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SUPPLEMENT ARTICLE

How Unavoidable Are Analytical Treatment Interruptions in HIV Cure–Related Studies?

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In this discussion, 2 established researchers and clinical trialists debate their opposing views on the utility, benefits, and risks of the use of analytical interruption of antiretroviral therapy as a clinical trial end point and outcome measure in human studies seeking to induce remission of or eradicate human immunodeficiency virus infection.

Keywords. Analytical treatment interruption; antiretroviral therapy; viral outgrowth assay.

FOR THE TIME BEING, CAPITALIZING ON SENSITIVE ASSAYS MAY REMOVE THE NEED TO RISK HUMAN IMMUNODEFIENCY VIRUS (HIV) TRANSMISSION IN MANY CURE-RELATED STUDIES: DAVID MARGOLIS' PERSPECTIVE

Antiretroviral therapy (ART) interruption poses risks to both study participants and their sex partners. It is the ultimate way to assess whether an intervention has achieved either human immunodeficiency virus (HIV) eradication or tight restriction of HIV replication, but thus far, no practical intervention short of transplantation protocols has substantially reduced the frequency of latent persistent infection. Therefore, in the near future it is unlikely that any intervention(s) will achieve a cure or a clinically relevant viral remission of HIV [1, 2]. Further, the phenomenon of "posttreatment control" has recently been recognized in a small minority of HIV-infected participants without any intervention but standard ART [3]. Therefore, studies aimed at achieving clinically relevant viral remission, defined as periods of clinical aviremia without ART that are measured in months to years, require large study groups with sham treatments or placebo arms and extensive monitoring and follow-up, exacerbating the burdens and risks for the study participant.

However, tractable assays are already available to directly or indirectly measure latent, persistent infection and can be used in intensive, single-center studies [4–7]. While such assays are not simple or cheap, they should be the end point of current cure-related studies. There is no need to interrupt ART and deal with the attendant risks of viral rebound for the study participants and their partners. Only if substantial depletion of persistent infection can be demonstrated in these near-term studies should further studies that include ART interruption as an end point be considered.

If the goal of interventions is to create drug-free remission without viral eradication, it is prudent to first ask whether people with immune-based viral control experience adverse health effects due to the need to mobilize chronic antiviral immune responses [8, 9]. This concern is serious enough to warrant a study that compares health outcomes between those who initiate ART and those who do not, in a cohort with long-term innate control of HIV infection. Nevertheless, there may be some HIV-positive people who are now willing to undergo the risks of an analytical treatment interruption (ATI) for the sake of a research protocol aimed at inducing control of viremia, not cure. Such protocols must then deal with the challenges that were previously faced by therapeutic vaccine protocols: How much viremia during ATI will be tolerated? For how long? How will this be monitored? Study designs might mitigate some concerns by using laboratory assays and reserving ART interruption for study participants demonstrated to have gained an antiviral response that may lead to viral control.

Overall, it is important to be realistic about the current state of HIV cure science. Considering the risks of ATI to participants, their sex partners, and any other individuals later exposed in a potential chain of HIV transmission, the scientific benefits of a study must be substantial to justify a study that includes ATI, even if clinical safety parameters can be met for the individual participants. Given the early state of cure research and the low likelihood that anything tested in the near future is likely to have clinical benefits, research should first focus on measurements of progress that can be achieved without ATI. The serious risks

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to study participants, as well as to nonparticipants, demand nothing less.

WITH APPROPRIATE PRECAUTIONS, ANALYTICAL TREATMENT INTERRUPTIONS REMAIN UNAVOIDABLE IN SOME CURE-RELATED STUDIES: STEVEN DEEKS' PERSPECTIVE

ATIs carry risks to participants and to nonparticipants, but there is no substitute for them if we are to make progress toward a cure for HIV. Cure-related assays do not directly measure the relevant reservoir (eg, the replication-competent virus population that initiates new rounds of infection). Even assays that probably provide reasonable, albeit unproven, quantification are laborious, have limited range, are difficult to apply to tissue specimens, and have yet to be validated. Immunologic assays that might predict remission are also lacking, in part because the correlates of posttreatment control remain unknown. Even if a promising virologic or immunologic assay emerged, the clinical trials necessary for its validation as a legitimate surrogate marker do not exist.

Given the lack of a valid surrogate marker for cure-related research, the only real option is to rely on validated surrogate markers of the disease, namely plasma HIV RNA levels. Since the goal of any curative intervention is to extend the degree of ART-free virus suppression, the inconvenient truth is that there really is no viable way to truly define how a drug works other than to interrupt therapy and measure the outcome.

Only heroic interventions such as stem cell transplantation [10] or very early ART [11, 12] have moved the dial in terms of time to rebound, stemming either from the failure of most interventions to affect the reservoir size (the likeliest explanation) or from the insensitivity of this outcome to anything short of a multiple-log reduction in the reservoir [13]. I agree that, for interventions that are not expected to affect time to rebound and for which other outcome measures are available (eg, virus production in the case of latency-reversing agents), ART interruptions are unnecessary and should be avoided. However, in contrast to reservoir-reducing interventions (ie, those that seek to alter the postinterruption set point), the correlates of posttreatment control are not known, and an interruption of ART is often necessary.

Risks to study participants from treatment interruptions are generally well known and easy to quantify. Truly informed consent is possible because most study participants have experience with both treated and untreated HIV and an instinctive understanding regarding the risks of interrupting therapy. This contrasts with the substantial, new, and often difficult-to-quantify risks of the many curative interventions being tested. When done in a well-resourced and highly monitored setting, many of these risks to study participants can be mitigated. Risks to sex partners are also known, but how to inform those partners and how to reduce that risk remain to be defined.

In summary, because no biomarker for cure research exists, we need to turn to other outcomes. Although ATIs have many limitations, they are informative, and their risks for participants and, to some degree, for nonparticipants, can be managed through informed consent and careful monitoring.

RESPONSE TO STEVEN DEEKS, BY DAVID MARGOLIS

The statement that viral outgrowth assays have yet to be validated is simply wrong [5–7]. The harsh reality is that substantial depletion of persistent infection—a change that would register as an indisputable success in viral outgrowth assays—has thus far only been achieved by the heroic interventions mentioned, such as early ART or bone marrow transplantation. And while in some cases even these interventions did not substantially delay rebound, at least the favorable assay metric justified the hope that there might be a delay. At the same time, it appears likely that, at minimum, a result of such magnitude would be required, to induce a very durable viral remission or even viral eradication. Until such an early signal of success is achieved, only careful, costly, demanding studies of cure-related interventions should be done, and they should be limited to small, extensively monitored cohorts.

However, if cure is not the goal of an experimental trial, and all that is sought is control of viremia without ART, then that is another matter. Individuals participated in therapeutic vaccine studies over a decade ago with the goal of replacing ART. These were never presented as studies to achieve cure or remission. In such studies, assays to measure the frequency of persisting viral infection might or might not be useful. And in such studies, then and now, the issue of the infectiousness of participants following an ATI must be dealt with.

RESPONSE TO DAVID MARGOLIS, BY STEVEN DEEKS

The question of whether the current assays are "validated" depends on definitions. The field desperately needs an assay that can be used as the primary end point in the emerging spectrum of cure-related clinical trials. For such a biomarker to be transformative, the field will need to prove that changes in the measurement predict the clinical effectiveness of the intervention. A "chicken and egg" problem exists, however, in that we need an effective intervention to validate the capacity of a measurement to predict any treatment effect.

The plasma HIV RNA assay is a classic example of an effective surrogate marker. Once it was shown that changes in HIV RNA predict changes in morbidity and mortality [14], drug discovery and development became far easier, leading to where we are today, with dozens of approved drugs.

Given the experimental nature of most ongoing "probe" studies, using potential biomarkers such as the virus outgrowth assay or the next generation of DNA assays may be reasonable,

particularly for interventions aimed at reducing the reservoir, but how informative they truly are is not yet known.

A carefully performed treatment interruption will always provide valuable data regarding how an intervention works. These studies will also provide an outcome measure to help discover and validate any reservoir measurement. The only compelling reason not to do them is safety. In this clinician's experience, it is easy to explain the direct risks to the participant and the indirect risks to their sex partners. It is also easy to predict and manage any direct complications experienced by the participant if resources are available to do very careful monitoring. In contrast, it is not easy to explain risks to and manage them in sex partners, because partners are often not involved in the consent process and may not even be aware the study is happening. Our approach is to provide as much education as possible to the participant and to refer interested partners to local services that provide preexposure prophylaxis and other interventions. The time may come when those who fund and perform these studies will need to provide preexposure prophylaxis and other services to any and all partners. This may require separate protocols and consent forms and will require significant resources. The prevention field has struggled with similar issues and may be able to provide guidance on how those doing cure research should proceed.

Notes

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