Gut Microbiome Is Linked to Intact HIV-1 Reservoir Size

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BACKGROUND

- The gut microbiome is altered during HIV infection and plays a crucial role in modulating immune responses and systemic inflammation, which may influence the persistence of the HIV-1 reservoir that mainly resides in the gut lymphoid tissue.
- In this study, we explored the associations between the gut microbiome composition, its metabolic pathways and the intact HIV-1 reservoir size in people with HIV (PWH) on long-term ART, to reveal potential targets for reservoir modulation.

METHODS

- Blood and fecal samples were collected from 30 PWH (40% females) on long-term ART (median 8 years).
- Intact Proviral DNA Assay (IPDA) in blood (rCD4⁺ T cells) and shotgun metagenomic sequencing of fecal samples were performed to identify microbial species and metabolic pathways associated with intact reservoir size and ratio of intact to total provirus.
- Alpha diversity indices were calculated, and Linear discriminant analysis Effect Size (LEfSe) was used to identify abundant species and pathways.

RESULTS

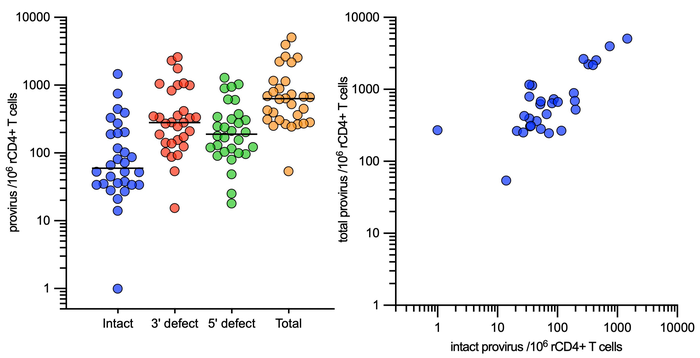


Fig 1. IPDA frequencies and ratio of intact to total provirus. Groups of higher and lower intact reservoir divided by the median (60 intact copies/10⁶ rCD4⁺ T cells; ratio 0.13).

Gut microbiome composition and metabolic function are associated with intact HIV-1 reservoir size, implicating microbiome-driven immune metabolism as a potential modulator of reservoir persistence

- Gut health–related species (e.g. *Lachnospira sp000437735, Phocaeicola spp.*) enriched in individuals with smaller intact reservoir.
- Species linked to chronic inflammation (e.g. *Prevotella spp.*) associated with larger intact reservoir.

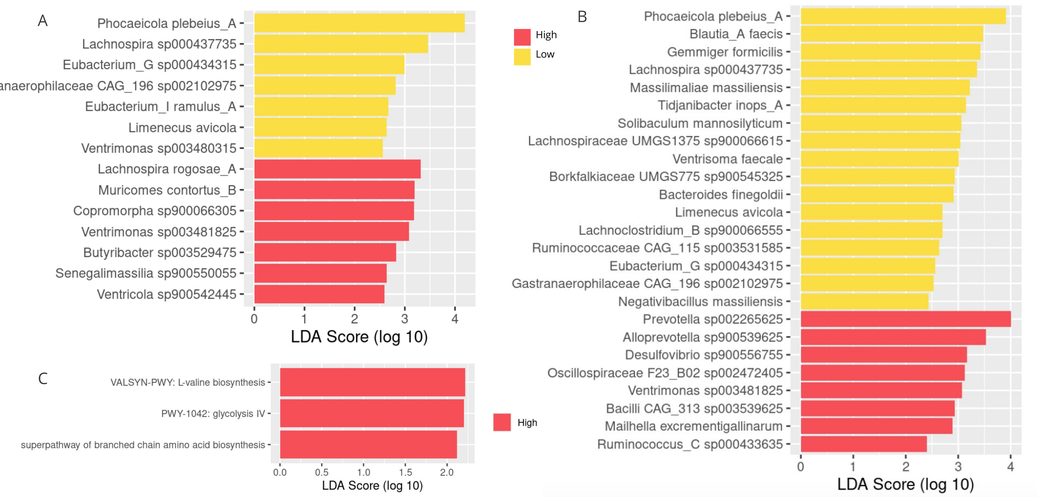


Fig 2. Abundant species and metabolic pathways. LEfSe (>2) of species showing significantly abundant organisms in (A) high and and low groups of intact reservoir size and (B) ratio of intact-to-total proviruses. (C) Significantly abundant pathways based on intact proviral reservoir size.

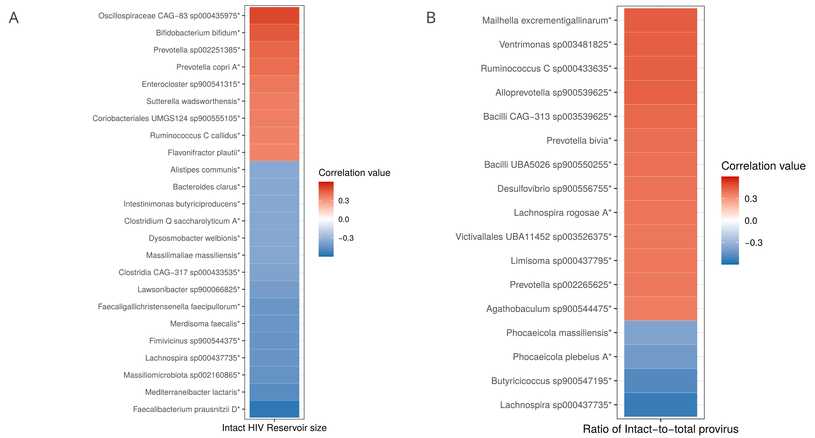


Fig 3. Spearman correlation of species and (A) intact reservoir size and (B) ratio of intact-to-total provirus.

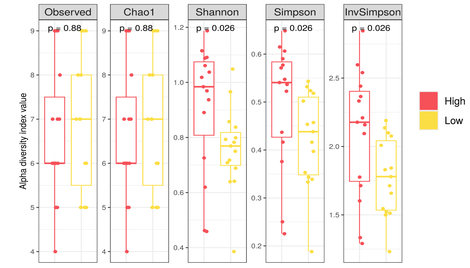


Fig 4. Alpha diversity according to intact reservoir size.

- Lower microbial evenness in individuals with smaller intact HIV-1 reservoir.

CONCLUSIONS

- Intact HIV-1 reservoir size in blood is associated with gut microbiome composition and metabolic pathways.
- Butyrate–producing and gut health–associated species were enriched in individuals with smaller reservoirs, whereas species more often associated to chronic inflammation were linked to larger reservoirs.
- Glycolysis and BCAA biosynthesis pathways may influence T-cell function via mTOR signaling, favoring HIV persistence.
- The gut microbiome may represent a potential target for HIV reservoir modulation.

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PLAIN LANGUAGE SUMMARY

People with HIV who had certain beneficial gut bacteria had a smaller latent HIV reservoir, while those with gut bacteria more often linked to inflammation had a larger reservoir. These findings suggest that the gut microbiome may influence how HIV persists in the body, raising the possibility that modifying gut bacteria could one day support HIV cure strategies.