

# REVOJUTION

AVANCES Y DESAFÍOS EN EL TRATAMIENTO DEL VIH

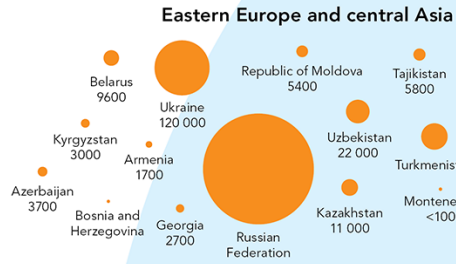
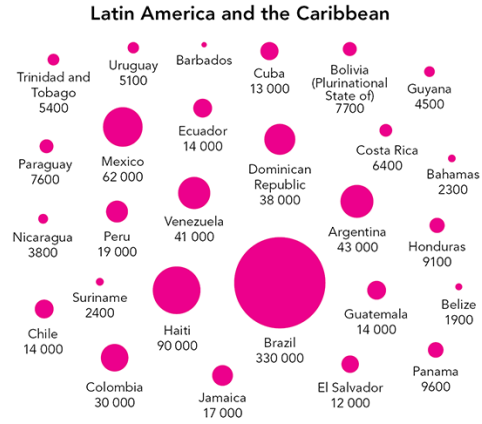
# Woman and HIV

**Impact of sex and gender in HIV infection**

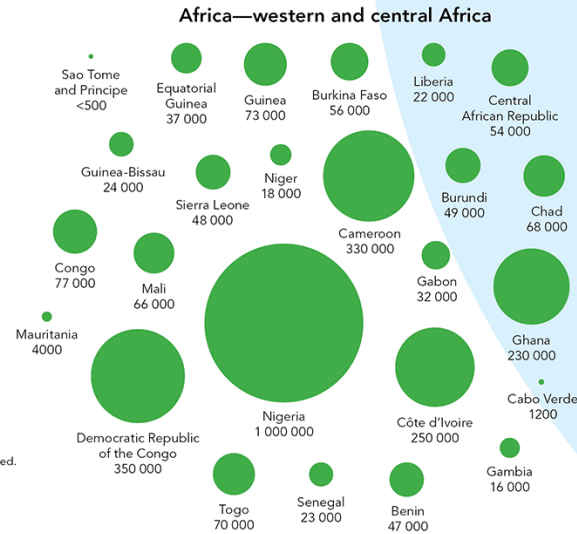
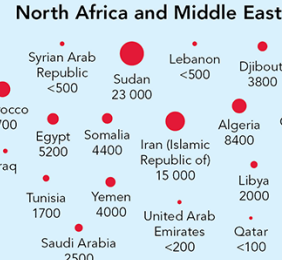
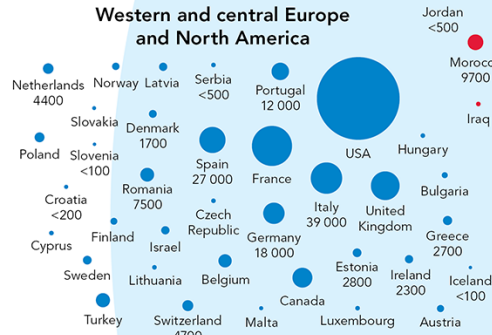
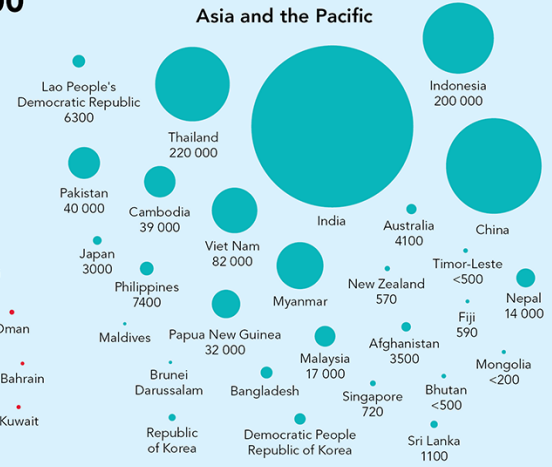
- He recibido honorarios para ponencias de Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals (Johnson & Johnson) y Merck Sharp & Dohme
- He recibido financiación para asistir a congresos de Gilead Sciences y GlaxoSmithKline
- He recibido financiación para becas de investigación de Gilead Sciences, GlaxoSmithKline y Merck Sharp & Dohme

# 20.2 MILLION GIRLS AND WOMEN LIVING WITH HIV

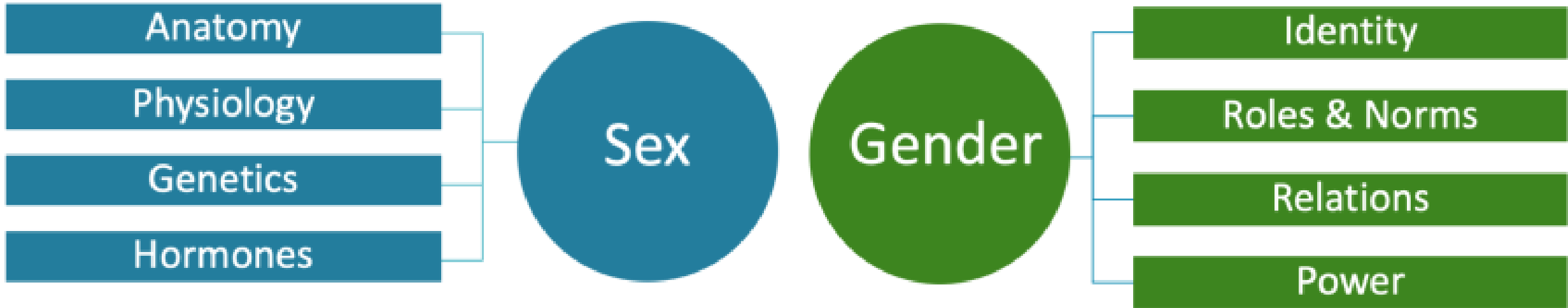
Girls and women make up more than half of the 37.7 million people living with HIV. Ending AIDS by 2030 requires that we address girls' and women's diverse roles by putting them at the centre of the response.



## Global 20 200 000



## Dimensions of Sex (Biological Variable) & Gender (Social and Cultural Variable)



Sex contributes to physiological and anatomical differences that **influence HIV exposure, immunological response and treatment tolerability**

Gender may reflect behaviours that influence **exposure to HIV, access to healthcare or health-seeking behaviours that affect the course of infection**

# Prevention: **feminine gender**

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- **Gender inequality** disproportionately affects women and girls
- In most societies, women have **lower status and have less control over decision-making about their bodies**, in their intimate relationships, families and communities, exposing them to **violence, coercion and harmful practices**
- Women and girls face high risks of **unintended pregnancies, sexually transmitted infections including HIV, cervical cancer, malnutrition and depression**, amongst others
- Gender inequality also poses **barriers for women and girls to access health information and critical services**, including restrictions on mobility, lack of decision-making autonomy, limited access to finances, lower literacy rates and discriminatory attitudes of healthcare providers

# Prevention: **feminine gender**

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- In studies of oral PrEP for HIV prevention, women have shown **lower real-world uptake** in comparison to men, demonstrating **adherence challenges** in this population
- In post exposure prophylaxis with doxycycline (DOXIEP), **the incidence of STIs was not significantly lower** with doxycycline PEP among cisgender women than with standard care, and **adherence was low**, as shown by levels of drug in hair samples (29% detection)
- On the other hand, in the HTPN 084 study, **cabotegravir LA for HIV prevention** in women was **effective and superior to TDF-FTC**

# PrEP in women

Hypothesis for lack of efficacy in trials including women vs men

- Different concentrations in vaginal vs rectal mucosa
- HIV Subtype C
- **Lack of adherence**

FEM-PrEP (TDF-FTC)	65	66.5	5	Non-partners	0.94 (0.59, 1.52)
VOICE (TDF-FTC)	71	92.1	4.2	Non-partners	1.04 (0.73, 1.49)
VOICE (TDF)	70	92.1	4.2	Non-partners	1.49 (0.97, 2.29)
TDF2 (TDF-FTC)	36	100	3.9	Non-partners	0.51 (0.19, 1.22)
Partners PrEP (TDF-FTC)	23	5.9	2.8	Partners	0.34 (0.16, 0.72)
Partners PrEP (TDF)	20	5.9	2.8	Partners	0.29 (0.13, 0.63)

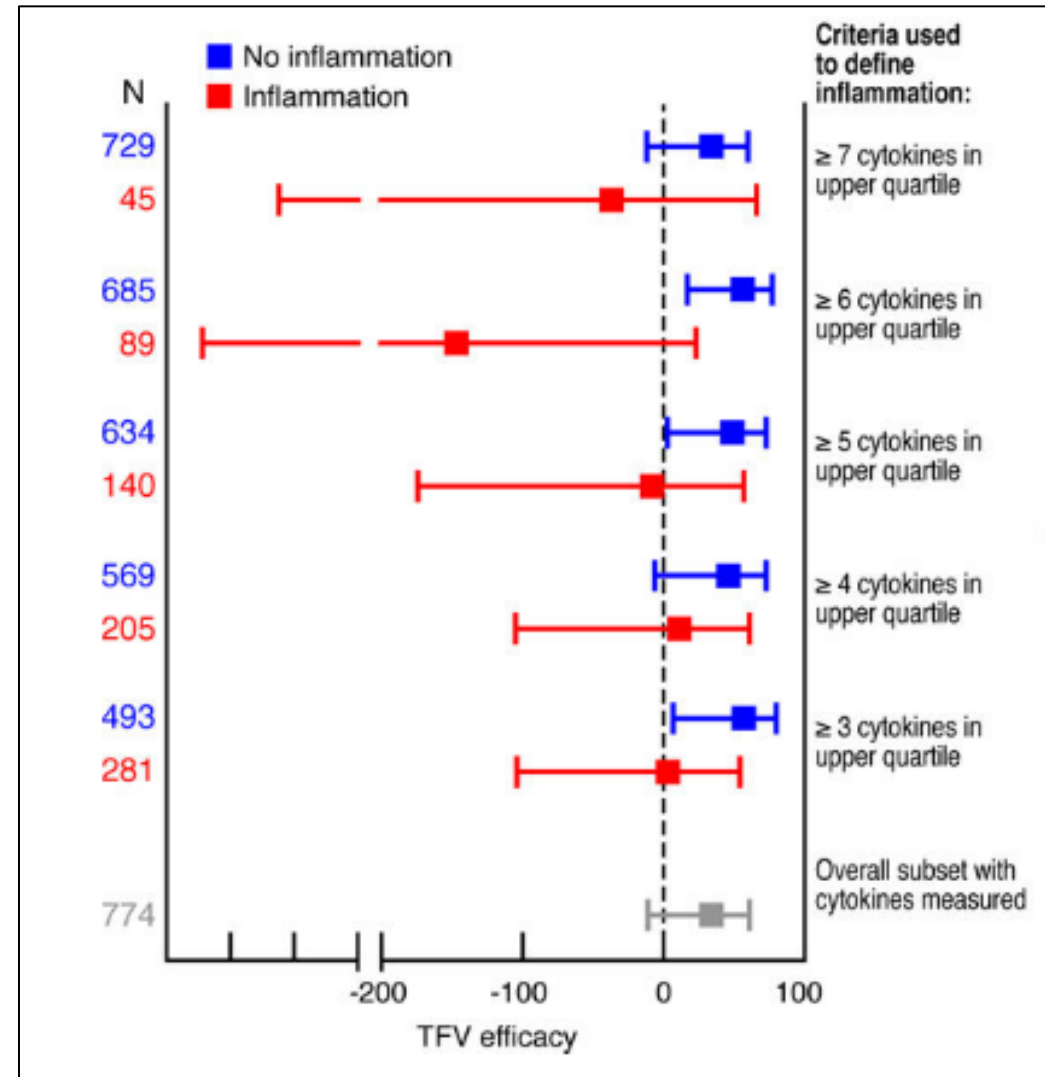
Undetectable (%)      Sub-type C (%)      Placebo HIV Incidence (%)      Non-partners vs. Partners      PrEP vs. Placebo HR (95% CI)



# Female genital tract and HIV infection

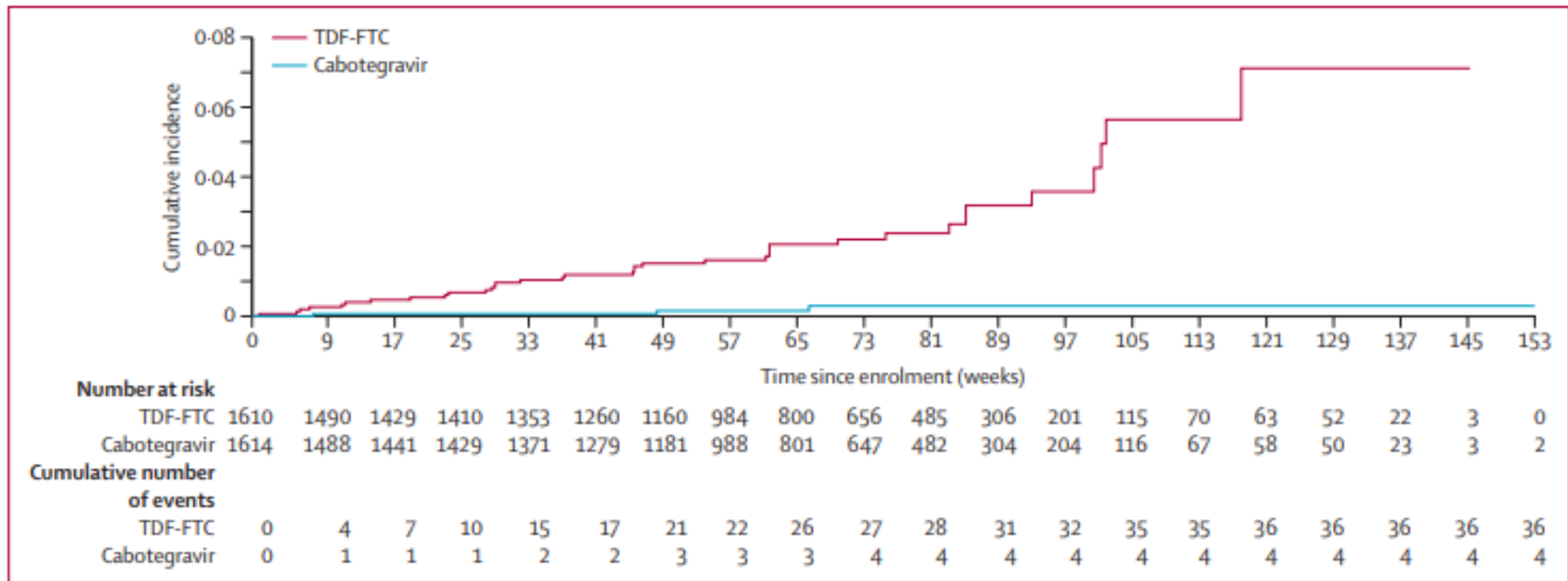
- **Inflammation in FGT** not only increases risk of HIV infection but also **can interfere with preventive measures**

*Mc Kinnon, Genital inflammation undermines the effectiveness of tenofovir gel in preventing HIV acquisition in women. Data from the CAPRISA trial. Nat Med 2018*



# PrEP in women: Cabotegravir LA

Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial



# PrEP in women: cabotegravir LA

Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial

0.08 ] — TDF-FTC  
— Cabotegravir

**Participants in the cabotegravir group had an 88% lower risk of HIV infection than those in the TDF-FTC group**

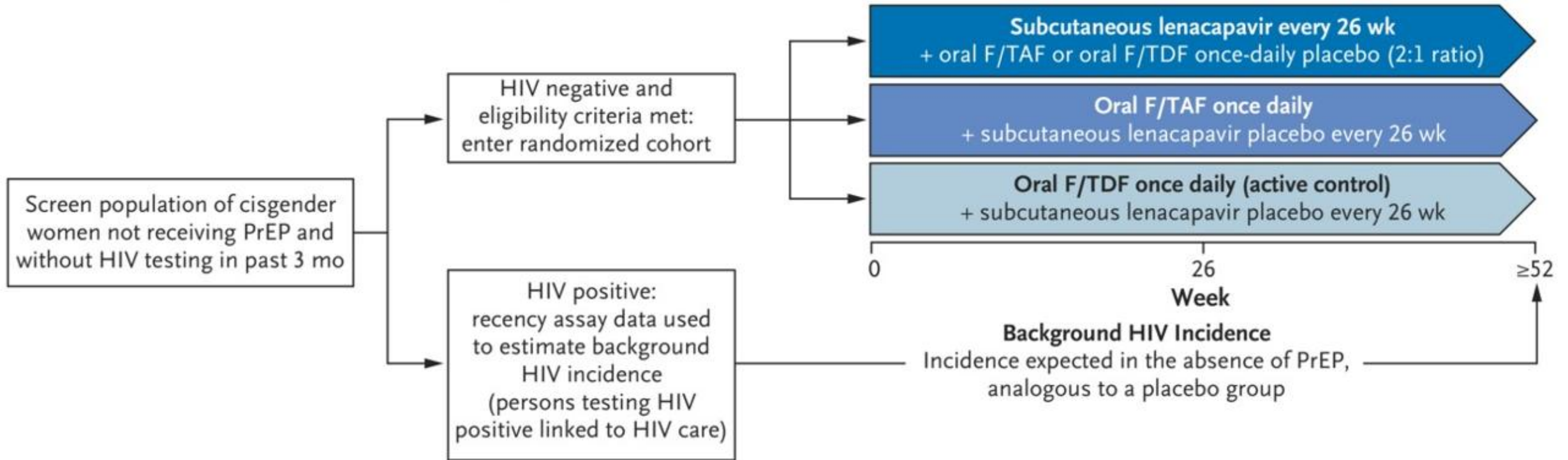
of events																				
TDF-FTC	0	4	7	10	15	17	21	22	26	27	28	31	32	35	35	36	36	36	36	36
Cabotegravir	0	1	1	1	2	2	3	3	3	4	4	4	4	4	4	4	4	4	4	4



# PrEP in women: Lenacapavir LA

## A Trial Design

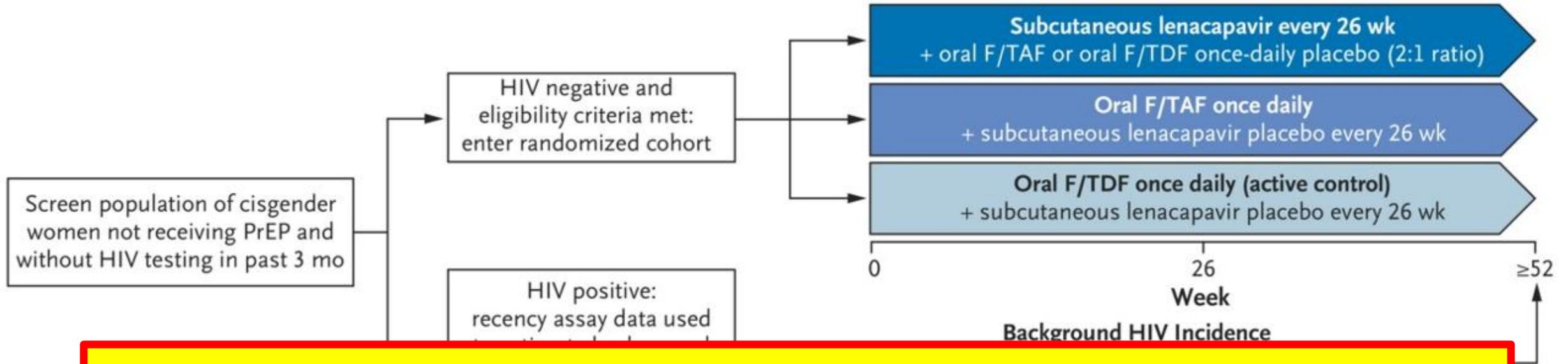
### Cross-Sectional Incidence Cohort



# PrEP in women: Lenacapavir LA

## A Trial Design

### Cross-Sectional Incidence Cohort



**No HIV infections in the Lenacapavir arm**

# Prevention: **feminine sex**

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- **Immune cell populations and functions** in the female genital tract (FGT) are tightly **regulated by sex hormones** and the tissue environment
- Women engaging in heterosexual intercourse are at a **higher risk of HIV infection compared to men**, specially in high endemic areas
- **STIs**, alteration in microbiome and disbalance in lactobacillus can **increase susceptibility of HIV** in female genital tract
- **Inflammation in FGT** not only increases risk of HIV infection but also **can interfere with preventive measures**

# Diagnosis: **feminine gender**

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- In some areas where the prevalence of HIV among men and women is similar, like **sub-Saharan Africa**, women tend to undergo **HIV test on their own initiative more frequently than men, however young women (14-24 yo. are disproportionately affected)** in comparison to men.
- Conversely, in the **European Union** women arrive later to diagnosis than men, probably representing **less test performance in women** in this area



# Diagnosis: **feminine gender**

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- Studies in **Spain** observed **lower rates of voluntary testing in women** and described **pregnancy as the main motivator** for HIV testing when analyzing factors related to voluntary screening
- Data from our Hospital showed **that 21% of women on active follow-up in our cohort** in December 2020 had **been diagnosed with HIV through reproductive health** screening

# Antiretroviral Treatment: **feminine gender**

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- Many **factors related to feminine gender** like HIV stigma, institutional violence, poverty, job precarity, high rates of caregivers in women, etc. **negatively impact in virological outcomes in WLWH**

# Antiretroviral Treatment: **feminine sex**

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- **Sex-based differences** are widely recognized in bioavailability, distribution, metabolism, and elimination of drugs, **contributing to sex differences in drug efficacy and toxicity profiles**
- Several studies report **higher adverse events with antiretroviral treatment** for HIV infection in women compared to men

# Antiretroviral Treatment: **feminine sex**

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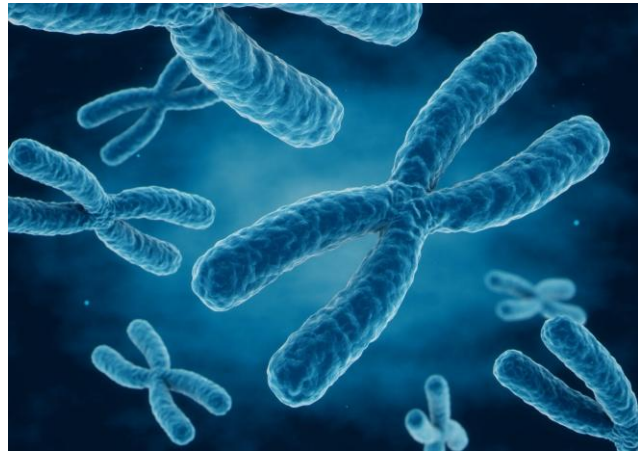
Efficacy of treatment in terms of viral load and CD4 count

- Similar to men (if equal access to treatment...) (*Moore, JAIDS 2003; Castilho, ARHR 2014*)

Immune response after ART initiation

- In **acute infection** faster decay of VL and earlier recovery of CD4 count. No difference in levels of HIV DNA with time (*Novelli, JIAS 2020*)
- Lower HIV-1 cell associated RNA, lower plasma HIV RNA and lower T-cell activation and PD-1 expression in women in relation to men (*Scully, JID 2019*)

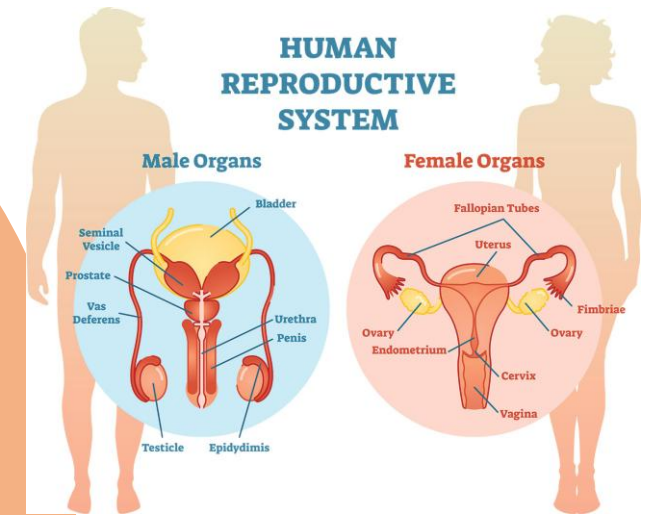
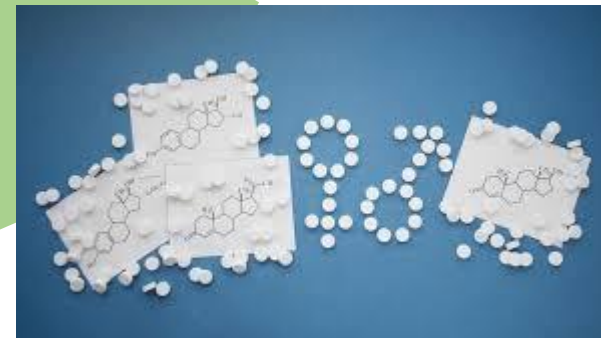
# Differences in immune responses related to **sex**



chromosomes

reproductive  
organs

sex steroids



# Differences in immune responses related to **sex**

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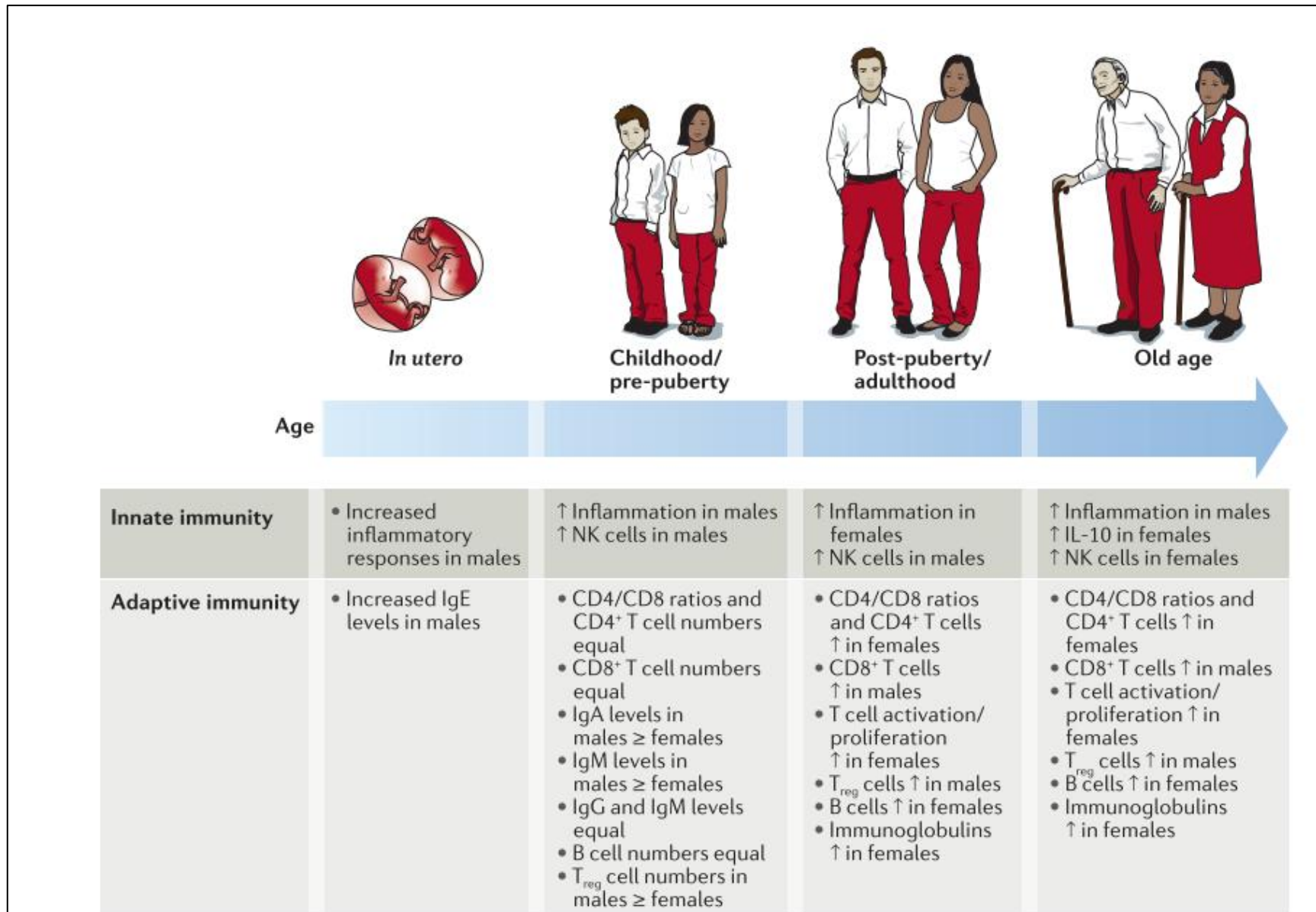
- The human **X chromosome** contains over 1,100 annotated genes, representing approximately 5% of the human genome, and **includes a significant number of immune related genes**
- In XX one X chromosome has to be silenced to ensure only a single copy functions in each sex
- **15% of X genes in humans escape X inactivation resulting in higher copy numbers in females than males**
- Many genes on the **X chromosome regulate immune function** and play an important role in modulating sex differences in the development of immune-related diseases

# Differences in immune responses related to **sex**

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- Androgen and estrogens receptors (AR and ER) are present in the promoters of several innate immune genes
- **Sex steroids may cause dimorphic innate immune responses**
- **ERs are expressed in various lymphoid tissue cells, in lymphocytes, macrophages, and DCs**
- Differential effects of oestrogens on immune function reflect, not only oestrogen concentration, but also the density, distribution and type of ERs in immune cells
- Levels of oestrogen, for example,  $17\beta$  oestradiol (E2), are **variable during the menstrual cycle, high during pregnancy and low after menopause in females.**

# Differences in immune responses related to **sex**





# Characteristics of HIV infection related to **feminine sex**

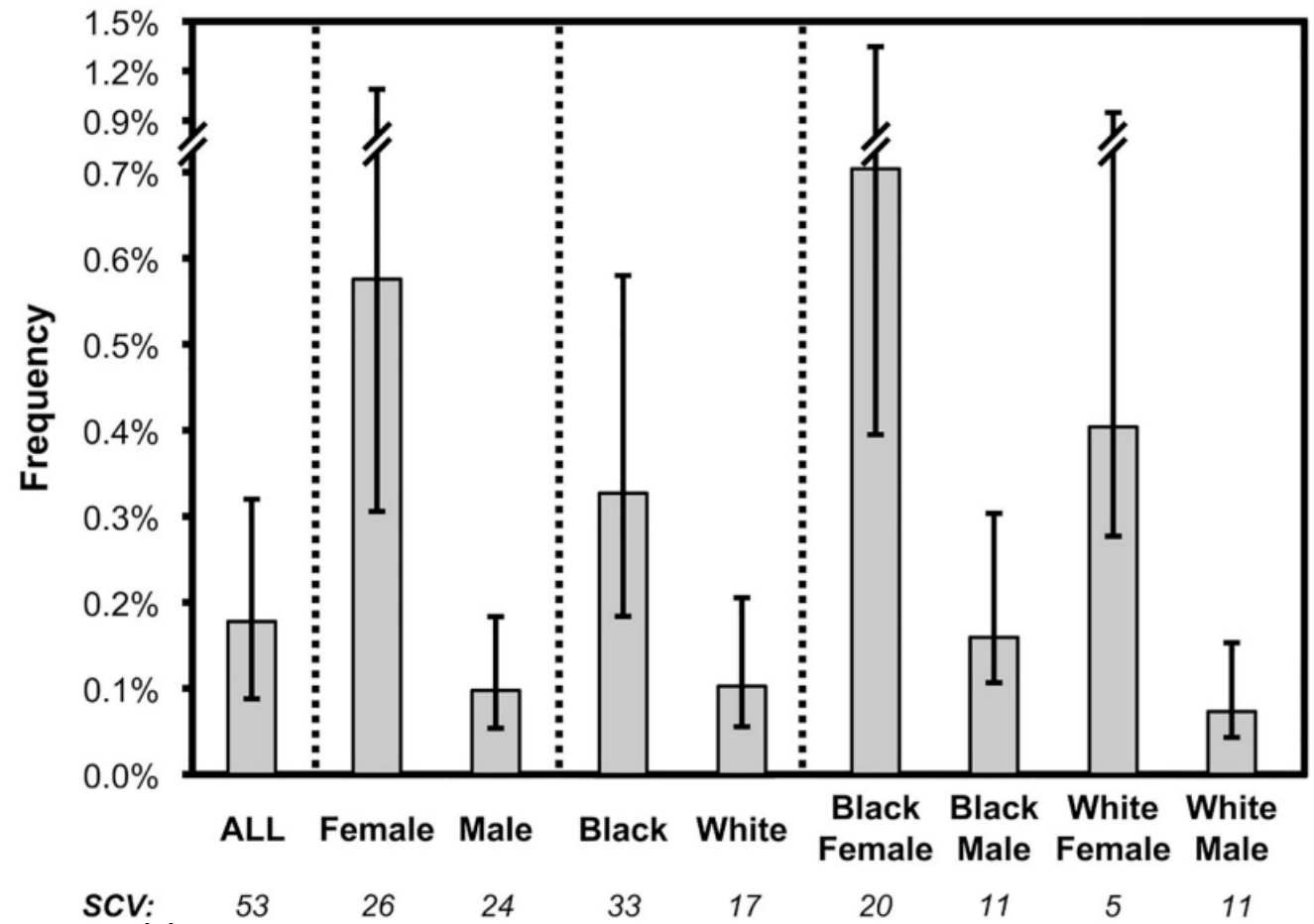
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- Among adults, untreated WLWH have **greater CD8+ T cell activation** than men when adjusted for viral load and over **40% less circulating HIV RNA** than men
- **Faster progression to AIDS without treatment** adjusted for viral load (1,6 fold higher risk of AIDS than men)
- **Higher proportion of elite controllers** in WLWH

# Characteristics of HIV infection related to **feminine sex**


**Female sex and black race** are associated with higher spontaneous control of viremia (SCV)

Of 46,524 medical records of HIV-1-infected persons reviewed, 29,811 had adequate viremia measurements for screening, of which **53 (0.18%)** were identified as persons with SCV (three consecutive plasma HIV-1 RNA tests



\*\* Only Black and White race and female and male gender are shown, given the small numbers of other races and transgender persons

# Characteristics of HIV infection related to **feminine sex**



**Oral Abstract Session-10**

Wednesday, March 6, 2024

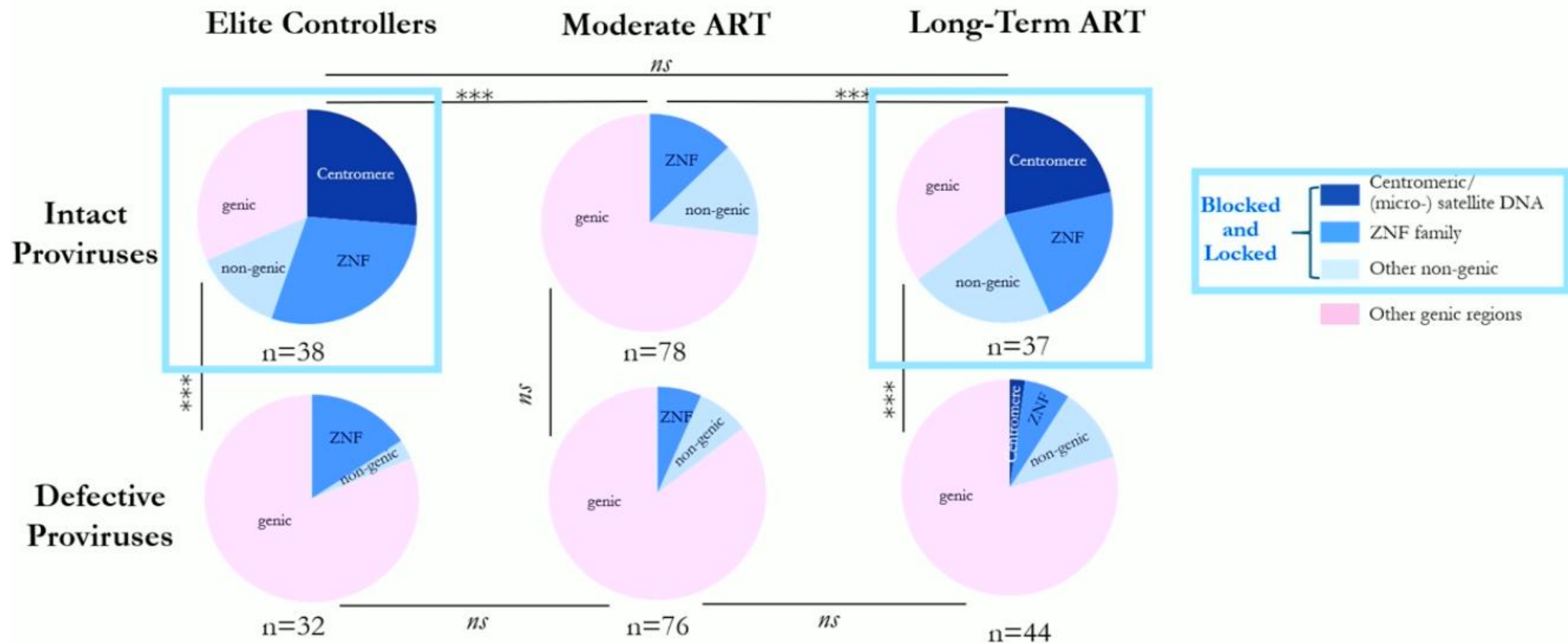
## **Sex-Based Differences in HIV-1 Reservoir Profile in Individuals With Long-Term ART Suppression**

**Toong Seng Tan**  
Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA  
Brigham's and Women Hospital, Cambridge, MA, USA

*Disclosure: Dr Tan reported no relevant financial relationships with ineligible companies.*

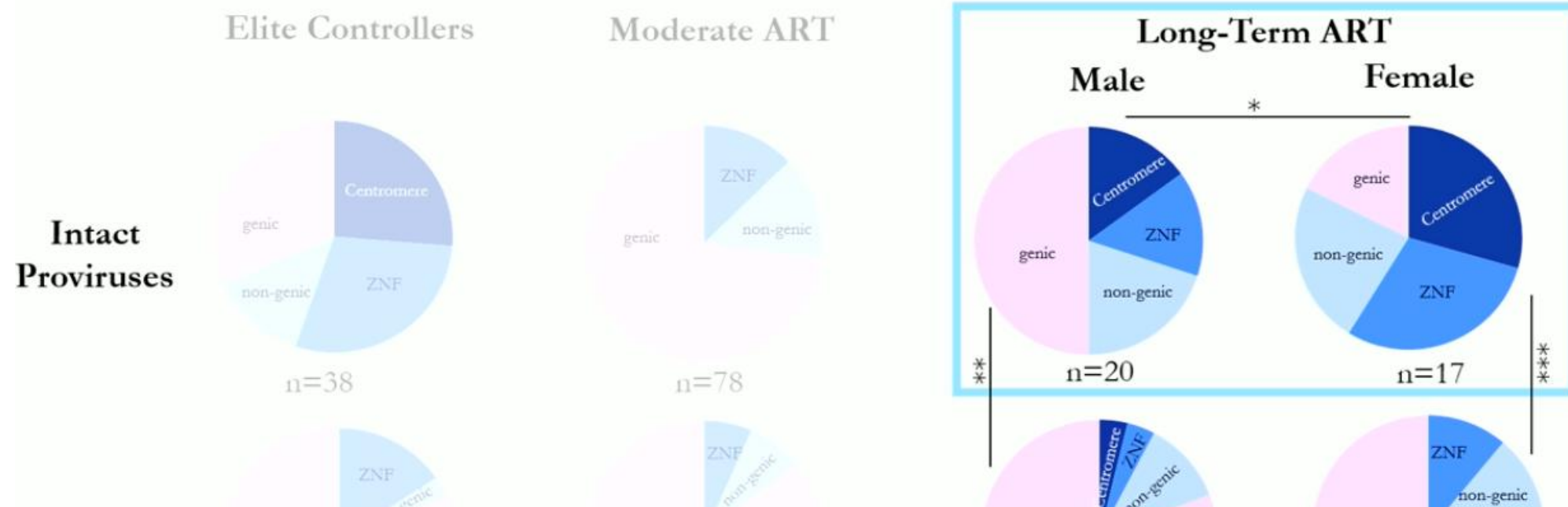
**CROI** 2024

# Significant Enrichment of Intact Proviruses in Heterochromatin during Long-Term ART



- \*\*\*p<0.001, chi-square test
- Unique single integration sites were used in the analysis

## Stronger Enrichment of Intact Proviruses in Heterochromatin in Females on Long-Term ART



- The **female sex** was associated in this study with a higher number of viruses in the reservoir at non-replicative gene positions.
- These results are important in the field of the possibility of a functional cure for HIV.

# Conclusions

- **Both, sex and gender**, can act as factors of vulnerability in women.
- **Gender inequalities pose women at higher risk for HIV**
- In settings where women represent low numbers of PLWH they are **less represented in preventive strategies** than men
- Due to roles and norms access to **healthcare and adherence to antiretroviral treatment/preventive treatment** is unacceptable **low** in some regions
- More preventive and linkage to care for HIV strategies adapted to the epidemiology of each local setting are needed

# Conclusions

- There are **important sex-based differences** that impact on **HIV acquisition risk, tolerability** to medication and **immunological response** that can impact on HIV infection outcome.
- Women are **underrepresented** in most HIV clinical trials in Western countries
- Participation of WLWH in HIV studies remains **crucial** as the lack of information on sex- and gender-specific effects may hinder
  - **knowledge** about HIV natural history in women
  - the **safety** and **efficacy** of antiretroviral treatments
  - new findings in **HIV cure strategies**



THANK YOU!!!