



Eileen Scully MD, PhD

19 January 2023

Rust Belt CFAR Sex and Gender Scientific Working
Group

Sex Differences in HIV Infection

Outline

- Brief historical discussion of sex/gender and inclusion in clinical trials
- How does sex/gender fit into the leading edge of HIV research
- Some data on the role of sex in HIV pathogenesis

Setting the stage: Inclusion of women in clinical trials

- 1977 FDA guidance:
 - *recommended excluding women with childbearing potential from participating in phase 1 and early phase 2 clinical studies until reproductive toxicity (segment 2) studies were conducted and some evidence of effectiveness had become available. The recommended exclusion was broadly applied to any "premenopausal female capable of becoming pregnant," but explicitly did not apply to women with life threatening diseases...*



Policy developed to: *reflect societal interests in protecting vulnerable populations*

<https://www.fda.gov/science-research/womens-health-research/gender-studies-product-development-historical-overview>

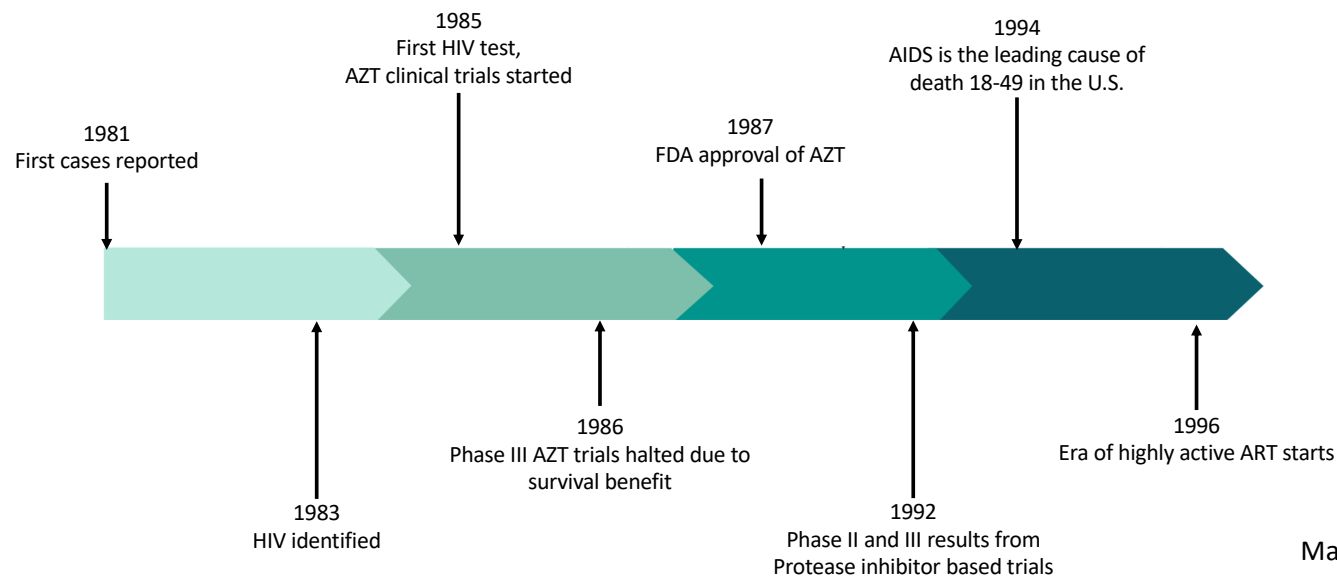
Does exclusion=protection?

- “A gender line keeps women not on a pedestal, but in a cage” - RBG, oral arguments, Supreme Court 1975
- *Even further:* there are not pedestals for many women, both cisgender and transgender, and in particular women of color

In biomedical science, information is power and without it, we are powerless to make specific recommendations about optimal therapy and the true risks of interventions.

Turning the focus to HIV...

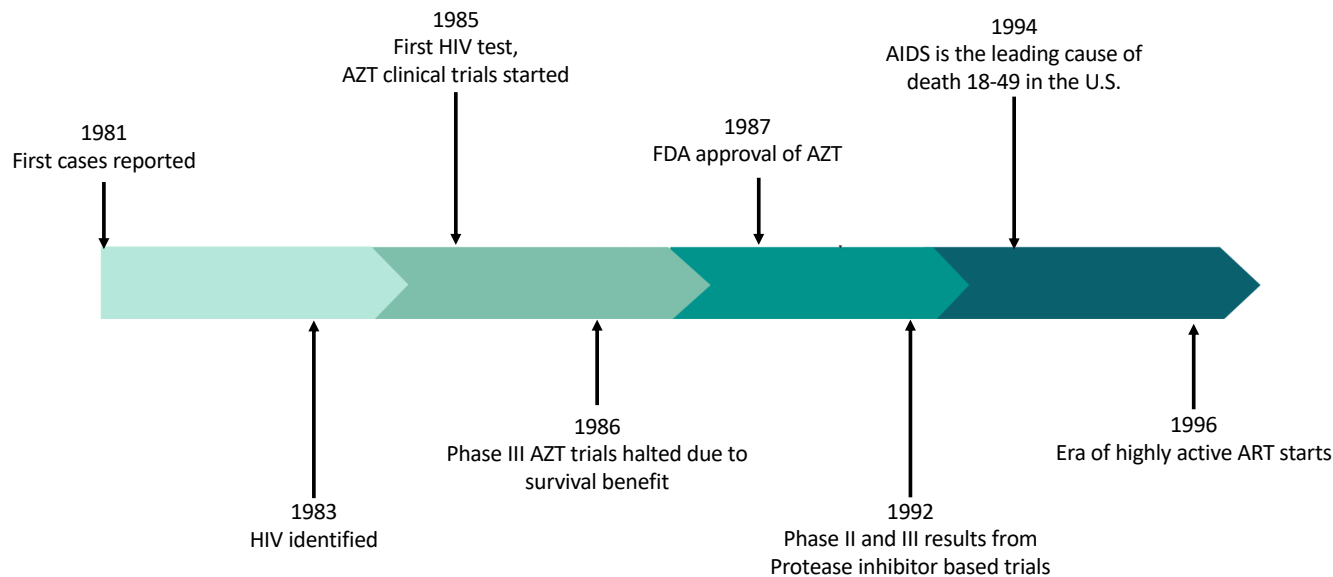
- **MMWR: June 5, 1981:** 5 cases of PCP pneumonia among men in Los Angeles, followed by reports from NYC, San Francisco and others.
- Between June of 1981 and January of 1983 the CDC received reports of 43 women with immunodeficiency syndromes



Masur et al., Ann of Int Med, 1982; MMWR 1983

The first treatment trials: AZT

- 1987 trial 282 participants, 13 cisgender women (4.6%)
- 1990 trial 524 participants, 25 cisgender women (4.7%)



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JULY 23, 1987

Number 4

THE EFFICACY OF AZIDOTHYIMIDINE (AZT) IN THE TREATMENT OF PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX

A Double-Blind, Placebo-Controlled Trial

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 AND THE AZT COLLABORATIVE WORKING GROUP

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A RANDOMIZED CONTROLLED TRIAL OF A REDUCED DAILY DOSE OF ZIDOVUDINE IN PATIENTS WITH THE ACQUIRED IMMUNODEFICIENCY SYNDROME

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 AND THE AIDS CLINICAL TRIALS GROUP*

The first treatment trials: AZT

TABLE 1. Number and percentage of persons with AIDS, by selected characteristics and period of report — United States, 1981–2000

Characteristic	1981–1987	
	No.	(%)
Sex		
Male	46,251	(92.0)
Female	4,029	(8.0)

Early trial participation required identification of the infection, and much of the surveillance was linked to epidemiological risks.

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The Epidemic Grows

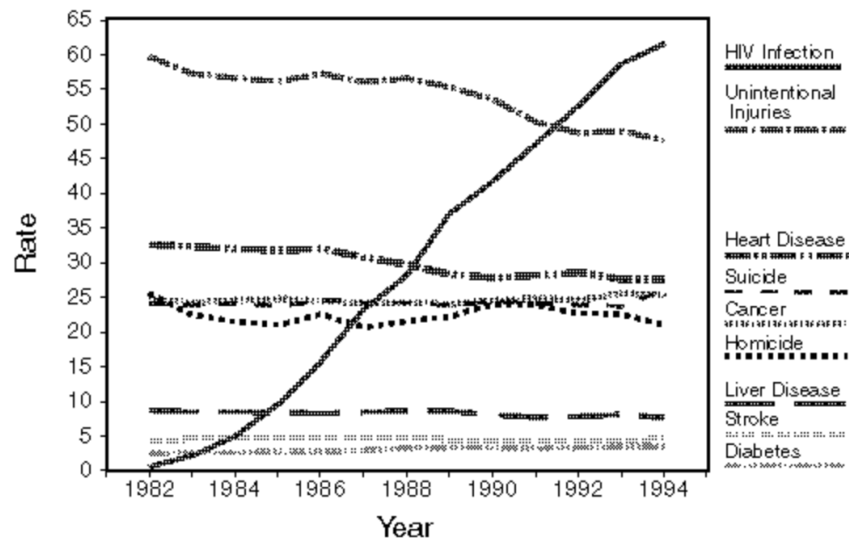
TABLE 1. Number and percentage of persons with AIDS, by selected characteristics and period of report — United States, 1981–2000

Characteristic	1981–1987		1988–1992		1993–1995		1996–2000	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Sex								
Male	46,251	(92.0)	177,132	(87.5)	211,909	(82.4)	204,730	(77.4)
Female	4,029	(8.0)	25,387	(12.5)	45,353	(17.6)	59,672	(22.6)

The Epidemic Grows:1993

- HIV is the leading cause of death among men ages 25-44

FIGURE 1. Death rates* from leading causes of death among men aged 25-44 years, by year — United States, 1982-1994†



The Epidemic Grows:1993

- HIV is the leading cause of death among men ages 25-44
- HIV is the leading cause of death among black women ages 25-44

FIGURE 1. Death rates* from leading causes of death among men aged 25-44 years, by year — United States, 1982-1994†

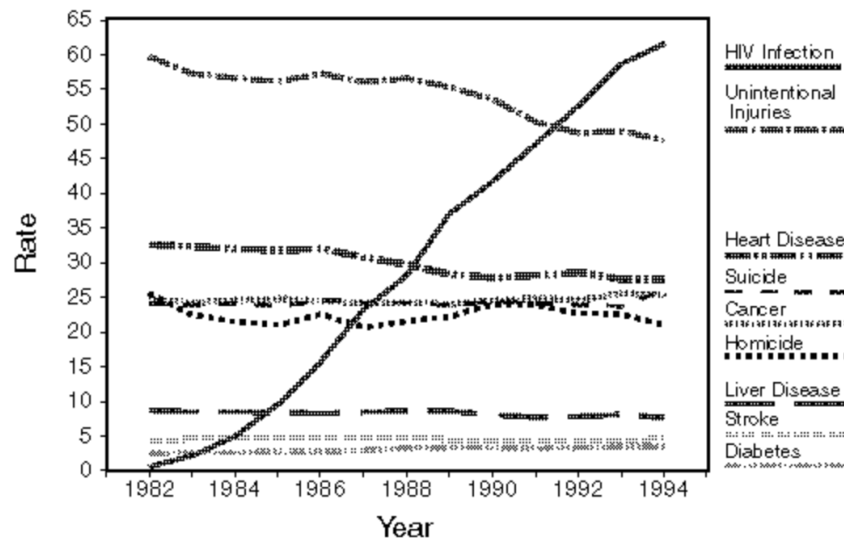
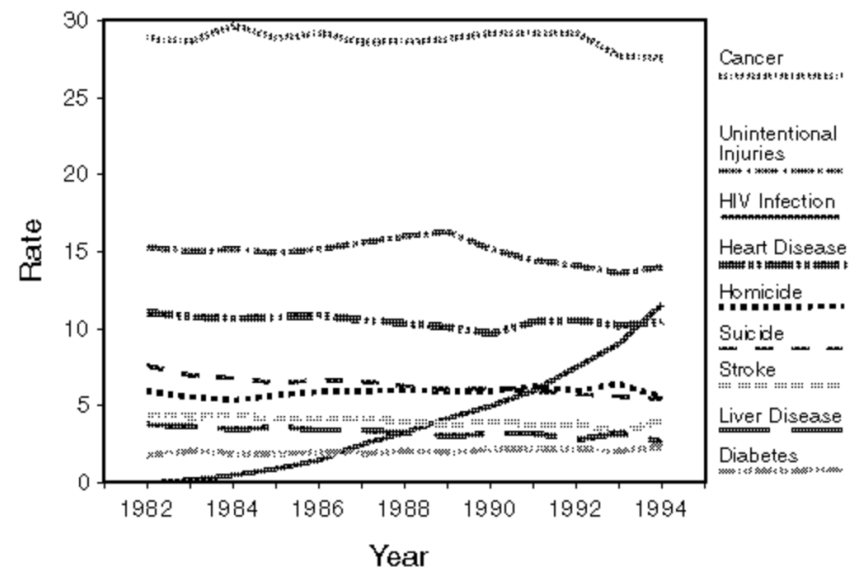


FIGURE 2. Death rates* from leading causes of death among women aged 25-44 years, by year — United States, 1982-1994†

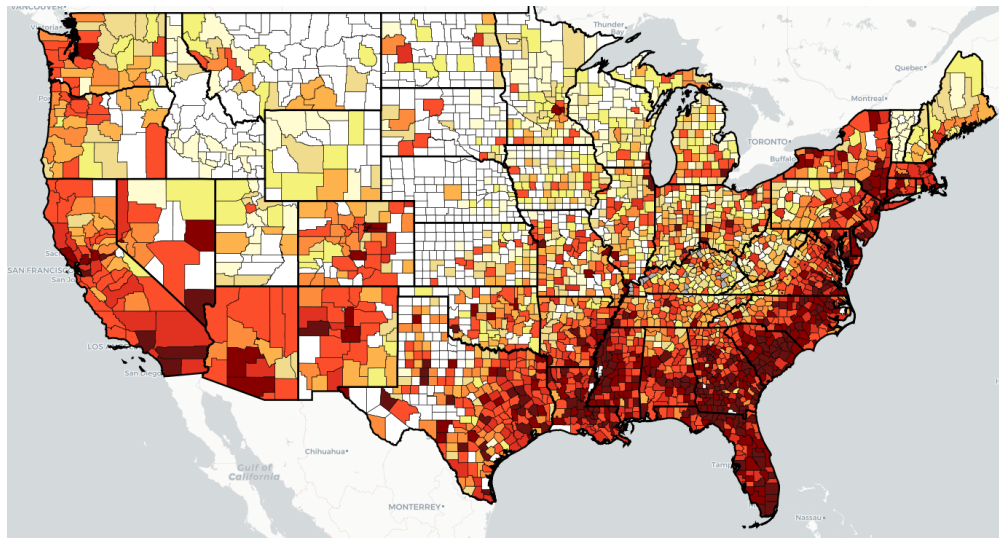


Summary of the changing epidemic

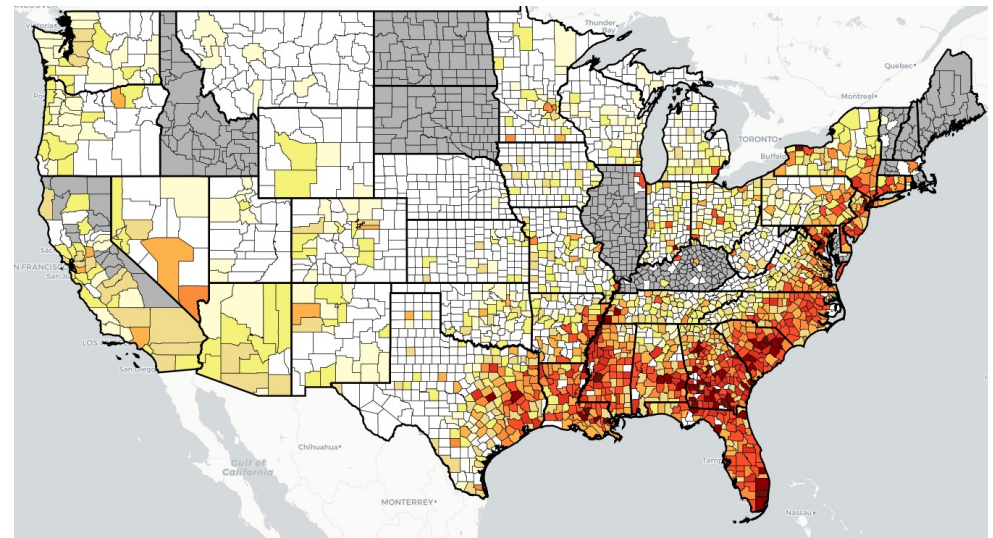
- Early cases were predominantly in males; first reports of cases in females in 1982, steady increase in proportion through the 1980s and 1990s
- Despite low prevalence, AIDS was the leading cause of death for young black women in the U.S. in 1993
- Since 2000 the proportion of people living with HIV who are cisgender women is ~23% in the US
- Data on Transgender women is inadequately collected, formal CDC guidance issued in 2012
- Regional differences in prevalence of HIV infection among women

Distribution of the burden of HIV in women

HIV infection

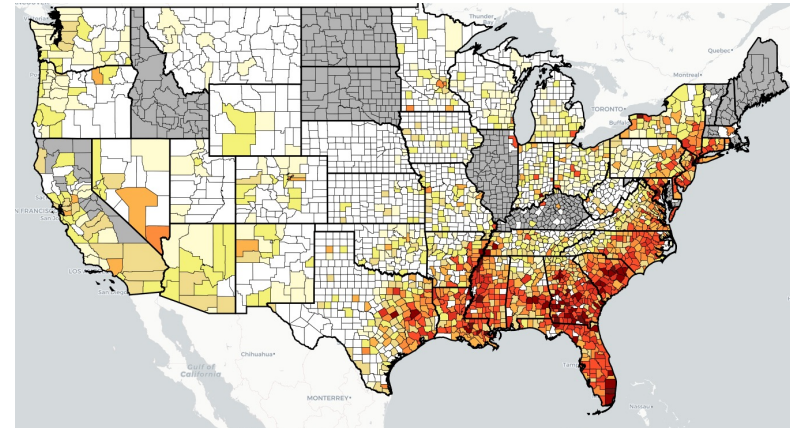
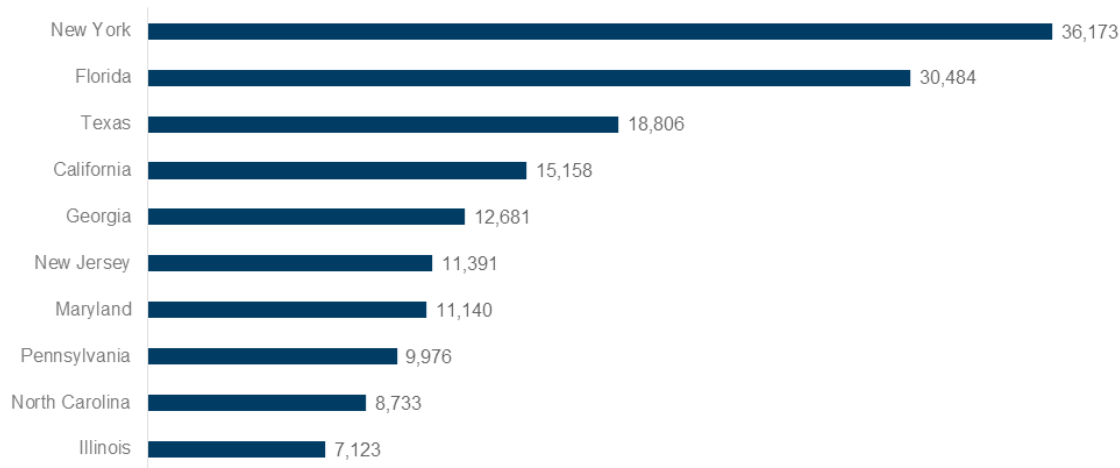


HIV infection in women



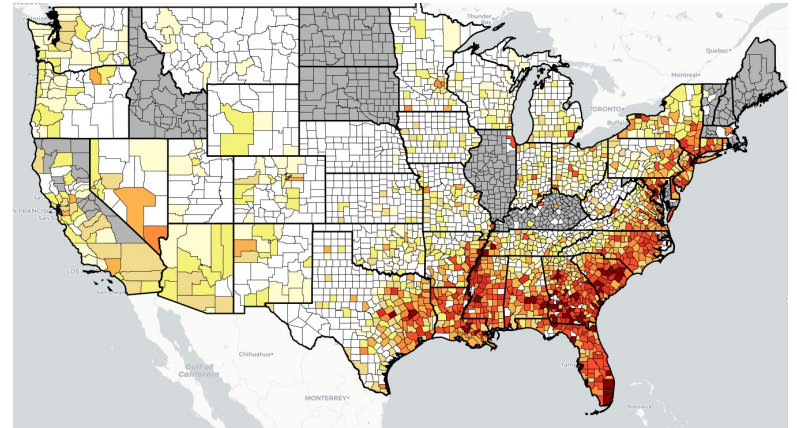
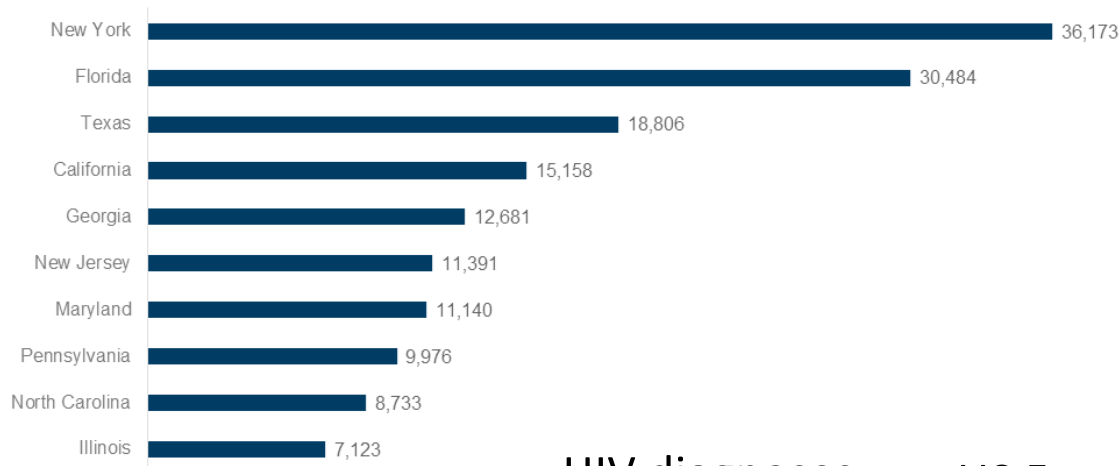
Women are an estimated 258,000 of the 1.1 million people living with HIV in the U.S. in 2019*

Distribution of the burden of HIV in women

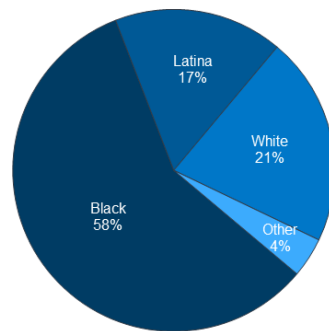


<https://www.kff.org/hiv/aids/fact-sheet/women-and-hiv-aids-in-the-united-states>

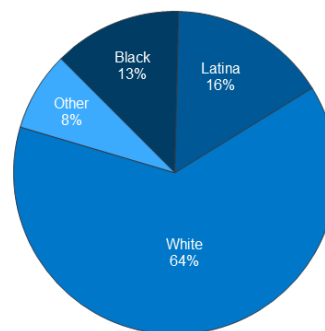
Distribution of the burden of HIV in women



HIV diagnoses



US Female population



<https://www.kff.org/hiv/aids/fact-sheet/women-and-hiv-aids-in-the-united-states>

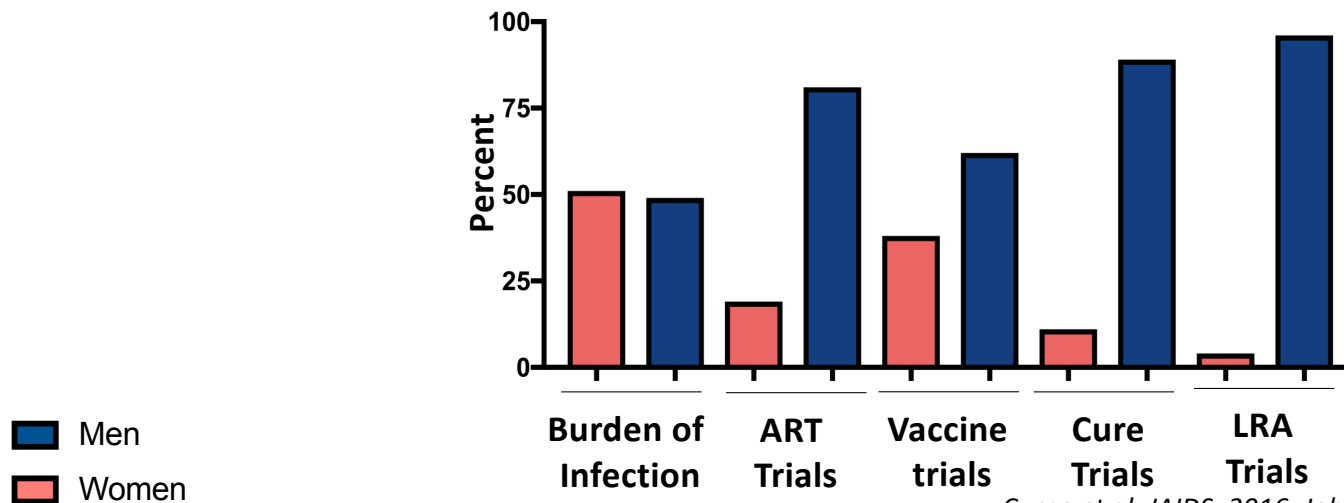
A decorative horizontal arrow graphic at the top of the slide, composed of four overlapping arrow shapes pointing to the right. The colors transition from light teal on the left to dark teal on the right.

1990s – A Shift in Policy

- In 1993 NIH reverses its 1977 policy and recommends inclusion of women
 - Highlights importance of informed consent
 - Contraception
 - Pharmacokinetic data in specific populations
 - Menstrual status data (lifespan)
- The Office for Research on Women's Health is established
- FDA reports that 1997-2000, 8 of 10 medications withdrawn from the market were due to adverse effects in women
- 2016 recommendation of inclusion of sex as a biological variable

Where does this leave consideration of sex and gender in HIV

- Seminal studies of HIV pathogenesis included few or no women
- Patient advocacy has been a key driver of HIV research and gender dynamics in epidemic limit cis and transgender women's role
- Changes in regulatory policy have shifted to favor inclusion of women



Curno et al, JAIDS, 2016; Johnston and Heitzeg, AIDS Res Hum Retroviruses, 2015

Does it matter?

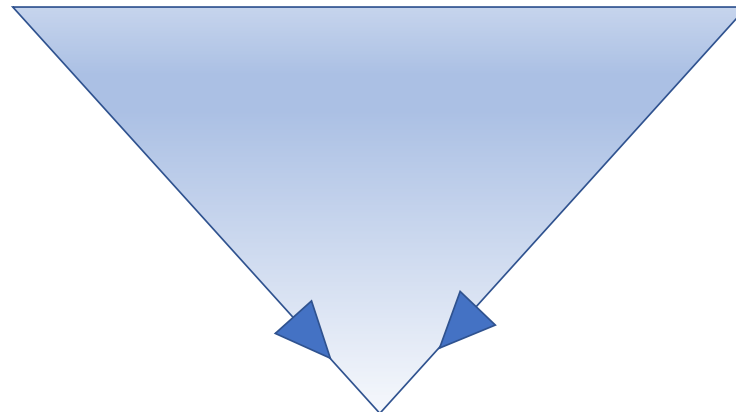
What is the evidence for the relevance of sex to HIV pathogenesis?

SEX

*Assigned at birth, anatomy
and chromosomes*

GENDER

*Internal sense of self with
respect to gender*



HEALTH

Sex versus Gender

Article | [Published: 26 August 2020](#)

Sex differences in immune responses that underlie COVID-19 disease outcomes

[Takehiro Takahashi](#), [Mallory K. Ellingson](#), [Patrick Wong](#), [Benjamin Israelow](#), [Carolina Lucas](#), [Jon Klein](#), [Julio Silva](#), [Tianyang Mao](#), [Ji Eun Oh](#), [Maria Tokuyama](#), [Peiwen Lu](#), [Arvind Venkataraman](#), [Annsea Park](#), [Feimei Liu](#), [Amit Meir](#), [Jonathan Sun](#), [Eric Y. Wang](#), [Arnau Casanovas-Massana](#), [Anne L. Wyllie](#), [Chantal B. F. Vogels](#), [Rebecca Earnest](#), [Sarah Lapidus](#), [Isabel M. Ott](#), [Adam J. Moore](#), [Yale IMPACT Research Team](#), ... [Akiko Iwasaki](#)  [+ Show authors](#)

[Nature](#) **588**, 315–320 (2020) | [Cite this article](#)

Matters arising


A finding of sex similarities rather than differences in COVID-19 outcomes

<https://doi.org/10.1038/s41586-021-03644-7>

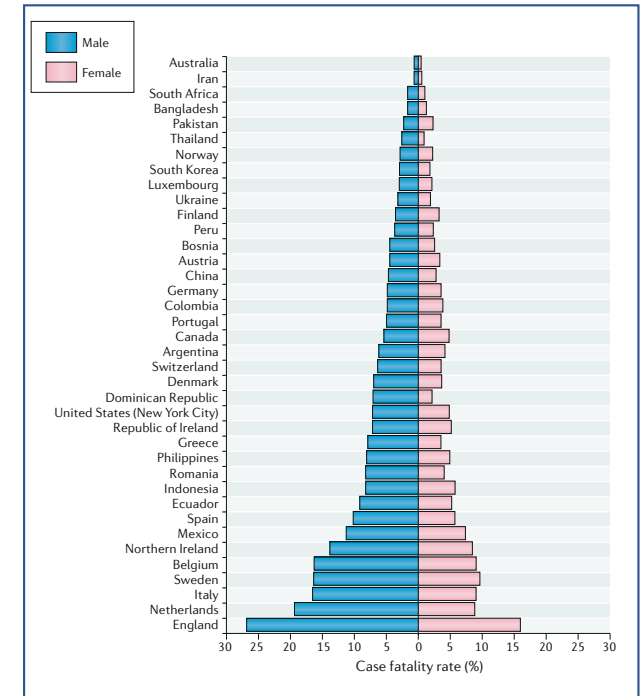
Received: 13 November 2020

Accepted: 11 May 2021

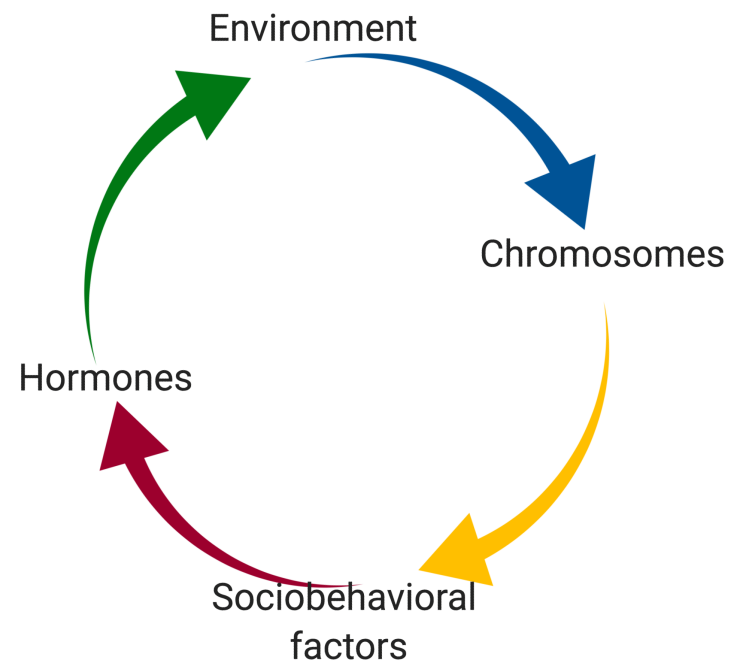
Published online: 22 September 2021

[Heather Shattuck-Heidorn](#)^{1,2} , [Ann Caroline Danielsen](#)³, [Annika Gompers](#)⁴, [Joseph Dov Bruch](#)⁵, [Helen Zhao](#)⁵, [Marion Boulicault](#)⁶, [Jamie Marsella](#)⁷ & [Sarah S. Richardson](#)^{2,7}

ARISING FROM T. Takahashi et al. *Nature* <https://doi.org/10.1038/s41586-020-2700-3> (2020)

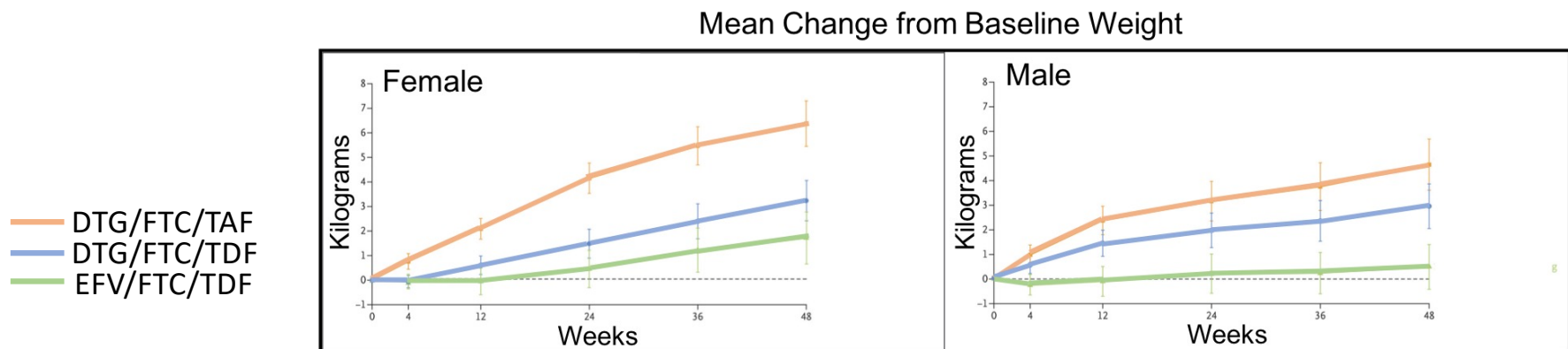


Sex versus Gender

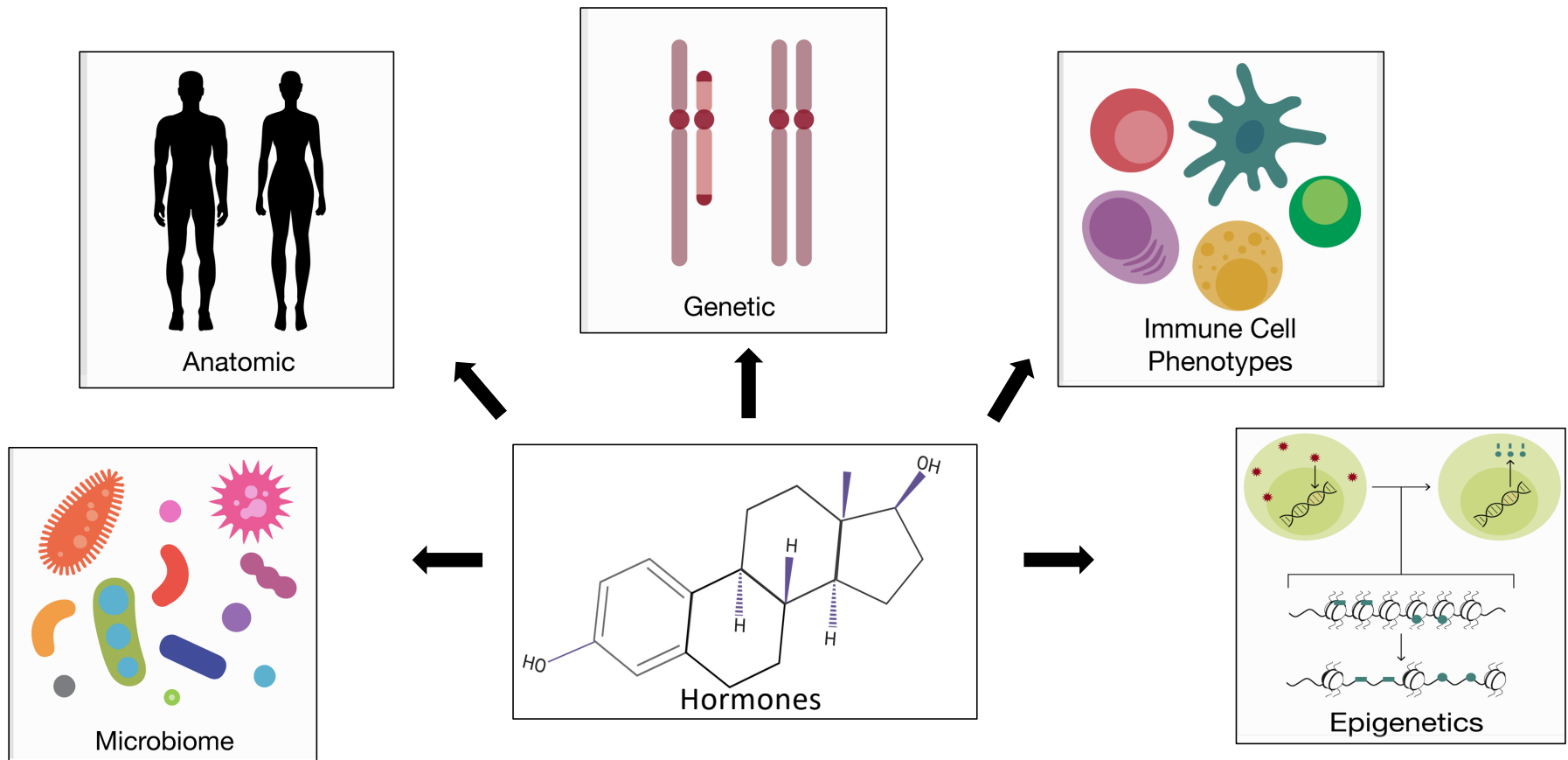


Frontiers in HIV research

- Prevention of transmission
- Optimal deployment of long-acting therapeutics
- Management of weight gain associated with ART
- Management of aging and comorbidities
- Cure



Biological determinants of sex differences

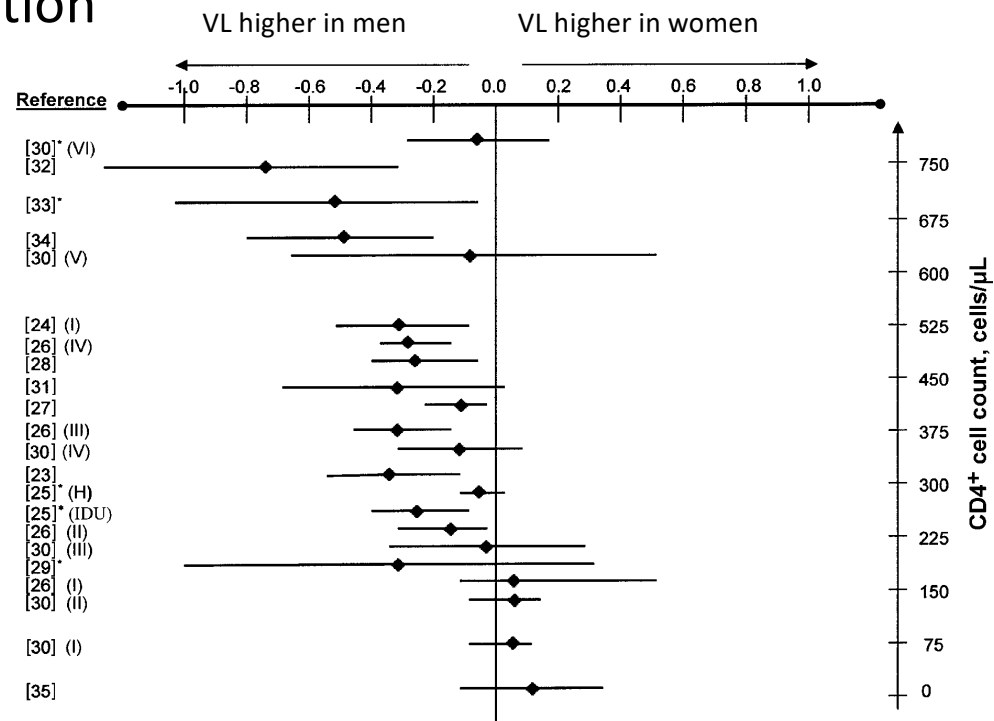


Scully, E *Curr HIV/AIDS Reports*, 2018, *Pathogens and Immunity* 2019; Schmiedel et al., *Cell* 2018



Sex differences in HIV pathogenesis and cure

- Untreated infection





Sex differences in HIV pathogenesis and cure

- Untreated infection

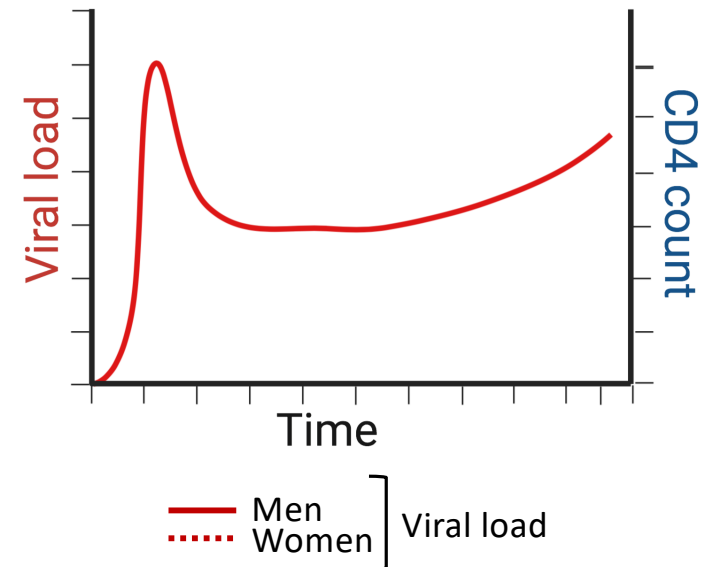
	Median Initial Viral Load	
	Progressing to AIDS	Not progressing
Men	77,822	40,634
Women	17,149	12,043



Sex differences in HIV pathogenesis and cure

- Untreated infection

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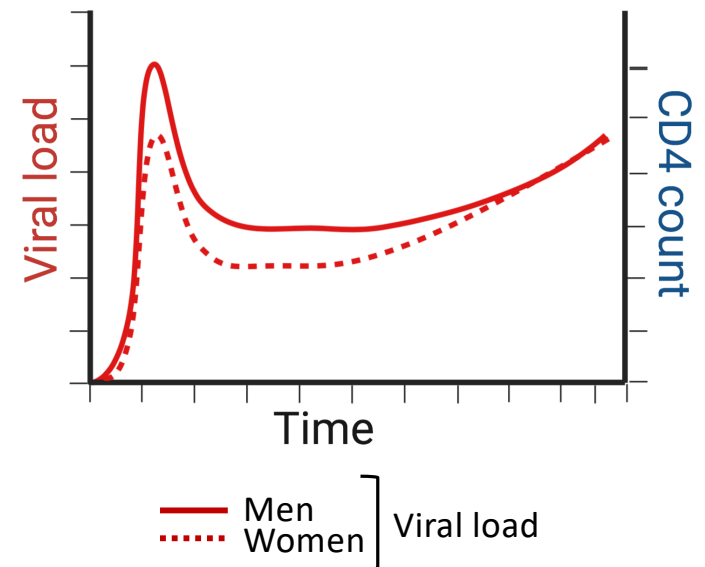
Sterling et al., NEJM 2001



Sex differences in HIV pathogenesis and cure

- Untreated infection

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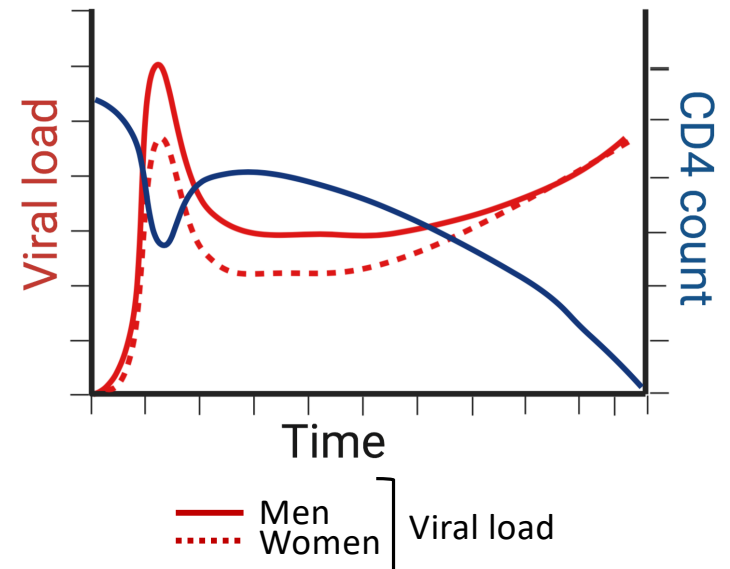


Sterling et al., NEJM 2001



Sex differences in HIV pathogenesis and cure

- Untreated infection:
 - Lower set point VL
 - Equivalent rate of disease progression

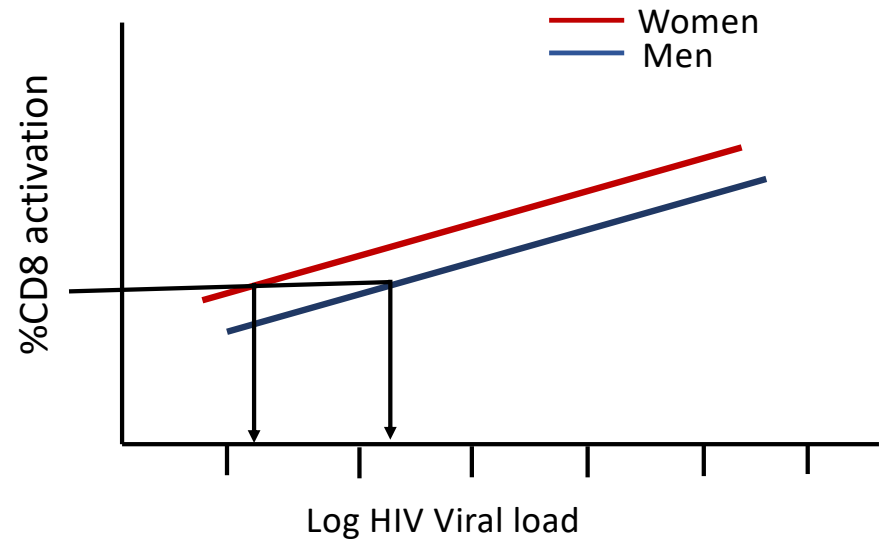


Sterling et al., NEJM 2001



Sex differences in HIV pathogenesis and cure

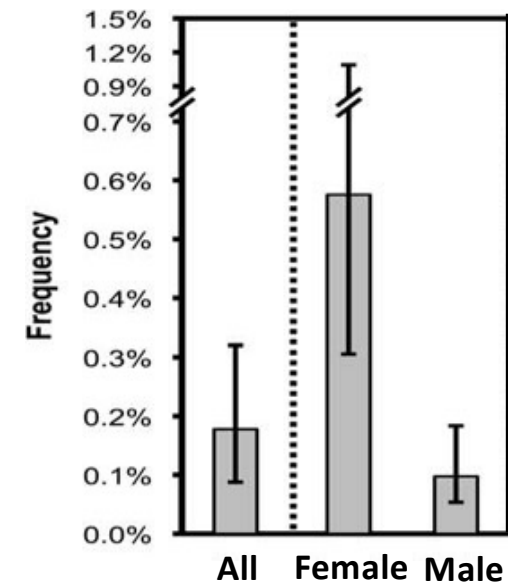
- Untreated infection: **mechanisms?**
 - ♀ Higher T cell immune activation per viral load
 - ♀ More IFN α production per HIV RNA stimulation
 - ♂ More per cell HIV RNA production





Sex differences in HIV pathogenesis and cure

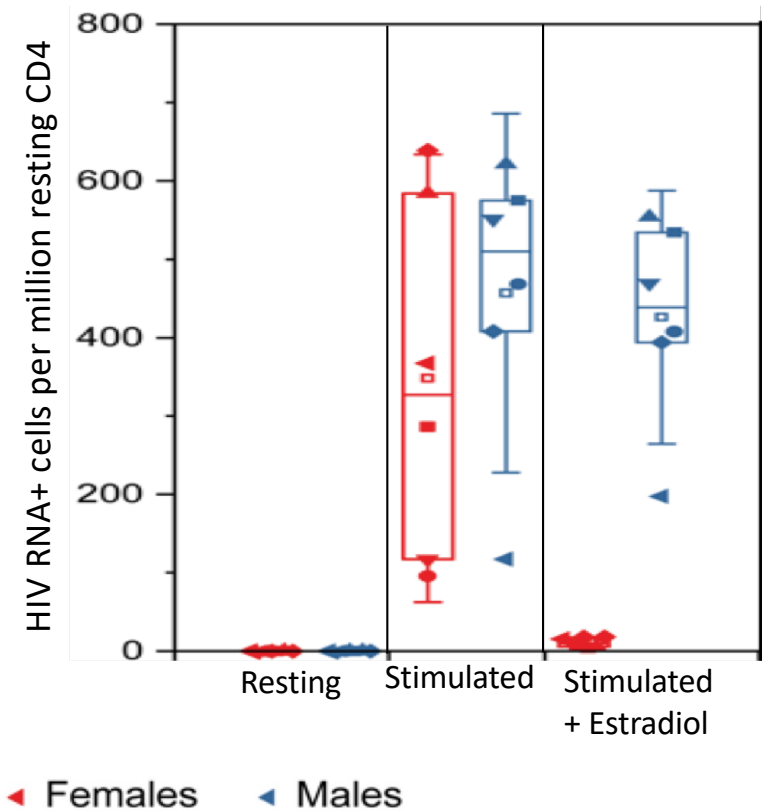
- Untreated infection clinical phenotypes
 - Women are overrepresented in phenotypes of viral control OR ranging 1.9 to 5 across different cohorts
 - Medical record review of 29,811 cases¹
 - Primary seroconversion in 2176 individuals (CASCADE)²
 - Primary infection cohort in sub-Saharan Africa 590³
 - Medical record review of 23,461⁴



¹Yang et al., *AIDS* 2017; ²Madec et al., *AIDS* 2005; ³Price et al., *JID* 2019; ⁴Crowell et al., *J Infec Dis*, 2015

Sex differences in HIV pathogenesis and cure

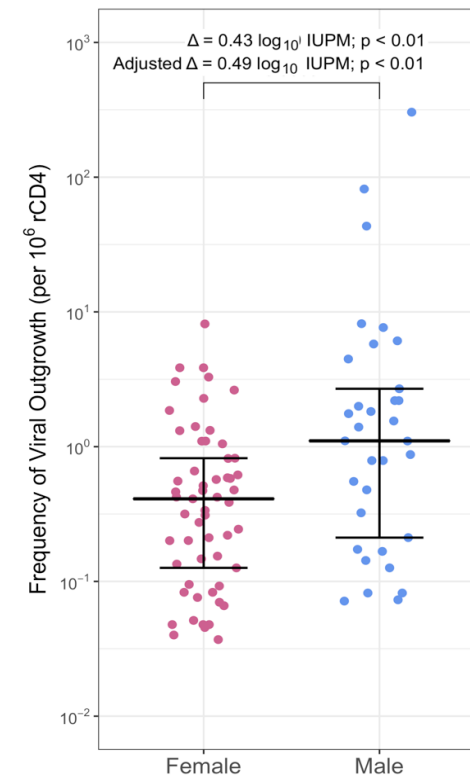
- Treated disease
 - Matched prospective ART treated cohort
 - lower single copy assay
 - lower multiple spliced HIV RNA
 - Lower inducible HIV RNA production
 - *Ex vivo* HIV RNA production blocked by 17β estradiol exposure



Scully et al., JID, 2019; Gandhi et al, Plos Path 2017; Das et al, PNAS 2018

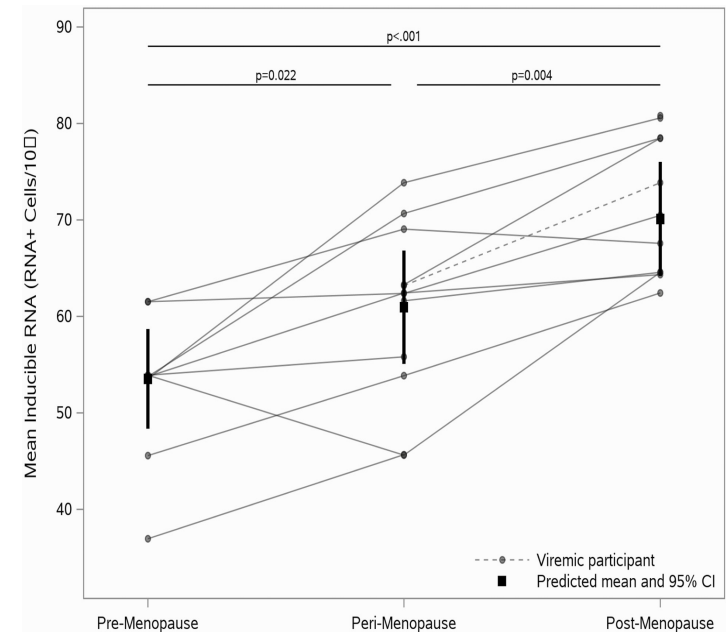
Sex differences in HIV pathogenesis and cure

- Treated disease
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 - Lower replication competent virus production



Sex differences in HIV pathogenesis and cure

- Treated disease
 - Matched prospective ART treated cohort
 - lower single copy assay
 - lower multiple spliced HIV RNA
 - Lower inducible HIV production RNA
 - *Ex vivo* HIV RNA production blocked by 17β estradiol exposure
 - Lower replication competent virus production
 - Increasing inducible HIV RNA through menopause

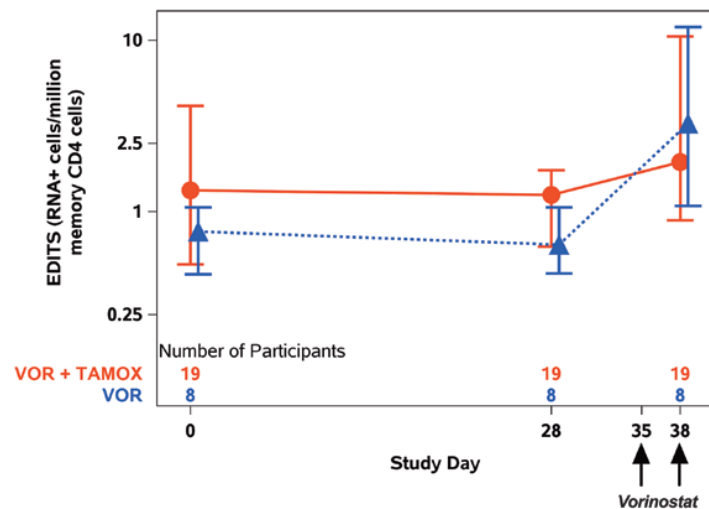


Sex Differences in Treated Disease

- Lower levels of residual virus activity ♀
- Ex vivo induction of HIV RNA is sensitive to estradiol exposure ♀ > ♂
- Reservoir activity changes over the lifecourse ♀
- Lower levels of PD1 expression in ♀

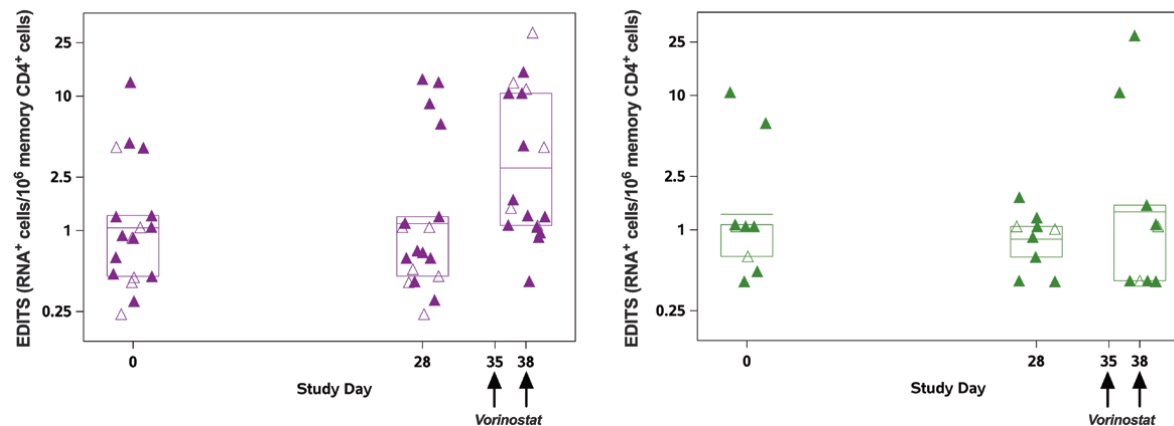
Sex differences in HIV pathogenesis and cure

- ACTG 5366: The MOXIE trial
 - 31 ART-treated postmenopausal women
 - Randomized 2:1 to receive tamoxifen + vorinostat versus vorinostat alone
 - No augmentation of vorinostat response with tamoxifen



Sex differences in HIV pathogenesis and cure

- ACTG 5366: The MOXIE trial
 - 31 ART-treated postmenopausal women
 - Randomized 2:1 to receive tamoxifen + vorinostat versus vorinostat alone
 - No augmentation of vorinostat response with tamoxifen
 - Response to vorinostat highest in those with increase in H4 acetylation



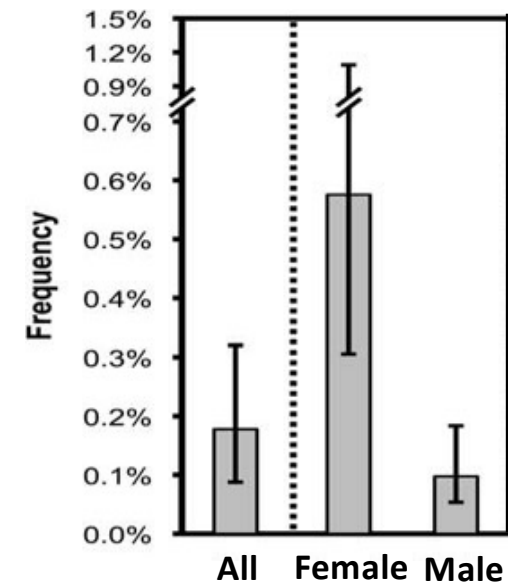
Conclusions

- LRAs are not very potent
- Baseline HIV RNA levels were lower than observed in prior ACTG studies
- Women can be enrolled in cure trials



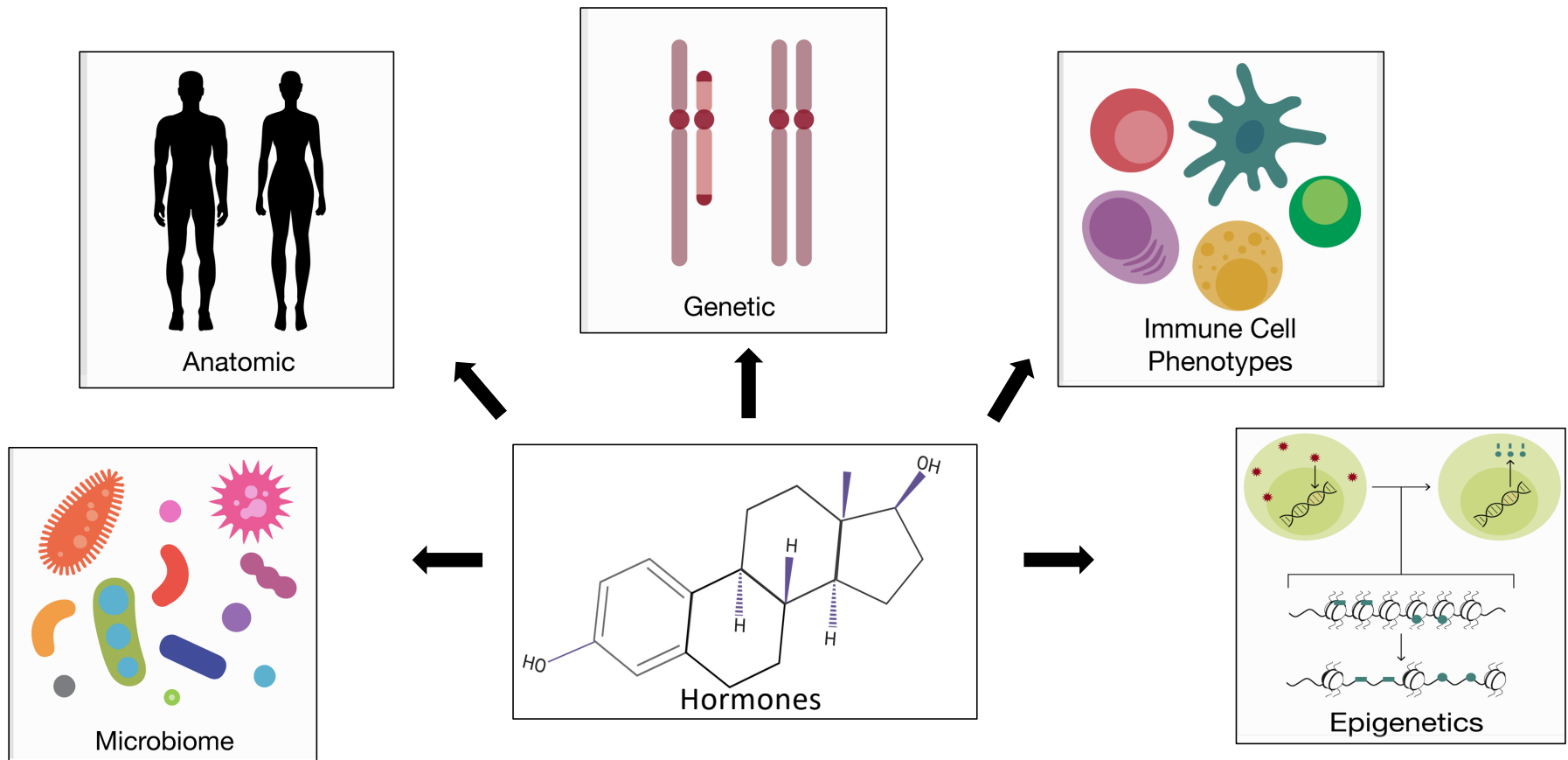
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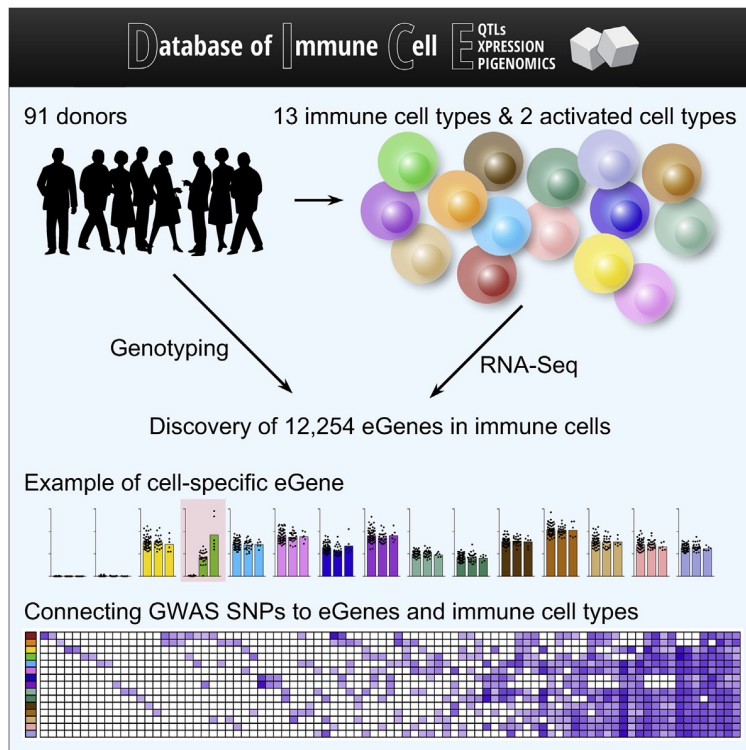
¹Yang et al., *AIDS* 2017; ²Madec et al., *AIDS* 2005; ³Price et al., *JID* 2019; ⁴Crowell et al., *J Infec Dis*, 2015

Biological determinants of sex differences



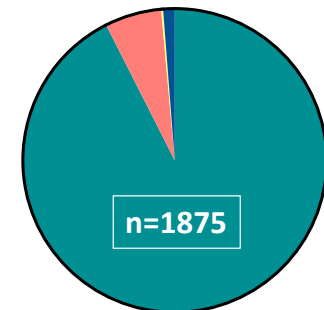
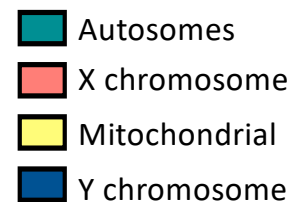
Scully, E *Curr HIV/AIDS Reports*, 2018, *Pathogens and Immunity* 2019; Schmiedel et al., *Cell* 2018

Mechanisms of sex variation: Gene expression



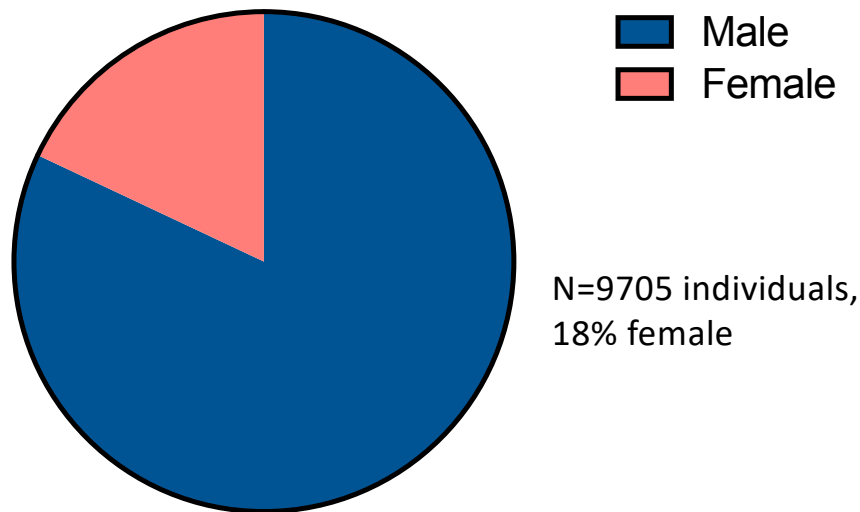
- Focused analysis of gene expression in immune cells
- Identified significant sex based variation in gene expression profiles

Differentially Expressed Genes



International Collaboration for the Genomics of HIV

- Candelaria Vergara, Jeffrey Tuff, Paul McLaren



Cohort	Autosomal analysis (N=9,705)		X chromosome analysis (N=6,953)		Ancestry Group	Genotyping Platform
	N	%Female	N	%Female		
The International HIV Controllers Study & The AIDS Clinical Trials Group	2,824	19.2	2,019	14.3	EUR/AA	Illumina 550, Illumina 1M
The AIDS Linked to the IntraVenous Experience (ALIVE) Cohort, The Multicenter Hemophilia Growth and Development Study (MHGDS), The Multicenter Hemophilia Cohort Studies (MHCS), & the D.C. Gays cohort (DCG)	1,356	5.8	1,328	4.2	EUR/AA	Affymetrix 6.0
Center for HIV/AIDS Vaccine Immunology (EuroCHAVI)	1304	25.1	1,304	25.1	EUR	Illumina 650, Illumina 1M
The Multicenter AIDS Cohort Study	1117	0.0	1,117	0.0	EUR/AA	Illumina 1M
Urban Health Study: Genetics Cohort	769	24.6	0.0	0.0	EUR/AA	Illumina 650
The nonprogressor Genomics of Resistance to Immunodeficiency Virus Study & The ANRS PRIMO cohort	581	12.6	0.0	0.0	EUR	Illumina 300
Center for HIV/AIDS Vaccine Immunology (CHAVI)	515	4.5	0.0	0.0	EUR/AA	Illumina 1M
The Amsterdam Cohort Studies on HIV infection and AIDS	384	7.8	382	7.8	EUR	Illumina 300
The Swiss HIV Cohort Study	340	67.9	340	67.9	AFR	Illumina H3A African array
The Internatioanl AIDS Vaccine Initiative	242	40.5	463	38.8	AFR	Illumina 1M
The Pumwani Sex Workers Cohort, University of Nairobi	147	100.0	0.0	0.0	AFR	Affymetrix 5.0
Wellcome Trust Sanger Institute	126	61.9	0.0	0.0	AFR	Illumina 1M

Are there genetic variants with a sex-specific impact on HIV viral load?

- X chromosome variants
- Sex stratified analysis of autosomal variants, gene based analysis and analysis of heterogeneity of effects

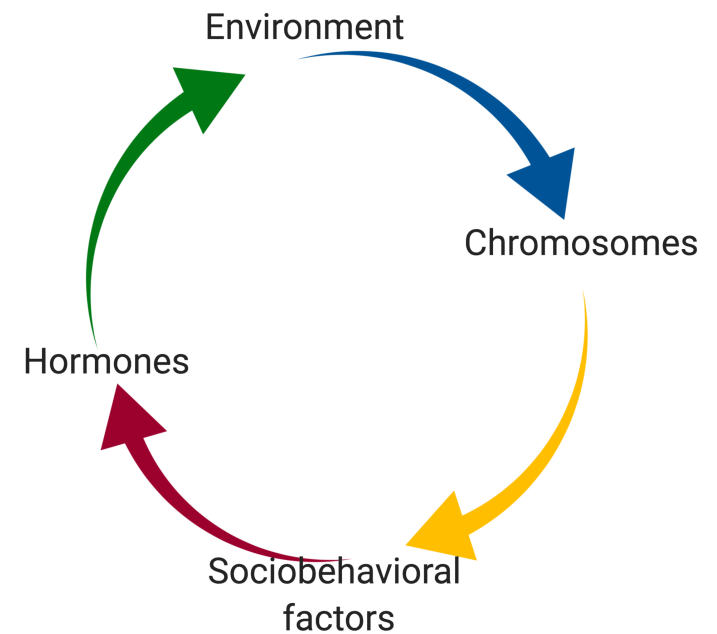
Summary

- Novel genetic variants (chr 19) associated with set point viral load were identified in males only in sex-stratified analysis
- Regions on chr 1 and chr 6 had sex differential associations on set point viral load (positive in females and neutral/negative in males)
- Sample size likely limited the analysis of female specific genetic effects

Sex specific effects of autosomal genes have an impact on HIV set point viral load and may point to mechanisms of viral control

Sex and gender in HIV

- Recognizing the rich scientific opportunity
- The mandate that equity and advancing care requires representation
- Mandatory reporting, stopping rules
- Early stage repetition of key concepts *before* moving forward
- Stratified analysis
- Collaboration



Thank you!!

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