Abacavir-Lamivudine-Zidovudine vs Indinavir-Lamivudine-Zidovudine in Antiretroviral-Naive HIV-Infected Adults
A Randomized Equivalence Trial

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The current goal of antiretroviral therapy is to achieve prolonged suppression of human immunodeficiency virus (HIV) replication. The rational selection of antiretroviral agents used to initiate the treatment of HIV infection is critical for 2 reasons. First, the magnitude and duration of antiretroviral response is greatest for initial therapy, and second, sequencing of therapy must allow for effective second-line treatment regimens if the initial therapy fails. A

Context Abacavir, a nucleoside analogue, has demonstrated suppression of human immunodeficiency virus (HIV) replication alone and in combination therapy. However, the role of abacavir in a triple nucleoside combination regimen has not been evaluated against a standard protease inhibitor–containing regimen for initial antiretroviral treatment.

Objective To evaluate antiretroviral equivalence and safety of an abacavir-lamivudine-zidovudine regimen compared with an indinavir-lamivudine-zidovudine regimen.

Design and Setting A multicenter, phase 3, randomized, double-blind trial with an enrollment period from August 1997 to June 1998, with follow-up through 48 weeks at 73 clinical research units in the United States, Canada, Australia, and Europe.

Patients Five hundred sixty-two antiretroviral-naive, HIV-infected adults with a plasma HIV RNA level of at least 10000 copies/mL and a CD4 cell count of at least 100 \( \times 10^6 \)/L.

Interventions Patients were stratified by baseline HIV RNA level and randomly assigned to receive a combination tablet containing 150 mg of lamivudine and 300 mg of zidovudine twice daily plus either 300 mg of abacavir twice daily and indinavir placebo or 800 mg of indinavir every 8 hours daily plus abacavir placebo. After 16 weeks, patients with confirmed HIV RNA levels greater than 400 copies/mL were eligible to continue receiving randomized treatment or receive open-label therapy.

Main Outcome Measure Virologic suppression, defined as HIV RNA concentration of 400 copies/mL or less at week 48.

Results The proportion of patients who met the end point of having an HIV RNA level of 400 copies/mL or less at week 48 was equivalent in the abacavir group (51% [133/262]) and in the indinavir group (51% [136/265]) with a treatment difference of −0.6% (95% confidence interval [CI], −9% to 8%). In patients with baseline HIV RNA levels greater than 100000 copies/mL, the proportion of patients achieving less than 50 copies/mL was greater in the indinavir group than in the abacavir group with 45% (45/100) vs 31% (30/96) and a treatment difference of −14% (95% CI, −27% to 0%). The 2 treatments were comparable with respect to their effects on CD4 cell count. There was no difference between groups in the frequency of treatment-limiting adverse events or laboratory abnormalities. One death in the abacavir group was attributed to hypersensitivity reaction, which occurred following rechallenge with abacavir, approximately 3 weeks after initiating study treatment.

Conclusions In this study of antiretroviral-naive HIV-infected adults, the triple nucleoside regimen of abacavir-lamivudine-zidovudine was equivalent to the regimen of indinavir-lamivudine-zidovudine in achieving a plasma HIV RNA level of less than 400 copies/mL at 48 weeks.

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conventional approach to initial antiretroviral treatment has been with 2 nucleoside analogues and a protease inhibitor.\textsuperscript{1,3} While protease inhibitor–containing regimens have contributed substantially toward delaying progression of the acquired immunodeficiency syndrome (AIDS) and increasing duration of survival,\textsuperscript{4,7} several problems can limit their long-term effectiveness and contribute to incomplete viral suppression. These problems include poor tolerability, metabolic toxic effects, drug interactions due to inhibition or induction of cytochrome P450 enzymes, and incomplete adherence due to the complexity of dosing regimens.\textsuperscript{8,11} Incomplete viral suppression in the presence of selective pressure exerted by antiretroviral therapy promotes the development of resistance mutations, which may confer cross-resistance to other drugs of the same class.

Abacavir is a potent inhibitor of HIV reverse transcriptase (RT),\textsuperscript{12,13} it does not rapidly select resistant viruses in vitro, and multiple mutations are required to confer high-level reduction (10-fold) in susceptibility of HIV strains.\textsuperscript{14-17} Initial studies among therapy-naive HIV-infected patients demonstrated that, as monotherapy, abacavir has antiretroviral activity comparable with that of protease inhibitors, decreasing HIV RNA level by 1.7 to 2.2 \log_{10} \text{copies/mL}.\textsuperscript{18} Marked antiretroviral activity of abacavir also has been demonstrated in combination regimens with lamivudine and zidovudine.\textsuperscript{19,20} This study compares the efficacy and safety of a triple nucleoside analogue regimen of abacavir-lamivudine-zidovudine with the conventional regimen of indinavir-lamivudine-zidovudine in previously untreated HIV-infected patients.

**METHODS**

**Study Participants**

Adults who were seropositive for HIV and who had not received previous antiretroviral therapy were screened for enrollment. Additional criteria for enrollment included a plasma HIV RNA level of at least 10,000 copies/mL within 21 days of study drug administration, a CD4 cell count of at least 100 $\times 10^6$/L within 21 days of study drug administration, a hemoglobin level exceeding 10 g/dL (100 g/L) for men or 9 g/dL (90 g/L) for women, a neutrophil count exceeding 1000 $\mu$L, a platelet count exceeding 75,000 $\times 10^9$/L, an estimated creatinine clearance of greater than 40 mL/min (0.67 mL/s), a serum amylase level of less than 1.5 times the upper limit of normal, a total bilirubin level of less than 1.5 times the upper limit of normal, and levels of hepatic aminotransferases of less than 5 times the upper limit of normal.

Patients were excluded from consideration for the study if they had previously received any antiretroviral treatments, received any HIV vaccine within 90 days before study entry, or received immunomodulatory drugs or treatment with radiation therapy or cytotoxic chemotherapeutic agents within 30 days before study entry (with the exception of local treatment for Kaposi sarcoma). Patients were also excluded if they were pregnant or breastfeeding, had clinical pancreatitis or hepatitis (within 6 months before study entry), or had active HIV-related illness as defined by Centers for Disease Control and Prevention category C.\textsuperscript{21}

**Study Design**

This 48-week, double-blind, randomized, multicenter trial was conducted at 73 centers in the United States, Canada, Australia, and Europe. The institutional review boards and independent ethics committee at each site approved this study, and all patients gave written informed consent before initiating the study.

Randomization was performed after screening using a block size of 8 and was stratified according to initial HIV RNA level (\leq 10000-100000 \text{ copies/mL} or > 100000 \text{ copies/mL}) by a centralized randomization procedure (FIGURE 1). Study personnel called a center established by Clinphone (Nottingham, England) to enter patients' eligibility data and to receive treatment number assignment. Patients were randomly assigned on a 1:1 ratio to receive a combination tablet containing 150 mg of lamivudine and 300 mg of zidovudine twice daily and either a 300-mg tablet of abacavir twice daily plus indinavir placebo or 800 mg of indinavir every 8 hours daily (200-mg capsule formulation) plus abacavir placebo. The patient, the investigator, and the sponsor were blinded to treatment allocation. Breaking the blind was permitted in cases of medical emergency only if knowledge of a patient's treatment assignment was essential for

![Figure 1. Profile of Patient Enrollment and Discontinuations Through 48 Weeks of Treatment](http://jama.jamanetwork.com/pdfaccess.ashx?url=/data/journals/jama/4774/ on 06/16/2017)
appropriate clinical management or upon diagnosis of a probable hypersensitivity reaction. All patients received 16 tablets per day and followed the diet restrictions and fluid requirements recommended for indinavir. In brief, indinavir (or indinavir placebo) was administered with water 1 hour before or 2 hours after a meal and patients were instructed to drink 1.5 L of water during the course of 24 hours to ensure adequate hydration. Patients who had confirmed HIV RNA levels of 400 copies/mL or higher on 2 occasions at week 16, or thereafter, selected 1 of 3 options: (1) continuation of randomized therapy; (2) discontinuation of randomized therapy to receive open-label therapy consisting of abacavir or indinavir or both, with lamivudine plus zidovudine combination tablet (or alteration of background therapy); or (3) discontinuation of all study medication and withdrawal from the study. Patients who chose open-label therapy (as well as those who completed the study per protocol) were able to receive treatment until (1) they permanently withdrew from the study; (2) discontinued the study for any reason; or (3) the last patient had completed 48 weeks of randomized therapy.

**Study Monitoring**

Patients were assessed every 2 weeks for the first 4 weeks and every 4 weeks through week 48. Plasma HIV RNA level was measured using a standard RT polymerase chain reaction assay (Amplicor HIV Monitor, Roche Molecular Systems, Branchburg, NJ) with a limit of quantification of 400 copies/mL. The ultrasensitive PCR assay with a quantification limit of 50 copies/mL was also used to analyze plasma samples collected at weeks 16, 24, 36, and 48. CD4 cell counts were measured by flow cytometry. Safety assessments were based on evaluations of medical histories, vital signs, hematology, clinical chemistry, urinalysis, and clinical adverse experiences. Adverse events were evaluated using the Division of AIDS Table for grading severity of adult adverse experiences. Ajudication of safety and adverse event data were performed by study investigators blinded to patient treatment assignment, except in cases of medical emergencies. All plasma samples for efficacy and safety laboratory evaluations were analyzed by Covance Central Laboratories (Geneva, Switzerland; Indianapolis, Ind; and Sydney, Australia).

Genotypic analysis was performed on plasma samples from patients with confirmed HIV RNA levels of greater than 400 copies/mL. The HIV RT and protease coding regions and gag cleavage sites were amplified by RT polymerase chain reaction, as described previously. Mutations were also identified by the OpenGene genotyping system (Visible Genetics, Toronto, Ontario).

**Study Assessments**

The primary end point in the assessment of efficacy was virologic suppression defined as a plasma HIV RNA level of 400 copies/mL or less at week 48. The secondary end points included the proportion of patients with HIV RNA levels of 50 copies/mL or less at week 48, changes in HIV RNA levels and CD4 cell counts over 48 weeks, clinical progression, the proportion of patients with moderate (grade 2) to severe (grade 4) adverse events, and time to viral rebound. The time to viral rebound analysis was assessed for all patients using a standard threshold level of 400 copies/mL, and a less stringent one evaluated previously of 5000 copies/mL. Viral rebound was confirmed when 2 consecutive HIV RNA values exceeded the threshold level. Patients who did not have HIV RNA levels below the threshold level on randomized therapy were considered virologic failures at time zero.

**Statistical Analysis**

Efficacy variables were analyzed on an intent-to-treat basis (excluding patients who were randomized but did not initiate therapy) and on an as-treated basis. In the intent-to-treat analysis, patients were considered treatment failures if they made any treatment changes, prematurely discontinued randomized treatment for any reason, or had missing data for 2 consecutive evaluations. In the as-treated analysis, only data from patients continuing randomized treatment were considered for analysis.

As with HIV surrogate marker studies evaluating treatment interventions, the established standard practice is to compare treatment groups with respect to the proportion of antiretroviral-naive patients with undetectable plasma viral loads. In this study, the viral load was measured using the Amplicor HIV monitor (the only assay approved at the time this study was conducted), which had a lower limit of detection of 400 copies/mL. The study was powered to assess treatment equivalence for the primary end point (ie, a plasma HIV RNA level of ≤400 copies/mL at week 48 for the intent-to-treat population). For the primary end point, treatments were considered equivalent if the 95% confidence interval (CI) was within the bound of −12% to 12%. As a result of discussions with clinical investigators and with the Food and Drug Administration, the margin for equivalence was preselected as the largest difference that would be considered clinically acceptable. Based on these parameters, the study was designed to enroll approximately 550 patients, with 275 in each treatment group. The CIs were similarly generated for secondary and subgroup analyses for descriptive purposes.

The HIV RNA values were log_{10} transformed before analysis. The magnitude and duration of changes in HIV RNA levels and CD4 cell counts were summarized by the average area under the curve minus baseline calculation. The area under the curve minus baseline calculation difference between groups and the corresponding 95% CIs were calculated using non-parametric methods. The time to confirmed viral rebound was compared between groups using Kaplan-Meier estimates and was stratified by the baseline HIV RNA level.

**RESULTS**

**Baseline Characteristics**

Five hundred sixty-two patients were enrolled in the study between August
From the study (Figure 1).

The median decreases in HIV RNA area under the curve minus baseline calculation values were comparable between groups: −1.96 log_{10} copies/mL in the abacavir-lamivudine-zidovudine group and −1.84 log_{10} copies/mL in the indinavir-lamivudine-zidovudine group with a median difference of −0.03 (95% CI, −0.15 to 0.08).

**CD4 Cell Counts**

The median increases in CD4 cell count area under the curve minus baseline calculation for CD4 cell counts were comparable between groups: 107 × 10^{6}/L in the abacavir-lamivudine-zidovudine group and 93 × 10^{6}/L in the indinavir-lamivudine-zidovudine group with a median difference of −3 (95% CI, −24 to 19). At week 48, the median change from baseline in CD4 cell counts was similar between groups (Figure 3).

**Time to Viral Rebound**

At 48 weeks, there were no differences between groups in the proportion of patients who did not have viral rebound with HIV RNA levels greater than 400 copies/mL or less than 5000 copies/mL among all patients (Figure 4) or in the subgroups. In the high baseline HIV RNA stratum, proportions for the abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine groups were 55% vs 61% (400 copies/mL) and 75% vs 79% (5000 copies/mL), respectively. Likewise, no differences were observed between groups in the low baseline HIV RNA stratum and were 68% vs 68% (400 copies/mL) and 84% vs 78% (5000 copies/mL).

1997 and June 1998. Thirty-five patients (6%) did not take study drugs at the start of the trial (Figure 1). The treatment groups were balanced with respect to demographic and baseline characteristics (Table 1). Approximately one third of patients enrolled had baseline HIV RNA levels greater than 100000 copies/mL. There were no differences between groups in the reasons for premature discontinuation from the study (Figure 1).

**Plasma HIV RNA Levels**

At week 48, the proportion of patients who had sustained suppression of HIV RNA levels to less than 400 copies/mL in the abacavir-lamivudine-zidovudine group was equivalent to that in the indinavir-lamivudine-zidovudine group by the intent-to-treat analysis: 51% (133/262) vs 51% (136/265) with a treatment difference of −0.6% (95% CI, −9% to 8%) (Figure 2A). In the as-treated analysis, proportions were 86% (125/145) vs 94% (130/139) for the abacavir-lamivudine-zidovudine group vs indinavir-lamivudine-zidovudine group with a treatment difference of −7% (95% CI, −14% to 0%) (Figure 2A). No difference was observed between the 2 groups in the proportion of patients with HIV RNA levels of less than 400 copies/mL regardless of baseline HIV RNA level (Figure 2B).

At week 48, the proportion of patients who had HIV RNA levels of 50 copies/mL or less in the abacavir-lamivudine-zidovudine group was comparable with that in the indinavir-lamivudine-zidovudine group by intent-to-treat analysis: 40% (104/262) vs 46% (121/265) with a treatment difference of −6% (95% CI, −15% to 2%) (Figure 2C). By the as-treated analysis, proportions were 69% (104/150) vs 82% (121/147) for the abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine groups with a treatment difference of −13% (95% CI, −23% to −4%) (Figure 2C).

In the intent-to-treat analysis, the proportion of patients in the high baseline HIV RNA stratum who had HIV RNA levels of 50 copies/mL or less at 48 weeks was greater in the indinavir-lamivudine-zidovudine group than in the abacavir-lamivudine-zidovudine group: 31% (30/96) vs 45% (45/100) with a treatment difference of −14% (95% CI, −27% to 0%) (Figure 2D). This was not observed in the low baseline HIV RNA stratum: 43% (74/166) vs 46% (76/165) with a treatment difference of −2% (95% CI, −13% to 9%). In the as-treated analysis, the proportion of patients who had HIV RNA levels of 50 copies/mL or less was greater in the indinavir-lamivudine-zidovudine group for both strata: 76% (74/97) vs 88% (76/86) with a treatment difference of −12% (95% CI, −23% to −1%) for the high baseline HIV RNA stratum and 57% (30/53) vs 74% (45/61) with a treatment difference of −17% (95% CI, −34% to 0%) for the low baseline HIV RNA stratum.

The median decreases in HIV RNA area under the curve minus baseline calculation values were comparable between groups: −1.96 log_{10} copies/mL in the abacavir-lamivudine-zidovudine group and −1.84 log_{10} copies/mL in the indinavir-lamivudine-zidovudine group with a median difference of −0.03 (95% CI, −0.15 to 0.08).

**Time to Viral Rebound**

At 48 weeks, there were no differences between groups in the proportion of patients who did not have viral rebound with HIV RNA levels greater than 400 copies/mL or less than 5000 copies/mL among all patients (Figure 4) or in the subgroups. In the high baseline HIV RNA stratum, proportions for the abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine groups were 55% vs 61% (400 copies/mL) and 75% vs 79% (5000 copies/mL), respectively. Likewise, no differences were observed between groups in the low baseline HIV RNA stratum and were 68% vs 68% (400 copies/mL) and 84% vs 78% (5000 copies/mL).

**CD4 Cell Counts**

The median increases in CD4 cell count area under the curve minus baseline calculation for CD4 cell counts were comparable between groups: 107 × 10^{6}/L in the abacavir-lamivudine-zidovudine group and 93 × 10^{6}/L in the indinavir-lamivudine-zidovudine group with a median difference of −3 (95% CI, −24 to 19). At week 48, the median change from baseline in CD4 cell counts was similar between groups (Figure 3).

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Genotypic Resistance

Of the 59 patients who had confirmed HIV RNA levels exceeding 400 copies/mL by week 48 of therapy, 47 had 2 plasma samples collected (at baseline and at the time of confirmed failure). In both treatment groups, the RT mutation most frequently observed was M184V, which was detected in viral isolates from 31 patients overall (66%), including 21 of 27 patients in the abacavir-lamivudine-zidovudine group and 10 of 20 patients in the indinavir-lamivudine-zidovudine group. Additionally, 22 (71%) of 31 patients had viral isolates with the M184V mutation alone, including 15 of 21 patients in the abacavir-lamivudine-zidovudine group and 7 of 10 patients in the indinavir-lamivudine-zidovudine group. Overall, 14 patients (30%) with viral rebound had wild-type virus, including 6 of 27 patients in the abacavir-lamivudine-zidovudine group and 8 of 20 patients in the indinavir-lamivudine-zidovudine group. Two patients in the indinavir-lamivudine-zidovudine group developed the protease mutation L10V or M461 without evidence of M184V. Mutations selected also included other RT-associated mutations (6 patients from the abacavir-lamivudine-zidovudine group) and protease-associated mutations (5 patients from each group).

Progression of Disease

Four (<1%) of 562 patients had confirmed AIDS-defining events during the study. Three patients in the abacavir-lamivudine-zidovudine group had clinical progressions to Centers for Disease Control and Prevention category C that
included Kaposi sarcoma (2 patients) and cryptococcosis (1 patient). One patient in the indinavir-lamivudine-zidovudine group had clinical progressions to category C (lymphoma). In addition, there were 4 deaths that were not HIV-related disease progressions as described below.

**Adverse Events**

The study treatments were equally well tolerated for up to 48 weeks. The most common (≥5%) drug-related adverse events that were of moderate to severe intensity (grades 2-4) included nausea (with or without vomiting), malaise and fatigue, headache, and renal signs and symptoms (TABLE 2). The proportion of patients with severe laboratory abnormalities was similar between groups (Table 2).

Four deaths were reported during the study. In the abacavir-lamivudine-zidovudine group, 1 death was attributed to hypersensitivity reaction that occurred following rechallenge with abacavir approximately 3 weeks after initiating study treatment, and 2 were attributed to cardiac arrhythmia and myocardial infarction occurring 30 to 35 weeks after initial study treatment. The latter 2 events were not considered to be related to abacavir. In the indinavir-lamivudine-zidovudine group, 1 death was attributed to drug overdose (heroin and cocaine), which occurred approximately 6 weeks after initiating study treatment.

Nineteen patients (7%) in the abacavir-lamivudine-zidovudine group and 6 patients (2%) in the indinavir-lamivudine-zidovudine group were identified as having symptoms that were consistent with or similar to a possible abacavir hypersensitivity reaction. In the abacavir-lamivudine-zidovudine group, symptoms generally occurred within 6 weeks of initiating abacavir, and included fever and rash accompanied by gastrointestinal tract–related symptoms, such as nausea, vomiting, and diarrhea. In the indinavir-lamivudine-zidovudine group, symptoms were less severe, were gastrointestinal in nature, and included rash or fever but not both concurrently.

**COMMENT**

This randomized trial is the first, to our knowledge, to evaluate the antiretroviral...
eral equivalence of atrope nucleoside analogue regimen against the conventional regimen of a protease inhibitor plus 2 nucleoside analogues for initial treatment in antiretroviral-naive HIV-infected adults. Results demonstrate that the abacavir-lamivudine-zidovudine regimen provides equivalent virologic suppression to the indinavir-lamivudine-zidovudine regimen at 48 weeks based on the primary analysis of the proportion of patients with plasma HIV RNA levels of 400 copies/mL or less. Secondary analyses by baseline HIV RNA stratification demonstrated comparable antiretroviral activity among patients with baseline HIV RNA levels below 100,000 copies/mL, as assessed by the standard or ultrasensitive assays. A greater proportion of patients in the high baseline HIV RNA stratum had undetectable HIV RNA levels with the indinavir-lamivudine-zidovudine regimen than with the abacavir-lamivudine-zidovudine regimen by the ultrasensitive assay. Kaplan-Meier analysis of the time to viral rebound (>400 or 5000 copies/mL of HIV RNA) was not different between groups when analyzed for all patients or by the subgroups.

The double-blind, randomized nature of this study and the use of CIs to estimate treatment similarities provided a rigorous assessment of treatment effects. The validity of the study conclusions is further demonstrated by the consistency of results obtained from the various analyses. Because of the placebo-control design of the study, all patients were required to receive 16 tablets per day with the diet restrictions and fluid requirements associated with indinavir therapy. Although treatment adherence was not evaluated in the present study, other studies have demonstrated that increased pill burden is correlated with decreased treatment adherence. Thus, the study results may underestimate the potential impact of the abacavir-lamivudine-zidovudine regimen as the increased pill count (16 tablets daily vs 2 tablets twice daily in clinical practice) may have affected treatment adherence.

While cross-study comparisons are limited by differences in populations, methods, and availability of long-term data, the results of this study of a single-class regimen are generally comparable with those from several trials of multiclass regimens. In these studies, triple therapy regimens containing a protease inhibitor plus 2 nucleosides have reduced plasma HIV RNA levels to less than 400 copies/mL in 41% to 70% of patients and 34% to 57% of patients for 50 copies/mL or less by intent-to-treat analysis. Median HIV RNA level reductions of 1.7 to 3 log_{10} copies/mL and median CD4 cell count increases of 130 × 10^6/L to 227 × 10^6/L were observed in these trials. Likewise, both groups in our study showed substantial and sustained increases in CD4 cell counts over 48 weeks.

In this study, few patients in either treatment group had confirmed virologic failure. Genotypic resistance analyses of these patients indicated that virologic failure was associated with the development of a single RT mutation (M184V). Similar results have been seen in patients receiving protease inhibitor-containing regimens. The finding that patients with viral rebound had wild-type virus implies that factors other than the selection of resistant mutant viruses may be responsible for virologic failure. Our study showed that viral isolates from most patients did not contain mutations that were associated with resistance to other drugs, implying that virologic response to subsequent treatments might be successful.

Several studies have shown that suppression of HIV RNA levels to less than 20 to 50 copies/mL was associated with a more durable virologic response compared with suppression to below 400 copies/mL. Our study showed no difference in the durability of response between treatment groups despite a difference in the proportion of patients who had undetectable HIV RNA levels by the

<table>
<thead>
<tr>
<th>Table 2. Adverse Events by Treatment Group</th>
<th>No. (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abacavir-Lamivudine - Zidovudine</strong> (n = 262)</td>
<td><strong>Indinavir-Lamivudine - Zidovudine</strong> (n = 264)</td>
</tr>
<tr>
<td>Drug-related grade 2 to 4 of ≥5% incidence</td>
<td>Drug-related grade 2 to 4 of ≥5% incidence</td>
</tr>
<tr>
<td>Nausea</td>
<td>41 (16)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>21 (8)</td>
</tr>
<tr>
<td>Malaise and fatigue</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Headache</td>
<td>25 (10)</td>
</tr>
<tr>
<td>Renal signs and symptoms</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Permanent discontinuation of the study drug</td>
<td>45 (17)</td>
</tr>
<tr>
<td>Serious events</td>
<td>55 (21)</td>
</tr>
<tr>
<td>Severe laboratory abnormalities</td>
<td>43 (16)</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>13 (5)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Platelets</td>
<td>3 (1)</td>
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<tr>
<td>White blood cell count</td>
<td>0</td>
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<tr>
<td>Hepatic aminotransferases</td>
<td>16 (6)</td>
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<tr>
<td>Aspartate transaminase</td>
<td>16 (6)</td>
</tr>
<tr>
<td>Alanine transaminase</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Creatine phosphokinase</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Total serum bilirubin</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Amylase</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>

Subjects are counted only once, even if they have 2 or more episodes of the same adverse event. In the indinavir group, 1 subject was considered lost to follow-up when he failed to return after the first study visit.

These events were judged by a blinded investigator to be possibly, probably, or definitely related to the study treatment.

1See “Methods” for further details.

Denotes grade 3 and 4 or grade 2 for amylase as defined according to the Division of AIDS toxicity grading scale.

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ultrasensitive assay. Although the reason for this difference is unclear, we speculate that treatment differences may take longer to emerge or may be due to variability associated with the use of a single measure (as in the proportion of patients with HIV RNA levels below the limit of detection of the assay).

Among patients who had high baseline HIV RNA, less than 50% of patients achieved viral suppression to below 50 copies/mL in both treatment groups, although a better response was observed for patients receiving the indinavir-lamivudine-zidovudine regimen. Several studies have shown that the likelihood of achieving undetectable viral load with an initial treatment regimen is reduced if patients have high HIV RNA levels and lower CD4 cell counts at baseline. The difficulty in achieving an undetectable viral load among patients with high baseline HIV-1 RNA levels supports the need to initiate antiretroviral treatment in a manner consistent with treatment guidelines from the Department of Health and Human Services (ie, treatment in a manner consistent with the need to initiate antiretroviral therapy). The difficulty in achieving an undetectable viral load with an initial treatment regimen is reduced if patients have high HIV RNA levels and lower CD4 cell counts at baseline. The selection of an antiretroviral treatment strategy including possible increased serious adverse effects, tolerability, potential drug interactions, and likelihood of nonadherence, treatment costs associated with managing adverse effects, and the potential for future treatment options will continue to provide long-term virologic suppression comparable with the indinavir-lamivudine-zidovudine regimen.

The virologic benefit derived from an HIV treatment regimen also must be balanced against other factors that impact treatment strategy including possible increased serious adverse effects, tolerability, potential drug interactions, and likelihood of nonadherence, treatment costs associated with managing adverse effects, and the potential for future treatment options. Given these considerations, the abacavir-lamivudine-zidovudine regimen offers several potential advantages, including twice daily dosing, low pill burden, low drug interaction risk, and the potential to reserve other drug classes for future therapy. However, this regimen also has several potential disadvantages including limited data on long-term efficacy, clinical progression, or toxicity, and the risk for hypersensitivity reactions. Recent data also suggest that another nonprotease inhibitor–containing triple therapy is an option for patients who are treatment-naïve or who are moderately treatment experienced. In conclusion, the results of this 48-week randomized trial demonstrate that in previously untreated HIV-infected adults, the triple nucleoside combination regimen of abacavir-lamivudine-zidovudine administered twice daily is equivalent to a conventional regimen of indinavir-lamivudine-zidovudine in achieving plasma HIV RNA levels of less than 400 copies/mL at 48 weeks, and is comparable with respect to their CD4 cell count effects.

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COMPARISON OF ABACAVIR VS INDIANINO TRIPLE THERAPIES

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In Reply: We agree with all these authors that it would be useful to calculate an overall accuracy of ultrasound screening for fetal Down syndrome when structural abnormalities and ultrasonographic markers are used together. Unfortunately, studies that reported a composite ultrasound score (n=18) reported statistically inconsistent results, and thus a reliable summary estimate could not be generated. The mean sensitivity (68%) and mean false-positive rate (8%) are not reliable, and we did not include them in the expected outcome data. It is meaningless to use these values to generate positive and negative LRs as the authors of these letters suggest. Although it is likely that a normal ultrasound result demonstrating no structural abnormalities or markers can reduce the likelihood of Down syndrome, the amount of this reduction is not known, and Dr Nyberg’s estimate of a negative LR of 0.34 is not supported by our data.

Furthermore, there are reasons to believe that the true accuracy of the composite score is lower than we reported. First, we found significant differences in the sensitivity by study design, and if we excluded the case control studies, which are likely to overestimate accuracy,1 the mean detection was only 58%. Second, most included studies were confined to high-risk pregnancies, and if ultrasound screening was used in a lower-risk population, the detection rate would likely be lower than we reported.2

We focused on isolated ultrasonographic markers because these results showed the most consistent data, and because in clinical practice, this is the most common occurrence. Most pregnant women are at low risk of having a fetus with Down syndrome, and markers will predominantly be identified as isolated abnormalities. We agree with Nyberg that the presence of a single ultrasonographic marker in most patients should not alter treatment. However, we strongly disagree about the nature of the current clinical practice. Detection of these markers has dramatically increased the use of invasive testing,3 and many physicians counsel their patients that they are at an elevated risk of carrying a fetus with Down syndrome based on the presence of a single marker. In addition to unnecessary invasive tests performed because of the presence of markers, the psychological impact cannot be overstated.4

We defined high risk as 1:300, equivalent to the risk of Down syndrome in a 35-year-old woman, and the same threshold used by many serum testing programs.5 If we had used the mean risk among all women older than age 35 years instead, this would have resulted in a higher PPV but would not have altered the low-detection rate or low LRs.

We agree with Dr Egan and colleagues that advanced maternal age–based screening for Down syndrome is not accurate, but there is no evidence that ultrasound screening would be as accurate as biochemical screening.5 If women who are at an elevated risk of carrying a fetus with Down syndrome based on serum testing results are dissuaded from undergoing amniocentesis because of the absence of ultrasonographic markers, the detection of affected pregnancies will decrease. There are no data confirming the accuracy of ultrasound screening as the primary screening test for Down syndrome. If ultrasound screening is used with serum testing, the false-positive rate will increase with no evidence whether detection will increase. Contrary to what Dr Bahado-Singh and colleagues suggest, there are no good data on whether ultrasound screening and serum markers used together would improve the performance of detection. Their study6 included only high-risk women, and thus it cannot be used to evaluate whether ultrasound screening can detect cases missed by other screening methods.

Finally, when continuous variables are used to define an abnormal test result, it is possible to choose a threshold to correspond to a particular false-positive rate, as Bahado-Singh et al suggest. For categorical variables, such as choroid plexus cysts, it is not possible to do this, and we reported the summary estimate that corresponded to that reported in the literature. Thus, it is unlikely that the sensitivity of the markers is higher than we report.

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