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CROI Conference on Retroviruses and Opportunistic Infections

Fatty Acid and Amino Acid Pathways Link to SIV Reservoir and Rebound in Infants

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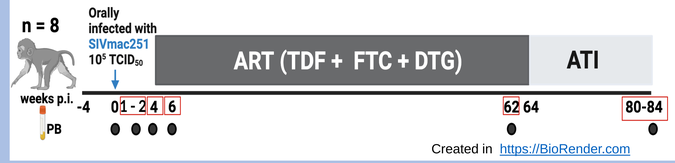
CCIV Center for Childhood Infections & Vaccines

BACKGROUND

Inflammation persists during antiretroviral therapy (ART) in HIV infection. Host soluble mediators (i.e. cytokines, chemokines and metabolites) are known to impact immune function, however, their interactions with reservoir size and viral rebound dynamics are lesser known. We hypothesize that specific cytokine/chemokine and microbial/host-derived metabolites may influence viral reservoir size on ART and rebound magnitude post-analytical treatment interruption (ATI). To explore this, we evaluated associations between these host immune determinants, reservoir size on ART and post-ATI viral rebound in a pediatric HIV model to address this knowledge gap in children living with HIV (CLWH).

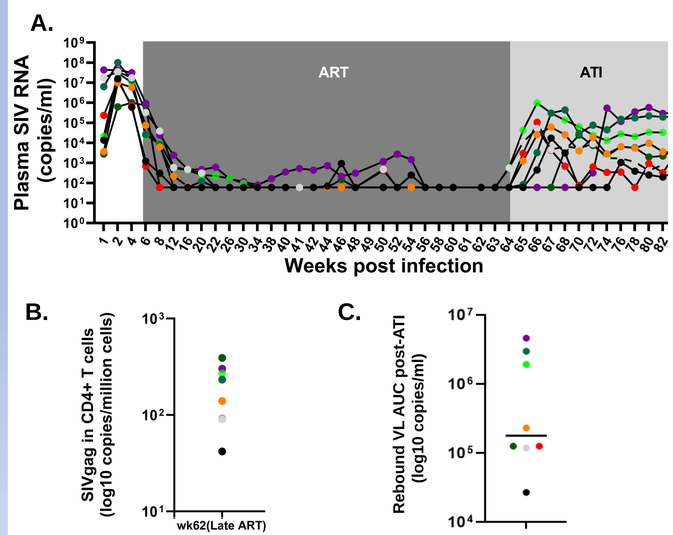
METHODS

Figure 1. Experimental Design



RESULTS

Figure 2. (A) Longitudinal plasma viral load of ART-suppressed SIV-infected rhesus macaques. (B) Viral DNA in peripheral blood CD4+ T cells after 1 year on ART and (C) Rebound viral load area under the curve (VL AUC) post-ATI.



GRAPHICAL ABSTRACT

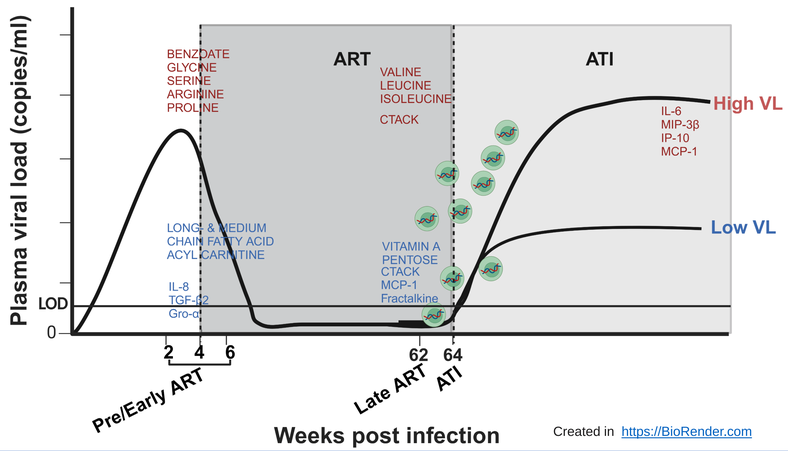
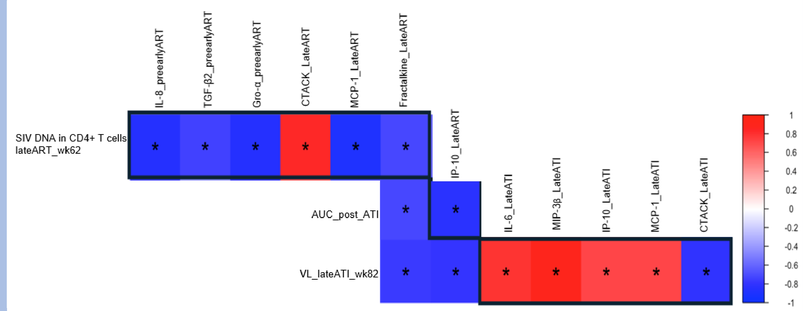


Figure 3. Both pro- and anti-inflammatory cytokines/chemokines are associated with SIV reservoir and rebound (correlation heatmap).



CONCLUSIONS

- During acute infection (pre/early ART) both pro- and anti-inflammatory cytokines/chemokines (IL-8, TGF-β2 and Gro-α) were negatively correlated with SIV reservoir size while chemoattractant and type I IFN responsive chemokines (IP-10, Fractalkine) during late ART were negatively correlated with rebound post ATI (Fig. 3).
- Lipids and amino acids were noticeably downregulated at pre/early ART suggesting consumption/degradation of associated metabolites during viremia and/or age-related longitudinal modulation of metabolites (Fig. 4A & B).
- During acute infection, benzoate and amino acid pathways were positively correlated with the SIV reservoir late ART (Fig. 5A). In contrast, fatty acid pathways were negatively correlated with the SIV reservoir late ART (Fig. 5B).
- A different set of amino acid pathways in late ART were positively correlated viral load AUC post-ATI (Fig. 5C) while vitamin A and pentose pathways were negatively correlated with viral load AUC post-ATI (Fig. 5D).
- These data indicate that host-specific immune responses and microbial/host metabolites influence reservoir size during ART and viremia off ART. Future work to define mechanistic interactions is underway.

Figure 5. Benzoate, amino acids, fatty acids (A – B), branched-amino acids, vitamin A and pentose (C – D) are associated with viral reservoir and rebound, respectively.

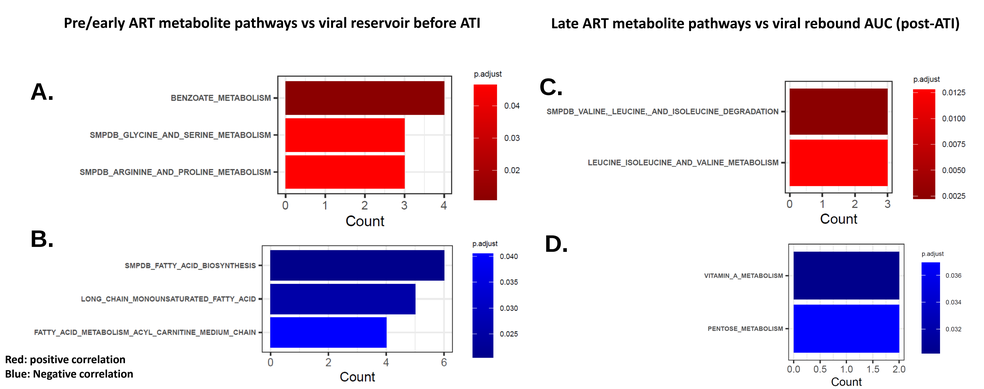
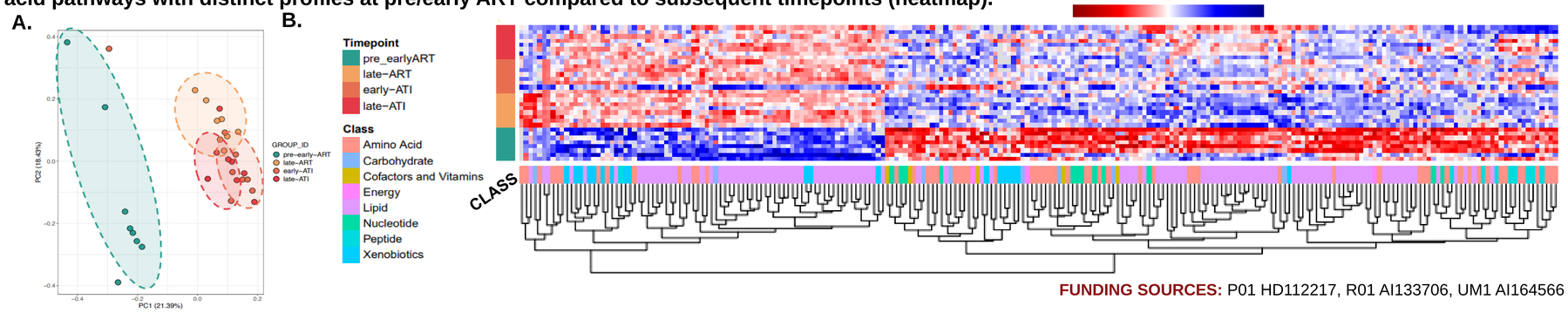


Figure 4. (A) Pre/early ART metabolites separated from later timepoints (PCA). (B) Longitudinal metabolite modulation by class was driven by lipid and amino acid pathways with distinct profiles at pre/early ART compared to subsequent timepoints (heatmap).



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