Impact of Hormone Therapy and HIV on the Immunometabolic Landscape in a Cohort of Transgender Women

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BACKGROUND

- **Transgender women (TW) are a key population that is impacted by HIV[1].**
- **Little is known about immune response and activation in transgender individuals.**
- **Estrogen has been shown to modulate development, differentiation, and functionality of immune cell types[2].**
- **Studies of HIV-1 pathogenesis have found differences in set point viral load, immune activation, and latency reversal between cisgender men and women that may be influenced by hormones[3].**
- **A lived gender experience may contribute to differences in immune activation between transgender women and cisgender women.**

METHODS

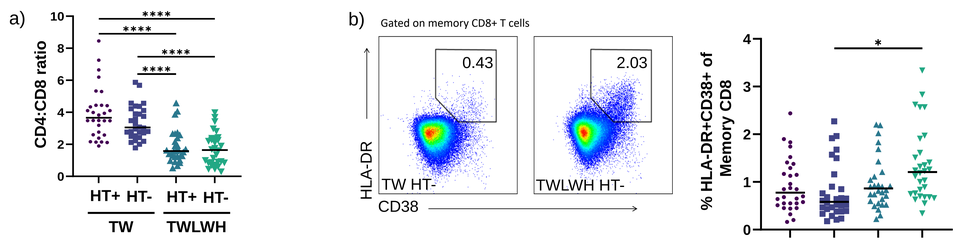
- IRB approval was obtained to recruit participants assigned male at birth and living with a female identity from the Brazilian Transcendo[4] cohort in 4 groups:
  - Transgender women on hormone therapy (TW HT+)
  - Transgender women not currently on hormone therapy (TW HT-)
  - Transgender women living with HIV on hormone therapy (TWLWH HT+)
  - TWLWH not currently on hormone therapy (PLWH HT-).
- Cryopreserved PBMCs were immunophenotyped with a 32-color panel using the Cytek Aurora.
- RNA was isolated from bulk CD4 T cells and cDNA was prepared for qPCR analysis of *CPT1a* mRNA quantification. qPCR was normalized to RPLP1.
- Metabolic dependence was quantified using the Scenith assay[5].

	TW HT+	TW HT-	TWLWH HT+	TWLWH HT-
Number of participants	30	30	30	30
Age (years)	38.52 [27.5, 40]	32.7 [26, 29]	24.2 [28, 33]	41.9 [36, 41]
Race/Color				
Black	9 (29%)	10 (33%)	13 (45%)	4 (12%)
Pardo	9 (29%)	7 (23%)	12 (41%)	18 (60%)
Indigenous	0 (0%)	1 (3%)	0 (0%)	0 (0%)
White	12 (39%)	11 (37%)	3 (10%)	8 (67%)
Asian	1 (3%)	1 (3%)	1 (3%)	0 (0%)
Length of suppression (years)			4.04 [0.83,4]	5.01 [2,4]
Fully Suppressed (ART>1yr)			22	22
ART <1 yr			8	7
Reported viral load detected			0	1
CD4 Nadir <200			5	6
CD4 Nadir >200			25	24
Medications				
non-HIV medications	11 (35%)	8 (27%)	4 (13%)	20 (66.6%)
PrEP	17 (55%)	14 (46%)		
Antiretroviral therapy (ART)			30	30
Hormone therapy				
Estradiol	15		6	
Estradiol + progesterone	12		21	
Antiandrogen only	3		3	

Hormone therapy in Transgender Women Living with HIV (TWLWH) reduces Fatty Acid Oxidation (FAO) in memory T cells.

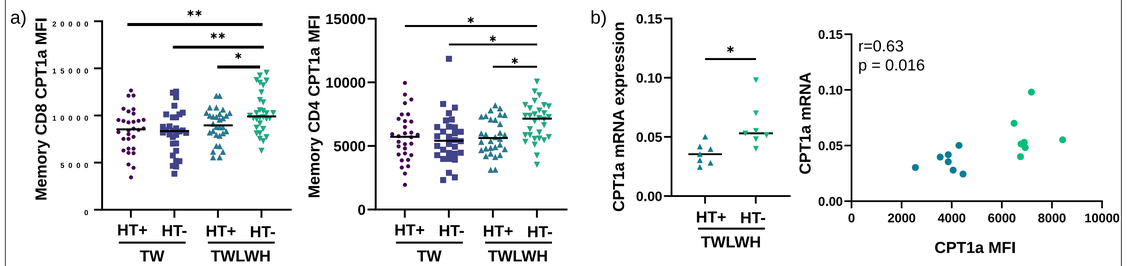
RESULTS

Fig 1 – Hallmarks of HIV are present in Transgender Women (TW) living with HIV



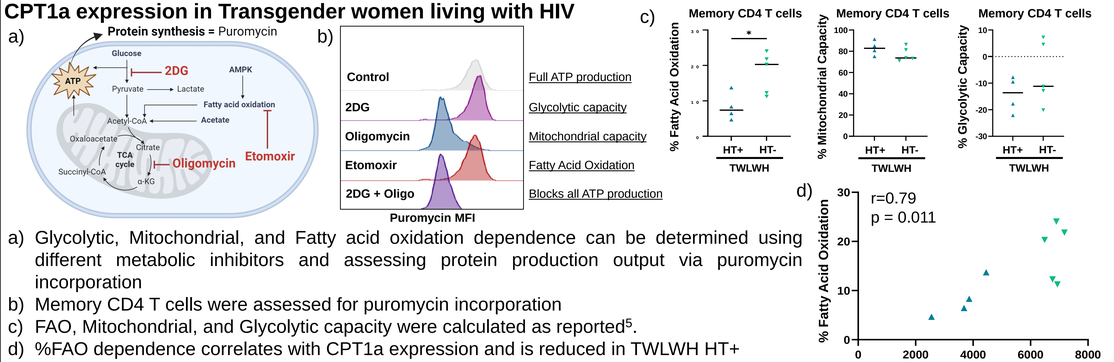
a) CD4:CD8 ratios are decreased in TWLWH.
b) HLA-DR+CD38+ Memory CD8 T cells are increased in TWLWH.
* p < 0.05, **** p < 0.0001 by Tukey's multiple comparisons test following significant one-way ANOVA.

Fig 2 – Immune cell metabolism is affected by HIV and hormone therapy



a) CPT1a is upregulated in TWLWH in CD4/CD8 T cells. **TWLWH HT+ have diminished CPT1a protein levels compared to TWLWH HT-**. CPT1a expression did not decrease with hormone treatment in any other cell type (e.g. B cells, NK cells, etc) data not shown.
b) *CPT1a* mRNA levels are reduced in TWLWH HT+ and correlates with protein expression levels.
* p < 0.05, ** p < 0.01 by Tukey's multiple comparisons test following significant one-way ANOVA or T test

Fig 3 – Fatty acid oxidation levels in resting CD4 T cells are reduced after hormone therapy and correlate with CPT1a expression in Transgender women living with HIV

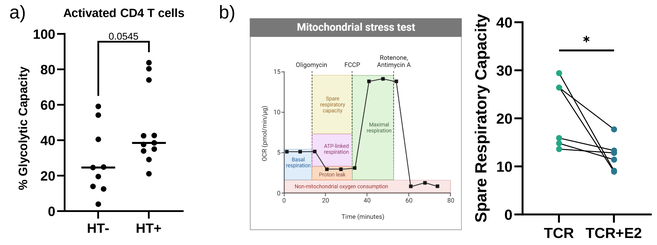


a) Glycolytic, Mitochondrial, and Fatty acid oxidation dependence can be determined using different metabolic inhibitors and assessing protein production output via puromycin incorporation
b) Memory CD4 T cells were assessed for puromycin incorporation
c) FAO, Mitochondrial, and Glycolytic capacity were calculated as reported[5].
d) %FAO dependence correlates with CPT1a expression and is reduced in TWLWH HT+
* p < 0.05 by T test

ADDITIONAL DATA

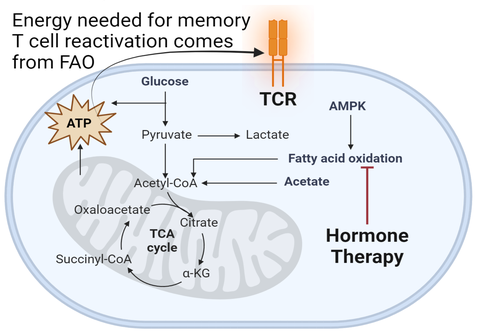
Fig 4 – Metabolism is modulated *ex vivo* and *in vitro* in response to hormones following T cell activation.

a) Glycolytic capacity of Transgender women on hormone therapy is enhanced regardless of HIV status following T cell activation.
b) In vitro exposure to 17-β estradiol reduces Spare Respiratory Capacity (SRC) following T cell activation. Lower SRC is associated with lower FAO in long lived T cells.



CONCLUSIONS

- Hormone therapy reduces CPT1a expression in TWLWH at the protein and mRNA levels.
- Fatty acid oxidation capacity is reduced in TWLWH on hormone therapy and correlates with reduced CPT1a expression.
- Hormone exposure *in vitro* reduces SRC in T cells after activation and potentially causes a need for enhanced glycolytic capacity that can be seen with *ex vivo* hormone exposure.
- **Impact** - Fatty acid oxidation is critical for memory cell reactivation upon stimulus. Decreased fatty acid oxidation may impact energy availability for re-activation in TWLWH on hormone therapy.



Acknowledgments and Funding

We would like to acknowledge the participants of the cohort for their time and samples.
This work was supported by R01AI154541 to ES from NIAID/ORWH.
Figures generated in Biorender

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