

A^{PhA} Special Report

Optimizing Adherence to HIV/AIDS Medication Regimens

Introduction

Worldwide, an estimated 33 million people are infected with the human immunodeficiency virus (HIV).¹ Estimates of prevalence in the United States in 2006 suggest that 1.1 million diagnosed and undiagnosed adults and adolescents are infected, with an estimated 38,000 individuals diagnosed with acquired immune deficiency syndrome (AIDS).^{2,3} The U.S. incidence of HIV infection has been relatively stable since 1999 and mortality remains high: 56,300 new infections and more than 14,600 HIV/AIDS-related deaths in 2006.^{3,4}

Highly Active Antiretroviral Therapy

The first antiretroviral drug, zidovudine, was introduced in 1987. HIV/AIDS-related morbidity and mortality, however, dramatically declined only after the advent of highly active antiretroviral therapy (HAART) in 1996.^{5,7} HAART regimens are combinations of three or more different antiretroviral agents from at least two drug classes.⁶ Preferred regimens for treatment-naïve patients include a dual nucleoside reverse transcriptase inhibitor backbone combined with either a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor often boosted with ritonavir. Antiretroviral agents from other drug classes (i.e., fusion inhibitors, chemokine coreceptor 5 antagonists, and integrase inhibitors) are approved for use in treatment-experienced patients.⁶

The success of HAART lies not in its ability to eradicate the virus, but in its ability to suppress viral replication. When compared with monotherapy or dual-agent therapy, combinations of three or more agents achieve maximal suppression with less risk of resistance mutations.⁶ When viral load is suppressed to undetectable, morbidity and mortality decline, immune function improves, and vertical transmission is prevented. Factors that predict undetectable viral load in the first 12 to 24 months of HAART include low baseline viral load, higher baseline CD4 T-cell count, rapid viral load reduction, and optimal adherence. Adherence is one of the most important alterable predictors of treatment outcome.⁸

Adherence and Outcome

The relationship between adherence and HIV treatment outcome is based on the premise that drug exposure (plasma and intracellular drug concentrations) must be maintained at a level sufficient to suppress viral replication.⁹ Consistently taking a HAART regimen exactly as prescribed ensures optimal drug levels. Consequences of suboptimal adherence and the resultant insufficient drug levels are significant: failure to suppress viral replication, rebound replication, development of resistance with the accompanying limitation on future treatment options, and loss of clinical and immune benefits of therapy.¹⁰

Patients who are less than 95% adherent are 3.5 times more likely to have treatment failure, defined as a detectable viral load, compared with patients who are 95% to 100% adherent.¹¹ This 95% threshold represents the traditional target level of adherence required for successful HAART, meaning that a patient must take at least 95% of prescribed doses to achieve maximal viral suppression.⁶ This target is based on early studies of combination therapy. Further studies are needed to determine whether it similarly applies to or should be adjusted for newer regimens, including once-daily regimens or regimens that contain nonnucleoside reverse transcriptase inhibitors or ritonavir-boosted protease inhibitors. Pending those studies, however, this target level remains the working definition of optimal adherence.^{6,9}

Mannheimer et al. reported on the findings of two randomized multicenter trials enrolling a total of 1,095 treatment-naïve and treatment-experienced patients with HIV infection beginning initial HAART or salvage antiretroviral regimens, respectively.¹² Patients who reported 100% adherence at each visit during the 12-month follow-up period achieved HIV RNA level reductions of 2.77 log₁₀ copies/mL and CD4 count increases of 179 cells/μL. Lower levels of adherence had significantly smaller HIV RNA reductions and CD4 count increases. Similarly, an earlier study by Low-Beer demonstrated a linear relationship between adherence and viral suppression, with 84% of patients who adhered to 95% to 100% of prescribed therapy achieving viral suppression compared with only 64% of patients with 90% to less than 95% adherence.¹³

As the study by Mannheimer et al. demonstrated with its tracking of CD4 counts, the immune benefit of HAART is compromised by poor adherence.¹² Clinical benefits are also compromised. In a population-based analysis of 1,282 patients with HIV infection,

STOP!

What is the advantage of HAART over single- or dual-agent antiretroviral therapy?