HIV Eradication: Progress and Challenges

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The ultimate goal of human immunodeficiency virus (HIV) therapy is to eradicate the virus from infected individuals. The introduction of highly active antiretroviral therapy (HAART) in mid 1990s provided, for the first time, the hope that eradication is an achievable reality. The widespread use of HAART dramatically changed the clinical course of HIV infection in a significantly large proportion of infected individuals, leading ultimately to measurable decreases in the incidence of death and acquired immunodeficiency syndrome (AIDS)-defining conditions.

The Eradication Optimism

Early predictions that the infection might be curable were based on the widespread belief that if combination therapy could reduce and maintain the plasma virus to below the limit of detection with available assays, then prolonged treatment should eradicate the virus. This was the expectation in 1997, when after a careful analysis of the dynamics of HIV replication in peripheral blood of individuals receiving HAART, Perelson et al showed that HIV clearance follows a biphasic decay process (1). The first phase of decay lasts for about 2 weeks after initiation of therapy. During this period, the plasma viremia drops by almost 99%. The estimated half-life of free virus in this phase is less than 6 hours and the half-life of cells that produce most of the plasma virus is about 1.6 days. This rapid initial decay is followed by a slower second phase decay of plasma viremia. The half-life of the infected cells in this phase was estimated to be 1-4 weeks. Based on these estimates, it was predicted that 2.3-3.1 years would be required to eradicate the virus. However, the prediction was made with the caveats that 1) virus replication remains completely suppressed by HAART, 2) there is no possible existence of viral reservoirs with decay rates slower than that of the second phase or reservoirs that are impermeable to the antiretroviral drugs, and 3) there are no latently infected cells that could be activated to produce infectious virus (1). Unfortunately, all of these predictions have proven to be incorrect, and serious doubts have been raised regarding the feasibility of complete eradication with HAART.

Obstacles to Eradication

What has become increasingly clear is that despite the impressive clinical results and widespread acceptance as the standard of care for HIV-infected individuals, HAART is no magic bullet. An estimated 30%-50% of all individuals taking HAART do not show complete suppression of plasma viremia. Included among the factors that can lead to this type of failure are: prior resistance from mono- or bi-therapy, prior infection with drug resistant strains, nonadherence to HAART, cross-resistance among the inhibitors, and certain other unidentified factors. On the other hand, even if a patient achieves undetectable plasma viermia by HAART, it does not necessarily mean that full control over the virus replication has been achieved. In a number of studies, a

Table 1. Obstacles to HIV Eradication in Infected Individuals on HAART.

1) Latent HIV reservoirs
   a) $CD4^+$ T cells
   b) monocytes/macrophages
   c) follicular dendritic cells
   d) anatomical sites such as CNS, testis, etc.
2) Emergence of resistant HIV strains
3) Drug toxicity
4) Poor bioavailability
   a) inefficient cellular activation of nucleoside inhibitors to active antiviral form
   b) affinity of antiviral drugs for the multidrug transporter proteins
5) Lack of adherence to therapy

quick rebound of virus replication has been seen in patients who interrupted HAART therapy or in those on maintenance therapy trials (2,3).

Several lines of evidence suggest that virus replication continues, albeit at a significantly low level, in individuals who appear to be aviremic on HAART. This led to the identification of cellular and anatomical reservoirs of HIV, where the virus continues to survive either because these reservoirs are impermeable to anti-HIV drugs or the virus is present in a physical form in which it can survive for prolonged periods despite therapeutic concentrations of these drugs (Table 1). Other explanations for the stability of the reservoirs include the reseeding of the reservoirs by a low level of ongoing viral replication and a reduced rate of infected cell clearance due to a decline in HIV-1 specific immune response (3).

The three cellular reservoirs that have received the most consideration as the major barriers to achieving HIV-1 eradication are resting $CD4^+$ T cells, monocytes/macrophages, and follicular dendritic cells (FDCs). Among these, the reservoir of latently infected resting $CD4^+$ T cells appears to be the major barrier to achieving HIV eradication in patients on combination therapy. HIV-1 replication in a resting $CD4^+$ T cell is less efficient than in an activated cell. Many of the activated T cells die within a few weeks after activation, but if these cells escape the death pathways, they return to a resting stage and persist as memory T cells. Memory cells survive much longer because their fundamental role is to provide protection against previously encountered pathogens. The estimated half-life of productively infected T cells in HIV-1 infected individuals receiving HAART is 1.6 days. On the other hand, the average half-life of the latent reservoir is approximately 44 months, and according to this estimate, eradication could take as long as 60 years, assuming that the reservoir contains only 1×10^5 cells and that no other viral reservoirs exist (4). Finzi et al have estimated that during the asymptomatic phase of infection the mean number of resting $CD4^+$ T cells with replication competent HIV is 1.4×10^6, suggesting that 60 years for eradication is a highly conservative estimate and, in fact, it may take much longer to achieve eradication (5). These findings are based on the reservoirs of viruses that are fully replication competent and have the potential to produce virus in patients who fail therapy or experience immune challenge, such as infection with opportunistic pathogens. Although reactivation of HIV from the latent $CD4^+$ T cell reservoir may not contribute much to the viral burden in an infected individual, these latently infected cells are the potential barrier to virus eradication in patients whose plasma viremia is successfully suppressed by HAART to levels below the detection limits for prolonged periods of time.

During the entire course of HIV infection, cells of the monocyte/macrophage lineages play an important role in mucosal transmission of the virus, in transporting virus across the blood-brain barrier, and in establishing viral infection within several anatomical sites in the body, in particular the central nervous system compartment. Macrophages are also among the most frequently infected cells in other organs such as liver, gut, lung, spleen, lymph node, etc. HIV-infected monocytes/macrophages have been detected in the genital tissues and secretions of men and women who had undetectable plasma viremia, suggesting that these cells could be a potential source for the infectious virus. Monocytes/macrophages can serve as long-lived sources of HIV infection because of their relative resistance to the cytopathic effects of the virus. The estimated lifespan of productively infected macrophages is about 14 days compared with 1.6 days for the productively infected $CD4^+$ T cells. Although no information exists on the precise lifespan of latently infected macrophages, it is predicted to be several months. There are also reports that relatively higher concentrations of protease inhibitors are required to inhibit virus replication in infected monocytes/macrophages compared with that in lymphocytes, making these cells a good source for virus escape in individuals on HAART.

Another potential reservoir that must be considered is the FDC network in the germinal centers of lymph nodes. Extracellular virions trapped on FDCs have the potential to perpetuate infection to activated $CD4^+$ T cells trafficking through germinal centers. According to the estimates, FDCs may harbor as many as 10^{11} virions during the initial stages of infection. Although the conventional antiretroviral therapies that block viral transcription and assembly have no direct effect on FDC-bound HIV, earlier studies showed that as much as four orders of magnitude decrease

can be achieved after 6 months of therapy with an estimated 30-month period required for eradication (6). More recently, however, based on an elegant mathematical model of the highly variable rate of dissociation of virions from the FDCs, Hlavacek et al have predicted that HAART may not be able to clear all HIV trapped on FDCs, or several more years of treatment might be necessary to achieve eradication (7).

The Road to Eradication

Clinical experience with HAART has, no doubt, provided us with a better understanding of the management of HIV disease. However, it is also a turning point in our awareness of the key obstacles that we now face on our road to eradication (Table 1). Although, in patients on HAART, maintaining plasma viremia below the detection limit for extended periods is a measure of successful therapy, it is in no way an assurance that complete control over virus replication has been achieved. Thus, while we strive for solutions to achieve eradication, we should not give up hope for absolute control over the virus without rebound viremia and with the possibility of treatment cessation. To achieve this goal, we need more effective HAART regimens and a new generation of therapies that will complement the existing armamentarium against HIV and overcome problems of drug toxicity, interactions, resistance, and poor bioavailability.

With regard to the new directions, recent advancements in the molecular mechanisms of the virus–cell interactions have provided helpful clues to the development and testing of effective drugs and HIV-specific vaccines that target viral entry: a complex multistep process that starts with the binding of the viral envelope to both the CD4 receptor and a specific chemokine receptor and ends with the fusion of the viral envelope and target cell membrane. In addition, vaccines should elicit antibody responses that will neutralize HIV and cytotoxic T lymphocyte responses that will kill virus-infected host cells. Although there is evidence that HAART regimens provide enough immune restoration, new approaches are being developed and tested with the hope of achieving complete normalization of immune function in infected individuals. One of these approaches is the use of intermittent interleukin 2 (IL-2) in combination with HAART. Previous studies have shown that this combination can produce marked sustained increases in CD4 counts. More recently, Chun et al have shown that, in a small number of patients, this treatment also resulted in substantial reduction in the pool of latently infected resting $CD4^+$ T cells (8).

There is no question that new therapeutic strategies will present new challenges. However, despite these challenges, the development of new armamentarium against HIV should help to achieve durable remission of HIV infection in the near future, perhaps similar to what we observe in infected individuals with long-term nonprogressive disease, while we continue to move ahead on our road to achieve eradication.

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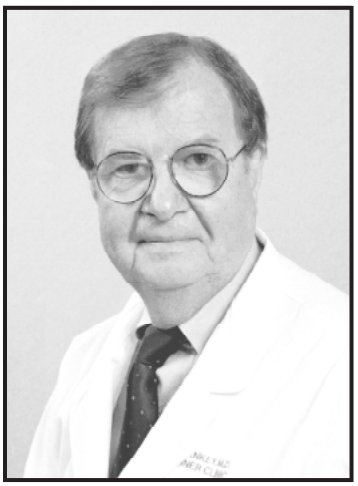

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