Can we avoid treatment interruption studies in the search for an HIV cure?

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Although combined antiretroviral therapy (cART) is able to achieve sustained control of viral replication in blood plasma and to significantly reduce HIV-associated mortality and morbidity, it cannot, to date, yield viral eradication. Indeed, during the earliest phases of primary HIV infection (PHI), HIV establishes a reservoir in its target cells, particularly in the $CD4^+$ memory T-cell subsets [1,2]. The half-life of these latent cells can reach up to several years and supplies to the persistence of the infection. cART has small or no impact on this cell-associated HIV-DNA (CA-HIV-DNA) even after several years of sustained viral suppression [3,4]. In addition, anatomical sites, such as the male genital tract [5,6] and the central nervous system [7], may also act as viral sanctuaries, contributing to HIV persistence despite cART, partly because of the poor penetration of antiretroviral drugs in these anatomical compartments [8]. Thus, cART is a life-long treatment for people living with HIV (PLHIV). Although new generation antiretroviral drugs are more potent, better tolerated, and with a lower pill burden, concerns still remain about long-term toxicity of these drugs, the need for long-term adherence to cART to avoid the emergence of HIV resistance, and cost issues, especially in low-income countries with a high prevalence of PLHIV. Thus, one of the major goals of researchers in the field of HIV infection is the evaluation of new strategies to achieve a cART-free remission of HIV infection. In this issue, Li *et al.* [9] address the critical roles of treatment interruption studies and biomarker identification in the search for an HIV cure. Achieving HIV eradication or at least a cART-free remission has been indeed priority issue in the research field of HIV infection since the last decade. HIV cure has been achieved in one single case, in the Berlin patient [10]. This patient remains free from HIV in blood plasma as well as in HIV target cells and in anatomical compartments several years after cART discontinuation following two total body irradiations and two allograft marrow transplantations from a donor who was homozygous for CCR5 Δ32 deletion [11]. Unfortunately, such a cure strategy did not prove to be reproducible to date, particularly with graft from donor with wild-type CCR5-positive cells [12,13]. There are two other populations of PLHIV that achieved HIV remission: the HIV controllers, who control spontaneously viral replication [14] and the posttreatment controllers (PTC), in whom cART was initiated early during PHI, and who were subsequently able to control viral replication for several years after cART interruption [15]. The first population exhibits specific host genetic and immune features, whereas the latter population does not [15,16]. Finally, a small proportion of patients treated during chronic infection was also able to achieve cART-free remission [17]. The only way so far to identify PTC or PLHIV able to achieve such a cART-free remission is through cART interruption.

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As mentioned by Li *et al.*, cART interruption usually yields viral rebound, thus raising concerns about patient safety [18], replenishment of HIV reservoirs [19], selection of HIV drug resistance, and increased risk for HIV transmission [20], especially if treatment interruption duration is long. Li *et al.* therefore propose an appealing strategy of monitored antiretroviral pause (MAP) using the time to first detectable viremia rebound as the primary outcome. In such a MAP study, participants would be monitored intensively after cART is stopped (i.e. three times a week viral load monitoring), and cART would be restarted as soon as the viremia threshold is reached. They also propose a series of biomarkers to identify the best candidates for such a MAP.

Total CA-HIV-DNA measured in peripheral blood mononuclear cells (PBMCs) is, to date, the most widely used marker. Indeed, a common feature of HIV controllers, PTC and PLHIV treated during the chronic phase of infection who were subsequently able to achieve cART-free remission, is their low total CA-HIV-DNA load in PBMC [14,17,21]. However, many authors have raised the issue of the composition of this total CA-HIV-DNA, that is, the proportion of defective proviruses [22]. Nevertheless, the level of total CA-HIV-DNA correlates with disease progression [23] and with the time to viral rebound after cART interruption [24]. Cell-associated HIV-RNA, which may be considered as the 'active reservoir' in patients with full plasma viral suppression on cART, has recently proved to be a promising marker [25]. Finally, viral outgrowth assay, although relevant, is not easy to perform because it is time-consuming; it needs specific equipments and a large quantity of blood drawn from the patients [26]. Other relevant markers could be the overall cumulative viremia (provided that data are available since PHI) and the duration of fully suppressed blood plasma HIV-RNA using ultrasensitive assays (with a lower limit of quantification as low as 1 copy/ml).

Host markers can also be used to identify the best candidates prior to enrolment in such MAP studies: human leukocyte antigen status, presence of CCR5 Δ32 deletion, and presence of specific $CD8^+$ T-cell anti-HIV responses. As suggested by Li *et al.*, the most appropriate marker may differ by the class of intervention. Patients who were diagnosed at the time of PHI and who initiated cART then and maintained it for a prolonged period might also be good candidates with regards to recent results suggesting that the earliness of cART initiation during PHI is key to achieving low levels of CA-HIV-DNA [27].

The ideal approach would be to be able to identify markers that would serve as outcomes without the need for cART interruption. In the mean time, to date, the only way to address the search for an HIV cure is through cART interruption. MAP studies design proposed by Li *et al.* allows for intensive monitoring and strict criteria for cART resumption. One critical point is the risk of viral transmission to the partner(s) during cART interruption. This information is very difficult to collect during trials but should be comprehensively documented and communicated [28]. The study design should also include the active participation of the regular(s) sexual partner(s) to comprehensive counseling and interventions to reduce the risk of HIV transmission, such as a preexposure prophylaxis offer to the negative regular(s) partner(s) [29].

Finally, one should keep in mind the ethical aspect of enrolling patients in these intensive – and sometime aggressive – studies with regards to the current excellent quality of life of PLHIV on well tolerated and less burdensome modern cART.

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Conflicts of interest

There are no conflicts of interest.

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