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The Future of HIV Treatment

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Abstract

Antiretroviral therapy has transformed the management of HIV-infected individuals over the past quarter century. However, important challenges remain. These include attempts to eradicate HIV from reservoirs within the body, thereby eliminating the need for lifetime therapy. In addition, improvements in drug development, clinical trial, and regulatory pathways are necessary to expeditiously evaluate novel therapeutic regimens and strategies. Antiretroviral drug scarcity remains a major problem in underserved populations worldwide, and partnerships among pharmaceutical companies, academic investigators, and both governmental and nongovernmental agencies are necessary to improve access to these lifesaving regimens.

Keywords

Antiretroviral Therapy; HIV Treatment; Eradication; Development of Therapeutics

In the global response to HIV/AIDS to date, development and implementation of effective antiretroviral therapy have been the premier accomplishments. Not only has antiretroviral therapy (ART) transformed a once near universally fatal disease into a manageable infection, it now shows great promise as an approach to preventing infection in those at greatest risk. Mother-to-child transmission of HIV has been nearly eliminated in resource-rich settings,[1] and recent studies suggest that sexual transmission among discordant couples can be prevented by treating the infected partner.[2]

Progress in ART was the result of years of laboratory and clinical investigations, including large, carefully controlled clinical trials. No single drug or class of drugs was instrumental to the advances; rather, it was the study and use of combination regimens employed over the past 20 years that yielded the progress that is now evident.[3]

Although we can rightfully take pride in this progress, many important challenges remain: Can we eradicate virus from HIV-infected individuals, eliminating the need for a lifetime of expensive, potentially toxic drugs? Are there problems with the pipeline leading to new and more effective antiretroviral drugs? If so, how can the pipeline be repaired? How can we

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improve access and adherence to lifesaving ART in at-risk populations? These are some of the questions we will address in this report.

SEARCH FOR A CURE

A few years ago, the concept of ridding an infected individual of HIV was considered highly unlikely, if not impossible. However, one improbable medical experiment has changed our attitude and once again raised the possibility of cure.[4,5] In a remarkable series of events, one infected individual appears to have been cured by a stem cell transplantation procedure involving the use of donor cells homozygous for the Δ32 deletion in the chemokine receptor 5 (CCR5) gene, making these cells resistant to HIV infection. The individual had acute myeloid leukemia (AML) and now, several years after transplantation, shows no evidence of HIV or HIV RNA in plasma or organs, despite discontinuation of ART. Moreover, he has shown successful reconstitution of CD4 T cells in blood and gut.

The procedure utilized in this patient—justified by the need for bone marrow transplantation to treat his relapsed AML—would be too risky and expensive to translate into routine clinical practice. However, this anecdotal case has inspired researchers to consider less arduous approaches directed toward eradicating HIV from latent virus reservoirs.[6] Several experimental approaches are being studied, including activation of HIV in latently infected cells by reversing the epigenetic silencing of HIV transcription[7]; the use of immune-based therapies to boost HIV-specific immunity or dampen HIV-associated immune activation[8]; and the use of genetically modified CD4+ T cells or bone marrow–derived stem cells that are rendered resistant to HIV infection.[9] The National Institutes of Health (NIH) has launched an initiative involving pharmaceutical, academic, and governmental partners in an effort to stimulate the search for a cure.

Designing clinical trials to test experimental approaches for HIV eradication poses special challenges: selecting appropriate participants for study; defining end points for proof-of-concept studies; and balancing the potential benefits of novel treatments with unknown risks. Several virological and immunological markers may serve as appropriate end points for proof-of-concept trials, but tests of cure or functional cure eventually will require analytical treatment interruptions. Criteria for advancing from proof-of-concept trials to analytical treatment interruption trials require careful consideration, with particular attention to the informed consent process to ensure that potential participants are fully aware of potential risks and not unduly influenced by the chances for a cure, which remain hypothetical.

THE ANTIRETROVIRAL DRUG PIPELINE

Over the past 25 years, more than 30 antiretroviral drugs and coformulated drug combinations have been approved in the United States, leaving little doubt that when the history of HIV/AIDS is written, this quarter century will be seen as the “golden age” of HIV therapeutics. However, the momentum in HIV drug development appears to be slowing, and fewer drugs are in an advanced stage of development than in years past. Paradoxically, the availability of many convenient, highly effective, and generally well-tolerated antiretroviral regimens has raised the bar for demonstrating the potential advantages of new drugs in an already crowded market—thereby increasing the risks for pharmaceutical companies and reducing potential profit margins. Moreover, pending competition from low-price combination regimens as current first-line agents go off patent over the next few years means that in order to justify premium pricing, newer drugs will need to show superiority to established regimens, not just equivalence. In addition, the focus of several pharmaceutical companies has turned to other infectious agents (eg, the hepatitis C virus, or HCV, where many targets have proven accessible and virological cure seems attainable). Nevertheless,

HIV/AIDS continues to be an enormous global problem, and current ART regimens remain costly, potentially toxic, and associated with the development of viral drug resistance.

What can be done to overcome obstacles to development of new ART regimens? One approach to repair the drug pipeline is to design less complex, less costly clinical trials of investigational agents, leading to faster and easier drug approval.[10] The US Food and Drug Administration (FDA), pharmaceutical companies, physicians, and patients share the desire for trials to be less cumbersome without sacrificing the collection of essential safety and efficacy data. Simplifying clinical trials is particularly important for the development of new drugs needed to treat highly drug-resistant HIV infection. The activity of a novel agent against drug-resistant virus can generally be demonstrated by monitoring the drop in plasma HIV-1 RNA levels over 10 to 14 days; long-term virological response depends on the activity of the other drugs in the regimen and adherence. Thus, an approach advocated by many is to assess drug activity in a 14-day trial in which the new drug or placebo are added to a failing regimen. Thereafter, all participants are given access to the new drug; allowed to optimize the “background” ART regimen to include other drugs to which the virus remains susceptible; and followed for 24 to 48 weeks to determine the new regimen’s longer-term safety and durability. It will be important to evaluate such novel trial designs in a variety of populations, including children, pregnant women, and those with comorbid conditions, such as HCV infection.

Improving the delivery of antiretroviral drugs through the development of depot formulations, being studied by several pharmaceutical companies, could have a dramatic impact on the challenge of sustaining high levels of treatment adherence and might significantly improve outcomes in difficult-to-treat populations. Local subcutaneous drug depots that require only infrequent replenishment are one such approach,[11] and intravaginal drug-containing rings to reduce transmission are another.[12] Important biological safety and regulatory issues related to depot preparations need to be addressed before they are employed widely.

It has been encouraging to watch partnerships arise between pharmaceutical companies to coformulate antiretroviral drugs, reducing pill burdens for patients who require prolonged therapy. Partnerships among pharmaceutical companies, academic investigators, and both governmental and nongovernmental agencies have also facilitated access to lifesaving regimens in both resource-rich and resource-poor settings. Organized efforts such as the United States President’s Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria have made the promise of ART a reality for millions of infected persons in developing countries; concerted efforts by groups such as the Clinton Foundation have reduced the cost of treatment. International efforts must be expanded to build infrastructures that ensure treatment programs’ sustainability, that make greater use of point-of-care diagnostics, and that continuously monitor drug resistance and toxicity in order to anticipate problems before they emerge.

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