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Letter to the Editor

Delayed CD4 cell recovery in HIV-associated disseminated nontuberculous mycobacterial disease

Dear Editor,

We read the manuscript describing the retrospective case-control study by Katzschner et al. [1] and their call for renewed attention to HIV-associated disseminated non-tuberculous mycobacterial disease (dNTMd) with great interest. The authors stated that specific contribution of dNTMd to delayed CD4-cell restoration remains understudied; however, they did not cite two studies that outlined this issue before. Lazaro et al. did a study within the ANRS Co3 Aquitaine Cohort, a prospective cohort of people with HIV-1 initiated in 1987 in five hospitals in Aquitaine, France. They formed two groups of individuals who started for the first time a combination of three antiretroviral drugs; the exposed group with disseminated *Mycobacterium avium* complex (dMAC) infection (to which 18 of the 20 dNTMd infections in Katzschner et al.'s study were due) [1] included 51 people with such a diagnosis made between 12 months before and 6 months after antiretrovirals initiation [2]. These patients were individually matched to 145 individuals without any history of dMAC infection by CD4 cell count, previous experience of antiretroviral treatment, AIDS clinical stage at the time of antiretrovirals initiation, age and gender. The study showed that dMAC infection at the time of antiretrovirals initiation importantly impaired immune reconstitution, whereas the 6-months decline of plasma HIV-RNA was not significantly different [2]. After 6 months on antiretrovirals, the median increase of CD4 cell count was +28 cells/mm^3 (interquartile range [IQR]: 1-63) in people with dMAC infection and +72 cells/mm^3 (IQR: 34-120) in people without (P<0.0001) [2], The independent effect of dMAC infection was confirmed also at 12 and 24 months [2]. We retrospectively reviewed the records of 73 antiretroviral-naïve individuals with AIDS presenting with CD4 counts of <100 cells/mm^3 at two Infectious Diseases Units in Italy and investigated whether opportunistic infections or cancers recorded at presentation influenced subsequent immune reconstitution on antiretrovirals [3]. The median CD4 cell count at the time of antiretrovirals start was 60.68 cells/ mm^3 and the median viral load was 572,633 HIV-1 RNA copies/mL. After a median follow-up period of 36 months, all 67 individuals who had been adherent to antiretroviral treatment had sustained viral load suppression (HIV RNA <50 copies/mL), and their median CD4 cell count was 391.79 cells/mm^3. A lower increase in CD4 cell count (median 59.75 cells/mm^3) and total lymphocyte count (median 74.21 cells/mm^3) was found only in the 9 individuals who had experienced dMAC infections [3]. In both the above studies the diagnosis of disseminated MAC infection was based on the isolation of MAC from cultures of blood, bone marrow, or other normally sterile tissue or body fluids.

The underlying reasons for the negative influence of dNTM infections on immune recovery remain unknown. In addition to the two explanations proposed by Katzschner et al. (higher immunodeficiency in people with dNTM infection despite similar CD4 cell counts and viral suppression rates, and granulomatosis in lymphatic tissues leading to impaired immunological remodeling) [1], other factors may contribute to impaired immune recovery. These are the induction of immunosuppressive cytokines, tumor necrosis factor (TNF)-alpha or apoptosis [4], the long-lasting effects of anti-dNTM drugs, and the dNTM-induced low-level chronic immune activation. The latter could influence T-cell life span [5] and diminish bone marrow function through TNF-alpha and transforming growth factor (TGF)-beta released by activated dendritic cells, natural killer cells and T cells. As outlined by Katzschner et al., further multicenter studies are needed [1]; they should be international, prospective, and involve investigation of different immune cell populations/subpopulations and of cytokines in blood, bone marrow and lymphatic tissues.

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Ethical approval

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Author contributions

All authors contributed to drafting, reviewing, and providing final approval of this letter.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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