

# Effect of Lamivudine in HIV-Infected Persons with Prior Exposure to Zidovudine/Didanosine or Zidovudine/Zalcitabine

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## ABSTRACT

Nucleoside analog-based regimens remain an integral component of combination therapy for use in both antiretroviral treatment-naive and experienced HIV-infected patients. To further define treatment responses to new antiretroviral therapy in patients with long-term experience to dual nucleoside analog therapy (zidovudine [ZDV] plus didanosine [ddI] or ZDV plus zalcitabine [ddC]), 325 subjects derived from the AIDS Clinical Trials Group (ACTG) 175 trial were randomized to three different combination regimens: (1) continuation of ZDV + ddI or ZDV + ddC (continuation arm), (2) addition of 3TC to ZDV + ddI or ZDV + ddC (addition arm), or (3) a switch to ZDV + 3TC therapy (switch arm). Both the addition and switch arms sustained significantly greater short-term (baseline to week 4) mean CD4<sup>+</sup> cell count increases compared with the continuation arm (+36, +28 versus -4 cells/mm<sup>3</sup>;  $p = 0.012$ ) and long-term CD4<sup>+</sup> cell count responses (baseline to weeks 40/48: +32, +19 versus -9 cells/mm<sup>3</sup>;  $p = 0.003$ ). Superior short-term (baseline to week 8) mean decreases in plasma HIV RNA ( $p < 0.001$ ) were achieved by both the addition and switch arms (0.53 log<sub>10</sub> and 0.54 log<sub>10</sub> copies/ml, respectively) compared with the continuation arm (0.13 copies/ml) whereas no differences in long-term virologic suppression were observed ( $p = 0.30$ ). At week 48, no differences were observed in the proportions of subjects who had HIV RNA levels below 500 copies/mL: 18% of subjects in each treatment arm (3-way  $p = 1.0$ ). Overall, the treatments were well tolerated and only nine subjects (3%) died or developed one or more AIDS-defining events. While this study confirms the intrinsic antiretroviral activity of 3TC, only modest marker changes and limited short-term viral suppression are seen with incremental addition of the drug. The current approach of using 3TC in maximally suppressive regimens is preferred.

## INTRODUCTION

GIVEN THE MODEST BENEFITS conferred by zidovudine (ZDV) monotherapy in HIV disease, attributed to its limited potency and the emergence of resistance,<sup>1</sup> combination dual nucleoside regimens were targeted for extensive clinical trial evaluation in both treatment-naive and ZDV-experienced HIV-infected individuals prior to the widespread introduction of nonnucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI) agents.<sup>2-5</sup>

The AIDS Clinical Trials Group (ACTG) 175, Delta, and NuCombo trials enrolled adult HIV-infected subjects with CD4<sup>+</sup> cell counts of 200-500, <350, and <200 cells/mm<sup>3</sup> and compared ZDV/didanosine (ddI) and ZDV/zalcitabine (ddC) with ZDV monotherapy.<sup>2-4,6</sup> These three trials established that ZDV plus ddI was superior to ZDV monotherapy in both nucleoside-naive and -experienced patients and that ZDV plus ddC was superior in antiretroviral drug-naive patients. After the introduction of two additional NRTI agents, stavudine (d4T) and lamivudine (3TC), alternative dual nucleoside combinations,

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such as ZDV/3TC, were then evaluated in treatment strategies that involved the addition of 3TC or a switch to 3TC-containing regimens. ZDV/3TC combination therapy exhibited both greater and more durable increases in CD4<sup>+</sup> cell counts and achieved greater reductions in viral loads compared with ZDV monotherapy or ZDV/ddC.<sup>7-12</sup>

The ACTG 303 trial, a rollover study from the earlier ACTG 175 trial, was implemented in advance of later studies conducted with NNRTI- and PI-containing regimens, and was designed to evaluate the short-term and long-term virologic responses in subjects previously treated with either ZDV/ddI or ZDV/ddC to changes in their nucleoside-based regimens. Three hundred and twenty-five subjects who remained on combination ZDV/ddI and ZDV/ddC therapy when ACTG 175 was completed were subsequently randomized to one of three treatment regimens: (1) continuation of their ACTG 175 therapy, (2) addition of 3TC to their original ACTG 175 therapy, or (3) a switch to ZDV/3TC therapy.

## MATERIALS AND METHODS

### *Study design and population*

In the ACTG 175 trial, a total of 2467 HIV-infected subjects without AIDS and with CD4<sup>+</sup> cell counts between 200 and 500 cells/mm<sup>3</sup> were randomized to one of four treatment arms: ZDV alone, ZDV plus ddI, ZDV plus ddC, or ddI monotherapy. The primary end point of the study was a  $\geq 50\%$  decline in CD4<sup>+</sup> cell count, progression to AIDS, or death.

ACTG 303 was a phase II, randomized, partially blind, follow-up study for ACTG 175 subjects who remained on their originally randomized combination nucleoside analog therapy or who crossed over to combination therapy after reaching a study end point in ACTG 175, and who took the same combination therapy until enrollment into this study. ACTG 175 subjects were eligible to participate if they met the following criteria: acceptable hematology and chemistry laboratory measurements, no history of  $\geq$  grade 2 peripheral neuropathy as defined by the standardized rating scale of the AIDS Clinical Trials Group, and no prior 3TC exposure; women who were pregnant were excluded from study participation.

Subjects were randomized to one of three treatment arms and were monitored for 48 weeks:

*Continuation arm:* ZDV 200 mg three times daily, plus ddI 200 mg twice daily; or ZDV 200 mg three times daily plus ddC 0.75 mg three times daily

*Addition arm:* ZDV 200 mg three times daily, plus ddI 200 mg twice daily, plus 3TC 150 mg twice daily; or ZDV 200 mg three times daily, plus ddC 0.75 mg three times daily, plus 3TC 150 mg twice daily

*Switch arm:* ZDV 200 mg three times daily plus 3TC 150 mg twice daily

The study was partially blind: Subjects who received ZDV/ddI (ZDV/ddC) in ACTG 175 received either ddI (ddC) or a matching placebo to ddI (ddC) in ACTG 303; all subjects received either 3TC or a matching placebo to 3TC. The randomization was stratified by the combination therapy (ZDV + ddI versus

ZDV + ddC) that subjects received in ACTG 175. The primary end points were to compare the short-term and long-term changes in plasma HIV RNA and CD4<sup>+</sup> cell counts across the three treatment arms. The secondary end points were to assess safety as measured by the occurrence of adverse events among the three treatment arms and to capture any new AIDS-defining events among the three treatment arms. Adverse events (signs, symptoms, or laboratory abnormalities) were graded according to the rating scale of the AIDS Clinical Trials Group.<sup>13</sup> The levels of severity varied according to the grade assigned: grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (life threatening). Sites were required to report peripheral neuropathy  $\geq$  grade 2 and all other signs and symptoms or laboratory abnormalities of grade 3 or higher.

### *Evaluations*

Subjects were examined for medical history and adverse experiences including hematological and chemistry abnormalities, on two occasions prior to study entry, at weeks 2, 4, 8, and then every 8 weeks thereafter through week 48. CD4<sup>+</sup> cell counts were obtained on two occasions prior to study entry and at weeks 4, 16, 24, 40 and 48 while plasma for HIV RNA levels was collected twice prior to study entry and at weeks 8, 24, 40 and 48. Baseline HIV RNA and CD4<sup>+</sup> cell count were determined as the geometric mean of the two pretreatment measurements. Short-term change was evaluated at week 4 for CD4<sup>+</sup> cell count and at week 8 for HIV RNA minus baseline. Long-term change was the geometric mean of weeks 40 and 48 (or the single measurement if only one was available) minus baseline for both markers.

### *Plasma HIV RNA measurements*

HIV-1 RNA was measured in citrated plasma, separated within 6 hr of collection and stored at  $-70^{\circ}\text{C}$ . All samples from each study participant were run in a single assay, including standards containing 15,000 and 150,000 copies of HIV RNA. Plasma HIV RNA levels were measured by the Roche (Nutley, NJ) Amplicor Monitor assay. The lower limit of quantification was 500 copies/ml. Viral load assays were performed at the conclusion of the study in three laboratories, certified in the performance of the Roche Amplicor RNA Monitor test, by Roche, and the Virology Quality Assurance Program, supported by the Division of AIDS (NIAID, NIH, Bethesda, MD).

### *Statistical analysis*

Distributions of times to events were estimated with the method of Kaplan and Meier and the log-rank test. HIV RNA analyses were conducted on a log base 10 scale. Analyses of short-term and long-term CD4<sup>+</sup> cell count and HIV-1 RNA changes from baseline used a linear regression analysis, adjusted for ACTU and prior ACTG 175 treatment; for HIV-1 RNA, values outside the range of quantification of the assay (500 to 750,000 copies/ml) were considered as censored data.<sup>14</sup> Interactions between treatment and prior ACTG 175 treatment were tested to determine whether the difference between treatments in ACTG 303 depended on the treatment received in ACTG 175. The Cochran-Mantel-Haenszel test was used to analyze the proportion of subjects with HIV-1 RNA levels

<500 copies/ml. For efficacy analyses, an intent-to-treat approach was used including all randomized subjects and all available follow-up to 48 weeks. Analyses of adverse events, however, were censored at 8 weeks after study treatment discontinuation if this was before 48 weeks. "Three-way" *p* values are for the test of hypothesis that the response evaluated is identical in all three treatment arms. All other *p* values are for pairwise comparisons and are unadjusted for multiple comparisons.

## RESULTS

### Baseline features

A total of 325 subjects were randomized. Table 1 lists the baseline characteristics of the study population. The median duration of antiretroviral therapy prior to ACTG 303 entry was 47 months. The mean CD4<sup>+</sup> cell count was 370 cells/mm<sup>3</sup> at ACTG 175 baseline compared with 358 cells/mm<sup>3</sup> at entry into ACTG 303. Of the 286 subjects who had HIV-1 RNA mea-

surements at entry into ACTG 303, the mean HIV-1 RNA was 4.12 log<sub>10</sub> copies/ml; 24 (8%) had a baseline value below 500 copies/ml and 3 (1%) had a value above 750,000 copies/ml. Overall, the baseline characteristics were well balanced across the three treatment groups.

### Follow-up and treatment status

Of the 325 subjects, 305 (94%) completed the protocol follow-up (48 weeks after starting treatment), 2 subjects died and the remaining 18 (6%) were lost to follow-up. There was no significant difference between the three treatment arms (three-way *p* = 0.21). Two hundred and fifty-seven subjects (79%) completed 48 weeks of study treatment, 1 subject died while on treatment due to a cardiac arrhythmia not attributed to study treatment, and 67 subjects (21%) permanently discontinued treatment before 48 weeks for reasons other than death. The discontinuation rate was 28% in the continuation arm, 19% in the addition arm, and 15% in the switch arm (three-way *p* = 0.063).

TABLE 1. SELECTED BASELINE CHARACTERISTICS BY TREATMENT

	Total (n = 325)	Continuing 175 treatment (n = 108)	Adding lamivudine (n = 109)	Switching to zidovudine plus lamivudine (n = 108)
Male sex: number (%)	278 (86%)	96 (89%)	93 (85%)	89 (82%)
Race				
White non-Hispanic: number (%)	236 (73%)	80 (74%)	78 (72%)	78 (72%)
Black non-Hispanic: number (%)	51 (16%)	17 (16%)	14 (13%)	20 (19%)
Hispanic: number (%)	35 (11%)	8 (7%)	17 (16%)	10 (9%)
Other: number (%)	3 (1%)	3 (3%)	0	0
Previous or current IV drug use: number (%)	21 (6%)	6 (6%)	8 (7%)	7 (6%)
Hemophiliac: number (%)	20 (6%)	7 (6%)	7 (6%)	6 (6%)
HIV symptoms				
AIDS: number (%)	2 (1%)	0	1 (1%)	1 (1%)
Symptomatic <sup>a</sup> : number (%)	50 (15%)	16 (15%)	17 (16%)	17 (16%)
Asymptomatic: number (%)	273 (84%)	92 (85%)	91 (83%)	90 (83%)
Age, years: Mean (SD)	40 (9)	39 (9)	41 (10)	40 (10)
Prior antiretroviral drug use, months: Median (Q1-Q3)	47 (42-68)	47 (41-70)	46 (42-66)	49 (42-69)
CD4 <sup>+</sup> cell count, cells/mm <sup>3</sup>				
At ACTG 175 baseline:				
Mean (SD)	370 (105)	368 (105)	369 (97)	372 (113)
At entry into ACTG 303:				
Mean (SD)	358 (195)	365 (194)	356 (189)	353 (202)
HIV-1 RNA level, <sup>b</sup> log <sub>10</sub> copies/ml				
≤500 copies/ml: Mean (SD)	4.12 (0.05)	4.07 (0.09)	4.19 (0.09)	4.08 (0.10)
500-750,000 copies/ml: Mean (SD)	24 (8%)	6 (7%)	6 (6%)	12 (12%)
≥750,000 copies/ml: Mean (SD)	259 (91%)	85 (93%)	89 (93%)	85 (86%)
3 (1%)	0	1 (1%)	2 (2%)	
ACTG 175 treatment (ZDV + ddI): number (%)	167 (51%)	55 (51%)	56 (51%)	56 (52%)
Switched from monotherapy to combination therapy in ACTG 175: number (%)	36 (11%)	11 (10%)	12 (11%)	13 (12%)

<sup>a</sup>Symptomatic was defined having candidiasis, oral hairy leukoplakia, or herpes zoster.

<sup>b</sup>Available for 286 subjects (91 in continuing arm, 96 in adding lamivudine arm, and 99 in zidovudine plus lamivudine arm).

*CD4<sup>+</sup> cell count responses and HIV RNA changes*

**CD4<sup>+</sup> cell count responses.** There were significant differences between the treatment arms for both short-term and long-term mean CD4<sup>+</sup> cell count changes (Fig. 1). With respect to short-term (baseline to week 4) changes, the addition arm and the switch arm demonstrated significantly greater mean increases in CD4<sup>+</sup> cell counts of +36 and +28 cells/mm<sup>3</sup>, respectively, compared with -4 cells/mm<sup>3</sup> for the continuation arm (three-way *p* = 0.012). Compared with the continuation arm, the addition arm (*p* = 0.008) and switch arm (*p* = 0.027), respectively, demonstrated higher mean CD4<sup>+</sup> cell increases. The difference in mean CD4<sup>+</sup> cell count increases between the addition and the switch arm was not significant (*p* = 0.67).

Similar results were obtained for long-term (baseline to weeks 40–48) changes. The addition arm and the switch arm had significantly greater mean CD4<sup>+</sup> cell count increases of +32 and +19 cells/mm<sup>3</sup>, respectively, compared with -9 cells/mm<sup>3</sup> observed in the continuation arm (three-way *p* = 0.003). Compared with the continuation arm, the addition arm (*p* = 0.001) and the switch arm (*p* = 0.02), respectively, had higher mean CD4<sup>+</sup> cell count increases. The difference between the addition arm and the switch arm was not significant (*p* = 0.33). At week 48, there was however, no difference in mean CD4<sup>+</sup> cell count change from baseline between the switch and continuation arms (Fig. 1).

Analyses of short-term and long-term changes in HIV RNA among subgroups of the study population defined by baseline characteristics showed that subjects with lower baseline CD4<sup>+</sup> cell counts had significantly greater mean increases in short-term and long-term CD4<sup>+</sup> cell counts (*p* = 0.006 and *p* = 0.001, respectively). There was no significant association with

other baseline characteristics nor was there evidence that differences between treatment arms varied by subgroup.

**Plasma HIV RNA changes.** A total of 268 subjects (82%) had short-term (baseline to week 8) HIV-1 RNA measurements and 253 subjects (78%) had long-term (baseline to weeks 40 and 48) measurements.

Subjects assigned to the addition arm and the switch arm sustained a mean short-term reduction in HIV RNA of 0.53 and 0.54 log<sub>10</sub> copies/ml, respectively (Fig. 2), compared with a mean reduction in plasma viral load of 0.13 log<sub>10</sub> copies/ml for subjects in the continuation arm (three-way *p* < 0.001). Subjects in the continuation arm had smaller mean short-term decreases in HIV-RNA compared with the addition arm (*p* < 0.001) and with the switch arm (*p* < 0.001). The difference between the addition arm and the switch arm was not significant (*p* = 0.86).

The long-term mean decreases in HIV RNA in the addition arm and the switch arm were 0.40 and 0.33 log<sub>10</sub> copies/ml, respectively, compared with the long-term mean decrease of 0.25 log<sub>10</sub> copies/ml for the continuation arm. The difference in long-term mean change among the three arms was not significant (three-way *p* = 0.30).

While the addition and the switch arms sustained significantly greater mean short-term plasma viral load declines than that observed in the continuation arm, the proportions of subjects in the addition and switch arms demonstrating plasma HIV RNA levels below 500 copies/ml at week 8 were 21% (19 of 91 subjects) and 24% (23 of 96 subjects), respectively, compared with 12% (10 of 86) in the continuation arm; these differences among the three treatment arms were not significant

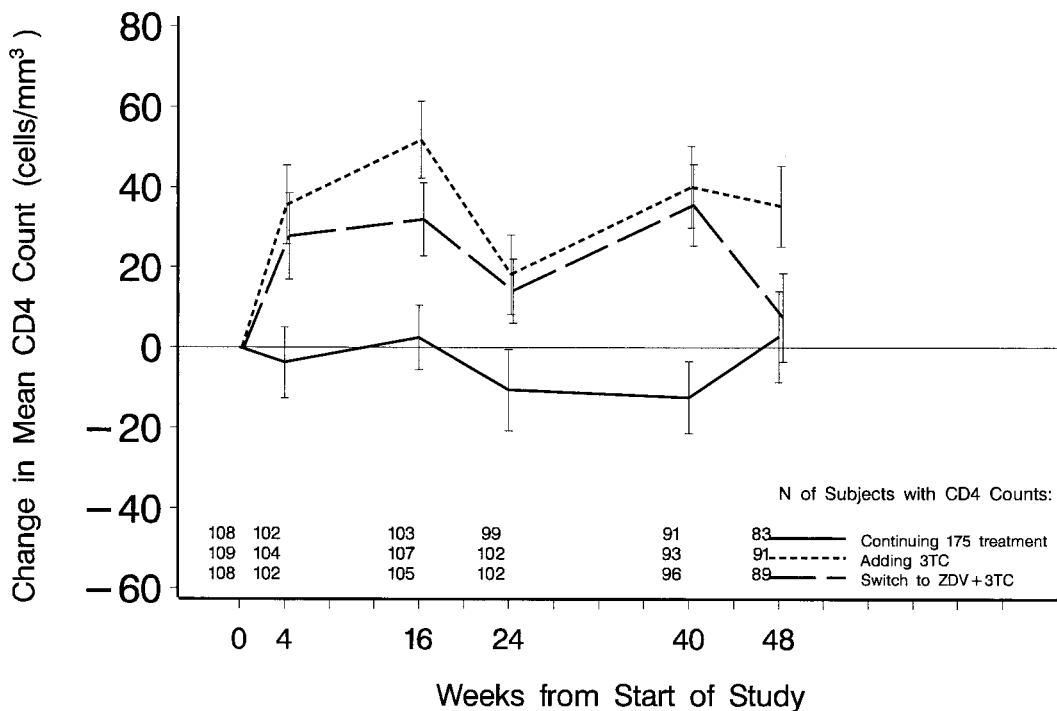


FIG. 1. Mean CD4<sup>+</sup> cell count change over time. Bars represent ± standard error.

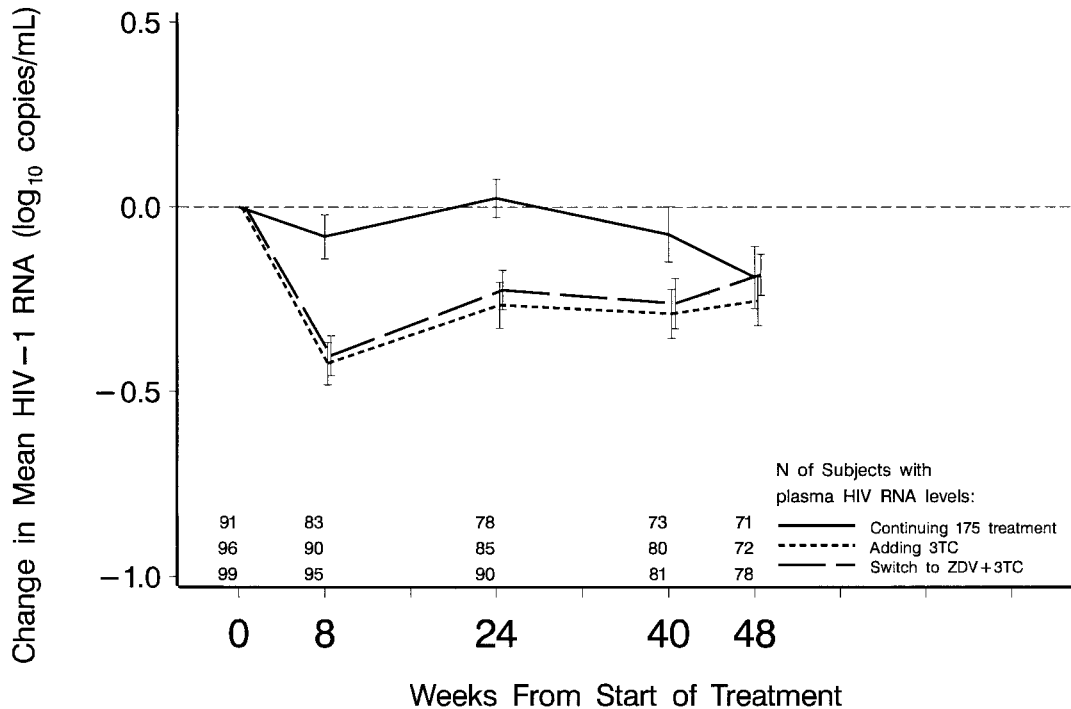


FIG. 2. Mean log<sub>10</sub> HIV-1 RNA change over time. Bars represent  $\pm$  standard error.

(three-way  $p = 0.16$ ). There were no differences observed in the proportions of subjects with suppression of plasma HIV RNA viral load below 500 copies/ml at week 48: 18% of subjects in each treatment arm (three-way  $p = 1.00$ ).

Short-term and long-term changes in HIV RNA were analyzed to evaluate whether the difference between treatments was associated with CD4<sup>+</sup> cell count, HIV RNA, prior duration of ZDV + ddI or ZDV + ddC treatment, or HIV-related symptoms. For subjects who had taken ZDV + ddI compared with subjects who had taken ZDV + ddC, mean reductions in HIV-1 RNA were significantly greater both in the short term (0.52 versus 0.30 log<sub>10</sub> copies/ml;  $p = 0.009$ ) and the long term (0.49 versus 0.17 log<sub>10</sub> copies/ml;  $p < 0.001$ ). In addition, subjects who had increasing trends in CD4<sup>+</sup> cell counts during follow-up in ACTG 175 had significantly greater reductions in the short term ( $p = 0.002$ ), but not the long term ( $p = 0.23$ ). There were no significant associations with any of the other baseline characteristics, nor was there any evidence that differences between treatments varied according to any baseline characteristic.

#### Adverse events and clinical disease progression

A total of 39 (12%) subjects had grade 3 or 4 signs/symptoms in the study, with 16 (15%) in the continuation arm, 12 (11%) in the addition arm, and 11 (10%) in the switch arm; signs and symptoms of a musculoskeletal nature were reported most frequently. Time to the first grade 3 or 4 sign or symptom did not differ among the treatment arms (three-way  $p = 0.49$ ). Twenty-six subjects (8%) developed grade 2 or 3 peripheral neuropathy. No grade 4 peripheral neuropathy was reported. There was no significant difference among treatment

arms in the incidence of neuropathy (6 in the continuation arm, 8 in the addition arm, and 12 in the switch arm; three-way  $p = 0.34$ ).

A total of 68 (21%) subjects experienced a grade 3 or 4 laboratory abnormality, with 20 (19%) of subjects in the continuation arm, 25 (23%) in the addition arm, and 23 (21%) in the switch arm. Elevations in creatine phosphokinase (CPK) levels were the most frequently reported grade 3 and 4 laboratory abnormalities. The time to first grade 3 or 4 laboratory abnormality did not differ significantly among treatments (three-way  $p = 0.69$ ). Overall, the study medications were well tolerated with only three subjects (two in the continuation arm and one in the addition arm) permanently discontinued from study treatment because of protocol-defined toxicities.

A total of nine subjects (3%) died or developed one or more AIDS-defining events: five in the continuation arm, two in the addition arm, and two in the switch arm. Two subjects died without a prior AIDS-defining event. Three subjects developed *Pneumocystis carinii* pneumonia (PCP); one subject developed disseminated mycobacterium infection (species not identified); one subject developed esophageal candidiasis; two subjects had cytomegalovirus (CMV) disease; and one subject developed concurrent HIV wasting and progressive multifocal leukoencephalopathy.

## DISCUSSION

The addition of 3TC or a switch to ZDV + 3TC conferred modest improvement in marker responses in patients with pro-

longed dual nucleoside exposure. Significantly greater short-term and long-term mean CD4<sup>+</sup> cell count increases were observed in the addition and switch arms compared with the continuation arm. Adding 3TC and switching to ZDV + 3TC resulted in superior mean short-term decreases in HIV RNA compared with continuing ZDV + ddI or ZDV + ddC but no long-term differences in virologic suppression were seen. At week 48, no differences in the proportions of subjects who had suppression of viral load below 500 copies/ml were seen (18% of subjects in each arm). A higher CD4<sup>+</sup> cell count at study entry was associated with greater declines in short-term HIV RNA levels ( $p = 0.002$ ). The addition of 3TC or a switch to ZDV + 3TC was well tolerated with a low toxicity rate.

The duration of prior ZDV experience in ACTG 303 subjects at study entry (median duration, 47 months) would be expected to increase the likelihood of baseline ZDV-associated mutations at codons 215, 70, and 41 that would confer high-level ZDV resistance.

The uniform development of the M184V mutation in the viral RT associated with the administration of 3TC, either alone or in combination with ZDV,<sup>15-17</sup> typically delays the development of ZDV resistance in ZDV-naïve patients and renews ZDV susceptibility in patients with previously acquired ZDV-associated resistance mutations.<sup>18,19</sup> The acquisition of dual M184V and 215Y codon mutations in viral isolates from selected patients receiving combination therapy with ZDV and 3TC has also been associated with reduced phenotypic susceptibility to both drugs.<sup>20</sup> The presence of baseline ZDV resistance mutations prior to the receipt of 3TC, therefore, may have limited or attenuated the extent of viral suppression achieved by adding 3TC or switching to ZDV + 3TC.

Similar trends in marker results with respect to those derived from the ACTG 303 study have been observed in prior studies conducted in both naïve and ZDV-experienced patients featuring dual ZDV plus 3TC nucleoside combination. In the NUCA 3001 and NUCB 3001 trials,<sup>9</sup> HIV-infected patients with <4 weeks of ZDV experience who received ZDV + 3TC combination therapy sustained superior mean CD4<sup>+</sup> cell count rises and achieved significantly greater long-term HIV RNA reductions through 1 year of follow-up compared with those who received ZDV alone.

In patients with more extensive ZDV pretreatment (at least 24 weeks of prior ZDV experience), greater mean CD4<sup>+</sup> cell count increases that persisted for up to 1 year but only short-term decreases in HIV RNA levels, as seen in this study, were conferred by ZDV/3TC therapy compared with ZDV/ddC or ZDV alone, respectively, in the NUCA 3002<sup>10</sup> and NUCB 3002<sup>11</sup> trials.

Despite the important differences in patient populations with respect to HIV disease stage and prior duration of antiretroviral therapy, our study and these other studies demonstrate that the dual combination of ZDV plus 3TC in ZDV-experienced patients consistently provides durable, sustained increases in CD4<sup>+</sup> cell counts of +20 to +41 cells/mm<sup>3</sup> above baseline but affords limited, short-term decreases in plasma viral load ranging from 0.5 to 0.9 log<sub>10</sub> copies/ml.<sup>10-12</sup> This study, based on the finding that only 18% of subjects in each of the three arms achieved HIV RNA levels <500 copies/ml at week 48, suggests that subsequent combination therapy that is limited to nucleoside agents, even in the setting of relatively low baseline viral loads (mean HIV RNA level of 4.12 log<sub>10</sub> copies/ml), will

confer only partial and short-term viral suppression in patients with extensive and prolonged NRTI experience.

In the ACTG 303 trial, the subjects on the ACTG 175 ZDV + ddI arm sustained significantly greater declines in both short-term and long-term HIV RNA changes ( $p = 0.009$  and  $p < 0.001$ , respectively) than those on the ZDV + ddC arm whereas no differences were noted in CD4<sup>+</sup> cell count responses. The reasons for this superior treatment response are unclear. The RT mutation L74V, which has been shown to develop during ddI monotherapy, typically results in diminished susceptibility to ddI while renewing ZDV susceptibility in the presence of ZDV mutations.<sup>21</sup> With concurrent administration of ZDV and ddI, however, the development of the 74 codon mutation would be suppressed, which may partially explain the continued antiviral activity of ddI for >3 years in this dual NRTI combination. Since the switch arm (ZDV + 3TC) and the addition arm (ZDV + ddI + 3TC), however, achieved similar declines in HIV RNA levels, the continuation of ddI on study entry did not appear to confer additional potency to the ZDV + 3TC regimen. The superior viral load responses observed in patients who had received ZDV + ddI versus ZDV + ddC in ACTG 175 may potentially relate to issues of greater *in vivo* efficacy of ddI relative to ddC.

The current approach to HIV therapy has been redefined with the recent use of increasingly more potent combination regimens<sup>22</sup> that are initiated at earlier stages of HIV infection with the aim of achieving viral suppression to below the limit of detection. In treatment-naïve patients, triple nucleoside regimens featuring potent agents, such as abacavir,<sup>23-25</sup> have achieved reductions in plasma viral load that compare favorably with those observed with protease inhibitor-based regimens. NRTI-alone regimens, however, in treatment-experienced patients, such as those comprising the ACTG 303 study population, are known to be only partially suppressive, and are associated with substantial RNA expression in lymph nodes<sup>26-27</sup> and the evolution of resistant virus.

Despite the limited short-term reductions in HIV RNA conferred by adding 3TC or by switching to ZDV + 3TC, this highly selected study population maintained mean CD4<sup>+</sup> cell counts at or above baseline levels of 370 cells/mm<sup>3</sup> and remained clinically stable with minimal HIV disease progression.

The results of the ACTG 303 study need to be interpreted in the context of the era in which the trial was performed. Although incremental nucleoside analog therapy is no longer considered optimal therapy, defined populations may do clinically well for prolonged periods. Further, ACTG 303 illustrates that strategic thinking over time is important in planning antiretroviral regimens, as those who received ZDV/ddI in ACTG 175 had improved responses to the addition of, or the switch to 3TC, in comparison with the ZDV/ddC group. The modest marker responses seen in ACTG 303, as illustrated by the lack of a durable viral load response, indicate that a more aggressive approach to therapy, in which drugs such as 3TC are used in maximally suppressive regimens, is preferred.<sup>22,28</sup>

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