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Commentary

Early antiretroviral treatment of infants to attain HIV remission: Not just a matter of timing

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Over the past few years, the concept of HIV remission has arisen and sparked expectations towards an HIV cure. Several HIV-infected adults and children have shown sustained control of viral replication after antiretroviral treatment (ART) interruption. In adults, patients initially treated for HIV primary infection in a cohort named "Visconti", were described as "HIV post-treatment controllers" as they had a median 7-year period of undetectable viral load (VL) after interruption of ART [1]. A similar posttreatment control pattern has been reported in approximately 9.5% of adults [2]. In children, a few case reports of posttreatment control have been published [3–5]. The first of them was the "Mississippi Baby"; ART was started very early, 30 h after birth, and continued up to 18 months. Then, the child had an undetectable viral load with a very low cell-associated HIV reservoir for more than 2 years after interruption of the treatment before experiencing viral rebound [4]. In HIV-infected infants, transmission occurs mainly at delivery but also *in utero* during late pregnancy. Thus, compared to adults with a primary infection, ART can be initiated very early after contamination. There is much evidence that early treatment reduces the HIV viral reservoir, particularly latently infected resting CD4+ T cells, in adults and children [6,7]. Moreover, in neonates, the tolerogenic immunological environment of early life could limit immune activation, which would be less favourable for the establishment of the latent infection of T cells [8].

Although the mechanisms of posttreatment control are unclear, it could be hypothesized that a very early effective ART at birth could be the first step to achieving HIV remission. As a proof of concept, Kuhn et al. tested the hypothesis that a substantial number of HIV-infected neonates who initiated ART at < 14 days after birth and were maintained on ART would meet favourable virologic and immunologic endpoints to be included in a further planned analytic treatment interruption trial [9]. Such a trial could subsequently allow the identification of posttreatment controllers. The primary virologic endpoint was VL < 400 copies/ml by 24 weeks after ART initiation and < 50 copies/ml by 48 weeks of age and no confirmed VL > 50 copies/ml after suppression was attained. The primary immunologic endpoint was a CD4+ T-cell percentage > 30% by 24 weeks that was sustained through follow-up. Seventy-three HIV-infected neonates were included. At 48 weeks, just over half of the followed patients attained and sustained a VL <50 copies/ml, and half of these patients sustained a CD4+ T-cell percentage > 30%. Moreover, the proportion of infants who achieved the primary endpoints was similar in the infants treated before 48 h and the infants treated between 48 h and 14 days. Thus, despite very early treatment, the number of children meeting the study virologic and immunologic endpoints was low.

The main finding from this study was that the precocity of ART initiation was not itself sufficient to achieve the virologic and immunologic prerequisites to consider a treatment interruption. Of course, this study does not question the need for early treatment in HIV-infected infants, which is associated with an indisputably clinical benefit compared to delayed treatment. However, it raises many questions about the possibility of reaching HIV remission through a posttreatment control period. First, in infants, achieving an undetectable VL is more difficult than in adults. In addition to the inappropriate galenic form and poor palatability of ART, starting a planned lifelong treatment just after birth might lead to adherence difficulties. Second, *in utero* HIV infection of infants could be associated with immunological damage, such as early thymic dysfunction, which was not evaluated in this study and could prevent the achievement of immunologic endpoints. Third, because the immune system is immature in young children, a longer ART than 48 weeks in this study, might be necessary to achieve an optimal balance between a small pool of infected cells and potent specific immune responses. Fourth, it cannot be excluded that a very early treatment initiation might reduce the duration of exposure to viral antigens able to induce specific T and memory B cell responses, which could contribute to reducing the pool of infected cells and maintaining a status favourable for posttreatment control. Finally, two case reports of posttreatment control suggest that factors other than the early initiation of ART

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could be involved in HIV remission, as ART was started at 2 and 4 months of age in these cases [4,5]. These two cases are almost similar to the "Visconti" patients with very weak HIV-specific CD8+ T cell responses, which differentiated the profile of posttreatment controllers from the spontaneous HIV controllers or the "elite controllers" described in cohorts of patients naïve to treatment [10]. In elite controllers, the HIV-specific CD8+ T cell response seemed to be restricted by "protective" MHC class 1 molecules, that were not present in the two paediatric cases, one of them even displaying a pattern considered to be disadvantageous for HIV progression [10].

HIV remission is associated with many unresolved questions. This study shows that early initiation is not itself sufficient to attain an appropriate virologic and immunologic status to hope HIV remission after ART interruption. Finally, such study reflects the complexity of posttreatment control, likely involving subtle interactions between virologic, immunologic and host factors.

Declaration of Competing Interest

No conflicts of interest to declare (AF).

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