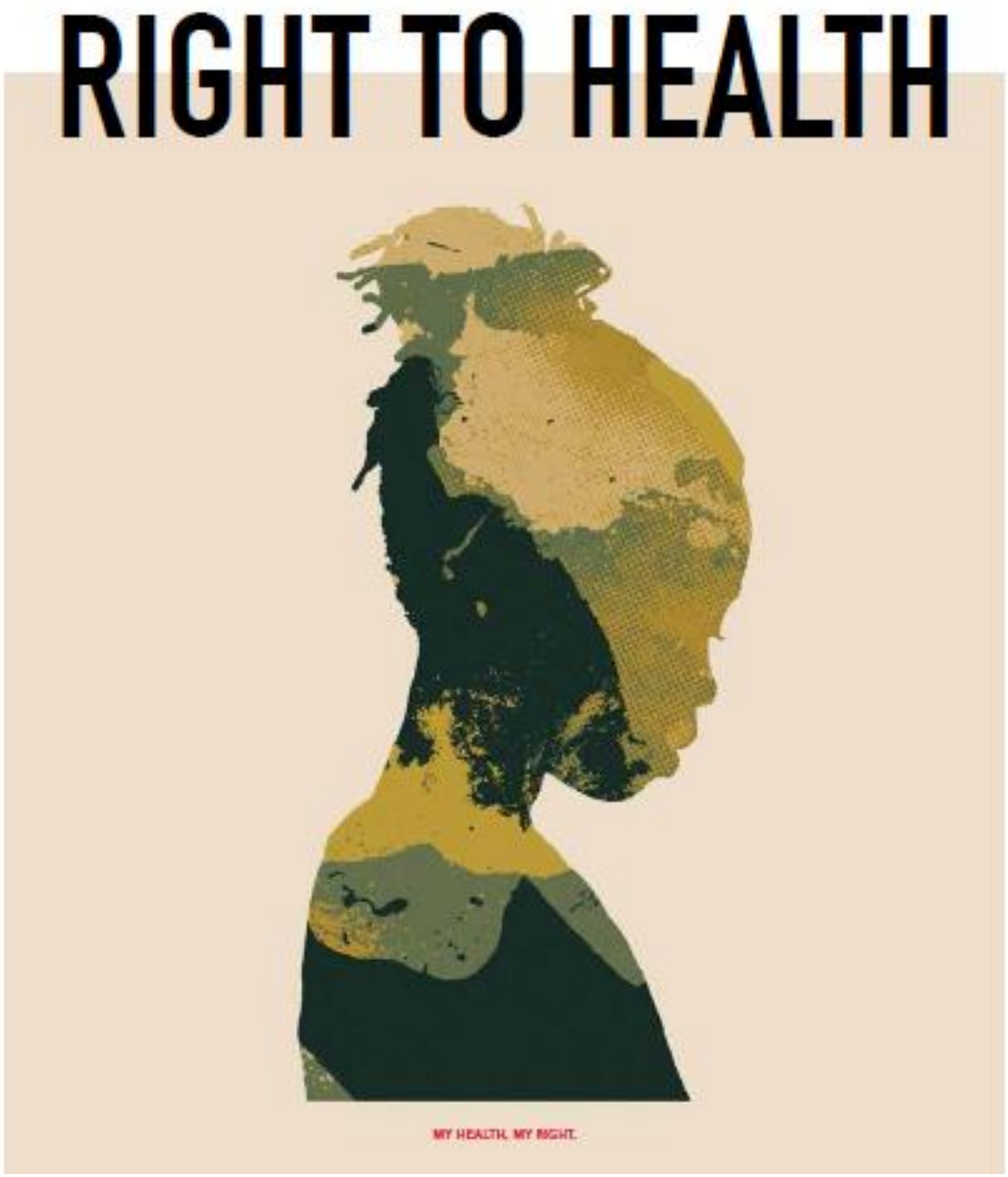
July 30, 2021

Monica Gandhi MD, MPH

Professor of Medicine, UCSF

Division of HIV, Infectious Diseases, and Global Medicine

Medical director, “Ward 86” HIV Clinic, San Francisco General Hospital

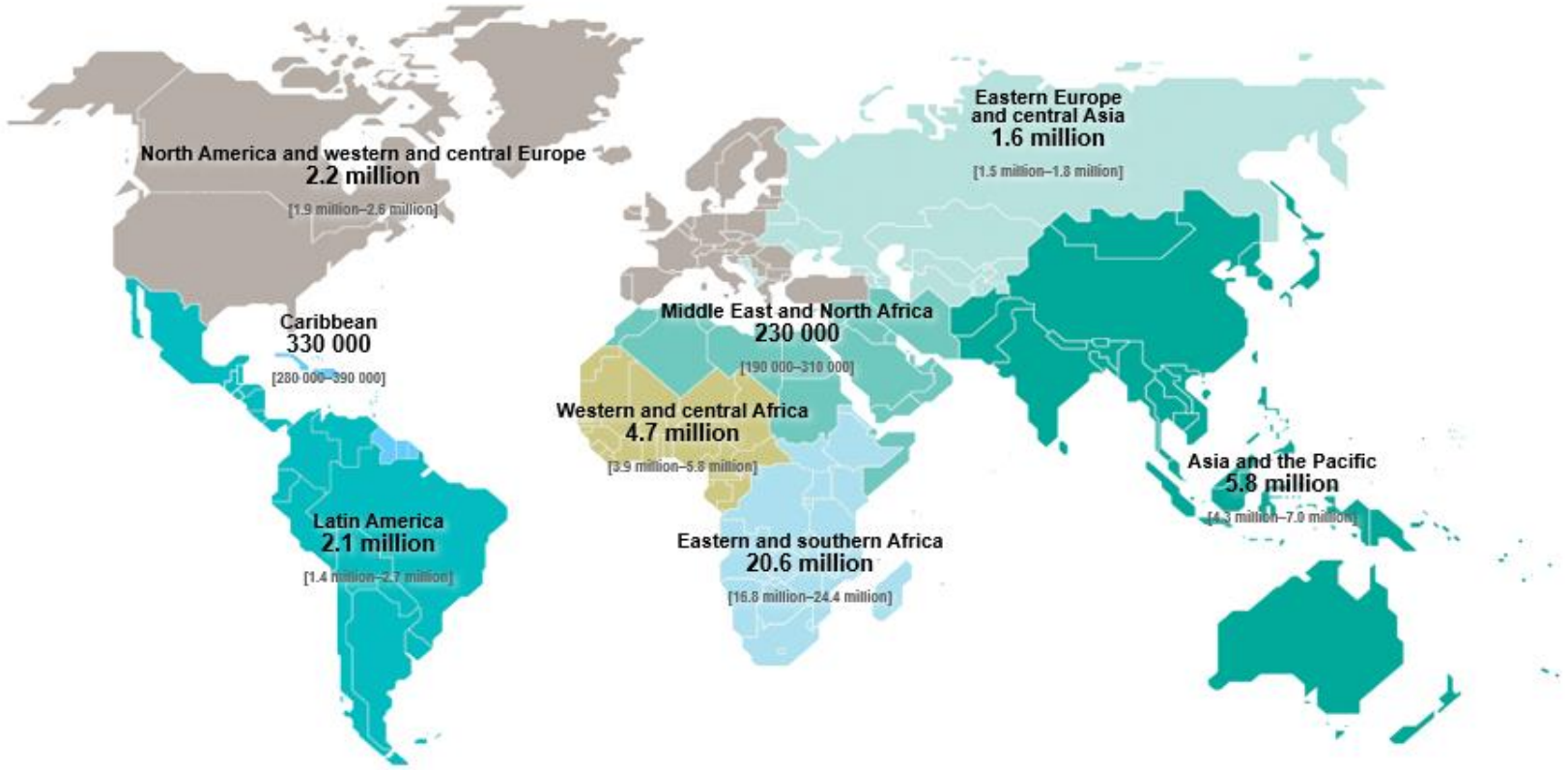


Outline

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
- **ART and pregnancy**
  - Update this year
- **Primary care for women**
  - Breast and cervical cancer screening, menopause

Adults and children estimated to be living with HIV | 2020

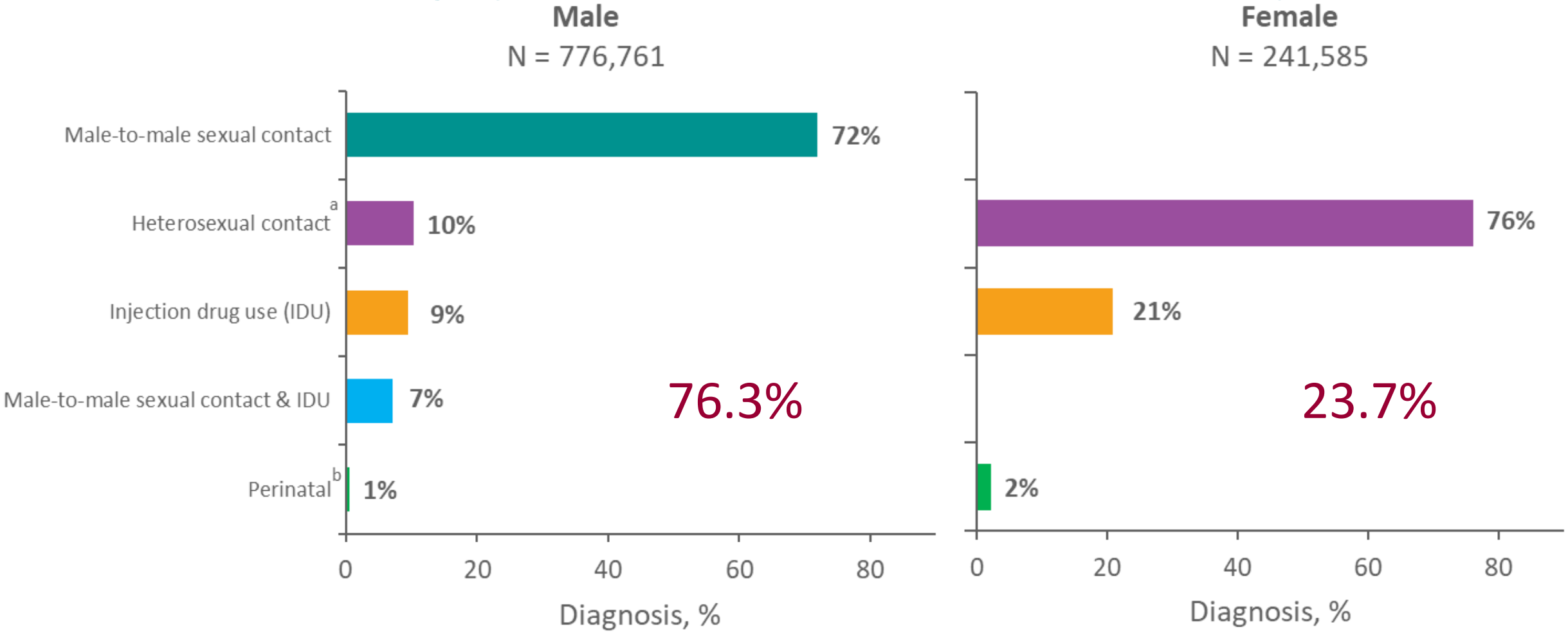


Total: 37.7 million [30.2 million–45.1 million]

19.3 million women (51.2%) out of 37 million adults

UNAIDS

Adults and Adolescents Living with Diagnosed HIV Infection, by Sex and Transmission Category, Year-end 2017—United States and 6 Dependent Areas



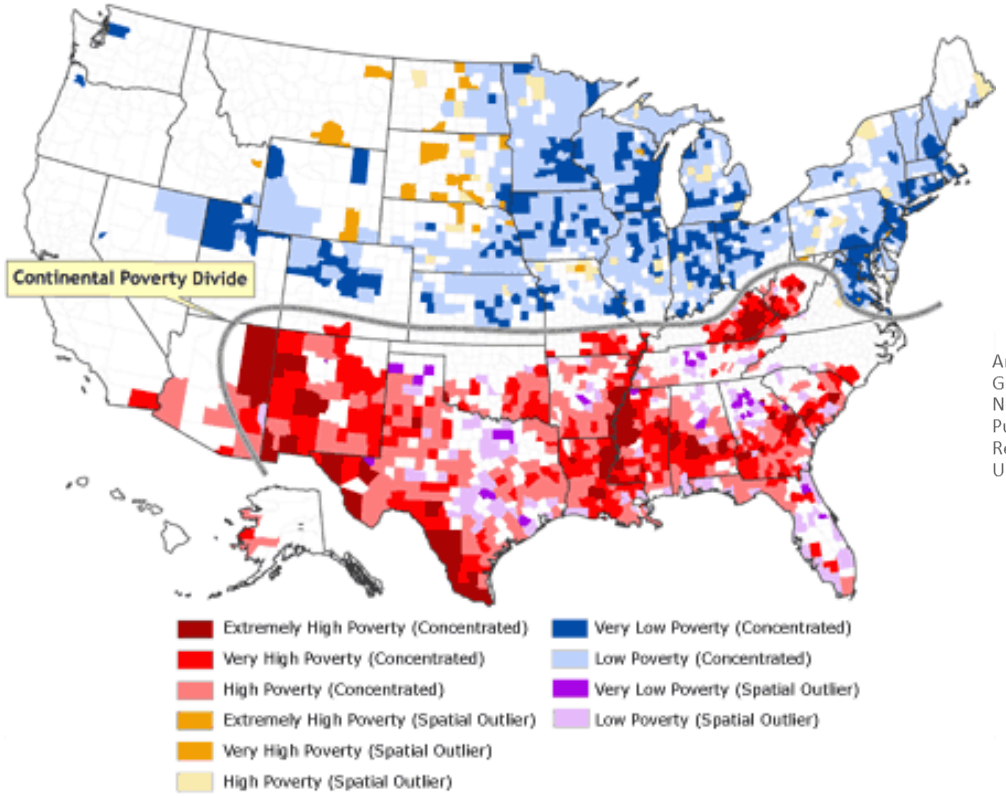
Note. Data have been statistically adjusted to account for missing transmission category. "Other" transmission category not displayed as it comprises 1% or less of cases.

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

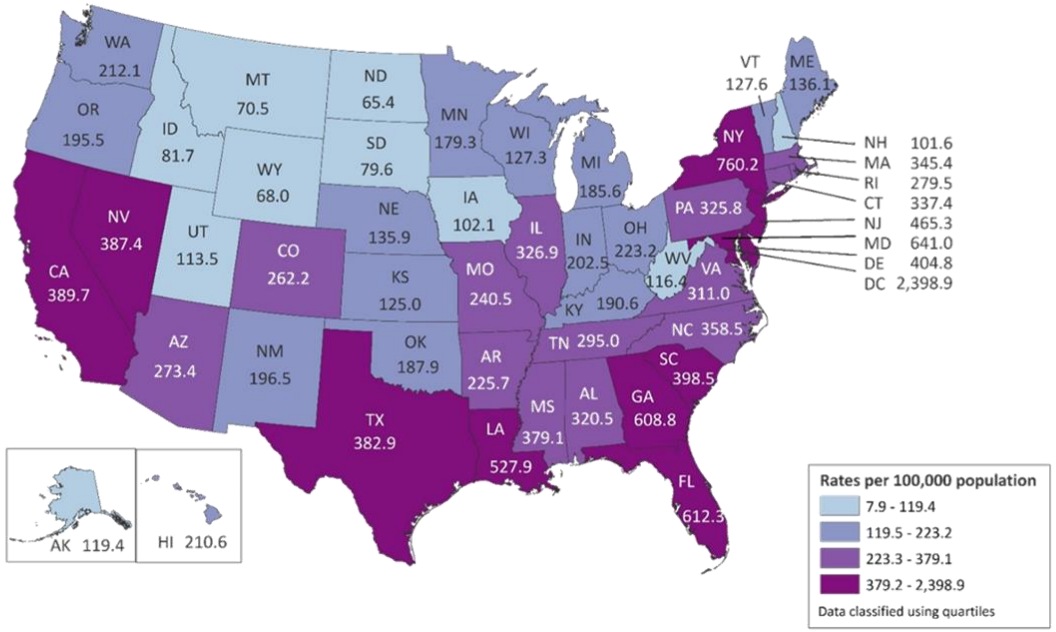
[b] Perinatal includes persons whose infections were attributed to perinatal transmission, but were aged 13 years and older at the end of 2017.

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

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



American Samoa	7.9
Guam	74.9
Northern Mariana Islands	34.8
Puerto Rico	553.5
Republic of Palau	50.1
U.S. Virgin Islands	610.8



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

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4 PrEP options either available or in works

- TDF/FTC – many clinical trials
- TAF/FTC – DISCOVER Trial
- Vaginal dapivirine ring- ASPIRE, RING and now HOPE
- Intramuscular cabotegravir- HPTN083 and HPTN084

Placebo-controlled PrEP trials of TDF/FTC

Trial	Population/Setting	Intervention	Reduction in HIV Infection Rate, %
iPrEX[1] (N = 2499)	MSM, 11 sites in US, S. America, Africa, Thailand	▪ Daily oral TDF/FTC	44% (95% CI 15-63, p 0.005)
Partners PrEP[2] (N = 4747)	Serodiscordant couples in Africa (men, women)	▪ Daily oral TDF ▪ Daily oral TDF/FTC	▪ Women: 71%; men: 63% ▪ Women: 66%; men: 84%
TDF2[3] (N = 1219)	Heterosexual males and females in Botswana	▪ Daily oral TDF/FTC	62%* (underpowered for sex differences)
Bangkok TFV Study[6] (N= 2413)	IDU (use in last year) in Bangkok (men, women)	▪ Daily oral TDF	49% (95% CI 9.6-72.2, p 0.01)
FEM-PrEP[4] (N = 2120)	High-risk women, Africa	▪ Daily oral TDF/FTC	▪ Study stopped early due to futility (adherence)- no efficacy
VOICE[5] (N = 5029)	High-risk women, Africa	▪ Daily oral TDF ▪ Daily oral TDF/FTC ▪ 1% TFV gel	▪ 1% TDF gel & daily oral TDF arm both stopped early, futile ▪ Daily TDF/FTC arm – no efficacy (adherence)

1. Grant RM. N Engl J Med. 2010. 2. Baeten JM. N Engl J Med. 2012 3. Thigpen MC. N Engl J Med. 2012; 4. Van Damme. N Engl J Med. 2012 5. Marrazzo J, N. Engl J. Med. 2015; 6. Choopanya Lancet June 2013; 7. McCormack. CROI 2015

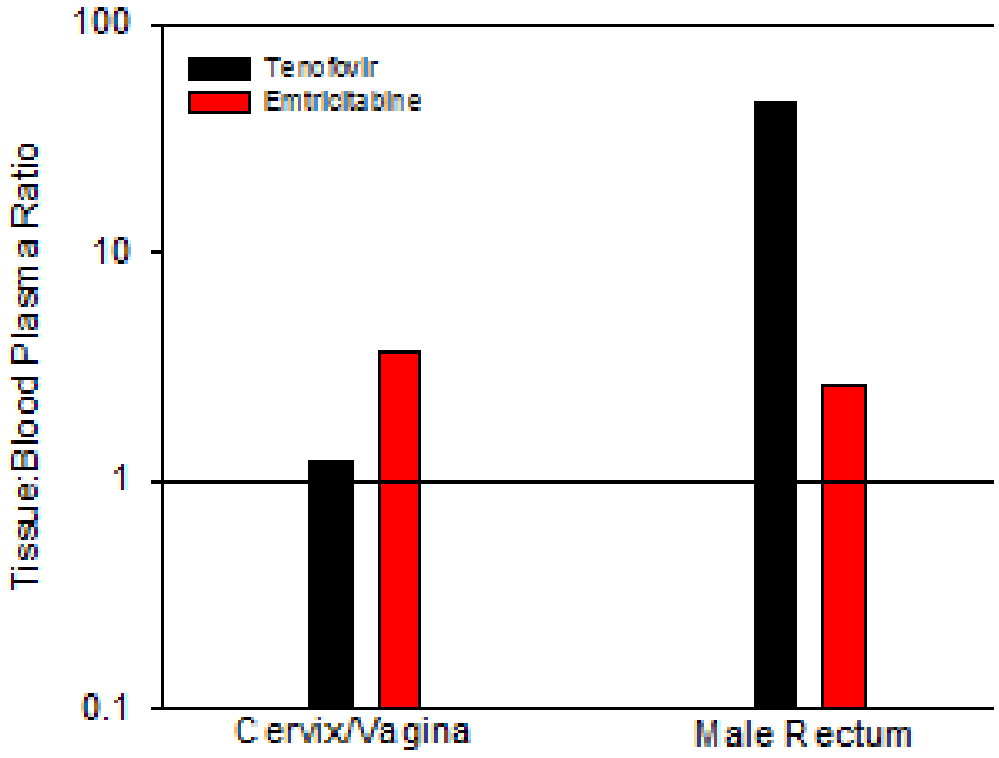
FEM-PrEP and VOICE: Pharmacologic monitoring indicated adherence was issue

Adherence Measure	VOICE	FEM-PrEP
Self-report	91%	95%
Returned pill counts	92%	88%
Plasma TFV detection	29%	24%

Marrazzo et al. NEJM 2015; Van Damme et al. NEJM 2012

Idea that adherence to TDF/FTC may need to be higher in women on PrEP came from PK modeling and surprising results of FEM-PrEP/VOICE

- TFV concentrations are higher in rectal than vaginal tissue[1]
- Cumulative exposure of rectal tissue to TFV and TFV-DP 30x and 120x higher, respectively, vs vaginal tissue in same women[2]
- Modeling of 4 doses/wk okay for men may not apply for women[3]



[1]Patterson KB. *Sci Transl Med* 2011; [2]Louissaint NA *AIDS Res Hum Retroviruses*. 2013; [3]Anderson P. Sci Transl Med 2012; [4]Grant. Lancet ID 2014; Cortrell JID 2016

What did PrEP demonstration projects in women tell us?

HPTN 082: Evaluation of daily oral PrEP as a primary prevention strategy for young African women

Study Population

Uninfected women
Ages 16-25 yrs

Johannesburg & Cape Town, South Africa
Harare, Zimbabwe

Target Enrollment

- 400 women who accept PrEP at enrollment
- ≤200 women who decline PrEP at enrollment

Standard adherence support

Standard adherence support *plus* drug level feedback

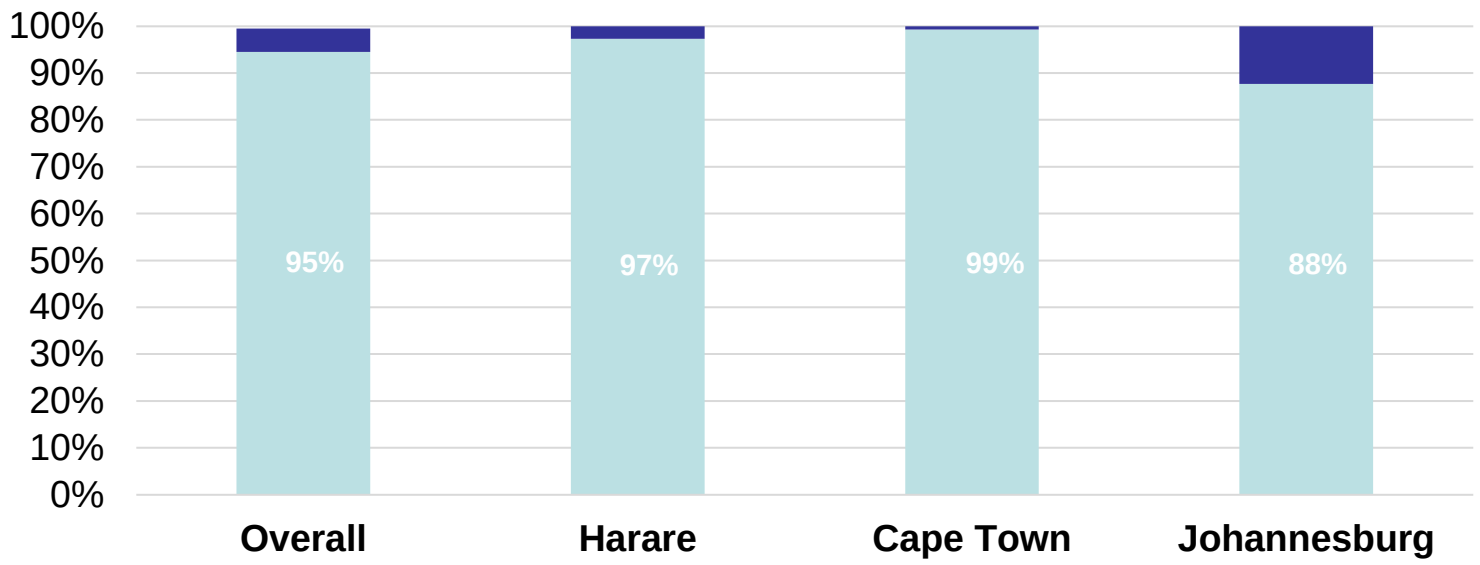
Eligibility criteria: Sexually active in past month; VOICE risk score ≥5; interest in PrEP; normal creatinine clearance; hepatitis B seronegative; access to mobile phone

Slide courtesy C. Celum

HPTN
HIV Prevention
Trials Network

HPTN 082: PrEP uptake

Figure 1: PrEP uptake overall and by site



Slide courtesy C. Celum

HPTN Q82
HERS

Tenofovir levels at 3, 6, & 12 months

	3 months N=371	6 months N=363	12 months N=347
Tenofovir diphosphate (TFV-DP), DBS			
Detectable	83.6%	56.5%	31.4%
≥700 fmol/punch* (4 doses/week;among those with detectable TFV-DP)	24.8%	20.9%	8.6%

* TFV-DP ≥700 fmol/punch was associated with 100% efficacy among MSM in the iPrEX OLE study & the 25th percentile of 4 doses/week on average (Grant Lancet HIV 2014)

Slide courtesy C. Celum

HIV seroconversions

- Four HIV seroconverters observed in 404 person-years of follow-up (at months 3, 6, and two at 9)
- HIV incidence of 1.0/100 person-years (95% CI 0.3-2.5)
- 2 had undetectable DBS TFV-DP concentrations and 2 detectable but low concentrations (74 and 243 fmol/punch) in the visit at or prior to when they were first detected HIV seropositive
- Three had no resistance mutations & one had D67N (NRTI mutation) and four NNRTI mutations (K101E, K103N, E138A, and G109A)
  - No resistance mutations associated with TDF or FTC

Slide courtesy C. Celum

HPTN 082: Summary

- Very high PrEP uptake (95%) among young women at risk for HIV, a majority of whom took PrEP in the first 6 months
- Women who perceived themselves to be at risk of HIV and were motivated to use PrEP had higher adherence at 6 months
- Low HIV incidence (1%) given risk profile of this cohort
  - 4 doses a week seemed to be enough

Slide courtesy C. Celum

The 3P study:

Social marketing & conditional incentives to increase PrEP adherence

3P cohort characteristics
N=200

- Young (median age 19)
- Most had a primary partner; 71% of whom reported suspecting he had other partners
- 30% had CT, GC or trichomonas at baseline
- 19% reported IPV in the past year
- All but one had detectable TFV-DP in first 3 months

Slide courtesy C. Celum

Incentives conditioned on tenofovir levels to increase adherence among young women on PrEP in Cape Town

Celum, C[1], Gill, K[2], Morton, J[1], Stein, G[1], Myers L[2], Thomas, K[1], McConnell, M[3], van der Straten, A[4], Baeten, J[1], Duyver, M[2], Mendel, E[2], Naidoo, K[2], Dallimore, J[2], Wiesner, L[5], Bekker, LG[2]

[1]University of Washington, Seattle, WA, USA, [2]Desmond Tutu HIV Foundation, University of Cape Town, Cape Town, South Africa, [3]Harvard University, Boston, MA, USA, [4]Woman's Global Health Imperative, RTI and UCSF San Francisco, CA, USA, [5]University of Cape Town, Cape Town, South Africae

Table 1: PrEP adherence, as assessed by TFV-DP levels at 3 months by study arm

Tenofovir diphosphate in DBS at mo	Total	Incentive Arm	Control Arm
Concentration i			
Median (IQR)			969.0)
N Undetectable			
N Detectable			

1 HIV seroconversion in 3P so 4 doses a week may be enough…argues for pharmacodynamic rather than pharmacokinetic evaluations for efficacy (e.g. trials in women)

- All but
- At 3 m
- 80% had medium or greater adherence at 2 and 3 months.

Slide courtesy C. Celum

Bottom line on TAF/FTC for PREP, women- DISCOVER trial

- Only 74 TGW in this study of 5200 (rest MSM) so hard to make comment and no cisgender women
- Safety at 48 and 96 weeks – bit better, renal/bone issues resolve after d/c of PrEP so unclear significance; weight gain more in TAF/FTC arm
- FDA approved 10/3/19 but NOT for receptive vaginal sex

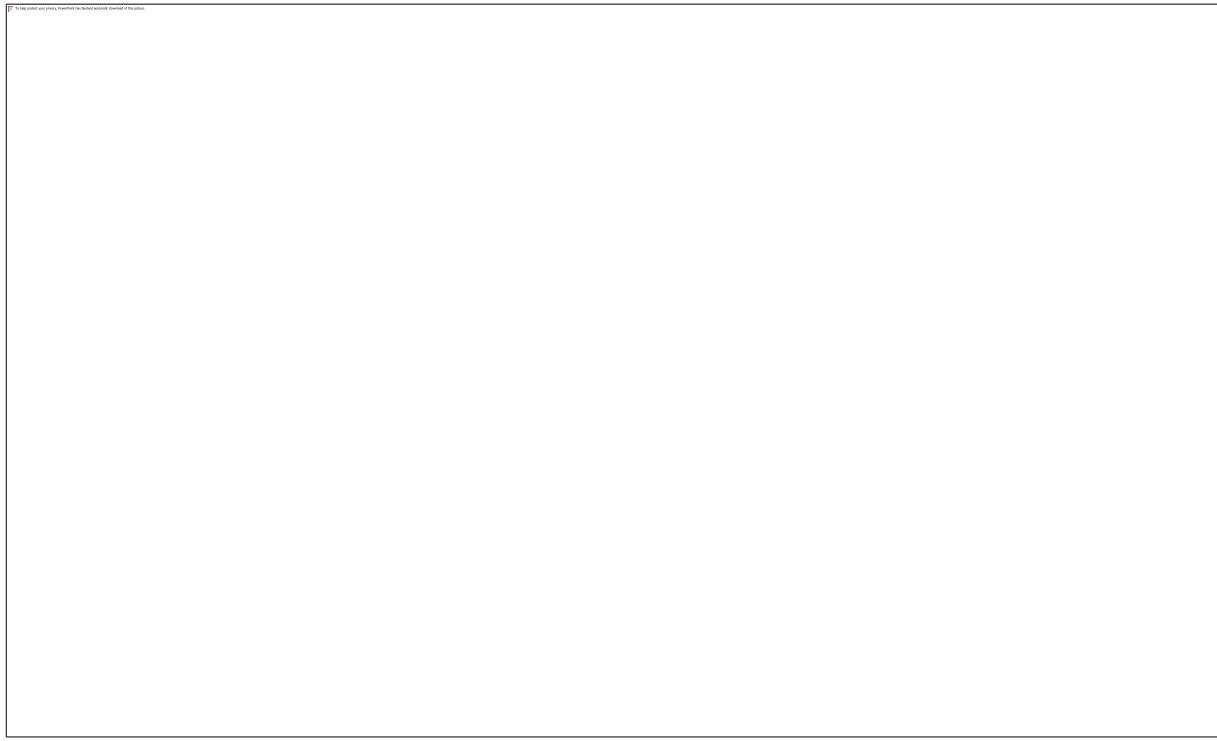
FDA NEWS RELEASE

FDA approves second drug to prevent HIV infection as part of ongoing efforts to end the HIV epidemic

What about safety with TAF/FTC? World Health Organization Treatment Guidelines – July 2019

- First-line treatment with either: TDF/FTC/DTG or TDF/3TC/DTG
- PrEP with either:
- TAF/FTC not recommended for routine treatment, WHO
  - No clear safety data for pregnant women
  - Concerns over weight gain
  - After 96 weeks, participants on TAF/FTC had gained average 1.7kg compared to 0.5kg TDF/FTC
- TAF/FTC should only be used for people with impaired renal function or osteoporosis

ADVANCE study



IPM-027 (Ring) & MTN-020/ASPIRE:
Dapivirine vaginal ring

Silicone ring containing 25 mg dapivirine (NNRTI) exchanged Q4 weeks

Randomized, double-blinded, placebo-controlled **Phase III** trials

- Women in Malawi, South Africa, Uganda, Zimbabwe
- Median age 26,[1,2] ~50% did not use condom with last sex act[2]
- Worked in open-label trials, adherence is everything

	Ring Study (N = 1959)	ASPIRE (N = 2629)
HIV incidence per 100 py, DPV v PBO	4.1 vs. 6.1	3.3 vs. 4.5
Overall reduction in HIV-1	31% (0.9-51.5)	27% (1-46)
Remove 2 low adhering sites	--	37% (12-56)
Women >21 years	37% (3.5-59)	56% (31-71)
Women 18-21 years	15% (-60, 55)	-27% (-133, 31)

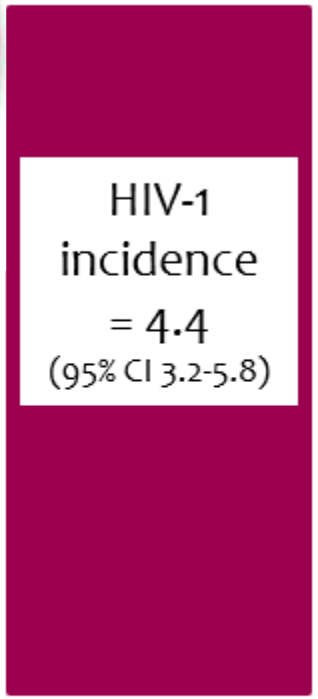
1. Nel A, et al. NEJM 2016. 2. Baeten J, NEJM 2016.

HOPE open-label extension study

ASPIRE

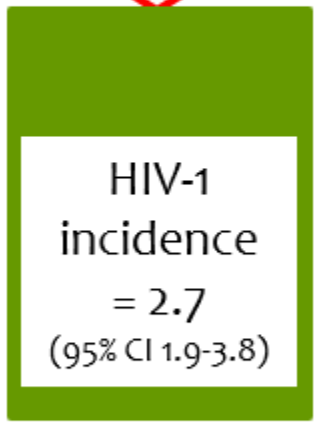
27% reduction

31% reduction



Placebo based on MTN-020/ASPIRE
EXPECTED

39% reduction
95%CI 14-65%



MTN-025/HOPE
OBSERVED

European Medicines Agency (EMA) approval of the dapivirine ring for HIV prevention for women in high HIV burden settings

24 July 2020 | Departmental news | Reading time: 3 min (740 words)

July 24, 2020

NIH Study is First Large Trial to Find Long-Acting HIV Prevention Highly Effective--Companion Study in Women Is Ongoing

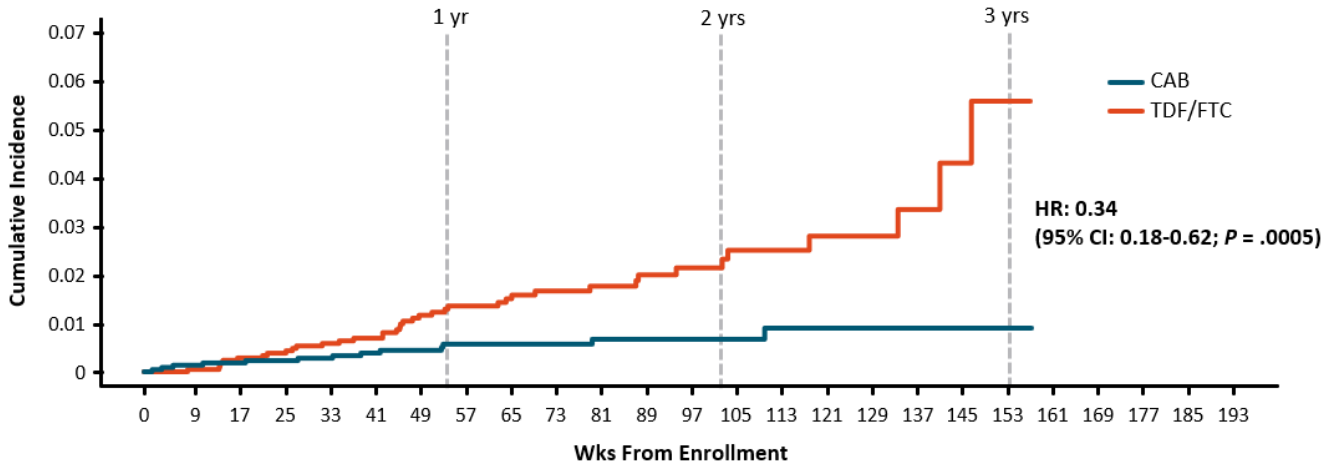
May 18, 2020

HPTN 083

an HIV prevention clinical trial

Study stopped year early due to efficacy

- HPTN083 phase 2b/3 study enrolled MSM and transgender women to compare long-acting cabotegravir IM q8 weeks vs daily TDF/FTC
- Launched 2016, enrolled 4,570 ppts throughout world
- CAB superior to TDF/FTC in prevention




U=U
UNDETECTABLE = UNTRANSMITTABLE

Undetectable = Untransmissable (U=U)

>150,000 condomless sex acts

Study	Population	Condomless Sex Acts	Transmissions within Partnership
PARTNER (JAMA 2016)	888 couples, 38% MSM; 62% heterosexual	58,000	**0**
Opposites Attract (Lancet 2018)	343 couples, 100% MSM	17,000	**0**
PARTNER2 (Lancet 2019)	783 couples 100% MSM	77,000	**0**

Undetectable = Untransmissable (U=U)

Dear Colleague

INFORMATION FROM CDC'S DIVISION OF HIV/AIDS PREVENTION

When ART results in viral suppression, defined as less than 200 copies/ml or undetectable levels, it prevents sexual HIV transmission. Across three different studies, including thousands of couples and many thousand acts of sex without a condom or pre-exposure prophylaxis (PrEP), no HIV transmissions to an HIV-negative partner were observed when the HIV-positive person was virally suppressed. ***This means that people who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively no risk of sexually transmitted the virus to an HIV-negative partner.***

CDC

CENTERS FOR DISEASE CONTROL AND PREVENTION

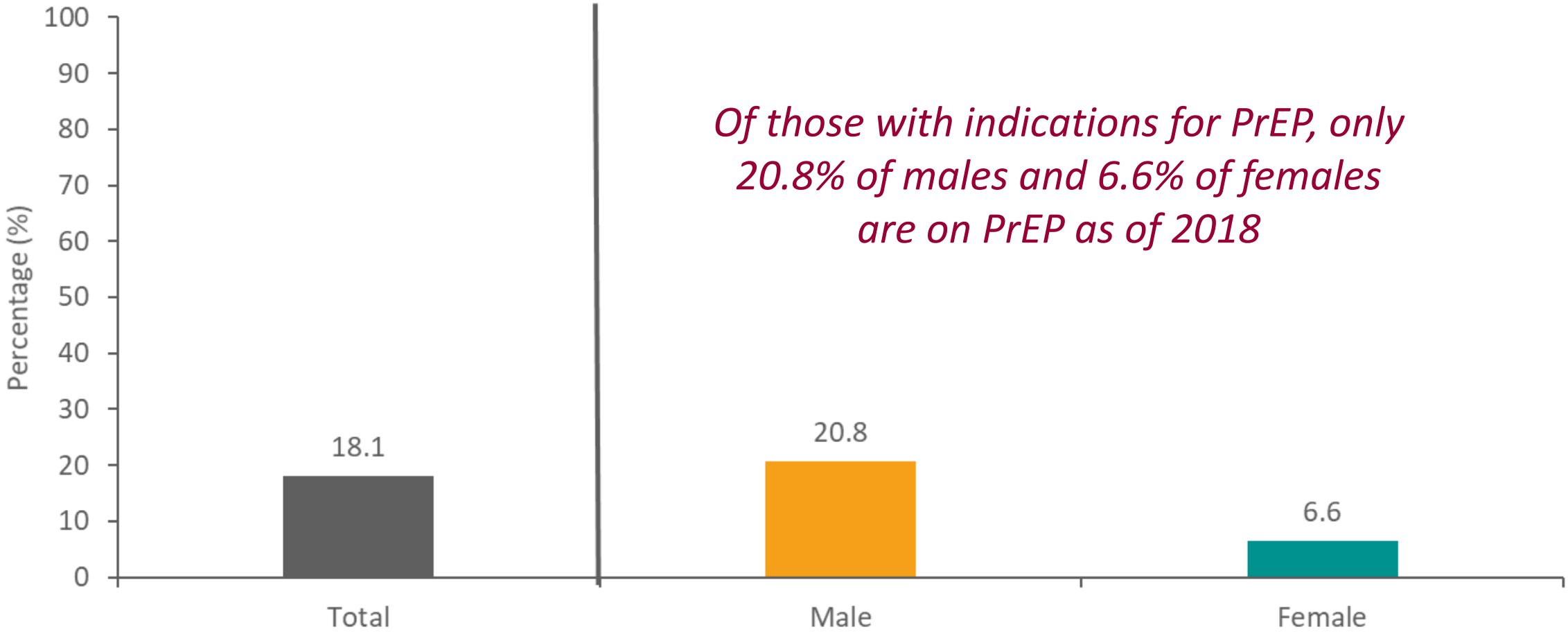
Gender-based inequalities

- 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 LIMC, average HIV prevalence among sex workers is ~12%, with an OR for HIV infection of 13.5 compared to all women aged 15–49 (violence and criminalization big contributors)

UNAIDS

2014

PrEP Coverage among Persons Aged ≥16 Years, by Sex at Birth 2018—United States

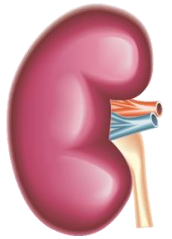


Of those with indications for PrEP, only 20.8% of males and 6.6% of females are on PrEP as of 2018

Abbreviation: PrEP, preexposure prophylaxis.

Note. PrEP coverage, reported as a percentage, was calculated as the number who have been prescribed PrEP divided by the estimated number of persons who had indications for PrEP. Different data sources were used in the numerator and denominator to calculate PrEP coverage.

Safety Issues of PrEP in women



- Effect on **renal** function
  - Partners PrEP study (TDF/FTC): average decline of -1.59 mL/min in eGFR vs placebo over median 18 months[1]
- Effect on **BMD**
  - 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[2]
  - iPrEX study: patients taking TDF had a 1.1% net decrease in mean BMD at femoral neck at 24 months[3]; in iPrEx OLE, -1.42% net decrease in spine at 24 wks.

[1]Mugwanya KK, et al. *JAMA Intern Med* 2015; [2]Brown TT. *AIDS*. 2006; [3]Liu AY *PLoS One.* 2011; [4]Mulligan K CID 2015

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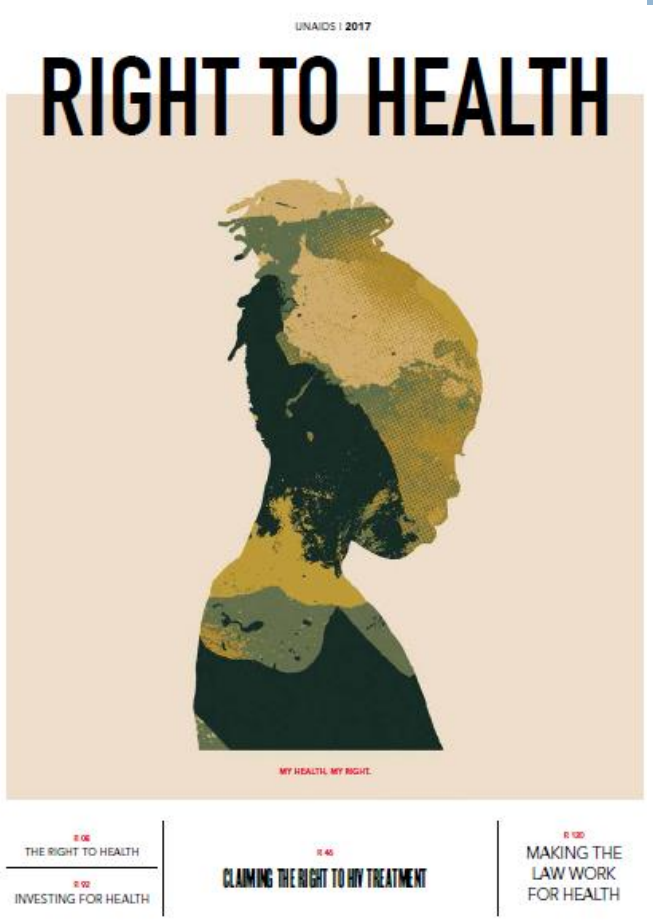
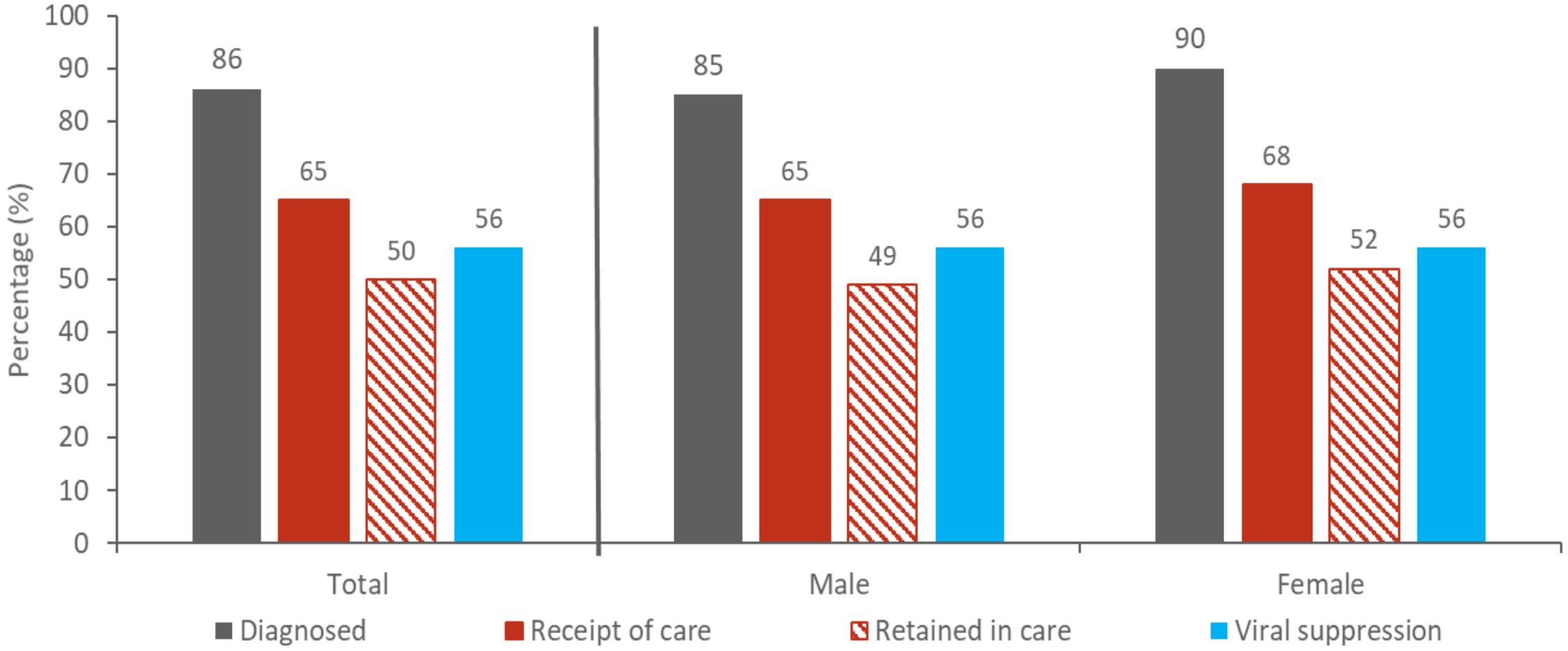
Half of all HIV infections globally are in women yet…



- Women still underrepresented in clinical trials of new HIV medications
  - Elvitegravir[1] and Bictegravir[2] (latter published 2017) both with <15% women in pivotal start studies
- Only 8.3% of participants enrolled in cure studies are women[3]
- When women are at the table to plan trials (e.g. important GRACE study[4]), women are enrolled

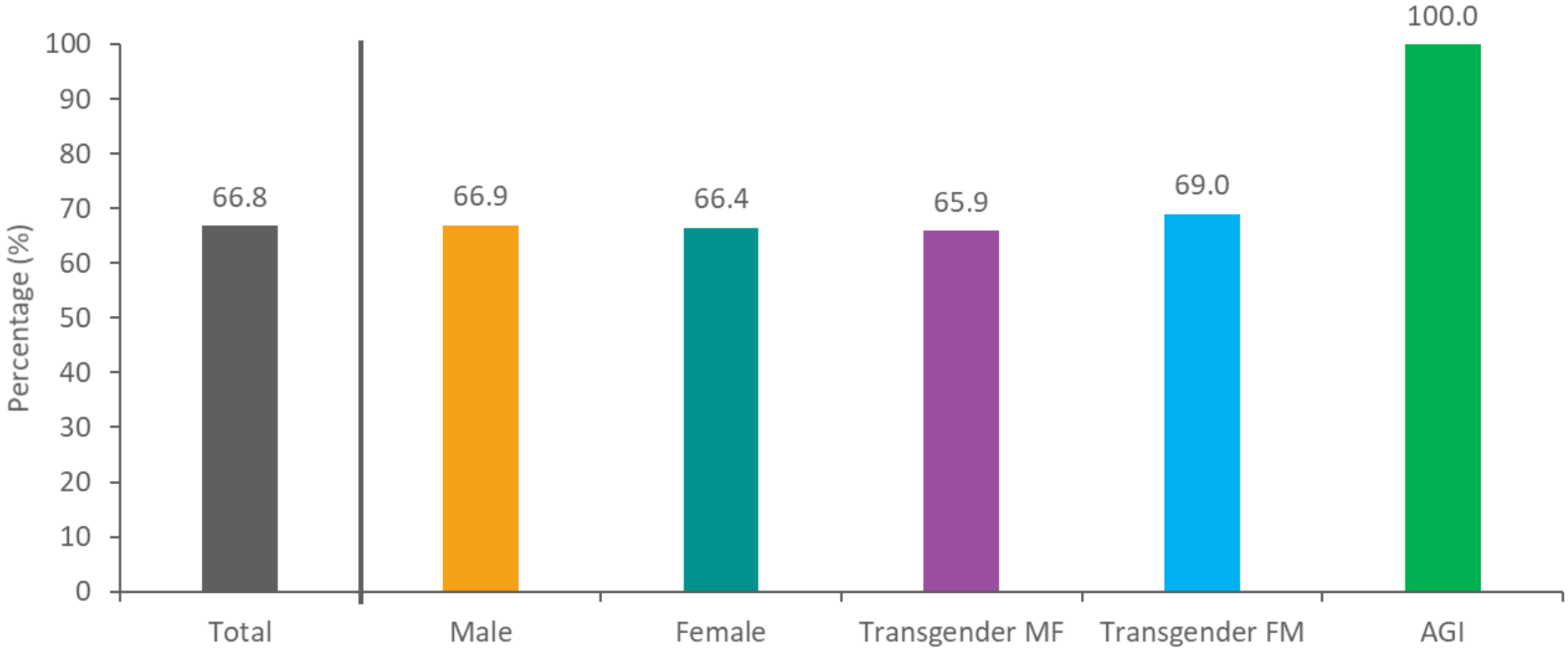
[1]Sax PE. Lancet 2012; [2]Sax PE. Lancet 2017; [3]Johnston RE. ARHR 2015; [4]Currier J. Ann Intern Med 2010

Persons Living with Diagnosed or Undiagnosed HIV Infection
HIV Care Continuum Outcomes, by Sex, 2018—United States



Note. Receipt of medical care was defined as ≥1 test (CD4 or VL) in 2018. Retained in continuous medical care was defined as ≥2 tests (CD4 or VL) ≥3 months apart in 2018. Viral suppression was defined as <200 copies/mL on the most recent VL test in 2018.

Viral Suppression within 6 Months of HIV Diagnosis among Persons Aged ≥13 Years, by Gender—41 States and the District of Columbia



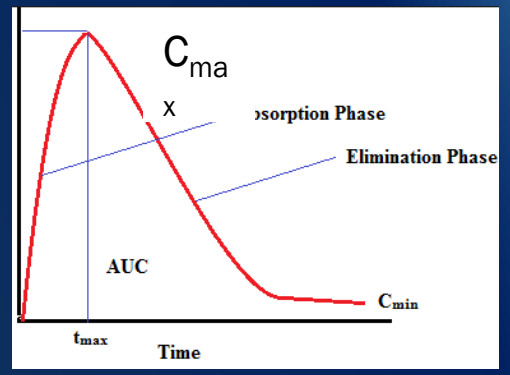
Abbreviations: MF, male-to-female; FM, female-to-male; AGI, additional gender identity.
Note. Viral suppression was defined as <200 copies/mL on a VL test within 6 months of HIV diagnosis in 2018.

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 DRV/r- therapy
- 32.8% of women (vs 23.2% men, p 0.042) d/c'd ART
- Trend - worse virologic responses in women (ITT), driven by higher d/c rates[1,2]
- Conclusion (many studies): Real world and even clinical studies in HIV lose HIV-infected women, discontinuation rates high, adverse effects higher[3]

[1]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; [2]Squires K. AIDS Patient Care and STDS 2013; Smith K. J Nat Med Assoc 2012; [3]Loutfly MR. J Intl AIDS Society 2013*

Sex differences in PK



Pharmacokinetics

Absorption

- Women ↓ acid, slower gastric emptying time (OCPs, cycle)
- Diet differences
- No consistent differences in gut CYP or p-gp

Distribution

- Women weigh less
- More proportional fat
- Varying plasma volumes
- Less organ flow
- Estrogen has effects on plasma binding proteins (↓ AAG)

Metabolism

- In vitro: F>M trend
- Progesterone ↑ CYP3A4 activity
- Hepatic p-gp M>F

Elimination

- M>F trend
- Smaller organs

Gandhi. Annu Rev Pharm Tox 2004
Franconi. Clin Med Chem 2017

Administration of concomitant medications can affect each stage & vary by sex

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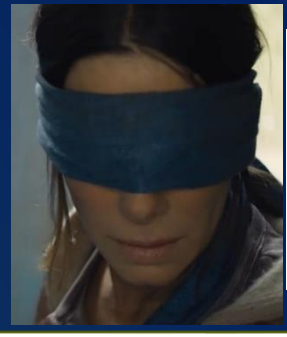
Key background points



There are very few TRUE teratogens known (high rate of causing congenital malformations)

- *Formerly labeled by FDA as "Category X"*
- *Examples are isotretinoin, valproic acid, warfarin, methotrexate (thalidomide)*

Most drugs have simply not been studied in pregnancy, making PLLR (Pregnancy and Lactation Labeling) difficult; may only have post-marketing cases (e.g. 4 cases on DTG), not well-designed human studies.

"Physicians often left flying blind when trying to determine whether a drug has a favorable risk-benefit profile in pregnancy"
Rita Rubin, JAMA 2018
(Addressing Barriers to Inclusion of Pregnant Women in Clinical Trials)

"The first thing we have had to do is to argue that the status quo is unethical. You must do research with pregnant women because NOT doing so is unethical", Anne Lyerly MD (Rubin JAMA 2018), Director of Bioethics, UNC

Tsepamo Study Update (End of April 2020)

- Update to the ongoing observational cohort study
  - Additional data from 39,200 women and 28 neural tube defects
- Trend in the incidence of neural tube defects with dolutegravir taken at contraception
  - April 2018 (n=426): 0.94%
  - May 2018-March 2019 (n=1683): 0.30%
  - April 2019-2020 (n=3571): 0.19%
- Risk of neural tube defects among infants born to women on dolutegravir at conception
  - Approximately 2 per 1000 women in this cohort

Additional Neural Tube Defects and Exposures (April 2020)

	NTDs (number)	Exposures (number)
Conception		
Dolutegravir	2	1908
Non-dolutegravir	6	4569
Efavirenz	5	2999
At pregnancy		
Dolutegravir	1	741
Women without HIV	17	30,258

Zash R, et al. *J Int AIDS Soc*. 2020;23(suppl 4):183-184. Abstract OAXLB0102.

Which drugs preferred, alternative in guidelines?

NRTIs
Zidovudine (AZT, ZDV)- Alternative
Epzicom (ABC/3TC)
Truvada (TDF/FTC)

NNRTIs
Efavirenz (EFV)- Alternative
Rilpivirine (RPV)- Alternative

INSTIs
Raltegravir (RAL)
Dolutegravir (DTG)

PIs
Atazanavir/r (ATV/r)
Lopinavir/ritonavir (LPV) – Alternative
Darunavir/r (DRV/r)

Single pill combinations
Triumeq (DTG/ABC/3TC)- Preferred after 1st trimester
Complera (RPV/TDF/FTC) - Alternative
Atripla (EFV/TDF/FTC) - Alternative

Dolutegravir first line by WHO as of July 2019

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

Not recommended vs not enough data

Not recommended	Not enough data
Elvitegravir/cobicistat/TAF/FTC	Tenofovir alafenamide (TAF)
Elvitegravir/cobicistat/TDF/FTC	Bictegravir (BIC)
Atazanavir/cobicitat	Doravirine (DOR)
Darunavir/cobicistat	BIC/TAF/FTC
DRV/cobi/TAF/FTC	DOR/TDF/3TC
Nevirapine	RPV/TAF/FTC
Etravirine	Ibalizumab
Maraviroc	(Fostemsavir)
T20	(Cabotegravir)
DTG/RPV	

Often used in non-pregnant adults

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

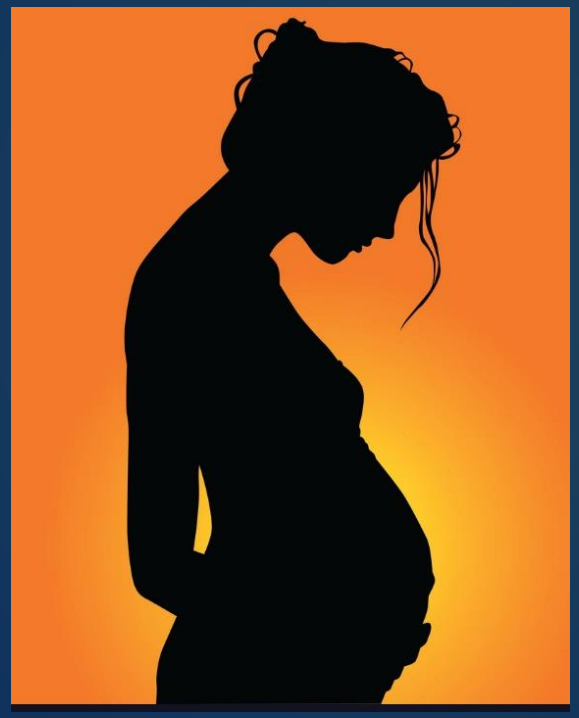
Pregnancy changes pharmacokinetic parameters further

Absorption

- Slower GI motility (progesterone)
- ↓ Gastric acid secretions
- ↑ Intestinal pH

Metabolism

- Progesterone ↑ hepatic metabolism



Distribution

- Expanded intravascular volume
- Decreased albumin
- Body fat ↑ in pregnancy

Elimination

- ↑ renal blood flow and GFR
- ↑ cardiac output

Pariente. PLOS Med. 2016;
Sheffield. CID 2014

In general (not always), these changes lead to lower drug levels in pregnancy

What should you consider?

1. Patient preference

2. Switching (can be disruptive)

3. GI concerns (N/V with PIs) and GERD

4. PK and drug-drug interactions

5. HepB (needs TDF/FTC)

6. Really needs SPC (only DTG/ABC/3TC and alternative EFV/TDF/FTC, RPV/TDF/FTC) or can't take BID (RAL and DRV/r in US, BHIVA)

BMJ Open

Values and preferences of women living with HIV who are pregnant, postpartum or considering pregnancy on choice of antiretroviral therapy during pregnancy

15 qualitative studies

1. Distress about side effects (10 studies)
2. Desire to reduce vertical transmission (9 studies)
3. Concern about side effects to child (8 studies)
4. Desire for child to be healthy (5 studies)
5. Desire for oneself to be healthy (5 studies)
6. Pill burden (2 studies)

1. Patient preference

Lytvyn et al. BMJ Open 2017

Other considerations in pregnancy

3. 4,5,6. Heartburn, nausea, PK, BID, SPC

ARV Class	ARV	Consideration
NNRTI (alternative SPCs)	*Efavirenz*	• Primate studies raised concern about NTDs; not seen in human studies, deemed safe • Watch for intra-and postpartum depression
	Rilpivirine	• Don't use if CD4 count <200 or HIV RNA >100,000 • Heartburn? Can't use PPI and stagger dosing with H2 blocker • PK lower in 2nd and 3rd trimester, unclear significance- use standard dose and monitor VL, be vigilant
INSTI	*Raltegravir*	• Change dose from 1200mg po daily to 400mg po **BID** in pregnancy • Separate doses from iron and don't use aluminum/magnesium antacids • INSTIs reduce VL fast– can add to suppress; no clear class effects for NTDs
	Dolutegravir	• Not in 1st trimester; **DTG/ABC/3TC only preferred SPC**
PI	*Atazanavir + ritonavir*	• PK changes not significant so use standard dosing, hyperbilirubinemia • Heartburn? Atazanavir concentrations lowered by PPIs, H2 blockers
	Darunavir + ritonavir	• US and BHIVA guidelines recommend darunavir 600 mg **BID**/ ritonavir 100 mg **BID** in pregnancy (European AIDS Clinical Society does not)

Monitoring of HIV labs during pregnancy

- HIV RNA at first antenatal visit, 2 to 4 weeks after initiating or changing ART, monthly until undetectable , then q3 months in pregnancy and at 34-36 weeks
- CD4 at first antenatal visit and then only repeat (q3-6 months) if <300 or detectable viral loads
- Drug resistance testing if HIV viral load detectable (>500) during pregnancy (and if initiating ART during pregnancy but don't delay(
- Labs per typical adverse effects of the ART agent
- Standard glucose screening at 24-28 weeks' gestation (some experts say earlier for those on PIs)
- Ultrasound to confirm dating especially given dolutegravir
- Increasing calls for more frequent VL testing in pregnancy/postpartum in low-income settings (guidelines currently variable, most frequent q6 months)

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

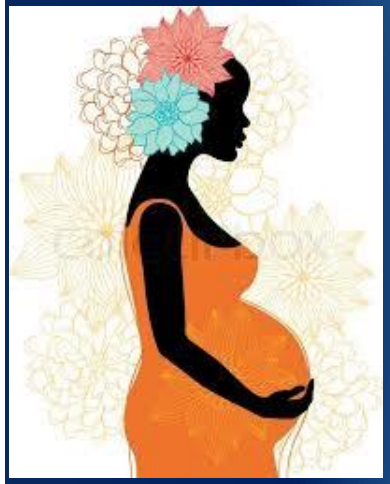
1. Myer. PLOS Medicine 2017
2. Lesosky. CROI 2019. Abstract 674

Comment on PrEP

2017

Safety of Tenofovir Disoproxil Fumarate–Based Antiretroviral Therapy Regimens in Pregnancy for HIV-Infected Women and Their Infants: A Systematic Review and Meta-Analysis

Jean B. Nachega, MD, PhD, MPH,†‡ Olalekan A. Uthman, MD, PhD,§‖¶ Lynne M. Mofenson, MD,# Jean R. Anderson, MD,** Steve Kanters, PhD, MSc,††‡‡ Francoise Renaud, MD,§§ Nathan Ford, MPH, PhD,§§ Shaffiq Essajee, MD,§§ Meg C. Doherty, MD, PhD,§§ and Edward J. Mills, MSc, PhD‡‡*



- TDF/FTC generally safe in pregnancy for both women and infants (consider bone effects)
- Given high incidence of HIV pregnant and postpartum in many settings, oral PrEP during this critical time important

Heffron. AIDS 2018; Machekano. PLOS ONE 2018; Thomson JID 2018

Pre-conception period

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

Preconception Counseling and Care for Women of Childbearing Age Living with HIV (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations

- Discuss reproductive desires with all women of childbearing age on an ongoing basis throughout the course of their care (**AIII**).
- Provide information about effective and appropriate contraceptive methods to reduce the likelihood of unplanned pregnancy (**AI**).
- During preconception counseling, provide information on safe sex and encourage the elimination of alcohol, tobacco, and other drugs of abuse; if elimination is not feasible, clinicians should provide appropriate treatment (e.g., methadone or buprenorphine) or counsel patients on how to manage health risks (e.g., use of syringe services program) (**AII**).
- All women living with HIV who are contemplating pregnancy should be receiving antiretroviral therapy (ART) and have a plasma viral load below the limit of detection prior to conception (**AII**).
- When selecting or evaluating ART for women of childbearing age living with HIV, consider a regimen's effectiveness, a woman's hepatitis B status, teratogenic potential of the drugs in the ART regimen, and possible adverse outcomes for the mother and fetus (**AII**).
- HIV infection does not preclude the use of any contraceptive method; however, drug-drug interactions between hormonal contraceptives and ART should be considered (**AII**).

Contraceptives and ART (simplified)

ARV class (commonly-used)	Interactions with contraceptives (combination OCPs, progestin-only POPs, DMPA, implants)
NRTIs	No interactions although feminizing hormone therapy for TGW may reduce TFV-DP levels intracellularly
NNRTIs	Rilpivirine – no interactions Efavirenz – DPMA preferred (oral, implants not)
PIs	DRV/r - DPMA preferred (oral, implants not) ATV/r – All methods (cOCPs, POPs, DMPA, implants) LPV/r – All methods retain efficacy DRV/c and ATV/c – POPs not studied; drug-drug interactions with others (use alternative)
INSTIs	All okay with all forms of contraceptives

Slide courtesy of
Anne Lyerly MD

Women of reproductive potential

The 'fundamental misconception':

all women are always pregnable and therefore (through the magical operation of the mind characteristic of unconscious sexism) *always pregnant*."

-Vanessa Merton, *AJLM* 1993

HIV: Women represent 23% of participants in ARV research (median/study = 19%)
Curno et al, JAIDS 2016

Slide courtesy of
Anne Lyerly MD

Burden of justification

- Shifting burden – require justifying *exclusion*

INCLUSION → EXCLUSION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2018
Clinical/Medical
Revision 1

Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials

Guidance for Industry

Designing Drug Trials: Considerations for Pregnant Women

Jeanne S. Sheffield,[1] David Siegel,[2] Mark Mirochnick,[3] R. Phillips Heine,[4] Christine Nguyen,[5] Kimberly L. Bergman,[6] Rada M. Savic,[7] Jill Long,[8] Kelly E. Dooley,[9] and Mirjana Nesin[8]

Clinical Infectious Diseases

2014

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
- **ART and pregnancy**
  - Update this year
- **Primary care for women**
  - Breast and cervical cancer screening, menopause

Primary care screening for HIV-infected women

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, *n*	Incidence Rate per 100 000 Person-Years	Persons, *n*	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

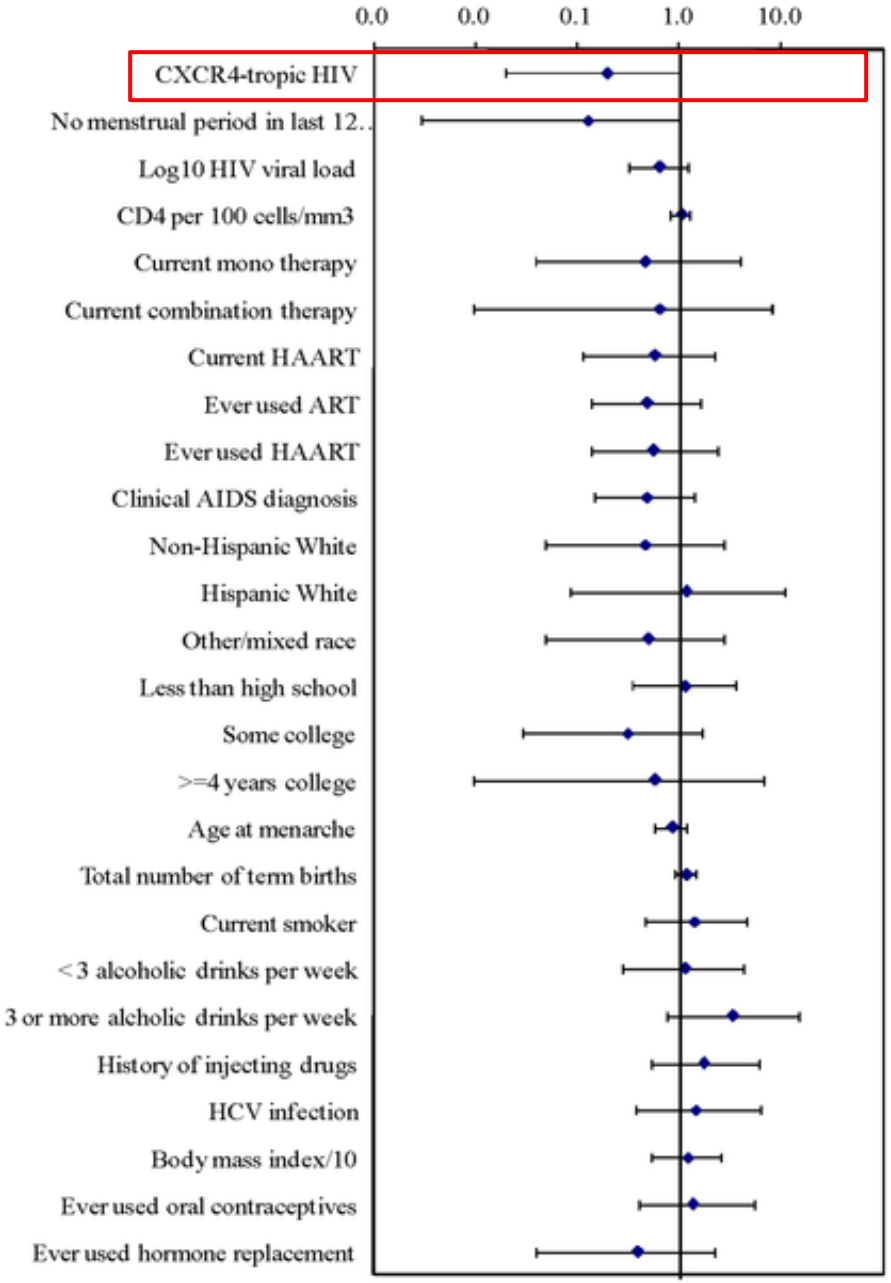
NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.

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

Silverberg. Annals of Intern Med 2015

Possible mechanism

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



Hessol. PLOS One 2010; Goedert. JAIDS 2015

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

Aberg JA, et al. *Clin Infect Dis.* 2014

Menopause

- Menopause: physical and psychological symptoms, accelerated development of other age-related comorbidities, particularly cardiovascular disease, neurocognitive dysfunction, and bone mineral disease
- Symptoms of menopause heightened by HIV
- Menopause and HIV: additional considerations of acquisition and transmission risk, progression of infection, changes in antiretroviral pharmacokinetics, response, and toxicities

The menopause transition in women living with HIV: current evidence and future avenues of research

Shema Tariq[1]*, Jane Anderson[2], Fiona Burns[1], Valerie Delpech[3], Richard Gilson[1] and Caroline Sabin[1]

[1] Research Department of Infection and Population Health, University College London, UK
[2] Centre for the Study of Sexual Health and HIV, Homerton University Hospital NHS Foundation Trust, London, UK
[3] Public Health England, London, UK

Physical function

Physical function worse in older women than men with HIV, despite better CD4 recovery

- :

9th International Workshop on HIV and Aging, September 13-14, 2018, New York

CONCLUSION

Immunological recovery measured by CD4 T cell count and CD4/CD8 ratio

CVD and CV risk factors

Their physical function and their quality of life are worse.

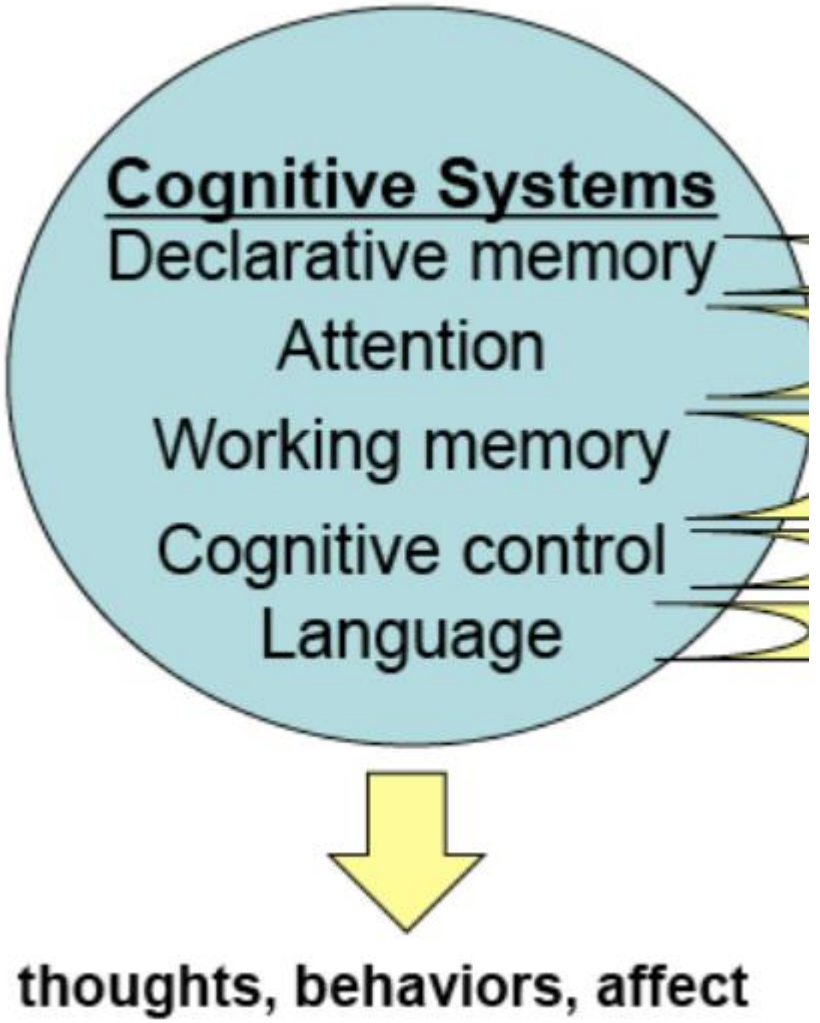
Cognition (WIHS study)

Cognitive aging in the era of effective antiretrovirals

Leah H. Rubin, PhD, MPH Associate Professor of Neurology & Epidemiology

PATTERNS

- Heterogeneity in cognitive aging is the rule not the exception
- Women living with HIV may be more cognitively vulnerable than men living with HIV
- Cognitive impairment persists despite continued viral suppression



Bone health

Recommendations for Evaluation and Management of Bone Disease in HIV

Table 4. Bone Mineral Density T- and Z-Score Thresholds for Determination of Osteopenia and Osteoporosis

Population	Interpretation: Use of T-Score or Z-Score	Normal	Osteopenia	Osteoporosis
Postmenopausal women and men ≥50 y of age	T-score (compared with a young healthy adult)	≥ −1 SD	Between −2.5 and −1 SD	≤ −2.5 SD
All others	Z-score (age-, sex-, ethnicity-matched)		Low BMD for chronological age if ≤ −2 SD[a]	

Sources: [4, 8].

Abbreviations: BMD, bone mineral density; SD, standard deviation.

[a] In premenopausal women, men <50 years of age, and children, the diagnosis of osteoporosis should not be made by BMD criteria alone [4].

Conclusion

Epidemiology:

- Global and U.S.

HIV prevention in women

- Sex differences

HIV treatment in women

- Sex differences in outcomes, toxicities, pharmacokinetics

ART and pregnancy

- Update this year

Primary care for women

- Breast and cervical cancer screening, menopause