

Jessica Prodger, Western University

Pathways to an HIV cure: Research and advocacy priorities

Considerations for cis-Women in HIV Cure Research



Affiliated Independent Event

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



Towards an HIV Cure **XIAS**





Towards

RIAS

an HIV Cure

Pathways to an HIV cure: Research and advocacy priorities

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



Affiliated Independent Event

"Female" Biological Sex

	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 hormonesEffect of pregnancy, menopause, etc.		

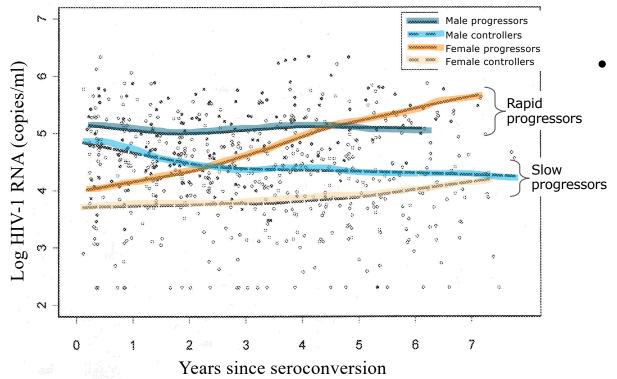
Towards

RIAS

an HIV Cure

Post-Zygote Modifiabil

Sex & HIV Pathogenesis



• Female sex

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

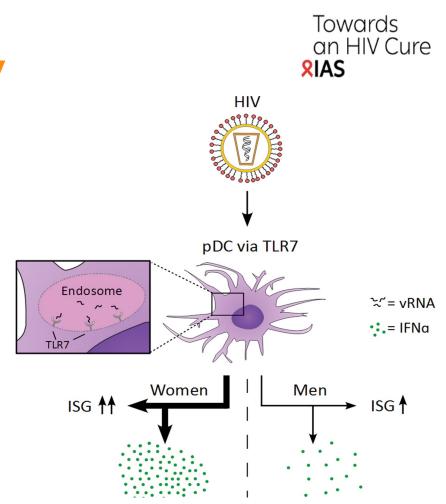
AIDS 2022 Affiliated Independent Event

Adapted from Sterling et al. JID 1999

Towards an HIV Cure **<u><u>RIAS</u>**</u>

Sex & Immunology

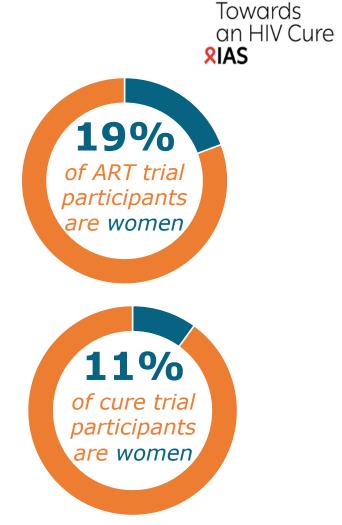
- X chromosome genes
 - TLR7, FOXP3, and 10% of all microRNAs
- Epigenetic modification
 - Methylation patterns and transcriptomes
- Female = higher IFNa
 - Bi-allelic expression = more TLR7
 - Estrogen enhances response to TLR7



Adapted from Addo et al. JID 2014

Sex & Cure Research

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



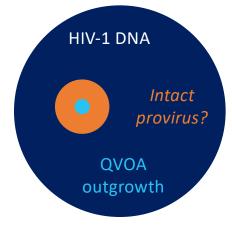
AIDS 2022 Affiliated Independent Event

Curno et al JAIDS 2016

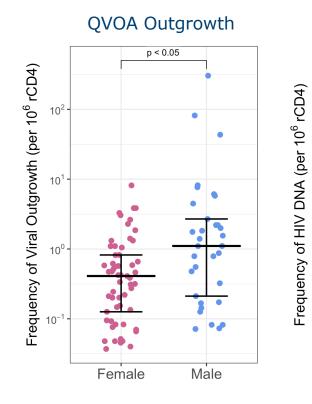
Sub-Saharan Africa & Biological Sex



- 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.



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



AIDS 2022 Affiliated Independent Event

С	h	ar	a	ct	eri	sti	С
						_	

10⁶

10⁵

10⁴

10³

10²

HIV-1 DNA Age (per years)= 0.1

Pre-ART viral load (per log₁₀ copy/ml) Females (n = 47); Males (n = 28) Nadir CD4 T cell count (per 100 cells/µl) Time on ART (per log₁₀ year) CD4 T cell count at QVOA (per 100 cells/µl) CD4/CD8 T cell ratio at QVOA (per 0.1 proportion increase) PD1+ CD4 T cells (per 1% PD1+ CD4 T cells

(per 1% PD1+ CD4 T cells) Females (n = 34); Males (n = 13) IL2+ CD4 T cells

(per 1% IL2+ CD4 T cells) Females (n = 34); Males (n = 13)

FENELCD4 T cells (per 1% TNF+ CD4 T cells) Females (n = 34); Males (n = 13)

IL2+ CD8 T cells (per 1% IL2+ CD8 T cells) *Females (n = 34); Males (n = 13)*

TNF+ CD8 T cells

(per 1% TNF+ CD8 T cells) Females (n = 34); Males (n = 13)

Univariate Regression	Stelphniksær Falteg	Stepwis	
(n = 57) Males (n = 33)	Fe Freates (n (=12957) adj. R ² = 0.27 adj		Females (n = 29) adj. R ² = 0.
Aୁଦ୍ର ପ୍ତେ3* 0.01	-0.03*	0.01	-
(-୦(ଇଞ୍ଚ,୪ୟମ୍ଟାଦ୍ରୀ) (-0.04, 0.07)	(-0.05, -0.01)	(-0.04, 0.07)	
Prœ-ØXRT viral load 0.16	0.30*07		0.33*
(- Ø₽₱5,!@129 9>ppy/ml()-0.22, 0.53)	(0. 06,1556) 29)(-((0.08, 0.58
Nadio*CD4 T cell ഡിൻ	-0.10*	-0.10	-
(ഗാല, 10.2 ഴിട/ലം) (-0.35, 0.14)	(0.00, 0.21)	(-0.35, 0.14)	
Tifnæ1ón ART 0.31	-2.411.21*		-2.11*
(-10 83 ,l og ₁ 59 ≽ar) (-0.93, 1.55)	(-3(58,83).603,59)(-8		(-3.58, -0.6
CED4010 cell count a0CIVOA	-0.00	-0.10	
(-@c@7,100079lls/µl)(-0.34, 0.14)	(-0.07, 0.07)	(-0.34, 0.14)	
CD4J2D8 T cell ratio 1&*QVOA (-{0pi/0017#pporticer01r23ea8e033)		0.13* (-0.23, -0.03)	
P0.064CD4 T cells 0.040*	0.004	0.050.040*	
(-0.069.1% ርዋጅ1+ ርውደን በ49 (ውደን በ20)	(-0.009, 0.016)(0	0.0(10,000#0)0.072)	
ID29-2℃D4 T cells -0.036	9.027*	-0.036	-
(0.0000.10%0543)+ CI240.71066‼s0.041)	(0.000, 0.054)	(-0.106, 0.041)	
TONE 14CD4 T cells -0.012	0.014*	-0.012	-
(0.0092.10%0210F+ ୧୮୦୬/0742୧୩୨୦୦19)	(0.002, 0.026)	(-0.042, 0.019)	

 IL2+22D8 T cells
 -0.14*
 -0.12*
 -0.16*0.14*

 (0.0277.10%2068)*
 CD0.24¢9!!≤0.023)
 (0.027, 0.2050)-0.800,200,0023)

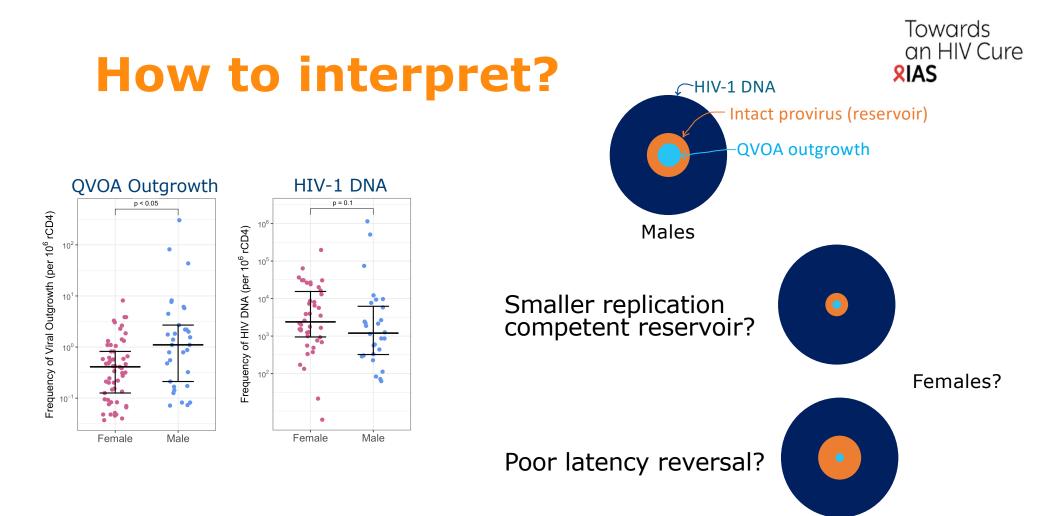
 TONEF#8CD8 T cells-0.018
 0.00.018*
 -0.018
 0.01

 (0.0000,10%085)F+ (208,052¢,150017)
 (-00000,003035)
 (-0.052, 0.017)
 (-0.00, 0.0

* denotes p<0.05

* denotes p<0.05 Prodger JL et al JCI Insight 2020

- denotes variables included in the stephysical equivalence of the stephysical stephysical

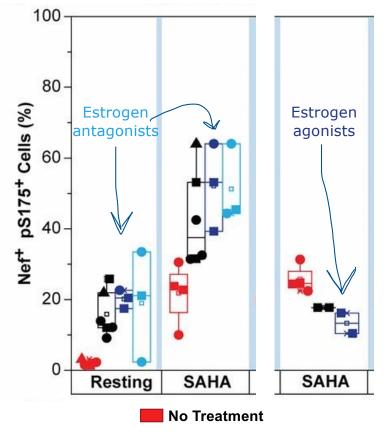


Estrogen & HIV Transcription

- 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)
- $\beta\text{-estradiol} \downarrow LRA\text{-induced HIV expression}$
- MOXIE Trial

in vitro

 No effect of tamoxifen on vorinostat reactivation in <u>post-menopausal</u> females



Adapted from Das et al. PNAS 2018

Towards

an HIV Cure

Considerations for Research

Towards an HIV Cure **RIAS**

- 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, transitionrelated hormone therapy...
 - Community engagement: novel agents with risk



Thomas Quinn Andrew Redd Steven Reynolds



Ron Gray Maria Wawer **Eileen Scully Robert Siliciano** Janet Siliciano Adam Capoferri Kyungyoon Kwon Jun Lai

AIDS 2022 Affiliated Independent Event



Katherine Yu Yun-Hee Choi Sarah Gowanlock



David Serwadda Jingo Kasule Taddeo Kityamuweesi Paul Buule Sarah Kalibbala Margaret Anyokorit Anthony Ndyanabo Aggrey Anok





RIAS

Towards

an HIV Cure

Research Enterprise to Advance a Cure for HIV

GILEAD CANADA RESEARCH CHAIRS CHAIRES DE RECHERCHE DU CANADA

People of Rakai, who participated in research