Impact of Raltegravir Intensification on the gut Microbiota of Subjects with Chronic HIV-1 Infection

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BACKGROUND

Raltegravir (RAL) intensification may improve intestinal and overall health by increasing intestinal microbial richness.

METHODS

This was a prospective, double-blind, placebo-controlled, 2-arm randomized trial, where aviremic subjects with HIV-1 under stable NNRTI- or PIr-based ART were randomized 2:1 to add RAL (1200 mg QD) or placebo to their ongoing ART, stratified by NNRTI vs PIr ART at study entry. We evaluated the longitudinal effect of RAL intensification on the gut microbiome by shotgun metagenomics as well as on soluble markers of immune activation and gut integrity (sCD14, D-Dimer, IFABP, IP10, IL-6 and LBP) and surface lineage, activation, exhaustion, and polarization T cell markers at weeks 0, 12, 24, and 48 by spectral cytometry.

RESULTS

Changes in the microbiota

57 subjects were included, 38 received RAL and 19 placebo. Microbial gene richness did not change in subjects receiving RAL but increased in placebo (LMM p=0.009). In subjects receiving RAL, 3 *Roseburia* species (*R. hominis*, *intestinalis* and *unilivorans*) decreased over time, whereas *Bifidobacterium longum* and *Paraprevotella xylaniphila* increased. RAL was associated with lower *Streptococcus termophilus* abundance than placebo from week 12 onwards (**Figure 1**).

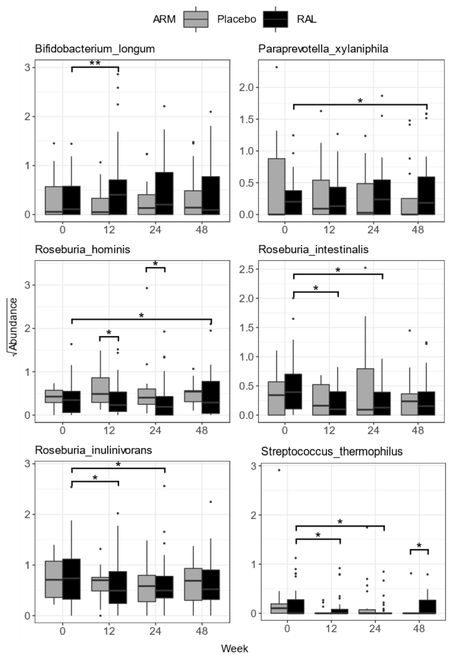

Figure 1. Species abundance which significantly changed respective to baseline in the RAL group or respective to placebo

Raltegravir intensification is associated with changes in *Roseburia* abundance and reduced T-cell activation, exhaustion and senescence

Changes in the T cell response

RAL intensification was not associated with changes in CD4+, CD8+, sCD14, D-Dimer, IFABP, IP10, IL-6 or LBP.

In the spectral cytometry analyses, CD8 EM and TEMRA cells were relatively increased in RAL vs. placebo (**Figure 2**). CD4+ Th1 CM and Th17 CM cells were longitudinally decreased in the placebo group between w.12 and w.48, while CD4+ Th2 CM cells were increased between baseline and w.24 (**Figure 3**). When the Mean Fluorescence Intensity (MFI) of activation, exhaustion, and senescence markers relative to baseline was analysed, we found (**Figure 4**): **A)** An increase in CD4 Naive CD38+ cells at w.12 in placebo vs. RAL, and an increase in CD4 TEMRA CD57+ cells at w.24. **B)** An increase in CD8 EM HLADR+, PD-1+, and CD57+ cells in placebo vs. RAL at w.24, and a decrease in a subpopulation of CD8 EM PD1+ cells at w.12 in placebo vs. RAL. **C)** An increase in Th17 CM PD-1+ cells in RAL vs. placebo at w.48.

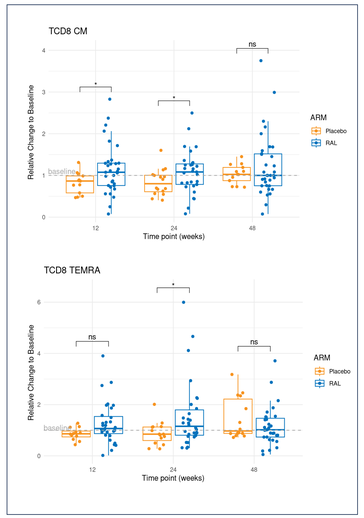

Figure 2. % of CD8+ T cells subpopulations with changes between study groups

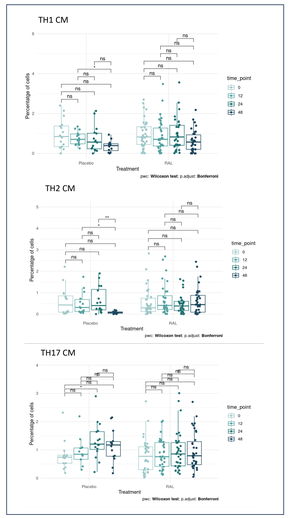

Figure 3. % of CD4 + T cell subpopulations showing longitudinal changes

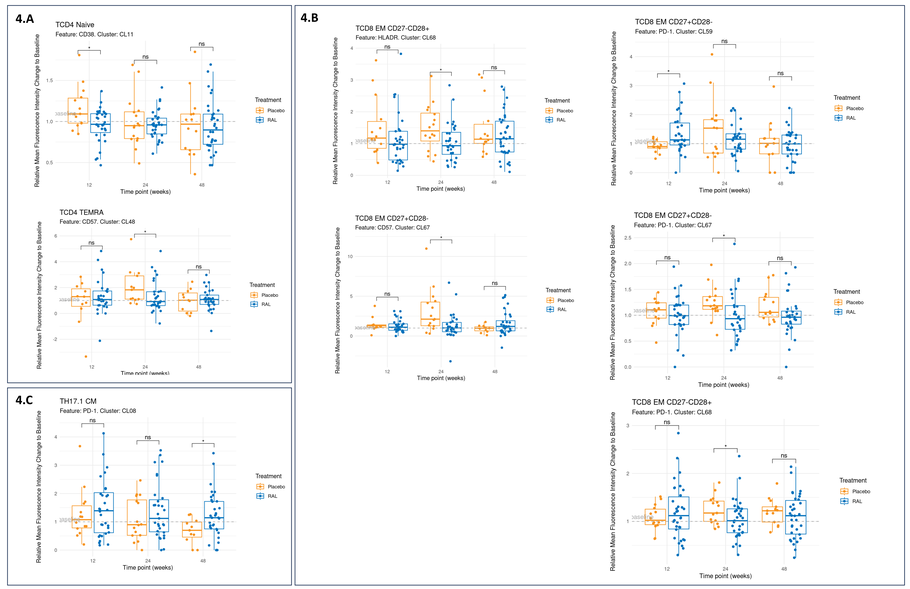

Figure 4. Relative MFI change to baseline

Correlation between microbiota and inflammation markers

When correlating the relative abundance of bacterial species that significantly changed over time with soluble inflammation markers, we found a strong positive correlation between three species of *Roseburia* and D-Dimer and IL-6 levels in placebo (**Figure 5**).

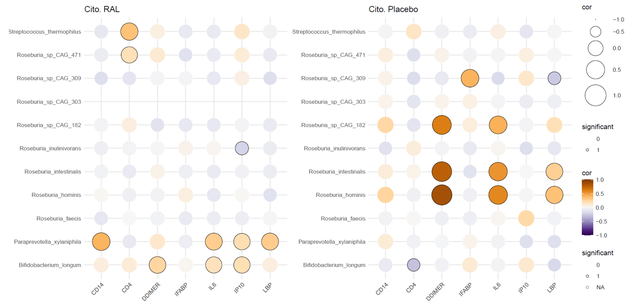

Figure 5. Pearson correlation analysis between differentially abundant species and inflammatory markers.

CONCLUSIONS

RAL intensification of PI/r or NNRTI-based regimens is associated with reduced immune activation, exhaustion, and senescence of CD8+ EM T-cells, as well as changes in CD4 T cell polarization, coupled with changes in the gut microbiome composition.

Roseburia is more able to cope with oxidative environments than other butyrate producers, being a potential surrogate marker of intestinal inflammation.

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