

## 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

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### ABSTRACT

**Background** We studied measures of human immunodeficiency virus (HIV) replication, the viral phenotype, and immune function (CD4 cell counts) and the relation of changes in these indicators to clinical outcomes in a subgroup of patients in a controlled trial of early antiretroviral treatment for HIV, the AIDS Clinical Trials Group Study 175.

**Methods** The 391 subjects, each of whom entered the study with a single screening CD4 cell count of 200 to 500 per cubic millimeter, were randomly assigned to receive zidovudine alone, didanosine alone, zidovudine plus didanosine, or zidovudine plus zalcitabine. Plasma concentrations of HIV RNA were assessed in 366 subjects, and viral isolates from 332 subjects were assayed for the presence of the syncytium-inducing phenotype.

**Results** After eight weeks, the mean ( $\pm$ SE) decrease from base line in the concentration of HIV RNA, expressed as the change in the base 10 log of the number of copies per milliliter, was  $0.26 \pm 0.06$  for patients treated with zidovudine alone,  $0.65 \pm 0.07$  for didanosine alone,  $0.93 \pm 0.10$  for zidovudine plus didanosine, and  $0.89 \pm 0.06$  for zidovudine plus zalcitabine ( $P < 0.001$  for each of the pairwise comparisons with zidovudine alone). Multivariate proportional-hazards models showed that higher base-line concentrations of plasma HIV RNA, less suppression of plasma HIV RNA by treatment, and the presence of the syncytium-inducing phenotype were significantly associated with an increased risk of progression to the acquired immunodeficiency syndrome and death. After adjustment for these measures of viral replication and for the viral phenotype, CD4 cell counts were not significant predictors of clinical outcome.

**Conclusions** Both the risk of the progression of HIV disease and the efficacy of antiretroviral therapy are strongly associated with the plasma level of HIV RNA and with the viral phenotype. The changes in the plasma concentration of HIV RNA predict the changes in CD4 cell counts and survival after treatment with reverse-transcriptase inhibitors. (N Engl J Med 1996;335:1091-8.)

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THE AIDS Clinical Trials Group Study 175 (ACTG 175) provides direct evidence, in the clinical report elsewhere in this issue of the *Journal*,<sup>1</sup> of the clinical and immunologic benefits (e.g., increased CD4 cell counts) of the treatment of human immunodeficiency virus (HIV) infection with didanosine, zidovudine plus didanosine, and zidovudine plus zalcitabine, as compared with zidovudine monotherapy. Although changes in CD4 cell counts have provided a basis for the initiation of antiretroviral treatment and have been used to help define the acquired immunodeficiency syndrome (AIDS),<sup>2</sup> the plasma HIV RNA concentration is increasingly used as a measure of viral replication in order to evaluate the activity of antiviral drugs.<sup>3-10</sup> In trials comparing zidovudine with placebo in symptomatic subjects with CD4 cell counts of 200 to 500 per cubic millimeter, increasing plasma HIV RNA concentrations and decreasing CD4 cell counts have been associated with the development of AIDS.<sup>11</sup> In addition, the presence of the syncytium-inducing phenotype of HIV, associated with advanced disease and resistance to zidovudine, may contribute to the rapid progression of disease.<sup>12,13</sup>

In order to determine the relation of virologic and immunologic factors to clinical progression in a subgroup of subjects enrolled in ACTG 175, we evaluated plasma HIV RNA concentrations, CD4 cell counts, and viral phenotype both at entry to the study and during treatment. The associations among virologic and immunologic responses, viral phenotypes, survival, and the progression of disease were examined in HIV-infected patients being treated with nucleoside reverse-transcriptase inhibitors at an intermediate stage of HIV disease.

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## METHODS

### Trial Design

The entry criteria, treatment regimens, and clinical characteristics of subjects in ACTG 175 are described in the study's clinical report.<sup>1</sup> The study's virology subgroup comprised 391 subjects enrolled at 11 of the study sites. Blood was collected in acid citrate dextrose on two occasions, at least 72 hours apart, during the 14 days preceding treatment, to determine plasma HIV RNA concentrations; the geometric mean of these two measurements was defined as the base-line value. Plasma HIV RNA concentrations were measured at weeks 8, 20, and 56, provided that the subjects continued to receive the assigned treatment.

### Virologic Studies

Syncytium-inducing viruses were detected by the cocultivation of supernatant fluid from cell-culture isolates in MT-2 cells. These were observed for 14 days, when the presence or absence of signs of cytopathology led us to identify the isolates as syncytium-inducing or non-syncytium-inducing isolates, respectively.<sup>12,13</sup> Plasma samples frozen at  $-70^{\circ}\text{C}$  were assayed for their plasma HIV RNA concentrations with the Amplicor polymerase-chain-reaction test (Roche Molecular Systems, Branchburg, N.J.).<sup>14</sup> All samples from individual subjects were tested in the same assay with control samples containing 15,000 and 150,000 copies of HIV RNA. The laboratories were certified in the performance of the assay by the Virology Quality Assurance Program of the ACTG.<sup>15</sup>

### Statistical Analysis

Analyses of plasma HIV RNA concentrations were undertaken after log (base 10) transformation of the values. Throughout this article, HIV RNA concentrations are expressed as the log of the number of copies per milliliter. Analysis of variance and two-sample *t*-tests were used to test associations among base-line characteristics, including CD4 cell counts and plasma HIV RNA concentrations, and the mean changes in CD4 cell counts and plasma HIV RNA concentrations associated with the different treatments. The associations between the base-line characteristics and the presence of the syncytium-inducing phenotype were evaluated with the chi-square test and logistic regression.<sup>16</sup> The distribution of times to events was compared with use of the log-rank test and Cox proportional-hazards models, with stratification according to history of antiretroviral treatment and the assigned treatment regimen.<sup>17</sup> Base-line levels and changes from base line to week 8 and week 56 in plasma HIV RNA concentrations and CD4 cell counts were included in the proportional-hazards models as continuous variables, but the hazard ratios are presented as those associated with a decrease of 1.00 log in the HIV RNA concentration and with an increase of 100 CD4 cells per cubic millimeter. Tests of interaction were used to assess whether the strength of the associations varied according to treatment and history of antiretroviral therapy.<sup>18</sup> All *P* values are two-sided and have not been adjusted for multiple comparisons.

## RESULTS

### Study Subjects

This study included 391 of the subjects enrolled in ACTG 175; of these, 216 reported having had one week of previous antiretroviral therapy or less, and 175 had received more than one week of antiretroviral therapy, usually with zidovudine. Of the group, 89 subjects were randomly assigned to receive zidovudine alone; 107, didanosine alone; 102, zidovudine plus didanosine; and 93, zidovudine plus zalcitabine. Selected characteristics of the 391 subjects are shown in Table 1. As compared with all 2467 subjects in ACTG 175, this subgroup had some differences in

characteristics attributable to its slower rate of accrual and site selection. Although a larger percentage of subjects in the virology subgroup had little or no previous antiretroviral therapy, as compared with the overall study group, the subjects in the two groups who had had such therapy received treatment of similar duration. The median duration of treatment during the study was 122 weeks; 17 percent of the virology subgroup was lost to follow-up, and 51 percent discontinued the study treatment. There was a significantly greater rate of discontinuation of treatment among subjects assigned to receive zidovudine alone (71 percent) than among those assigned to receive didanosine alone (41 percent,  $P<0.001$ ), zidovudine plus didanosine (45 percent,  $P=0.002$ ), or zidovudine plus zalcitabine (48 percent,  $P<0.001$ ). Analyses of changes in plasma HIV RNA concentrations were restricted to the first 56 weeks of follow-up, during which 68 percent of the subjects were still taking their assigned medications.

### Virologic and Immunologic Markers at Base Line

Plasma HIV RNA concentrations were assessed at base line, in two separate measurements, for 366 of the subjects. Four subjects had values (at both the measurements) below the limit of detection (2.30 log copies per milliliter). The mean plasma HIV RNA concentration was 4.20 log (15,971 copies per milliliter), and the values ranged as high as 6.16 log. For 80 percent of the subjects, the difference in the log concentration between the two base-line measurements was less than 0.26, and for 90 percent it was less than 0.41. For each additional 100 cells per cubic millimeter in a patient's CD4 count, the mean plasma HIV RNA concentration at entry was 0.14 log lower ( $P<0.001$ ), but subjects with similar CD4 counts had HIV RNA concentrations that varied by about  $\pm 1$  log from the average.

Syncytium-inducing virus was detected in 59 (18 percent) of the 332 viral isolates from samples taken at entry to the study. The subjects with syncytium-inducing virus in isolates had significantly lower mean CD4 cell counts than those without such virus ( $296\pm 12$  vs.  $352\pm 6$  cells per cubic millimeter,  $P<0.001$ ) and significantly higher plasma HIV RNA concentrations ( $4.53\pm 0.10$  vs.  $4.18\pm 0.04$  log,  $P<0.001$ ).

The association between base-line characteristics and plasma HIV RNA concentrations, CD4 cell counts, and the presence or absence of syncytium-inducing virus is shown in Table 1. The presence of signs and symptoms related to HIV infection (oral hairy leukoplakia, candidiasis, or herpes zoster) was significantly associated with increased HIV RNA concentrations ( $P<0.001$ ) and decreased CD4 cell counts ( $P=0.006$ ). Homosexuality was associated with a significantly higher plasma concentration of HIV RNA ( $P=0.002$ ), and intravenous drug use

**TABLE 1.** PLASMA HIV RNA CONCENTRATION, CD4 CELL COUNT, AND VIRAL PHENOTYPE ACCORDING TO THE CHARACTERISTICS OF THE SUBJECTS AT BASE LINE.\*

CHARACTERISTIC	No. (%) OF SUBJECTS	HIV RNA†	CD4 CELLS/ mm <sup>3</sup>	SUBJECTS WITH SYNCYTIUM- INDUCING VIRUS (%)
No. with data	391	366	391	332
Age				
20–29 yr	88 (23)	4.13±0.08	360±12	12
30–39 yr	190 (49)	4.21±0.06	339±7	18
40–49 yr	83 (21)	4.27±0.08	334±12	22
≥50 yr	30 (8)	4.18±0.15	344±16	24
P value		0.90	0.11	0.10
Sex				
Male	320 (82)	4.27±0.04	343±6	18
Female	71 (18)	3.92±0.09	346±14	18
P value		<0.001	0.83	0.93
Race or ethnic group				
Non-Hispanic white	282 (72)	4.27±0.04	343±6	18
Non-Hispanic black	57 (15)	3.99±0.10	347±14	24
Hispanic	45 (12)	4.17±0.11	342±16	8
Other	7 (2)	3.61±0.30	347±40	20
P value		0.013	0.99	0.17
Homosexuality				
Yes	283 (72)	4.28±0.04	345±6	16
No	108 (28)	4.01±0.07	338±10	23
P value		0.002	0.52	0.16
Intravenous drug use				
Yes	56 (14)	3.94±0.10	348±12	19
No	335 (86)	4.25±0.04	343±6	18
P value		0.003	0.72	0.86
Early symptoms of HIV‡				
Yes	60 (15)	4.50±0.09	309±13	22
No	331 (85)	4.15±0.04	349±6	17
P value		<0.001	0.006	0.35
Previous antiretroviral therapy				
None or ≤1 wk	216 (55)	4.24±0.05	363±7	13
>1 wk–12 mo	53 (14)	4.12±0.10	316±14	24
13–24 mo	51 (13)	4.13±0.11	312±14	20
25–36 mo	46 (12)	4.13±0.11	320±15	24
>36 mo	25 (6)	4.37±0.16	341±22	40
P value		0.50	0.001	0.023

\*Plus-minus values are means ±SE. In calculating the P values, age was treated as a continuous variable; all other P values are for comparisons of the subgroups shown.

†Plasma HIV RNA concentrations are expressed as the log of the number of copies per milliliter.

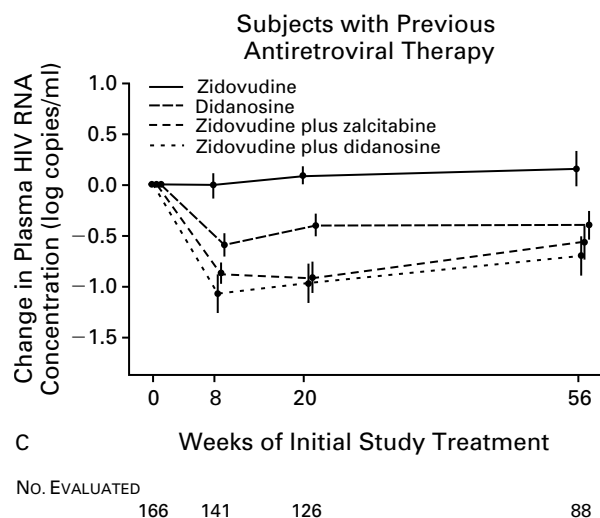
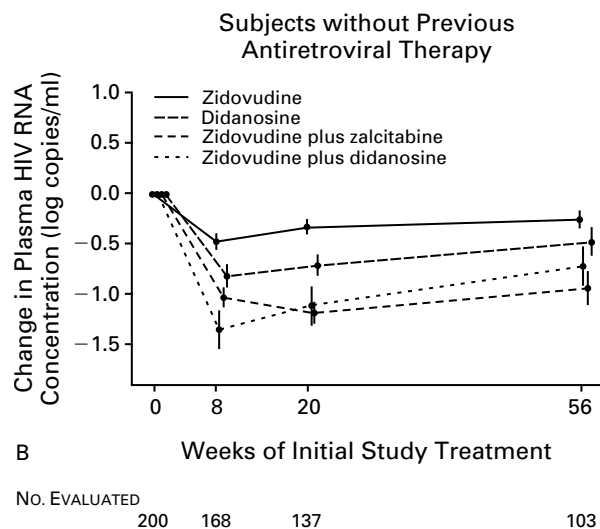
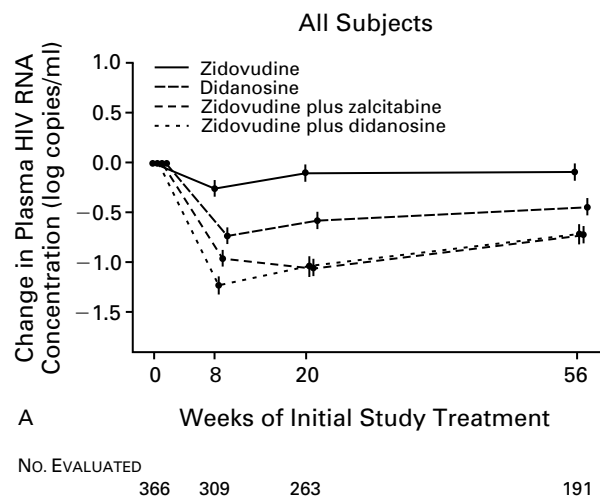
‡The symptoms of early-stage infection were oral candidiasis, hairy leukoplakia, or herpes zoster within 30 days before randomization.

with a significantly lower concentration ( $P = 0.003$ ). Women had significantly lower plasma HIV RNA concentrations ( $P < 0.001$ ), as did black subjects ( $P = 0.013$ ). However, there were no significant associations of these risk factors, sex, or race with the CD4 cell count. Antiretroviral treatment before entry into the study was associated with lower CD4 cell counts and a higher rate of the presence of syncytium-inducing phenotype, but not with differences in plasma HIV RNA concentrations.

**Multivariate Model of the Variation in Base-Line Plasma HIV RNA Concentrations**

A stepwise selection procedure for variables was used to develop a multivariate model for assessing factors associated with different base-line plasma HIV

RNA concentrations. In this model, the presence of early symptoms related to HIV was independently associated with an HIV RNA concentration, in copies per milliliter, that was 0.28 log higher ( $P = 0.006$ ); a decrease of 100 cells per cubic millimeter in the CD4 count was associated with an HIV RNA concentration that was 0.17 log higher ( $P < 0.001$ ); female sex was associated with an HIV RNA concentration that was 0.28 log lower ( $P = 0.003$ ); and intravenous drug use was associated with an HIV RNA concentration that was 0.26 log lower ( $P = 0.013$ ). Race and ethnic group were not significantly associated with a difference in HIV RNA concentrations. The presence of the syncytium-inducing phenotype, however, was associated with an HIV RNA concentration that was 0.28 log higher ( $P = 0.004$ ).



**Changes in Plasma HIV RNA Concentrations during Treatment**

Study treatment was associated with a decrease in plasma HIV RNA concentrations and an increase in CD4 cell counts. Measurements made eight weeks after the start of treatment revealed significant differences in the response of plasma HIV RNA concentrations to antiretroviral therapy among the treatment groups. There was a mean decrease of  $0.26 \pm 0.06$  log (45 percent) in the HIV RNA concentration in 65 subjects who received zidovudine alone, a decrease of  $0.65 \pm 0.07$  (78 percent) in 87 subjects who received didanosine alone, a decrease of  $0.93 \pm 0.10$  (88 percent) in 81 subjects who received zidovudine plus didanosine, and a decrease of  $0.89 \pm 0.06$  (87 percent) in 76 subjects who received zidovudine plus zalcitabine ( $P < 0.001$  for each of the pairwise comparisons with zidovudine alone).

The changes from base line in HIV RNA concentrations during the first 56 weeks of treatment are shown in Figure 1. Subjects without a history of antiretroviral treatment who took zidovudine alone had a mean reduction at week 8 of 0.47 log; subjects with that history had a mean reduction of 0.02. Pairwise comparisons of the changes in plasma HIV RNA concentrations between the other three treatments and zidovudine alone showed no significant differences between subjects with and without a history of antiretroviral treatment. At week 8 and week 56, as compared with subjects taking zidovudine alone, subjects who were taking didanosine alone, zidovudine plus didanosine, and zidovudine plus zalcitabine all had significantly greater reductions in plasma HIV RNA concentrations. The two combination therapies were associated with significantly greater mean reductions than was didanosine alone at week 8, but these differences were not significant at week 56.

**Virologic Predictors of the Progression of Disease**

During follow-up, 78 of the 391 subjects (20 percent) had a 50 percent decrease in the CD4 cell count, were given a diagnosis of AIDS, or died; 48 (12 percent) were given a diagnosis of AIDS or died; and 28 (7 percent) died. The pattern of end points found among the four treatment groups in our study of the virology subgroup was not significantly different from that in the overall study of 2467 subjects. The associations between the base-line characteristics of the virology subgroup and the progres-

**Figure 1.** Changes in Plasma HIV RNA Concentrations in the Four Treatment Groups over 56 Weeks.

Values are shown for all subjects, subjects without previous antiretroviral therapy, and subjects with previous antiretroviral therapy. Concentrations are expressed as the log of the number of HIV RNA copies per milliliter.

**TABLE 2.** OUTCOMES ACCORDING TO BASE-LINE VIROLOGIC AND IMMUNOLOGIC MARKERS IN A UNIVARIATE ANALYSIS.\*

MARKER	No. OF SUBJECTS	50% DECREASE IN CD4 CELLS, AIDS OR DEATH		
		AIDS, OR DEATH	AIDS OR DEATH	DEATH
			number (percent)	
Plasma HIV RNA (log copies/ml)				
4.74 to 6.16	91	39 (43)	30 (33)	20 (22)
4.28 to 4.74	92	16 (17)	7 (8)	3 (3)
3.71 to 4.28	92	10 (11)	4 (4)	1 (1)
<3.71	91	6 (7)	3 (3)	2 (2)
Hazard ratio†		0.25 (P<0.001)	0.17 (P<0.001)	0.15 (P<0.001)
CD4 cell count (cells/mm <sup>3</sup> )‡				
131 to 255	98	32 (33)	19 (19)	10 (10)
256 to 335	98	15 (15)	12 (12)	6 (6)
336 to 412	98	16 (16)	8 (8)	7 (7)
413 to 666	97	15 (15)	9 (9)	5 (5)
Hazard ratio§		0.68 (P=0.002)	0.61 (P=0.003)	0.70 (P=0.081)
Syncytium-inducing phenotype				
Present	59	27 (46)	18 (31)	11 (19)
Absent	273	45 (16)	27 (10)	15 (5)
Hazard ratio¶		0.28 (P<0.001)	0.25 (P<0.001)	0.24 (P<0.001)

\*P values are for the hazard ratios.

†The hazard ratios are those associated with a 1.0 lower base-line concentration, in log copies per milliliter.

‡These base-line values are the means of two measurements of the CD4 cell count, excluding the screening value of 200 to 500 cells per cubic millimeter required for entry into the study.

§The hazard ratios are those associated with a base-line CD4 cell count that is 100 cells per cubic millimeter higher.

¶The hazard ratios are those associated with the absence of syncytium-inducing virus.

sion of disease are shown in Table 2. The risk of disease progression was greatest among subjects in the lowest quartile of CD4 counts ( $\leq 255$  CD4 cells per cubic millimeter), with little change in the risk of progression found over the remainder of the range of CD4 counts. An increased risk of disease progression was associated with each successively higher quartile of base-line plasma HIV RNA concentrations and with the presence of syncytium-inducing virus. The risk of progression was examined with multivariate proportional-hazards models that considered the base-line plasma HIV RNA concentration, the base-line CD4 cell count, and the presence or absence of the syncytium-inducing phenotype at base line as variables.

Model 1 in Table 3 shows the hazard ratios for adverse clinical outcome associated with these variables. Lower base-line plasma HIV RNA concentrations and the presence of the non-syncytium-inducing phenotype at base line were significant predictors of a decreased hazard of disease progression. After adjustment for base-line plasma HIV RNA concentrations and viral phenotype, CD4 cell counts were not significantly associated with the risk of progression. Further analyses (data not shown) indicate that the associations of disease progression with base-line plasma HIV RNA concentrations, CD4

cell counts, and the viral phenotype were not significantly different between subjects who did and subjects who did not have a history of antiretroviral treatment, nor did they differ among the four treatment groups.

#### Responses to Treatment and the Progression of Disease

Responses to treatment, measured as the suppression of plasma HIV RNA or increases in CD4 cell counts, were included in proportional-hazards models (model 2 in Table 3). A decrease of 1.0 log in the concentration of HIV RNA from base line to week 8 was associated with a significant lowering to 0.35 in the hazard ratio for AIDS or death (i.e., a 65 percent reduction in the risk of AIDS or death). In model 2, the reduction in the risk of the specified clinical outcomes associated with changes in CD4 cell counts was not significant. The hazard ratios associated with base-line plasma HIV RNA concentrations and base-line viral phenotype were similar in models 1 and 2; both lower base-line plasma HIV RNA concentrations and a decrease in the concentration between base line and week 8 were associated with a significant reduction in the risk of disease progression (Table 4).

A proportional-hazards model similar to model 2 was fitted to the data, which included changes in plas-

**TABLE 3.** TWO MULTIVARIATE PROPORTIONAL-HAZARDS MODELS FOR PREDICTING OUTCOMES.\*

MARKER	50% DECREASE IN CD4 CELLS, AIDS, OR DEATH	AIDS OR DEATH	DEATH
	hazard ratio (95% confidence interval)		
<b>Model 1: base-line variables only</b>			
Lower plasma HIV RNA†	0.23 (0.14–0.38) P<0.001	0.17 (0.08–0.32) P<0.001	0.17 (0.07–0.40) P<0.001
Higher CD4 cell count‡	0.80 (0.59–1.09) P=0.15	0.80 (0.54–1.19) P=0.27	0.89 (0.53–1.49) P=0.66
Absence of syncytium-inducing phenotype	0.31 (0.18–0.54) P<0.001	0.34 (0.17–0.69) P=0.003	0.38 (0.15–0.96) P=0.041
<b>Model 2: base-line variables and changes at week 8</b>			
Plasma HIV RNA			
Lower base-line concentration†	0.22 (0.13–0.37) P<0.001	0.12 (0.05–0.28) P<0.001	0.13 (0.05–0.38) P<0.001
Decrease from base line to week 8§	0.22 (0.12–0.41) P<0.001	0.35 (0.17–0.72) P=0.005	0.29 (0.11–0.79) P=0.015
CD4 cell count			
Higher base-line count‡	0.89 (0.63–1.25) P=0.50	1.14 (0.74–1.75) P=0.57	1.45 (0.78–2.69) P=0.24
Increase from base line to week 8¶	0.68 (0.48–0.97) P=0.031	0.68 (0.43–1.08) P=0.10	0.70 (0.39–1.26) P=0.24
Absence of syncytium-inducing phenotype at base line	0.38 (0.20–0.71) P=0.003	0.40 (0.18–0.91) P=0.028	0.55 (0.17–1.79) P=0.32

\*P values are for the hazard ratios.

†The hazard ratios are those associated with a 1.0 lower base-line concentration, in log copies per milliliter.

‡The hazard ratios are those associated with a base-line CD4 cell count that is 100 cells per cubic millimeter higher.

§The hazard ratios are those associated with a decrease of 1.0, in log copies per milliliter.

¶The hazard ratios are those associated with an increase of 100 cells per cubic millimeter.

ma HIV RNA concentrations and CD4 cell counts from base line to week 56. There was a 90 percent reduction in the risk of progression of disease associated with a reduction of 1.0 log in the plasma HIV RNA concentration between base line and week 56 ( $P=0.007$ ). In this model the change in the CD4 count was not an independent predictor of the risk of progression to AIDS or death ( $P=0.52$ ).

## DISCUSSION

The measurement of plasma HIV RNA concentrations provides a sensitive indicator of the risk of disease progression and death in subjects with asymptomatic HIV infection, both before and after treatment with reverse-transcriptase inhibitors. Although zidovudine monotherapy in subjects with 200 to 500 CD4 cells per cubic millimeter has relatively limited immunologic and clinical benefits,<sup>19,20</sup> treatment with zidovudine plus didanosine, zidovudine plus zalcitabine, or didanosine alone results in a more sustained virologic and immunologic response. Our virologic findings support the hypothesis that treatment of the early stages of HIV infection with antiretroviral drugs, as assessed by the measurement

of plasma HIV RNA concentrations, is associated with protection against immunologic deterioration, AIDS, and death.

The ability to measure plasma HIV RNA concentrations may permit a more targeted, rational use of antiretroviral drugs before the onset of severe immunodeficiency. The risk of disease progression among the mostly asymptomatic subjects enrolled in this study was better indicated by the plasma HIV RNA concentration than by the CD4 cell count, which was not as strong a predictor of clinical events. The gradient of risk for disease progression in the early stages of HIV infection as indicated by plasma HIV RNA concentrations (Table 2) provides a rationale for the use of antiretroviral therapy in patients with higher plasma concentrations of HIV RNA, regardless of the CD4 cell count, although further studies are needed to determine whether it is wise to defer antiretroviral treatment when there are lower concentrations of plasma HIV RNA.

These results regarding the predictive value of plasma HIV RNA concentrations support the findings of other recent studies. In the analysis of a placebo-controlled study of therapy with zidovudine in

**TABLE 4.** PROGRESSION TO AIDS OR DEATH ACCORDING TO BASE-LINE PLASMA HIV RNA CONCENTRATION AND DECREASE IN CONCENTRATION AT WEEK 8.

BASE-LINE HIV RNA CONCENTRATION (log copies/ml)	DECREASE IN HIV RNA CONCENTRATION AT WEEK 8 (log copies/ml)		
	>0.63	≤0.63	ALL
	% with progression (no. with progression/ total in category)		
≤4.28	1 (1/81)	5 (4/76)	3 (5/157)
>4.28	13 (10/76)	28 (23/81)	21 (33/157)
All	7 (11/157)	17 (27/157)	24 (38/157)

270 symptomatic subjects with 200 to 500 CD4 cells per cubic millimeter, O'Brien et al. concluded that both the base-line levels of CD4 cells and plasma HIV RNA and the changes in these levels over six months were predictors of the development of AIDS.<sup>11</sup> Over a longer observation period, Mellors et al. observed in the Multicenter AIDS Cohort Study that the risk of AIDS and death was strongly associated with increased plasma HIV RNA concentrations.<sup>3</sup> Our study found a significant association between a reduction in the plasma HIV RNA concentration after the initiation of therapy with antiretroviral drugs and a reduction in the risk of AIDS and death, but there was less evidence that changes in the CD4 cell count in response to drug therapy provided a useful indication of the risk of clinical progression.

The presence of lower base-line plasma HIV RNA concentrations among women and among intravenous drug users is an interesting but unexplained observation. However, risk factors for HIV infection, sex, ethnic group, and a history of previous antiretroviral treatment were not independently associated with differences in clinical outcome. Neither are the clinical results of ACTG 175 fully explained by the overall comparison of the changes in HIV RNA concentrations in the different treatment regimens. Therapy with didanosine alone led to clinical results comparable to those with the combination of zidovudine and didanosine, although patients treated with the latter regimen had a clearly larger mean decrease in plasma HIV RNA concentrations (Fig. 1). The reduction in plasma HIV RNA concentrations after treatment with zidovudine plus zalcitabine was similar to that after zidovudine plus didanosine, yet the latter regimen was more effective in the subjects with a history of antiretroviral therapy,<sup>1</sup> and similar results have been observed in a recently reported study of combination therapies in subjects with more advanced disease, but without a history of antiretroviral therapy.<sup>21</sup>

These differences point to the importance of other

factors in the treatment of HIV infection, including the development of drug resistance, adherence to assigned treatment, and the durability of antiretroviral activity. Overall, the specific treatment assignment was of less importance as a predictor of clinical progression than was the reduction in the plasma HIV RNA concentration after antiretroviral therapy.

Besides HIV RNA, other virologic factors also have a role in the pathogenesis and treatment of HIV. Syncytium-inducing virus has been associated with an accelerated rate of CD4 cell depletion, reduced CD4 cell responses, and resistance to zidovudine.<sup>12,13,22-25</sup> In our study, the presence of syncytium-inducing virus was a risk factor for disease progression independent of the CD4 cell count and the plasma HIV RNA concentration. Whether more aggressive antiretroviral intervention can prevent or suppress the development of the syncytium-inducing phenotype requires additional study.

The observations in ACTG 175 are limited to patients treated with zidovudine, didanosine, and zalcitabine. Studies of therapy with other nucleoside reverse-transcriptase inhibitors, stavudine and lamivudine, used in combination with protease inhibitors, have found large decreases in plasma HIV RNA and proportional increases in CD4 cells.<sup>11,26,27</sup> As additional drugs and combinations of drugs are tested, studies are needed to confirm that decreases in the rate of disease progression are proportional to the suppression of plasma HIV RNA. However, our results provide evidence that in the treatment of HIV infection with reverse-transcriptase inhibitors, clinical benefits come about through the suppression of viral replication and the reduction of plasma HIV RNA concentrations.

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#### APPENDIX

Other members of the ACTG 175 Virology Study Team were: Janet Lathey, Ph.D., University of California, San Diego; Walter Scott, Ph.D., University of Miami; Brigitte Griffiths, M.D., Yale University; Mark Winters, M.S., Stanford University; Tim Spahlinger, Case Western Reserve University; Jacqueline Gillis, New England Deaconess Hospital; and Richard D'Aquila, Harvard Medical School.

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CORRECTION

**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**

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 . On page 1094, Figure 1 is incorrect. The revised figure appears below.

Figure 1.

