Changes in Plasma HIV RNA Levels and CD4$^+$ Lymphocyte Counts Predict Both Response to Antiretroviral Therapy and Therapeutic Failure

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Background: Markers are needed for assessing response to antiretroviral therapy over time. The CD4$^+$ lymphocyte count is one such surrogate, but it is relatively weak.

Objective: To assess the association of changes in plasma human immunodeficiency virus (HIV) RNA level and CD4$^+$ lymphocyte count with progression to the acquired immunodeficiency syndrome (AIDS).

Design: Analysis of data from a subset of patients in a multicenter, randomized, clinical trial.

Setting: Six Veterans Affairs medical centers and one U.S. Army medical center.

Patients: 270 symptomatic HIV-infected patients from the Veterans Affairs Cooperative Study on AIDS.

Intervention: Patients were randomly assigned to receive zidovudine or placebo initially; a cross-over protocol was established for patients receiving placebo who had disease progression.

Measurements: Reverse transcriptase polymerase chain reaction on cryopreserved plasma samples, previously obtained CD4$^+$ lymphocyte counts, and clinical events.

Results: For each decrease of 0.5 $\log_{10}$ copies/mL in plasma HIV RNA level, averaged over the 6 months after randomization, the relative risk (RR) for progression to AIDS was 0.67 ($P < 0.001$). In a subset of 70 treated patients with long-term follow-up, a return to baseline plasma HIV RNA levels within 6 months of randomization was associated with progression to AIDS (RR, 4.28; $P = 0.004$). Plasma HIV RNA levels or CD4$^+$ lymphocyte counts over time were more strongly associated with progression to AIDS than were baseline levels or counts.

Conclusions: An adequate virologic response after initiation of antiretroviral therapy seems to require a decrease in plasma HIV RNA level of at least 0.5 $\log_{10}$ copies/mL that is sustained for at least 6 months. The independent relation between plasma HIV RNA level and CD4$^+$ lymphocyte count over time and clinical outcome suggests that the measurement of plasma HIV RNA level, in addition to the CD4$^+$ lymphocyte count, has a role in guiding the management of antiretroviral therapy.

Disease resulting from human immunodeficiency virus (HIV) infection typically evolves over several years (1). The goal of current antiretroviral therapy is to halt viral replication and, it is hoped, produce modest immune restoration and clinical stabilization or improvement. Treatment with combinations of antiretroviral drugs can reduce levels of viral replication more substantially than monotherapy can (2–4) and is associated with improved clinical outcome (2, 4–6). Unfortunately, the duration of benefit derived from antiretroviral therapy has been limited, at least in part, by the emergence of resistance to this therapy (7). An increasing array of antiretroviral agents available for the treatment of HIV infection has resulted in many potential therapeutic regimens. Thus, to optimize therapy, we need to develop markers that can identify drug failure before clinical progression. The CD4$^+$ lymphocyte count is one such surrogate, but it has been shown to be an incomplete marker of initial antiretroviral response (8) and does not reflect the level of viral load (9, 10).

Direct and sensitive measures of plasma HIV RNA have recently become available, and these hold promise as a method for guiding antiretroviral therapy (11–13). A single measurement of the plasma HIV RNA level has important prognostic value (9, 10) and is strongly correlated with rates of progression to the acquired immunodeficiency syndrome (AIDS), regardless of treatment. In general, low levels of plasma HIV RNA (<5000 to 10 000 copies/mL) are associated with relatively low rates of progression to AIDS, although progression does occur in some persons with very low baseline levels (9, 13, 14). In a previous study (10), we showed that antiretroviral treatment–induced changes in plasma HIV RNA levels were the best indicators of drug efficacy. In the present study, we used samples and data from the completed Veterans Affairs Cooperative Study Program 298 (VACSP 298), which showed

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that rates of progression to AIDS were reduced in patients randomly assigned to immediate zidovudine therapy compared with patients randomly assigned to placebo (15). In VACSP 298, a 75% reduction in plasma HIV RNA level explained 59% of the clinical benefit seen with immediate zidovudine treatment (10). Here, we evaluate 1) how changes in plasma HIV RNA levels and $CD4^+$ lymphocyte count correlate with progression to AIDS and 2) the usefulness of these measures in assessing antiretroviral drug failure during the course of therapy.

Methods

The details of VACSP 298, including the techniques for collecting and analyzing serum specimens, have been described elsewhere (10, 15, 16). Clinical events and $CD4^+$ lymphocyte counts were monitored during the original study (15, 16); plasma HIV RNA levels were measured by Amplicor HIV-1 Monitor (Roche Diagnostic Systems, Branchburg, New Jersey) retrospectively in stored specimens for the second study (10). A subset of participants from the second study was eligible for longitudinal analysis of markers if the participants had at least four plasma samples, obtained over at least 1 year, available for quantitative HIV RNA determination and if they had had $CD4^+$ lymphocyte counts measured at least four times during the same period.

Baseline characteristics were compared by using the chi-square test or the Fisher exact test for discrete variables and the Wilcoxon rank-sum test for continuous variables. As in our previous work (10), all RNA values were $\log_{10}$-transformed before analysis. The initial response to treatment was determined by averaging all measurements of plasma HIV RNA level or $CD4^+$ lymphocyte count obtained during the first 6 months of treatment and comparing these average values with the one or two baseline, prerandomization values that were available. Treatment failure was defined as progression to AIDS according to the 1987 criterion (17). The two measures examined as surrogate markers of treatment failure were 1) return to baseline values within 6 months and 2) changes in values within 18 months after the initial 6-month response to treatment. Clinical follow-up was limited to 60 months. Analyses of the time to progression to AIDS were conducted using Cox proportional-hazards modeling procedures (18). Time-dependent analyses are Cox models in which the marker values are entered into the model at the time they are measured and are assumed to be constant until remeasured. In the present study, only measurements obtained within the first 24 months of the study and before the occurrence of AIDS were considered. We used SAS software, versions 6.09/6.11 (SAS Institute, Cary, North Carolina), for statistical analysis.

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Results

Patient Characteristics

The 270 patients from VACSP 298 who had samples available for plasma HIV RNA analysis are described elsewhere (10). The patients in the two treatment groups (the immediate treatment group and the deferred treatment group) did not differ significantly in age, race, $CD4^+$ lymphocyte count, or plasma HIV RNA level at entry. A trend toward a difference in mean baseline plasma HIV RNA levels was seen: Levels were higher in the immediate therapy group than in the deferred therapy group (4.04 $\log_{10}$ copies/mL compared with 3.89 $\log_{10}$ copies/mL; $P = 0.07$). The 70 patients in the immediate therapy group who were suitable for longitudinal HIV marker analysis had a median duration of clinical follow-up of 54 months (range, 18 to 60 months), a median age of 41 years, a median plasma HIV RNA level of 4.23 $\log_{10}$ copies/mL, and a median $CD4^+$ lymphocyte count of 374 cells/mm^3. Baseline characteristics in this subset, including body weight, percentage of $CD3^+$ lymphocytes that were $CD4^+$ cells, $CD8^+$ lymphocyte count, and β_2-microglobulin, did not differ from those in patients who were not selected.

HIV Marker Response to Antiretroviral Treatment and Progression to AIDS

For all 270 patients, regardless of treatment, if the postrandomization response is measured by the mean levels of the markers over the first 6 months of the study, the relative risk (RR) for progression to AIDS is 0.67 (95% CI, 0.56 to 0.80; $P < 0.001$) for each decrease of 0.5 $\log_{10}$ copies/mL in HIV RNA level from baseline (**Table 1**, model 1). The relative risk for each 10% increase in $CD4^+$ lymphocyte counts from baseline (model 2) is 0.82 (CI, 0.76 to 0.89; $P < 0.001$). If changes in both markers are considered together in the same model (model 3), then the relative risk for each decrease of 0.5 $\log_{10}$ copies/mL in HIV RNA level is 0.70 (CI, 0.59 to 0.84) and the relative risk for each 10% increase in $CD4^+$ lymphocyte count is 0.85 (CI, 0.78 to 0.92). This means that, after adjustment for the changes in $CD4^+$ lymphocyte count, each decrease of 0.5 $\log_{10}$ copies/mL in HIV RNA level decreases the risk for progression to AIDS by about 30%. After adjustment for the changes in HIV RNA level, each 10%

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Table 1. Mean Change in Markers from Baseline over 6 Months and Progression to AIDS*

Cox Proportional Hazards Model	Change from Baseline†	Relative Risk (95% CI)	*P* Value
1	Decrease in HIV RNA plasma level of 0.5 $\log_{10}$ copies/mL	0.67 (0.56–0.80)	<0.001
2	Increase in $CD4^+$ lymphocyte count of 10%‡	0.82 (0.76–0.89)	<0.001
3	Decrease in HIV RNA plasma level of 0.5 $\log_{10}$ copies/mL‡	0.70 (0.59–0.84)	<0.001
	Increase in $CD4^+$ lymphocyte counts of 10%‡	0.85 (0.78–0.92)	<0.001

* All study patients (n = 270). AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.
† Baseline values for both markers are included in all Cox proportional hazards models.
‡ If changes in both HIV RNA plasma level and $CD4^+$ lymphocyte count are considered in the model.

increase in $CD4^+$ lymphocyte count decreases the risk for progression to AIDS by about 15%. The interaction between plasma HIV RNA level and $CD4^+$ lymphocyte count was not significant ($P >$ 0.2). In patients who had both a decrease of 0.5 $\log_{10}$ copies/mL in HIV RNA level and a 10% increase in $CD4^+$ lymphocyte count, the relative risk for progression to AIDS was 0.33 ($P = 0.019$) compared with persons who did not have both of these changes. In patients who had neither of these changes, the risk for progression was significantly increased compared with the group in which at least one of these changes did occur (RR, 2.3; $P = 0.001$) and did not differ from the group that did not receive immediate therapy.

Durability of HIV Marker Changes over Time and Progression to AIDS

After the initial changes in markers seen after the start of zidovudine therapy in the selected subset ($n = 70$), most patients experienced a return to baseline levels; 23 of these patients progressed to AIDS within 60 months. We examined the relation between the rate of return toward baseline values from the initial post-treatment level and progression to AIDS. Plasma HIV RNA levels returned to baseline within 6 months in 32 patients (46%), 13 of whom had progression to AIDS; $CD4^+$ lymphocyte counts returned to baseline within 6 months in 49 patients (70%), 17 of whom had progression to AIDS. Using Cox regression and adjusting for baseline values, we found that persons whose plasma HIV RNA levels returned to baseline within 6 months had a greater risk for progression to AIDS (RR, 4.28 [CI, 1.59 to 11.6]; $P = 0.004$) than did those whose levels returned to baseline after 6 months (**Figure**). Return of the $CD4^+$ lymphocyte count to baseline within 6 months did not distinguish patients who progressed to AIDS from those who did not (RR, 1.62 [CI, 0.63 to 4.15]; $P > 0.2$).

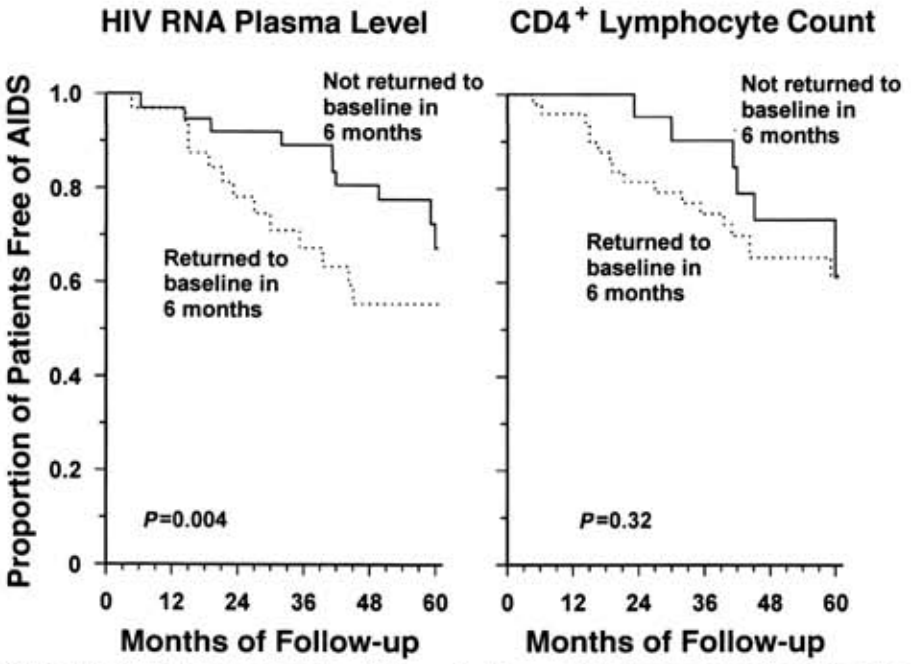

Figure. Kaplan–Meier analysis of the time to progression to the acquired immunodeficiency syndrome (*AIDS*) in 70 patients whose human immunodeficiency virus (*HIV*) RNA plasma levels did or did not return to baseline (*left*) or whose $CD4^+$ lymphocyte counts did or did not return to baseline (*right*) in less than 6 months. The *P* value for the difference between the groups is shown for each marker.

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The relative risk for each individual marker was essentially unaffected if we adjusted for a return to baseline of the other marker in the Cox regression analysis.

Changes in markers from the 6-month post-treatment mean values were also examined as potential indicators of drug failure. Analysis of marker values was limited to the first 24 months after randomization, during which time a median of 8 plasma HIV RNA measurements (range, 3 to 14 measurements) and a median of 8 $CD4^+$ lymphocyte counts (range, 3 to 11 counts) were performed. After adjustment for the initial response, a decrease in $CD4^+$ lymphocyte count of 30% or more during this 18-month period (months 6 to 24 of follow-up after initiation of treatment) was associated with progression to AIDS (RR, 3.64; $P = 0.012$) (**Table 2**). Although a single measurement demonstrating an increase in plasma HIV RNA levels as great as 1.0 $\log_{10}$ copies/mL since the 6-month post-treatment mean did not seem to distinguish patient outcomes, larger plasma HIV RNA increases of 1.5 or 2.0 $\log_{10}$ copies/mL markedly increased the risk for progression to AIDS (RR, 4.63 [$P = 0.002$] and RR, 11.87 [$P < 0.001$], respectively).

Time-Dependent Analysis of Marker Change and Clinical Progression

To assess the value of changes in HIV markers over time and progression to AIDS, we performed a Cox regression analysis of time to progression using the sequence of HIV marker values after the initiation of therapy (**Table 3**). Progressive increases in plasma HIV RNA level (RR, 3.80 per 1.0 $\log_{10}$ copies/mL; $P < 0.001$) or decreases in $CD4^+$ lymphocyte count (RR, 0.84 per 25 $CD4^+$ lymphocytes/mm^3) predicted the development of AIDS more strongly than did baseline values. In an adjusted multivariate Cox model, changes in plasma HIV RNA level and $CD4^+$ lymphocyte count remained more predictive than baseline measurements and were independent predictors of progression to AIDS (RR for increase in HIV RNA level, 2.9 per $\log_{10}$ copies/mL [$P = 0.003$]; RR for decrease in $CD4^+$ lymphocyte count, 0.87 per 25 $CD4^+$ lymphocytes/mm^3 [$P < 0.001$]).

Table 2. Relation between Changes from the Mean Post-Treatment Value over 6 Months and Progression to AIDS*

Change from Mean Post-Treatment Value	Patients	Patients with AIDS	Relative Risk (95% CI)	*P* Value
	n	*n* (%)		
Increase in HIV RNA plasma level				
≥0.5 $\log_{10}$ copies/mL	59	20 (34)	2.27 (0.64–7.94)	0.20
≥1 $\log_{10}$ copies/mL	40	11 (28)	1.06 (0.43–2.64)	>0.2
≥1.5 $\log_{10}$ copies/mL	20	9 (45)	4.63 (1.75–12.29)	0.002
≥2 $\log_{10}$ copies/mL	10	6 (60)	11.87 (3.51–40.13)	<0.001
Decrease in $CD4^+$ lymphocyte count				
≥20%	51	18 (35)	2.09 (0.75–5.80)	0.16
≥30%	42	18 (43)	3.64 (1.33–9.96)	0.012
≥40%	33	14 (42)	2.44 (1.05–5.71)	0.039
≥50%	25	12 (48)	2.90 (1.26–6.65)	0.012

* Selected patients in the group receiving immediate treatment with zidovudine ($n = 70$). AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

Discussion

In this report, we show that the risk for progression to AIDS decreases as the response of plasma HIV RNA levels and $CD4^+$ lymphocyte counts to therapy increases. In addition, we show that the durability of the virologic response to therapy and progressive worsening in both markers over time are more predictive of clinical stability and progression to AIDS, respectively, than is any single measurement, including baseline measurements. Decreases in $CD4^+$ lymphocyte count during therapy remain an important predictor of progression to AIDS.

Studies using various antiretroviral agents, alone or in combination, have shown that the magnitude of the effect of antiretroviral therapy on viral load is associated with clinical end points (3, 5, 10, 13, 19). Viral load reductions may soon become the standard measure for assessing the initial response to antiretroviral therapy. Because the risk for clinical progression to AIDS is greater in persons who do not experience a reduction of at least 0.5 $\log_{10}$ copies/mL in plasma HIV RNA levels upon the initiation of zidovudine therapy, alternate antiretroviral regimens should be considered in these nonresponding patients. In patients with a high initial viral load, a reduction of 0.5 $\log_{10}$ copies/mL may not achieve a level below the target level (<5000 to 10 000 copies/mL). It is desirable to reduce viral load as much as possible (9, 13).

One measure of antiretroviral response is the magnitude of virologic decline; another is the durability of viral suppression. No previous studies have addressed the relative importance of durability of the antiretroviral response with respect to clinical end points. By analyzing a subset of persons enrolled in VACSP 298 and controlling for baseline plasma HIV RNA levels, we have demonstrated that persons whose plasma HIV RNA levels returned to baseline within 6 months of the initiation of zidovudine therapy had a greater risk for progression to AIDS than did those in whom the decrease in viral load was more sustained. Thus, despite an initial virologic response, a rapid return of plasma HIV RNA levels to baseline is an early indication of therapeutic failure. This suggests that both the durability and magnitude of the initial

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virologic response are important predictors of progression to AIDS. This finding is relevant because many different characteristics of the initial virologic response to therapy and the duration of effect have been described, especially as more drugs have become available. For example, viral burden often decreases by at least 1.0 $\log_{10}$ copies/mL in response to therapy with non-nucleoside analogue reverse transcriptase inhibitors, only to rebound to baseline during the first several weeks of therapy (20). In contrast, such therapeutic combinations as zidovudine and lamivudine result in reductions in viral load of approximately 1.0 $\log_{10}$ copies/mL that seem to be sustained for more than 1 year (21). It is likely that if the reduction of the viral load is greater and is more sustained, the clinical benefit will be increased. This remains to be more formally demonstrated by additional antiretroviral trials that correlate clinical and virologic outcomes.

To define the usefulness of monitoring viral and immune markers in treated patients, we determined whether a single measurement of change in plasma HIV RNA level or $CD4^+$ lymphocyte count from post-treatment values could predict drug failure. In a subset of evaluable persons enrolled in the early treatment arm of VACSP 298, we found that a 30% decline in $CD4^+$ lymphocyte count during therapy resulted in a nearly 40-fold increase in risk for clinical progression. In our study, progression was not predicted by a single measurement of an increase in viral load of at least 1.0 $\log_{10}$ copies/mL but was predicted by greater increases (that is, $\geq$1.5 or 2.0 $\log_{10}$ copies/mL). A single measurement of an increase in plasma HIV RNA levels of at least 1.0 $\log_{10}$ copies/mL from post-treatment values in our study is unable to predict outcome, even though it is generally accepted that a change in viral load of at least 0.5 $\log_{10}$ copies/mL is significant (13). Although there is little apparent fluctuation in plasma HIV RNA levels over short periods in clinically stable patients (19, 22, 23), our understanding of the biological variation of viral load over long periods is still inadequate. Another potential explanation for the inability of a single plasma HIV RNA measurement to predict drug failure is that viral load, over the short term, can be transiently affected by various factors that result in immunologic activation (23–26). These factors include immunizations, such as those for influenza and tetanus, and acute infectious processes, such as herpes simplex virus infection and possibly tuberculosis (27–29). Many other factors not yet identified may also influence HIV replication in vivo. Because $CD4^+$ lymphocyte counts reflect the level of immunocompetence in patients with HIV infection, it is not surprising that a 30% decrease in $CD4^+$ lymphocyte count was more closely associated with the development of AIDS.

Table 3. Time-Dependent Analyses of Sequential Values of Markers for Response to Antiretroviral Therapy and Progression to AIDS*

Variable	Marker Alone		Markers Combined	
	Relative Risk (95% CI)	*P* Value	Relative Risk (95% CI)	*P* Value
HIV RNA plasma level				
Baseline	0.92 (0.56–1.51)	>0.2	0.86 (0.50–1.48)	>0.2
Over time	3.80 (1.98–7.30)	<0.001	2.90 (1.45–5.81)	0.003
$CD4^+$ lymphocyte count				
Baseline	0.96 (0.84–1.10)	>0.2	0.98 (0.86–1.12)	>0.2
Over time	0.84 (0.77–0.91)	<0.001	0.87 (0.80–0.94)	<0.001

* Markers were assessed for 2 years or until AIDS was diagnosed, whichever came first. For this analysis, $CD4^+$ lymphocyte count was transformed by dividing by 25. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

Our study also supports the use of a 50% decline in $CD4^+$ lymphocyte count as an end point for clinical trials (5). Immunologic perturbations that increase viral load are less likely to have a substantial effect on $CD4^+$ lymphocyte counts (23–25).

Although single measurements of viral load have limited usefulness, we have demonstrated that changes in viral load over time are more predictive of drug failure. This hypothesis was tested by a Cox regression analysis done to determine the ability of a time-dependent analysis of viral load and $CD4^+$ lymphocyte count to predict clinical progression. These analyses demonstrated that plasma HIV RNA changes over time can be a good marker of underlying disease progression and probably also of antiretroviral therapy failure, independent of trends in $CD4^+$ lymphocyte count. In fact, progressive changes in plasma HIV RNA levels, as well as $CD4^+$ lymphocyte counts, are more predictive for the development of AIDS than are baseline values. Monitoring both plasma HIV RNA levels and $CD4^+$ lymphocyte counts over time may thus be a useful way to assess drug failure. Because these markers will be used together, it seems reasonable to obtain simultaneous measurements of $CD4^+$ lymphocytes and plasma HIV RNA at 3- to 4-month intervals (13).

This study has several limitations, including the use of data from a trial that used only zidovudine monotherapy; the performance of a subgroup analysis limited to patients for whom multiple, sequential samples were available; and the lack of direct assessment of the effect of using changes in measured levels of surrogate markers as guides to management. Although zidovudine monotherapy is now seldom used in the United States, this clinical trial did show clinical benefit and our virologic and immunologic analysis is therefore likely to apply to other antiretroviral agents. For analysis of the initial 6-month response, most patients had three or more plasma samples available; however, some patients

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were included if only one sample was available in this period. In some cases, samples were not available at 1 and 2 months, which are the time points after the initiation of reverse transcriptase inhibitor therapy when the peak response in viral load reduction usually occurs. To include all study participants in the analysis, we averaged marker values from all samples available during the first 6 months; this may underestimate short-term response. For longitudinal analysis, plasma samples were not routinely collected after progression to AIDS occurred or the $CD4^+$ lymphocyte count decreased to less than 200/mm^3 and a patient was given open-label zidovudine. Therefore, the analysis of plasma HIV RNA levels and $CD4^+$ lymphocyte counts was limited to 2 years after randomization, during which time the number of samples available for these two biological variables was similar. Prospective trials are needed to specifically determine those measures that perform best for monitoring antiretroviral therapy. None of these limitations, however, negates the overall conclusion that changes in these markers predict response to, and failure of, antiretroviral therapy.

Increasing numbers of antiretroviral therapeutic agents are now available for the management of HIV-infected persons. It is therefore timely that assays are available to quantify plasma HIV RNA levels and provide an opportunity to directly monitor the virologic effects of these drugs in treated patients. Plasma HIV RNA measurements are being increasingly used in clinical practice, despite our limited knowledge of their clinical usefulness. We believe that measurements of plasma HIV RNA can be used for three purposes: staging disease and determining when to initiate therapy, assessing initial response to therapy, and identifying drug failure. Recent studies have shown that baseline levels of this virologic marker are similar to or better than $CD4^+$ lymphocyte counts in predicting the likelihood of clinical progression (9, 10, 14, 30). In addition, the effect of antiretroviral therapy on plasma HIV RNA levels has also been shown to predict clinical outcome (10). The present study analyzed the relation between the durability of the virologic response to antiretroviral therapy and clinical outcome and suggests that the change in quantitative plasma HIV RNA levels over time may be a good marker of antiretroviral failure. Although a single measurement of viral load may not always indicate drug failure, repeated measurements of both plasma HIV RNA levels and $CD4^+$ lymphocyte counts that show progressive, unfavorable trends are a strong indication of drug failure. The ability to monitor the initial response to treatment and changes in viral load over time may thus allow clinicians to individualize and optimize antiretroviral therapy in HIV-infected persons. We need to learn how to interpret the virologic response to therapy in patients at different stages of disease, with different treatments, and with different previous antiretroviral experience. Prospective trials will help to establish specific measures for drug failure for the increasingly complex therapeutic regimens used in practice. In addition, future studies should assess the cost-effectiveness of this new monitoring strategy.

Appendix

For this report, the VA Cooperative Study Group on AIDS included M. Edgington, P. Scali, and T. Economou, Cooperative Studies Coordinating Center, West Haven Veterans Affairs Medical Center, West Haven, Connecticut; C. Lahart and N. Wray, Houston Veterans Affairs Medical Center, Houston, Texas; S.M. Finegold and W.L. George, West Los Angeles Veterans Affairs Medical Center, Los Angeles, California; G.M. Dickinson and N. Klimas, Miami Veterans Affairs Medical Center, Miami, Florida; G. Diamond, New York Veterans Affairs Medical Center, New York, New York; P.C. Jensen, San Francisco Veterans Affairs Medical Center, San Francisco, California; C. Hawkes and C. Oster, Walter Reed Army Hospital, Washington, D.C.; F. Gordin and A.M. Labriola, Washington, D.C., Veterans Affairs Medical Center, Washington, D.C.; and P. Spivey, Durham, North Carolina, Veterans Affairs Medical Center, Durham, North Carolina.

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