# Impact of an Educational Program on Efficacy and Adherence With a Twice-Daily Lamivudine/Zidovudine/Abacavir Regimen in Underrepresented HIV-Infected Patients

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**Abstract:** A 24-week open-label clinical trial was conducted in 195 HIV-infected adults commonly underrepresented in research (35% female, 71% African American, 21% Hispanic, and 20% injection drug users [IDUs]) to evaluate the effect of an HIV educational program on efficacy and adherence with a simple, compact, twice-daily triple nucleoside regimen containing a lamivudine (150 mg)/zidovudine (300 mg) combination (COM) tablet plus abacavir (ABC), 300 mg. At baseline, the patients' median plasma HIV-1 RNA level was 4.18 $\log_{10}$ copies/mL and the median $CD4^+$ cell count was 379 cells/$mm^3$. Patients were randomized 1:1 to 4 modules of the Tools for Health and Empowerment HIV education intervention plus routine counseling (EI + RC; n = 96) or to routine counseling alone (RC; n = 99). No differences between the EI + RC and RC treatment arms were observed with respect to the proportion of patients achieving plasma HIV-1 RNA levels <40 copies/mL (60% [33/55] vs. 55% [38/69]; $P = 0.529$) or <400 copies/mL (80% [44/55] vs. 80% [55/69]; $P = 0.689$) at week 24 (intent-to-treat observed analysis), increase in median CD4 cell count above baseline at week 24 (78.3 vs. 104.8 cells/$mm^3$; $P = 0.498$), or mean overall adherence rates as measured by the Medication Event Monitoring System (MEMS) (70% vs. 74%). COM + ABC was generally well tolerated, and no association was observed between interruptions in treatment and the development of ABC hypersensitivity (5 suspected cases). In conclusion, in underrepresented patients, the EI used in this study did not affect the efficacy and adherence results with ABC + COM to any greater degree than did RC.

**Key Words:** lamivudine, zidovudine, abacavir, underrepresented populations, adherence, hypersensitivity reaction

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To date, many clinical trials evaluating highly active antiretroviral therapy (HAART) regimens have underrepresented certain groups of patients—notably, ethnic minorities, women, and injection drug users (IDUs).[1] This oversight is problematic, because over the past 15 years, the number of new cases of HIV and AIDS among these underrepresented patients has increased disproportionately compared with the total HIV-infected population.[2–4]

Several studies have reported poorer adherence in African American patients compared with white patients[5–8] and in IDUs compared with non-IDUs[9–11] due to a multiplicity of factors, including inconsistent access to antiretroviral medications and medical care in general, lack of medication or disease counseling, literacy problems, unstable or unsupportive home environments, distrust of medical caregivers, and/or attitudinal issues. In one study of an underrepresented HIV-infected population, the reasons most often mentioned by patients for refusing to take HAART regimens were unreadiness for strict adherence to a complex regimen (44%) and fear of adverse effects (38%).[12]

Adherence, and hence virologic suppression, would be expected to be at least partially improved in underrepresented patients if they were given proper education about their treatment and were prescribed simple, easy-to-remember, and well-tolerated HAART regimens. Education programs have

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been developed to motivate patients to adhere to their antiretroviral drug regimens and comply with scheduled clinic visits, although these have only rarely factored in the special needs and causes of nonadherence in underrepresented populations.[13–15] A simple and compact (4 tablets per day) triple nucleoside reverse transcriptase inhibitor (NRTI) regimen has been available for several years that combines 1 lamivudine (150 mg)/zidovudine (300 mg) tablet (COM) plus 1 abacavir 300-mg tablet (ABC). In clinical trials, this regimen administered twice daily has proved to suppress viral load maximally while preserving other classes of antiretrovirals as options for subsequent or salvage therapy.[16–18] The objective of the present study, Glaxo Wellcome Protocol NZTA4006, was to evaluate the impact of an HIV education intervention (EI; 4 modules of the Tools for Health and Empowerment [THE] course[19]) plus routine adherence counseling versus routine counseling (RC) alone on efficacy and adherence with the twice-daily COM + ABC regimen in an underrepresented HIV-infected population.

## METHODS

### Patient Selection

Male and nonpregnant female outpatients were eligible for study enrollment if they were aged 18 years or older; had HIV-1 infection documented by HIV-1 antibody enzyme-linked immunosorbent assay (ELISA) and Western blot testing; had a plasma HIV-1 RNA level >40 copies/mL and <100,000 copies/mL (according to the NucliSens assay; Organon Teknika, Durham, NC) and CD4 cell counts $\geq 50/mm^3$ within 14 days of study drug administration; were antiretroviral naive or had limited antiretroviral experience (used for up to 6 months) with anti-HIV drugs other than lamivudine, zidovudine, abacavir, non-NRTIs, or protease inhibitors (PIs); and were from an underrepresented population. Underrepresented populations included men from ethnic minorities (specifically African Americans, Latinos/Hispanics, or Asians), IDUs, and any women. All patients had to be able to read, comprehend, and record information at the level of fifth-grade English. Patients were excluded if they were unable to comply with the study schedule; unlikely to be able to attend the required sessions of the THE course during weeks 1 through 4 of the study; were diagnosed with AIDS, acute hepatitis, or chronic hepatitis; were concurrently enrolled in another investigational drug study; were pregnant (confirmed by a serum β-human chorionic gonadotropin test) or lactating; had a malabsorption syndrome affecting drug absorption; had clinically significant laboratory abnormalities; required radiation therapy, cytotoxic chemotherapy, or immunomodulating agents within 4 weeks prestudy; had received an HIV immunotherapeutic vaccine within 3 months prestudy; or required foscarnet or other agents with documented activity against HIV-1 in vitro.

### Study Design and Treatment

In this multicenter, phase 3, open-label, parallel-arm, comparative trial, all eligible patients received 1 COM tablet plus an ABC 300-mg tablet twice a day for 24 weeks. The COM was supplied as Combivir and the ABC as Ziagen (both brand name products from Glaxo Wellcome, Inc., Research Triangle Park, NC). The study was conducted between July 14, 1998 and February 28, 2000 at 25 outpatient treatment sites in the United States. All patients provided written informed consent to participate, and the protocol for the study was approved by the institutional review boards at each treatment site.

All study candidates underwent a medical history and physical examination at the pre-entry visit (2 weeks prestudy [week −2]) for determination of study eligibility. HIV-1 RNA levels and CD4 cell counts were determined at this time and at weeks 0 (baseline), 2, 5, 8, 12, 16, and 24. The mean of all measurements taken prior to or on the baseline day (day 1) constituted the baseline HIV-1 RNA and CD4 values used in data analysis.

### Education Intervention

In addition to their medication, patients were randomized 1:1 to receive either an EI (4 modules of the THE course) plus RC (EI + RC) or RC alone. The THE course is an 11-module educational program for HIV-infected patients and their informal caregivers in which there are interactive small-arm sessions facilitated by a health care professional trained in the principles of adult learning, skills-building exercises aimed at behavior change in participants, flip charts, videotapes, patient logbooks, and patient workbooks.[19] Program materials are designed at a fifth-grade reading level (English only). The goal of the THE course is to empower people living with HIV/AIDS and their informal caregivers with the knowledge, skills, attitudes, and resources to improve self-care, adherence, quality of life, and satisfaction with care, leading to improved quality of care. The following 4 modules focusing on patient empowerment, HIV pathogenesis and treatment, and medication management and adherence were delivered (1 session per week) during weeks 1 through 4 of this clinical trial: "Who's In Charge Here?," "How Does HIV Work?," "Attacking the Virus," and "Managing Your Medications." The shortening of the THE course was done for logistic reasons in the belief that adherence-related issues would be sufficiently addressed with the study patients with just the 4 modules and that the study would be facilitated by the abridgment. Modules of the THE course not chosen as part of the EI focused on positive coping techniques, information about preventing opportunistic infections, recognizing HIV-related symptoms that can be managed at home versus those that should be reported to a health care provider, identifying/evaluating available health care delivery services, and legal and child care issues.

RC consisted of provision of the following information at each study visit: names and physical descriptions of the

study drugs; instructions on how best to take the study drugs, including dosage and dosage schedules (taking the patient's daily routine into account) as well as how/when to remove the medications from bottles using Medication Event Monitoring System (MEMS) TrackCaps (APREX Corporation, Union City, CA); importance of taking the study drugs exactly as prescribed; and potential adverse events as well as actions to take if study participants experienced any of these. To avoid crossover of effect of the THE course to patients randomized to receive RC only, the site personnel who were trainers for the THE course could not be involved in the delivery of RC to the patients. To ensure consistency in delivery of RC information to all patients, the same person(s) delivered RC information to patients at each site.

## Efficacy Assessment

The primary efficacy measure was the proportion of patients attaining plasma HIV-1 RNA levels below the 40-copy/mL lower limit of quantitation (LLOQ) of the NucliSens assay and below the 400-copy/mL LLOQ of the HIV-1 MONITOR version 1.0 polymerase chain reaction (PCR) assay (Roche, Nutley, NJ) at 24 weeks after starting treatment with COM + ABC. Viral load response (HIV-1 RNA in plasma) was the primary study end point. Treatment failure was defined by 4 criteria: (1) nonachievement of a 0.5-$\log_{10}$ drop in HIV-1 RNA by week 8, (2) nonachievement of undetectable (<40 copies/mL) HIV-1 RNA by week 24, (3) 2 consecutive 0.5-$\log_{10}$ increases of HIV-1 RNA after attaining undetectability (<40 copies/mL), and (4) 2 consecutive 0.5-$\log_{10}$ increases of HIV-1 RNA over nadir. Virologic failures had to be confirmed by a repeat HIV-1 RNA measurement within 4 weeks of the initial measurement. A secondary efficacy measure was an assessment of changes in the number of CD4 lymphocyte counts (immunologic response).

## Adherence Assessment

Adherence was evaluated using MEMS TrackCaps. At each visit, study medications were dispensed by the site pharmacist in bottles equipped with MEMS TrackCaps, which monitored and electronically recorded the date and time at which each dose of medication was removed from the bottle. Weekly, monthly, and overall adherence rates were calculated by dividing the total number of doses taken (observed) by the total number of doses that should have been taken (expected). The expected number of doses of study drugs that should have been taken on a daily basis was 4 (2 COM + 2 ABC). For days between the first and last MEMS dates when no data were present, adherence was set equal to 0. Patients returned study medication bottles with MEMS TrackCaps to clinical site personnel at each visit for reuse or shipment to APREX Corporation for downloading and evaluation of the electronic adherence data.

## Safety Assessment

The patients were monitored for adverse events, laboratory abnormalities, and any HIV-related illnesses at weeks 5, 8, 12, 16, and 24. Patients who experienced ACTG grade 4 toxicities[20] were withdrawn from the study, as were patients who failed to achieve resolution of ACTG grade 3 toxicities[20] after interruption of therapy.

## Statistical Analysis

The intent-to-treat (ITT) population underwent statistical analysis. A sample size of 200 patients was sought on the basis of practical considerations rather than statistical considerations. These patients were to be recruited and enrolled from 15 to 20 sites in the United States (10–15 patients enrolled per site). Demographics and baseline characteristics were summarized using descriptive statistics. Both an ITT observed analysis and an ITT missing-equals-failure (M = F) analysis were used for assessing the proportion of patients with a plasma HIV-1 RNA level <40 copies/mL or <400 copies/mL. In the ITT observed analysis, only available assessments were used (no imputation for missing values), regardless of whether the patient was still receiving original therapy. In the ITT M = F analysis, all missing values were considered as failure. Means (± standard deviations [SDs]), medians, and 25th and 75th percentiles were calculated for plasma HIV-1 RNA levels and CD4 cell counts as well as for change from baseline for each of these parameters. Differences between the EI + RC and RC treatment arms regarding change from baseline in plasma HIV-1 RNA levels and CD4 cell counts were compared at each study visit using the Van Elteren test, controlling for investigational site. A Kaplan-Meier product-limit estimate of the survival function was used to estimate the median time to first occurrence of HIV-1 RNA ≤40 copies/mL. The log-rank test was used to assess the significance of the difference between treatment arms in median time to first occurrence of HIV-1 RNA <40 copies/mL. Differences between the 2 treatment arms with respect to the proportion of patients achieving HIV-1 RNA levels <40 copies/mL and <400 copies/mL were compared at each visit using the Cochran-Mantel-Haenszel test, controlling for investigational site. Differences between treatment arms in the average area under the curve minus baseline (AAUCMB) for HIV-1 RNA plasma levels and CD4 cell counts were evaluated using an analysis of covariance (ANCOVA) model with baseline as the covariate. The ANCOVA model also included a factor for treatment. The Cochran-Armitage trend test was used to investigate a relationship between MEMS-derived adherence rate ranges (<70%, 70% to <80%, 80% to <90%, %90 to <95%, and ≥95%) observed at study week 24 and the proportion of patients achieving HIV-1 RNA <40 copies/mL and <400 copies/mL, respectively, at this time. This analysis was performed only for patients who had both MEMS and viral load data at week 24. A probability value of <0.05 was considered statistically significant. Statistical

analyses were performed using SAS version 6.12 (SAS Institute, Inc., Cary, NC).

## RESULTS

### Patient Characteristics and Disposition

Of 195 patients randomized to treatment, 99 were in the RC arm and 96 were in the EI + RC arm. The 2 treatment arms did not differ with respect to demographic or baseline disease characteristics (Table 1). Most of the patients were of an ethnicity other than white (71% African Americans and 21% Hispanics), 35% were female, and 20% were current IDUs. At baseline, median HIV-1 RNA and CD4 cell counts were 4.25 $\log_{10}$ copies/mL and 365.5 cells/mm$^3$, respectively, in the RC arm; 4.14 $\log_{10}$ copies/mL and 384.3 cells/mm$^3$, respectively, in the EI + RC arm; and 4.18 $\log_{10}$ copies/mL and 379 cells/mm$^3$, respectively, in the total patient population. Ninety-one percent of the total patient population was antiretroviral naive; of the antiretroviral-experienced patients, 12 had previously received zidovudine, 3 had received lamivudine, and 1 had received the COM tablet. Attendance at the EI sessions was high by the patients (93%–97%) but relatively low by their caregivers (26%–28%). RC was received by 95%–100% of all patients during the trial. More patients in the EI + RC treatment arm than in the RC arm (31 [32%] vs. 23 [23%]) withdrew prematurely from the study for reasons delineated in Table 1, most of which were unrelated to adverse events.

### Virologic Measurements of Efficacy

Virologic failure was observed in 33 patients (33%) in the EI + RC arm and in 17 (18%) in the RC arm. There were no apparent differences between the EI + RC and RC treatment arms with respect to the number of patients who failed virologically according to the 4 protocol-defined criteria: nonachievement of a 0.5-$\log_{10}$ drop in HIV-1 RNA by week 8 (1 vs. 3 patients), nonachievement of HIV-1 RNA levels <40 copies/mL by week 24 (5 vs. 11 patients), 2 consecutive 0.5-$\log_{10}$ increases of HIV-1 RNA after attaining levels <40 copies/mL (5 vs. 12 patients), and 2 consecutive 0.5-$\log_{10}$ increases of HIV-1 RNA over nadir (6 vs. 7 patients). Furthermore, the EI + RC and RC arms were similar with regard to the number of patients who experienced no clinical disease progression (93 [97%] vs. 97 [98%]), the number experiencing progression from U.S. Centers for Disease Control and Prevention (CDC) class A to new class B (3 [3%] vs. 1 [1%]), and the number experiencing progression from CDC class A to death (0 vs. 1 [1%]).

Between weeks 2 and 24, a steadily increasing percentage of patients in each treatment arm achieved undetectable HIV-1 RNA levels (Fig. 1). ITT observed analysis showed no differences between the EI + RC and RC treatment arms with respect to the proportion of patients achieving plasma HIV-1 RNA levels <40 copies/mL (60% [33/55] vs. 55% [38/69]; $P$ = 0.529) or <400 copies/mL (80% [45/55] vs. 80% [55/69]; $P$ = 0.689) at week 24. Similarly, in the ITT M = F analysis, undetectability was achieved at week 24 in the EI + RC and RC arms in a comparable number of patients according to both the 40-copy/mL assay (33% [32/96] vs. 34% [34/99]; $P$ = 0.233) and 400-copy/mL assay (42% [40/96] vs. 44% [44/99]; $P$ = 0.186).

Median HIV-1 RNA plasma levels decreased rapidly over the first 2 weeks of treatment. Median time to first occurrence of HIV-1 RNA ≤40 copies/mL was 9 weeks (95% confidence interval [CI]: 8.0, 10.0) in the EI + RC arm and 10 weeks (95% CI: 9.0, 12.0) in the RC arm ($P$ = 0.124). From weeks 5 through 24, HIV-1 RNA remained −1.95 to −2.10 $\log_{10}$ copies/mL below baseline in the EI + RC arm and −2.00 to −2.30 $\log_{10}$ copies/mL below baseline in the RC arm (Fig. 2). Comparison of the $\log_{10}$ HIV-1 RNA AAUCMB showed no significant difference between the EI + RC and RC arms (least squares mean: −0.93 vs. −0.88; $P$ = 0.393).

### Immunologic Measurements of Efficacy

In the AAUCMB analysis, the EI + RC and RC arms did not differ with respect to CD4 cell count changes observed over the entire study period (least squares means: 44.3 vs. 45.2; $P$ = 0.93). Median CD4 cell counts and changes in these counts from baseline were also similar in the treatment arms at almost all times during the study, remaining consistently >40 cells/mm$^3$ above baseline from weeks 5 through 24 (see Fig. 2). At week 24, the median change from baseline in CD4 cell counts was 78 cells/mm$^3$ and 105 cells/mm$^3$ in the EI + RC and RC arms, respectively.

### Adherence Assessment

Adherence did not differ between the treatment arms at any point during the study. MEMS data showed that the mean overall adherence rates in the EI + RC and RC treatment arms were 70% and 74%, respectively. When MEMS data for the entire treatment population were evaluated, the overall adherence rate was 72%. Analysis of MEMS data by various adherence ranges generally showed a direct relationship between percentage adherence to all medication doses and achievement of virologic suppression according to both the 40-copy/mL assay ($P$ = 0.008) and the 400-copy/mL assay ($P$ = 0.028) (Fig. 3). In patients who were 70% to <80% adherent, however, this trend was not apparent, because the percentage of patients achieving undetectable HIV-1 RNA levels according to 400-copy/mL assay results was approximately the same (100% [10/10]) as that for patients who were ≥95% adherent (95% [19/20]).

Adherence was limited by treatment interruptions: 83 patients (52%) had >4 drug interruptions lasting ≥2 days, 24 patients (15%) had 1 interruption lasting ≥5 days, and 40 patients had more than 1 interruption lasting ≥5 days. Mean ad-

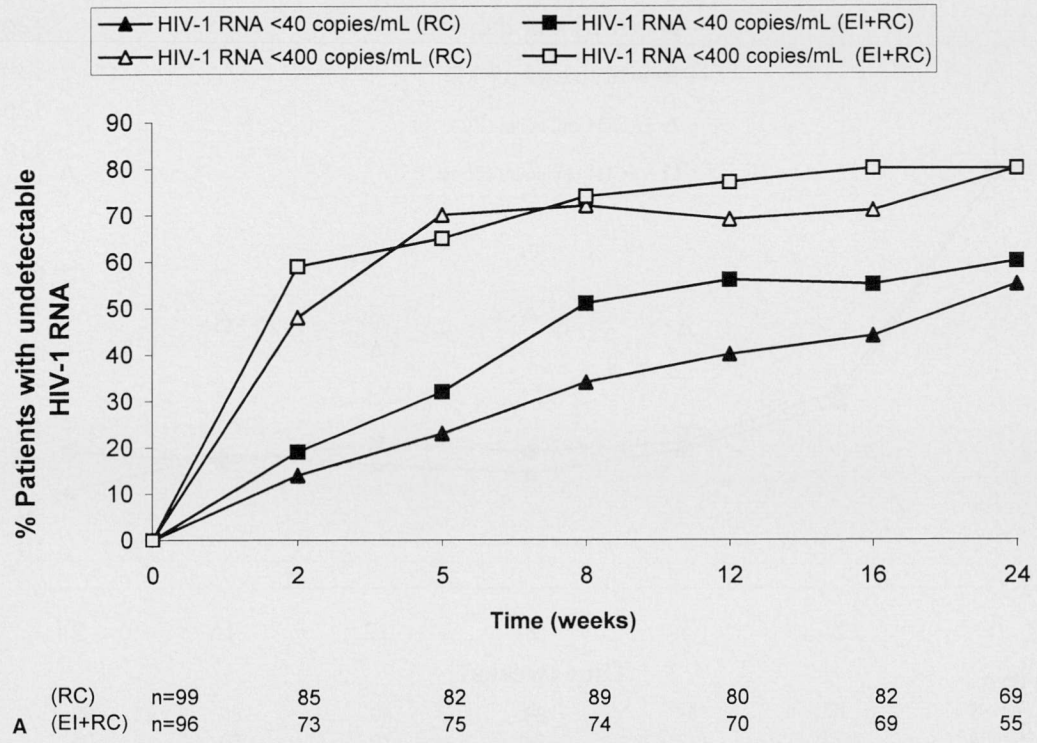
**TABLE 1.** Baseline Characteristics of the Study Patients (Intent-to-Treat Population)

| Characteristic | RC Arm (n = 99) | EI + RC Arm (n = 96) | Total (n = 195) |
|---|---|---|---|
| Age, y | | | |
| Mean ± SD | 37.7 ± 8.2 | 35.7 ± 9.1 | 36.7 ± 8.7 |
| Range | 20–52 | 18–53 | 18–53 |
| Sex, No. (%) | | | |
| Male | 68 (69) | 59 (61) | 127 (65) |
| Female | 31 (31) | 37 (39) | 68 (35) |
| Race, No. (%) | | | |
| African American | 71 (72) | 67 (70) | 138 (71) |
| Hispanic | 19 (19) | 22 (23) | 41 (21) |
| White | 6 (6) | 7 (7) | 13 (7) |
| Asian | 1 (1) | 0 | 1 (<1) |
| Other | 2 (2) | 0 | 2 (1) |
| Injection drug user | 19 (19) | 19 (20) | 38 (20) |
| HIV-1 RNA, $\log_{10}$ copies/mL | | | |
| Mean ± SD | 4.16 ± 0.62 | 3.98 ± 0.66 | 4.07 ± 0.65 |
| Median (range) | 4.25 (1.92–5.06) | 4.14 (1.93–5.16) | 4.18 (1.92–5.16) |
| HIV-1 RNA undetectability, No. (%) | | | |
| <400 copies/mL | 2 (2) | 2 (2) | 4 (2) |
| <40 copies/mL | 0 | 0 | 0 |
| CD4 cell count, cells/$mm^3$ | | | |
| Mean ± SD | 410.2 ± 216.3 | 408.0 ± 192.2 | 409.1 ± 204.3 |
| Median (range) | 365.5 (61–1133) | 384.3 (52.5–1083) | 379 (52.5–1133) |
| CDC classification | | | |
| Asymptomatic or lymphadenopathy | 74 (75) | 82 (86) | 156 (80) |
| Symptomatic, not AIDS | 21 (21) | 13 (14) | 34 (18) |
| AIDS | 4 (4) | 0 | 4 (2) |
| Any risk factor | 95 (96) | 91 (95) | 186 (95) |
| Heterosexual contact | 47 (47) | 50 (52) | 97 (50) |
| Homosexual contact | 39 (39) | 44 (46) | 83 (43) |
| Intravenous drug use | 22 (22) | 20 (21) | 42 (22) |
| Transfusion | 2 (2) | 3 (3) | 5 (3) |
| Occupational exposure | 0 | 1 (1) | 1 (<1) |
| Other | 4 (4) | 0 | 4 (2) |
| Prior antiretroviral experience | 7 (7) | 11 (11) | 18 (9) |
| Lamivudine | 0 | 3 (3) | 3 (2) |
| Zidovudine | 4 (4) | 8 (8) | 12 (6) |
| Lamivudine/zidovudine tablet | 0 | 1 (1) | 1 (<1) |
| Other* | 9 (9) | 7 (7) | 16 (8) |
| Premature study drug discontinuation | 25 (26) | 31 (32) | 56 (29)† |
| Premature withdrawal from study | 23 (23) | 31 (32) | 54 (28) |
| Adverse event | 6 (6) | 4 (4) | 10 (5) |
| Consent withdrawn | 3 (3) | 4 (4) | 7 (4) |
| Lost to follow-up | 9 (9) | 12 (13) | 21 (11) |
| protocol violation | 2 (2) | 2 (2) | 4 (2) |
| Virologic failure | 0 | 0 | 0 |
| Other | 3 (3) | 9 (9) | 12 (6) |

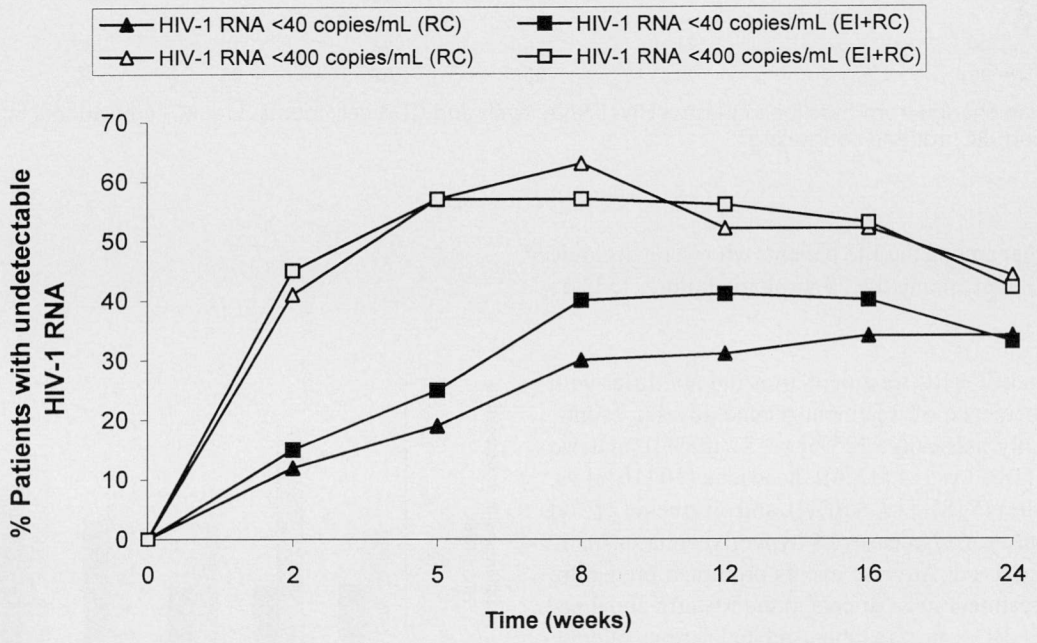
*RC arm: didanosine (3), stavudine (3), indinavir (1), hydroxyurea (1), nevirapine (1); EI + RC arm: didanosine (2), stavudine (2), zalcitabine (1), ritonavir (1), saquinavir (1) (some patients received more than 1 of these antiretroviral drugs).

†Two other patients were not included in this number because they never began therapy and so would not have been listed as having prematurely stopped study drug.

ART, antiretroviral therapy.

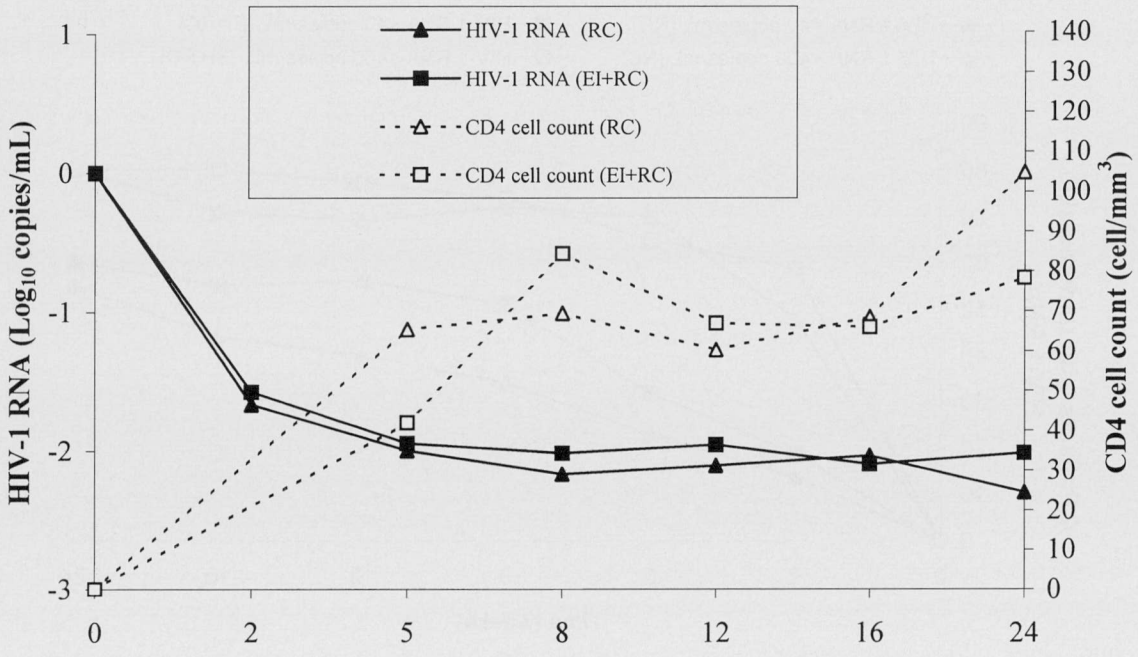



| A | | | | | | | |
|---|---|---|---|---|---|---|---|
| (RC) | n=99 | 85 | 82 | 89 | 80 | 82 | 69 |
| (EI+RC) | n=96 | 73 | 75 | 74 | 70 | 69 | 55 |




| B | | | | | | | |
|---|---|---|---|---|---|---|---|
| (RC) | n=99 | 99 | 99 | 99 | 99 | 99 | 99 |
| (EI+RC) | n=96 | 96 | 96 | 96 | 96 | 96 | 96 |

**FIGURE 1.** Percentage of patients with plasma HIV-1 RNA levels below the limit of assay quantitation in the intent-to-treat (ITT) observed analysis (A) and ITT missing = failure (M = F) analysis (B). EI + RC, educational intervention plus routine counseling; LLOQ, lower limit of quantitation; RC, routine counseling.




| | | | | | | |
|---|---|---|---|---|---|---|
| **HIV-1 RNA**: | | | | | | |
| RC n= 99 | 85 | 82 | 89 | 80 | 82 | 69 |
| EI+RC n= 96 | 73 | 75 | 74 | 70 | 69 | 55 |
| **CD4**: | | | | | | |
| RC n= 99 | | 73 | 85 | 74 | 77 | 62 |
| EI+RC n= 96 | | 69 | 65 | 62 | 66 | 50 |

**FIGURE 2.** Median change from baseline in plasma HIV-1 RNA levels and CD4 cell counts. EI + RC, educational intervention plus routine counseling; RC, routine counseling.

herence was higher among the 145 patients who were virologic successes (79%) than among the 50 virologic failures (53%).

## Safety

The RC and EI + RC treatment arms did not differ with respect to the incidence of treatment-related adverse events, which were mainly nausea (25 [25%] vs. 27 [28%]), malaise and fatigue (18 [18%] vs. 14 [15%]), headache (10 [10%] vs. 15 [16%]), diarrhea (8 [8%] vs. 6 [6%]), and dizziness (7 [7%] in each treatment arm). No cases of hyperglycemia or lactic acidosis were observed. Adverse events prompted premature withdrawal of treatment in 8 patients in the RC arm and 4 patients in the EI + RC arm. Treatment-related serious allergic reactions included allergic reaction to medicinal substance (3 patients), allergy and allergic reaction (2 patients), malaise and fatigue (1 patient), skin rash (1 patient), and feeding problems (1 patient) in the RC arm and allergic reaction to medicinal substance (1 patient), abnormal liver function test (1 patient), and anemia (1 patient) in the EI + RC arm. Five patients (2.6%) developed signs and symptoms suggestive of an ABC-related hypersensitivity reaction at 5, 6, 9, 14, and 46 days, respectively, following treatment initiation. In each of these patients,

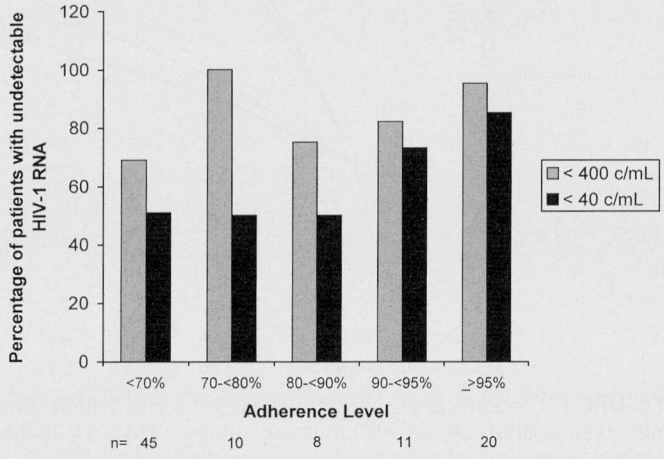



**FIGURE 3.** Correlation of HIV-1 RNA detectability and adherence level. Data are plotted only for the 94 patients with both Medication Event Monitoring System (MEMS) data and a viral load measurement at week 24.

hypersensitivity symptoms resolved without sequelae following discontinuation of ABC.

### Effect of Interruption of Abacavir Dosing on Hypersensitivity Reaction Incidence

Among 161 patients for whom MEMS data were available, 74% (119/161) had treatment interruptions lasting ≥2 days and 40% (64/161) had interruptions lasting ≥5 days. None of these patients experienced a hypersensitivity reaction. Among the 3 patients with MEMS data who experienced a suspected ABC-related hypersensitivity reaction, none had had a treatment interruption. The other 2 patients in whom a suspected hypersensitivity reaction was reported did not have MEMS data, and they discontinued treatment on days 6 and 40, respectively. Pill count records showed that 1 patient did not miss any doses, whereas the other patient's overall adherence was 59% (it is unknown when the doses of COM and ABC were missed).

## DISCUSSION

The results of this study indicate that the EI + RC and RC alone treatment arms did not differ significantly with respect to virologic suppression, immunologic changes, or adherence in the treatment of underrepresented HIV-infected patients. Several reasons may have accounted for this. First, the EI used, which abbreviated the THE course to just 4 modules, may have been insufficient to promote improvement in adherence comparable to that reported with the entire 11-module version.[19,21] Rice et al[21] showed that 3 months following their completion of the 11-module THE course, an ethnically diverse population of 54 HIV-infected patients (44% African American, 19% Hispanic, and 32% white) missed fewer doses of PIs ($P = 0.03$) and reverse transcriptase inhibitors ($P = 0.09$) compared with a population that did not participate in this EI (n = 33). Second, sessions of the THE course were supposed to have been attended by both patients and their caregivers. Although almost all the patients cooperated with this requirement, approximately three quarters of the caregivers did not. Thus, lack of participation by the caregivers could have negated any positive effects that the EI potentially could have had. Third, the time over which adherence was measured may have been too short for significant differences to become manifest. Thus, as in our study, Tuldrà et al[13] found no significant differences in adherence rates at 24 weeks in a study population that was predominantly white and male when comparing those patients who received an EI (n = 55) and those patients who received only RC (n = 61). At 48 weeks, the adherence rate in the EI group remained similar to what it was at 24 weeks, but the adherence rate was significantly lower in the RC group because that group began to miss increasing numbers of doses between weeks 24 and 48.

Adherence-focused educational programs administered to African American patients with HIV infection have met with varying degrees of success.[14,15,22–24] Cheever et al[14] conducted a 6-month EI trial aimed at increasing adherence to medication for *Pneumocystis carinii* pneumonia (PCP) prophylaxis in 120 HIV-infected patients at an inner-city hospital-based HIV clinic. Although the EI improved patient knowledge about PCP compared with the control group ($P < 0.04$), it did not affect the MEMS-determined adherence rate (75% in both groups). These investigators found that a key problem impairing adherence was poor health literacy of the population: 22% could read their medication label but incorrectly interpreted the instructions, and 4% were unable to read a label at all. Similar health literacy deficiencies that impaired adherence to HAART regimens among African American patients were also noted by Kalichman et al.[22] In contrast, literacy issues in our study were unlikely to account for nonadherence because of the protocol stipulation requiring all patients to be able to read, comprehend, and record information at a fifth-grade level of English. In a retrospective review of patient charts and computerized pharmacy records at an urban hospital, Del Rio et al[23] observed that many HIV-infected patients from ethnic minorities have several concurrent adherence-impairing conditions, such as affective disorders, drug abuse, alcoholism, lack of transportation to clinics, inconvenient clinic appointments, and lack of social support and stable housing, all of which need to be factored into HAART adherence-enhancement programs. It is noteworthy that 2 modules from the THE course that were not used as part of the EI in the present study—"When to Call for Help" and "Choices in Health Care Delivery"—addressed some of the aforementioned problems and might have been appropriate for enhancing adherence to treatment in the particular underrepresented population evaluated.

The efficacy results of this clinical trial show that many underrepresented HIV-infected patients with a baseline viral load <100,000 copies/mL were able to achieve virologic suppression over a 24-week treatment period with the twice-daily COM + ABC regimen (80% with <400 copies/mL at week 24 [ITT observed analysis] and increase in median CD4 cell count above baseline >78 cells/mm$^3$ at week 24). These viral load levels are superior to those reported by Lucas et al[5] in PI-naive nonwhites, women, and IDUs receiving HAART (PI + 1 other antiretroviral drug to which the patient had not previously been exposed) at an urban clinic (44% with ≤500 copies/mL at 3–7 months). The efficacy results of COM + ABC in NZTA4006 are consistent with the interim efficacy findings with twice-daily ABC/lamivudine/zidovudine (as Trizivir) in ACTG5095, a double-blind placebo-matched clinical trial that also evaluated an ethnically diverse population of antiretroviral-naive patients (36% African American and 21% Hispanic).[25] ITT switch-included analysis in the latter study showed that at 48 weeks, 74% of patients treated with ABC/lamivudine/zidovudine achieved HIV-1 RNA <200 copies/mL and mean CD4 cell counts increased above baseline

by 174 cells/mm$^3$. Nevertheless, cross-comparisons of the results of NZTA4006 with those of ACTG5095 must be tempered by the fact that ACTG5095 had a stricter definition of virologic failure (2 successive HIV-1 RNA levels ≥200 copies/mL at week 16 or later), evaluated a population with more advanced HIV disease (mean baseline HIV-1 RNA, 4.85 $\log_{10}$ copies/mL [42% ≥100,000 copies/mL]; mean CD4 cell count, 238 cells/mm$^3$ [48% ≤200 cells/mm$^3$]) and used a double-blind design requiring patients to take 7 pills per day of the ABC/lamivudine/zidovudine combination tablet instead of 2 pills per day as prescribed in clinical practice. It is to be noted that the National Institute of Allergy and Infectious Diseases Data and Safety Monitoring Board (DSMB) overseeing ACTG5095 discontinued the ABC/lamivudine/zidovudine arm after an average of 32 weeks because the proportion of the 167 antiretroviral-naive patients who had experienced virologic failure up to that time point was larger in the ABC/lamivudine/zidovudine arm than in the 2 comparator arms (COM + efavirenz or ABC/lamivudine/zidovudine + efavirenz) combined (21% vs. 10%).[26] The DSMB considered potency alone in their decision and did not factor in ease of use, patient satisfaction, regimen simplicity, toxicity, or sequenceability issues.

In this study, the overall MEMS-determined adherence rate was 72%, a rate comparable to that reported in other clinical trials evaluating HAART regimens and utilizing MEMS technology[27,28] but less than the adherence rates reported with less rigorous patient self-report adherence tools.[29] It is reassuring that despite this moderate level of adherence, 80% of patients were able to achieve an HIV-1 RNA <400 copies/mL while receiving treatment with COM + ABC. In our evaluation of viral load suppression at different adherence ranges, the percentage of patients achieving undetectable HIV-1 RNA at the adherence range of 70% to <80% was 100% with the 400-copy/mL LLOQ assay and 50% with the 40-copy/mL LLOQ assay, virologic results that are superior to those reported for the same adherence ranges in studies evaluating regimens combining 2 NRTIs with a PI.[27,29] Thus, in the large British Columbia Center for Excellence HIV/AIDS Drug Treatment Program (n = 886), the same adherence range in patients receiving a triple combination consisting of 2 NRTIs plus either a PI or an nonnucleoside reverse transcriptase inhibitor (NNRTI) resulted in only 24% of patients achieving an HIV-1 RNA level <500 copies/mL.[29] Similarly, in a study by Paterson et al,[27] 81 patients taking HAART consisting of 2 NRTIs plus 1 PI, with an adherence level ranging from 70% to 79.9%, resulted in only 29% of patients achieving HIV-1 RNA levels ≤400 copies/mL.

The safety results of this study showed no new or unexpected adverse events. As with other studies of COM + ABC, gastrointestinal complaints were the most commonly reported adverse events.[16–18] The 2.6% incidence of hypersensitivity reactions is lower than the 3.7% incidence that has been observed in ABC-treated patients in general.[30] This might be expected, because in a review of all cases of ABC-related hypersensitivity reactions reported to date in clinical trials (197 of 5332 patients), both univariate and multivariate statistical analyses showed a significantly lower incidence in African American patients than in the general population.[31] Interruptions in treatment did not result in an ABC-related hypersensitivity reaction in any patient, nor did treatment interruptions precede any case of this reaction reported in this study, as is consistent with the findings of Loeliger et al.[32] Thus, it appears unlikely that such treatment interruptions increase the risk of developing an ABC-related hypersensitivity reaction and that a rechallenge type hypersensitivity reaction, without previous symptoms, would occur.

Overall, when tested in a rigorous way, the EI in this 24-week clinical trial did not affect the virologic response or MEMS-determined adherence to COM + ABC to any greater degree than RC alone in underrepresented patients, perhaps because the prime focus of the intervention was limited to patient empowerment and improving knowledge about HIV and its treatment. To have more impact, EIs for use in underrepresented patients with HIV infection may need to address additional adherence-impairing factors, including inadequate social support, poor health literacy, and concurrent health problems specific to underrepresented patients, especially ethnic minorities.

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## REFERENCES


1. Gifford AL, Cunningham WE, Heslin KC, et al. Participation in research and access to experimental treatments by HIV-infected patients. *N Engl J Med*. 2002;346:1373–1382.
2. UNAIDS AIDS Epidemic Update, December 2000 AIDS Summary, No. 3 (Published: 2001.01):7 Available at: http://www.unaids.org/epidemic_update/report_DECOO/index_dec.html.
3. Centers for Disease Control and Prevention (CDC). *HIV/AIDS Surveillance Report*. 2003;13:1–44.
4. Association of State and Territorial Health Officials (ASTHO) Infectious Disease Policy Committee. ID-5. Injection drug use-related blood borne infection. Available at: http://www.astho.org/infectious/documents/hivaids/InjectionPolicy.pdf. Accessed January 10, 2002.
5. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Ann Intern Med*. 1999;131:81–87.
6. Singh N, Berman SM, Swindells S, et al. Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. *Clin Infect Dis*. 1999;29:824–830.
7. Singh N, Squire C, Swek C, et al. Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: prospective assessment with implications for enhancing compliance. *AIDS Care*. 1996;8:261–269.
8. Gifford AG, Bormann JE, Shively MJ, et al. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *J Acquir Immune Defic Syndr*. 2000;23:386–395.
9. Tuldrà A, Ferrer MJ, Rodriguez C, et al. A proposed model to predict compliance with antiretroviral therapy [abstract I-177]. Presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, September 1998.
10. Lucas GM, Cheever LW, Chaisson RE, et al. Detrimental effects of continued illicit drug use on the treatment of HIV-1 infection. *J Acquir Immune Defic Syndr*. 2001;27:251–259.
11. Malow RM, Baker SM, Klimas N, et al. Adherence to complex combination antiretroviral therapies by HIV-positive drug abusers. *Psychiatr Serv*. 1998;49:1021–1022,1024.
12. Maisels L, Steinberg J, Toias C. An investigation of why eligible patients do not receive HAART. *AIDS Patient Care STDs*. 2001;15(Suppl): L185–L191.
13. Tuldrà A, Fumaz CR, Ferrer MJ, et al. Prospective randomized two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2000;25:221–228.
14. Cheever LW, Barnes GL, Chaisson RE. A randomized educational intervention to improve adherence with medication [abstract I-178]. Presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, September 1998.
15. Kunches L, Mazzullo JM, Miller-Mack E, et al. Educational and support needs of people living with HIV (PLWH) to improve adherence to highly active antiretroviral therapy (HAART) [abstract 32333]. Presented at the 12th World AIDS Conference, Geneva, June–July 1998.
16. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naïve HIV-infected adults. A randomized equivalence trial. *JAMA*. 2001;285: 1155–1163.
17. Matheron S, Brun-Vezinet F, Katlama C, et al. 48-Week results of the CNAF 3007/Ecureuil open label study: efficacy and safety of the triple nucleoside combination Combivir/abacavir versus Combivir/nelfinavir as first line antiretroviral therapy in HIV-1 infected adults [abstract/poster 121]. Presented at the 5th International Congress on Drug Therapy in HIV Infection, Glasgow, October 2000.
18. Vibhagool A, on behalf of the CNA3014 International Study Team. Abacavir/Combivir (ABC/COM) is comparable to indinavir/Combivir (IDV/COM) in HIV-1-infected antiretroviral therapy naïve adults: results of a 48-week open-label study (CNA3014) [abstract/poster 063]. Presented at the 1st International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment, Buenos Aires, July 2001.
19. Igboko E, Scott-Lennox J, Pham DV, et al. Impact of T.H.E. course (Tools for Health and Empowerment) on medication adherence: pilot study [poster 14274]. Presented at the 12th World AIDS Conference, Geneva, June–July 1998.
20. Table for Grading of Adult Adverse Experiences. Washington, DC: National Institute of Allergy and Infectious Diseases, Division of AIDS; August 1992.
21. Rice MM, Hardy WD, Igboko EF, et al. Impact of T.H.E. (Tools for Health and Empowerment) COURSE on medication adherence: a pilot study [poster R13]. Presented at the 11th Annual Conference of the Association of Nurses in AIDS Care, San Antonio, November 1998.
22. Kalichman SC, Ramachandran B, Catz S. Adherence to combination antiretroviral therapies in HIV patients of low health literacy. *J Gen Intern Med*. 1999;14:267–273.
23. Del Rio C, Green S, Abrams C, et al. From diagnosis to undetectable: the reality of HIV/AIDS care in the inner city [abstract S21]. Presented at the 8th Conference on Retroviruses and Opportunistic Infections, Chicago, February 2001.
24. Gifford AL, Bormann JE, Shively MJ, et al. Effects of group HIV patient education on adherence to antiretrovirals: a randomized controlled trial [abstract 479]. Presented at the 8th Conference on Retroviruses and Opportunistic Infections, Chicago, February 2001.
25. Gulick RM, for the ACTG 5095 Team. Phase III, randomized, double-blind comparison of three protease inhibitor-sparing regimens for the initial treatment of HIV infection [oral presentation 41]. Presented at the 2nd IAS Conference on Pathogenesis and Treatment, Paris, July 2003.
26. Trizivir compared to efavirenz plus Combivir: 48 weeks interim study results from ACTG5095. March 10, 2003. Available at: www.natap.org/2003/march/031103_2.htm.
27. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133:21–30.
28. Wagner GJ. Predictors of antiretroviral adherence as measured by self-report, electronic monitoring, and medication diaries. *AIDS Patient Care STDs*. 2002;16:599–608.
29. Low-Beer S, Yip B, O'Shaughnessy MV, et al. Adherence to triple therapy and viral load response [letter]. *J Acquir Immune Defic Syndr*. 2000;23:360–361.
30. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther*. 2001;23:1603–1614.
31. Symonds W, Cutrell A, Edwards M. Risk factor analysis of hypersensitivity reactions to abacavir. *Clin Ther*. 2002;24:565–573.
32. Loeliger AE, Steel H, McGuirk S, et al. The abacavir hypersensitivity reaction and interruptions in therapy [letter]. *AIDS*. 2001;15:1325.