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The critical roles of treatment interruption studies and biomarker identification in the search for an HIV cure

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Role of antiretroviral treatment interruption studies in HIV cure research

The evaluation of new therapies to achieve an antiretroviral therapy (ART)-free remission of HIV infection will require demonstration of efficacy through ART interruption studies. However, there are concerns about stopping ART, including patient safety, selection of HIV drug resistance and increased risk for HIV transmission. In this article, we highlight the importance of identifying biomarkers of ART-free remission for cure research and present an updated approach to treatment interruption that should identify predictive markers while minimizing negative consequences for participants. The proposed approach, termed an intensely monitored antiretroviral pause (MAP), has the potential to accelerate progress towards an HIV cure.

Learning from past treatment interruption studies

Initially, ART interruption studies were performed either to reduce ART exposure with the hope of prolonging the durability of ART regimens and minimizing side effects or as a therapeutic intervention to induce long-term ART-free HIV remission [1]. These studies were spurred by a report published in 1999 of a patient who achieved ART-free HIV remission after several patient-initiated treatment interruptions. To assess the potential benefits of treatment interruption and reduced exposure to anti-retrovirals, a large treatment interruption trial, known as the SMART study, was conducted [2]. Unfortunately, the study demonstrated that participants who underwent prolonged treatment interruption had significantly increased risk of opportunistic disease, cardiovascular and other non-AIDS defining events, and death [2]. As a consequence, treatment interruption strategies were largely abandoned, especially with the advent of better tolerated ART regimens. The results of the SMART study have continued to colour the perceptions of the risks involved in treatment interruption studies despite the SMART study's limited generalizability to newer treatment interruption studies designed to evaluate HIV curative strategies.

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Conflicts of interest

J.Z.L. has served as a consultant for Quest Diagnostics, SeraCare Life Sciences and TherapyEdge. J.W.M is a consultant to Gilead Sciences and a shareholder of RFS Pharmaceuticals. D.M.S. has served as a consultant for Hologic and Testing Talent Services.

There are key aspects of the SMART study that largely contributed to the negative outcomes of treatment interruption and can be avoided when conducting treatment interruptions to evaluate a curative strategy [3]. In the SMART study, participants underwent repeated cycles of prolonged ART interruption with limited monthly postinterruption monitoring. In contrast, treatment interruption studies aimed at understanding viral rebound generally require single, shorter durations of ART interruption and significantly more frequent plasma viral load monitoring after interruption. There are generally two types of ART interruption study designs used today to test potential HIV curative interventions. Over the past decade, the most common study design has a preset duration of ART interruption (e.g. up to 24 weeks of treatment interruption) with the viral load set point, $CD4^+$ cell count or ART reinitiation as the primary efficacy outcomes [4–7], and such studies have generally had an excellent safety record. However, these studies still expose participants to extended periods of viremia, which raise concerns about replenishment of HIV reservoirs, HIV transmission [8], immune damage and clinical risks [9,10]. By contrast, a carefully MAP can be designed to minimize potential risks to the participants by using the time to first detectable viremia rebound as the primary outcome. In such a MAP study, participants would be monitored intensively after treatment is stopped, and ART would be restarted as soon as the viremia threshold is reached. A preliminary study of this type has already been conducted by Rothenberger *et al*. [11] in a small number of individuals treated during chronic infection. In this study, 12 patients underwent a treatment interruption with subsequent three times a week viral load monitoring and restarted ART within 5 days of their plasma viral load becoming detectable. The authors noted no clinical symptoms in any patient and all participants had rapid viral suppression after ART reinitiation [11]. This type of intensive posttreatment interruption study design has also been used in the monitoring of viral rebound after haematopoietic stem cell transplantation [12]. This study design reduces the duration of viremia, especially for individuals whose immune systems are functionally naive to HIV (e.g. those treated during acute infection or have undergone a bone marrow transplant) and are at a greater risk of high-level viremia and acute retroviral syndrome [12,13]. In addition, treatment interruption studies have led to the discovery of posttreatment controllers (PTCs) who exhibit sustained HIV suppression despite the lack of protective human leukocyte antigen (HLA) alleles [14]. Elucidating the mechanisms of viral control in these PTCs may lead to novel approaches for inducing sustained ART-free HIV remission in the general HIV-infected population.

Biomarkers of HIV disease and implications for curative strategies

The discovery of biomarkers for HIV disease progression was instrumental in discovering effective ART and improving clinical care. One major advance was the identification that plasma HIV RNA levels predicted the risk of HIV disease progression and that reducing these levels (i.e. viral load) was associated with reduced risk of disease progression [15,16]. Prior to 1997, the approval of ART required reduction in clinical endpoints, including AIDS-defining events and death. These studies typically required thousands of participants and years of follow-up. In 1997, the U.S. Food and Drug Administration (FDA) agreed that plasma HIV RNA could serve as primary endpoints for FDA-registration trials [17]. This

change allowed for smaller and shorter trials, improved participant acceptance and significantly accelerated HIV drug development.

As the HIV field increasingly turns towards developing therapies to achieve sustained ART-free HIV remission, biomarkers that can reliably predict meaningful outcomes are once again urgently needed. Therapeutics to achieve a sterilizing or functional HIV cure will require initial validation in treatment interruption trials, but the risks, expense and required duration of the treatment interruptions are obstacles for their use in early-phase clinical studies and a barrier for investment from the pharmaceutical industry. The discovery of virologic, immunologic, host or other biomarkers of the duration of ART-free remission could greatly streamline the allocation of limited resources and avoid the exposure of patients to ineffectual and potentially toxic therapies. In a small MAP study of participants treated during chronic HIV infection, the duration of infection, length of ART suppression and $CD4^+$ cell count nadir were significantly associated with time to viral rebound [11]. In addition, an analysis of SPARTAC trial participants who received ART during primary infection, levels of total HIV DNA were predictive of time to viral rebound during an ATI [18]. Finally, a recent pooled analysis of treatment interruption studies from the AIDS Clinical Trials Group demonstrated that the size of the active HIV reservoir, as reflected by cell-associated HIV RNA (CA-RNA) and residual plasma viremia, was predictive of the timing of viral rebound after treatment interruption [19]. These findings suggest that biomarkers can be identified that are predictive of outcome after MAP [20].

Biomarkers currently used to evaluate HIV curative strategies are generally categorized as either reflective of the size of the HIV reservoir [21] or host immune response to HIV. The most commonly used biomarker of HIV reservoir status is cell-associated HIV RNA and it has been used to reflect the efficacy of HIV latency-reversing agents, including the histone deacetylase inhibitors (HDACi) vorinostat [22], romidepsin [23], panobinostat [24], among others [25]. Other commonly used biomarkers of viral persistence include levels of residual plasma viremia [22,24], cell-associated HIV DNA [24,26] and quantitative viral outgrowth assays of infectious virus [27]. Although there is evidence that levels of HIV DNA and RNA may predict viral rebound kinetics after treatment interruption [18,19,28,29], data are very limited for the other HIV reservoir biomarkers, and the optimal HIV reservoir biomarker for the prediction of time to viral rebound off ART is still unclear.

Host immune factors associated with control of viral rebound have been most closely studied in HIV elite controllers, whose viral control is associated with strong HIV-specific T cell activity [30]. Similarly, HIV-specific T cell responses have been associated with posttreatment interruption viral load set point in several therapeutic vaccine studies [5,6] and in the spontaneous control of HIV [31]. Other immune factors being evaluated as potential biomarkers of HIV persistence and post-ART viral control include HIV antibody levels, and natural killer cell and dendritic cell profiles. All of these immunologic factors represent potentially promising biomarkers that should be evaluated as predictors of time to rebound during MAP studies.

Given the number and diversity of available biomarkers, the systematic evaluation of the optimal biomarkers to predict post-ART viral rebound kinetics should be a high priority for

the field. Although biomarkers are an integral part of drug development programmes, it should be noted that the reliance on biomarkers entails limitations and risks. The most appropriate biomarker may differ by the class of intervention. For example, the optimal biomarker for a latency-reversing agent may differ from that of a therapeutic vaccine or gene-modifying therapy. It is also possible that combinations of biomarkers will be needed to achieve the optimal sensitivity, specificity and predictive value that are unattainable by any one biomarker. It is therefore vital that the validation of potential biomarkers be performed in multiple phases, including preclinical exploratory studies to identify potentially useful markers, retrospective or prospective studies to correlate the biomarker with outcomes, and controlled studies to confirm that changes in the biomarker are associated with improved outcome. These steps were used in the validation of plasma HIV RNA as a surrogate endpoint by showing the correlations between HIV RNA levels and clinical outcome [15], as well as the relationship between HIV RNA suppression and clinical response [16].

Identifying a biomarker that is able to reliably predict time to viral rebound when ART is stopped could greatly accelerate the engagement of industry and other stakeholders in HIV cure efforts. The process of identifying and validating such a biomarker will require some risk to participants who are willing to volunteer to have their ART stopped for this effort. Therefore, such endeavours must proceed with caution and as safely as possible. Further, overcoming these challenges will require a multidisciplinary effort with an input from all stakeholders, including academia, industry and regulatory agencies, but these hurdles can be overcome with collaborative and systematic effort as an integral part of the quest for a cure of HIV.

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