Metabolic Shifts Potentiate Accelerated Aging in Successful Long-term HIV treatment

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BACKGROUND

- **Are people living with HIV (PLWH) with successful therapy potentiate accelerated aging compared to the HIV-negative counterpart?**

Despite successful antiretroviral therapy (ART), persistent low-grade immune activation together with inflammation and toxic antiretroviral drugs can lead to long-lasting metabolic adaptation in people living with HIV (PLWH). The successful short-term cART reported abnormalities in the metabolic reprogramming in PLWH, but the long-term consequences are unknown.

METHODS

- Plasma samples were collected from 138 PLWH on cART with more than 5 years), 126 HC, and 45 untreated HIV-infected patients with viremia from Cameroon (n=171) and India (n=138).
- Untargeted and targeted metabolomics: Ultra-high-performance liquid chromatography/mass spectrometry (UHPLC/MS/MS) and LC-MS/MS respectively.
- Machine learning models, Network analysis

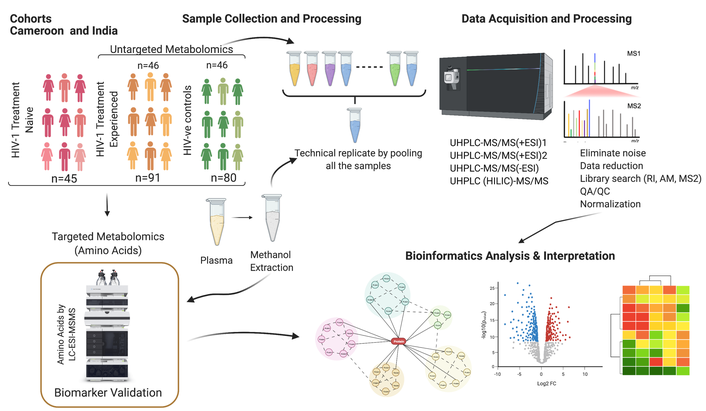


Figure 1. Study designing.

A switch in glutaminolysis as the alternative pathway for energy production with long-term treatment can lead to increased co-morbidities and potentiate accelerated aging in PLWH with successful therapy from LMICs.

Significantly lower levels of neuro-steroids like 5α−androstan−3α,17β−diol mono-sulfate, androsterone sulfate potentiate cognitive aging.

RESULTS

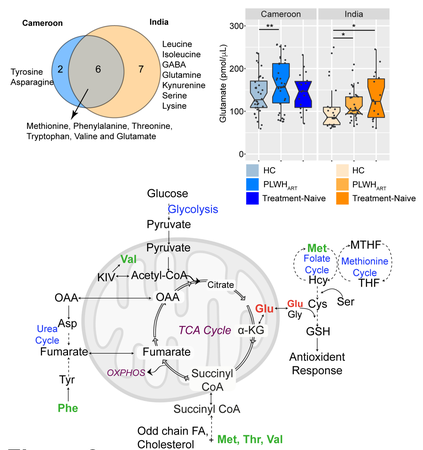


Figure 2.

Figure 2: Targeted amino acid in the larger HIV-1 cohorts from Cameroon and India. Venn diagram representing the overlap of AA significantly differing in HC compared to cART between Cameroon and Indian cohort. The box plots showing the abundance of glutamate between HC and cART (Mann-Whitney U test) (* FDR<0.1, ** FDR<0.05): Schematic representation of the altered AA linked with the key metabolic pathways.

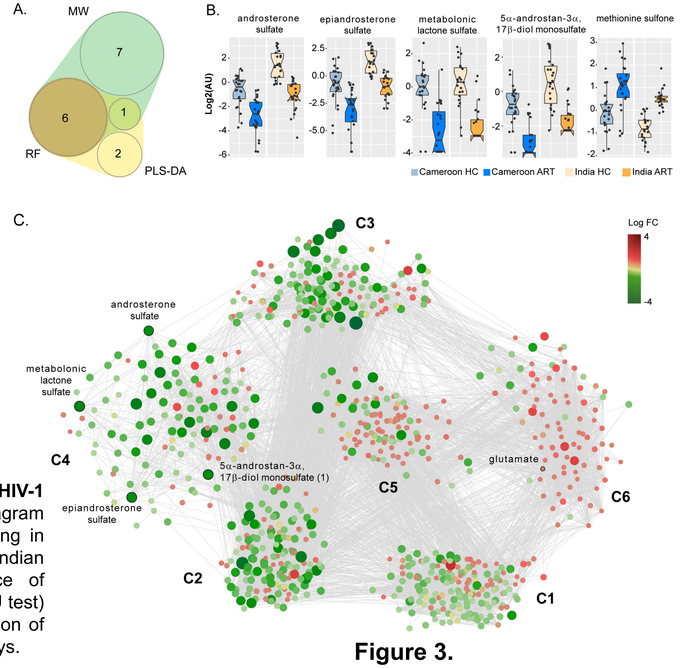


Figure 3.

Figure 3: Identification of biomarkers associated with HIV status and impact of cART compared to HC. (A) A 4-dimensional, quasi-proportional Venn diagram showing the number of overlapping metabolites (N = 6) differing HC/cART from three methodologies (Mann-Whitney U Test, RF and PLS-DA) in Indian and Cameroon cohort. Analysis was performed separately in Indian and Cameroon cohorts. **(B)** Boxplots of significant biomarkers shared by Indian and Cameroon patients: androsterone sulfate, epiandrosterone sulfate, metabolomic lactone sulfate, 5-α-androstan-3α,17β-diol monosulfate and methionine sulfone. In all the comparisons, FDR<0.001 **(C)** Global association analysis network and identified communities. Potential biomarkers and glutamate are indicated.

CONCLUSIONS

- The present study based on cohorts (India and Cameroon) indicated altered amino acid metabolism and more potentially a switch in glutaminolysis as the alternative pathway for energy production following a long-term antiretroviral therapy.
- Altered glutaminolysis with long term treatment and it's association with metabolic syndrome (1), diminished immune recovery (2).
- The glutamate excitotoxicity mediated neuro-cognitive impairments can lead to increased co-morbidities and accelerated aging in PLWH with successful therapy.
- A decrease in neurosteroids causes major depressive syndrome (3) leading to diminished quality of life despite successful therapy.

REFERENCES

1. Gelpi M, *et al.* Central role of the glutamate metabolism in long-term antiretroviral treated HIV-infected individuals with metabolic syndrome: a cross-sectional cohort study. ***Aging***, 2021.2004.2001.21254778 (2021).
2. Rosado-Sánchez I, *et al.* Glutaminolysis and lipoproteins are key factors in late immune recovery in successfully treated HIV-infected patients. ***Clinical science (London, England** : 1979)* **133**, 997-1010 (2019).
3. Mukerji SS, *et al.* Low Neuroactive Steroids Identifies a Biological Subtype of Depression in Adults with Human Immunodeficiency Virus on Suppressive Antiretroviral Therapy. ***The Journal of infectious diseases*** **223**, 1601-1611 (2021).

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