
Current perspectives in HIV therapeutics

In the 30 years since the first recognition of acquired immune deficiency syndrome (AIDS), extraordinary and unprecedented progress has been made in understanding the pathogenesis of human immunodeficiency virus (HIV) and in the development of medications to treat the virus. These advances have transformed HIV from what was previously considered a uniformly fatal disease to a chronic viral infection that can be effectively managed with antiretroviral therapy (ART). As a result of improved HIV therapeutics, patients are experiencing improved quality of life and longer life expectancy. Ongoing progress in the field of HIV medicine also has made it challenging for clinicians to keep pace with current clinical issues and approaches (see "Practical Applications for the Practicing Allergist-Immunologist" in this issue). Several selected advancements in HIV therapeutics are discussed further in the following paragraphs.

Although patients with HIV may be asymptomatic, particularly early in the course of infection, persistent inflammation and immune activation have been shown to have multiple detrimental effects, including renal dysfunction, premature cardiovascular disease, liver failure, neurocognitive decline, and osteoporosis.¹ Many T cells display an activated phenotype, with the number of activated T cells predictive of HIV disease progression independent of plasma viral load.^{2,3} In late-stage disease, T cell activation also predicts the risk of developing AIDS or death.⁴ Immune activation can be a direct result of HIV infection but also can be driven by other processes such as HIV-mediated disruption of mucosal barriers, which then leads to translocation of gut microbial products into the systemic circulation.⁵ Long-term control of HIV replication with ART can significantly reduce immune activation; however, patients successfully treated with ART were found to have higher levels of immune activation compared with the HIV-uninfected population.⁶ Thus, treatment with ART improves but does not fully restore immunologic health in patients with HIV.

The recognition and understanding of immune activation and its associated effects has been one of several contributing factors swinging the pendulum back in favor of earlier initi-

ation of ART. Several studies have shown that treating at higher CD4 cell counts is associated with a reduced risk of AIDS and death.^{7,8} In addition, lower CD4 cell counts have various detrimental effects, including an association with non-AIDS malignancies,⁹ HIV-associated dementia,¹⁰ and reduced CD4 cell gains during ART.¹¹ The "hit HIV, early and hard" approach¹² originated with the advent of 3-drug therapy; however, a shift toward delayed therapy occurred in the early 2000s because of ART toxicities, high pill burdens, challenges with patient adherence, and concerns for the development of drug resistance.

In recent years, the improved toxicity profiles and potency of newer antiretroviral agents, as well as recognition of ongoing morbidity associated with HIV infection, has led to a renewed aggressiveness in treating HIV. Co-formulation of antiretrovirals has lowered the pill burden for most patients and allowed for a once-daily single-tablet regimen (efavirenz/tenofovir/emtricitabine). In addition to nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors, newer drug classes have been developed, resulting in the availability of the integrase strand transfer inhibitor raltegravir and the chemokine receptor-5 (CCR-5) inhibitor maraviroc. Because of the improved potency, tolerability, and adherence of available ART regimens, suppression of plasma viral load below the limit of detection generally occurs in over 90% of treatment-naïve patients in clinical trials.^{13,14} As a result of improved regimens and the goal to reduce the morbidity associated with HIV infection, current treatment guidelines recommend initiating ART at CD4 cell counts below 500 cells/mm³, whereas some experts advocate starting ART at CD4 cell counts above 500 cells/mm.^{3,15,16}

Life expectancy for patients with HIV may now approximate that of age-matched persons without HIV.¹⁷ In a French HIV cohort, a normal lifespan can be expected once patients are on effective ART for several years and achieve CD4 cell counts greater than 500 cells/mL.^{3,18} Patients with HIV are also able to work and have greater stability in their occupations because of improved overall health. A study of 200 patients with HIV showed that 40% of patients were actively employed, and 66% of those without work were seeking employment.¹⁹ Work stability is even evident in the military setting. For example, more than 200 men and women with HIV infection are able to continue active duty service in the United States Air Force. The increasing longevity in individuals with HIV has led to an increased recognition of non-AIDS conditions. An analysis of over 154,000 patients in 13 HIV cohorts showed that 49.5% of deaths were AIDS related,

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with the remaining attributable to non-AIDS malignancies (11.8%), non-AIDS infections (8.2%), violence or drug-related causes (7.7%), liver disease (7%), and cardiovascular disease (6.5%).²⁰ Future management of HIV infection will have increased focus on prevention and management of non-AIDS diagnoses.

Despite the multitude of advances in the field, the pursuit of a cure for HIV has remained elusive. ART is not curative for several reasons, but mainly because of the persistence of latently infected, resting CD4+ T cells, which serve as a stable reservoir for the virus. The traditional approach applied to many infectious diseases is to develop a “sterilizing cure,” which, in the case of HIV, would eliminate the virus from all sites and sanctuaries in the infected host. The only known example of a potential sterilizing cure comes from a report of an HIV-infected patient in Germany who acquired acute myeloid leukemia.²¹ After receiving a bone marrow transplant from a donor homozygous for a 32-base-pair deletion in the CCR-5 gene, the patient had maintained a viral load of less than 1 copy/mL without ART. An alternative approach to a cure for HIV involves maintenance of low-level viremia below 50 copies/mL, an approach termed “functional cure.” Elite controllers are patients infected with HIV who are able to spontaneously control plasma viremia in the absence of ART. Elite controllers represent less than 1% of HIV-infected patients²² and are being intensively studied as a model for functional cure.

Advances in HIV therapeutics have transformed HIV from a “death sentence” into a chronic illness. Treatment successes are being witnessed in the areas of improved life expectancy and decreased AIDS-associated morbidity and mortality. However, new areas of clinical focus include conditions that result in or are impacted by chronic inflammation, immune activation, and aging. ART continues to improve in the areas of potency, tolerability, and patient adherence, but novel strategies and approaches are necessary to eventually discover a cure for HIV.

JASON F. OKULICZ, MD
Jason.okulicz@amedd.army.mil

Infectious Disease Service
San Antonio Military Medical Center
San Antonio, Texas

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