Impact of Three Different ART Regimens on the GALT: a Randomized Clinical Trial

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ABSTRACT

Background

Acute HIV infection leads to depletion of the gastrointestinal-associated lymphoid tissue (GALT), driving bacterial translocation, chronic T-cell activation and disease progression. The aim of this study was to evaluate whether ART initiation regimen might determine mucosal recovery, and whether intensification with a fourth drug may achieve better immune reconstitution.

Methodology

In this clinical trial, 33 ART naïve HIV-infected subjects were randomized to three different ART strategies: EFV, MRV or MRV+RAL, each in combination with TDF/FTC. Peripheral blood (PB), rectal biopsies, and duodenal biopsies were obtained at baseline and after 9 months of ART. Tissue was digested into single-cell suspensions for flow cytometry of lymphocyte subsets and activation (HLADR+CD38+) phenotypes.

Results

Twenty-six HIV+ subjects completed the follow-up: 8 on the EFV arm, 10 on the MRV arm and 8 on the MVC+RAL arm. Median age was 37 years [25-42] without significant differences between groups. In the EFV, MVC and MVC+RAL arms, median preART CD4 counts were 322, 440 and 453 cell/mm3, (between-group comparisons, P=ns.). All patients achieved complete HIV suppression. Absolute CD4 T-cell counts significantly increased on PB after 9 months of ART by 151 cell/uL [43-386], 239 [128-288] and 281 [120-342], as well as did the %CD4 (delta: 14%, 11%, 17%). The %CD8 significantly declined (delta: 13%, 9%, 17%). However, all between-group comparisons were non-significant, even after adjustment for baseline CD4 T-cell counts. In EFV, MVC and MVC+RAL arms, ART resulted in substantial increases in %CD4 in the GALT, both in duodenal (delta: 10%, 10%, 19%) and rectal mucosa (delta: 21%, 18%, 18%), as well as declines in %CD8 (duodenal delta: -11%, -12%, -20%, and rectal: -21%, -18%, -22%). In the adjusted analysis, the extent of preART %CD4 depletion in duodenal mucosa determined CD4 T-cell recovery, both in PB and GALT (Beta 0.48, P=0.02 and Beta 0.42, P=0.042, respectively), but no effect of treatment was identified. Peripheral %HLADR+CD38+ CD8+ T-cells significantly decreased in blood at 9 months post ART, the largest decrease was observed in the MVC+RAL arm (delta: -25%, -24%, -34%; between-group comparisons, P=ns). Changes in CD8+ T-cell activation in the GALT were modest compared to those observed in blood [duodenum, delta: -6%, -9%, -29%; colon, delta: -19%, -5%, -5% (between-group comparisons, P=ns)].

Conclusions

Results of this pilot clinical trial in HIV-infected subjects suggest that CD4 depletion at GALT at ART initiation determine CD4 recovery. Overall, initiation with a quadruple ART regimen showed better immunological restoration in blood and GALT, but the differences remained non-significant and larger studies will be needed to confirm this hypothesis.

METHODS

- Peripheral blood (PB), duodenal and rectal biopsies were obtained from 33 ART nave HIV+ subjects at baseline and after 9 months of treatment.
- Intestinal biopsies underwent digestion to single-cell suspension for polychromatic flow cytometry.
- Lymphocyte maturational subsets were defined as follows: naive T cell (T_N, CD45RA+CCR7+), central memory (T_{CM}, CD45RA-CCR7+), transitional memory (T_{TM}, CD45RA-CCR7-), effector memory (T_{EM}, CD45RA-CCR7-), terminally differentiated (T_{EMRA}, CD45RA+CCR7-) for CD4+ and CD8+ cells.
- T-cell activation was defined as co-expression of HLA-DR and CD38 on respective lymphocyte population.
- Gating strategy included using an FMO (fluorescenceminus-one) to determine the cut-off for positive cells for CCR7, CD38, and HLA-DR for each run.

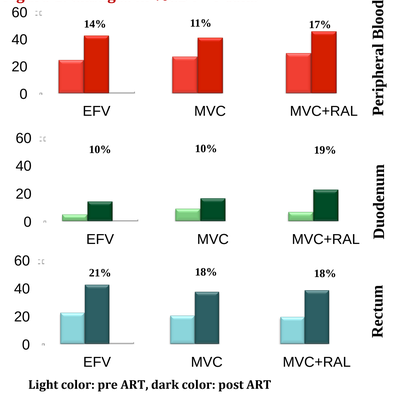
BACKGROUND

- Acute HIV infection leads to depletion of the gastrointestinal-associated lymphoid tissue (GALT) (1). Despite initiation of ART, persistent damage of the mucosa has been suggested as a major driver of bacterial translocation, chronic T-cell activation and disease progression (2).
- Although the extent to which ART achieves GALT recovery is not well known (3), treatment intensification has been suggested as a strategy potentially leading to decrease viral reservoir. Maraviroc has good gut-associated lymphoid tissue penetration (4) and recently, used as intensification has shown to induce a decrease in circulating bacterial products. However, while some results show an increase on % CD38+HLA-DR+CD8+ Tcells in rectum and peripheral blood after MRV intensification (5), others did not found such an effect (6) .
- The aim of this study was to evaluate the effect of three different initiation regimen on mucosal recovery, and to analyze whether intensification with a fourth drug may achieve better mucosal immune reconstitution.

RESULTS: immune recovery

26 HIV+ patients completed the follow-up period, 22 (84.6%) were male.
8 started EFV, TDF/FTC, 10 MRV, TDF/FTC and 8 MVC+RAL, TDF/FTC
Median age was 37 years [25-42] without significant differences between groups.
Median preART CD4 counts were 322, 440 and 453 cell/mm3 respectively (between-group comparisons, P=ns.).
All patients achieved complete HIV suppression.

Figure 1: Changes in %CD4+ T cells

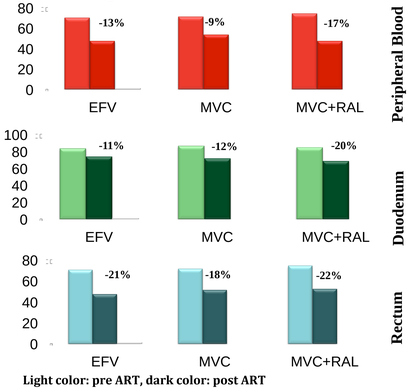


Light color: pre ART, dark color: post ART

After 9 months, ART resulted in substantial increases in %CD4 on PB (**Figure 1, top**), as well as duodenal (**Figure 1, middle**), and and rectal mucosa (**Figure 1, bottom).** However, differences between treatment group were non-significant, even after adjustment for baseline CD4 T-cell counts.

The %CD8 significantly declined on PB (delta: -13%, -9%, -7%), duodenal (delta: -11%, -12%, -8%) and rectal mucosa(-21%, -18%, -22%) (**Figure 2**)

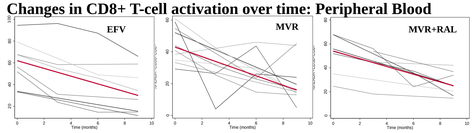
Figure 2: Changes in %CD8+ T cells



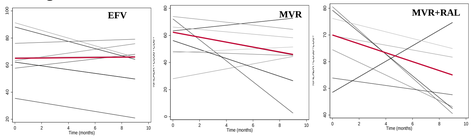
Light color: pre ART, dark color: post ART

RESULTS: immunoactivation

Changes in CD8+ T-cell activation over time: Peripheral Blood



Changes in CD8+ T-cell activation over time: Duodenum



Changes in CD8+ T-cell activation over time: Rectum

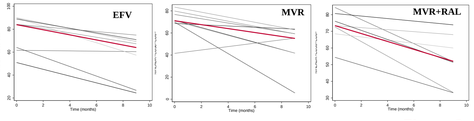


Figure 3

Peripheral %HLADR+CD38+ CD8+ T-cells significantly decreased in blood at 9 months post ART **Figure 3, top).**
The largest decrease on peripheral CD8+ T cell activation was observed in the MVC+RAL arm (PB delta: -25%, -24%, -34%, respectively). However, between-group comparisons were all non-significant

Changes in CD8+ T-cell activation in the GALT were modest compared to those observed in blood (**Figure 3, middle and bottom**). Duodenum delta: -6%, -9%, -29%; colon, delta: -19%, -5%, -5%, respectively]. No effect of treatment was identified.

In the adjusted analysis, the extent of pre ART %CD4 depletion in duodenal mucosa determined CD4 T-cell recovery, both in PB and GALT (Beta 0.48, P=0.02 and Beta 0.42, P=0.042, respectively), but no differences among treatment arms were identified.

CONCLUSIONS

- **In this pilot study, three different ART regimens achieve similar immune recovery in blood and GALT.**
- **Overall, initiation with a quadruple ART regimen showed slightly better immunological restoration in blood and duodenum, but the differences remained non-significant.**
- **Treatment with MRV was associated to a decrease in CD8+ T cells coexpressing HLADR+CD38+ on PB, duodenum and rectum, in this study.**
- **CD4 depletion at GALT at ART initiation and not ART regimen determine CD4 recovery.**
- **Sample size is a main limitation of this study. Larger studies will be needed to confirm this hypothesis.**

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