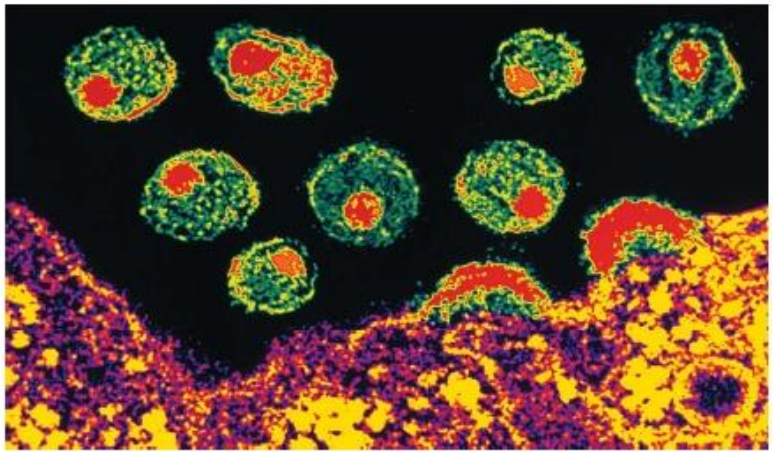
The HIV Latent Reservoir in Ugandans: Implications for HIV Cure



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30+ ANNIVERSARY

Acknowlegements

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Improved Health Through Research

NIH National Institute of Allergy and Infectious Diseases

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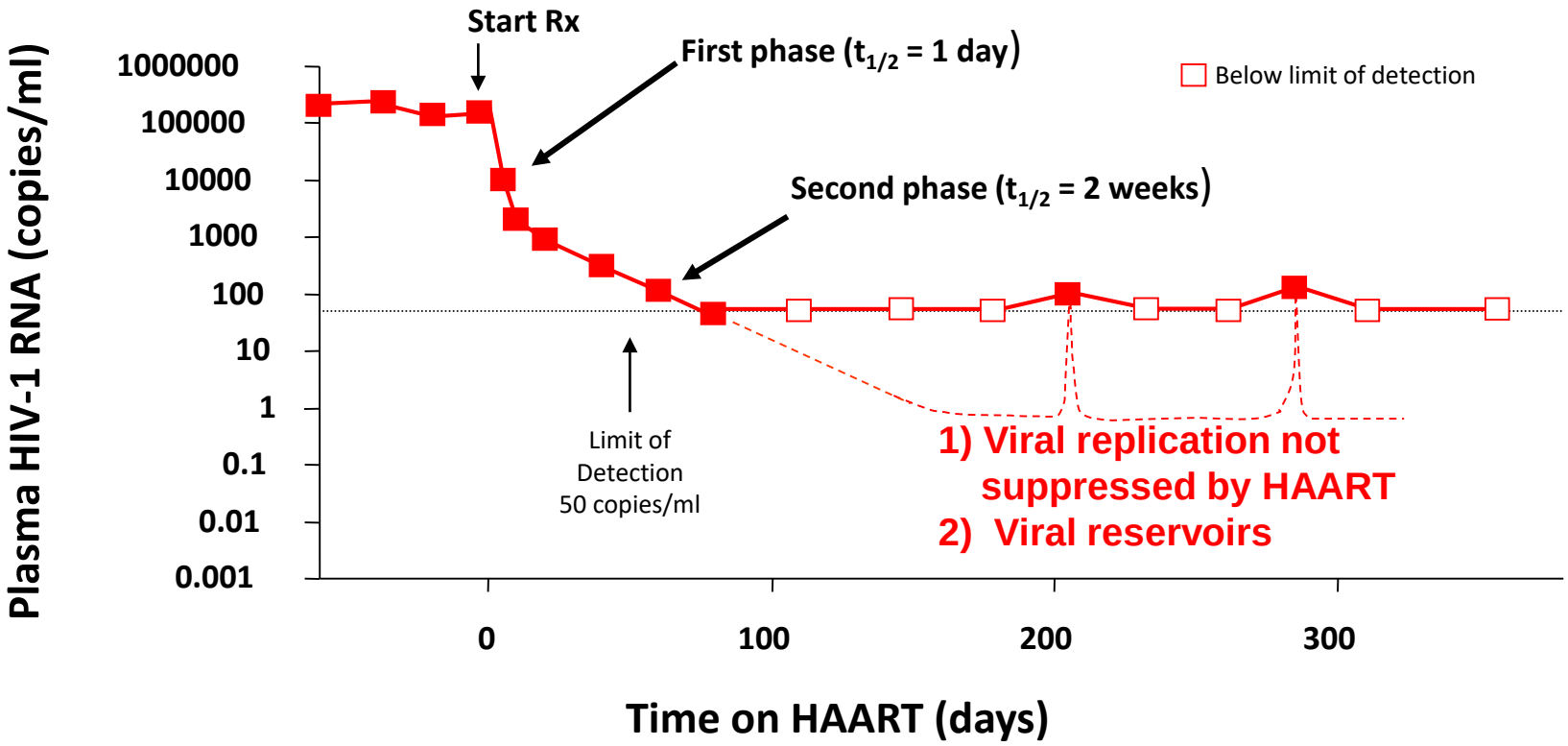
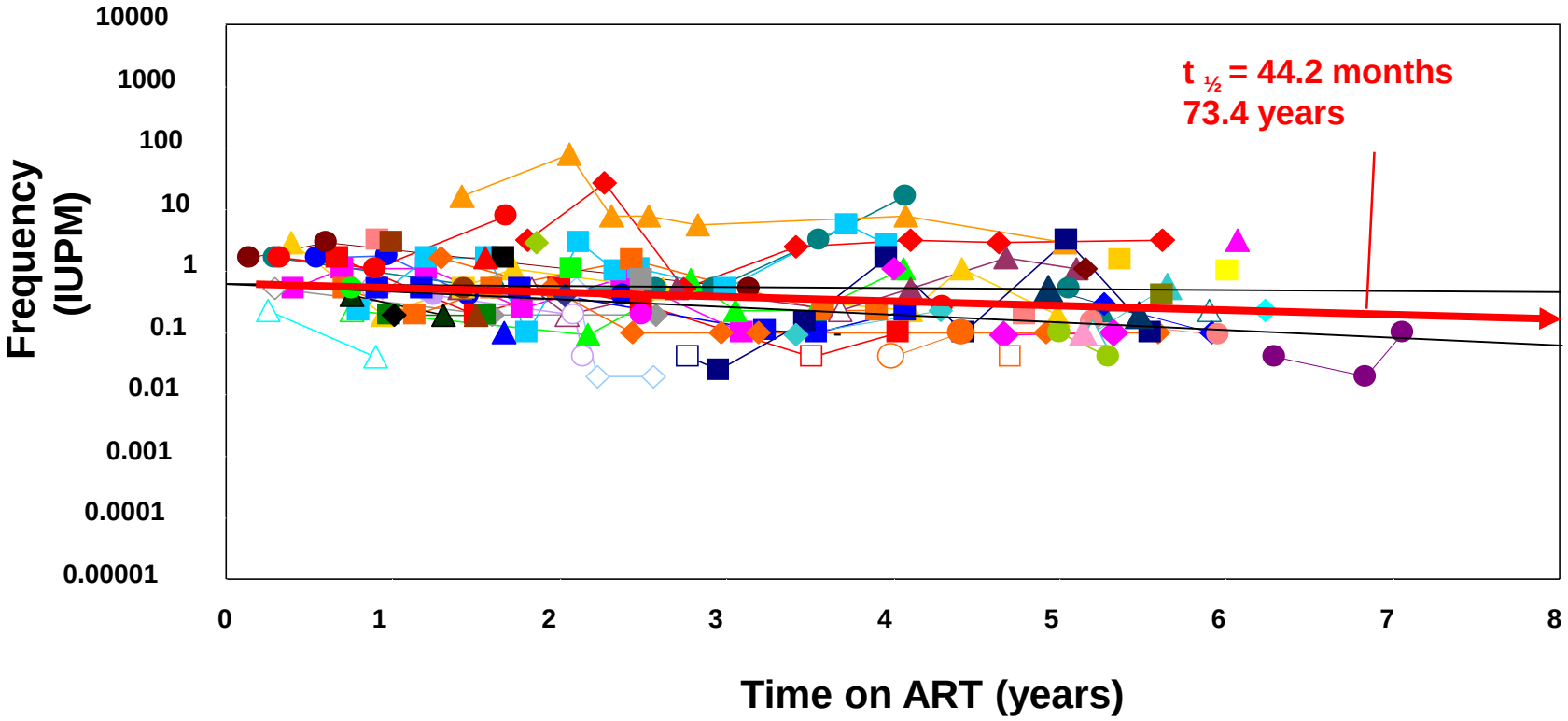
Dynamics of HIV-1 Replication in Patients on ART Therapy



Latent Reservoir Poses the Greatest Barrier to Cure



Siliciano JD, Nat Med, 2003.

Latent Viral Reservoir (LVR) in Sub-Saharan Africans

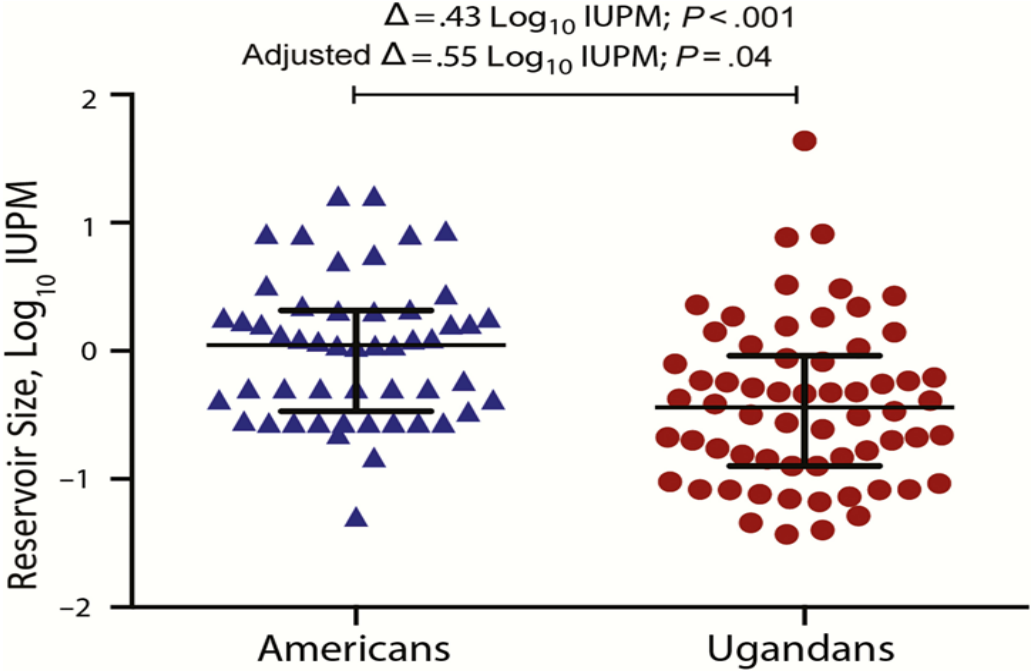
- **HIV cure research is dependent on accurate measurements of the LVR. However, no studies had previously quantified LVR in sub-Saharan Africans.**
- **High burden of endemic infections and other regional differences (viral subtype) may affect size of the LVR and efficacy of cure strategies.**
- **Quantitate the LVR size and dynamics over time, and measure correlates of immune parameters in SSA in order to tailor cure strategies as they develop.**

Study Populations

- Rakai, Uganda:
  - 70 HIV+ individuals on ART; >two VL <40 copies 12-18 months apart.
    - LVR quantification: Quantitative viral outgrowth assay (Q-VOA)
    - Retested annually for 5 years to determine decay curves

- Baltimore, USA:
  - 51 Moore Clinic patients studied using same techniques (Q-VOA)
    - Decay curves already calculated

Frequency of Resting CD4+ T cells Infected with Latent, Replication-Competent HIV-1 in Americans and Ugandans as Measured by QVOA



Median: 1.08 IUPM
Range: 0.72 – 1.49 IUPM

Median: 0.36 IUPM
Range: 0.26 – 0.55 IUPM

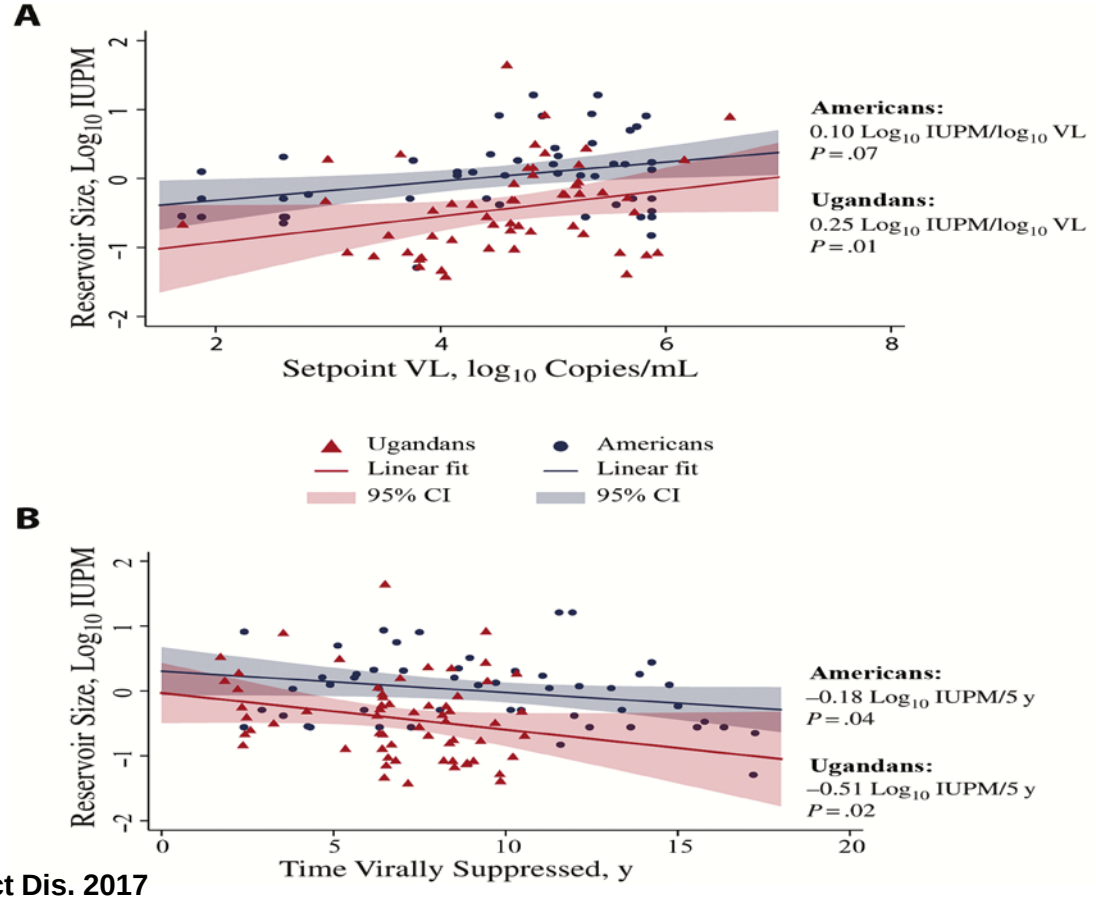
Prodger, et al, Clin Infect Dis. 2017

Subtyping: Sequencing Outgrowth Virus

- Isolates were sequenced in gp41 and pol using MiSeq NGS sequencing protocol
- No difference in IUPM between A, D, recombinants (p=0.3)
  - A: median = 0.46 IUPM (IQR: 0.21 – 1.55 IUPM)
  - D: median = 0.34 IUPM (IQR: 0.15 – 0.79 IUPM)
  - Recombinants: 1.10 IUPM (IQR: 0.24 – 2.20 IUPM)
- Continuing to sequence additional outgrowth wells from all participants for clonality

Prodger et al., Clin Infect Dis. 2017

Direct Correlation of Reservoir Size (IUPM) with Set-point Viral Load and Inverse Correlation with Time Virally Suppressed



Slopes not significantly different, p=0.3

Prodger, et al, Clin Infect Dis. 2017

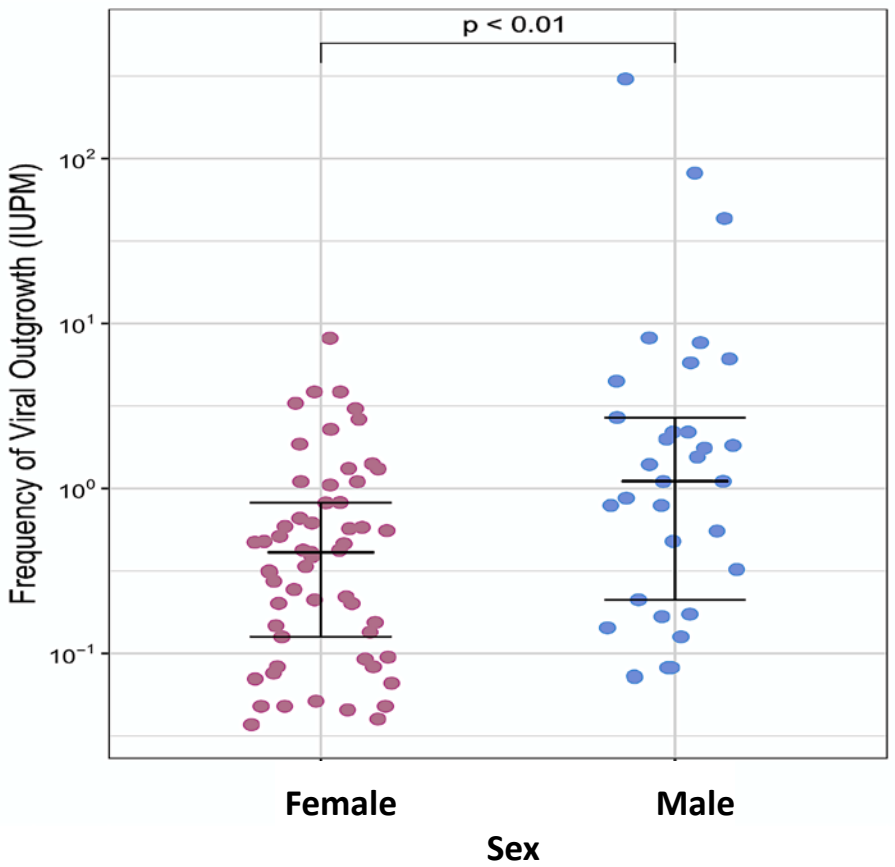
Latent Reservoir Size by Gender

- In this original study, Ugandan women had a much smaller reservoir size than American women, but the difference was not significant due to the few women in the US study.
- Thus we expanded the study to include a total of 90 Ugandans (57 women and 33 men).
- Ugandan women had a significant lower median reservoir size (0.53 IUPM) compared to men (1.01 IUPM) ($p<0.01$).

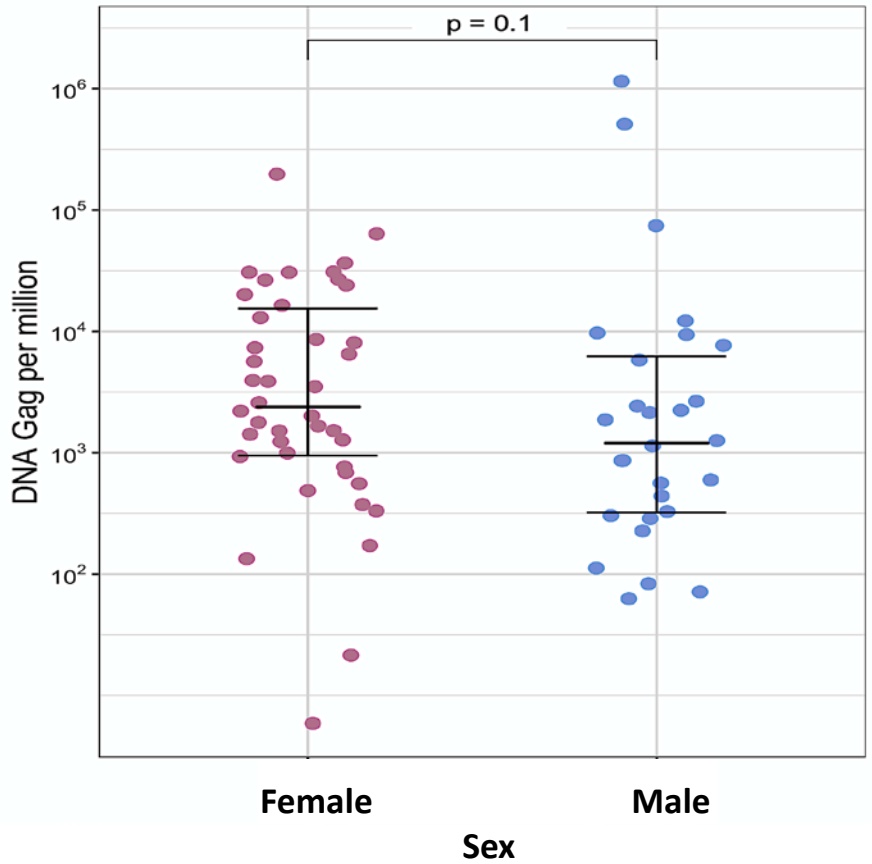
Ugandan Study of HIV Latent Reservoir by Sex

Characteristic Median (IQR)	Females (n = 57)	Males (n = 33)	P-value
Age (years)	41.1 (37.4, 47.2)	44.2 (40.3, 47.1)	0.15
Subtype, n (%)			0.76
A	9 (15.8)	5 (15.2)	
C	2 (3.5)	1 (3.0)	
D	26 (45.6)	17 (51.5)	
A/D	7 (12.3)	3 (9.1)	
A/F	1 (1.8)	0	
A/C	0	1 (3.0)	
Unknown	12 (21.1)	6 (18.2)	
Pre-ART Viral Load (log_{10} copies/mL) *Females (n = 47); Males (n = 28)*	4.62 (3.88, 4.93)	4.72 (4.17, 5.22)	0.18
Nadir CD4+ T cell count (cells/µL)	180 (109, 232)	168 (129, 238)	0.92
Time on ART (years)	7.0 (5.3, 8.5)	6.9 (3.3 9.3)	0.86
CD4+ T cell count at QVOA (cells/µL)	594 (461, 740)	458 (380, 559)	<0.01
CD4+/CD8+ T cell ratio at QVOA	0.89 (0.65, 1.12)	0.63 (0.56, 0.84)	<0.01
Viremic time (years) *Females (n = 16); Males (n = 16)*	6.1 (4.2, 10.2)	5.6 (3.7, 7.8)	0.46

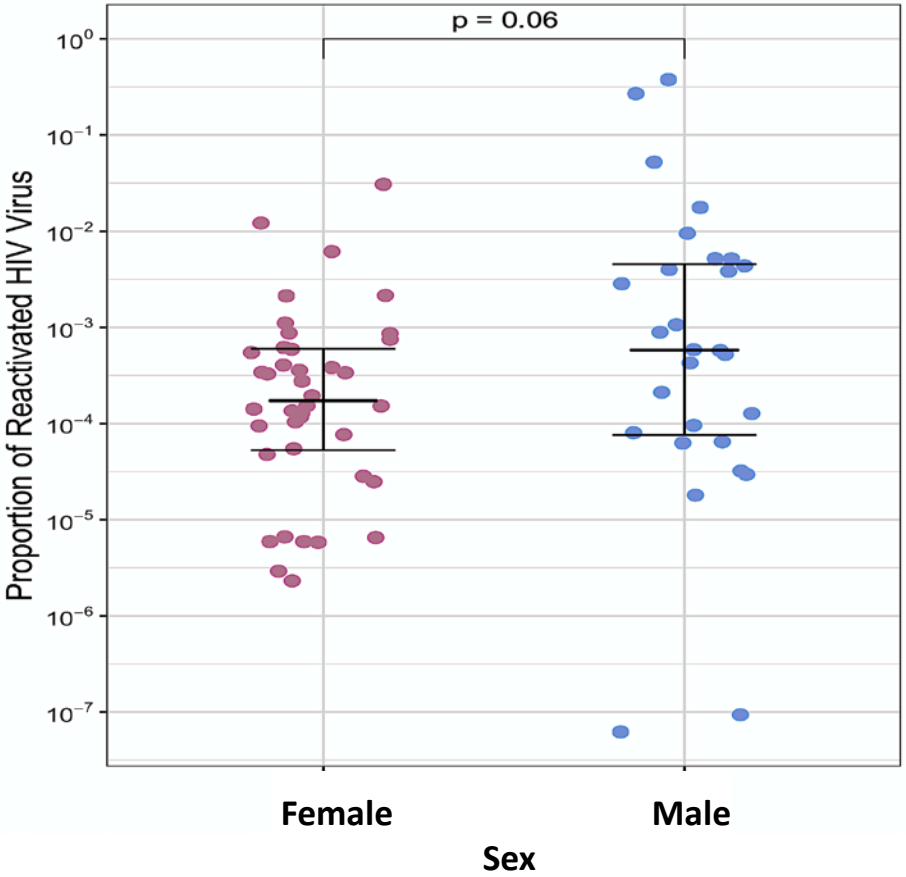
Frequency of Viral Outgrowth by Sex



Measurement of HIV DNA gag per million cells



Proportion of Reactivated HIV per DNA



Summary and Future Studies

- **HIV latent reservoir was smaller in Ugandans compared to Americans, and differed significantly by gender among Ugandans, but not by subtype**
- **Further studies on gender differences in latent reservoir activation.**
  - **As shown by others, estrogen receptor-1 is a key regulator of HIV-1 latency that imparts gender-specific restrictions on the latent reservoir (Das et al, PNAS 2018; Scully et al, JID 2019)**
  - **Accurate measurements of intact, replication-competent virus, total integrated viral DNA and intact proviral DNA (IPDA)**
- **Sequencing of the viral outgrowths for clonality and timing with ARV use**