Published in final edited form as:

Curr Opin HIV AIDS. 2011 January ; 6(1): 1–3. doi:10.1097/COH.0b013e328340ffa6.

Introduction: challenges to finding a cure for HIV infection

Douglas D. Richman, M.D.

VA San Diego Healthcare System and Distinguished Professor of Pathology and Medicine,
University of California San Diego, Director, Center for AIDS Research Florence Seeley Riford
Chair in AIDS Research

Abstract

Purpose of review—Renewed interest has emerged to address the latent reservoir of HIV to achieve a cure.

Recent findings—The integrated proviral genome is a fundamental component of the retroviral replication cycle. The establishment of latently infected CD4+ lymphocytes, and perhaps other as yet poorly characterized cells, represents a reservoir of HIV infection that is not appreciably affected by effective antiretroviral chemotherapy. Effective management of HIV infection thus will require lifelong treatment unless an approach to purging this reservoir is identified. Although substantial insights about the latent reservoir have been made, our understanding about the details of the reservoirs, the mechanisms of latency, and potential targets to eliminate latently infected cells is too primitive to achieve a cure without a great deal of basic research to elucidate some of these areas.

Summary—A resurgence of interest in latent infection and its treatment promises progress in addressing the challenge of a cure, although realistically this will require a prolonged period of investigation in many areas.

Keywords

HIV; latency; viral reservoirs; HIV cure; antiretroviral therapy

Introduction

HIV chemotherapy has been a major medical accomplishment over the past 2 decades and has dramatically reduced the morbidity and mortality of those with access to care. Major scientific challenges for both HIV-infected and HIV-uninfected individuals confront the future of the management of HIV. These challenges are sufficiently imposing that successfully addressing them may not be achievable. For HIV uninfected people, the development an HIV vaccine is imperative if a truly substantial reduction in epidemic transmission is to be achieved. For HIV infected people, the two challenges are the provision of effective treatment for those without access, which is a major operational and economic challenge, and the development of approaches to cure the latent reservoir for those on treatment, which is a major scientific challenge. Treatment, despite its remarkable success in dramatically reducing morbidity and mortality, is expensive, must be taken with reliable adherence for life, and often results in side effects or toxicity. An intervention that could purge the latent reservoir during effective antiretroviral suppression of virus replication would have a profound impact on medical care and HIV transmission. The

prospect of such an intervention, however, is a distant one, because the limitations of our understanding about latency and how to address it are substantial.

What we know about the latent reservoir

Since the original documentation of the existence of the latent reservoir (1), a number of important insights have been generated as will be summarized in more detail in the subsequent reviews in this issue. As delineated in a recent review on the subject (2•), we know that

1. Latently infected resting memory CD4+ T cells are the best characterized latent reservoir for HIV-1.
2. Less than 1 cell per million resting CD4+ T cells from patients on potent antiretroviral therapy harbor latent, replication competent HIV-1 provirus.
3. Other drug-insensitive reservoirs, including brain, macrophages and hematopoietic stem cells, may also exist.
4. The nucleotide sequences of latent proviruses do not evolve, which suggests no ongoing viral replication (3–5). Discontinuation of antiretroviral therapy permits the relapse of viral replication originating from this latent reservoir.
5. Patients successfully treated with antiretroviral therapy for a decade or more exhibit no appreciable decrease in the size of the latent reservoir.
6. The persistence of the latently infected reservoir precludes its elimination by antiretroviral therapy for the lifetime of the patient.
7. Latency is likely established and maintained by numerous steps in the HIV-1 replication pathway, which potentially complicates eradication strategies.

Our limited understanding of the mechanism of latency

This last point in reality reflects a level of ignorance that explains why success in purging the latent reservoir is a long-term aspiration, if possible at all. As discussed in detail in reviews in this issue, several mechanisms for the maintenance or latency have been described in various cell model systems. These include transcriptional blocks to the virus mediated by condensed chromatin, sequestration of transcription factors, restricted nuclear RNA export, and transcriptional inhibition by miRNA. These mechanisms may act in various combinations and may not represent all the mechanisms responsible for maintaining latency. Even should any of these mechanisms be responsible for maintaining latency, in part or completely, there is no intervention that has provided a compelling depletion of the latent reservoir, even in cell model systems. For example the histone deacetylase complex of enzymes is extensive and inhibitors of these enzymes vary in their specificity, as well as their toxicity and none has depleted latency in a model system by more than 90%, while we know that at least 10^6 latently infected cells must be eliminated for a cure (6). Thus a fundamental requirement to address the challenge of a cure is more basic insight into mechanisms of latency, targets for intervention and the identification of useful drugs that can safely and effectively hit those targets.

Our limited understanding of the composition of the latent reservoir

Our ignorance also extends to the nature of the latent reservoir itself. With the concerns about our primitive understanding about mechanisms stated above, the latent CD4+ T cell reservoir has been well documented and characterized. This reservoir may represent only the first and perhaps the largest of the reservoirs that must be addressed. Latently infected cells

may reside in anatomic compartments like the central nervous system, perhaps because they exist in a pharmacologic sanctuary. Macrophages have been proposed to undergo latent infection. Recently evidence for latent infection of hematopoietic stem cells was proposed (7). These cells could be the source of the increasingly appreciated subset in well-suppressed patients of circulating virions that are monophyletic.(8–9). This population of genotypically monoclonal virions suggests a persistently infected cell that can homeostatically proliferate without undergoing lytic cell death. Thus another fundamental requirement to address the challenge of a cure is more basic insight into the nature, magnitude and possibly the anatomic location of the cellular components of the latent reservoir.

The challenge of perturbing this reservoir

Should progress be achieved in understanding the composition of the reservoir, the mechanisms of latency, the targets for intervention and the discovery of potentially effective drugs to address these targets, the challenge of proof of concept *in vitro* and *in vivo* remains. With only approximately 1 in a million CD4+ T cells latently infected, many studies of latency can only be conducted with cell culture models. Does a latency model in a proliferating cell line with a molecular construct reflect a latent provirus in a primary CD4+ lymphocyte that is not activated or dividing? Few models of latency have been developed in primary human CD4+ lymphocytes using infectious HIV-1. Do these models, in which primary CD4 lymphocytes can only be maintained for a few weeks, reflect cells *in vivo* that persist for years?

Because testing a potentially ineffective and toxic investigational intervention in subjects who are living well with suppressive antiretroviral therapy poses potential ethical and study design concerns, preclinical testing in an animal model might provide proof-of-concept and guidance regarding treatment design in a clinical trial. The ultimate proof of a successful depletion of the latent reservoir is the withdrawal of antiretroviral therapy without a subsequent rebound of viral replication. A murine model, like the bone marrow-liver-thymus (BLT) mouse, might prove to have some utility in latency studies (10). Simian immunodeficiency virus infection of rhesus macaques has been shown to closely reflect HIV in humans, including the establishment of latent infection (11) and most classes of antiretroviral drugs have activity in this model. We do not know that all the host mechanisms participating in latency are identical or will respond to drugs targeting human proteins or sequences. In addition the small size of monkeys restricts the size and frequency of specimen collection needed to investigate the latent reservoir.

Conclusion

The search for a cure will be prolonged and challenging. In fact, it may not be possible; nevertheless, like the search for a vaccine, the challenge should not preclude the effort. Achieving a cure would have a dramatic impact on morbidity, mortality, health care costs and transmission. The effort to investigate this challenge intensively, regardless of the ultimate outcome, will yield significant insights into latency and reservoirs. Nevertheless, success, should it be possible, will take years if not decades. Despite intense skepticism Emil Frei and Emil Freireich embarked on a sequential series of clinical studies in the mid-1950's in children with acute lymphocytic leukemia (12). Studying various drug combinations, central nervous system prophylaxis and supportive care interventions, the prognosis of this disease changed over a period of 20 years from uniformly fatal to >75% cured. Two decades elapsed from when skepticism that zidovudine (AZT) would work at all to when successful rates of viral suppression approaching 90% in HIV-infected patients were broadly achieved. The emerging successes of new drugs for hepatitis C virus infection indicate a similar promise of cure rates, which will have required decades of discovery and development. With

precedents like these, the payoff of success justifies the intense efforts to cure HIV, despite the difficulty and likely timeline of this endeavor.

Acknowledgments

This work was supported by the Department of Veterans Affairs and grants AI69432 (the UCSD Center for AIDS Research), AI047745, and AI080193 from the National Institutes of Health.

References

1. Chun T-W, Carruth L, Finzi D, et al. Quantification of Latent Tissue Reservoirs and Total Body Viral Load in HIV-1 Infection. *Nature*. 1997; 387:183–188. [PubMed: 9144289]
2. Richman DD, Margolis DM, Delaney M, et al. The Challenge of Finding a Cure for HIV Infection. *Science*. 2009; 323:1304–1307. Review of the state of the art in the field of HIV latency and a proposal to establish a collaborative program involving academia, industry and government to address the challenge. [PubMed: 19265012]
3. Hermankova M, Ray SC, Ruff C, et al. HIV-1 Drug Resistance Profiles in Children and Adults With Viral Load of <50 Copies/mL Receiving Combination Therapy. *JAMA*. 2001; 286:196–207. [PubMed: 11448283]
4. Persaud D, Siberry GK, Ahonkhai A, et al. Continued Production of Drug-Sensitive Human Immunodeficiency Virus Type 1 in Children on Combination Antiretroviral Therapy Who Have Undetectable Viral Loads. *J Virol*. 2004; 78:968–979. [PubMed: 14694128]
5. Kieffer TL, Finucane MM, Nettles RE, et al. Genotypic Analysis of HIV-1 Drug Resistance at the Limit of Detection: Virus Production without Evolution in Treated Adults with Undetectable HIV Loads. *JID*. 2004; 189:1452–1465. [PubMed: 15073683]
6. Han Y, Wind-Rotolo HY, Yang HC, et al. Experimental Approaches to the Study of HIV-1 Latency. *Nat Rev Microbiol*. 2007; 5:95–106. [PubMed: 17224919]
7. Carter CC, Nuga-Onafuwa A, McNamara LA, et al. HIV-1 Infects Multipotent Progenitor Cells Causing Cell Death and Establishing Latent Cellular Reservoirs. *Nat Med*. 2010:446–551. [PubMed: 20208541]
8. Tobin NH, Learn GH, Holte SE, et al. Evidence That Low-Level Viremias during Effective Highly Active Antiretroviral Therapy Result from Two Processes: Expression of archival Virus and Replication of Virus. *J Virol*. 2005; 79:9625–9634. [PubMed: 16014925]
9. Bailey JR, Sedaghat AR, Kieffer T, et al. Residual Human Immunodeficiency Virus Type 1 Viremia in Some Patients on Antiretroviral Therapy is dominated by a Small Number of Invariant Clones Rarely Found in Circulating CD4+ T cells. *J Virol*. 2006; 80:441–457.
10. Melkus MW, Estes JD, Padgett-Thomas A, et al. Humanized Mice Mount Specific Adaptive and Innate Immune Responses to EBV and TSST-1. *Nat Med*. 2006; 12:1316–1322. [PubMed: 17057712]
11. Shen A, Yang H-C, Zhou Y, et al. Novel Pathway for Induction of Latent Virus from Resting CD4⁺ T Cells in the Simian Immunodeficiency Virus/Macaque Model of Human Immunodeficiency Virus Type 1 Latency. *J Virol*. 2003; 77:4938–4949. [PubMed: 12663799]
12. Laszlo, J. *The Cure of Childhood Leukemia: Into the age of miracles*. New Brunswick, N.J: Rutgers University Press; 1995. p. 287