Curing HIV: Moving Forward Faster

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Abstract

There is enormous enthusiasm in the scientific community for finding a cure for HIV. Although much remains to be discovered regarding the mechanisms of viral persistence and how it may be disrupted, some assumptions regarding the goals of a cure, applicability to target populations, and what is required of the assays we employ, may lead to missed opportunities and discoveries and hamper the discovery of a product that will safely cure tens of millions of HIV-infected people around the world. The field will benefit from an awareness and critical interrogation of assumptions that may be implicit in their scientific pursuits.

HIV CURE RESEARCH has gained enormous momentum since the acceptance by the field that the “Berlin Patient”¹ represented the first case of cure. Researchers are working toward a number of different modalities to cure HIV, ranging from immunological and pharmacological to gene therapy. Attendant on these approaches are a number of assumptions that may need to be closely examined.

Is a Functional Cure, or Remission, Good Enough?

An HIV cure has been thought of as either “sterilizing,” achieved by ridding the body of any replication-competent HIV, or “functional,” in which virus that persists is controlled in the absence of antiretroviral therapy (ART). Increasingly, researchers are speaking of a remission as a more achievable outcome, during which virus remains undetectable for a protracted period until rebound.

One assumption is that a functional cure or remission will represent an improvement in the health and well-being of an HIV-positive person. However, a functional cure necessarily means that HIV remains in the body even if viremia is suppressed. Evidence over the past several years suggests that elite controllers (ECs), the rare group of people who are able to control their virus without the use of ART, are more susceptible to comorbidities and are hospitalized more often than HIV-negative people.^{2–4} It is thought that cryptic viral processes, including low-level replication,⁵ lead to immune activation resulting in higher incidence of cardiovascular disease and other morbidities.^{6–9} The recognized effects of immune activation in ECs have led to new recommendations by some in the field to start these patients on ART to prevent the associated comorbidities of the activated immune system.^{2,10,11}

Remission, a term coopted from the cancer field, refers to an atypically protracted period¹² after ART withdrawal, during which the virus remains undetectable and is thus presumed to be doing no harm. Such remission was achieved in the two Boston patients¹³ as well as the Mississippi child.¹⁴ However, these patients, as with ECs, may be susceptible to immune activation and comorbidities associated with a persisting viral reservoir. In addition, in the absence of biomarkers of imminent rebound, patients are at risk of significant adverse consequences if and when such a recrudescence occurs.¹³ Achieving remission without knowing if or when the virus will rebound may thus impose the need for *more* frequent monitoring than is currently necessary for patients on ART. Current estimates proposed by Hill *et al.* at the sixth Annual HIV Persistence during Therapy meeting in Miami suggest that patients must be tested at least four times a week during the first 7 weeks of therapy to be sure of viral suppression.¹⁵ While in this model, the need for testing decreases as time on remission increases, even a person on remission for 1.5 years may still be required to undergo bi-monthly testing. Thus, a “cure” with these constraints and the medical and social complexities of possible viremia may not be a desirable cure.

Is a functional cure or remission a satisfactory goal? Will it be “good enough” for the 36.9 million people living with HIV/AIDS (PLWHA)? Recent small surveys conducted primarily in men who have sex with men suggest that, while they are interested in promoting cure research by participating in cure trials, by and large they are motivated by the hope of a sterilizing rather than a functional cure. A 2012 study of 458 respondents found that 84% thought a sterilizing cure desirable compared with 51% and 56% who found remission

or a functional cure desirable, respectively.¹⁶ More recently, a 2014 UK-based study found that 91% favored a sterilizing cure versus 60%–70% who favored a functional cure.¹⁷ Thus, the assumption that *any* form of cure to HIV will be desirable both to patients and their caretakers should be reexamined.

Is Precise Measurement of the Reservoir Necessary or Sufficient to Evaluate an Intervention?

The hallmark of any definition of a cure is a delay to pathology-associated viral rebound following treatment interruption. In the case of a sterilizing cure, the delay to rebound results from the absence of replication-competent virus, whereas in a functional cure, the delay to rebound is due to enhanced immune control or virologic silencing.

Assessing delay to rebound requires a voluntary treatment interruption, which may place the patient at risk of acute viral syndrome, increased transmission, expansion of the viral reservoir, or resistance to ART, in addition to more frequent and burdensome monitoring of viral load. Thus, identifying biomarkers that predict rebound delay has been a recent research priority. To this end, negative immune regulators as well as other immunologic readouts^{18,19} have been studied and found to correlate with delay to rebound. However, stronger emphasis has been placed on direct measurement of the viral reservoir under the assumption that a smaller reservoir predicts a longer delay to rebound^{20–22} and a great deal has been invested in accurately measuring the reservoir.²³

The quantitative viral outgrowth assay is cited as the gold standard, but has well-recognized shortcomings,²⁴ whereas measuring proviral DNA itself captures defective as well as replication-competent virus.²⁵ As a result, other assays to measure replication-competent virus have been developed.²⁶ However, is accurately measuring the reservoir sufficient to know whether the curative intervention has resulted in a change that will prolong delay to rebound?

Undetectable measures of proviral DNA or viral outgrowth failed to predict the eventual viral rebound after ART interruption in two patients receiving stem cell transplants¹³ and in the “Mississippi Baby” who also had an undetectable reservoir.²⁷ In other cases, readily detectable viral reservoirs are found in patients who have controlled viremia after ART cessation: the VISCONTI cohort,²⁸ and the more recently described Parisian teenager.²⁹ While the sensitivity of assays to measure reservoir size may be an issue, the apparent stochasticity of rebound^{14,30} suggests that even the most accurate and sensitive measure of reservoir size may not predict delay to rebound. Rather, a combination of biomarkers, perhaps including reservoir size, but also immune function and other, as yet undiscovered, host factors should be more aggressively pursued. To date, few studies looking for biomarkers of delay to rebound include nonhypothesis-driven approaches or look to bridge fields, such as bioengineering, for the development of synthetic biomarkers, although recent mathematical approaches have been intriguing.^{31–35}

Must Viremia be Fully Suppressed to Effect a Cure?

The goal of HIV treatment is the suppression of viremia³⁴ associated with halting the progression to AIDS and/or other comorbidities and a decrease in transmission risk.³⁵ Despite the welcome broadening of the availability of ART, we may never reach a point at which every in-

dividual’s viremia is well suppressed. Will viral suppression be a prerequisite for a cure?

Clinical trials testing shock and kill or gene therapy approaches generally require full viral suppression before the intervention, as a change in viral reservoir size, which is most easily measured in the absence of ongoing viral replication, is usually the primary, or at least a main, trial endpoint (www.clinicaltrials.gov). However, as discussed above, reservoir size—at least as a single measure—may not predict delay to rebound.

Another argument for full viral suppression is that it may be associated with a smaller reservoir and reversing latency in a smaller number of HIV genomes, in the case of shock and kill, may minimize the dose and toxicity of such an intervention, as well as facilitating immune control of viral production from any remaining infected cells. However, it has recently been suggested that latency reversing agents (LRAs) may work more efficiently before a patient starts ART, while viral genomes are actively producing virus,³⁶ a concept that will soon be tested (O. Sogaard, pers. comm. December 28, 2015).

The case for full viral suppression before a gene therapy intervention is not as clear-cut (other than as it pertains to the general health of the study subject). In fact, it has been argued that for some forms of gene therapy (such as the removal of functional CCR5), the withdrawal of ART may facilitate the positive selection of successfully edited cells.³⁷

Since universal viral suppression is unlikely to be achieved, interventions should be tested in a range of viral suppression scenarios.

Will One Size Fit All?

Shock and kill, currently the most widely researched cure approach, relies on LRAs to shock the virus out of latency and immune-modulating approaches to enhance the killing of virus-producing cells. Until recently, analyses addressing whether this approach will be equally effective across all populations have been lacking. A recent study indicated that physiological levels of estrogen can affect the ability of LRAs to reverse latency.³⁸ Other demographic factors, such as race,³⁹ age, duration of infection, or the stage of infection at which ART was initiated, may also affect the success of a cure intervention that relies on the integrity of the immune system.⁴⁰

People who initiated ART early in infection likely have smaller and probably less virally diverse⁴¹ reservoirs, and retain more robust immune function.⁴² It is widely believed that curing people whose reservoirs are small may be an easier place to start, but to the extent that a cure tested in those treated during acute infection relies on a largely intact immune system to control or clear persistent virus, such an intervention may not be efficacious in the vast majority of PLWHA. The converse, however, may not be true. An intervention that relies on (boosted or existing) an immune function that is efficacious in those who started ART during chronic infection is likely to be efficacious in those whose immune function is even better preserved. A faster path to a more widely applicable cure may thus be developed in more typical patients, those who initiated treatment during chronic infection and who have larger viral reservoirs.

In terms of scalability, many believe a pharmacologically based cure, such as shock and kill, would be more practical than one based on cell or gene therapy. While we support the

goal of developing a cure that is available at a reasonable cost to all PLWHA, it may be premature to shift our attention away from a line of inquiry that resulted in the only case of (suspected sterilizing) cure to date. Advances in science, as well as in the political and social landscape, can make seemingly unscalable interventions available around the world. The provision of ART worldwide, once thought unrealistic,^{43,44} is now considered the standard of care⁴⁵ facilitated by advances in science (e.g., one-a-day pill formulations), political commitment (e.g., PEPFAR), and other forces (e.g., manufacturers of generic medications, increases in donor participation).

Conclusions

In these early days of HIV cure research, with only one documented case of apparent sterilizing cure, and a diverse and incompletely characterized smattering of elite and post-treatment controllers, it is difficult to back-validate the tools—including assays as well as *in vitro* and animal models—that the field needs to predict cure efficacy and thus to decide which assumptions are correct. In the absence of such cases, it is too soon to make assumptions that close potentially valuable avenues of research.

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