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Framing expectations in early HIV cure research

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Abstract

Language used to describe clinical research represents a powerful opportunity to educate volunteers. In the case of HIV cure research there is an emerging need to manage expectations by using the term ‘experiment’. Cure experiments are proof-of-concept studies designed to evaluate novel paradigms to reduce persistent HIV-1 reservoirs, without any expectation of medical benefit.

Keywords

HIV cure research; experiments; trials; expectations

When Jerome Horwitz experimented with azidothymidine (AZT) in the early 1960s as a potential chemotherapy for leukemic patients [1], he could not have predicted that the compound would become the first FDA-approved drug to suppress HIV 25 years later. AZT failed to show efficacy in oncology experiments in 1964, but the compound became revolutionary to treat HIV in Horwitz’ lifetime. The example of AZT illustrates the unpredictability of drug development in complex diseases such as cancer or HIV.

Over the 25 years since the emergence of AZT the field of HIV research has evolved towards finding a cure – conferring long-term remission by the elimination of latent HIV proviral reservoirs and/or augmentation of antiviral immunity, resulting in virological suppression in the absence of antiretroviral treatment. Experimental approaches currently being investigated to cure HIV-1 infection in adults involve: (i) highly active antiretroviral therapy (HAART) or megaHAART during acute infection (Fiebig stages I–IV), (ii) the induction of expression by latent HIV viral genomes using latency-reversing compounds, (iii) gene editing to confer innate resistance to HIV via modifications such as the genetic alteration of the chemokine (C-C motif) receptor 5 (CCR5), (iv) administration of broadly neutralizing antibodies, (v) therapeutic vaccines, and/or (vi) combinations of the above.

At this time, clinical experiments in HIV-1 cure research consist of proof-of-concept activities involving no expectation of clinical benefit accruing from the experimental interventions. These experiments nonetheless represent a pivotal step in translational medicine. They allow the transfer of interventions from cell and animal models to initial human testing. The goal of these clinical experiments is to convert basic science discoveries into eventually therapeutic or curative applications. These experiments are also designed to gather scientific information using surrogate endpoints (or, less often, clinical endpoints) and evaluate hypotheses in small groups of patients using the paradigms of experimental medicine. These efforts allow scientists to assemble the tools and the methods necessary to prepare for future HIV-1 cure clinical studies.

In this context, what is the best term to describe HIV-1 cure research? Almost two decades ago an investigation into human radiation experiments in the USA documented that patients have very different responses to language associated with medical research. Interviews found that terms such as ‘clinical investigation’ and ‘study’ are judged to convey less uncertainty and greater chance of personal benefit than ‘experiment’ – which is linked to unproven treatments of greater risk, and often invokes the image of human ‘guinea pigs’ [2]. Since then, considerable research has documented that participants in early-phase clinical experiments are often highly susceptible to underestimating risk and overestimating possible medical benefits [2]. Therefore, we argue that it is time to start using the term ‘experiment’ when it is the most appropriate label, and highlight the fact that altruistic HIV-positive patients are volunteers in experiments that will contribute to translational science but not to their own personal benefit. In fact, early-phase HIV cure research is often designed as small parallel experiments to evaluate novel molecules and/or repurposed drugs, such as those borrowed from oncology research. The knowledge gained from these proof-of-concept experiments is highly cumulative and iterative. Hypotheses are usually tested, rejected, and regenerated at every stage.

Although several different types of designs and modalities are currently included under the umbrella of HIV cure research, most are safety experiments with efficacy endpoints of uncertain validity, and are thus too weak to claim any relationship to expected therapeutic benefits. The calculation of potential risk of harm from participation in early-phase HIV-1 cure experiments is often uncertain (involving both known and unknown risks), and may be unfavorable when compared with standard treatment (e.g., ART for individuals with long-term viral suppression). Risks might be compounded if an HIV cure experiment involves an analytic treatment interruption (ATI), a research strategy recently repackaged under the term ‘intensively monitored antiretroviral pause’ (IMAP). The treatment interruptions may be necessary to assess the effect of the pilot experiments and determine whether HIV viral rebound is recurrent, delayed, or remains absent following the intervention. Even in HIV-1 cure experiments not requiring treatment cessation, the prospect of benefit to participants may remain low to nonexistent. Early-stage or pilot experiments then differ from later-stage clinical studies, which may entail some expectations of positive clinical effects or a proof of true clinical efficacy. In the case of latency-reversing agents, for example, scientists are measuring molecular effects *in vivo* – such as reactivation of the expression of the latent proviral HIV-1 genome. Whether such an intervention, which is thought to be a required

first step in purging persistent, latent infection, will lead to the reduction of the size of the latent reservoir, and whether a partial reduction that does not clear all latent infection would confer a direct clinical benefit remains highly uncertain. In these and other cure experiments, benefit is evaluated in terms of the production of scientific knowledge for society and not for the individual patient.

We have learned a great deal from past HIV-1 cure clinical experiments that started in the 1990s, shortly after the advent of antiretroviral treatment. Because most of these experiments have represented early clinical testing, the safety aspect has been at the forefront of investigation. For example, in 1999, Prins and colleagues [3] found that reversing HIV latency using global T cell activation was too toxic and harmful for HIV-positive patients. This study involved three HIV-positive patients receiving potent ART, who were treated with a combination of recombinant interleukin 2 (IL-2) and Muromonab-CD3 (OKT3), a murine monoclonal antibody of the immunoglobulin IgG2a isotype. Periodic ART interruptions, a paradigm for current ATI, were tested as a treatment strategy in the SMART study [4], and showed clear evidence of harm, even in patients with near-normal CD4 cell counts. Clearly, safety assessments should remain a priority in early-stage cure experiments, and are as important as other clinical endpoints – such as those related to efficacy or surrogate efficacy. Although safety assessments are not inherently tied to the use of the term ‘experiments,’ scientists should take all measures possible to ensure that the principles of safety and nonmaleficence are respected.

There is only one known case of definitive HIV cure that involved a unique set of circumstances, yet to be replicated. Timothy Brown, ‘the Berlin patient’ [5], received high-dose induction and consolidation chemotherapy and engraftment with allogeneic stem cells from a donor who was homozygous for the CCR5 $\Delta 32/\Delta 32$ mutation [5]. In this patient, complete chimerism was achieved and the therapy resulted in a sterilizing cure with complete reconstitution of CD4⁺ T cells at the systemic level.

By contrast, in July 2014, researchers announced that the child in Mississippi, known at the time as the ‘Mississippi baby,’ presented with viral rebound after being seemingly ‘cured’ of HIV infection by the administration of ART (<http://www.niaid.nih.gov/news/newsreleases/2014/pages/mississippibabyhiv.aspx>). The child had previously received ART 30 h after birth and was treated for several months. The child then presented, following ART cessation, with undetectable levels of HIV-1 plasma RNA (pRNA) and proviral DNA at 28 months of age [6]. Although evidence of HIV infection remained undetectable for 27 months without ART, this case of prolonged HIV remission proved to be a ‘transient cure.’ By contrast, the Canadian HIV Research Network reported a failure to cure a newborn treated in very similar circumstances (<http://news.ca.msn.com/top-stories/hiv-cure-for-babies-tested-in-canada>). These cases of viral rebound in infants remind us of the need to tread cautiously in the search for a cure. Issues pertaining to HIV cure experiments in infants may require special consideration. These experiments also teach us that we must plan for long-term follow-up and close monitoring of patients following treatment cessation.

One modality currently being investigated in HIV-1 cure experiments involves the use of latency-reversing agents. This method may represent the safest, most scalable, and

accessible strategy to eradicating HIV-1 in the longer term. Latency-reversing agent experiments are performed with the intent of disrupting HIV latency without inducing global T cell activation and without disrupting the host gene expression program. The selected compounds also need to have acceptable toxicologic and pharmacological properties. Scientists are considering the use of compounds and/or biologic agents in combination to create optimal synergies for induction and clearance, as well as serial disruption of HIV latency, similarly to serial rounds of chemotherapy for cancer patients.

Latency-reversing agents are the most developed approach currently under study in the several HIV-1 cure clinical experiments, which nevertheless are still few in number. These experiments involve a group of compounds, the histone deacetylase inhibitors (HDACs), that are already in use or under investigation as anticancer drugs. A pioneering proof-of-concept experiment published in 2005 involved the use of valproic acid (an HDAC inhibitor) in four HIV-positive volunteers taking ART [7]. More recently, Dr Archin and colleagues validated HDAC inhibitors as a therapeutic class to disrupt HIV latency by directly measuring this effect in patients [8]. This study involved eight volunteers treated with a single dose of Vorinostat, and showed a 4.8-fold increase in HIV RNA expression in resting CD4⁺ T cells. Building on this experiment, Dr Archin and colleagues evaluated serial dosing of Vorinostat in five volunteers to explore the ability to disrupt latent infection repeatedly [9]. Although the magnitude of reinduction from resting CD4⁺ T cell-associated HIV RNA was reduced compared to that following single-dose Vorinostat, this experiment allowed the refinement and redesign of current ongoing research. In concert with latency-reversing agents, scientists are investigating immune-based therapies to ensure an effective immune response to clear infected cells. Vaccines to enhance the HIV-specific immune response may offer an encouraging approach. Alternatively, HIV-specific immune cells could be expanded *ex vivo* and reinfused into HIV-infected patients, an approach similar to that used in oncology for selected viral infections [10].

Undoubtedly, ongoing HIV-1 cure research experiments described above will provide scaffolds to spur the development of therapies that might eradicate HIV-1 infection. Framing these studies as clinical experiments rather than as clinical trials, investigations, or studies helps us calibrate expectations of what is possible at this stage. This cautionary approach also takes into account that a cure for HIV might come from the basic and translational sciences – as revolutionary treatment came from the surprising application of AZT. Although we remain hopeful that a cure is within reach, we should be reminded that we are still in the early stage of HIV cure research and at the dawn of a new phase for HIV therapy. Hopes to be ‘cured’ should not be part of decision-making or referral process in early-phase clinical experiments. We should be realistic about what these novel approaches will deliver for HIV-positive patients in the shorter term to avoid risks of therapeutic or curative misconceptions [11,12], and to ensure an ethical and informed recruitment process.

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References

1. Horwitz JP, et al. Nucleosides. V. The monomesylates of 1-(2'-deoxy-beta-D-lyxofuranosyl)thymidine. *J. Org. Chem.* 1964; 29:2076–2078.
2. Advisory Committee on Human Radiation Experiments. Final Report. US Government Printing Office; 1995.
3. Prins JM, et al. Immuno-activation with anti-CD3 and recombinant human IL-2 in HIV-1 infected patients on potent antiretroviral therapy. *AIDS.* 1999; 13:2405–2410. [PubMed: 10597782]
4. Gordin F, et al. CD4⁺ count-guided interruption of antiretroviral treatment. *N. Engl. J. Med.* 2006; 355:2283–2296. [PubMed: 17135583]
5. Allers K, et al. Evidence for the cure of HIV infection by CCR5^{-/-} stem cell transplantation. *Blood.* 2011; 117:2791–2799. [PubMed: 21148083]
6. Persaud D, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N. Engl. J. Med.* 2013; 369:1828–1835. [PubMed: 24152233]
7. Lehrman G, et al. Depletion of latent HIV-1 infection *in vivo*: a proof-of-concept study. *Lancet.* 2005; 366:549–555. [PubMed: 16099290]
8. Archin NM, et al. Expression of latent HIV induced by the potent HDAC inhibitor suberoylanilide hydroxamic acid. *AIDS Res. Hum. Retroviruses.* 2009; 25:207–212. [PubMed: 19239360]
9. Archin NM, et al. HIV-1 expression within resting CD4⁺ T cells after multiple doses of vorinostat. *J. Infect. Dis.* 2014 <http://dx.doi.org/10.1093/infdis/jiu155>.
10. Saglio F, et al. The time is now: moving toward virus-specific T cells after allogeneic hematopoietic stem cell transplantation as the standard of care. *Cytherapy.* 2014; 16:149–159. [PubMed: 24438896]
11. Appelbaum PS, et al. The therapeutic misconception: informed consent in psychiatric research. *Int. J. Law Psychiatry.* 1982; 5:319–329. [PubMed: 6135666]
12. Henderson GE, et al. Clinical trials and medical care: defining the therapeutic misconception. *PLoS Med.* 2007; 4:1735–1738.