Impact of Gender-Affirming Hormone Therapy on HIV Reservoirs and Inflammation in Transgender Women

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BACKGROUND

- Transgender women (TW) are disproportionately affected by HIV but underrepresented in HIV cure research[1]
- **Estradiol inhibits HIV transcription in a sex-specific way[2]**
  - Immune cells from women are more responsive to estrogen
- Effect of exogenous estradiol on HIV persistence is unknown

Study Question: How does the initiation of gender-affirming hormone therapy (GAHT) impact HIV reservoir measure (size & activity) and immune milieu?

METHODS

- **Study Participants (n=22):** TW with HIV virally suppressed on ART starting GAHT from San Diego and Houston (Table 1)
- **Controls (n=18):** Cisgender men with HIV virally suppressed on ART (matched by age, CD4⁺ T-cell count, and time to ART start)
- **Samples:** Blood
- **Timing:** Prior to starting GAHT (month 0) and months 2, 4, 6, 9, 12, and 18
- **Measurements:**
  - Estradiol and testosterone by ELISA
  - Cell-associated HIV RNA and DNA by ddPCR
  - 41 cytokines and chemokines by Luminex,16 included (Table 2)
- **Statistics:**
  - Linear mixed effects model with HIV reservoir as outcomes. Time, group, and their interaction as predictors.
  - PLS-DA to predict gender groups using cytokines/chemokines with an error rate estimated using k-fold cross-validation

Table 1. Participants Demographics

	Cases	Controls	p-value
Age (years)	39.0 (23 - 57)	37.0 (25 - 57)	0.906
Hispanic or Latino/a	12 (57%)	8 (44%)	0.639
Race			0.078
White	10 (48%)	14 (78%)	
Black	5 (24%)	0 (0%)	
Asian	1 (4.8%)	1 (5.6%)	
American Indian	2 (9.5%)	0 (0%)	
Pacific Islander	1 (4.8%)	0 (0%)	
Unknown	2 (9.5%)	3 (17%)	
Time from HIV Diagnosis to ART Initiation (days)	91 (0 - 5844)	11.5 (0 - 3635)	0.871
ART Regimen			0.387
Integrase Based	19 (90%)	14 (78%)	
Non-Integrase Based	2 (9.5%)	4 (22%)	
Hormone Regimen			
Estradiol Alone	10 (67%)	-	
Estradiol + Other	5 (33%)	-	

Table 2. Cytokines & Chemokines Included in Analysis

I-TAC
IL-8
MIP-1b
MIP-3b
IL-18
MCP-1
TRAIL
CD163
CRP
IL-16
IP-10
LBP
MIG
MIP-1a
RANTES
sCD14

16 cytokines met lower limit detection threshold of 70% and were included in analysis

Transgender women had higher levels of HIV DNA and unique immune signatures compared to cisgender men.

Initiation of gender-affirming hormone therapy did not impact dynamics of cellular HIV RNA and total HIV DNA, but we observed an accelerated decay in 2-LTR circles.

Figure 1. HIV 2-LTR over time

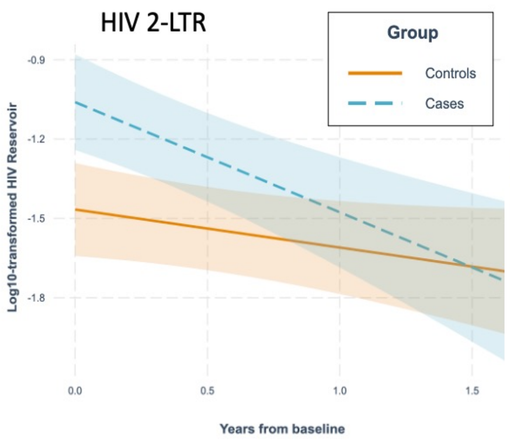
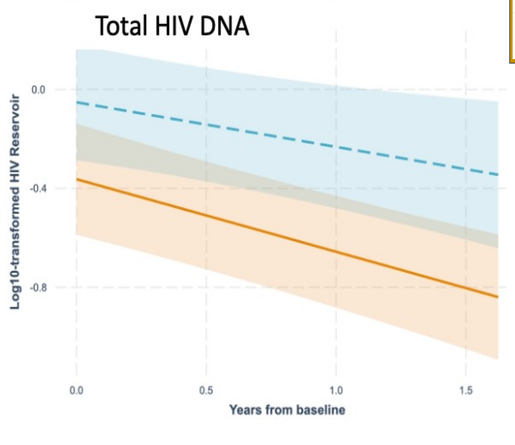


Figure 2. Total HIV DNA over time



Trend in log-transformed HIV 2-LTR (Fig.1) and total HIV DNA (Fig. 2) after initiation of GAHT (baseline) in TW (blue) and over time in controls (orange). Shaded areas represent 95% confidence interval.

TW had higher HIV DNA levels, both total (p = 0.060) and 2-LTR (p = 0.002). We observed a significant interaction between time and gender group for 2-LTR (p = 0.036) but not for total HIV DNA (p = 0.228). There was a faster decline in 2-LTR in TW after starting GAHT compared to cisgender men.

RESULTS

- **22 transgender women enrolled**
  - 9 lost to follow-up (1 suicide, 1 homicide, 2 imprisonments)
- 77 samples collected from TW; 79 samples from controls
- **TW had overall higher estradiol**
  - 145.83 pg/mL vs. 45.62 pg/mL (p < 0.001)
- **TW had lower testosterone with sharp decline after baseline**
  - 226 ng/dL vs 436 ng/dL (p < 0.001)
- **No difference in cellular HIV RNA between groups**

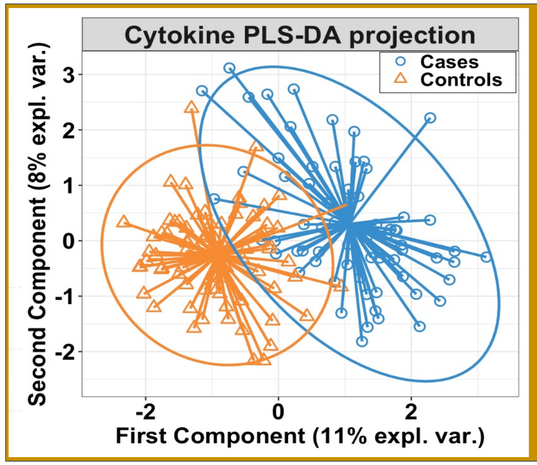


Figure 3. Cytokine partial least squares-discriminant analysis projection with confidence ellipses for TW (blue) and controls (orange).

Gender group accurately predicted with an error rate of 10%.

CONCLUSIONS

- TW had unique immune signatures, which might impact HIV disease outcomes and comorbidities
- Faster decline in 2-LTR after initiating GAHT may support estradiol's inhibition of residual HIV replication
- **Limitations:** Small sample size, variability in hormone regimens, recruitment and retainment
- Our study underscores the challenges associated with recruiting and studying this unique population
  - There is a need for improved trauma-informed care and tailored research efforts

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