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Deciphering the association between HIV-specific immunity and immune reconstitution

Ole S. Søgaard

Department of Infectious Diseases, Aarhus University Hospital, Denmark
Institute of Clinical Medicine, Aarhus University, Denmark

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Numerous observational studies have reported elevated risk of cardiovascular disease, chronic lung disease, infections and cancers among people living with HIV (PLWH) compared to non-HIV infected individuals [1,2]. The association between HIV infection and increased risk of these non-AIDS related comorbidities is strongest for viraemic individuals as highlighted by two pivotal randomized trials, the Strategies for Management of Antiretroviral Therapy (SMART) study and Strategic Timing of Antiretroviral Treatment START study [3,4]. However, even PLWH on long-term ART with suppressed viral replication and high CD4 cell counts appear to have a moderately higher risk of these common comorbidities than people without HIV infection [2]. The cause of this excess comorbidity remains unknown and may be multifactorial. Several causative mechanisms not directly related to the virus have been proposed including life-style factors which can be difficult to account for in epidemiological studies, socioeconomic status, and drug-related toxicities. Indeed, some antiretroviral drugs have been associated with increased risk of specific medical conditions such as myocardial infarction, renal insufficiency, and osteoporosis [5]. However, studies have also shown that HIV itself, despite suppressed plasma HIV RNA, can lead to low-level immune activation which may be a potential driving force for increased risk of non-AIDS related comorbidity [6].

All PLWH harbour a latent HIV reservoir which is not eliminated by antiretroviral therapy (ART) [7]. Low level immune activation can be induced by continuous release of viral proteins from the latent proviral reservoir which triggers a detrimental inflammatory response [6]. The frequency of intact proviruses in individuals on long-term ART is often as low as 1-100 intact proviruses per 1 million CD4 T cells whereas the frequency of defect proviruses may be up to 50 times higher than that of intact proviruses [8]. However, a recent study suggests that even defective proviruses can give rise to HIV proteins suggesting that individuals with large HIV reservoirs may be particularly prone to HIV antigen-induced inflammation [9].

In the present issue of *EBioMedicine*, Tripiciano and colleagues report the findings from an interesting prospective, longitudinal cohort study in which they investigate the interplay of anti-Tat immunity, low-level viremia, immune activation, and CD4+ T-cell dynamics in PLWH on long-term ART [10]. The hypothesis behind the study was that extracellular HIV Tat protein could drive immune activation, inhibit tat-specific T cell immunity, and fuel low-level viremia through reactivation of latent proviruses. In the study, the investigators follow 118 long-term ART treated individuals over a 3-year period. The study participants were stratified by residual viremia, anti-Tat serostatus and frequency of anti-Tat cellular immune responses and complementary statistical methods were used to determine potential associations between the biological covariates. The authors main findings were that anti-Tat immunity was significantly associated with higher nadir CD4+ T-cell numbers, control of low-level viremia and CD4+ T-cell recovery over time.

The authors speculate whether the greater longitudinal increase in CD4 T cell counts and the absence of detectable plasma viremia could be due to presence of anti-Tat Abs. In support of a beneficial effect of HIV Tat-specific immunity on immune reconstitution following ART initiation, the authors also report that anti-Tat cell-mediated immunity, alone or combined with anti-Tat humoral immunity, was found to predict increases in the levels of circulating NK cells or B cells. In contrast to anti-Tat immune responses, both cellular and humoral against HIV Env were present in >99% of all participants. Anti-Env antibody titres were also considerably higher than anti-Tat antibodies suggesting dominant immune responses against HIV Env compared to HIV Tat.

These findings are intriguing and suggest a potential window for pharmaceutical intervention by boosting anti-Tat immunity in people on ART. However, there may also be other potential mechanisms that could partially account for the observed findings. For instance, another cause of the positive association between levels of anti-Tat Abs and frequency of B cells and nadir (the lowest recorded value) CD4+ could be that anti-Tat antibodies are a marker of intact and well-preserved B cell functions. It is well-documented that PLWH who start ART early after the time of infection have better-preserved immune functions than those who start ART late after the time of infection [1,3,4]. Nadir CD4+ cell count, which is used as a marker of immune dysfunction prior to starting ART, was in fact higher among the anti-Tat

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E-mail address: olesoega@rm.dk

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antibody positive compared to the anti-Tat antibody negative group. This seems to indicate that the levels of anti-Tat antibody might depend on the level of immune dysfunction prior to starting ART. In addition, levels of anti-Tat immunity were not associated with persistent immune activation which argue against anti-Tat antibodies as a mechanism for eliminating HIV Tat-driven low level inflammation.

As the authors propose, future clinical trials could test therapeutic strategies such as vaccination using an HIV Tat-protein based vaccine or administration of anti-Tat antibodies to determine whether anti-Tat humoral or cellular immunity can lower residual viremia and restore immune functions in PLWH and ultimately reduce non-AIDS-related comorbidity.

Contributors

OSS soley wrote this commissioned Commentary.

Declaration of Competing Interest

The author declares no conflicts of interest.

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