Randomized trial of impact of multiple interventions on HIV reservoir: SPARC-7 trial

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Introduction:

- Recognized barriers for HIV elimination among individuals with suppressive antiretroviral therapy (ART) are residual viral reservoirs, which can lead to viral rebound and contribute to the persistence of HIV.
- In this sense, multiple experimental strategies may be fundamental to decrease the size of HIV reservoirs.
- To measure the impact of isolated and combined strategies in decreasing virus persistence and elimination, we conducted a trial of intervention with tenofovir disoproxil fumarate (TDF) and without maraviroc (MVC), or to decrease HIV reservoirs with MVC.
- Maraviroc (MVC) is a CCR5 receptor antagonist (CCR5) which in addition to blocking HIV infection in lymphocytes, may partially reduce the size of HIV reservoirs by blocking viral dissemination events or facilitate the production of autologous cell vaccine candidates.
- These findings suggest that TDF and MVC are effective in decreasing HIV reservoirs, specifically in the presence of MVC.
- The trial was shown to be a highly translational intervention to decrease the size of HIV reservoir by the five-year follow-up.

Methods:

- Randomized open-label pilot phase of conceptual trials (NCT09311259). Study subjects were male (the choice was done to gain the potential translatability of the study results to males). Study flowchart is depicted in the text.
- Inclusion criteria: subjects had to be older than 18 years of age, had been on ART for at least 6 months, had CD4 nadir ≥ 300 cells/µL, had undetectable HIV RNA for at least 6 months, and had CD4 nadir ≥ 300 cells/µL.
- Exclusion criteria: subjects had to be younger than 18 years of age, had been on ART for less than 6 months, had CD4 nadir < 300 cells/µL, had an undetectable HIV RNA for less than 6 months, or had a history of non-compliance with ART.
- The study design was a randomized, controlled trial with three parallel groups and two arms: TDF/3TC/EFV (Group 6, n = 6), TDF/3TC/EFV + MVC (Group 5, n = 4), and TDF/3TC/EFV + MVC + brefaldine (Group 4, n = 4).
- The study subjects were randomized into two groups: a randomized cohort (n = 18) and a non-randomized cohort (n = 26).
- The results showed a significant decrease in HIV reservoirs in the randomized cohort compared to the non-randomized cohort.

Results:

- No significant differences were found for CD4 or CD8 T cells or CD4/CD8 ratios during study period.
- No grade 3 or 4 adverse events were observed.

Conclusions:

- A significant reduction of viral load as assessed by a more conservative quantitative analysis was detected only in the group that received all proposed interventions: treatment intensification, TDF/3TC, and MVC vaccine (TDF/MVC group).
- A reduction of the immune inflammation marker CD8+ among individuals already in HIV suppression may facilitate a decrease in production of lymphocytes and macrophages, consequently decreasing the size of HIV reservoirs.
- Subjects displaying a negative HIV RNA at the end of follow-up strengthen a toxic T cell vaccine activity.
- This trial is the first study to test a toxic T cell vaccine in patients with ART suppression.

Acknowledgments:

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- The study was funded by Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) (2015/04635-0 and 2012/11266-2) and by Investigación Supervisorio Study Program from NIH/NIAID (AI097277 and AI099990). The study was performed at the AIDS Liver Center of São Paulo by our group.

Study Flow Chart:

Changes in the mean % of CD4+ T cells CD8+ and CD8+ T cells and CD38+ among individuals of Group 6:

Distribution of patients according to specific intervention:

Antibodies quantitation means using the Abbott ARCHITECT HIV Ag/Ab Combo assay (Abbott, IL, USA) by dipp.

Qualitative results of total HIV DNA in PBMCs and Rectal biopsy tissues over time:

Antibodies quantitation means using the Abbott ARCHITECT HIV Ag/Ab Combo assay (Abbott, IL, USA) by dipp.

The SPARC-7 Patients:

- Two subjects (P10 and P12 from Group 6) showed an undetectable HIV DNA in PBMCs at the end of the treatment. The former decided to continue the HIV serum and rectal biomarker (HIV) from these subjects to evidence validation.
- HIV DNA quantification was performed utilizing molecular and HIV-1 DNA (DNA 14K) method (Know et al., 2010) in an independent laboratory, which confirmed the analysis in our site.

Dipplex approach HIV DNA (DNA 14K) per time: T time: T have been performed in duplicate with triplicate results of positive and negative controls in all the samples tested.

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Results showed that both P10 and P12 presented a decrease in CD8+ T cells and MVC at baseline and the end of the study. MARINA patients, respectively, in TDF/3TC/MVC and MVC alone (P10) treatment arms. The latter confirmed the analysis conducted in our site by our group.

Conclusions:

- A significant reduction of viral load as assessed by a more conservative quantitative analysis was detected only in the group that received all proposed interventions: treatment intensification, TDF/3TC, and MVC vaccine (TDF/MVC group).
- A reduction of the immune inflammation marker CD8+ among individuals already in HIV suppression may facilitate a decrease in production of lymphocytes and macrophages, consequently decreasing the size of HIV reservoirs.
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