Efficacy and Safety of Adefovir Dipivoxil With Antiretroviral Therapy
A Randomized Controlled Trial

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Context Adefovir dipivoxil is a nucleotide analog that has demonstrated effective antiretroviral activity against human immunodeficiency virus (HIV) with once-daily administration.

Objective To determine if adefovir confers antiretroviral or immunologic benefit when added to stable antiretroviral therapy.

Design Multicenter, 24-week, randomized, double-blind, placebo-controlled study. Enrollment was conducted from June 3, 1996, through May 6, 1997.

Setting Thirty-three US HIV treatment centers.

Participants Of 1171 patients screened, 442 patients infected with HIV receiving stable antiretroviral therapy for at least 8 weeks with plasma HIV RNA greater than 2500 copies/mL and CD4+ cell count above 0.20 \(10^9/L\) were randomized.

Intervention Patients were randomized to receive either a single 120-mg/d dose of adefovir dipivoxil (n = 219) or an indistinguishable placebo (n = 223). All patients received L-carnitine, 500 mg/d. Open-label adefovir was offered after 24 weeks and was continued until the end of the study.

Main Outcome Measures Changes in HIV RNA from baseline, based on area under the curve and CD4+ cell levels, adverse events, and effect of baseline genotypic resistance on response to adefovir.

Results Patients assigned to adefovir demonstrated a 0.4-log10 decline from baseline in HIV RNA compared with no change in the placebo group (\(P<.001\)), which continued through 48 weeks. CD4+ cell counts did not change. During the initial 24 weeks, elevated hepatic enzyme levels (\(P<.001\)), gastrointestinal tract complaints (\(P<.001\)), and weight loss (\(P<.001\)) were associated with use of adefovir. Between 24 weeks and 48 weeks elevations in serum creatinine occurred in 60% of patients, usually returning to baseline after discontinuation of adefovir. Patients with lamivudine or lamivudine and zidovudine resistance mutations demonstrated anti–HIV effects with adefovir (\(P<.01\) vs placebo group).

Conclusions This study suggests that once-daily adefovir therapy reduces HIV RNA and is active against isolates resistant to lamivudine or lamivudine and zidovudine. Nephrotoxicity occurred when treatment extended beyond 24 weeks but was reversible.

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Adefovir dipivoxil is a nucleotide (nucleoside monophosphate) analog, a member of a unique class of anti-HIV compounds that have potent in vitro activity against HIV-1, HIV-2, hepatitis B, and herpes viruses. Adefovir also demonstrates antiviral activity against HIV-infected cells from monocyte/macrophage lineage. The active intracellular metabolite, adefovir diphosphate, inhibits HIV reverse transcriptase (RT) at concentrations of almost 1 log10 lower than concentrations that inhibit human DNA polymerases. Adefovir replaces deoxyadenosine monophosphate, ultimately resulting in DNA chain termination. Adefovir maintains in vitro activity against most nucleoside-resistant strains of HIV. The pharmacokinetic profile of the oral prodrug, adefovir dipivoxil, demonstrated an intracellular half-life of 18 hours, making it suitable for administration once daily. Initial clinical studies of adefovir demonstrated effective antiretroviral activity following a 125-mg dose. We conducted this study to determine if adefovir conferred antiretroviral benefit when added to a stable ART regimen.

METHODS

We conducted a 33-center, 24-week, randomized, double-blind, placebo-controlled trial in the United States to evaluate the virologic and immunologic efficacy and the safety of adefovir when added to stable ART. Adults infected with HIV with at least 8 weeks of stable ART were enrolled from June 3, 1996, through May 6, 1997. Inclusion criteria were plasma HIV RNA levels of at least 5000 copies/mL by branched-chain DNA assay (bDNA version 2.0, Chiron Corp, Emeryville, Calif); CD4+ cell counts of between 0.20 and 0.50 × 10^9/L; ambulatory performance status at least 80% on the Karnofsky scale; serum creatinine levels of less than 132.6 µmol/L (1.5 mg/dL); hepatic transaminase levels of less than 3 times the upper limit of normal; absolute neutrophil count of more than 0.75 × 10^9/L; platelet counts of more than 50.0 × 10^9/L; hemoglobin greater than 80 g/L; and serum amylase of less than 1.5 times the upper limit of normal. Women were required to have a negative serum pregnancy test result. Patients were excluded if they had a new AIDS-defining event during the 2 months before enrollment, had an active infection, received immunomodulating agents within 4 weeks before entry, were pregnant or breastfeeding, or had gastrointestinal malabsorption, malignancy, or impaired judgment. To accelerate patient accrual and improve generalizability of the study’s findings early, during the accrual period and with the approval of the data safety and monitoring board, the inclusion criterion for HIV RNA was reduced from 5000 to 2500 copies/mL, and the upper limit on CD4+ cell count was eliminated. These changes were implemented before examination of any efficacy data. Randomization was by permuted blocks, with stratification by CD4+ cell count, HIV RNA, and concomitant ART and with dynamic balancing by site. Study protocol and consent form were approved by the institutional review boards of each of the participating institutions and each patient provided written informed consent.

Treatment Regimen

Once a day for 24 weeks patients received 120 mg of adefovir or an identical appearing placebo. After completion of the 24-week blinded phase, all patients were offered open-label adefovir. Throughout the study, all patients received concomitant open-label l-carnitine. Based on other long-term studies, the dosage of l-carnitine was increased from 250 to 500 mg/d during the study. Patients were encouraged to continue their current ART during the first 24-week period. Blinding of original treatment assignment was maintained until the last patient had completed 48 weeks.

Patients were evaluated within 14 days before randomization, on the day treatment began, and every 4 weeks through week 24. Screening and baseline evaluations included a full medical history and HIV confirmation. Subsequent visits included an interval medical assessment and physical examination, a complete blood cell count, urinalysis, common laboratory tests, CD4+ and CD8+ cell counts, and quantitative plasma HIV RNA levels. Following the initial 24-week blinded treatment period, the same evaluations were performed every 4 or 8 weeks until the study drug was discontinued or the study was completed.

Primary Criteria for Efficacy

Determination of virologic efficacy (HIV RNA log10 transformed) and immunologic efficacy (CD4+ cell counts) was based on changes from baseline using the area under the curve, relative to baseline, through week 24. In both analyses, a patient’s area under the curve was standardized by the duration of follow-up, and thus represents an averaged post-baseline change in the response variable. Secondary virologic analyses included absolute changes of HIV RNA levels from baseline and verification of the primary HIV RNA assay with quantitative RT polymerase chain reaction (PCR) technology (AmpliC, Roche Diagnostic Systems Inc, Branchburg, NJ) (lower limit of quantification, 400 copies/mL). The baseline value for HIV RNA and CD4+ cells was defined as the average of the last screening and week 0 (pretreatment) values. Adverse events were calculated for patients who received at least 1 dose of randomized treatment (n = 437). Toxicity scales originated from the AIDS Clinical Trials Group, available via e-mail request at wwwadm@s-3.com.

Baseline HIV Genotype

One hundred ninety-one consecutively enrolled patients were selected from 2 enrollment periods for genotypic resistance analyses of plasma HIV. Analyses were performed without knowledge of treatment assignment. A PCR product could not be obtained from 5 patients (4 adefovir, 1 placebo) and 20 patients had no week 24 sample (14 adefovir, 6 placebo). Of the remaining 166 patients, 24 did not complete 24 weeks of assigned therapy (10 adefovir, 14 placebo), leaving 142 patients who received 24 weeks of assigned treatment with baseline and week 24 samples for analysis. The preparation of HIV RNA from patient plasma, generation of a 1.1-
kilobase (kb) PCR fragment containing HIV RT, and analyses of the DNA sequences of these PCR fragments have been previously described. Briefly, RT PCR fragments from plasma samples were amplified by 2 rounds of PCR and subjected to population-based dideoxy automated sequencing (ALFExpress, Amersham Pharmacia Biotech, Piscataway, NJ) using overlapping single-dye (Cy5) labeled primers. Nucleotides 1-900 (amino acids 1-300) of the HIV RT gene were analyzed.

**Statistical Analysis**

ICON Clinical Research Inc, North Wales, Pa, conducted data management for this study. Statistical analyses were conducted by an independent statistical center (S.L., E.N., and D.C.). An independent data and safety monitoring board reviewed interim study results for safety. After both interim analyses, in February 1997 and July 1997, the data and safety monitoring board recommended that the study continue. All investigators (except for the statistical center), as well as the sponsor and the data management team, were blinded to all efficacy results until the week 24 database was frozen on March 31, 1998. Safety data were monitored through January 22, 1999.

The study was designed to enroll 400 subjects, with equal allocation to the 2 study arms. This sample size was based on achieving a power of 90% to detect a 0.13 log10 average decrease in viral load and an average improvement of 0.03×109/L CD4+ cells, based on a 2-sided test at the P = .05 level, and allowing for a 10% dropout rate. All analyses were prespecified in the study protocol and based on intent to treat. The primary analyses of HIV viral load and CD4+ cell count were based on computing the normalized area under the curve relative to baseline through study week 24 and then comparing the placebo and adefovir groups using the Van der Waerden nonparametric test. A variety of secondary and other analyses of HIV and CD4+ cell count were conducted for consistency with the primary analyses. These included the proportions of subjects with viral load levels below the limit of quantification at week 24, regression analyses of area under the curve, which incorporated baseline patient characteristics, and repeated measures analyses to assess for possible effects of background ART. Secondary efficacy end points included changes in Karnofsky status and body weight. Time-to-event end points were analyzed using the log-rank test, and proportions were compared using Fisher exact test. All reported P values are 2-sided.

The study sponsor, Gilead Sciences Inc, Foster City, Calif, provided the support for the conduct of the study, including adefovir and L-carnitine, and conducted the genotypic testing, blinded to knowledge of study drug assignment. Representatives from the sponsor participated as members of the study team; however, the scientific leadership of the study was the responsibility of independent investigators (J.K. and S.L.).

**RESULTS**

A total of 442 patients enrolled in this study from 33 sites in the United States; 223 were assigned to receive placebo and 219 were assigned to receive adefovir (Figure 1). Table I summarizes the distribution of patients by several baseline characteristics. Patients were predominantly white (68%) and male (93%), with a median baseline CD4+ cell count of 0.32×109/L (range, 0.11-1.01×109/L) and median HIV RNA of 9800 copies/mL (3.99 log10). At baseline, 243 patients (55%) were receiving combination therapy limited to RT inhibitors (RTIs); of these 117 patients (26%) were receiving zidovudine and lamivudine, 97 patients (22%) were receiving lamivudine and an RTI other than zidovudine, and 31 patients (7%) were receiving zidovudine with an agent other than lamivudine or as monotherapy. At baseline, 171 patients (38%) were receiving a protease inhibitor in combination with RTIs (39% placebo; 38% adefovir). The 2 treatment groups were well balanced by each of these baseline characteristics and by site. Figure 1 shows the disposition of patients. The rate of discontinuation of treatment or loss to

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**Figure 1. Profile of Adefovir Trial**

- 1171 Patients Screened for Study
- 729 Not Randomized (Did Not Meet Protocol Criteria)
- 442 Randomized
- 221 Received Placebo as Allocated
  - 2 Did Not Receive Placebo as Allocated
- 216 Received Adefovir Dipivoxil as Allocated
  - 3 Did Not Receive Adefovir as Allocated
- 38 Discontinued During Double-Blind Treatment
  - 10 Intervention Stopped but Followed Up
  - 2 Developed Nephrotoxicity
  - 23 Lost to Follow-up
- 47 Discontinued During Double-Blind Treatment
  - 26 Intervention Stopped but Followed Up
  - 1 Developed Nephrotoxicity
  - 21 Lost to Follow-up
- 163 Completed 24 wk Double-Blind Period
  - 187 Entered Open Label Phase
- 169 Completed 24 wk Double-Blind Period
  - 176 Entered Open Label Phase
- 135 Completed 48 wk and Received Adefovir for 24 wk
  - 52 Discontinued Treatment With Adefovir
    - 24 Due to an Adverse Event, Including 3 With Nephrotoxicity
    - 28 Due to Patient Request or Lost to Follow-up
- 104 Completed 48 wk and Received Adefovir for 48 wk
  - 72 Discontinued Treatment With Adefovir
    - 55 Due to an Adverse Event, Including 37 With Nephrotoxicity
    - 17 Due to Patient Request or Lost to Follow-up
- 40 Completed 72 wk and Received Adefovir for 48 wk
  - 8 Discontinued Treatment With Adefovir
    - 54 Due to an Adverse Event, Including 40 With Nephrotoxicity
    - 41 Due to Patient Request or Lost to Follow-up
- 43 Completed 72 wk and Received Adefovir for 72 wk
  - 61 Discontinued Treatment With Adefovir
    - 54 Due to an Adverse Event, Including 21 With Nephrotoxicity
    - 35 Due to Patient Request or Lost to Follow-up
follow-up between groups did not significantly differ \( (P = .23, \ P = .78, \text{log rank test, respectively}) \).

During the initial 24-week portion of the study, 122 (28%) of the patients (57 placebo, 65 adefovir; \( P = .34 \)) initiated a new antiretroviral agent into their stable regimen. Among this group of 122 patients, 50 patients in the placebo and 49 in the adefovir groups added a new protease inhibitor \( (P = .32) \); 60% of those did so on or after study week 16. Five patients receiving adefovir and 3 receiving placebo developed an AIDS-defining clinical event during the initial 24-week portion of the study. No deaths occurred during this period.

### HIV RNA and CD4+ Cell Counts

As seen in Figure 2, A, the mean plasma HIV RNA level in the placebo group remained relatively constant during the initial 24 weeks of therapy, whereas HIV RNA levels in the adefovir group declined by 0.4 \( \log_{10} \) below baseline \( (P < .001) \). The estimated changes at a given time point are based on the number of patients with a marker value at baseline and at that time point, and thus are in general lower than the total number of patients randomized. The time-weighted average postbaseline change of HIV RNA during the initial 24-week blinded phase was \(-0.24 \log_{10}\) for those randomized to adefovir and \(-0.04 \log_{10}\) for those receiving placebo \( (P < .001) \).

Among the patients randomized to adefovir, 34 (19%) of the 178 had HIV RNA less than 500 copies/mL at week 24 compared with 11 (6%) of 182 receiving placebo \( (P < .001, \text{Fisher exact test}) \). The group of patients initially receiving adefovir had a sustained reduction of HIV RNA that extended through the 48-week study period (Figure 2, A). Patients initially receiving placebo who then began to receive adefovir after 24 weeks achieved a mean HIV RNA reduction of approximately 0.4 \( \log_{10} \) during the open-label period of treatment.

### Table 1. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adefovir</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients randomized</td>
<td>219</td>
<td>223</td>
<td>442</td>
</tr>
<tr>
<td>Age, y</td>
<td>40.5</td>
<td>39.6</td>
<td>40.0</td>
</tr>
<tr>
<td>Weight, kg (lb)</td>
<td>78.7 (174.9)</td>
<td>77.0 (171)</td>
<td>78.0 (173.4)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>153 (70)</td>
<td>147 (65)</td>
<td>300 (68)</td>
</tr>
<tr>
<td>Black</td>
<td>34 (16)</td>
<td>44 (20)</td>
<td>78 (18)</td>
</tr>
<tr>
<td>Other</td>
<td>31 (14)</td>
<td>32 (14)</td>
<td>63 (14)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>202 (92)</td>
<td>208 (93)</td>
<td>410 (93)</td>
</tr>
<tr>
<td>Women</td>
<td>17 (8)</td>
<td>15 (7)</td>
<td>32 (7)</td>
</tr>
<tr>
<td>Antiretroviral therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine monotherapy</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Other nRTI monotherapy</td>
<td>10 (5)</td>
<td>12 (5)</td>
<td>22 (9)</td>
</tr>
<tr>
<td>Combination nucleoside with or without nRTI</td>
<td>123 (56)</td>
<td>122 (55)</td>
<td>245 (55)</td>
</tr>
<tr>
<td>Protease inhibitors (not saquinavir) plus nRTI</td>
<td>66 (30)</td>
<td>68 (31)</td>
<td>134 (30)</td>
</tr>
<tr>
<td>Saquinavir plus nRTI</td>
<td>18 (8)</td>
<td>19 (8)</td>
<td>37 (8)</td>
</tr>
<tr>
<td>HIV-1 RNA, copies/mL \times 10^3, median (range)</td>
<td>10.0 (2.6-591)</td>
<td>9.3 (2.5-372)</td>
<td>9.8 (2.5-591)</td>
</tr>
<tr>
<td>CD4+ cell count, \times 10^9/L, median (range)</td>
<td>0.32 (0.11-0.93)</td>
<td>0.32 (0.13-1.01)</td>
<td>0.32 (0.11-1.01)</td>
</tr>
</tbody>
</table>

*All data are presented as number (percentage) unless otherwise indicated. HIV indicates human immunodeficiency virus; nRTI, nucleoside reverse transcriptase inhibitor; nnRTI, nonnucleoside reverse transcriptase inhibitor.

Figure 2. Changes From Baseline in HIV-1 RNA Levels and CD4+ T Cell Counts

At week 24, adefovir was provided to all patients. Bars are 95% confidence intervals. bDNA indicates branched DNA.
eral data obtained using the bDNA assay, the virologic response was repeated using PCR technology and yielded similar results to those obtained with bDNA technology (data not shown).

To assess consistency of the primary efficacy analysis, a variety of secondary analyses of viral load were undertaken. Linear regression models were fitted with treatment group, age, sex, baseline weight, initial CD4+ cell count, baseline HIV RNA level, use of a protease inhibitor, and Karnofsky scale as independent variables. In these analyses, older patients (P = .04), patients with higher screening viral loads above 5000 copies/mL (P < .01), and patients with higher baseline Karnofsky status (P = .04) had greater declines in viral loads. After adjusting for these factors the adefovir group continued to demonstrate significantly greater reduction in viral load than the placebo group (mean reduction, 0.20 log; P < .001). Additional analyses included comparisons of the placebo and adefovir groups at weeks 16 and 20 and comparisons that accounted for changes in the use of concomitant antiretrovirals. All of these analyses gave results that were very similar to the primary efficacy analysis (data not shown).

The time-weighted average postbaseline change in CD4+ cell counts did not significantly differ during the 24 weeks of randomized therapy between the 2 groups (P = .11). There was no substantial change from baseline in mean CD4+ cell counts over the entire 48-week period of follow-up in the group randomized to receive adefovir (Figure 2, B). Among patients randomized to receive adefovir, serum carnitine levels were lower than those randomized to receive placebo but generally were maintained in the normal range, and there were no reports consistent with carnitine deficiency (data not shown). As a group, patients receiving adefovir exhibited a steady decline in body weight, with a mean reduction of 2.4 kg (5.3 lb) at week 24, compared with no change among those receiving placebo (P < .001). Weights stabilized after 24 weeks of adefovir treatment.

### Toxic Effects

As shown in Table 2, a total of 250 (57%) of 437 patients experienced laboratory adverse events that were considered moderate to severe (grades 2, 3, or 4) during the 24-week blinded portion of the study. More patients receiving adefovir (n = 216) developed laboratory adverse events than those receiving placebo (n = 221) (137 [63%] vs 113 [51%], respectively; P = .04). Significantly more patients receiving adefovir than placebo experienced serum liver transaminase (AST or ALT) elevations. There were no other significant laboratory adverse events between the 2 groups. Overall, there were significantly more clinical events that were grade 2 or higher occurring in at least 5% of the study population among the patients treated with adefovir than placebo (179 [83%] vs 165 [75%], respectively; P = .04) (TABLE 3). There were significantly more gastrointestinal tract adverse events among the patients randomized to receive adefovir (123 [57%]) than placebo (64 [29%]; P < .001), including diarrhea, nausea, vomiting, and dyspepsia. Grade 2 dysuria also occurred more commonly among those receiving adefovir than those receiving placebo (10 [5%] vs 1 [1%], respectively; P = .02).

Following 24 weeks of adefovir treatment, there was an increasing incidence of renal toxic effects, manifested primarily by elevations in serum creatinine levels or hypophosphatemia. A Kaplan-Meier plot of the time to reach a serum creatinine increment of greater than 0.42 µmol/L (0.5 mg/dL) from baseline is shown in Figure 3, A, and indicates that more than a 0.42 µmol/L (0.5 mg/dL) increase from baseline can be expected in 35% of patients following 48 weeks and 50% of patients following 72 weeks of adefovir treatment. A scatter plot representing the temporal pattern of the individual patient values constituting the adefovir group with serum creatinine level elevation greater than 44.2 µmol/L (0.5 mg/dL) is shown in Figure 3, B. A Kaplan-Meier plot of the time to resolve the serum creatinine level elevation to less than 44.2 µmol/L (0.5 mg/dL) above baseline is shown in Figure 3, C, and estimates that 24 weeks after the laboratory abnormality and in response to the toxicity management (mostly consisting of drug discontinuation), 88% of cases of increased serum creatinine levels will have resolved. Hypophosphatemia occurred in 50% of patients after 48 weeks and in 61% of patients after 72 weeks of adefovir treatment, and hypophosphatemia’s onset and resolution followed a similar course as creatinine levels. Kaplan-Meier plot of the time to reach a serum phosphate level less than 2.0 mg/dL is shown in Figure 4, A. A delayed onset similar to the creatinine elevation is observed and the estimated incidence after 72 weeks of ADV treat-

### Table 2. Laboratory Adverse Events Grade 2 or Higher Occurring in at Least 5% of the Patients

<table>
<thead>
<tr>
<th>Component</th>
<th>Adefovir (n = 216)</th>
<th>Placebo (n = 221)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine kinase</td>
<td>34 (15)</td>
<td>31 (14)</td>
<td>.76</td>
</tr>
<tr>
<td>ALT</td>
<td>44 (20)</td>
<td>44 (20)</td>
<td>.001</td>
</tr>
<tr>
<td>AST</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>.05</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>18 (8)</td>
<td>18 (8)</td>
<td>.42</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>6 (3)</td>
<td>4 (3)</td>
<td>.81</td>
</tr>
<tr>
<td>Urine protein</td>
<td>24 (11)</td>
<td>24 (11)</td>
<td>.11</td>
</tr>
</tbody>
</table>

*ALT indicates alanine transaminase; AST, aspartate transaminase.

### Table 3. Clinical Adverse Events Grade 2 or Higher Occurring in at Least 5% of the Patients

<table>
<thead>
<tr>
<th>System</th>
<th>Adefovir (n = 216)</th>
<th>Placebo (n = 221)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal tract</td>
<td>123 (57)</td>
<td>64 (29)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>110 (51)</td>
<td>99 (45)</td>
<td>.20</td>
</tr>
<tr>
<td>Skin</td>
<td>58 (26)</td>
<td>68 (31)</td>
<td>.20</td>
</tr>
<tr>
<td>Neurologic</td>
<td>44 (20)</td>
<td>36 (16)</td>
<td>.27</td>
</tr>
<tr>
<td>Urologic</td>
<td>27 (13)</td>
<td>13 (6)</td>
<td>.02</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>14 (7)</td>
<td>11 (5)</td>
<td>.50</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>13 (6)</td>
<td>12 (5)</td>
<td>.48</td>
</tr>
<tr>
<td>Sensory nervous</td>
<td>8 (4)</td>
<td>12 (5)</td>
<td>.39</td>
</tr>
<tr>
<td>Any event</td>
<td>179 (83)</td>
<td>165 (73)</td>
<td>.04</td>
</tr>
</tbody>
</table>
ment is 59%. The corresponding scatter plot is shown in Figure 4, B. As shown by the Kaplan-Meier plot in Figure 4, C an estimated 97% resolution of the hypophosphatemia (>2.0 mg/dL) occurs within 24 weeks. One patient experienced renal failure requiring hemodialysis. This patient had hepatitis and pancreatitis and received an iodinated radiocontrast agent preceding the onset of acute renal failure and eventually died of multiorgan failure.

Analyses of Baseline HIV Genotypic Resistance
The baseline plasma HIV RT genotypes for the 142 patients in the virology substudy were determined, and the patients were grouped according to their zidovudine and lamivudine resistance mutations (TABLE 4). Consistent with the extensive pretreatment history of these patients, baseline virus from 79% and 76% of the patients expressed zidovudine or lamivudine resistance mutations, respectively. Patients with zidovudine resistance mutations were grouped according to the genetic patterns typically associated together: none, low-level (<10-fold), or high-level (>10-fold).28-30 All groups of patients randomized to receive adefovir with HIV expressing the lamivudine resistance mutation M184V and any level of zidovudine resistance mutations (none, low, high) showed a statistically significant decline in plasma HIV RNA compared with those patients receiving placebo ($P = .001$, $P = .01$, and $P = .002$, respectively, Van der Waerden test). Patients randomized to receive adefovir with wild-type virus or with only low-level zidovudine resistance mutations demonstrated a $0.65 \text{log}_{10}$ decline in HIV RNA. Patients with high-level zidovudine resistance mutations without an M184V mutation did not appear to suppress HIV RNA (Table 4).

**COMMENT**
This study was performed to determine the efficacy, as measured by changes in HIV RNA and CD4+ cell counts, and safety of adefovir. The data demonstrate that the addition of adefovir significantly reduced HIV RNA by $0.4 \text{log}_{10}$ and increased the proportion of subjects with viral load below 500 copies/mL, the lower limit at which the virus would be detected at the time this study was initiated. A variety of secondary analyses of viral load that accounted for baseline characteristics, changes in background ARTs, and duration of follow-up shorter than 24 weeks all corroborated the primary analysis. Patients with HIV expressing lamivudine resistance or lamivudine and zidovudine resistance in their baseline plasma sample received significant benefit from adefovir treatment. CD4+ cell counts did not significantly change from baseline during the study period.

The activity of adefovir suggests that nucleotide analogs may confer advantages to an effective treatment regimen. First, adefovir demonstrated effective anti-HIV activity for 24 weeks and appeared to be durable for 48 weeks, although changes in background therapy with other anti-HIV medications also were permitted after 24 weeks. The anti-HIV activity is similar to data reported for abacavir, with a comparable study design involving nucleoside-experienced patients.31 Second, adefovir was active in combina-
tion with a variety of anti-HIV medications. Third, adefovir is active when administered in once-daily dosing. Fourth, genotypic resistance data showed that adefovir retains activity against HIV that is resistant to lamivudine or the combination of lamivudine and zidovudine, a common resistance profile in patients experienced with ART. Developing effective agents to treat patients infected with HIV resistant to nucleoside analogs represents the next challenge for investigators and clinicians.

The activity and durability of adefovir must be balanced with its adverse events. The increased occurrence of liver enzyme abnormalities and gastrointestinal tract adverse effects were clinically important but manageable. The origin of the weight loss is unknown but was not clinically significant. Nephrotoxic effects were unanticipated and characterized by the slow but steady increase in serum creatinine and a decline of serum phosphate levels following 24 weeks of therapy. The resulting renal dysfunction was generally mild and resolved toward baseline, usually when adefovir was discontinued. Recently, adefovir prescribed at 60 mg/d was reported to have similar anti-HIV activity but lower incidence of elevated serum creatinine levels and serum hypophosphatemia.32

Identification and subsequent management of the nephrotoxic effects are essential for all patients receiving adefovir. Recommendations for the early identification of nephrotoxic effects include monthly determinations of serum creatinine and phosphate levels. Drug interruption or discontinuation should be considered if the serum creatinine levels exceed, or if serum phosphate levels drop below, their normal ranges. When the abnormal laboratory value returns to within normal limits, adefovir may be considered at a reduced dosage and with close clinical monitoring. Presently, there are no clinically useful predictors for patients likely to develop renal dysfunction; however, caution is warranted before initiating adefovir.

Table 4. Influence of Baseline Reverse Transcriptase (RT) Resistance Mutations on Mean Change in HIV RNA Log_{10} at 24 Weeks

<table>
<thead>
<tr>
<th>Baseline RT Mutations</th>
<th>No. of Patients</th>
<th>Mean Change*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lamivudine</td>
<td>Zidovudine</td>
<td>Total</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>9</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>Low‡</td>
<td>5</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>High§</td>
<td>20</td>
</tr>
<tr>
<td>M184V</td>
<td>None</td>
<td>None</td>
<td>21</td>
</tr>
<tr>
<td>M184V</td>
<td>Low‡</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>M184V</td>
<td>High§</td>
<td>75</td>
<td>39</td>
</tr>
<tr>
<td>Total</td>
<td>Lamivudine</td>
<td>Zidovudine</td>
<td>142</td>
</tr>
</tbody>
</table>

*Changes in human immunodeficiency virus (HIV) RNA expressed as log_{10} copies/mL branched DNA.
†P value is obtained from the Van Der Waerden test.
‡D67N, K70R, or L210W/S RT mutations. Low-level zidovudine resistance is defined as less than 10-fold; high-level zidovudine resistance, greater than or equal to 10-fold. M184I/L/T215Y/F or more than 3 zidovudine-associated mutations.
Efficacy and Safety of Adefovir Dipivoxil

In patients with preexisting renal disease and those receiving other potentially nephrotoxic agents.

Based on this study, the antiretroviral activity of adefovir in a single, once-daily regimen suggests that it may be a useful additional medication for patients who need to build effective treatment combinations to reduce viral replication. Adefovir should be used with close clinical and laboratory monitoring, and it may be especially useful in patients with resistance to lamivudine with or without zidovudine resistance.

This study demonstrates that adefovir treatment may be considered when constructing a treatment regimen for patients who have ongoing viral replication despite receiving approved antiretroviral medication.

**REFERENCES**


