specimens from HIV-1–seropositive individuals who have been treated effectively but suddenly die in vehicle accidents or from other traumas or causes (6). We envision a federal repository of HIV research tissue, funded and organized perhaps by the National Institutes of Health (NIH) and a consortium of governmental and private agencies, located at a single site with a national or international scope for specimen acquisition and distribution. This resource would be advertised to emergency rooms, surgical services, and medical providers likely to encounter victims of trauma or other acute fatal conditions and would function (on a smaller scale) like the United Network for Organ Sharing [UNOS (*10*)] for HIV-infected individuals who are excluded from transplant organ donation. HIV care clinics could offer patients the opportunity to carry cards identifying a willingness to become a "scientific tissue donor" in the event of untimely death. Tissues would be obtained from HIV-1–positive individuals, both treated and untreated controls, by attending physicians who would telephone a 24-hour hotline for emergency consent forms and instructions on harvesting, preserving, and shipping tissues along with blood and CSF, plus a relevant medical history to the repository. Because retention of cellular morphology and small quantities of labile viral nucleic acids is critical, establishing the infrastructure for meticulous tissue preservation by snap freezing and rapid fixation is of paramount importance. A central repository would provide the coordination to ensure uniformity and quality in processing samples. The specimens would then be catalogued, stored, and made available to all qualified investigators via a distribution system maintained by the repository.

The uncertain potential for eradication and immune reconstitution in response to antiretroviral therapy renders even more pressing the need to implement the recommendation of the NIH AIDS Research Program Working Group to develop a central repository of biological specimens (*11*). Based on sudden-accident mortality statistics and national HIV-1 seroprevalence data, we estimate that it might be possible to obtain tissues from 10 to 30 cases for this critical resource over a 2-year period at an estimated cost of $1 million per annum. In our view, the tissue bank proposal is responsive to the urgent need for such a repository. And it has reasonable prospects for success, drawing as it does on the inspiring history, throughout the AIDS pandemic, of the many HIV-1–seropositive individuals who have contributed to the advances in knowledge on which current successes and future hopes are based.

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Toward HIV Eradication or Remission: The Tasks Ahead

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With the advent of combination therapy, it is now possible to achieve durable control of human immunodeficiency virus–type 1 (HIV-1) replication in vivo. This development has led to a substantial decline in AIDS incidence and mortality in the United States in the past 2 years (*1*). The potent antiretroviral agents have also served as a tool to define the kinetics of HIV-1 turnover in infected persons (Fig. 1). When de novo infection is inhibited by drug treatment, cell-free virions are cleared rapidly and productively infected CD4 lymphocytes die after a short life-span (*2*, *3*). Complete elimination of these viral pools could be expected in ~2 months. But slower decay rates have been estimated for additional compartments carrying HIV-1, including infected tissue macrophages, CD4 lymphocytes that harbor infectious genome in a pre-integrated form, and virions trapped on follicular dendritic cells in lymphoid tissues (*4*, *5*). Nevertheless, mathematical projections suggest that these pools could also be eliminated if effective treatment is continued for 2 to 3 years (*4*), thereby raising the possibility of eradication. Recent studies show, however, that infectious HIV-1 persists latently in resting, memory CD4 lymphocytes in a post-integrated form despite 1 to 2 years of combination therapy (6). This latent reservoir of HIV-1, denoted L (Fig. 1), represents the major documented hurdle to virus eradication, although other obstacles such as viral sanctuaries may exist (*7*).

How do such virus-carrying CD4 lymphocytes arise? Do they represent rare survivors of productive infection? Or were they infected at a particular juncture during reversion from an activated state to the resting state? These questions remain unanswered, but it is known that L is small in size, generally ranging from 10^4 to 10^6 cells per host (8) and typically no larger than 10^7 cells (9). Its decay rate, μ (Fig. 1), has not been directly measured with any degree of accuracy, although several studies are now under way. It is known, nonetheless, that memory CD4 lymphocytes have a mean half-life ($t_{1/2}$) of ~3 to 4 months (*10*), which should mirror μ. Although much of the proviral DNA harbored within memory CD4 lymphocytes of infected persons exists as defective forms (9), the decay rate of this DNA may, nevertheless, serve as a surrogate to estimate μ. With this in mind, the decay $t_{1/2}$ of proviral DNA in peripheral blood mononuclear cells of patients receiving effective therapy has been found to be ~3 to 5 months (*4*, *11*), consistent with previous $t_{1/2}$ estimates of memory lymphocytes (*10*). Simple calculations based on these numbers are quite revealing. Approximately 14 to 20 half-lives are required for a pool size of 10^4 to 10^6 to decay to <1. Using 4 months as the $t_{1/2}$, it follows that 5 to 7 years of continuous, completely inhibitory therapy will be necessary to eliminate L. Treatment interruptions that permit HIV-1 replication to resume will rapidly restore the size of L. For larger pool sizes or greater values of $t_{1/2}$, more than 10 years of continuous treatment will be required. A treatment duration this protracted is unacceptable because of the complexity, toxicity, and cost of the current drug regimens, especially when the concept of "maintenance therapy" with a simplified regimen does not seem viable (*12*).

Increasing μ while continuing antiretroviral therapy is a strategy that should be explored. Activation of resting cells results in HIV-1 replication and cell death, whereas the spread of virus remains inhibited by antiretroviral agents. Infectious proviruses are undoubtedly harbored within a diverse

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population of resting CD4 lymphocytes with memory for a large array of exogenous antigens. Thus, administration of a limited set of antigens is unlikely to activate a sufficient number of these cells to replicate virus and thereby facilitate their rapid death. On the other hand, the use of a large panel of antigens would be impractical. What about the administration of cytokines? Interleukin-2 (IL-2) alone is not expected to activate resting lymphocytes because such cells do not express the appropriate high-affinity receptor. However, mixtures of certain cytokines, such as IL-2 plus IL-6 and tumor necrosis factor, have been shown to activate resting T cells in vitro (*13*). Polyclonal activators such as lipopolysaccharide, bacterial superantigens, and CD3 monoclonal antibodies (mAbs) should be considered, because each has the potential to increase μ by stimulating a fraction of L to make virus and thus die. Although each of the activators is associated with clinical toxicity, their utility in this setting should be carefully examined. In particular, a mouse CD3 mAb, OKT3, is already a licensed clinical product. Relatively high doses of OKT3 are routinely used to deplete T cells to prevent transplant rejection, but lower doses are known to be a polyclonal activator of T lymphocytes. Thus, low-dose OKT3 should be judiciously tested not only to define its safety profile in this context, but also to determine the magnitude of T cell activation achievable without prohibitive toxicity. Numerous courses of OKT3 administration are likely required to "flush out" the entire latent reservoir, and thus a humanized version of the mAb will later be needed to bypass the problem of inducing antibodies directed against mouse immunoglobulins. It is worrisome, however, that calculations indicate that each course of activation must stimulate more than 10% of the resting CD4 lymphocytes to make this strategy a viable one in the long run (*14*). Ultimately, the success of this type of activation strategy will be measured by the disappearance of culturable HIV-1 in CD4 lymphocytes and by the lack of the recurrence of viremia after discontinuation of antiretroviral therapy.

A second possible strategy to deal with the latent pool of HIV-1 is to achieve control without eradication, that is, to induce remission. In the presence of HIV-1–specific immunity, it is conceivable that L need not be reduced to a pool size of <1. There might be a threshold level L_T (Fig. 1) below which the spread of virus from intermittent activation of a small fraction of the reservoir population could be controlled by the immune system without continuing antiretroviral therapy. Here again, a rough calculation is revealing. If the decay $t_{1/2}$ of L is indeed about 4 months, as described above, then this is equivalent to a rate constant of 0.006 day^{-1}. With pool sizes of L ranging from 10^4 to 10^6 cells, it follows that a maximum of 60 to 6000 cells would be turned on each day to replicate virus. A number of these individual bursts of HIV-1 replication may be contained by immune responses. It stands to reason that the higher the virus-specific immunity, the higher the number of these activation events that could be controlled. Therefore, boosting specific immune responses may increase L_T, thereby improving the chance of inducing HIV-1 remission. Recent anecdotal reports of viral breakthrough when combination therapy was stopped after 1 to 2 years suggest that the critical threshold has not been reached. Moreover, an added concern is the recent observation that specific immunity to HIV-1, both cellular and humoral, wanes after effective drug therapy (*15*). Thus, exploring ways to increase L_T by boosting specific immunity using candidate HIV-1 vaccines seems particularly worthwhile. Alternatively, it has been suggested that antiretroviral therapy may be intermittently disrupted so that the resultant viremia could boost specific immune responses (*7*). Such a strategy, however, is unlikely to substantially shrink the pool size of L. Ultimately, in our effort to achieve long-term suppression of HIV-1 replication, it seems sensible to explore the feasibility of substituting enhanced virus-directed immunity for antiretroviral drugs.

The road to eradicating HIV-1 or inducing its remission is undoubtedly a bumpy one, replete with hidden challenges. Although the obstacles may be daunting, solutions to each must be vigorously pursued.

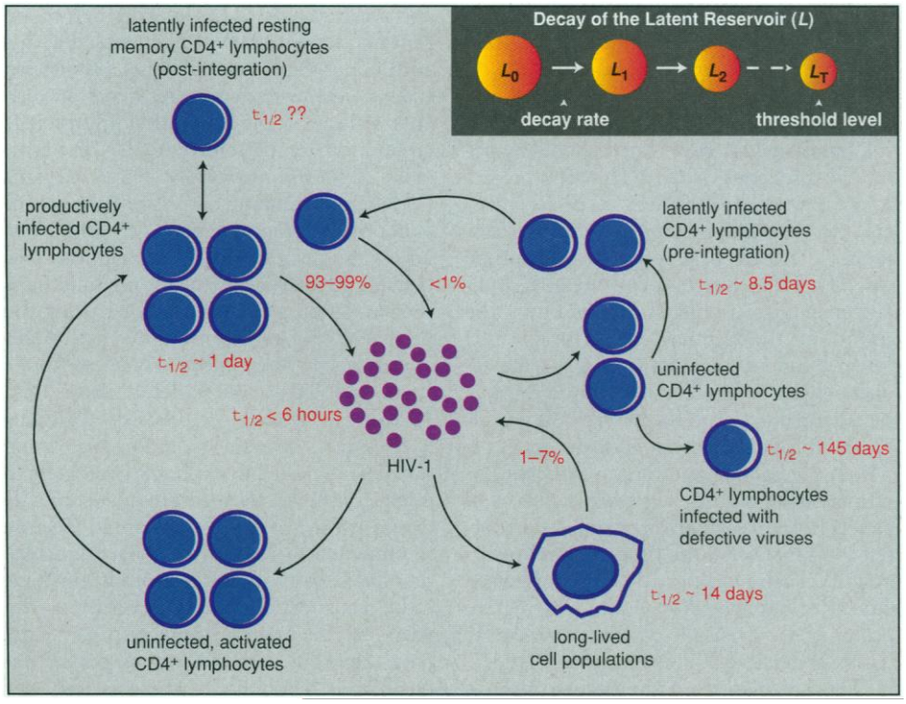

Fig. 1. A schematic representation of the dynamics of HIV-1 replication in vivo [adapted from (*3*)]. The latent reservoir L is shown at the top left, and its decay is hypothetically depicted in the insert.

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