Pre-Exposure Prophylaxis for HIV Does Not Affect the Immune Response, For the Good or the Bad

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Several trials have demonstrated the efficacy of the administration of antiretroviral drugs as pre-exposure prophylaxis to subjects at high risk of acquiring HIV. Partners PrEP, a placebo-controlled, randomized trial conducted in Kenya and Uganda on serodiscordant couples, showed that the reverse transcriptase (RT) inhibitor tenofovir disoproxil fumarate alone or in combination with emtricitabine, also an RT inhibitor, substantially reduced the risk of HIV acquisition. Although the main mechanism of protection is thought to be the inhibition of HIV replication at a very early stage of infection, the administration of the drugs could also provide an effect described as chemo-vaccination, where the virus, although unable to replicate, can be presented to the immune system. In a concerted effort with Dr. Baeten's group at the University of Washington, members of the Lund Lab in the Vaccine and Infectious Disease Division (VIDD) compared the immune responses in the groups of subjects receiving placebo and PrEP. The results of this study were published in December in Journal of Infectious Diseases.

"As PrEP is rolled out to high risk populations and likely will be offered as part of standard prevention packages in HIV vaccine trials, it is increasingly important to understand any potential influence PrEP may have on immunity, particularly when used together with new candidate vaccines", explained Dr. Pamela Murnane, who conducted the statistical analyses of the study. "Our unique study population provided for a robust evaluation of this hypothesis in humans," continues Dr. Murnane. "Participants had a known exposure to HIV, a high risk of HIV acquisition, were randomly assigned to PrEP or placebo, and had a high level of adherence to study drug." A total of 224 participants from the study were selected, half from the placebo and half from one of the treatment arms, and their immune responses were characterized.

Three cell types were the main focus of the investigation: CD4+ and CD8+ T cells, and natural killer (NK) cells. CD4+ T-cell responses are unique in HIV infection, in that they are targets for HIV infection and thus, they might be detrimental for HIV acquisition. CD4+ T cells from placebo and PrEP groups were thus characterized in order to verify if PrEP use modified their phenotype or function. The results showed that the frequencies of HIV-specific CD4+ T cell responses were

comparable in PrEP and placebo group (8.7% and 9.6%, respectively). In the same way, magnitude and breath of the responses were not statistically different. Activation status and maturation of CD4+ T-cells were compared as well and again, they were similar in the two groups.

CD8+ T cells have been shown to inhibit infection in non-human primate studies and are elevated in HIV-infected long-term non-progressors; thus, their role is supposed to be protective against HIV. No modification was detected in the PrEP group as compared to placebo, for the HIV-specific CD8+ T cell responses, whose frequencies were 20% for PrEP and 17.4% for placebo, as well as for the maturation or the activation of such cell type.

Finally, follow-up studies on a recent HIV vaccine efficacy trial suggested a protective effect mediated by HIV-specific, non-neutralizing antibodies. This finding shed light on the possibly protective role of antibody dependent cellular cytotoxicity, which involves recognition of HIV peptides on the surface of infected cells by antibodies, followed by cytotoxic activity by NK cells. This finding led the authors to characterize the pattern of activating/inhibitory receptors expressed on NK cells, but they found that it was not modified by PrEP.

In sum, while not being potentially dangerous in the context of a vaccine trial, PrEP does not seem to offer any chemo-vaccination effect, so it continuous administration is advisable during periods of high HIV-exposure.

Pattacini L, Murnane PM, Baeten JM, Fluharty TR, Thomas KK, Bukusi E, Katabira E, Mugo N, Donnell D, Lingappa JR, Celum C, Marzinke M, McElrath MJ, Lund JM, for the Partners PrEP Study group. 2014. Antiretroviral Pre-Exposure Prophylaxis Does Not Enhance Immune Responses to HIV in Exposed but Uninfected Persons. *J Infect Dis*. Epub ahead of print.

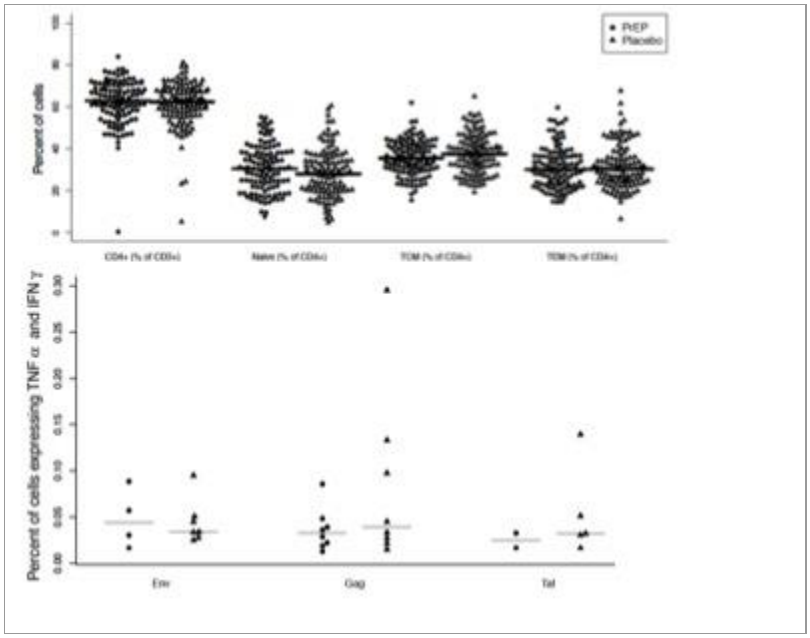

Image provided by Dr. Pamela Murnane

CD4+ T cell maturation and HIV-specific immune responses in PrEP and placebo groups.