GUT MICROBIOME ASSOCIATIONS WITH INTESTINAL HIV PERSISTENCE IN ART-SUPPRESSED PEDIATRIC MACAQUES

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Nicole Soo[1], Alexander Grier[1], Veronica Obregon-Perko[2], Zain Gohar Siddiqi[2], Gloria Mensah[2], Bhrugu Yagnik[2], Diane G Carnathan[2], Julia T. Ngo[2], Rama R Amara[2], Genevieve G. Fouda[1], Guido Silvestri[2], Sallie R. Permar[1], Ann Chahroudi[2], and Ria Goswami[1].

[1]Weill Cornell Medicine, New York, NY, USA, [2]Emory University School of Medicine, Atlanta, GA, USA.

BACKGROUND

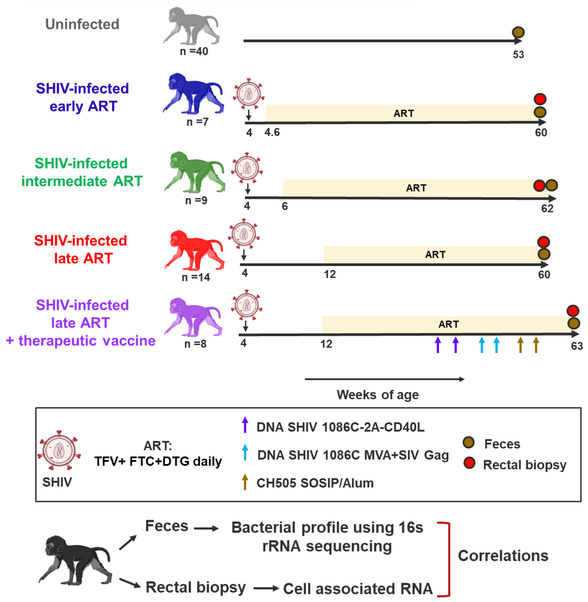
- Each year ~130,000 infants are newly infected with HIV, >50% during breastfeeding.
- HIV reservoir is established immediately upon infection and cannot be eliminated by treatment with ART, resulting in life-long adherence to ART from early life.
- HIV induces gut microbial dysbiosis, leading to inflammation and immune activation, key immune parameters that impact viral persistence.
- Using pediatric rhesus macaques, our group demonstrated the presence of transcriptionally active HIV in intestinal tissues, even after long-term ART.
- Understanding the role of gut microbiome on HIV persistence on ART will lead to **development of strategies to achieve ART-free HIV control** in the pediatric population.

OBJECTIVES

- Employ a physiologically relevant oral SHIV infection model of infant RMs that mimics breast milk transmission, to evaluate HIV-mediated gut bacterial dysbiosis.
- Define microbiome-based correlates of intestinal HIV persistence

METHODS

Oral SHIV infection and therapy of RMs.



RESULTS

ART initiation timing and gut bacterial dysbiosis in orally SHIV-infected infant RMs

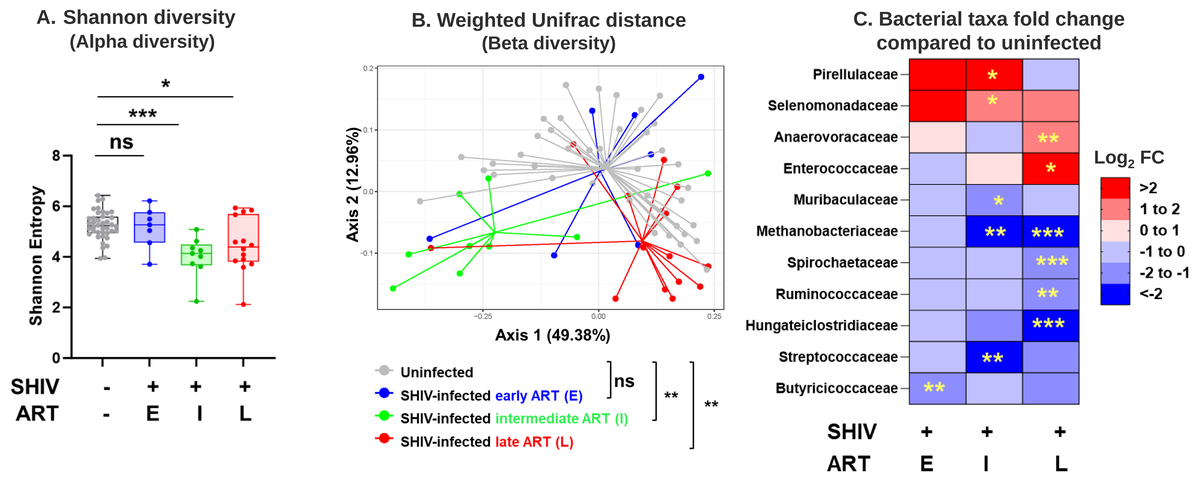


Figure 1. Delay in initiation of ART post oral SHIV infection is associated with gut bacterial dysbiosis that does not repair even after long-term ART. Fecal bacterial **(A)** alpha diversity **(B)** beta diversity principal component analysis and **(C)** bacterial families altered in each indicated treatment group compared to uninfected infant RMs. E, I, and L indicate early, intermediate, and late ART initiation, respectively. *: p<0.05; **: p<0.01; ***: p<0.001; ns: not significant.

DNA/MVA/SOSIP-based therapeutic vaccination and gut bacterial dysbiosis

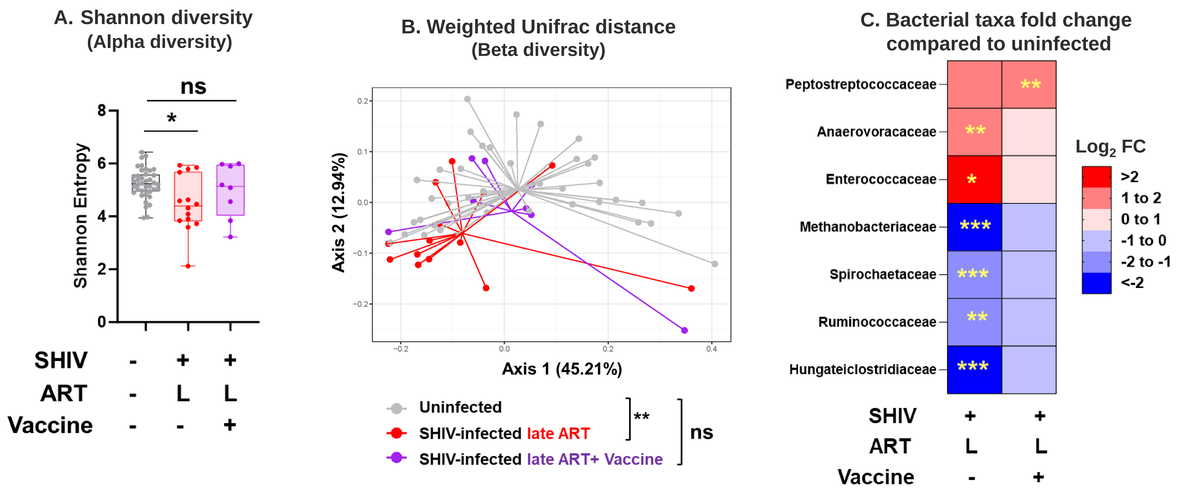


Figure 2. HIV therapeutic vaccination on ART repairs gut bacterial dysbiosis associated with delayed ART initiation. Fecal bacterial **(A)** alpha diversity **(B)** beta diversity principal component analysis and **(C)** bacterial families altered in late ART and late ART+ therapeutic vaccination group compared to uninfected infant RMs. L indicate late ART initiation. *: p<0.05; **: p<0.01; ***: p<0.001; ns: not significant.

RESULTS

Gut microbiome correlates with intestinal HIV persistence

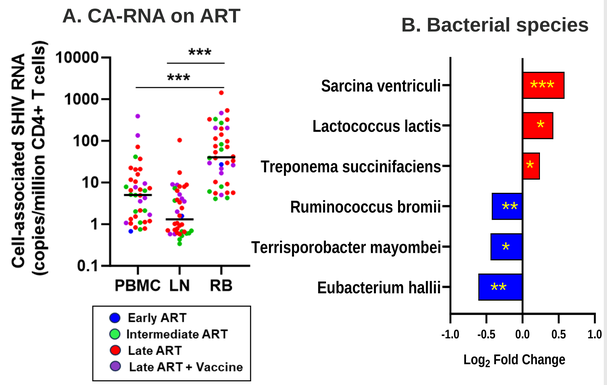


Figure 3. Gut microbiome is associated with transcriptionally active HIV in rectal biopsies. (A) Cell-associated HIV RNA (CA-RNA) in CD4+ T cells of PBMCs, lymph node (LN) and rectal biopsies (RB) from RMs on ART or ART+ vaccine. **(B)** Fecal bacterial species associated with CA-RNA from rectal biopsies, after correcting for therapy-based differences. *: p<0.05; **: p<0.01; ***: p<0.001

CONCLUSIONS

- Novel study of gut bacterial dysbiosis upon postnatal SHIV infection and therapy in a physiologically relevant animal model.
- Delay in ART initiation after SHIV infection is associated with gut bacterial dysbiosis, which cannot be repaired even after long-term ART.
- A DNA/MVA/SOSIP-based HIV therapeutic vaccine on ART can improve SHIV-mediated gut dysbiosis.
- Specific gut microbiome species correlate with intestinal HIV persistence.

Implication: Gut microbial signature can be used as a non-interventional correlate of reduced HIV persistence to facilitate pediatric ART interruption studies. Additionally, microbiome modulation in early life that can reduce HIV persistence may achieve drug-free HIV remission.

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