Effects of three Regimens of PEP on the Immune System of HIV Seronegative Individuals

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Introduction

• According to studies in animal models, Postexposure Prophylaxis (PEP) has to be maintained 4 weeks to be effective. However, with the diversity of the actual regimens, the consequences of those temporary window treatments at immunological level are not well characterized. The development of different classes of treatment agents for combating HIV infection has increased the alternatives to avoid the infection after accidental exposure.

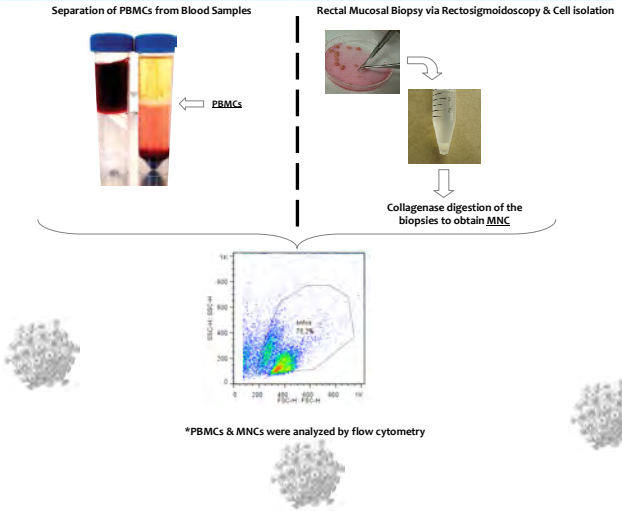
• According to UNAIDS, the vast majority of people newly infected with HIV are infected during unprotected intercourse (1). In almost all the infections sexually transmitted the virus has a CCR5 tropism (2). Since the binding of HIV to CCR5 is necessary to infection, a CCR5 inhibitor could be used in this setting. Additionally, modern integrase inhibitors (raltegravir) has been shown to be extremely well tolerated, with potent antiretroviral activity (3). We want to compare immunological consequences of such regimens in our cohort of HIV seronegative individuals.

Goal

➢ ***The objective of this pilot study was to assess the immunological effects of antiretroviral therapy during 28 days of PEP comparing the standard of care Lopinavir/r (LPV/r) vs Maraviroc (MVC) or vs Raltegravir (RAL), all of them with Tenofovir/Emtricitabine (TVD).***

Material and Methods

- Peripheral blood mononuclear cells (PBMCs) and mononuclear cells (MNC) from rectal biopsy specimens were collected from 30 men who have sex with men (MSM) with a potential sexual exposure. All of them were selected from two different PEP randomized clinical trials (NCT 01533272-MARAVIPEP & NCT01576731-RALPEP). Three arms (TVD plus LPV/r (n=9) or plus MVC (n=11) or plus RAL (n=10)) and four follow-up visits were scheduled (days 3, 8, 28 and 90 (as baseline).
- Flow cytometry was used to measure immune activation (CD38 and HLA-DR), senescence (CD57 and CD28) and CCR5 expression in both CD4 and CD8 T cells. Additionally levels of naïve, effector and memory T cells (CCR7 and CD45RA) were also evaluated.



Results

In PBMCs, no differences were detected at basal time among arms. Senescence and activation of CD4 T cells improved significantly in RAL arm between baseline and day 28 (CD28: 93.5% vs 97.5%, p= 0.02; CD57: 4.8% vs 1.5%, p=0.03; CD38+DR+: 5.8% vs 2.6%, p=0.05, respectively) whereas no changes were observed in the other two regimens. Only RAL arm reduced significantly the mentioned percentage of CD4+CD38+DR+ in comparison with MVC arm at day 28 (7.4% vs 2.6%, p=0.02, respectively). (Fig.1). At the same time points, MVC arm increased significantly the expression of CCR5 in both lineages CD4 (4.7% vs 15%, p=0.002) and CD8 (6.3% vs 16.1%, p=0.004) T cells, probably as a consequence of blockade of its internalization (Fig.2). Regarding rectal biopsies not significant differences were detected among arms except for a marked increase in the proportion of CD4 naïve T cells in MVC arm (RA+CCR7+:15% vs 46%, p=0.03) (Fig.3).

Figure 1.- Activation and senescence markers in CD4 T cells after 28 days of treatment. *Differential expression of CD28 (a), CD57 (b) or CD38 (c) are depicted below. Mann-Whitney-U test or Wilcoxon rank test were performed in each case where corresponded , all P values of statistically significant differences are indicated in bold (* p< 0.05).*

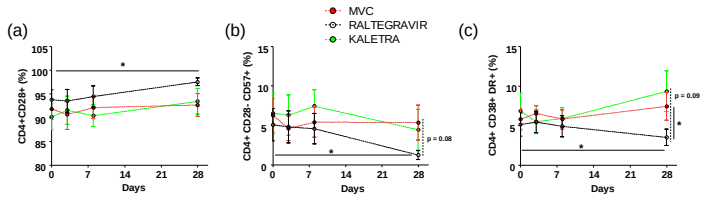


Figure 2.- MVC increased significantly the expression of CCR5 in both lineages (CD4 and CD8). *(a) CCR5 expression level determined longitudinally (basal, 3, 8 and 28 days) in CD4 and CD8 T cells. (b) At 28 days of treatment differences between MVC arm and the other two regimens increased dramatically. Mann-Whitney-U test or Wilcoxon rank test was performed where corresponds, all P values of statistically significant differences are indicated in bold (* p< 0.05; ** p< 0.01; *** p< 0.001).*

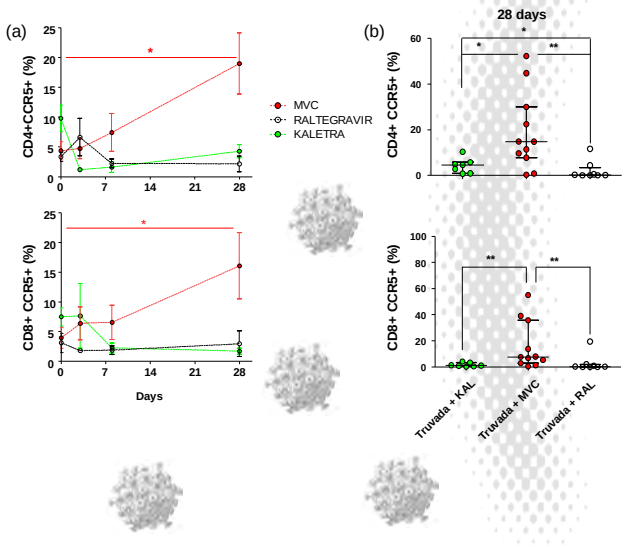
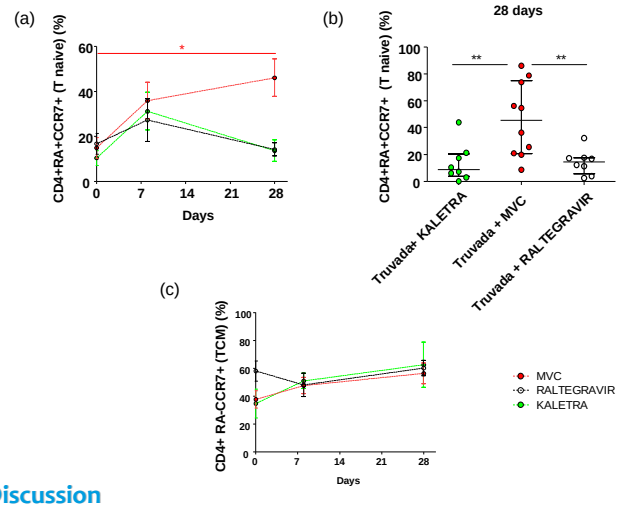


Figure 3.- Expression of CCR7 and CD45RA on MNCs. *The combination of both markers distinguishes three subsets of T cells: naive T cells (CCR7+ CD45RA+); central memory T cells (TCM: CCR7+ CD45RA-); and effector memory T cells (TEM: CCR7- CD45RA-). (a) Naive T cells in MVC arm clearly increase their percentage after 28 days of treatment (b) even in comparison with the other two regimens. They migrate very efficiently through lymph nodes using a 'combination code' of L-selectin (an adhesion molecule) and CCR7 (a chemokine receptor). CCR5 blockade could be improving this process. On the other hand central memory T cells, who maintained similar levels (c), probably migrate through lymph nodes where CCR5 blockade could be less relevant.*



Discussion

• Immunological studies measuring the effect of HAART in healthy individuals are not very frequent. Our results have shed some light on the problem using cells from two different sources: PBMCs and MNCs. There were no significant changes in the percentage and absolute numbers of CD4 and CD8 T cells, CD8 CD38 and CD8 CD28 T cells (4). But also other important aspects have been modified with different implications. For instance, CD4 T cell activation reduced in RAL regimen and different redistribution of T naïve cells in mucosal from MVC arm could be relevant to improve PEP choices and to reduce both, side effects and infections.

Conclusion

The rates of activation and senescence of the immune system were significantly lower in CD4 T cells from HIV seronegative individuals on PEP with TVD plus RAL as compared with those with the other two regimens. Although these data should be confirmed due the low number of patients, our findings in combination with the results of adequate adherence and tolerance (reported in Abstract 2095205-CROI 2015) strongly support RAL regimens for PEP.

References

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