Impact of Gender-Affirming Hormone Therapy on Cytokines and T-Cell Phenotypes in Transgender Women With HIV

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BACKGROUND

- Transgender women (TW) have a high HIV prevalence (20% globally).
  - Gender-affirming hormone therapy (GAHT) improves well-being, ART adherence, and viral suppression.
- **Estradiol modulate immune responses and suppresses HIV transcription in sex-specific ways.**
  - Immune cells from women are more responsive to estrogen.
- The impact of GAHT on immune phenotypes and HIV pathogenesis in TW remains unclear.

Study Question: What is the impact of GAHT on T-cell phenotypes and cytokine profiles in TW with HIV?

Distinct immune signatures were observed in transgender women on GAHT with HIV compared to cisgender men.

Transgender women exhibited ↑ Ki67 (T-cell proliferation) CD107a (cytotoxicity), and IL-17, indicating heightened immune activation, and ↓ sCD163 suggesting reduced myeloid activation.

METHODS

- Study Participants **(Table 1):**
  - **TW with HIV (n=18):** Virally suppressed on ART starting GAHT from San Diego and Houston.
  - **Controls (n=18):** Cisgender men (CM) with HIV, virally suppressed, matched by age, CD4⁺ T-cell count, and ART duration.
- Samples & Timing:
  - Blood collected at baseline (pre-GAHT), months 2, 4, 6, 9, 12, 18.
- Measurements:
  - **Hormones:** Estradiol and testosterone (ELISA).
  - **Cytokines/Chemokines (Table 2):** 41 markers (Luminex).
  - **T Cell Markers** (Flow Cytometry):
    - **Cytotoxicity/Degranulation:** CD107a
    - **Regulation:** CD25, FoxP3
    - **Cellular Cycling:** Ki67
    - **Exhaustion:** TIGIT, PD-1
  - Statistical Analysis: **PLS-DA** to predict gender groups using cytokines/chemokines and flow markers. **Generalized mixed-effects models** for markers with VIP ≥ 1, adjusted for multiple comparisons.

Table 1. Participants Demographics

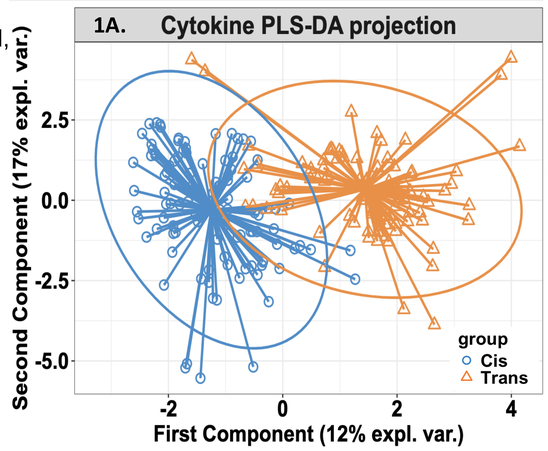
	TW (N = 18)	CM (N = 18)	p-value
Age (years)	39.0 (23 - 57)	37.0 (25 - 57)	0.987
Hispanic or Latino/a	10 (56%)	8 (44%)	0.739
Race			0.066
White	9 (50%)	14 (78%)	
Black	4 (22%)	0 (0%)	
Asian	1 (5.6%)	1 (5.6%)	
American Indian	2 (11%)	0 (0%)	
Pacific Islander	1 (5.6%)	0 (0%)	
Unknown	1 (5.6%)	3 (17%)	
Time from HIV Diagnosis to ART Initiation (days)	76.5 (0 - 5844)	11.5 (0 - 3635)	0.756
ART Regimen			>0.999
Integrase Based	15 (83%)	14 (78%)	
Non-Integrase Based	3 (17%)	4 (22%)	

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

Figure 1. PLS-DA Projections of Cytokine (1A) and Flow Cytometry (1B) Data. The partial least squares-discriminant analysis projections show separation between TW (orange) and CM (blue). Ellipses represent 95% confidence intervals for each group.



Cytokine and T-cell phenotypes distinctly separate transgender women on GAHT from cisgender men.

Table 3. Cytokines (2A) and Flow Markers (2B) with Significant Adjusted p-Values. Positive effect sizes indicate higher expression of the marker in TW compared to CM. Adjusted p-values account for multiple comparisons.

3A. Cytokine	Est. Effect Size	Adjusted p-Value
sCD163	-0.99	0.006
IL-17	0.50	0.009

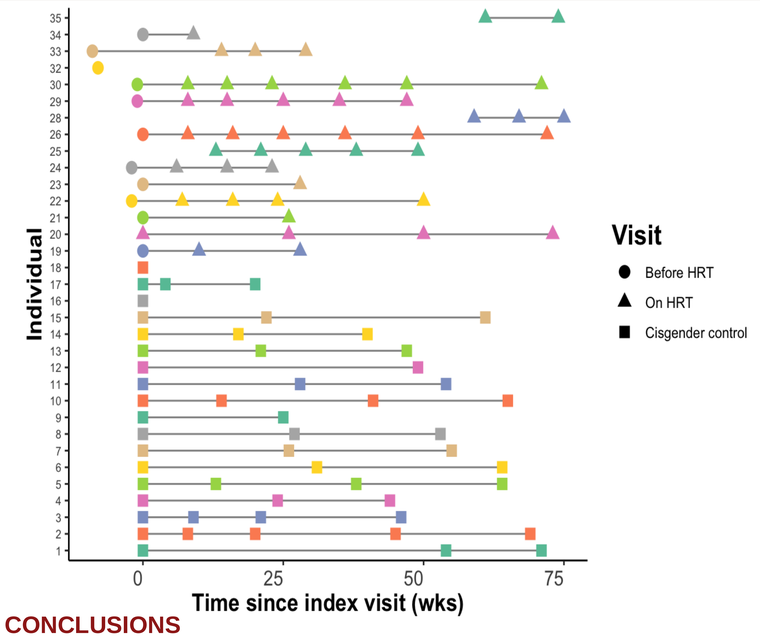
3B. Flow Marker	Functional Classification	Est. Effect Size	Adjusted p-Value
CD8⁺ Terminally Differentiated (CD3⁺, CD107a⁺)	Cytotoxicity/ Degranulation	0.42	0.015
CD8⁺ Central Memory (CD3⁺, CD107a⁺)	Cytotoxicity/ Degranulation	0.30	0.033
CD4⁺ Central Memory (CD3⁺, CD107a⁺)	Cytotoxicity/ Degranulation	0.40	0.006
CD4⁺ Effector Memory (CD3⁺, CD107a⁺)	Cytotoxicity/ Degranulation	0.42	0.008
CD4⁺ Effector Memory (CD25⁺, FoxP3⁺)	Regulatory T-cell	0.87	0.001
CD8⁺ Terminally Differentiated (CD3⁺, Ki67⁺)	Cellular Cycling	0.78	<0.001
CD4⁺ Effector Memory (CD3⁺, Ki67⁺)	Cellular Cycling	0.69	<0.001
CD4⁺ Central Memory (CD3⁺, Ki67⁺)	Cellular Cycling	0.67	<0.001
CD8⁺ Effector Memory (CD3⁺, Ki67⁺)	Cellular Cycling	1.03	<0.001
CD8⁺ Effector Memory (TGIT⁺, PD-1⁺)	Exhaustion	-0.55	0.031

TW have increased markers of T-cell cytotoxicity, cellular cycling, and regulation and reduced markers of exhaustion and monocyte activation.

RESULTS

- **22 transgender women enrolled (18 included in analysis)**
  - 9 lost to follow-up (1 suicide, 1 homicide, 2 imprisonments)
- 75 samples collected from TW; 53 from CM.
- Estradiol was significantly higher and testosterone lower in TW, reflecting GAHT use.
- PLS-DA Projections:
  - Cytokine profiles predicted gender groups with 7% error (Figure 1A).
  - Flow cytometry markers with an 18% error rate (Figure 1B).
- Significant differences in cytokines and flow markers between groups shown in **Table 3**.

Figure 2. Timing of Blood Sample Collection. Each row representing a participant. Circles indicate visits before starting hormone replacement therapy (HRT), triangles represent visits while on HRT, and squares indicate cisgender controls. The x-axis represents time since the index visit in weeks, and lines connect samples collected from the same participant over time.



CONCLUSIONS

- GAHT influences immune responses, but causality remains unclear.
- **Limitations:** Small sample size, varied hormone regimens, and retention challenges.
- **Clinical Implications:** Findings emphasize trauma-informed care and the need for tailored research to optimize HIV care in TW.
- **Future Research:** A planned R01 will expand on these findings, while my K23 will focus on GAHT's impact on innate immune cells.

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