ABSTRACT

Highly active antiretroviral therapy (HAART) has dramatically improved the prognosis for HIV-infected patients in the last 5 years, as demonstrated by several studies, including the EuroSIDA study—in which patients' CD4 cell counts of <20 cells/mL improved to 20 to 49 cells/mL and the projected 25% mortality rate over the following year was reduced to <10, and a collaborative effort among 8 European cohorts, in which researchers concluded that treatment with HAART had increased and maintained patients' CD4 cell counts and conferred clinical protection despite the discontinuation of a secondary prophylaxis.

To date, virologic failure has been managed in several ways, including switch therapy, continued therapy, interruption of HAART, and using interleukin-2 to boost CD4 counts. Trials examining the possibility of drug recycling are currently underway, as are trials examining the rate at which failing regimens increase plasma viral load, accumulation of resistant mutations, and immunologic failure.

Success or failure of treatment can be measured and defined in several ways; each method of definition should be explored and compared. Controlled trials must offer critical analyses of the efficacy and treatment-limiting toxicities of all treatments they examine.

>200 cells/mL. CD4 cell count levels were subsequently maintained at >200 cells/mL for a median of 11 months. After a median follow-up period of 13 months, CD4 cell counts remained at levels ≥ 200 cells/mL. Researchers concluded that treatment with HAART had increased patients' CD4 cell counts and clearly conferred clinical protection, despite elimination of disease-specific prophylaxis.

**Managing Virologic Failure**

To date, virologic failure has been managed in several ways, including switch therapy, continued therapy, interruption of HAART, and using interleukin-2 to boost CD4 counts. Each method has its strengths and weaknesses. Switch therapy offers renewed control, but may result in the defeat of a newly introduced class of drugs. Continued therapy may prevent toxicity and preserve the activity of new drugs, but bears the risk of additional resistance mutations and class resistance. Interruption therapy, on the other hand, is not costly, nor will it increase toxicity, but can cause the CD4 count to plummet and can increase the risk of clinical disease. Interleukin-2 can be effective regardless of the plasma viral load, but the clinical protection of this method is yet unproved.

Further controlled trials should increase our understanding of the effects and safety of treatment interruptions. Trials examining the possibility of drug recycling are currently under way, as are trials examining the rate at which failing regimens increase a patient's plasma viral load, accumulation of resistant mutations, and immunologic failure. We do know, however, that HAART has been successful: it keeps patients alive and increases CD4 cell counts. Even in patients who lack complete control of viral replication and are therefore at
increased risk of drug resistance, the plasma viral load still diminishes. Plasma viral load, however, remains a weak predictor of the risk of clinical disease progression; another strong predictor may be the current level of hemoglobin.

Most controlled trials analyze a regimen's ability to suppress plasma viral load and the tolerability of the regimen, since discontinuations are counted as virologic failures. Despite the important data often provided by trials that assess the efficacy and toxicity of drugs, trial design, small patient cohorts, and short duration of some studies may severely limit these data. An efficacy-only endpoint requires continued follow-up in patients who discontinue treatment. Treatment-limiting toxicity should be evaluated separately. Extended follow-up until the completion of the trial, regardless of whether the patient discontinues the study medication, should be encouraged to better determine the presence of late-onset adverse events and resistance. Moreover, studies that focus solely on effect, such as suppression of plasma viral load that is independent of discontinuations, may prove useful. The risk of virologic failure associated with numbers needed to treat vs. the numbers needed to treat to harm should also be examined.

Several definitions of treatment success and failure exist; however, each should be explored and compared. Controlled trials must offer critical analyses of the efficacy and treatment-limiting toxicities of all treatments they examine.

REFERENCES