Considerations for cis-Women in HIV Cure Research

Jessica Prodger, Western University

Pathways to an HIV cure: Research and advocacy priorities

I have no relevant financial relationships with ineligible companies to disclose.
Consideration of the attributes of biological sex associated with cis-Women in HIV Cure Research
"Female" Biological Sex

| Two X chromosomes | Cis women  
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<tbody>
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<td>XXY males and intersex peoples, trans men &amp; other gender diverse people</td>
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<th>Epigenetic Profile</th>
<th>Exogenous hormones can influence gene methylation: (X)XY people on feminizing hormones (transfeminine)</th>
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| 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

Adapted from Sterling et al. JID 1999
Sex & Immunology

- X chromosome genes
  - *TLR7*, *FOXP3*, and 10% of all microRNAs

- Epigenetic modification
  - Methylation patterns and transcriptomes

- Female = higher IFNα
  - 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

19% of ART trial participants are women

11% of cure trial participants are women

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:

\[ \Delta \log_{10} \text{IUPM} = 0.49, \ p < 0.01 \]
How to interpret?

- Smaller replication competent reservoir?
- Poor latency reversal?

![Graphs showing QVOA outgrowth and HIV-1 DNA frequency in males and females.](image)
Estrogen & HIV Transcription

- HIV-1 RNA levels vary with menses
  - lower in follicular when estrogen peaks

- Estrogen inhibits HIV transcription
  - $\beta$-estradiol $\rightarrow$ ER$\alpha$ (ESR1) suppresses HIV

- Blocking ER$\alpha$ enhances iHDAC (vorinostat = SAHA)

- $\beta$-estradiol ↓ LRA-induced HIV expression

- MOXIE Trial
  - No effect of tamoxifen on vorinostat reactivation in post-menopausal females

Adapted from Das et al. PNAS 2018
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
AIDS 2022 Affiliated Independent Event

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Andrew Redd
Steven Reynolds

Ron Gray
Maria Wawer
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Jun Lai

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

People of Rakai, who participated in research