Durability of Response to Treatment among Antiretroviral-Experienced Subjects: 48-Week Results from AIDS Clinical Trials Group Protocol 359

Roy M. Gulick,1 X. Joan Hu,2,4 Susan A. Fiscus,3 Courtney V. Fletcher,4 Richard Haubrich,5 Hailong Cheng,2,a Edward Acosta,7 Stephen W. Lagakos,2 Ronald Swanstrom,1 William Freimuth,6,a Sally Snyder,9 Charlotte Mills,11 Margaret Fischel,12 Carla Pettinelli,10 and David Katzenstein,6 for the AIDS Clinical Trials Group Protocol 359 Team

The 24-week extension of AIDS Clinical Trials Group Protocol 359, a study of human immunodeficiency virus (HIV)-infected, indinavir-experienced patients, was designed to study the durability of “salvage” treatment regimens. Patients received saquinavir in combination with either ritonavir or nelfinavir and, in addition, delavirdine, adefovir, or both. Patients who demonstrated a virologic response at weeks 12–16 were eligible to continue therapy in the extension through week 48. Of the 105 eligible subjects who were enrolled in the extension, 86 (82%) completed 48 weeks, and 49 (57%) of those 86 had HIV RNA levels <500 copies/mL at week 48. For these 86 subjects who completed 48 weeks, the median change in CD4 cell count from baseline was +72 cells/mm³. Greater body weight, higher CD4 cell count, and greater degree of phenotypic susceptibility to indinavir and saquinavir at baseline were significantly associated with durable virologic suppression. These results show that some patients who experience treatment failure can demonstrate durable virologic and immunologic responses with salvage antiretroviral regimens.

Current treatment guidelines recommend starting therapy for human immunodeficiency virus (HIV) infection with 2 nucleoside analogue reverse-transcriptase inhibitors in combination with 1 or 2 protease inhibitors or a nonnucleoside analogue reverse-transcriptase inhibitor [1, 2]. However, 20%–63% of patients from clinical cohorts experience virologic treatment failure while receiving combination antiretroviral therapy [3–7]. Recent prospective studies have attempted to identify strategies for treatment of the treatment-experienced patient [8–13], but these studies have focused primarily on 8–24-week virologic responses to treatment. The durability of virologic and immunologic responses to salvage antiretroviral therapy regimens is largely unknown. To address this, we prospectively followed up for an additional 24 weeks, as part of a treatment extension, indinavir-experienced patients who demonstrated an initial response to a new antiretroviral salvage therapy regimen by week 16 (determined at week 24).

Methods

Study design and population. AIDS Clinical Trials Group (ACTG) protocol 359 was a randomized, partially double-blind,
factorial, 48-week study (24-week primary study and 24-week extension) of 6 oral antiretroviral regimens that combined open-label saquinavir soft-gelatin capsule (sgc; 400 mg) with ritonavir (400 mg), given twice daily, or saquinavir sgc (400 mg) with ritonavir (400 mg), given twice daily, and, in addition, placebo-controlled delavirdine (600 mg twice daily), adefovir dipivoxil (120 mg once daily), or both delavirdine and adefovir dipivoxil (at the same dosages) (table 1). In addition, all subjects took L-carnitine, 500 mg daily.

Subjects eligible for the treatment extension had a documented virologic response during the initial period of ACTG 359, defined as the geometric mean of HIV RNA levels at weeks 12 and 16 being either \( \leq 5000 \text{ copies/mL} \) or \( \geq 1 \log_{10} \text{ copy/mL} \) below levels at baseline (week 0) (levels were measured with the Amplicor HIV Monitor Test; Roche Diagnostic Systems; limit of quantification, 500 copies/mL). If either the week 12 or the week 16 HIV RNA measurement was missing, the other was used as the level for the subject. Eligible patients were encouraged to continue the initial randomized therapy regimen for a total of 48 weeks.

**Study procedures.** Subjects had study visits every 4 weeks through week 48. At each visit, a clinical assessment and laboratory tests were done. Plasma was processed every 4 weeks through week 16 and every 8 weeks through week 48 and assayed in real time for HIV RNA (Amplicor HIV Monitor Test) at a central laboratory (University of North Carolina or University of Washington). Samples with HIV RNA levels of \( \leq 500 \text{ copies/mL} \) were retested with the Ultrasensitive HIV RNA assay (Roche Diagnostic Systems; limit of detection, 50 copies/mL). A subgroup of the study population, selected by stratified simple random sampling without replacement, underwent phenotypic resistance testing at baseline (Phenosense; ViroLogic). T lymphocyte subsets were quantified by flow cytometry every 4 weeks through week 16 and thereafter every 8 weeks through week 48.

Adverse events were graded using standardized ACTG guidelines. Adverse events of moderate (grade 2) or greater intensity were recorded so that the safety and tolerability of the study treatments could be evaluated. A protocol-specified definition of proximal renal tubular dysfunction was used that identified the disease by a serum creatinine level of \( \geq 0.5 \text{ mg/dL} \) above baseline and a serum phosphate level of \( < 2.0 \text{ mg/dL} \) or either of these abnormalities and 2 of the following: proteinuria (\( \geq 2+ \)), glycosuria (\( \geq 1+ \)) in the absence of hyperglycemia, hypokalemia (potassium level of \( < 3.0 \text{ mEq/L} \)), or a serum bicarbonate level of \( < 19 \text{ mEq/L} \).

**Statistical analysis.** The primary study objective of the treatment extension (weeks 16–48) of ACTG 359 was to evaluate the durability of virologic response among subjects who had plasma HIV-1 RNA levels of \( \leq 500 \text{ copies/mL} \) at 16 weeks. Durability of antiretroviral responses was evaluated in subjects who had demonstrated a virologic response (as defined above) by weeks 12–16. Safety analyses were based on data from subjects who received at least 1 dose of study medication. All tests were 2-tailed, and \( P < .05 \) was considered to be significant. Binary responses were analyzed using Fisher's exact test and the Pearson \( \chi^2 \) test; quantitative responses were analyzed using the Wilcoxon rank sum test and the \( F \) test for comparisons of 2 and \( > 2 \) groups, respectively.

**Results**

**Baseline characteristics and study disposition.** Of 277 subjects who enrolled in ACTG 359, 120 (43%) were eligible for the treatment extension, according to the prespecified criteria for virologic response (figure 1). A total of 105 (88%) of 120 eligible subjects entered the treatment extension at week 24, and 15 (12%) chose not to participate. There were no significant differences in baseline parameters between the eligible subjects who did and those who did not participate, with the exception of median age (extension participants, 40 years; extension nonparticipants, 45 years; \( P = .05 \), by the Wilcoxon rank sum test). Of the 156 subjects selected by stratified random sampling to participate, 154 (99%) began the study, and 152 (97%) completed the study.

Figure 1. Virologic responses in antiretroviral-experienced subjects included in a study of salvage therapy. HIV, human immunodeficiency virus.

### Table 1. Treatment regimens in AIDS Clinical Trials Group protocol 359 extension study of salvage antiretroviral therapy.

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Saquinavir + ritonavir + delavirdine + placebo</td>
</tr>
<tr>
<td>B</td>
<td>Saquinavir + ritonavir + placebo + adefovir dipivoxil</td>
</tr>
<tr>
<td>C</td>
<td>Saquinavir + ritonavir + delavirdine + adefovir dipivoxil</td>
</tr>
<tr>
<td>D</td>
<td>Saquinavir + nelfinavir + delavirdine + placebo</td>
</tr>
<tr>
<td>E</td>
<td>Saquinavir + nelfinavir + placebo + adefovir dipivoxil</td>
</tr>
<tr>
<td>F</td>
<td>Saquinavir + nelfinavir + delavirdine + adefovir dipivoxil</td>
</tr>
</tbody>
</table>
undergo phenotypic resistance testing at study entry, 56 eligible subjects participated in the study extension. At study entry, the median saquinavir IC\textsubscript{50} among these 56 subjects was 0.88 \( \mu \text{M} \), and the median indinavir IC\textsubscript{50} was 3.5 \( \mu \text{M} \).

Of the 105 treatment extension subjects, 70 (67%) had HIV RNA levels of \( \leq 500 \text{ copies/mL} \) at week 16, and 35 (33%) had HIV RNA levels that were \( >500 \text{ copies/mL} \) but were \( \geq 1 \log_{10} \text{ copy/mL} \) below baseline levels or \( \leq 5000 \text{ copies/mL} \). Eighty-six (82%) of 105 subjects completed the treatment extension through week 48, and 19 (18%) left the treatment extension early. The reasons for premature treatment discontinuation were as follows: death (\( n = 1 \); due to severe anemia at week 39 that was judged by the site investigator not to be related to study treatment), toxicity (proximal renal tubular dysfunction, \( n = 3 \); increased hepatic transaminase levels, \( n = 1 \); rash, \( n = 1 \); other, \( n = 1 \)), need for medication that was excluded by the protocol (\( n = 1 \)), and increase in HIV RNA levels (\( n = 11 \)). There were no significant differences in the proportions of subjects who discontinued study treatment early among the 6 treatment arms (\( P = .82 \), by Pearson \( \chi^2 \) test). Between weeks 16 and 48, 12 subjects chose to substitute stavudine for adefovir, and 8 subjects added nucleoside analogues (stavudine, \( n \); or lamivudine, \( n \); or lami-

**HIV RNA responses.** Of 105 eligible subjects who participated in the treatment extension, 86 (82%) completed 48 weeks of the study, and of these, 49 (57%) had HIV RNA levels of \( \leq 500 \text{ copies/mL} \) at week 48 (table 2 and figure 1). Of subjects with HIV RNA levels of \( \leq 500 \text{ copies/mL} \) at week 16, 43 (61%) of 70 (missing-equals-failure analysis, in which subjects with missing 48-week data were assessed as experiencing virologic failure in the analysis) and 43 (70%) of 61 (missing-equals-excluded analysis, in which subjects with missing 48-week data were excluded from the analysis) had HIV RNA levels of \( \leq 500 \text{ copies/mL} \) at week 48. Of subjects who had HIV RNA levels of \( >500 \text{ copies/mL} \) at week 16, 5 (14%) of 35 (missing-equals-failure analysis) and 5 (22%) of 23 (missing-equals-excluded analysis) had HIV RNA levels of \( \leq 500 \text{ copies/mL} \) at week 48 (figure 1). Of the 86 subjects who completed 48 weeks of study, the median change in HIV RNA levels from baseline through week 48 was \(-1.34 \log_{10} \text{ copies/mL} \) (table 2 and figure 2). Among the eligible subjects who participated in the study extension, who had HIV RNA levels of \( \leq 500 \text{ copies/mL} \), and for whom plasma samples were available for testing, HIV RNA levels were \( \leq 50 \text{ copies/mL} \) in 37 (60%) of 62 at week 16, 31 (62%) of 50 at week 24, and 35 (76%) of 46 at week 48.

For the treatment-extension study population, there were no significant differences in the proportions of subjects with HIV RNA levels of \( \leq 500 \text{ copies/mL} \) at either week 16 or 48 (missing-equals-failure or missing-equals-excluded analysis) between the pooled ritonavir and nelfinavir groups or among the pooled delavirdine, adefovir dipivoxil, and delavirdine/adefovir dipivoxil-combination groups. In a multivariate logistic regression analysis of the effects of various baseline parameters (race, sex, age, body weight, duration of prior indinavir use, HIV RNA level, CD4 cell count, and treatment assignment) on the durability of virologic response from week 16 to week 48, only the baseline CD4 cell count was significantly associated with the response (\( P = .01 \), missing-equals-failure analysis; \( P = .002 \), missing-equals-excluded analysis). After baseline HIV RNA level and CD4 cell count were replaced with week 16 values in the analysis, week 16 CD4 cell count was significantly positively associated with a durable virologic response (\( P = .03 \), missing-equals-failure analysis; \( P < .001 \), missing-equals-excluded analysis; \( \chi^2 \) test). After the week 16 CD4 cell count was accounted for, the baseline CD4 cell count was no longer significantly associated with HIV RNA levels of \( \leq 500 \text{ copies/mL} \) at week 48.

Of the 56 subjects selected by stratified random sampling from the study population to undergo phenotypic resistance testing, 38 had HIV RNA levels of \( \leq 500 \text{ copies/mL} \) at week 16. For those 38 subjects, a multivariate logistic regression analysis of the effects of the baseline parameters and the phenotypic susceptibility to indinavir or saquinavir (fold change in IC\textsubscript{50}) indicated that a greater baseline body weight (\( P = .03 \)), a higher CD4 cell count (\( P = .001 \)), and a lower baseline fold change in indinavir IC\textsubscript{50} relative to the drug-susceptible control virus (\( P = .04 \)) were significantly associated with the durability of virologic response. After the baseline HIV RNA and CD4 cell count were replaced with the week 16 HIV RNA and CD4 cell count in the analysis, a greater baseline body weight (\( P = .03 \)), a higher week 16 CD4 cell count (\( P = .001 \)), and a lower baseline fold change in both indinavir (\( P < .001 \)) and saquinavir (\( P = .002 \)) IC\textsubscript{50} values were positively associated with virologic response.

### CD4 cell count responses

The median change in CD4 cell

---

**Table 2.** Virologic and immunologic responses for 86 antiretroviral-experienced subjects included in a study of salvage therapy who completed 48 weeks of study.

<table>
<thead>
<tr>
<th>Study time point or period</th>
<th>No. (%) of subjects with HIV RNA levels ( \leq 500 \text{ copies/mL} )</th>
<th>Change in HIV RNA level, median copies/mL (IQR)</th>
<th>Change in CD4 cell count, median cells/mm\textsuperscript{3} (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 16</td>
<td>61 (71)</td>
<td>( -1.34 \log_{10} )</td>
<td>( +72 ) (5 to 129)</td>
</tr>
<tr>
<td>Week 48</td>
<td>49 (57)</td>
<td>( -0.13 ) (0.12 to 0.86)</td>
<td>( +9 ) (38 to 96)</td>
</tr>
<tr>
<td>Weeks 0–48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 16–48</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** HIV, human immunodeficiency virus; IQR, interquartile range.
count from baseline to week 48 for the 86 subjects who completed 48 weeks of study was +72 cells/mm$^3$ (interquartile range, +5 to +129 cells/mm$^3$; table 2). The median change in CD4 cell count from week 16 to week 48 for the 70 subjects with week 16 HIV RNA levels of ≤500 copies/mL was +29 cells/mm$^3$ (interquartile range, −36 to +103 cells/mm$^3$).

Subjects were stratified into 4 groups on the basis of the HIV RNA level at week 48: ≤50, >50 to 500, >500 to 5000, and >5000 copies/mL. Median CD4 cell count changes at week 48 for the 4 groups were significantly different from values at baseline ($P = .001$) and week 16 ($P = .033$) (table 3 and figures 3 and 4). There was a significant difference in the CD4 cell count changes from baseline to week 48 ($P = .001$; $t$ test) and from week 16 to week 48 ($P = .02$; $t$ test) between the groups with HIV RNA levels of ≤50 and >5000 copies/mL.

Linear regression analyses demonstrated that, of the baseline and week 16 parameters, only the week 16 CD4 cell count ($P < .001$; $t$ test) was significantly associated with the change in CD4 cell count from baseline to week 48. The changes in CD4 cell count at week 48 were also significantly correlated with HIV RNA level at week 48 ($P = .002$; $t$ test), with greater increases in CD4 cell counts associated with lower week 48 HIV RNA levels. For those subjects with baseline phenotypic resistance data available ($n = 48$), a lower baseline fold change in saquinavir IC$_{50}$ was significantly associated with the change in CD4 cell count from week 16 to week 48 ($P = .042$; $t$ test).

**Adverse events.** A total of 11 (10%) of 105 subjects had grade 3 or greater signs or symptoms at some point from week 16 through 48. The distribution among the treatment arms was as follows: 0 patients (arm A), 3 (arm B), 0 (arm C), 1 (arm D), 2 (arm E), and 5 (arm F) ($P = .01$; log-rank test). Of these symptoms, the most common were ache or pain and diarrhea or loose stools. Although only 3 (1%) of 277 subjects had experienced proximal renal tubular dysfunction by study week 16, 32 additional subjects experienced proximal renal tubular dysfunction between weeks 16 and 48. There were no differences in the occurrence of proximal renal tubular dysfunction among the 4 adefovir-containing treatment arms ($P = .26$) or between the pooled ritonavir and nelfinavir plus adefovir treatment arms ($P = .52$). A total of 29 (28%) of 105 subjects had grade 3 or greater laboratory abnormalities (other than those associated

### Table 3. Changes in CD4 cell counts, by human immunodeficiency virus (HIV) RNA level at week 48, among antiretroviral-experienced subjects included in a study of salvage therapy.

<table>
<thead>
<tr>
<th>HIV RNA level, copies/mL (no. of subjects)</th>
<th>Change in CD4 cell count, median cells/mm$^3$ (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤500 (49)</td>
<td>From week 0 to week 48: +102 (+36 to +154)</td>
</tr>
<tr>
<td>≤50 (15)</td>
<td>From week 16 to week 48: +51 (−90 to +105)</td>
</tr>
<tr>
<td>&gt;50 to 5000 (11)</td>
<td>+109 (+50 to +174)</td>
</tr>
<tr>
<td>&gt;5000 (26)</td>
<td>+65 (−32 to +109)</td>
</tr>
<tr>
<td>NOTE. IQR, interquartile range.</td>
<td>$^a$ No Ultrasensitive HIV RNA assay (Roche) results were available for 3 subjects.</td>
</tr>
</tbody>
</table>
Figure 3. Median changes in CD4 cell counts from baseline (week 0) to week 48, by human immunodeficiency virus (HIV) RNA level at week 48, among antiretroviral-experienced subjects included in a study of salvage therapy. Error bars represent 25th and 75th percentiles. Pairwise comparisons (t test) by group: Group 1 vs. group 2, \( P = .03 \); group 1 vs. group 3, \( P = .07 \); group 1 vs. group 4, \( P = .001 \); group 2 vs. group 3, \( P = .78 \); group 2 vs. group 4, \( P = .62 \); group 3 vs. group 4, \( P = .47 \).

with proximal renal tubular dysfunction) between weeks 16 and 48. The distribution among the treatment arms was as follows: 5 patients (arm A), 3 (arm B), 9 (arm C), 4 (arm D), 5 (arm E), and 3 (arm F) (\( P = .21 \); log-rank test). Of these abnormalities, the most common were triglyceride levels of \( >750 \text{ mg/dL} \), absolute neutrophil count of \( <750 \text{ cells/mm}^3 \), and creatine phosphokinase levels unrelated to exercise \( >4 \times \text{ the upper limit of normal} \).

Discussion

The durability of antiretroviral responses to salvage therapy in treatment-experienced patients is not well known. We found that in a group of patients taking indinavir-based regimens who had HIV RNA levels of 2000–200,000 copies/mL and who were randomly assigned to receive new antiretroviral regimens, 78 (31%) of 254 had HIV RNA levels of \( <50 \text{ copies/mL} \) at week 16 [9] and 49 (57%) of the 86 eligible subjects who completed the 24-week treatment extension had HIV RNA levels of \( \leq 50 \text{ copies/mL} \) at week 48. Of 70 subjects with HIV RNA levels of \( \leq 50 \text{ copies/mL} \) at week 16 who entered the treatment extension, 43 (61%) had HIV RNA levels of \( \leq 50 \text{ copies/mL} \) at week 48. The virologic treatment response rates may be underestimated in these results, because some subjects with suppressed viremia discontinued study treatment early for other reasons. In the same group, median CD4 cell counts increased by 19 cells/mm\(^3\) between baseline and week 16 for the entire study population [9] and by an additional 9 cells/mm\(^3\) between week 16 and week 48 for the treatment extension population. This study shows that some patients who responded initially to an antiretroviral salvage therapy regimen demonstrated durable virologic and immunologic treatment responses over the course of 48 weeks.

Several randomized studies of salvage antiretroviral regimens have been reported, but most have focused on short-term virologic end points. One of the first such trials, ACTG 333, a study of saquinavir-experienced subjects, was stopped early when a significant, though modest, difference in virologic response to the treatment regimens was detected at week 8 [8]. Other studies, such as the original report of the current study, ACTG 359 [9], GlaxoSmithKline 2007 [10], ACTG 372b [11], and ACTG 398 [12], focused on short-term end points at weeks 16–24 and showed disappointing virologic response rates. One small study by Tebas et al. [13] found a better virologic response rate among nelfinavir-experienced patients who changed to a regimen containing ritonavir and saquinavir. Benson et al. [14] recently found improved virologic responses among protease inhibitor–experienced subjects who began a regimen containing...
lopinavir/ritonavir. Because subjects who enter salvage studies have, by definition, already experienced virologic failure during prior treatment, a high treatment failure rate also may be expected when these patients begin a subsequent regimen. Using data from the EuroSIDA clinical cohort, Mocroft et al. [15] assessed response rates to second-line protease inhibitor regimens among 984 patients and found that only 43% suppressed virus loads to ≤500 copies/mL over the course of 6 months. Given that there are multiple reasons for virologic treatment failure (e.g., adherence, pharmacokinetics, and resistance and cross-resistance), it is notable that a durable response was achievable with a salvage regimen in the current study, albeit in a subgroup of patients.

The primary analysis at week 16 in this study showed a statistically significant difference in the virologic responses rates that favored the delavirdine-containing regimens [9]. One hypothesis for the difference in virologic response rates among the regimens was the demonstration of significant, although unanticipated, pharmacokinetic interactions among the study drugs [16]. Interestingly, the durability of the regimens, as measured by the antiretroviral responses from week 16 to week 48, was not different among the same study regimens. We speculate that the differences in drug concentrations led to early treatment failure in some patients but not in others, and that those in whom early treatment failure did not occur were able to achieve durable responses.

Clinical progression of HIV infection is strongly linked to CD4 cell count [17, 18]. The change in CD4 cell count that is associated with antiretroviral therapy occurs in 2 phases: a rapid increase during the first 8 weeks of treatment (phase 1) and a slower increase after 8 weeks (phase 2). Renaud et al. [19] found that, among nucleoside analogue–experienced subjects starting treatment with a protease inhibitor, both baseline CD4 cell count and the slope of CD4 cell decline before therapy was initiated predicted the phase 1 CD4 cell response but that reduction in virus load predicted the phase 2 CD4 cell response. In the EuroSIDA cohort, an HIV RNA level of <500 copies/mL was the strongest predictor of immunologic response (defined as an increase in CD4 cell count of at least 50 cells/mm³ over the baseline value) among patients receiving a second regimen including protease inhibitors [15]. Deeks et al. [20] studied a cohort of 380 patients who were taking protease inhibitors and found a significant correlation between mean changes in virus loads and CD4 cell counts over the course of 96 weeks.

In the present study, the week 16 CD4 cell count was significantly associated with durable virologic suppression from weeks 16 to 48, and the greater the degree of virologic suppression at week 48, the greater the increase in CD4 cell count from week
16 to week 48. In addition, changes in CD4 cell counts from baseline or week 16 to week 48 were significantly different among groups with week 48 HIV RNA levels of $\leq 50$, $>50-500$, $>500-5000$, and $>5000$ copies/mL; a greater degree of virologic suppression was associated with a larger increase in CD4 cell count.

Subjects who tolerated the study regimens for 16 weeks infrequently developed treatment-limiting toxicity responses after that time. The exception to this was the nephrotoxicity associated with adefovir dipivoxil, which occurred in only 3 (1%) of the original 277 study subjects by week 16 (dose, 120 mg of adefovir dipivoxil) but in 32 additional subjects during the treatment extension, between weeks 16 and 48 (dose, 60 mg of adefovir dipivoxil). Kahn et al. [21] noted similar results in a study of the effect of adefovir dipivoxil, 120 mg daily, in HIV-infected subjects; after 24 weeks of treatment, there was an increasing incidence of renal laboratory abnormalities, including elevations in serum creatinine levels (occurring in 60% of subjects by 48 weeks) and hypophosphatemia (occurring in 50% of subjects by 48 weeks). A more recent study of patients coinfected with HIV and hepatitis B virus in which adefovir dipivoxil was administered at a lower daily dose of 10 mg reported no treatment-related nephrotoxicity [22]. In general, the renal laboratory abnormalities associated with adefovir dipivoxil are consistent with a proximal renal tubular dysfunction and are mild to moderate in severity. The incidence of renal laboratory abnormalities associated with adefovir dipivoxil appears to be dose dependent (at 30, 60, or 120 mg), and the abnormalities usually resolve after the drug is discontinued.

The present study has several limitations, and the generalizability of the results is uncertain, given the highly selected study subject population. First, the study regimens were complex and involved taking 26–35 pills daily. It is notable that some study subjects who had a history of virologic failure that may have been due to poor adherence were able to take these complex study regimens and experience longer-term benefits. It is likely that adherence was important in maintaining the longer-term virologic and immunologic responses. Second, resistance testing was not used prospectively in this study. Current guidelines [1, 23] recommend use of resistance testing in patients who have experienced virologic failure to select subsequent treatment regimens, because this strategy has been associated with improvements in virologic treatment response [24, 25]. Third, most of our analyses of durability focus on subjects who achieved a prespecified virologic response at weeks 12 and 16, rather than on the entire study population. This was done to allow subjects who experienced early virologic failure to pursue other treatment options. Further investigation will explore the durability of virologic response for the entire study population. Despite the finding of prolonged benefits among subjects who had initial virologic responses, the overall response rates in this study were disappointing, and better salvage therapies and strategies are needed urgently.

In summary, this study showed that, in a group of treatment-experienced subjects who responded initially to a salvage regimen, some patients had durable virologic and immunologic responses through week 48. Further research efforts will help define the optimal strategies for using antiretroviral regimens to achieve higher rates of durable virologic and immunologic responses over the long term.

Acknowledgments

We thank Ernesto Scerpella, Allan Rodriguez, and Fernando Rivera (University of Miami, Miami); Charles John Gonzalez, Olivia T. Ortiz, Richard Hunt, and Candida T. Talabucon (New York University/Bellevue Hospital, New York); Janine Maenza, Rebecca Becker, Dorcas Baker, and Andrea Weins (Johns Hopkins University, Baltimore); Robert Kalajian, Margaret Nelson, and Kim Ingersol (Case Western Reserve University, Cleveland); Michael Saag and Sherree Wright (University of Alabama, Birmingham); Tammy Powell, Pamphos Kaul, Donna Thee, and Judith Feinberg (University of Cincinnati, Cincinnati); Joseph Wheat and Kristine Todd (Indiana University School of Medicine, Indianapolis); Linda Meixner, Bruce Coon, and Douglas Richman (University of California, San Diego); Neel French, Joseph Pulvirenti, Harold Kessler, and Jim Bruce (Northwestern University, Chicago); Aouie Carrera, Michael Borucki, John Fuchs, and Karen Waterman (University of Texas, Galveston); Joseph Eron, Jr., Charles van der Horst, Linh Ngo, and Janet Devine (University of North Carolina, Chapel Hill); M. Graham Ray, Beverly Putnam, Suzanne Fiorillo, and John Gerber (University of Colorado, Denver); Jane Norris, Debbie Slamowitz, and Thomas Merigan (Stanford University Medical Center, Palo Alto); Harvey Friedman, Doris Shank, and Chris Helker (University of Pennsylvania, Philadelphia); Daniel Rodriguez, Frances Canchola, John M. Leedom, and Liliana Aguinada (University of Southern California, Los Angeles); Scott A. Smith and Timothy Schacker (University of Minnesota, Minneapolis); Henry Sacks, Alice Mercado, Hilda Mendoza, and Steve Nowling (Mount Sinai Medical Center, New York); David Pearson, Laura Ponticello, Michael Giordano, and Brenda Greenhill (Weil Medical College, Cornell University, New York); Jorge L. Santana, Guillermo Vazquez, Ileana Lopez, and Virginia Ramirez (University of Puerto Rico School of Medicine, San Juan); Mary Albrecht, Don Craven, and Andrea-Christopher Belschner (Beth Israel Deaconess Medical Center, Harvard University, Boston); Michael F. Para, Robert J. Fass, and Jan Clark (College of Medicine and Public Health, Ohio State University, Columbus); Charles B. Hicks, Paulette MacDougall, and Stuart Carr (Duke University Medical Center, Durham, NC); Mary Shoemaker, Ross Hewitt, and Susan Cohn (University of Rochester, Rochester, NY); Juan J. Lertora, Mark Belk, David Mushatt, and Russell Strada (Tulane University School of Medicine, New Orleans); Gildon Beall, Dena Duran, and Mario Guerrero (Harbor–University of California, Los Angeles, Medical Center, Los Angeles); Mark A. Jacobson, Judy Aberg, Glenna Auerback, and Phyllis Barnett (University of California, San Francisco); Pablo Tebas, Genice Hamilton, and Michael Royal (Washington University School of Medicine, St. Louis); Lyle Oshita, Monica Millard, Scott Souza, and Debra Ogata-Arakaki (University of Hawaii, Honolulu); and Robert Delapenha, John McNeil, Lisa Alexis, and Judith Brown (Howard University, Washington, DC) as participating site personnel; Elizabeth Gimbel, Ann Walawander, and Kenneth Wood (Frontier Science and Technology Research, Amherst, NY); Jeff Taylor.
the patient volunteers. Hongyu Jiang (Statistical and Data Analysis Center, Harvard School of Public Health, Boston), for performing virologic assays. We also thank Antoinette Kenton and Sharon Shriver (Social and Scientific Systems, Silver Spring, MD), for assisting in protocol development; Dragavon, Michelle Jack, Vivian Yuan, and Robert Coombs (University of Washington, Seattle), for careful review of the manuscript; and the patient volunteers.

References


