No Cure Yet for HIV-1, But Therapeutic Research Presses On

Robert T. Schooley1 and John W. Mellors2
1Division of Infectious Diseases, Department of Medicine, University of California, San Diego, San Diego; 2Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, Pennsylvania

In this issue of the Journal, Siliciano et al. [1] have used sensitive culture methods to further evaluate whether the use of valproic acid (VA), an inhibitor of histone deacetylase, might activate HIV-1 from latently infected CD4+ memory T cells, thereby reducing the size of the latent viral reservoir in persons with chronic HIV-1 infection. Although the study design has limitations that are well delineated by the authors, the work does not support findings published earlier this year by Lehrman et al. [2] suggesting that VA, combined with the fusion inhibitor enfuvirtide, accelerates the decay of the latent viral reservoir. Although VA may hold less promise than previously hoped, the goal of depleting the latent viral reservoir should continue to be vigorously pursued. A recent finding that ~80% of patients receiving suppressive antiretroviral therapy have stable, persistent viremia of 1–20 copies/mL indicates that a long-lived reservoir of virus-producing cells may also exist [3]. At a minimum, eradication of HIV-1 infection will require the complete inhibition of virus expression and the killing or permanent inactivation of long-lived latently and productively infected cells. Although daunting, the goal of curing HIV-1 infection should not be abandoned. Such is the history of antiretroviral research, which continues to make enormous strides and is worth a closer look.

It has now been 20 years since the initial demonstration that reducing viral replication in patients improves clinical outcome and 10 years since the heady early days of the highly active antiretroviral therapy era, during which there was optimism that continued viral suppression would result in elimination of virus in-fection in as short a period as 2–3 years [4]. As more-accurate assessments of viral reservoirs were made, however, it became clear that suppression of viral replication alone would not be sufficient to cure HIV-1 infection [5, 6]. Nevertheless, key investments in antiretroviral drug discovery and development by industry and in rigorous clinical trials conducted by government and other entities—especially the National Institute of Allergy and Infectious Diseases and the National Institute of Child Health and Human Development—have led to major improvements in the efficacy, convenience, and cost of antiretroviral therapy [7, 8]. Despite these advances, once antiretroviral therapy is initiated, most patients can expect to be receiving it for the rest of their lives. Even though existing and new classes of small molecular inhibitors of HIV replication will continue to broaden treatment alternatives and to improve prognosis, none will break the current paradigm of combination therapy for life. What, then, are the alternatives to continuous life-long therapy?

Some had hoped that it would be possible to treat people intermittently over the course of their illness, either intervening only when CD4+ T cells decreased to levels that presage an increased risk for opportunistic infection or treating patients with fixed times of therapy administration and treatment interruption. The recent recommendation by an independent data and safety monitoring board that the Strategies for Management of Anti-Retroviral Therapy study be closed on the basis of significantly greater morbidity and mortality in the treatment-interruption arm is only the most recent demonstration that intermittent therapy has substantial
risks that may be prohibitive [9]. Although the results of intermittent studies have been mixed, recent trials, including several in resource-limited settings, have also cast serious doubt on the utility of this approach [10–12]. Studies of intermittent therapy will undoubtedly continue, but concerns about excess morbidity and mortality and the frequent selection of drug-resistant strains in treatment-interruption arms should provoke a careful look at trial designs and patient safety.

Whether more-prolonged treatment interruption will be possible with therapeutic vaccination remains a key area of active investigation. Several early studies have shown promise in this regard [13, 14]. Although enthusiasm has waned for therapy with interleukin (IL)–2, other contemporary approaches to immune restoration with such immune modulating agents as IL-7, IL-15, and keratinocyte growth factor hold potential and are worthy of further investigation. Clinical investigation of these agents is complicated and is best conducted by those with insights into the pathogenesis of the disease and the capacity to manage serious untoward events. As was recently shown with a ligand for CD28, engagement of the immune response can also have considerable downsides [15]. Without ongoing support by governmental and academic communities, the evaluation of potential promising biologics for the treatment of infectious disease is likely to be threatened.

Although both general and HIV-specific immune augmentation warrant ongoing research at both the basic and clinical science levels, neither of these approaches is likely to lead to elimination of the viral reservoir. Lehman et al. are to be commended for their pilot efforts with VA [2]. In pursuing these studies, they combined a plausible hypothesis with innovative preclinical studies and intensive, pathogenesis-focused clinical investigations in what should be a model for ongoing efforts in this area. Previous studies by Prins et al. [16] and van Praag et al. [17] of IL-2– and OKT3-based approaches are also commendable, although these, too, ultimately failed to achieve the initial goal. These studies should not be seen as failures but rather as examples of hypothesis-driven clinical investigation that should lay the groundwork for future work focused on achieving a cure. There are a multitude of tools to apply to this goal, including small interfering RNA, passive cellular immune augmentation, therapeutic vaccination, stem cell biology, cellular activation with combinations of more-selective ligands—as well as combinations of these approaches.

Other than pursuing a cure, what else remains to be accomplished in therapeutic research? Although we now have >20 antiretroviral agents, transmitted and acquired drug resistance coupled with acute and chronic toxicities of many of these agents call for ongoing drug discovery and development. In light of phase 1 and 2 data, chemokine-receptor antagonists and integrase inhibitors hold considerable promise. Although the pathway to drug registration is relatively clear, experience has shown that drug approval is only the first step in learning how to best use new agents across the spectrum of the disease. Some would argue that developing this information is the responsibility of the pharmaceutical industry, but few industry-supported clinical trials can be cited that have changed clinical practice on the basis of head-to-head comparisons of specific regimens. Such studies are, nonetheless, crucial to developing an understanding of how to best use new drugs and drug combinations. Clinical trials sponsored by the National Institutes of Health have filled this gap, leading to changes in clinical practice and optimizing the use of new antiretroviral drugs. Similarly, investigation into the best use of these new agents in resource-limited settings will largely be undertaken with support from US and European governmental agencies.

With >40 million persons already infected and few bona fide prospects for the early development of an effective vaccine, continued research on optimizing therapy is essential. It would be a grave error to dismantle the therapeutic research effort before life-long therapy is a memory and an effective vaccine is in hand. At this point, it can easily be argued that ongoing investment in clinical and translational therapeutic research, particularly innovative and rigorous investigator-initiated studies, shows more promise of ending the HIV-1 epidemic than does any other approach. We must press on.

References
10. Christine D, Moh R, Sorho S, et al. The CD4-guided strategy arm stopped in a randomized structured treatment interruption trial in


