



Jessica Prodger, Western University

Pathways to an HIV cure:
Research and advocacy priorities

Towards
an HIV Cure
IAS

Considerations for cis-Women in HIV Cure Research

*I have no relevant financial relationships
with ineligible companies to disclose.*



Affiliated Independent Event





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Consideration of *the attributes of biological sex associated with cis-Women in HIV Cure Research*



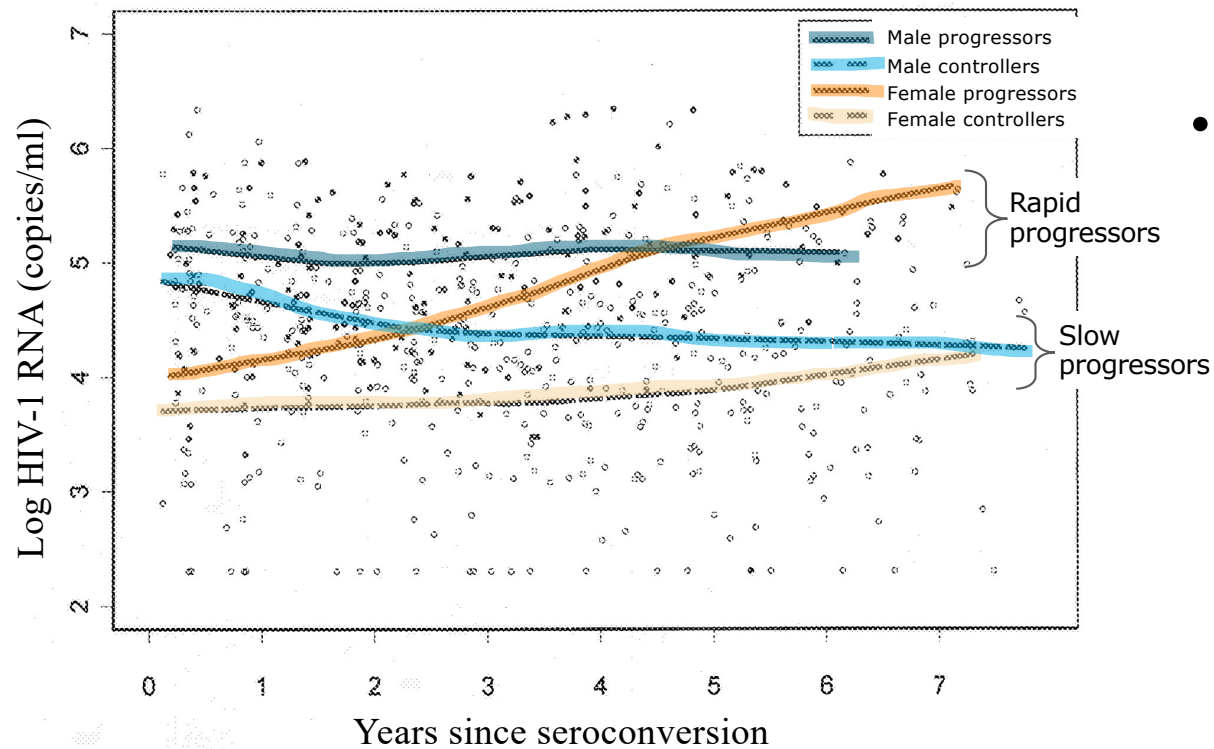
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“Female” Biological Sex

Post-Zygote Modifiability ↓	Two X chromosomes	Cis women XXY males and intersex peoples, trans men & other gender diverse people
	Epigenetic Profile	Exogenous hormones can influence gene methylation: (X)XY people on feminizing hormones (transfeminine)
	Sex hormones (estrogens progesterone)	(X)XY people on feminizing hormones (X)XX people on masculinizing hormones Effect of pregnancy, menopause, etc.

Sex & HIV Pathogenesis

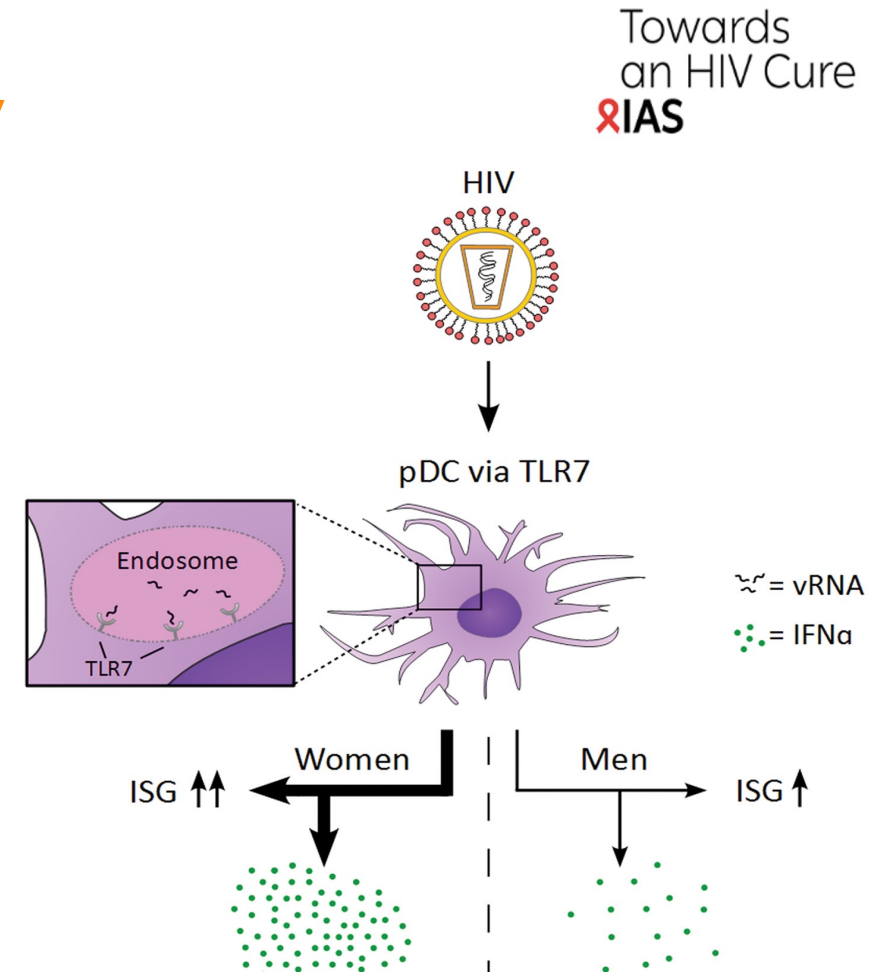


- Female sex

- High CD4 T cell counts & CD4/CD8 ratios
- Low early viral loads
- Faster progression at a given VL

Sex & Immunology

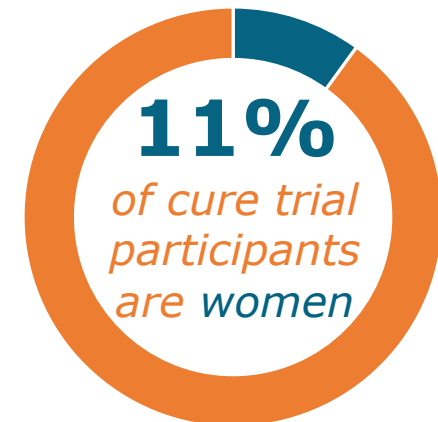
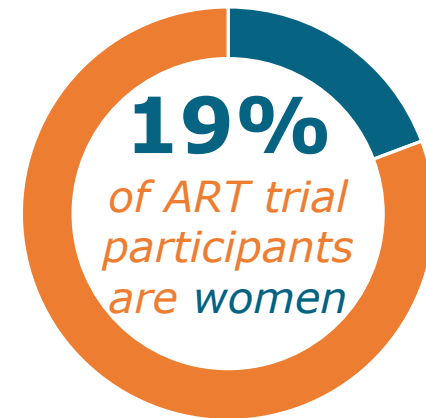
- X chromosome genes
 - *TLR7*, *FOXP3*, and 10% of all microRNAs
- Epigenetic modification
 - Methylation patterns and transcriptomes
- Female = higher IFN α
 - Bi-allelic expression = more TLR7
 - Estrogen enhances response to TLR7



Adapted from Addo et al. JID 2014

Sex & Cure Research

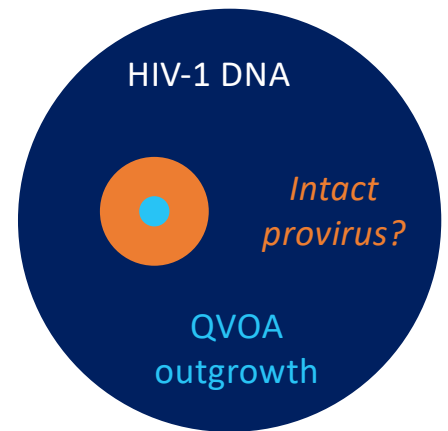
- Most ARTs target virus
- Many curative agents target host factors
 - Immune pathways (e.g., TLRs, PD-1)
 - Epigenetic pathways
 - Host genes



Sub-Saharan Africa & Biological Sex

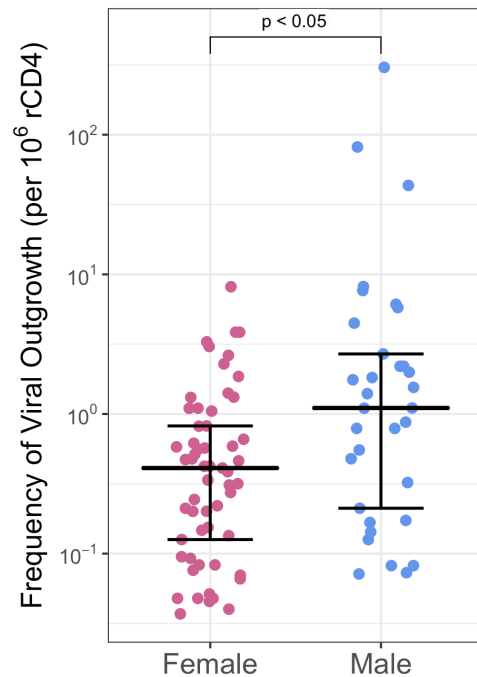


- Generalized epidemic, heterosexual transmission
 - Rakai Health Sciences Program (RHSP), Uganda
- 90 adults living with HIV
 - 57 females, 33 males
 - ART-suppressed
- Reservoir Quantification:
 - gag qPCR = all provirus (defective and intact)
 - QVOA: outgrowth = replication-competent only
 - Intact?? Problem = HIV subtype

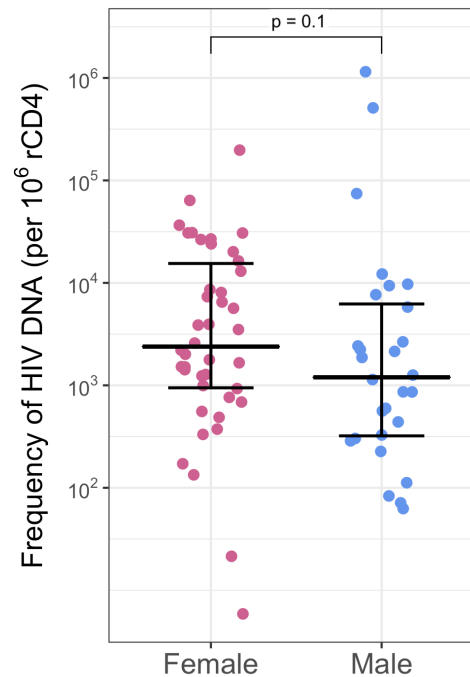


Adapted from Bruner et al.

QVOA Outgrowth



HIV-1 DNA



Controlling for:
pre-ART VL, nadir CD4, time on ART, CD4:CD8 ratio:

$$\Delta \log_{10} \text{IUPM} = 0.49, p < 0.01$$

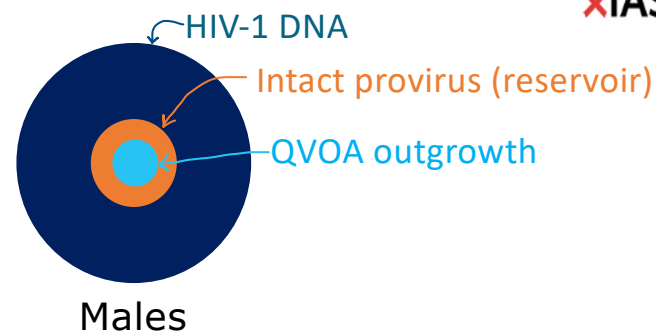
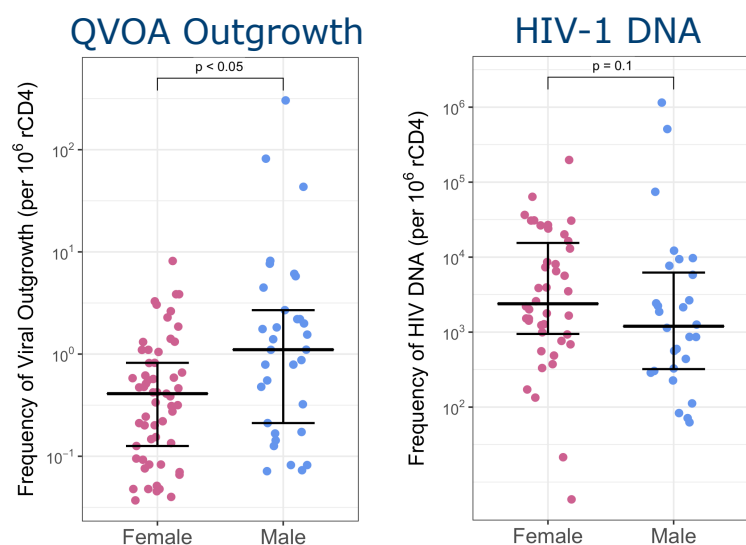
AIDS 2022 Affiliated Independent Event

Characteristic	Stepwise Regression	
	Females (n = 29) adj. R ² = 0.27	Males (n = 10) adj. R ² = 0.66
Age (per years)	-	-
Pre-ART viral load (per log ₁₀ copy/ml)	0.33* (0.08, 0.58)	0.43 (-0.30, 1.17)
Nadir CD4 T cell count (per 100 cells/ μ l)	-	-
Time on ART (per log ₁₀ year)	-2.11* (-3.58, -0.63)	-4.40* (-8.04, -0.76)
CD4 T cell count at QVOA (per 100 cells/ μ l)	-	-
CD4/CD8 T cell ratio at QVOA (per 0.1 proportion increase)	-	-
PD1+ CD4 T cells (per 1% PD1+ CD4 T cells)	-	0.05* (0.01, 0.10)
IL2+ CD4 T cells (per 1% IL2+ CD4 T cells)	-	-
TNF+ CD4 T cells (per 1% TNF+ CD4 T cells)	-	-
IL2+ CD8 T cells (per 1% IL2+ CD8 T cells)	-	-0.16* (-0.30, -0.03)
TNF+ CD8 T cells (per 1% TNF+ CD8 T cells)	0.01 (-0.00, 0.03)	-

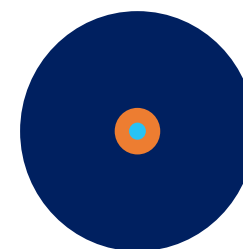
Prodger JL et al JCI Insight 2020

How to interpret?

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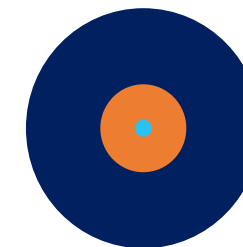


Smaller replication
competent reservoir?



Females?

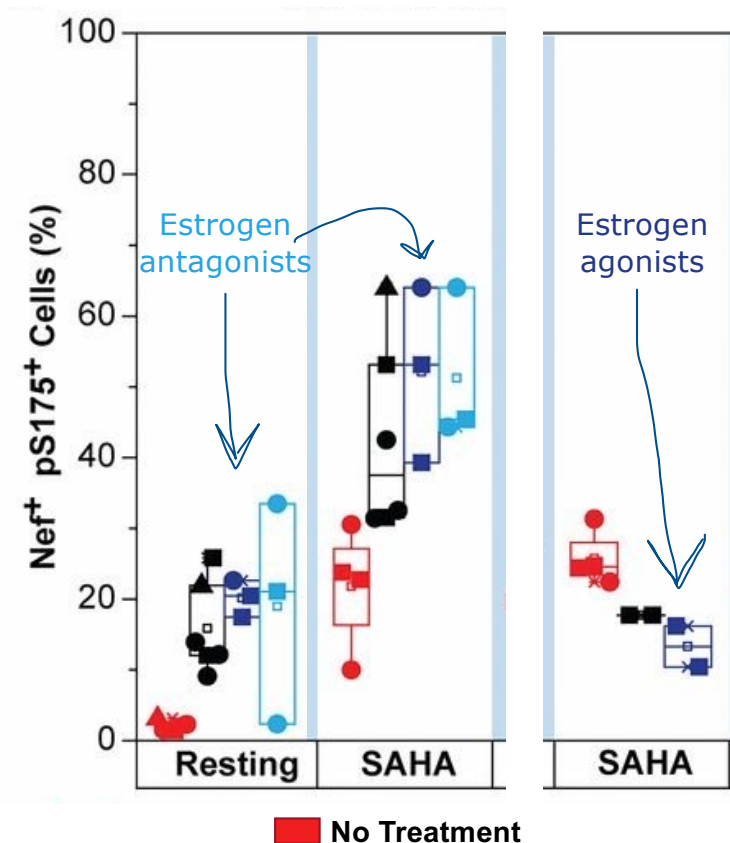
Poor latency reversal?



Estrogen & HIV Transcription

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- in vitro*
- HIV-1 RNA levels vary with menses
 - lower in follicular when estrogen peaks
 - Estrogen inhibits HIV transcription
 - β -estradiol \rightarrow ER α (ESR1) suppresses HIV
 - Blocking ER α enhances iHDAC (vorinostat = SAHA)
 - β -estradiol \downarrow LRA-induced HIV expression
 - MOXIE Trial
 - No effect of tamoxifen on vorinostat reactivation in post-menopausal females



Considerations for Research

- Estrogen may limit efficacy of latency reversal agents
 - interfere with reactivation-based quantification assays (QVOA)
- Hormones/chromosomes may impact immunomodulatory cures
 - e.g., TLR7 agonists, PD-1 inhibitors
- Subtype, layered on sex (sub-Saharan Africa)
- Need more diversity in cure research
 - Careful design: menses, puberty, pregnancy, menopause, hormonal contraception, transition-related hormone therapy...
 - Community engagement: novel agents with risk



Thomas Quinn
Andrew Redd
Steven Reynolds



Katherine Yu
Yun-Hee Choi
Sarah Gowanlock



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Maria Wawer
Eileen Scully
Robert Siliciano
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