Predictors of Virologic and Clinical Outcomes in HIV-1–Infected Patients Receiving Concurrent Treatment with Indinavir, Zidovudine, and Lamivudine

AIDS Clinical Trials Group Protocol 320

Lisa M. Demeter, MD; Michael D. Hughes, PhD; Robert W. Coombs, MD, PhD; J. Brooks Jackson, MD; Janet M. Grimes, MS; Ronald J. Bosch, PhD; Susan A. Fiscus, PhD; Stephen A. Spector, MD; Kathleen E. Squires, MD; Margaret A. Fischl, MD; and Scott M. Hammer, MD

Background: **A substantial proportion of patients with HIV infection will not respond to antiretroviral therapy. Early predictors of response to treatment are needed to identify patients who are at risk for treatment failure.**

Objective: **To determine predictors of virologic and clinical response to indinavir, zidovudine, and lamivudine therapy.**

Design: **Observational analysis of one treatment group in a phase III trial.**

Setting: **40 AIDS Clinical Trials units.**

Patients: **489 patients receiving indinavir, zidovudine, and lamivudine who had 1) a CD4 count of 0.200×10^9 cells/L or less after 8 or more weeks of study therapy and 2) plasma HIV-1 RNA measurements obtained at baseline and week 8.**

Measurements: **HIV-1 RNA level and CD4 cell count at weeks 0, 4, 8, 24, and 40. Clinical progression was defined as a new AIDS-defining illness or death.**

Results: **Patients' levels of HIV-1 RNA at the 8th study week of therapy predicted whether patients would achieve virologic suppression to below 500 (or 50) copies/mL at study week 24. An HIV-1 RNA level less than 500 copies/mL at week 24 was achieved in 71% of patients whose level at week 8 had been less than 500 copies/mL, 53% of those with a level of 500 copies/mL or more and at least 2–$\log_{10}$ copies/mL reduction since baseline, 29% of those with a level of 500 copies/mL or more with a 1– to 1.99–$\log_{10}$ copies/mL reduction, and 9% of those with a level of 500 copies/mL or greater and less than 1–$\log_{10}$ copies/mL reduction since baseline ($P < 0.001$). HIV-1 RNA level at week 8 also predicted clinical progression. HIV-1 disease progressed in 2.2% of the patients with a week-8 HIV-1 RNA level less than 500 copies/mL, 2.3% of patients with 500 copies/mL or greater and at least 2–$\log_{10}$ copies/mL reduction since baseline, 4.9% of patients with 500 copies/mL or greater and 1– to 1.99–$\log_{10}$ copies/mL reduction since baseline, and 10.6% of patients with 500 copies/mL or greater and less than 1–$\log_{10}$ copies/mL decrease since baseline ($P = 0.009$). After adjustment for HIV-1 RNA level, patients with a higher week-8 CD4 cell count were more likely to have a week-24 HIV-1 RNA level less than 500 copies/mL (relative risk for patients with a week-8 CD4 count $\geq 0.10 \times 10^9$ cells/L, 1.47 [95% CI, 1.00 to 2.16] compared with $<0.050 \times 10^9$ cells/L; relative risk for patients with a week-8 CD4 count of 0.05 to 0.099×10^9 cells/L, 0.98 [CI, 0.61 to 1.57] compared with $<0.050 \times 10^9$ cells/L). After adjustment for HIV-1 RNA level, patients with a week-8 CD4 count of 0.05×10^9 cells/L or greater (compared with $<0.05 \times 10^9$ cells/L) had a decreased hazard for clinical progression (hazard ratio, 0.25 [CI, 0.09 to 0.67]).**

Conclusions: **The HIV-1 RNA level and CD4 cell count achieved at 8 weeks of treatment are important predictors of subsequent virologic and clinical outcomes.**

Ann Intern Med. 2001;135:954-964. www.annals.org

For author affiliations, current addresses, and contributions, see end of text.

Potent antiretroviral regimens lead to viral load suppression in 60% to 90% of patients with HIV-1 infection (1–6). Several studies have analyzed early plasma HIV-1 RNA level and CD4 cell count as predictors of response to antiretroviral therapy (7–11). Few patients in these studies received protease inhibitors or achieved virologic suppression. To design maximally effective treatment strategies for patients with HIV-1 infection, more information is needed regarding factors that predict response to regimens that more closely reflect current standards of care (12, 13). We report factors that predicted virologic and clinical responses to treatment with indinavir, zidovudine, and lamivudine in a phase III clinical trial.

METHODS

Study Design

The AIDS Clinical Trials Group (ACTG) protocol 320 was a phase III trial in patients with at least 3 months of previous zidovudine therapy and a CD4 cell count of 0.200×10^9 cells/L or less. The study demon-

strated that indinavir, zidovudine, and lamivudine were superior to zidovudine and lamivudine in delaying clinical progression (2). A preliminary subset analysis of 190 patients (2) demonstrated that greater suppression of HIV-1 RNA level occurred in the study patients receiving indinavir. Because HIV-1 RNA level responses in the dual nucleoside group were poor, we limited our analysis to patients who initiated concurrent treatment with indinavir, zidovudine, and lamivudine. All participants gave informed consent, and the appropriate institutional review boards approved the study procedures.

Patient Selection

Study enrollment began in January 1996. A total of 583 patients were randomly assigned to receive indinavir, zidovudine, and lamivudine before 21 February 1997, when randomization and blinded study treatment were terminated. For the present study, we limited our analysis to 489 patients (84% of 583 patients), who initiated study treatment and had HIV-1 RNA measurements obtained at baseline and week 8. Sixteen patients (3%) were excluded because they did not start treatment or were randomly assigned too late to complete 8 weeks of treatment. Forty-four patients (8%) did not complete 8 weeks of study treatment because of death ($n = 2$), discontinuation of treatment after development of a new AIDS-defining event ($n = 7$), discontinuation due to adverse experiences ($n = 8$), or discontinuation at the request of the patient or loss to follow-up ($n = 27$). The remaining 34 patients (6%) had no baseline or no week-8 HIV-1 RNA measurement.

HIV-1 RNA Level Quantitation

At the conclusion of the study, researchers at six ACTG laboratories measured plasma HIV-1 RNA levels by using the Roche Amplicor Monitor assay (Roche Diagnostics, Branchburg, New Jersey) with a quantification limit of 500 copies/mL. Plasma samples with an HIV-1 RNA level of 2000 copies/mL or less according to the standard Monitor assay were retested by use of an ultrasensitive assay with a quantification limit of 50 copies/mL.

Statistical Analysis

Baseline HIV-1 RNA level was defined as the geometric mean of two measurements obtained before the patient started study treatment. If either measurement was less than 500 copies/mL, then 500 copies/mL was used as the baseline level (1% of patients); if either measurement was greater than 750 000 copies/mL, then 750 000 copies/mL was used (4% of patients).

To evaluate the associations between HIV-1 RNA level suppression at week 24 to less than 500 copies/mL (or to <50 copies/mL) and HIV-1 RNA level at week 8, including change in HIV-1 RNA level from baseline to week 8, we used the extension of the Fisher exact test. We used logistic regression to assess other potential predictors of virologic suppression at week 24. In developing a logistic regression model, we evaluated variables without and then with adjustment for baseline HIV-1 RNA level and the change in HIV-1 RNA level from baseline to week 8; we anticipated that these variables would best predict subsequent HIV-1 RNA suppression. In the models, we included a binary variable to identify two groups of patients on the basis of a week-8 HIV-1 RNA level less than 500 copies/mL versus a level of 500 copies/mL or greater (or a week-8 level of <50 copies/mL versus ≥ 50 copies/mL). To maximize the adjustment, we also included continuous variables for baseline $\log_{10}$ HIV-1 RNA level in each of these two groups and, for patients with 500 copies/mL or more at week 8, change in $\log_{10}$ HIV-1 RNA level from baseline. Because CD4 cell counts are widely used as a prognostic marker in clinical practice, we added the baseline and week-8 CD4 cell counts to the model by using standard clinical categories. We also evaluated sex, age, race/ethnicity, intravenous drug use, Karnofsky score, and length of previous zidovudine use according to ordered categories. To simplify the presentation of data, we provide results by using ordered categories for CD4 cell counts, patient age, and duration of previous zidovudine use; however, the same conclusions were obtained by using continuous variables.

We repeated all logistic regression analyses by using conditional logistic regression and generalized estimating equations (14) (with an exchangeable working correlation matrix) to allow for any possible clustering within clinical sites (data not shown). The estimated correlation within sites was extremely small (0.00 to 0.06, depending on the model). Results from the different modeling approaches did not differ sufficiently to affect our conclusions. Adjusted relative risks were obtained from the logistic regression models for patients

Table 1. **Proportion of Patients Who Achieved Suppression of Plasma HIV-1 RNA Level to Less Than 500 or 50 copies/mL***

Measurement	Patients with an HIV-1 RNA Level < 500 copies/mL	Patients with an HIV-1 RNA Level < 50 copies/mL
	n/n (%)	
Week 0	3/489 (0.6)	2/489 (0.4)
Week 4	139/466 (30)	28/466 (6)
Week 8	228/489 (47)	72/489 (15)
Week 24	201/412 (49)	123/412 (30)
Week 40	126/290 (43)	90/290 (31)

* The denominator is the number of patients who had an HIV-1 RNA measurement and who could have completed the given number of weeks of treatment before closure of the study; patients who discontinued use of indinavir, zidovudine, and lamivudine before week 8 are excluded. The numerator is the number of patients who achieved the stated level of suppression of HIV-1 RNA and were still taking indinavir, zidovudine, and lamivudine at the given week.

with HIV-1 RNA levels of 100 000 copies/mL at baseline and 500 copies/mL at week 8. (These values are very close to the median values for the study sample.) We used the multivariate delta method to derive variances for the log relative risk from the logistic regression model (15) and hence 95% CIs for the adjusted relative risks.

We analyzed differences in mean CD4 cell counts according to HIV-1 RNA profile groups by using analysis of variance. Predictors of progression to AIDS or death were evaluated by using the log-rank test and a Cox proportional hazards models with the date of the week-8 measurement as the time origin and censoring as the last follow-up visit. Baseline and week-8 HIV-1 RNA levels and CD4 cell count were included in the model as described for the logistic regression modeling. Because few clinical events occurred in the sample, we considered no other variables. The fit of all models was evaluated by visual inspection of residual plots and plots of the log cumulative hazard against time. We used SAS statistical software, version 6.12 (SAS Institute, Inc., Cary, North Carolina), for all statistical analyses. All *P* values were derived from two-sided hypothesis tests and were unadjusted for multiple comparisons.

Role of the Funding Sources

The ACTG of the National Institute of Allergy and Infectious Diseases funded the study. Merck and Co. and Roche Molecular Systems provided supplemental funding for virologic studies. Merck and Co. and Glaxo Wellcome provided study drugs. Members of the ACTG performed all assays. The authors analyzed and interpreted the data and had sole responsibility for submitting the manuscript for publication.

RESULTS

Patients

Eighty-three percent of the patients in this study were men, and the median age was 38 years (25th and 75th percentiles, 33 and 45 years, respectively). Fifty-four percent of patients were white, 26% were black, 18% were Hispanic, and 2% belonged to other nonwhite racial or ethnic groups. Fifteen percent of patients had previously used intravenous drugs. The median duration of previous zidovudine use was 24 months (25th and 75th percentiles, 12 and 44 months). At baseline, the median CD4 cell count was 0.082×10^9 cells/L (25th and 75th percentiles, 0.026 and 0.138×10^9 cells/L) and the median HIV-1 RNA level was 108 000 copies/mL (25th and 75th percentiles, 41 000 and 261 000 copies/mL). The median follow-up was 43 weeks (25th and 75th percentiles, 35 and 49 weeks).

Plasma HIV-1 RNA Responses

The baseline HIV-1 RNA level was less than 500 copies/mL in less than 1% of patients. Approximately half of the patients who completed 8 weeks or more of indinavir therapy had an HIV-1 RNA level less than 500 copies/mL by week 8; there was little change in the proportion of patients who had an HIV-1 RNA level less than 500 copies/mL at later times (**Table 1**). In contrast, a smaller proportion of patients had week-8 HIV-1 RNA levels suppressed to less than 50 copies/mL; the proportion of patients with less than 50 copies/mL of HIV-1 RNA subsequently increased.

Among the patients who achieved an HIV-1 RNA level less than 500 copies/mL at week 24 and who could have completed 40 weeks of therapy by the time of study closure, 90% (113 of 126) maintained suppression of HIV-1 RNA at week 40. The proportion of patients who maintained virologic suppression from weeks 24 to 40 was similar between the group with less than 500 copies/mL at week 8 (91% [82 of 90 patients]) and the group with 500 copies/mL or more at week 8 (86% [31 of 36 patients]). Few patients (10% [8 of 79]) who had not achieved virologic suppression to less than

Table 2. **Association of Baseline and Early Change in Plasma HIV-1 RNA with Suppression of HIV RNA to Less Than 500 copies/mL at Week 24***

HIV-1 RNA Category at Week 8	Patients with Week-24 HIV-1 RNA Level < 500 copies/mL, according to Baseline HIV-1 RNA Level				All Patients
	<5000 copies/mL	5000–49 999 copies/mL	50 000–499 999 copies/mL	≥500 000 copies/mL	
	← n/n (%) →				
<500 copies/mL	14/16 (88)	55/70 (79)	57/91 (63)	8/11 (73)	134/188 (71)
≥500 copies/mL and ≥2 $\log_{10}$ copies/mL below baseline level	–†	–†	32/56 (57)	9/21 (43)	41/77 (53)
≥500 copies/mL and 1–1.99 $\log_{10}$ copies/mL below baseline level	–†	8/17 (47)	10/42 (24)	1/7 (14)	19/66 (29)
≥500 copies/mL and <1 $\log_{10}$ copies/mL below baseline level	2/6 (33)	3/16 (19)	2/50 (4)	0/9 (0)	7/81 (9)
All patients	16/22 (73)	66/103 (64)	101/239 (42)	18/48 (38)	201/412 (49)
P value‡	0.025	<0.001	<0.001	0.003	<0.001

* Numerators are the number of patients at week 24 who were still taking indinavir, zidovudine, and lamivudine and had an HIV-1 RNA level less than 500 copies/mL; denominators are the number of patients who could have completed 24 weeks of treatment before closure of the study. Patients who discontinued treatment with indinavir, zidovudine, and lamivudine before week 8 are excluded.
† Baseline HIV-1 RNA level is too low to allow quantification of changes of the specified magnitude.
‡ *P* values were calculated by using the Fisher exact test to compare the proportion of patients with virologic suppression across the four categories of week-8 HIV-1 RNA for each baseline HIV-1 RNA level.

500 copies/mL by week 24 subsequently achieved suppression by week 40.

Predictors of Suppressed HIV-1 RNA Level

We evaluated the effect of early change (from baseline to week 8) in plasma HIV-1 RNA level on subsequent suppression (at week 24) of plasma HIV-1 RNA to less than 500 copies/mL (**Table 2**). Patients were categorized according to whether their week-8 HIV-1 RNA level was less than 500 copies/mL or 500 copies/mL or greater; for the latter group, categorization was also based on the magnitude of reduction in HIV-1 RNA level from baseline. This categorization took into account the fact that patients with a baseline HIV-1 RNA level of 5000 to 49 999 copies/mL, 50 000 to 499 999 copies/mL, or 500 000 copies/mL or more had to achieve reductions greater than 1 $\log_{10}$ copies/mL, greater than 2 $\log_{10}$ copies/mL, or greater than 3 $\log_{10}$ copies/mL, respectively, to have an HIV-1 RNA level less than 500 copies/mL at week 8. Lower baseline HIV-1 RNA level significantly predicted HIV-1 RNA suppression to less than 500 copies/mL at week 24 ($P < 0.001$, Fisher exact test). A further predictor of virologic suppression at week 24 was the magnitude of change in HIV-1 RNA level from baseline to week 8 ($P < 0.001$) (**Table 2**).

Measurement of HIV-1 RNA at week 4 added little value in predicting suppression of week-24 HIV-1 RNA level to less than 500 copies/mL beyond the predictive value provided by the week-8 HIV-1 RNA level. Virologic suppression to less than 500 copies/mL at week 24 occurred in 74% (74 of 100) of patients with HIV-1 RNA levels less than 500 copies/mL at weeks 4 and 8 compared with 67% (58 of 86) of patients with an HIV-1 RNA level less than 500 copies/mL at week 8 only (a 7–percentage point difference [CI, −7 to 20 percentage points]; $P > 0.2$, Fisher exact test). Among the 207 patients with a week-4 measurement and a week-8 HIV-1 RNA level of 500 copies/mL or greater, the week 4 value did not significantly predict week-24 suppression after adjustment for the week-8 level (data not shown).

We also evaluated whether other patient characteristics could predict virologic suppression at week 24 (**Table 3**). The proportion of patients with a suppressed HIV-1 RNA level at week 24 increased with increasing CD4 cell count at week 8. Across all categories of CD4 cell count, the association of the CD4 value with week-24 virologic suppression was stronger at week 8 than at baseline (**Table 3**). Furthermore, results of a multivariate analysis (adjusted for HIV-1 RNA levels) that included a patient's category of CD4 cell count at

baseline and at week 8 showed that an association between CD4 cell count and virologic suppression at week 24 was significant for the week-8 CD4 value ($P = 0.016$) but not for the baseline CD4 value ($P > 0.2$). Thus, higher CD4 cell counts at week 8, in addition to lower week-8 HIV-1 RNA levels, predicted greater odds of suppression of HIV-1 RNA level at week 24.

In the adjusted analyses, older patients had a higher probability of HIV-1 RNA suppression to less than 500 copies/mL at week 24 compared with younger patients (**Table 3**). The trend was slightly weaker with adjustment for HIV-1 RNA levels, as evidenced by the lower relative risks in the adjusted analysis than the unadjusted analysis. The significant association with older age persisted in logistic regression models that adjusted for CD4 cell count at baseline, week 8, or both, as well as HIV-1 RNA levels. After adjustment for HIV-1 RNA levels, plasma HIV-1 RNA suppression to less than 500 copies/mL at week 24 was not significantly associated with sex, race/ethnicity, history of intravenous drug use, Karnofsky score, or duration of previous zidovudine use. However, the large CIs suggest that these analyses may not detect modest associations between these variables and virologic outcome.

Both the baseline and week-8 HIV-1 RNA levels significantly predicted suppression of a patient's HIV-1

Table 3. **Suppression of HIV-1 RNA Level to Less Than 500 copies/mL at Week 24, according to Patient Characteristics***

Variable	Patients with Week-24 HIV-1 RNA Level < 500 copies/mL, *n/n (%)*	Relative Risk (95% CI)	
		Unadjusted	Adjusted†
Baseline CD4 cell count			
$<0.05 \times 10^9$ cells/L	58/155 (37)	1.00 (referent)	1.00 (referent)
$0.05–0.099 \times 10^9$ cells/L	44/90 (49)	1.31 (0.97–1.75)	1.04 (0.79–1.36)
$\geq 0.10 \times 10^9$ cells/L	99/167 (59)	1.58 (1.25–2.01)	1.20 (0.95–1.52)
Week-8 CD4 cell count‡			
$<0.05 \times 10^9$ cells/L	21/73 (29)	1.00 (referent)	1.00 (referent)
$0.05–0.099 \times 10^9$ cells/L	27/70 (39)	1.34 (0.84–2.14)	0.98 (0.61–1.57)
$\geq 0.10 \times 10^9$ cells/L	153/263 (58)	2.02 (1.39–2.94)	1.47 (1.00–2.16)
Age			
<35 y	52/141 (37)	1.00 (referent)	1.00 (referent)
35–39 y	45/98 (46)	1.25 (0.92–1.69)	1.18 (0.89–1.56)
40–44 y	35/67 (52)	1.42 (1.03–1.94)	1.27 (0.94–1.71)
≥45 y	69/106 (65)	1.77 (1.37–2.28)	1.44 (1.11–1.86)
Sex			
Male	173/346 (50)	1.00 (referent)	1.00 (referent)
Female	28/66 (42)	0.85 (0.63–1.15)	0.83 (0.61–1.13)
Race/ethnicity§			
White	124/230 (54)	1.00 (referent)	1.00 (referent)
Black	40/101 (40)	0.73 (0.56–0.96)	0.89 (0.68–1.17)
Hispanic	33/73 (45)	0.84 (0.63–1.11)	1.01 (0.79–1.29)
Intravenous drug use			
Never	175/353 (50)	1.00 (referent)	1.00 (referent)
Ever	26/59 (44)	0.89 (0.65–1.21)	0.77 (0.55–1.08)
Karnofsky score			
100	68/122 (56)	1.00 (referent)	1.00 (referent)
90	98/212 (46)	0.83 (0.67–1.03)	0.83 (0.68–1.01)
70 or 80	35/78 (45)	0.81 (0.60–1.08)	0.91 (0.71–1.18)
Duration of previous zidovudine use			
≤12 mo	56/117 (48)	1.00 (referent)	1.00 (referent)
13–24 mo	51/104 (49)	1.02 (0.78–1.35)	1.04 (0.81–1.33)
25–48 mo	48/112 (43)	0.90 (0.67–1.19)	0.93 (0.71–1.21)
>48 mo	46/79 (58)	1.22 (0.93–1.59)	1.18 (0.93–1.51)

* Numerators are the number of patients still taking indinavir, zidovudine, and lamivudine and having an HIV-1 RNA level less than 500 copies/mL at week 24. Denominators are the number of patients who could have completed 24 weeks of treatment before closure of the study. Patients who discontinued treatment with indinavir, zidovudine, and lamivudine before week 8 are excluded.
† Adjusted for baseline and week-8 HIV-1 RNA levels. Adjusted relative risks are given for a patient with a baseline HIV-1 RNA level of 100 000 copies/mL and a week-8 level of 500 copies/mL (these values are close to the medians for the study sample).
‡ Six patients who did not have a CD4 cell count measurement for week 8 were not included in the results for week-8 CD4 cell count presented in this table.
§ Eight patients (including four with a week-24 HIV-1 RNA level < 500 copies/mL) whose race or ethnicity was classified as "other" are not included in the results for race or ethnicity presented in this table.

Table 4. **Association of Baseline and Early Change in Plasma HIV-1 RNA Level with Suppression of HIV-1 RNA to Less Than 50 copies/mL at Week 24***

HIV-1 RNA Category at Week 8	Patients with Week-24 HIV-1 RNA < 50 copies/mL, according to Baseline HIV-1 RNA Level				All Patients
	<5000 copies/mL	5000–49 999 copies/mL	50 000–499 999 copies/mL	≥500 000 copies/mL	
	← n/n (%) →				
<500 copies/mL	11/16 (69)	37/70 (53)	38/91 (42)	2/11 (18)	88/188 (47)
≥500 copies/mL and ≥2 $\log_{10}$ copies/mL below baseline level	–†	–†	12/56 (21)	5/21 (24)	17/77 (22)
≥500 copies/mL and 1–1.99 $\log_{10}$ copies/mL below baseline level	–†	6/17 (35)	6/42 (14)	0/7 (0)	12/66 (18)
≥500 copies/mL and <1 $\log_{10}$ copies/mL below baseline level	2/6 (33)	2/16 (13)	2/50 (4)	0/9 (0)	6/81 (7)
All patients	13/22 (59)	45/103 (44)	58/239 (24)	7/48 (15)	123/412 (30)
P value‡	0.18	0.008	<0.001	>0.2	<0.001

* Numerators are the number of patients at week 24 who were still taking indinavir, zidovudine, and lamivudine and had an HIV-1 RNA level less than 50 copies/mL; denominators are the number of patients who could have completed 24 weeks of treatment before closure of the study. Patients who discontinued treatment with indinavir, zidovudine, and lamivudine before week 8 are excluded.
† Baseline HIV-1 RNA level is too low to allow quantification of changes of the specified magnitude.
‡ *P* values were calculated by using the Fisher exact test to compare the proportions of patients suppressed across the four categories of week-8 HIV-1 RNA for each baseline HIV-1 RNA level.

RNA level to less than 50 copies/mL at week 24 (**Table 4**). Across the range of baseline HIV-1 RNA levels, patients who had an HIV-1 RNA level less than 500 copies/mL at week 8 had the highest rate of suppression to less than 50 copies/mL at week 24, and patients who had 500 copies/mL or greater at week 8 and less than a 1–$\log_{10}$ copies/mL reduction from baseline had the lowest rate. A similar trend was seen within each category of baseline HIV-1 RNA level; however, small numbers of patients may explain the lack of statistical significance between week-8 HIV-1 RNA levels and week-24 virologic suppression to less than 50 copies/mL that occurred within some baseline HIV-1 RNA categories.

In multivariate logistic regression analysis after adjustment for the baseline HIV-1 RNA level and the change from baseline to week 8, only higher CD4 cell count at week 8 ($P = 0.015$) and older age ($P = 0.014$) significantly predicted an increased probability of suppression to less than 50 copies/mL at week 24. The rate of suppression of HIV-1 RNA level at week 24 increased with increasing CD4 cell count at week 8—from 15% of patients with week-8 CD4 counts less than 0.05×10^9 cells/L to 24% of patients with CD4 counts of 0.05 to 0.099×10^9 cells/L to 36% of patients with CD4 cell counts of 0.10×10^9 cells/L or greater. Among patients younger than 35 years of age, 21% achieved virologic suppression to less than 50 copies/mL at week 24 compared with 30%, 28%, and 43% of patients aged 35 to 39 years, 40 to 44, and 45 years or older, respectively. We found no significant associations between other patient characteristics at baseline and suppression of the plasma HIV-1 RNA level to less than 50 copies/mL at week 24, although the limited sample size means that modest associations are unlikely to be detected by this analysis.

Of the 188 patients with a week-8 plasma HIV-1 RNA level less than 500 copies/mL, 186 had a week-4 HIV-1 RNA value available. Of these 186 patients, 100 had a week-4 HIV-1 RNA level less than 500 copies/mL. The level of HIV-1 RNA was suppressed to less than 50 copies/mL at week 24 in 55% of patients (55 of 100) whose HIV-1 RNA level at week 4 was less than 500 copies/mL compared with 37% of patients (32 of 86) whose level at week 4 was 500 copies/mL or greater (difference between week-4 groups, 18 percentage points [CI, 4 to 32 percentage points]; $P = 0.019$, Fisher exact test). Thus, if a patient has a week-8 HIV-1 RNA level less than 500 copies/mL, knowledge that the patient's value was less than 500 copies/mL at week 4 provides some additional information in predicting virologic suppression to less than 50 copies/mL at week 24.

Fifty-six patients had a week-8 HIV-1 RNA level less than 50 copies/mL, including 54 patients who also

Table 5. **Association between Week-8 Plasma HIV-1 RNA Level and Clinical Progression of HIV-1 Infection***

HIV-1 RNA Category at Week 8	Patients with Progression to an AIDS-Defining Event or Death, *n/n (%)*
<500 copies/mL	5/228 (2.2)
≥500 copies/mL and ≥2 $\log_{10}$ copies/mL below baseline level	2/86 (2.3)
≥500 copies/mL and 1–1.99 $\log_{10}$ copies/mL below baseline level	4/81 (4.9)
≥500 copies/mL and <1 $\log_{10}$ copies/mL below baseline level	10/94 (10.6)

* $P = 0.009$, according to the Fisher exact test. ($P = 0.004$ by using the log-rank test.) Denominators represent the number of patients randomly allocated to receive indinavir, zidovudine, and lamivudine therapy who initiated study treatment, had baseline and week-8 HIV-1 RNA measurements, and had a week-8 HIV-1 RNA value that met the criteria for one of the categories listed in the table. Numerators are the number of patients with disease progression to an AIDS-defining event or death.

had an HIV-1 RNA measurement obtained at week 4. In assessing suppression to less than 50 copies/mL at week 4 among these 54 patients, we found that HIV-1 RNA level was subsequently suppressed to less than 50 copies/mL at week 24 in 69% (11 of 16) of those having a week-4 value less than 50 copies/mL compared with 63% (24 of 38) of those having a week-4 value of 50 copies/mL or greater (difference, 6 percentage points, [CI, −22 to 33 percentage points]; $P > 0.2$).

Changes in CD4 Cell Count

To evaluate the association between changes in CD4 cell count and the profiles of HIV-1 RNA response over time, we studied the subset of 353 patients who had completed 24 weeks of treatment by the time of study closure. We divided these patients into four mutually exclusive groups on the basis of the magnitude, rapidity, and durability of the week-24 HIV-1 RNA response. Patients with a pattern of rapid suppression achieved an HIV-1 RNA level less than 500 copies/mL at weeks 8 and 24 ($n = 134$ [38%]). We considered patients' rate of suppression to be slow if they had a week-24 value less than 500 copies/mL but a level of 500 copies/mL or greater at week 8 ($n = 67$ [19%]). Patients with a response of 1-log copies/mL were those with a week-24 HIV-1 RNA level greater than 500 copies/mL and at least a 1–$\log_{10}$ copies/mL decrease from baseline ($n = 62$ [18%]). Patients were considered to have had minimal or no response if their week-24 HIV-1 RNA value was 500 copies/mL or greater and was less than 1-$\log_{10}$ copies/mL below their baseline level ($n = 90$ [25%]).

Different HIV-1 RNA profiles were associated with significant differences in CD4 cell count changes from baseline to week 24 ($P < 0.001$, analysis of variance). Patients having minimal or no response had a significantly smaller increase in CD4 cell count (mean increase, 0.05×10^9 cells/L) than patients who achieved rapid suppression (mean increase, 0.101×10^9 cells/L), slow suppression (mean increase, 0.115×10^9 cells/L), or a 1-$\log_{10}$ copies/mL response (mean increase, 0.126×10^9 cells/L). Patients varied considerably in the magnitude of change in CD4 cell count associated with a given change in HIV-1 RNA level. However, when the change in HIV-1 RNA was compared with the change in CD4 cell count at week 24, only 13% of patients who were still receiving indinavir combination therapy at week 24 had discordant responses (decreases or increases in both CD4 count and HIV-1 RNA level).

Predictors of Clinical Progression

Of the 489 patients who received at least 8 weeks of indinavir, zidovudine, and lamivudine, 21 (4.3%) subsequently progressed to an AIDS-defining event or died. The rate of clinical progression was significantly higher in patients with lower HIV-1 RNA responses at week 8 ($P = 0.009$, Fisher exact test) (**Table 5**).

Of these 489 patients, 481 had a CD4 measurement obtained at week 8. Twenty of these 481 patients (4.1%) subsequently progressed to an AIDS-defining event or died. Eight percent (14 of 175) of patients with a CD4 cell count less than 0.050×10^9 cells/L at week 8 subsequently experienced clinical progression, compared with 4.6% (5 of 108) of patients with a count of 0.05 to 0.099×10^9 cells/L and 1% (2 of 206) of patients with a count of 0.10×10^9 cells/L or greater. In multivariate proportional hazards regression analysis, after adjustment for baseline HIV-1 RNA level and the change in HIV-1 RNA level from baseline to week 8, patients with a week-8 CD4 cell count of 0.05×10^9 cells/L or greater had a decreased hazard of progression to an AIDS-defining event or death compared with patients who had a week-8 CD4 cell count of less than 0.050×10^9 cells/L (hazard ratio, 0.25 [CI, 0.09 to 0.67]; $P = 0.006$). A further multivariate proportional hazards model showed that baseline HIV-1 RNA level

and baseline CD4 cell count were not significantly associated with clinical progression ($P > 0.2$ for both) when added to a model in which week-8 HIV-1 RNA level and week-8 CD4 cell count remained significant. However, because few patients in this study had clinical progression, we cannot rule out the possibility of clinically important associations between clinical progression and baseline HIV-1 RNA level or CD4 cell count.

DISCUSSION

Therapy for HIV-1 infection has dramatically improved since the introduction of protease inhibitors. Yet, a significant proportion of patients treated with protease inhibitor combination regimens still do not achieve HIV-1 RNA levels below the limits of detection. Most studies of protease inhibitor combination therapies have reported plasma HIV-1 RNA suppression in 60% to 90% of patients (1–3, 5), although more recent studies have reported suppression rates of only 40% to 50% (4, 16–18). The rates of RNA suppression seen in ACTG 320 were more consistent with those of the latter studies. Several factors could explain the lower response rates seen in ACTG 320 compared with those reported in earlier clinical trials; these factors include disease stage, previous nucleoside experience, demographic characteristics, and drug adherence of the patient population studied.

We have characterized early predictors of plasma HIV-1 RNA suppression in a subset of patients who received indinavir, zidovudine, and lamivudine for at least 8 weeks and had measurements of baseline and week-8 plasma HIV-1 RNA level; thus, our conclusions do not apply to patients who discontinue therapy early because of toxicities or concerns about treatment efficacy. The primary virologic end points we studied were suppression of plasma HIV-1 RNA level at week 24 to less than 500 copies/mL or to less than 50 copies/mL. We found that a lower level of HIV-1 RNA at baseline, a greater reduction in HIV-1 RNA at week 8, a higher CD4 cell count at week 8, and older age each independently predicted HIV-1 RNA suppression to less than 500 copies/mL at week 24. The results were similar when we constructed models that evaluated factors predictive of suppression to less than 50 copies/mL.

The strong predictive value of baseline plasma HIV-1 RNA on subsequent viral load suppression seen in our study was not surprising. Of interest, however, the CD4 cell count was associated with the likelihood of plasma HIV-1 RNA suppression independent of plasma HIV-1 RNA level. A lower CD4 cell count has been associated with a lower rate of virologic response in other studies of protease inhibitor–containing regimens (17–19). Low CD4 cell count may be a marker for other virologic factors, such as quasi-species diversity, that could increase the likelihood of developing drug-resistant HIV-1 variants. Alternatively, in patients with lower CD4 cell counts and more advanced disease, factors such as concomitant medications or illnesses might complicate adherence to antiretroviral therapy.

We also found that older age increased the likelihood of virologic suppression, independent of plasma HIV-1 RNA level. A similar correlation of age with virologic suppression was seen in a previous study of patients receiving combination antiretroviral therapy; however, the strongest predictor of virologic failure in that study was missed clinic appointments, which may reflect drug nonadherence (16). Because drug adherence was not formally assessed in ACTG 320, we cannot comment on the extent to which nonadherence contributed to the apparent association in our study between younger age and virologic failure. Previous zidovudine use did not predict HIV-1 RNA suppression, perhaps because most of these patients had previously used zidovudine for a fairly prolonged period.

Of interest, week-8 HIV-1 RNA level predicted virologic suppression at week 24 independently of the baseline value. If the combination of indinavir, zidovudine, and lamivudine therapy had the same activity in all patients, one would expect that HIV-1 RNA levels measured soon after initiation of therapy would depend on the baseline value and would not be predictive when the baseline value was taken into account. This finding implies that the magnitude of change in plasma HIV-1 RNA level in response to a given regimen must differ among patients, and, therefore, the plasma HIV-1 RNA level achieved by an individual patient in response to an antiretroviral regimen cannot be predicted solely on the basis of the specific regimen administered and the patient's baseline plasma HIV-1 RNA level. The variability in responses of individual patients to an antiretroviral regimen could be due to differences in drug adherence, drug metabolism, baseline HIV-1 drug resistance, or other as-yet uncharacterized host or viral factors.

Viral load suppression to less than 500 copies/mL at week 8 is a good predictor of suppression to either less than 500 or 50 copies/mL at week 24. However, if a patient has an HIV-1 RNA level suppressed to less than 500 copies/mL at week 8, knowledge of a week-4 plasma HIV-1 RNA level less than 500 copies/mL only provided additional prognostic information in predicting an increased rate of subsequent suppression to less than 50 copies/mL at week 24. Among patients without HIV-1 RNA suppression at week 8, greater changes from baseline to week 8 were predictive of suppression. However, in these patients, suppression at week 4 was rare, and the level achieved at week 4 did not significantly improve prediction of subsequent suppression to less than 500 copies/mL at week 24. Thus, obtaining a plasma HIV-1 RNA value at week 4 does not appear to add substantially to the predictive power of a week-8 value.

Virologic suppression achieved by week 24 appeared to be durable. Patients who achieved plasma HIV-1 RNA suppression by week 8 appeared to have the same likelihood of maintaining virologic suppression to less than 500 copies/mL at week 40 as those patients who did not achieve suppression until week 24. Thus, although early virologic responses are important in achieving virologic suppression, they may not be as important in maintaining this response. In addition, we found that patients who had not demonstrated virologic suppression by week 24 were unlikely to achieve suppression to less than 500 copies/mL. Patients achieved HIV-1 RNA suppression to less than 50 copies/mL more slowly than to less than 500 copies/mL, and few patients who ultimately achieved an HIV-1 RNA level less than 50 copies/mL at week 24 had also been suppressed to less than 50 copies/mL at week 8. We have no data to determine whether there are times between weeks 8 and 24, beyond which virologic suppression to less than 500 or 50 copies/mL is unlikely. One smaller study of patients receiving ritonavir suggested that the nadir in viral load is usually achieved by 12 weeks of therapy (20). In our study, the HIV-1 RNA profile groups differed significantly in CD4 cell responses at week 24 that appeared to be primarily driven by a reduced CD4 response in the patients who had no or minimal HIV-1 RNA response to indinavir at week 24. These data suggest that an antiretroviral regimen should not be judged as failing virologically until after 8 weeks of therapy and that alternative regimens should be considered if suppression to less than 500 copies/mL is not achieved after 6 months of therapy.

Both HIV-1 RNA level and CD4 cell count at week 8 independently predicted clinical response to therapy with a protease inhibitor. This analysis underscores the important contribution of CD4 cell count in predicting clinical outcome. Baseline HIV-1 RNA and CD4 cell counts were not significant predictors of clinical outcome after adjustment for week-8 HIV-1 RNA and CD4 cell counts. These data are consistent with our finding that early plasma HIV-1 RNA level is a better predictor of virologic suppression than the baseline plasma HIV-1 RNA level. However, the patients in our study had very few clinical events, and therefore an association with baseline levels cannot be ruled out. Our findings are, however, consistent with those from a previous study of patients primarily receiving nucleoside analogues (9), and support the use of HIV-1 RNA level and CD4 cell count achieved during therapy to assess the clinical effectiveness of an antiretroviral regimen.

From University of Rochester School of Medicine and Dentistry, Rochester, New York; Harvard School of Public Health, Boston, Massachusetts; University of Washington, Seattle, Washington; Johns Hopkins University, Baltimore, Maryland; University of North Carolina, Chapel Hill, North Carolina; University of California, San Diego, California; University of Alabama at Birmingham, Birmingham, Alabama; University of Miami School of Medicine, Miami, Florida; and Columbia University, New York, New York.

Note: Drs. Demeter and Hughes contributed equally to this work.

Disclosures: Dr. Demeter has received research support from Merck & Co. and Pharmacia-Upjohn and research support and honoraria from Glaxo Wellcome and Roche Molecular Systems and has served as a consultant to Glaxo Wellcome, Roche Pharmaceuticals, and Roche Molecular Systems. Dr. Hughes has received research support from Roche Pharmaceuticals and served as a consultant to Chiron. Dr. Jackson received an honorarium from Glaxo Wellcome. Dr. Fiscus has received research support from Glaxo Wellcome, Organon Technika, and Visible Genetics. Dr. Squires has received research support from Merck & Co., Abbott Laboratories, Agouron Pharmaceuticals, Bristol-Myers Squibb, Glaxo Wellcome, Gilead Sciences, Systemix, and Oxo-Chemie and has served as a consultant to Merck & Co., Bristol-Myers Squibb, Roxane, and Vertex. Dr. Fischl has received research support from Abbot Laboratories, Bristol-Myers Squibb, and Dupont and research support and honoraria from Agouron Pharmaceuticals, Glaxo Wellcome, and Merck & Co. and has served as an advisory board member to Bristol-Myers Squibb and Glaxo Wellcome.

Acknowledgments: The authors thank the patients and investigators at the 33 AIDS Clinical Trials units and 7 National Hemophilia Foundation sites, whose participation made this study possible. They also thank Luis Berrios, Michael Chiulli, and Robin Shepard for performance of HIV-1 RNA assays.

Grant Support: In part by the AIDS Clinical Trials Group and grants (AI-27658, AI-38855, AI-38858 [contracts 96VC006, 96VC009, 96VC010], AI-27664, AI-30731, RR-00044) from the U.S. National Institutes of Health. Supplemental support for some virology studies was provided by Merck & Co. and Roche Molecular Systems. Study medications were provided by Merck & Co. and Glaxo Wellcome.

Requests for Single Reprints: Lisa M. Demeter, MD, Infectious Diseases Unit, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Box 689, Rochester, NY 14642.

Current Author Addresses: Dr. Demeter: Infectious Diseases Unit, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Box 689, Rochester, NY 14642.
Drs. Hughes and Bosch: Harvard School of Public Health, 651 Huntington Avenue, Boston, MA 02115.
Dr. Jackson: Department of Pathology, Johns Hopkins University, 600 North Wolfe Street, Carnegie 420, Baltimore, MD 21287.
Dr. Coombs: Department of Laboratory Medicine, University of Washington, 1959 Northeast Pacific Avenue, Room NW 120, Seattle, WA 98195.
Ms. Grimes: Brown University, Box G8063, Providence, RI 02906.
Dr. Fiscus: Department of Microbiology and Immunology, University of North Carolina at Chapel Hill School of Medicine, 709 Mary Ellen Jones Building, Campus Box 7140, Chapel Hill, NC 27599.
Dr. Spector: Department of Pediatrics, Division of Infectious Diseases, University of California, San Diego, 9500 Gilman Drive, Room 430, La Jolla, CA 92093.
Dr. Squires: Los Angeles County University of Southern California Medical Center, Rand Schrader Clinic, 1300 North Mission Road, Room 349, Los Angeles, CA 90033.
Dr. Fischl: Department of Medicine, University of Miami School of Medicine, 1800 Northwest 10th Avenue, Box 016960 (R-60A), Miami, FL 33101.
Dr. Hammer: Division of Infectious Diseases, Columbia University, 630 West 168th Street, Mail Box 82, Room PH8-W876, New York, NY 10032.

Author Contributions: Conception and design: L.M. Demeter, M.D. Hughes, R.W. Coombs, S.A. Spector, M.A. Fischl, S.M. Hammer.
Analysis and interpretation of the data: L.M. Demeter, M.D. Hughes, J.M. Grimes, R.J. Bosch, S.A. Spector, M.A. Fischl, S.M. Hammer.
Drafting of the article: L.M. Demeter, M.D. Hughes, R.J. Bosch, S.A. Spector, M.A. Fischl, S.M. Hammer.
Critical revision of the article for important intellectual content: L.M. Demeter, M.D. Hughes, R.W. Coombs, J.B. Jackson, R.J. Bosch, S.A. Spector, K.E. Squires, M.A. Fischl, S.M. Hammer.
Final approval of the article: L.M. Demeter, M.D. Hughes, R.J. Bosch, S.A. Fiscus, S.A. Spector, K.E. Squires, M.A. Fischl, S.M. Hammer.
Provision of study materials or patients: J.B. Jackson, S.A. Spector, K.E. Squires, M.A. Fischl, S.M. Hammer.
Statistical expertise: M.D. Hughes, J.M. Grimes, R.J. Bosch.
Administrative, technical, or logistic support: M.D. Hughes, R.W. Coombs, J.B. Jackson, S.A. Fiscus, S.M. Hammer.
Collection and assembly of data: L.M. Demeter, M.D. Hughes, R.W. Coombs, J.M. Grimes, S.A. Spector, M.A. Fischl, S.M. Hammer.

References

1. **Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, et al.** Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med. 1997;337:734-9. [PMID: 9287228]

2. **Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, et al.** A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med. 1997;337:725-33. [PMID: 9287227]

3. **Ledergerber B, Egger M, Opravil M, Telenti A, Hirschel B, Battegay M, et al.** Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. Lancet. 1999;353:863-8. [PMID: 10093977]

4. **Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J, et al.** Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. N Engl J Med. 1999;341:1865-73. [PMID: 10601505]

5. **Hogg RS, Rhone SA, Yip B, Sherlock C, Conway B, Schechter MT, et al.** Antiviral effect of double and triple drug combinations amongst HIV-infected adults: lessons from the implementation of viral load-driven antiretroviral therapy. AIDS. 1998;12:279-84. [PMID: 9517990]

6. **Murphy RL, Gulick RM, DeGruttola V, D'Aquila RT, Eron JJ, Sommadossi JP, et al.** Treatment with amprenavir alone or amprenavir with zidovudine and lamivudine in adults with human immunodeficiency virus infection. AIDS Clinical Trials Group 347 Study Team. J Infect Dis. 1999;179:808-16. [PMID: 10068575]

7. **Katzenstein DA, Hammer SM, Hughes MD, Gundacker H, Jackson JB, Fiscus S, et al.** The relation of virologic and immunologic markers to clinical outcomes after nucleoside therapy in HIV-infected adults with 200 to 500 CD4 cells per cubic millimeter. AIDS Clinical Trials Group Study 175 Virology Study Team. N Engl J Med. 1996;335:1091-8. [PMID: 8813039]

8. An evaluation of HIV RNA and CD4 cell count as surrogates for clinical outcome. Delta Coordinating Committee and Virology Group. AIDS. 1999;13:565-73. [PMID: 10203381]

9. **Marschner IC, Collier AC, Coombs RW, D'Aquila RT, DeGruttola V, Fischl MA, et al.** Use of changes in plasma levels of human immunodeficiency virus type 1 RNA to assess the clinical benefit of antiretroviral therapy. J Infect Dis. 1998;177:40-7. [PMID: 9419168]

10. **Coombs RW, Welles SL, Hooper C, Reichelderfer PS, D'Aquila RT, Japour AJ, et al.** Association of plasma human immunodeficiency virus type 1 RNA level with risk of clinical progression in patients with advanced infection. AIDS Clinical Trials Group (ACTG) 116B/117 Study Team. ACTG Virology Committee Resistance and HIV-1 RNA Working Groups. J Infect Dis. 1996;174:704-12. [PMID: 8843206]

11. **O'Brien WA, Hartigan PM, Daar ES, Simberkoff MS, Hamilton JD.** Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. VA Cooperative Study Group on AIDS. Ann Intern Med. 1997;126:939-45. [PMID: 9182470]

12. **Carpenter CC, Cooper DA, Fischl MA, Gatell JM, Gazzard BG, Hammer SM, et al.** Antiretroviral therapy in adults: updated recommendations of the International AIDS Society-USA Panel. JAMA. 2000;283:381-90. [PMID: 10647802]

13. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services and Henry J. Kaiser Family Foundation. MMWR Morb Mortal Wkly Rep. 1998;47:43-82. [PMID: 9572121]

14. **Diggle PJ, Liang KY, Zeger S.** Analysis of Longitudinal Data. Oxford: Oxford Univ Pr; 1994.

15. **Agresti A.** Categorical Data Analysis. New York: Wiley; 1990.

16. **Lucas GM, Chaisson RE, Moore RD.** Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. Ann Intern Med. 1999;131:81-7. [PMID: 10419445]

17. **Deeks SG, Hecht FM, Swanson M, Elbeik T, Loftus R, Cohen PT, et al.** HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic: response to both initial and salvage therapy. AIDS. 1999;13:F35-43. [PMID: 10397555]

18. **Hirsch M, Steigbigel R, Staszewski S, Mellors J, Scerpella E, Hirschel B, et al.** A randomized, controlled trial of indinavir, zidovudine, and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapy. J Infect Dis. 1999;180:659-65. [PMID: 10438352]

19. **Miller V, Staszewski S, Sabin C, Carlebach A, Rottmann C, Weidmann E, et al.** CD4 lymphocyte count as a predictor of the duration of highly active antiretroviral therapy-induced suppression of human immunodeficiency virus load. J Infect Dis. 1999;180:530-3. [PMID: 10395876]

20. **Kempf DJ, Rode RA, Xu Y, Sun E, Heath-Chiozzi ME, Valdes J, et al.** The duration of viral suppression during protease inhibitor therapy for HIV-1 infection is predicted by plasma HIV-1 RNA at the nadir. AIDS. 1998;12:F9-14. [PMID: 9543434]

I love life too much to agree to early death; there were too many half-finished dramas whose completion I wished to know. I would have to submit to the surgery. Like one of those figures on the surgical table in an Eakins painting, the swamp of my slithery insides would be exposed, my darkest interior invaded. I recall telling my wife that I looked upon this surgery as tantamount to having to face a vicious bully, who was going to beat the hell out of me, but it was the price of getting back into school, and since I wanted back in, there was nothing for it but to take my beating.

Joseph Epstein
"Taking the Bypass"
The New Yorker. April 12, 1999:61

Submitted by:
Sigmund Weitzman, MD
Northwestern University Medical School
Chicago, IL 60611-3008

Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.–*The Editor*