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Virologic and CD4 Cell Response to Zidovudine or Zidovudine and Lamivudine Following Didanosine Treatment of Human Immunodeficiency Virus Infection

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ABSTRACT

To optimize nucleoside reverse transcriptase inhibitor (nRTI) antiretroviral therapy, 137 subjects who had been treated with didanosine monotherapy for more than 3 years in the AIDS Clinical Trials Group (ACTG) 175 study were randomized to zidovudine and didanosine (dual therapy) or zidovudine, didanosine, and lamivudine (triple therapy). Evaluation of early (8 week) change in HIV plasma RNA demonstrated that addition of lamivudine and zidovudine provided significantly greater virologic suppression compared to the addition of zidovudine alone (mean decrease of 1.27 vs. 0.74 $\log_{10}$ copies/ml, $n = 108$, $p = 0.007$). Both dual and triple therapy provided significant long-term decreases (from study entry to mean at Weeks 40 and 48) in HIV plasma RNA: 0.62 and 0.86 $\log_{10}$ copies/ml, respectively ($n = 110$). However, the difference between treatments was not significant ($p = 0.16$). At 48 weeks, 26% of subjects starting study treatment had <500 copies/ml of plasma HIV RNA. The CD4 count response was greater at 4 weeks for triple versus dual therapy: a mean increase of 51 vs. 12 CD4 cells/ml^3 ($n = 126$, $p = 0.039$). The difference at Weeks 40 and 48 was not significant (a 22 cell increase vs. a 1 cell decrease, $n = 129$, $p = 0.41$). Zidovudine and didanosine treatment, with or without lamivudine, was well tolerated and only 2 of 137 (1.5%) of study participants developed an AIDS-defining event over 48 weeks.

INTRODUCTION

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (nRTIs) remain an important component of combination antiviral therapy. The optimum use of these drugs, however, requires additional data on the relative merits of combinations and how best to use nRTIs sequentially. Current recommendations for antiretroviral therapy include the use of two nucleoside reverse transcriptase inhibitors and a protease or nonnucleoside reverse transcriptase inhibitor in initial therapy to provide highly active antiretroviral therapy.[1,2] Among patients with virologic failure, substitution of two new nRTIs with either a new protease inhibitor, nonnucleoside reverse transcriptase inhibitor, or both is recommended to achieve suppression of virus replication.[1,2] Only a few of the many possible nRTI combinations have been directly compared although some combinations are excluded from consideration based on pharmacologic antagonism or shared toxicities. With sequential nRTI drug regimens, zidovudine-experienced subjects have consistently shown inferior HIV RNA and CD4 cell responses to new nucleoside drug(s) compared to nRTI naive patients.[3,4]

There are currently six nRTI drugs used in the treatment of HIV infection: zidovudine (ZDV), didanosine (ddI), lamivudine (3TC), stavudine (d4T), zalcitabine, and abacavir. Combined use of these nRTI drugs is supported by the rapid development of resistance and poor long-term clinical outcome of treatment with lamivudine, zidovudine, and zalcitabine as monotherapies.[5–8] In contrast, in at least one large clinical comparison

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(ACTG 175), didanosine alone decreased mean HIV RNA levels and increased mean CD4 cell numbers for more than 2 years among zidovudine-experienced and naive subjects and compared favorably with respect to clinical outcomes to combinations of zidovudine and didanosine or zalcitabine.[4,8]

In 1995, prior to the era of highly active antiretroviral therapies, we initiated a clinical trial among subjects who had been treated with didanosine alone in the AIDS Clinical Trials Group (ACTG) 175 study. At enrollment to ACTG 175 in 1991–1992, these subjects had 200 to 500 $CD4^+$ cells/mm^3, about half had been treated with zidovudine before study entry, and most were asymptomatic. Although the overall results of the ACTG 175 study demonstrated the superiority of combinations versus zidovudine monotherapy, the clinical and virologic activity of didanosine was superior to zidovudine and not significantly inferior to combination treatments.[8] Subjects completing didanosine treatment were offered one or two additional nucleoside analog therapies to compare their activity in further reducing HIV replication. One hundred and thirty-seven subjects were randomized: 69 to the addition of zidovudine and 68 to the addition of zidovudine plus lamivudine for 48 weeks. The study was designed to evaluate the safety and antiviral activity of 2 and 3 nRTI regimens among patients previously treated with didanosine.

METHODS

Study design

ACTG 302 was a randomized, double-blinded clinical trial enrolling subjects who received either zidovudine or didanosine monotherapy in ACTG 175; this report concerns only the didanosine recipients. All subjects with acceptable hematology and serum chemistry measures who had remained on their originally assigned therapy in ACTG 175 were eligible to participate. Entry of subjects with clinically active infections was deferred for at least 14 days and subjects with either a neoplasm (other than minimal Kaposi's sarcoma) or a prior AIDS-defining opportunistic infection were excluded. All subjects continued treatment with didanosine 200 mg twice daily, added zidovudine 200 mg three times daily, and were randomized to add lamivudine 150 mg twice daily or a corresponding placebo. The randomization was stratified by nucleoside experience prior to entry into ACTG 175 (non vs. zidovudine experienced). Plasma HIV RNA and CD4 cell numbers were measured twice before starting the study treatment, and at 4 weeks (CD4 only), 8 weeks (HIV RNA only), 16 weeks (CD4 only), 24, 40, and 48 weeks after starting treatment. However, for 18 subjects, no plasma specimens were obtained prior to starting treatment and these subjects are excluded from analysis of change in HIV RNA. In addition, although subjects were asked to continue follow-up if they discontinued study treatment before 48 weeks, not all subjects did so.

Baseline $\log_{10}$ RNA and CD4 count was the mean of the two pretreatment measurements. Short-term change was defined as change from baseline to the Week 4 CD4 count and the Week 8 HIV RNA determination; long-term change was to the mean of the Week 40 and 48 determinations (or to a single determination if only one was available) for both markers. The study's primary objective was to compare the safety and short- and long-term plasma HIV RNA and CD4 cells changes in the two treatments.

Plasma HIV RNA measurements

HIV-1 RNA was measured in citrated plasma, separated within 6 hr of phlebotomy and stored at −70°C. All samples from each study participant were run in a single assay at the conclusion of the study in three laboratories, certified in the performance of the Roche amplicor RNA monitor test, by Roche as well as the Virology Quality Assurance program, supported by the Division of AIDS, NIAID, NIH.

Statistical methods

All analyses of HIV RNA were undertaken after log base 10 transformation. Changes in HIV RNA and CD4 cell count were analyzed using linear regression with adjustment for clinical site and nucleoside experience prior to entry into ACTG 175 (none versus experienced), and used maximum likelihood methods for censored data to handle HIV RNA values outside of the range of quantification of the assay.[9] To evaluate the potential sensitivity of results to subjects without measurements at both 40 and 48 weeks, analyses were also conducted using the last available measurement, carried forward. The proportion of subjects with HIV RNA levels below 500 copies/ml was analyzed using the Cochran–Mantel–Haenszel test, and logistic regression was used to evaluate predictors of suppression. Times to treatment discontinuation and to the development of signs and symptoms or laboratory abnormalities of grade 3 or higher according to the NIAID toxicity grading tables were compared between treatments using the log rank test[10] stratified by nucleoside experience prior to entry into ACTG 175. All analyses were intent to treat including all randomized subjects and all available follow-up to 48 weeks after starting study treatment, except that analyses of adverse effects were censored at 8 weeks after study treatment discontinuation if this was before 48 weeks.

RESULTS

Baseline characteristics of subjects

One hundred and thirty seven subjects who completed treatment in ACTG 175 with didanosine were randomized to the addition of new nucleoside therapies. All subjects continued didanosine; 69 added zidovudine and lamivudine placebo and 68 added zidovudine and lamivudine. They had received didanosine monotherapy in ACTG 175 for a median of 3.6 years (interquartile range 3.4–3.7). Seventy-five subjects (55%) had received zidovudine as monotherapy for a median duration of 2.0 years (interquartile range 1.0–2.6) prior to entry to ACTG 175, but had not taken zidovudine within the past 3 years. Demographic, virologic, and immunologic characteristics are shown in Table 1. Since entering ACTG 175 the mean CD4 count for these subjects had increased slightly from a mean (±SD) of 371 ± 100 $CD4^+$ to 383 ± 160 cells/mm^3. Mean HIV RNA at entry to ACTG 175 of 4.27 ± 0.06 $\log_{10}$ copies/ml had decreased to a mean value of 3.91 ± 0.08 $\log_{10}$ copies/ml at ACTG 302 study entry (equivalent to a decrease from 18,600 to 8,100 copies/ml).

TABLE 1. SELECTED BASELINE CHARACTERISTICS BY TREATMENT

	Total (N = 137)	*Zidovudine plus didanosine (N = 69)*	*Zidovudine plus didanosine plus lamivudine (N = 68)*
Sex: number (%)			
Male	119 (87%)	63 (91%)	56 (82%)
Race: number (%)			
White non-Hispanic	100 (73%)	54 (78%)	46 (68%)
Black non-Hispanic	25 (18%)	11 (16%)	14 (21%)
Hispanic	11 (8%)	4 (6%)	7 (10%)
Other	1 (1%)	0	1 (1%)
IV drug use: number (%)			
Previously or currently	8 (6%)	3 (4%)	5 (7%)
Hemophiliac: number (%)			
Yes	12 (9%)	8 (12%)	4 (6%)
HIV symptoms: number (%)			
AIDS	1 (1%)	1 (1%)	0
Symptomatic[a]	18 (13%)	11 (16%)	7 (10%)
Asymptomatic	118 (86%)	57 (83%)	61 (90%)
Age (years): mean (SD)	40 (9)	41 (8)	39 (10)
Antiretroviral use prior to ACTG 302 (years): median (Q1–Q3)	4.0 (3.5–5.8)	4.0 (3.5–5.8)	4.2 (3.6–5.8)
ZDV use prior to ACTG 175 (years): number (%)			
Experienced (>7 days)	75 (55%)	38 (55%)	37 (54%)
Naive (≤7 days)	62 (45%)	31 (45%)	31 (46%)
Median (Q1–Q3) (ZDV experienced subjects only)	2.0 (1.0–2.6)	2.0 (0.7–2.5)	2.0 (1.2–2.6)
ddI use prior to ACTG 302 (years): median (Q1–Q3)	3.6 (3.4–3.7)	3.6 (3.4–3.7)	3.6 (3.4–3.7)
CD4 (cell/mm^3) at ACTG 175 baseline: mean (SD)	371 (100)	375 (106)	367 (94)
CD4 (cell/mm^3): mean (SD)	383 (160)	386 (164)	380 (157)
HIV-1 RNA level[b] ($\log_{10}$ copies/ml): mean (SD)	3.91 (0.08)	3.99 (0.11)	3.83 (0.10)

[a]Symptomatic was defined having candidiasis, oral hairy leukoplakia, or herpes zoster.
[b]Available for 119 subjects (59 on zidovudine plus didanosine and 60 on zidovudine plus didanosine plus lamivudine).

Compared to the 127 subjects who completed ACTG 175 still taking didanosine monotherapy and so were eligible for ACTG 302, subjects who did enroll had significantly higher mean CD4 counts at completion of ACTG 175 (391 versus 346 cells/mm^3), were significantly more likely to have a Karnofsky score of 100 (66 vs. 35%), and were more often of white, non-Hispanic race/ethnicity (73 vs. 61%). Subjects who discontinued didanosine monotherapy in ACTG 175 and so were not eligible for ACTG 302 had significantly lower mean CD4 cell counts at the completion of ACTG 175 (236 cells/mm^3), lower Karnofsky scores (32% had scores of 100), and lower mean weight (68 vs. 73 kg.).

Follow-up and treatment status

Eleven subjects (8%) were lost to follow-up for vital status and adverse experiences, including AIDS-defining diagnoses: 6 assigned didanosine and zidovudine versus 5 assigned didanosine, zidovudine, and lamivudine. For CD4 cell count, 11 subjects (8%) did not have a short-term (Week 4) evaluation and 8 subjects (6%) were missing both 40- and 48-week evaluations and so did not have a long-term evaluation. The corresponding values for HIV-1 RNA changes, including the 18 subjects who were missing the baseline evaluation, were 29 subjects (21%) and 27 subjects (20%), respectively. Twenty-six subjects (including the 11 lost to follow-up) discontinued study treatment prior to 48 weeks: 12 versus 14, respectively ($p = 0.60$). Only one subject (assigned to didanosine and zidovudine) was withdrawn because of protocol-defined toxicity (grade 4 anemia).

RNA changes with new nucleoside therapies

Subjects assigned didanosine, zidovudine, and lamivudine had a mean short-term (to Week 8) and long-term (to mean of Weeks 40 and 48) reduction in HIV RNA of 1.27 and 0.86 $\log_{10}$ copies/ml compared with 0.74 and 0.62 $\log_{10}$ copies/ml, respectively, among subjects assigned didanosine and zidovudine (Fig. 1). The differences between treatments in short-term and long-term mean decrease in HIV plasma RNA were 0.45 (95% confidence interval: 0.12 to 0.78 decrease, $p = 0.007$) and 0.25 $\log_{10}$ copies/ml (95% confidence interval: 0.10 increase to 0.60 decrease, $p = 0.16$), respectively. In the analysis using the last

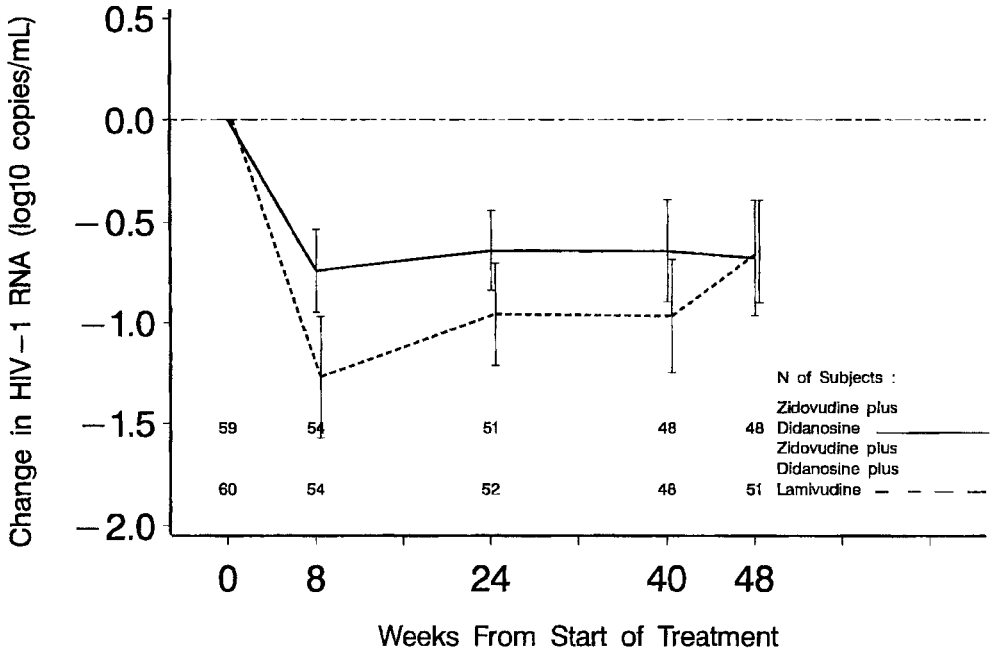

FIG. 1. Changes in HIV-1 RNA from baseline over 48 weeks in subjects treated with zidovudine plus didanosine compared to zidovudine, didanosine, and lamivudine.

available measurement if both the Week 40 and Week 48 were missing, the difference in mean long-term change was 0.20 $\log_{10}$ copies/ml (95% confidence interval: 0.12 increase to 0.52 decrease, $p = 0.23$). Short- and long-term changes in HIV RNA were analyzed to evaluate whether the difference between treatments was associated with CD4 count, HIV RNA, HIV-related symptoms at baseline. No significant associations were found and there was no significant evidence that any of these factors predicted change in HIV RNA across treatments.

Suppression of HIV RNA below 500 copies/ml

At enrollment, 10 of 119 (8%) of evaluable subjects had HIV RNA below 500 copies/ml on didanosine therapy: 6/59 (10%) were randomized to didanosine plus zidovudine and 4/60 (7%) to didanosine, zidovudine, and lamivudine. Subjects with short-term (8 week) suppression below 500 copies/ml increased to 30 (55%) in the three-drug arm as compared to 20 (36%) in the two-drug regimen ($p = 0.050$). However, by 48 weeks a similar number of subjects in the 3- and 2-drug arms had <500 copies/ml, 17/52 (33%) and 19/51 (37%), respectively ($p = 0.54$). Expressed as a proportion of subjects starting study treatment, the corresponding percentages are 44 vs. 29% at Week 8 ($p = 0.077$) and 25 vs. 28 ($p = 0.85$) at Week 48, respectively. Lower plasma HIV RNA, higher CD4 count, higher CD4 percentage, lower CD8 percentage, and no prior zidovudine experience were all significantly associated with increased odds of suppression below 500 copies/ml at Week 48, after adjusting for 302 treatment (Table 2).

CD4 cell change

The CD4 cell changes from baseline to Week 4 (short-term change) were significantly greater in the three-drug regimen, a mean (SE) of 51 (13) vs. 12 (12) $CD4^+$ cells/mm^3 in the two-drug regimen, a difference of 38 CD4 cells/mm^3 (95% confidence interval 2,74; $p = 0.039$) as shown in Figure 2. However, the difference of 23 cells/mm^3 in the mean long-term (average of week 40 and 48) CD4 cell increases between the treatment groups [22(13) increase versus 1 (14) decrease] was not significant (95% confidence interval −16,62; $p = 0.41$). The difference was very similar in the analysis using the last available measurement if both the Week 40 and Week 48 measurements were missing: 29 cells/mm^3 (95% confidence interval −10, 69; $p = 0.31$). There was no significant evidence that the difference in short-term change in CD4 count between treatments varied by CD4 count, HIV RNA, HIV-related symptoms, or prior zidovudine use, nor that any of these factors predicted the magnitude of change across treatments. These comparisons, however, are not well powered.

Prior zidovudine treatment, CD4 cell, and HIV RNA responses

Subjects in both treatment groups who were naïve to zidovudine had greater mean long-term increases in CD4 cell count than subjects who had previously taken zidovudine (28 vs. −4 cells/mm^3, $p = 0.092$). This difference was more pronounced in the zidovudine, didanosine, and lamivudine arm where the zidovudine naive subjects had significantly higher long-term CD4 increase compared to experienced subjects, 56 vs. −5 cells/mm^3 ($p = 0.015$), but this was not seen in the zidovudine plus didanosine arm (1 vs. −2 cells/mm^3, $p = 0.89$). In both treatment groups, subjects with lower CD4 cell counts at entry to ACTG 302 had significantly greater long-term increases in CD4 cell count ($p = 0.002$).

Among all subjects, those previously treated with zidovudine tended to have smaller decreases in HIV RNA than subjects who had not been previously treated with zidovudine both in the short term (0.87 vs. 1.15 $\log_{10}$ copies/ml, $p = 0.21$) and

TABLE 2. SELECTED BASELINE CHARACTERISTICS BY WEEK 48 RNA RESULTS

	RNA at Week 48		
	≤500 (N = 36)	*>500 (N = 67)*	p *Value*[a]
Sex: number (%)			
Male	33 (92%)	57 (85%)	0.360
Race: number (%)			
White non-Hispanic	29 (81%)	52 (78%)	0.776
Black non-Hispanic	4 (11%)	11 (16%)	
Hispanic	3 (8%)	3 (4%)	
Other	0	1 (1%)	
IV drug use: number (%)			
Previously or currently	2 (6%)	3 (4%)	0.792
Hemophiliac: number (%)			
Yes	2 (6%)	3 (4%)	0.827
HIV symptoms: number (%)			
AIDS	0	1 (1%)	0.541
Symptomatic[b]	6 (17%)	8 (12%)	
Asymptomatic	30 (83%)	58 (87%)	
Age (years): mean (SD)	41 (8)	41 (9)	0.802
ZDV use prior to ACTG 175 (years): number (%)			
Experienced (>7 days)	13 (36)	41 (61)	0.015
Naive (≤7 days)	23 (64)	26 (39)	
Antiretroviral use prior to ACTG 302 (years): median (Q1–Q3)	3.7 (3.4–4.3)	4.7 (3.5–5.9)	0.052
Change in CD4 per year[c]: mean (SD)	14 (49)	−1 (42)	0.124
CD4 (cell/mm^3) at ACTG 175 baseline: mean (SD)	392 (102)	360 (90)	0.111
CD4 (cell/mm^3): mean (SD)	427 (190)	356 (152)	0.049
Percent CD4: mean (SD)	25 (8)	22 (8)	0.026
Percent CD8: mean (SD)	49 (9)	55 (11)	0.017
HIV-1 RNA level[d] ($\log_{10}$ copies/ml): mean (SD)	3.15 (0.16)	4.24 (0.08)	<0.001

[a]*p* Value from logistic regression model, adjusted by 302 treatment.
[b]Symptomatic was defined having candidiasis, oral hairy leukoplakia, or herpes zoster.
[c]Based on a median of 3 years of follow-up in ACTG 175.
[d]Available for 99 subjects: 35 in ≤500 group and 64 in >500 group.

long term (0.61 vs. 0.97 $\log_{10}$ copies/ml, $p = 0.23$), but neither difference was significant. However, RNA responses among subjects with and without zidovudine experience at entry to ACTG 175 were significantly different within subjects randomized to the zidovudine plus didanosine arm. Fifty-four of these 69 subjects had RNA at both baseline and Week 8. The 20 subjects with prior zidovudine experience had a mean, short-term decline of 0.56 compared to 1.03 $\log_{10}$ copies of HIV RNA in 24 zidovudine naïve subjects ($p = 0.045$). These differences from baseline narrowed to a mean decrease of 0.51 and 0.81 $\log_{10}$ copies of HIV RNA ($p = 0.31$) in zidovudine experienced and naïve patients, respectively, at 40–48 weeks. Prior AZT experience in ACTG 175 was not associated with a significant difference in short- or long-term changes in zidovudine, didanosine, and lamivudine recipients.

Adverse experiences and clinical progression

Only 7 subjects (5%) experienced grade 3 signs or symptoms: 3 subjects assigned didanosine and zidovudine and 4 assigned to didanosine, zidovudine, and lamivudine. Seventeen subjects (12%) experienced laboratory abnormalities of grade 3 or higher: 12 subjects receiving didanosine and zidovudine and 5 subjects receiving didanosine, zidovudine, and lamivudine. Laboratory abnormalities that triggered protocol mandated treatment interruption included elevated liver function tests in 4 subjects, creatinine phosphokinase elevations in 3, and anemia or leukopenia in 4. All of these were reversible without evidence for lactic acidosis or mitochondrial toxicity. Nine subjects (7%) had symptoms consistent with a grade 2 or 3 peripheral neuropathy, 3 assigned to didanosine and zidovudine and 6 assigned the three drugs. There were two AIDS-defining events: both in subjects receiving zidovudine and didanosine, CMV retinitis diagnosed after 40 weeks on treatment and a clinical diagnosis of toxoplasmosis after 45 weeks on treatment.

DISCUSSION

The addition of zidovudine or zidovudine and lamivudine to long-term didanosine monotherapy resulted in a significant decline in mean HIV RNA that was sustained for 48 weeks. Mean

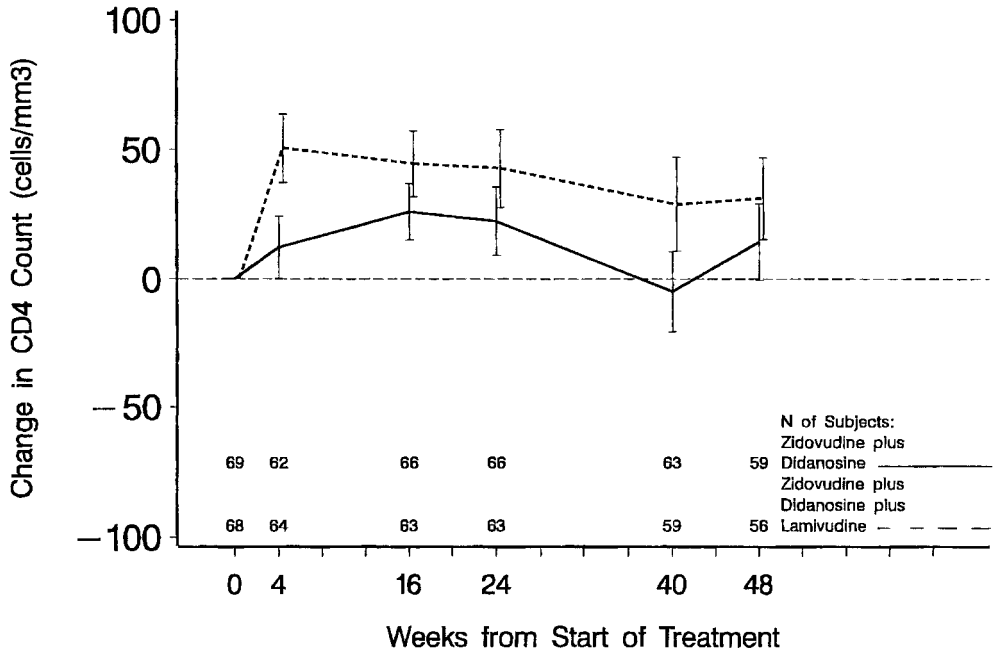

FIG. 2. Changes in HIV-1 RNA from baseline over 48 weeks in subjects treated with zidovudine plus didanosine compared to zidovudine, didanosine, and lamivudine.

CD4 cell numbers increased in the zidovudine, didanosine, and lamivudine arm but showed little change in the zidovudine plus didanosine arm. The most common, dose-limiting toxicity associated with didanosine therapy, peripheral neuropathy (11), was observed in 9 of 137 (7%) of subjects. With respect to long-term (40 and 48 week) changes, the addition of lamivudine to a regimen including didanosine and zidovudine did not provide significantly greater improvements in either HIV RNA or CD4 cell count. This result persisted in analyses, which included the last available measurement for subjects with missing data at Weeks 40 and 48. The two and three nucleoside regimens reduced HIV RNA to less than 500 copies/ml in 36 of 103 subjects (35%) evaluated at 48 weeks, corresponding to 26% of the 137 subjects who started study treatment.

Administration of didanosine in HIV infection has been examined in patients with advanced disease, as an alternative to zidovudine.[12–14] Among patients with less than 200 CD4 cells or clinical AIDS, early studies of didanosine treatment demonstrated significant benefits compared to zidovudine.[12,13] The ACTG 175 study tested didanosine in an earlier population of mostly asymptomatic subjects with 200 to 500 CD4 cells.[8] In that study, didanosine was virologically superior to zidovudine, irrespective of prior zidovudine experience.[4] Long-term mortality data from a recent meta-analysis of nucleoside therapies show among 1289 subjects from ACTG 175 a significant reduction in mortality among those randomized to treatment with didanosine vs. zidovudine, again, irrespective of prior zidovudine treatment.[15] Continued treatment of 137 of the 620 subjects initially randomized to receive didanosine in ACTG 175, with didanosine and either zidovudine or zidovudine and lamivudine, allows a comparison of the response to two or three nucleosides over 1 year.

It should be emphasized, however, that subjects who entered the current study had responded to treatment with a decrease in plasma HIV RNA and increase in CD4 cells with little change in HIV RNA and CD4 cell numbers over a median of 3 years since enrollment in ACTG 175. In contrast, subjects who discontinued didanosine monotherapy in ACTG 175 showed significantly greater declines in CD4 cell count and Karnofsky score. Subjects eligible for this study who declined participation also had more advanced disease by these measures. Thus, while these results cannot be generalized to all HIV-infected individuals, they do show that some patients maintain a stable disease state on didanosine-based nucleoside therapy. Similar virologic activity, with a mean 10-fold decrease in plasma HIV RNA among asymptomatic, antiretroviral naïve subjects receiving didanosine, has been reported over 24 weeks.[16,17]

In terms of prior zidovudine experience, there were no significant evidence that the differences between treatments in either short- or long-term changes in HIV RNA or CD4 count varied by whether a subject had taken zidovudine prior to entry into ACTG 175, though the power to detect differences is limited. However, in both treatment arms, subjects treated with zidovudine prior to didanosine in ACTG 175 tended to have smaller decreases in HIV RNA than subjects who had not been treated. Also, subjects who had previously taken zidovudine prior to ACTG 175 had smaller mean long-term increases in CD4 than subjects who had received only didanosine therapy.

Didanosine may be less likely to result in the development of drug resistance that significantly impacts subsequent nRTI therapies, preserving subsequent treatment options.[14,18,19] Treatment of HIV infection, with single, or combination nRTIs, has generally been discouraging compared to combinations including 2 nRTIs and either a protease or a nonnucleoside reverse transcriptase inhibitor. In part, the clinical and virologic failure of nucleoside monotherapies has been ascribed

to the development of drug resistance at rates, in zidovudine or didanosine monotherapy, of about 30% per year.[20–22] Zidovudine with or without concomitant didanosine treatment may result in the development of resistance mutations that extend to didanosine and other nucleoside drugs.[23–25] In contrast, the L74V mutation in RT, the predominant mutation selected by didanosine, may increase zidovudine susceptibility of HIV.[26] The results presented here, of a robust and sustained response in HIV RNA to the administration of zidovudine (with or without lamivudine) among didanosine-treated subjects, provides *in vivo* evidence consistent with continued zidovudine sensitivity after prolonged didanosine administration.

Experience with three nucleoside analogs is limited. Among 45 antiretroviral drug naïve subjects treated with zidovudine, didanosine, and lamivudine more than 80% of subjects achieved suppression of HIV RNA to less than 200 copies/ml.[27] Two recent studies suggest that three nucleosides suppress HIV RNA in a majority of drug naïve subjects.[28,29] Fischl and colleagues studied zidovudine, lamivudine, and abacavir[28] and Katlama and colleagues have shown that didanosine, stavudine, and lamivudine suppress plasma HIV RNA at 24 weeks to less than 500 copies/ml in the majority of drug naïve subjects.[29] In this study, the increased short-term activity of zidovudine, lamivudine, and didanosine suggests that these three nucleosides can be safely included in regimens in didanosine experienced subjects providing greater short-term initial suppression of HIV replication than zidovudine and didanosine.

Based on studies of HIV RNA suppression and the development of drug resistance, the goals of antiretroviral treatment in HIV infection have rapidly shifted to early suppression of HIV replication to the lowest possible levels with combination antiretroviral therapy regimens.[1,2] In this study, suppression of plasma HIV RNA to levels less than 500 copies/ml at 48 weeks was observed in 36/103 subjects (35%) with available data at 48 weeks. A more conservative interpretation, imputing a value above 500 copies/ml for subjects without data for any reason, demonstrates that 36/137 (26%) achieved virologic suppression. Dual and triple nucleoside therapies may provide prolonged reduction of HIV RNA, particularly in subjects with higher CD4 cell counts and lower HIV RNA levels.

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