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Immune activation and HIV: An enduring relationship

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Immune activation (IA) has been a central aspect of HIV pathogenesis from the early years of the epidemic. Well before the advent of combination antiretroviral therapy (ART) it was observed that CD8 T cell activation measured by co-expression of HLA-DR and CD38 was an independent predictor of mortality after adjustment for CD4 counts and plasma HIV viremia [1,2]. At the same time, markers of innate immune activation, beta2-microglobulin and neopterin, had also been identified as important biomarkers of inflammation and HIV prognosis [3,4]. More recently, the results of the SMART (Strategies for Management of Anti-Retroviral Therapy) trial highlighted a clear link between inflammatory and coagulation biomarkers and clinical events in HIV infected persons even after adjusting for HIV risk factors and comorbidities [5]. These results brought once again immune activation and inflammation at the forefront of disease pathogenesis as HIV is being converted to a chronic disease and the age of the people living with HIV is steadily rising.

It is now well established that despite the tremendous success of ART in reducing mortality and morbidity, HIV-infected persons remain at higher risk than age-matched controls for serious non-AIDS or non-infectious complications. These complications that overlap to some extent with diseases of aging have been associated with residual immune activation despite suppression of plasma HIV viremia and can be further accentuated by life style factors and comorbidities, such as smoking and hypertension. This is relevant to clinical care of people living with HIV as a large proportion of them worldwide is approaching or is already older than 50 years of age.

In this issue of Current Opinion in HIV and AIDS, an overview of the topic of immune activation in HIV is presented within the background of modern ART, knowledge of benefits of earlier treatment and sophisticated research tools to study pathogenesis. The association of residual immune activation with clinical outcomes has long been noted and continues to be evaluated. As highlighted by Utay et al., many factors contribute to the immune activation of treated patients and depending on the specific patient population, innate versus adaptive immune activation may be playing a different role in risk for AIDS versus non-AIDS events [6]. T cell activation, monocyte activation, type I interferons,

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Conflicts of interest

Dr Altfeld has MA has received speaker honoraria from MSD, Gilead, Jansen & Jansen, and BMS. Dr Sereti has no disclosures.

Indoleamine 2,3-dioxygenase-1 (IDO) activity and tissue fibrosis are all critical facets of the perpetual immune activation but it still remains elusive which pathways may be more amenable to successful intervention and in which patient subgroups this could substantially add to the tremendous benefit of ART.

Immune activation and inflammation in HIV-1-infected mothers can furthermore affect mother to child transmission of HIV-1, and even the subsequent immune development of the HIV-1-exposed but uninfected child [7]. Pediatric infection resulting from vertical transmission is a particularly intriguing area of immunologic studies given the consequences of the very early infection on the development of an immature immune system and disease progression [8]. During horizontal transmission of HIV-1, it is now well established that mucosal inflammation resulting from infections or dysbiosis can significantly impact the rate of HIV transmission [9]. Immune activation appears very early during acute HIV infection even prior to seroconversion or the development of a symptomatic acute retroviral syndrome, suggesting that the cascade of events triggered by the virus and aimed at achieving viral restriction can inadvertently fuel further viral replication [10]. ART in these very early stages may significantly decrease the inflammatory response of acute infection in periphery and the central nervous system (a nonrenewable site) but it remains still unclear whether this will change the course of disease and the long-term risk of serious non-AIDS events (SNAEs).

The etiology of persistent IA in the context of successful ART is considered multifactorial but the virus itself and the mechanisms it uses to evade innate responses play a central role [11]. In addition, microbial translocation, loss of Th17 and dysbiosis in mucosal barriers (gut and cervical) seem to contribute to the persistent state of IA [12]. Co-infections play an important role both in acute inflammatory responses known as IRIS early after ART initiation but also in chronic treated patients, with CMV and HCV being most extensively studied in that role [13].

Studies in non-human primates (NHP) have beautifully highlighted several cardinal aspects of HIV/SIV pathogenesis, showing how the role of IFN depends on the disease stage and is beneficial in acute infection, yet becomes detrimental in chronic infection [14]. Interventions in NHP studies have elucidated the role of IFN and microbial translocation, although these studies may not always be reproducible in humans given the complexity of human infection with various comorbities, genetics and life style factors. Sex differences in innate immune sensing and IFN responses by pDCs can also have a critical role in determining differences in HIV-1 disease manifestations between women and men during acute and chronic infection, and require further studying [15]. Cardiovascular disease [16] and neurocognitive disease [17] represent important morbidities in treated patients with HIV-1 infection and have been linked to both adaptive and innate immune activation. Finally, immune activation and inflammation appear to be important contributors to maintenance of HIV viral reservoirs [18], the biggest obstacle to viral eradication and cure. Aging of HIV patients will necessitate refined interventions in addition to ART to expand and normalize the life span of people living with HIV [19].

Despite extensive study of pathways of IA, multiple studies attempting to decrease persistent IA have not yet succeeded to alter clinical outcome. The best strategy to date to decrease IA and inflammation in HIV is early initiation of ART. A better understanding of the mechanisms underlying IA may allow targeted approaches to successfully address specific aspects of IA in HIV, namely decreasing the viral reservoir, improving dysbiosis or treating co-infections. As the Strategic Timing of Anti-Retroviral Treatment (START) trial showed, both AIDS and non-AIDS events decrease substantially with early treatment initiation making early ART the best approach to decrease morbidity and mortality [20]. It is plausible that in addition to ART, a careful individualized approach with strategies that minimize or eliminate the impact of comorbidities including smoking cessation, control of diabetes, obesity, hypertension, and treatment of hepatitis C, could probably further reduce morbidity and mortality in HIV-1-infected individuals. More targeted approaches for all or specific subgroups of HIV-infected persons may emerge through cutting edge studies that will clarify the role of different pathways of IA and their link to clinical events.

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