A Randomized, Double-Blind Study of Triple Nucleoside Therapy of Abacavir, Lamivudine, and Zidovudine Versus Lamivudine and Zidovudine in Previously Treated Human Immunodeficiency Virus Type 1-Infected Children

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ABSTRACT. *Objectives.* **Abacavir (ABC) is a potent inhibitor of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase. We compared the efficacy, safety, and tolerability of combination therapy with ABC, lamivudine (3TC), and zidovudine (ZDV) versus 3TC and ZDV in antiretroviral experienced HIV-1-infected children over 48 weeks.**

Methods. **Two hundred five HIV-1-infected children who had received previous antiretroviral therapy and had CD4$^+$ cell counts ≥100 cells/mm^3 were stratified by age and by previous treatment. Participants were randomly assigned to receive ABC (8 mg/kg twice daily [BID]) plus 3TC (4 mg/kg BID) and ZDV (180 mg/m^2 BID; ABC/3TC/ZDV group) or ABC placebo plus 3TC (4 mg/kg BID) and ZDV (180 mg/m^2; 3TC/ZDV group). Participants who met a protocol-defined switch criteria (plasma HIV-1 RNA >0.5 log$_{10}$ copies/mL above baseline at week 8 or >10 000 copies/mL after week 16) had the option to switch to open-label ABC plus any antiretroviral combination or continue randomized therapy or withdraw from the study.**

Results. **The Kaplan-Meier estimates (95% confidence interval) of the proportion of participants who maintained HIV-1 RNA levels ≤10 000 copies/mL for 48 weeks or more was significantly better in the ABC/3TC/ZDV group compared with the 3TC/ZDV group: 33% (23%–42%) versus 21% (13%–29%). At week 48, the proportions of participants with HIV-1 RNA ≤10 000 copies/mL were 36% versus 26% for the ABC/3TC/ZDV and 3TC/ZDV groups, respectively, by intent-to-treat analysis. For the subgroup of participants with baseline HIV-1 RNA >10 000 copies/mL, a significantly higher proportion of participants in the ABC/3TC/ZDV group had HIV-1 RNA ≤10 000 copies/mL compared with the 3TC/ZDV group (29% vs 12%) but no difference was observed in the subgroup of participants with baseline HIV-1 RNA ≤10 000 copies/mL (78% vs 72%). The median changes from baseline in CD4$^+$ cell counts were greater in the ABC/3TC/ZDV group than in the 3TC/ZDV group. Few participants (3%) experienced abacavir-related hypersensitivity reaction.**

Conclusions. **ABC, in combination with 3TC and ZDV, provides additional antiretroviral activity over 48 weeks, compared with combination therapy with 3TC and ZDV in antiretroviral experienced HIV-1-infected children. ABC was safe and generally well-tolerated and should be considered an active component of combination antiretroviral therapy in this pediatric population.** *Pediatrics* **2001;107(1). URL: http://www.pediatrics.org/cgi/content/full/107/1/e4;** ***human immunodeficiency virus type 1, abacavir, lamivudine, zidovudine, viral ribonucleic acid, CD4, antiretroviral therapy, pediatric.***

ABBREVIATIONS. HIV-1, human immunodeficiency virus type 1; RT, reverse transcriptase; ZDV, zidovudine; ddI, didanosine; 3TC, lamivudine; ABC, abacavir; BID, twice daily; ITT, intent-to-treat; AAUCMB, average area under the curve minus baseline; NAUC, normalized area under the curve; NRTI, nucleoside reverse transcriptase inhibitors.

A major goal of therapy for both children and adults with human immunodeficiency virus type 1 (HIV-1) infection is to achieve maximum suppression of HIV-1 replication through aggressive antiretroviral therapies. In initial pediatric trials of symptomatic patients, monotherapy with several nucleoside reverse transcriptase (RT) inhibitors—including zidovudine (ZDV), didanosine (ddI), stavudine, and lamivudine (3TC)—resulted in clinical, immunologic, and virologic benefits.[1–4] Subsequent comparative clinical trials conducted first in HIV-1-infected adults and later in symptomatic, antiretroviral naïve HIV-1-infected children demonstrated the superior efficacy of initial therapy with dual nucleosides, compared with nucleoside monotherapy.[5–11] More recently, studies of combination therapy with protease inhibitors and/or nonnucleoside RT inhibitors have yielded favorable results.[12–19]

Although combination antiretroviral therapies have improved survival and slowed disease progres-

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sion, treatment of HIV-1-infected children is still limited by several challenges. These include limited compliance to complex dosing regimens, lack of suitable drug formulations, and limited pediatric-specific data on pharmacokinetics, efficacy, and safety of effective combination antiretroviral therapies. The selection of antiretroviral-resistant HIV-1 because of inadequate suppression of viral replication and the limited number of therapies available, further constrains long-term treatment options. Therefore, the evaluation of novel antiretroviral therapies for children is critical.

Abacavir (ABC; formerly 1592U89) has been approved for the treatment of HIV-1 infection in adults and in children in the United States. ABC undergoes phosphorylation by a unique intracellular metabolic pathway to form its active moiety, carbocyclic guanosine triphosphate, which is a potent inhibitor of HIV RT.[20,21] High-level resistance to ABC does not develop rapidly in vitro and multiple mutations are required to confer a 10-fold reduction in susceptibility to ABC.[22,23] The availability of a liquid formulation for this drug and the potent suppressive effect on HIV-1 make ABC an attractive antiretroviral agent for use in children.

The present study (Glaxo Wellcome Protocol CNA3006) was designed to compare the efficacy, safety, and tolerability of a triple drug combination of ABC, 3TC, and ZDV (ABC/3TC/ZDV) versus the combination of 3TC and ZDV (3TC/ZDV) in HIV-1-infected children with previous antiretroviral experience.

METHODS

Participant Population

HIV-1-infected children between the ages of 3 months and 13 years were eligible for enrollment. The upper age limit selected was required to fulfill regulatory requirements. There were no restrictions with regard to gender, ethnicity, or mode of HIV-1 infection. Children at any clinical disease stage (Centers for Disease Control and Prevention classification N, A, B, or C)[24] could be enrolled if they had been on their current antiretroviral therapy for at least 12 weeks. Participants on a regimen that included a protease inhibitor could be enrolled; however, the protease inhibitor had to be discontinued at least 2 weeks before randomization. The following baseline laboratory values were required: hemoglobin concentration of $\geq$7 g/dL; neutrophil count of $\geq$400/μL; aspartate aminotransferase and alanine aminotransferase $<$10 times the upper limit of normal; bilirubin $<$3 times the upper limit of normal; serum creatinine concentration $<$1.2 (age 3 months to 2 years) or 1.7 mg/dL (age 2 to 6 years); and amylase or lipase $<$2 times the upper limit of normal.

Participants were excluded from the study if their $CD4^+$ % declined to $<$15% (the critical value for an increased risk for opportunistic infections in children) within 14 days before study drug administration, had documented hypersensitivity to a nucleoside analog, had an active ongoing opportunistic infection, had received investigational antiretroviral treatments within 14 days before study entry, had received a dose of any HIV-1 vaccine within 30 days before study entry, or were receiving immunodulatory drugs or treatment with radiation therapy or cytotoxic chemotherapeutic agents for an active malignancy. Also excluded were pregnant or breastfeeding females, as were participants with pancreatitis or hepatitis (within 6 months before entry into the study).

Study Design

This double-blind, randomized, multicenter, placebo-controlled study lasting 48 weeks was conducted at 28 centers in the United States and at 1 center in Panama. The study was designed to enroll 210 participants, with 105 participants in each treatment group. The protocol was approved by the institutional review boards at each study site. Written informed consent was obtained from the parent or legal guardian of each child before the initiation of the study.

Participants were stratified before randomization by age ($<$30 months or $\geq$30 months of age) and by treatment with 3TC and ZDV, either concurrently or sequentially, within the previous 6 months (yes or no). Participants discontinued previous antiretroviral therapy and were randomly assigned to 1 of 2 treatment groups: ABC (8 mg/kg twice daily [BID]), 3TC (4 mg/kg BID), and ZDV (180 mg/m^2 BID; ABC/3TC/ZDV group) or ABC placebo, 3TC (4 mg/kg BID), and ZDV (180 mg/m^2; 3TC/ZDV group). ABC was supplied as 20 mg/mL in a liquid formulation, ZDV as 10 mg/mL in a liquid formulation or 100-mg capsule, and 3TC as 10 mg/mL in a liquid formulation or 150-mg tablet. Participants could receive ZDV capsules or 3TC tablets instead of the liquid formulation if the calculated dose met or exceeded the recommended doses for adults and they were able to swallow the capsules or tablets.

Participants continued their randomized treatment for 48 weeks unless they met one of the protocol-defined switch criteria as follows: 1) at week 8, 2 consecutive plasma HIV-1 RNA measurements showing an increase of $>$0.5 $\log_{10}$ copies/mL from baseline performed at least 1 week apart, or 2) at week 16 and every 8 weeks thereafter, 2 consecutive HIV-1 RNA measurements $\geq$10 000 copies/mL performed at least 1 week apart. Participants who met one of the switch criteria were eligible for one of the following options: open-label triple combination therapy with ABC/3TC/ZDV; open-label ABC in combination with any other antiretroviral agent (which may or may not have included 3TC and/or ZDV); continued therapy on blinded, randomized study drugs; or withdraw from the study.

Adverse events occurring during the study were evaluated by the investigator and severity was graded according to the Division of AIDS Toxicity Grading Table for Pediatric Adverse Experiences. In brief, clinical and laboratory adverse events were graded on a 4-point scale from grade 1 (mild) to grade 4 (severe). Participants who developed a grade 3 clinical adverse event or laboratory abnormality had all study drugs temporarily discontinued except for participants with grade 3 anemia or neutropenia for whom ZDV was interrupted until the adverse event had returned to $\leq$grade 2. Participants who developed a grade 4 adverse event had their study drugs permanently discontinued unless the event was judged to be unrelated to ABC. Participants with grade 4 asymptomatic laboratory abnormalities could continue therapy if the toxicity was considered unrelated to study drugs.

Study Assessments

The primary efficacy assessment was the time to virologic event (defined as confirmed plasma HIV-1 RNA $>$10 000 copies/mL). Other assessments included the proportion of participants with plasma HIV-1 RNA levels $\leq$10 000 copies/mL after 48 weeks of treatment; the proportion of participants with plasma HIV-1 RNA $\leq$400 copies/mL; changes in plasma HIV-1 RNA levels; changes in $CD4^+$ cell count and percentage from baseline to week 48; disease progression based on the development of new or recurrent opportunistic infections; and changes in weight growth velocity. The safety assessment was based on the number of clinical or laboratory adverse events that were considered severe (grades 3 and 4). All adverse events were classified according to whether they resulted in permanent discontinuation, interruption, or other modification of study drugs and whether they were related to study drugs.

Clinical and Laboratory Monitoring

Blood samples were collected for plasma HIV-1 RNA analyses at baseline (day 1), weeks 2 and 4, and every 4 weeks thereafter until study discontinuation. Blood samples for lymphocyte subset analyses were obtained at baseline, weeks 2 and 4, every 4 weeks until week 48, and every 8 weeks thereafter until study discontinuation. Standard laboratory evaluations were performed at baseline, weeks 2 and 4, and every 4 weeks thereafter. Urinalysis was evaluated as clinically indicated throughout the study. Participants were monitored for disease progression based on the occurrence of new or recurrent opportunistic infections at each visit

using the 1994 Revised Classification System of the Centers for Disease Control and Prevention.[24]

Plasma HIV-1 RNA levels were measured using a commercially available RT polymerase chain reaction assay with a detection limit of 400 copies/mL (Amplicor HIV-1 Monitor, Primers 1.0, Roche Molecular Systems, Branchburg, NJ). $CD4^+$ analyses were performed using flow cytometry. All efficacy and safety laboratory analyses were performed at Covance Central Laboratories (Indianapolis, IN) except in Panama where chemistry, hematology, and lymphocyte subset analyses were performed at the local hospital laboratory (Hospital del Niño, Panama City, Panama).

Growth parameters (height, weight, and standard frontal occipital head circumference) were measured at baseline, weeks 2 and 4, and every 4 weeks thereafter. During the treatment period, head circumference was required for all participants ≤3 years of age. Weight/growth velocity was evaluated beginning at week 24 and at every 4 weeks thereafter.

Statistical Analyses

The study was designed to have >90% power to detect a difference between treatment groups with respect to the durability of the HIV-1 RNA response as measured by Kaplan-Meier estimates of the time to a confirmed HIV-1 RNA >10 000 copies/mL. The sample size calculation assumed that 25% of the 3TC/ZDV group and 50% of the ABC/3TC/ZDV group would remain event-free for at least 48 weeks with 10% of participants lost to follow-up. The distribution of time to virologic event was estimated using the Kaplan-Meier product-limit estimates and treatment differences were analyzed using a permutation-based log-rank test, controlling for randomization factors and baseline HIV-1 RNA group (≤10 000 or >10 000 copies/mL). Participants who never had plasma HIV-1 RNA ≤10 000 copies/mL while on study are considered failures at time 0.

Efficacy variables were analyzed on an intent-to-treat (ITT) basis, including all participants who were randomized into the study. Two ITT analyses were performed. In the switch=failure analysis (a conservative analysis), participants who prematurely discontinued randomized therapy for any reason, changed randomized treatment for any reason (including meeting switch criteria), or had missing values, were considered treatment failures. In the ITT switch-included analysis (the conventional ITT analysis), participants who prematurely discontinued randomized study medication were not automatically counted as a treatment failure. Instead, this analysis includes all data from study participants, even data collected after the randomized treatments have changed. In the as-treated analysis, only data from participants remaining on randomized treatment were considered for analysis.

Statistical comparisons of the differences between treatment groups in the proportion of participants with plasma HIV-1 RNA ≤10 000 copies/mL were performed at week 48 using the Cochran Mantel-Haenszel test, controlling for baseline plasma HIV-1 RNA group and randomization stratification factors (age and previous 3TC/ZDV experience). Differences between treatment groups in the proportion of participants with HIV-1 RNA levels ≤400 copies/mL were also compared using the Cochran Mantel-Haenszel test, controlling for the same variables.

The magnitude and duration of changes in virologic and immunologic markers were determined for each participant and summarized for each treatment group by the switch-included analysis. The average area under the curve minus baseline (AAUCMB) calculation was calculated for plasma HIV-1 RNA, $CD4^+$ %, and $CD4^+$ cell count. The normalized area under the curve (NAUC) was calculated using the trapezoidal rule and divided by baseline value for $CD4^+$ cell count. The median AAUCMB and NAUC values were compared between treatment groups using the extended Cochran Mantel-Haenszel test.

Growth parameters were converted to standardized z scores.[25] The z scores and change from baseline in z scores were summarized over time up to week 48. Wilcoxon rank-sum tests for change from baseline in z scores were performed to assess treatment differences. Linear mixed-effect models of z scores were used to further assess treatment effect.

RESULTS

Between June 1997 and September 1997, 205 participants were randomized to treatment with ABC/3TC/ZDV (n = 102) or 3TC/ZDV (n = 103). The study continued until the last participant reached 48 weeks. Seventeen participants were enrolled into the study despite a violation of one eligibility criterion ($CD4^+$ <15%). Of these, 13 were enrolled in Panama and were granted an exemption from this criterion because of limited treatment options available in that country.

Baseline Characteristics

The treatment groups were balanced with respect to baseline characteristics (Table 1). Of the 205 participants enrolled, 170 (83%) were 30 months of age or older (range: 2.6–13 years) and 162 (79%) had screening plasma HIV-1 RNA levels >10 000 copies/mL.

All participants had been pretreated with antiretroviral agents and at least 50% had been treated for >2 years. Most participants randomized to the no previous 3TC/ZDV stratum had received ZDV (61%)

TABLE 1. Baseline Demographics and Characteristics

Characteristic	ABC/3TC/ZDV (n = 102)	3TC/ZDV (n = 103)
Male/female, n	45/57	45/58
Age, y		
Median (range)	5.8 (.7–12.6)	5.3 (.6–13)
Race, n (%)		
Black	42 (41)	61 (59)
Hispanic	38 (37)	24 (23)
White	18 (18)	16 (16)
Other	4 (4)	2 (2)
CDC clinical classification, n (%)		
N (asymptomatic)	7 (7)	7 (7)
A (mildly symptomatic)	38 (37)	41 (40)
B (moderately symptomatic)	33 (32)	32 (31)
C (severely symptomatic)	24 (24)	23 (22)
Baseline plasma HIV-1 RNA		
Median $\log_{10}$ copies/mL HIV-1 RNA (range)	4.68 (2.60–6.25)	4.46 (2.60–6.45)
≤10 000 copies/mL, n (%)	18 (18)	25 (24)
>10 000 copies/mL, n (%)	84 (82)	78 (76)
Median $CD4^+$ cell, cells/mm^3 (range)	647 (28–6846)	724 (10–5707)
Median $CD4^+$ cell percentage (range)	27 (2–57)	27 (1–61)

CDC indicates Centers for Disease Control and Prevention.

in the previous 6 months, often in combination with ddI (48%).

Participant Accountability

Overall, 155 participants (76%) completed 48 weeks of study, except for 29 participants (28%) in the ABC/3TC/ZDV group and 21 participants (20%) in the 3TC/ZDV group. In the ABC/3TC/ZDV group, reasons for study discontinuation were adverse events (34%), unspecified factors (31%), insufficient plasma HIV-1 RNA response (17%), lost to follow-up (10%), and withdrawal of consent (7%). In the 3TC/ZDV group, reasons for study discontinuation were insufficient plasma HIV-1 RNA response (38%), adverse events (24%), clinical progression (14%), lost to follow-up (10%), unspecified factors (10%), and withdrawal of consent (5%).

A total of 117 participants (57%) met switch criteria at week 16 or thereafter: 51 in the ABC/3TC/ZDV group (50%) and 66 in the 3TC/ZDV group (64%). Of these, 34 (67%) and 41 (62%) in the ABC/3TC/ZDV and 3TC/ZDV groups, respectively, opted to continue their randomized treatment regimens despite meeting the switch criteria. The remaining participants discontinued randomized treatment in favor of open-label ABC in combination with other antiretroviral agents. Four additional participants who did not meet switch criteria (1 and 3 participants in the ABC/3TC/ZDV and 3TC/ZDV groups, respectively) also switched to open-label ABC in combination with other antiretroviral agents. For participants who switched study drugs, the most frequently prescribed antiretrovirals taken with open-label ABC were d4T and nelfinavir, with or without 3TC and ZDV.

Time to Virologic Event

The Kaplan-Meier estimates of the proportion of participants (95% confidence interval) who maintained plasma HIV-1 RNA ≤10 000 copies/mL for 48 weeks or more was significantly different between the ABC/3TC/ZDV and 3TC/ZDV groups: 33% (23%–42%) versus 21% (13%–29%; $P = .003$; Fig 1).

Plasma HIV-1 RNA

Randomized Period

Overall, the proportion of participants who had plasma HIV-1 RNA concentration ≤10 000 copies/mL was higher in the ABC/3TC/ZDV group than in the 3TC/ZDV group (Fig 2A) at week 48: 36% versus 26% ($P = .014$) for the switch=failure analysis and 65% versus 63% ($P = .25$) for the as-treated analysis (Table 2). In the retrospective subgroup analysis of participants with baseline HIV-1 RNA >10 000 copies/mL, a statistically significant difference in response was noted between treatment groups by the switch=failure analysis: 29% versus 12% for the ABC/3TC/ZDV and 3TC/ZDV groups, respectively ($P = .008$; Table 2). No statistically significant difference in response (78% vs 72%) was noted between treatment groups for those participants with baseline HIV-1 RNA ≤10 000 copies/mL.

At week 48, the proportion of participants with plasma HIV-1 RNA ≤400 copies/mL was significantly different between the ABC/3TC/ZDV and

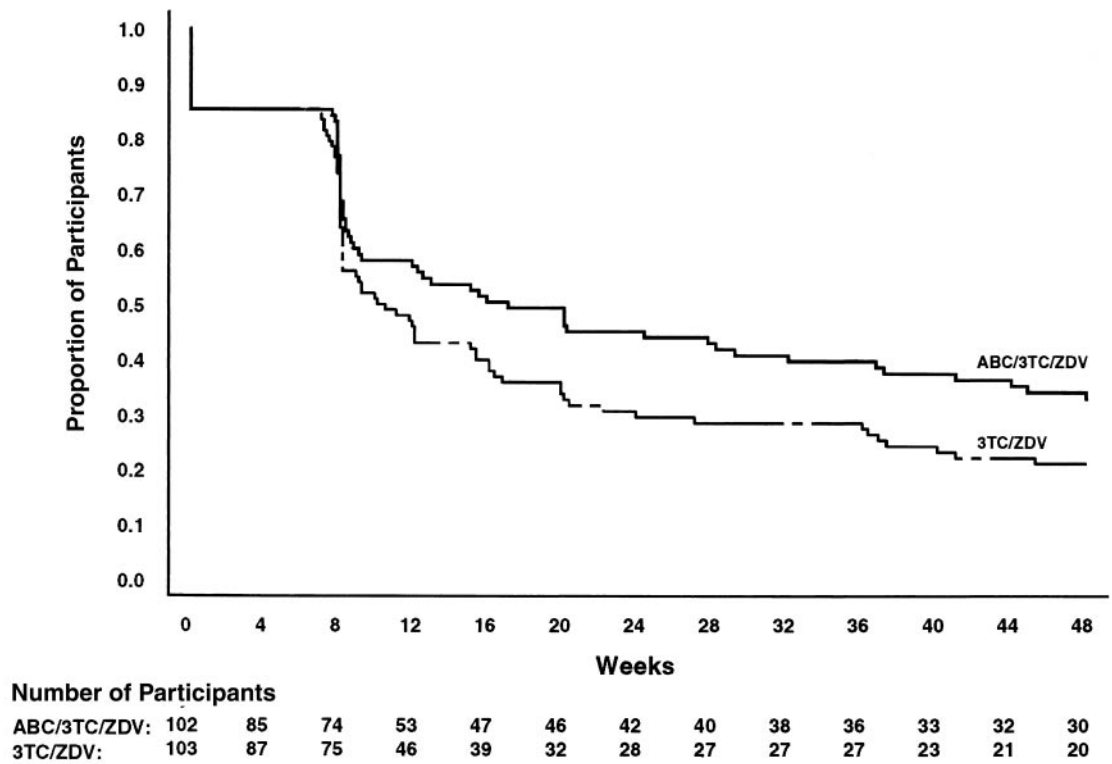


Fig 1. Kaplan-Meier estimates of the proportion of participants who maintained plasma HIV-1 RNA ≤10 000 copies/mL through 48 weeks. The number of participants given below the figure represents the number of participants at risk for having plasma HIV-1 RNA >10 000 copies/mL (in the future).

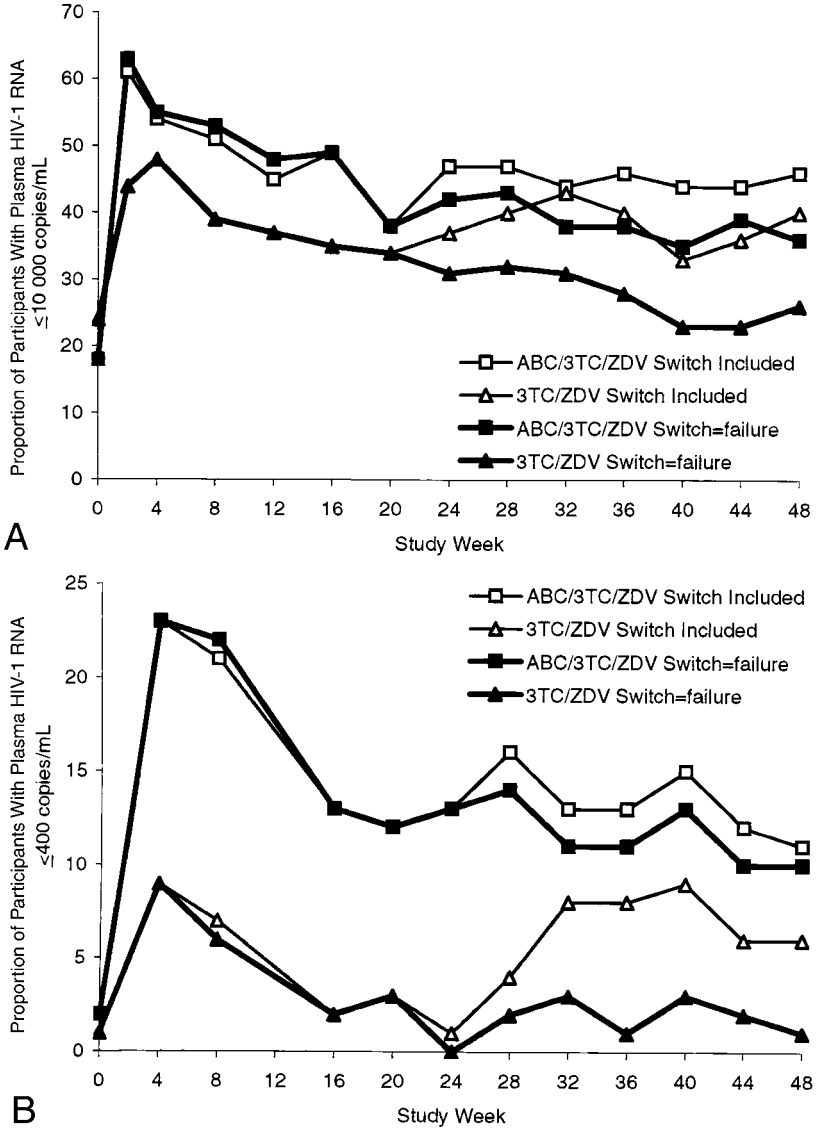


Fig 2. A, Proportion of participants with plasma HIV-1 RNA ≤10 000 copies/mL. B, Proportion of participants with plasma HIV-1 RNA ≤400 copies/mL.

TABLE 2. Proportion of Participants With Plasma HIV-1 RNA ≤10 000 Copies/mL at 48 Weeks Controlling for Baseline Plasma HIV-1 RNA*

	Baseline Plasma HIV-1 RNA ≤10 000 Copies/mL		Baseline Plasma HIV-1 RNA >10 000 Copies/mL		All Participants	
	ABC/3TC/ZDV	3TC/ZDV	ABC/3TC/ZDV	3TC/ZDV	ABC/3TC/ZDV	3TC/ZDV
Intent-to-treat analyses:						
Switch-failure	14/18 (78)	18/25 (72)	24/84 (29)	9/78 (12)	37/102 (36)	27/103 (26)
	$P = .77$		$P = .008$		$P = .014$	
Switch-included	14/18 (78)	19/25 (76)	33/84 (39)	22/78 (28)	47/102 (46)	41/103 (40)
	$P = .96$		$P = .14$		$P = .18$	
As-treated analysis	13/14 (93)	17/21 (81)	21/38 (55)	9/20 (45)	34/52 (65)	26/41 (63)
	$P = .47$		$P = .35$		$P = .25$	

* Values in parentheses are %. *P* values comparing the % among treatment groups are provided.

3TC/ZDV groups: 10% (10/102) versus <1% (1/103; $P = .001$) by the switch=failure analysis (Fig 2B) and 17% (9/52) versus 2% (1/41; $P = .005$) by the as-treated analysis. For participants with baseline plasma HIV-1 RNA level ≤10 000 copies/mL, statistically significant differences ($P \leq .05$) were noted for the ABC/3TC/ZDV group compared with the 3TC/ZDV group: 33% (6/18) versus 4% (1/25) by the switch=failure analysis and 36% (5/14) versus 5% (1/20) by the as-treated analysis. For participants with baseline HIV-1 RNA >10 000 copies/mL, the proportion of participants with plasma HIV-1 RNA ≤400 copies/mL in the ABC/3TC/ZDV and 3TC/ZDV groups were 5% (4/80) versus 0% by switch=failure analysis and 11% (4/36) versus 0% by as-treated analysis.

Over a period of 48 weeks, the median decreases from baseline in plasma HIV-1 RNA in the ABC/

3TC/ZDV group were twofold to threefold greater than those in the 3TC/ZDV group (Fig 3). At week 48, the median (range) change from baseline in plasma HIV-1 RNA was −.61 (−3.13,.84) $\log_{10}$ copies/mL and −.27 (−2.58,1.36) $\log_{10}$ copies/mL, for the ABC/3TC/ZDV and 3TC/ZDV groups, respectively. The median AAUCMB for plasma HIV-1 RNA was significantly lower in the ABC/3TC/ZDV group than in the 3TC/ZDV group through week 16 (−.51 vs −.27 $\log_{10}$ copies/mL) and through week 48 (−.47 vs −.21 $\log_{10}$ copies/mL; $P < .0001$).

Open-Label Period

At week 48, the proportion of participants who had switched to open-label ABC in the 3TC/ZDV group and had plasma HIV-1 RNA ≤10 000 copies/mL (40%) was similar to that observed in the ABC/3TC/ZDV group (46%; $P = .39$; Table 2). Similarly, the proportion of participants who had ≤400 copies/mL was not different between the ABC/3TC/ZDV and 3TC/ZDV groups: 11% (11/102) versus 6% (6/103; $P = .20$).

Among participants in the ABC/3TC/ZDV group who added other antiretroviral agents after week 16 ($n = 15$), 7 participants (47%) had plasma HIV-1 RNA ≤10 000 copies/mL and only 1 participant (7%) had plasma HIV-1 RNA ≤400 copies/mL at week 48. Among participants in the 3TC/ZDV group who added open-label ABC alone after week 16 ($n = 10$), only 1 participant (10%) had plasma HIV-1 RNA ≤10 000 copies/mL, and none had plasma HIV-1 RNA ≤400 copies/mL at week 48. By comparison, an improved response was observed among those who added open-label ABC plus other antiretroviral agents (including other NRTIs [non-nucleoside reverse transcriptase inhibitors], protease inhibitors, or non-NRTIs; $n = 22$): 11 participants (50%) had plasma HIV-1 RNA ≤10 000 copies/mL and 5 participants (23%) had plasma HIV-1 RNA ≤400 copies/mL.

CD4⁺ % and CD4⁺ Cell Count

Median increases in CD4⁺ % were greater in the ABC/3TC/ZDV group than in the 3TC/ZDV group over 48 weeks of treatment (Fig 4A). At week 48, the median increase from baseline in CD4⁺ percentage was 3.10 in the ABC/3TC/ZDV group, compared with .80 in the 3TC/ZDV group. The median AAUCMB for CD4⁺ percentage was higher in the ABC/3TC/ZDV group than in the 3TC/ZDV group through week 16 (1.95 vs 5.27; $P < .05$) but this difference was not significant through week 48 (1.9 vs 9.84).

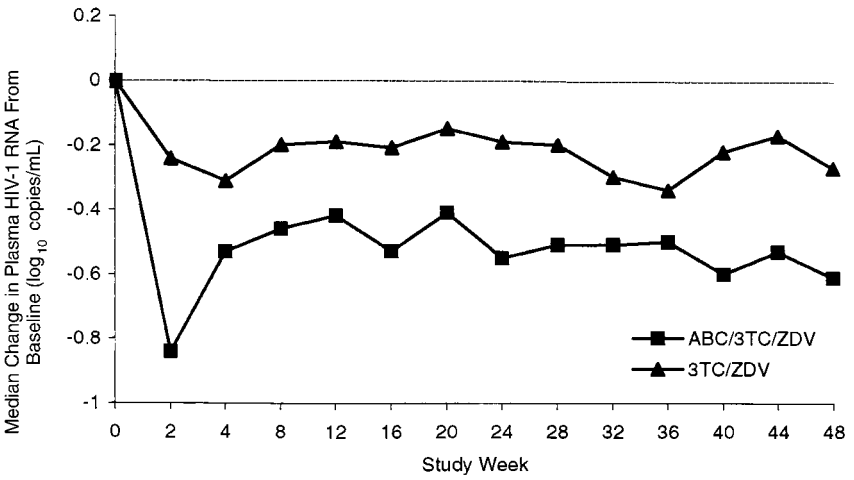
At week 48, the median change from baseline in CD4⁺ cell count (Fig 4B) was 99 cells/mm³ in the ABC/3TC/ZDV group, compared with −14 cells/mm³ in the 3TC/ZDV group. The median AAUCMB for CD4⁺ cell count was greater in the ABC/3TC/ZDV group than in the 3TC/ZDV group through week 48 (52 vs 2 cells/mm³), but the difference between treatment groups was not statistically significant ($P > .05$). The NAUC for CD4⁺ cell count was marginally higher in the ABC/3TC/ZDV group than in the 3TC/ZDV group through week 16 (1.1 vs 1.05; $P < .05$) but this difference was not significant through week 48 (1.11 vs 1.01).

Growth Effects

At week 48, no significant difference was noted between the ABC/3TC/ZDV and 3TC/ZDV treatment groups in the mean (± standard error) change from baseline in z scores for age-adjusted height (.14 ± .06 vs 6.14 ± .06), weight (.07 ± .06 vs 6.16 ± .06), and head circumference (.16 ± .17 vs 7.37 ± .16).

Disease Progression

Five participants (2%; 3, ABC/3TC/ZDV and 2, 3TC/ZDV) developed a new acquired immunodeficiency disease-defining event or died during the study. Two participants had clinical progression to class C events that included encephalitis (ABC/3TC/



Number of Participants:

ABC/3TC/ZDV	93	93	93	93	92	88	87	86	85	76	76	76	70
3TC/ZDV	97	100	96	99	98	96	89	91	92	88	81	79	77

Fig 3. Median change from baseline in plasma HIV-1 viral level ($\log_{10}$ copies/mL).

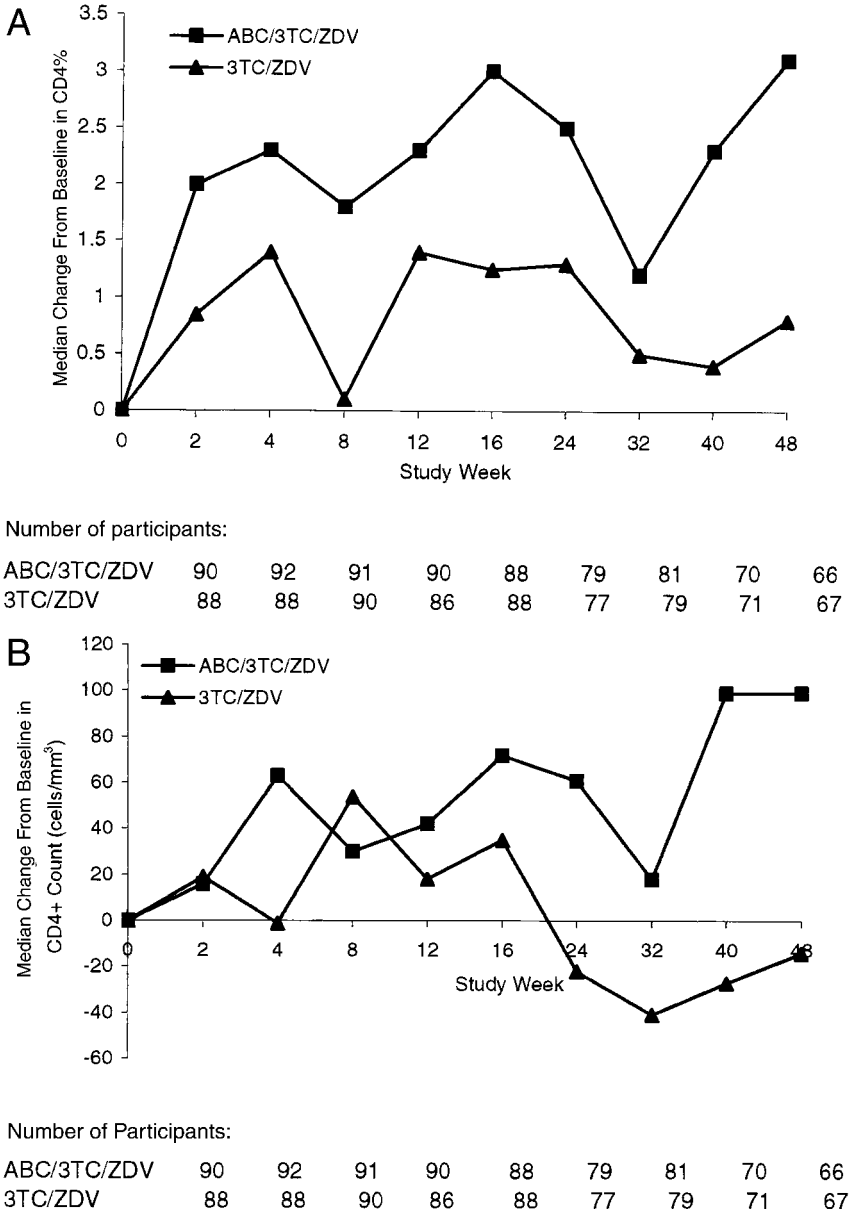


Fig 4. A, Median change from baseline in $CD4^+$ %. B, Median change from baseline in $CD4^+$ cell count (cells/mm^3).

ZDV group) and mycobacterium avium (3TC/ZDV group). Two participants in the ABC/3TC/ZDV group and 1 participant in the 3TC/ZDV group died, and they are described in the next section.

Safety

The most frequently reported adverse events (≥15%) among participants on randomized therapy are presented in Table 3. Incidences of nausea/vomiting and cough occurred more frequently in the ABC/3TC/ZDV group than in the 3TC/ZDV group ($P = .018$ and $P = .002$, respectively). The incidence of gastrointestinal discomfort and pain was significantly lower in the ABC/3TC/ZDV group than in the 3TC/ZDV group (4% vs 12%; $P = .034$). Adverse events were generally transient in nature and resolved within 3 weeks. Most of the adverse events were mild or moderate in intensity. Few adverse events led to permanent discontinuation of study drugs: nausea and/or vomiting (4 participants, ABC/3TC/ZDV), fever (3 participants, ABC/3TC/ZDV and 1 participant, 3TC/ZDV), and rash (2 participants, ABC/3TC/ZDV). These events affected no more than 4% of the study population.

Overall, 3 participants died during the study. Two deaths occurred during the first 16 weeks; one death was attributed to brain abscess (ABC/3TC/ZDV group) and the other death was attributed to acute renal failure (requiring dialysis) and nosocomial sepsis (3TC/ZDV group). Neither death was considered by the investigator to be related to study drugs. A third participant in the ABC/3TC/ZDV group died ~45 weeks after initiating study treatment. The cause of death was interstitial pneumonitis and was considered unrelated to the study drug by the investigator.

Overall, 4 cases (3%) of possible ABC-related hypersensitivity reaction were observed among 146 participants who received ABC during the study (2 during the randomized period in the ABC/3TC/

TABLE 3. Number (%) of Participants Reporting the Most Common (≥15%) Adverse Events and Grades 3 and 4 Laboratory Abnormalities

	Randomized Period	
	ABC/3TC/ZDV (n = 102)	3TC/ZDV (n = 103)
Clinical adverse events		
Nausea and vomiting	47 (46)	31 (30)†
Cough	47 (46)	26 (25)†
ENT infection	35 (34)	31 (30)
Fever and/or chills	37 (36)	28 (27)
Diarrhea	20 (20)	27 (26)
Nasal signs/symptoms	23 (23)	20 (19)
Headache	21 (21)	16 (16)
Skin rashes	16 (16)	16 (16)
Viral ENT infection	15 (15)	13 (13)
Grade 3 and 4 laboratory abnormalities		
Neutropenia	2 (2)	8 (8)
Leukopenia	4 (4)	2 (2)
Anemia	1 (<1)	3 (3)
Elevated ALT	2 (2)	2 (2)
Elevated AST	3 (3)	1 (<1)
Elevated bilirubin	2 (2)	1 (<1)
Hyperglycemia	2 (2)	—
Hypoglycemia	—	1 (<1)
Elevated amylase	4 (4)	7 (7)
Hyperkalemia	3 (3)	2 (2)
Hypokalemia	1 (<1)	—
Hypernatremia	5 (5)	1 (<1)
Hyponatremia	3 (3)	2 (2)
Elevated creatinine	—	1 (<1)

ENT indicates ear, nose, and throat; ALT, alanine aminotransferase; AST, asparate aminotransferase.
* Participants who added abacavir and/or other antiretroviral agents after week 16.
† $P < .05$.

ZDV group and 2 of 44 participants in the 3TC/ZDV group who switched to open-label ABC during the nonrandomized period). The onset of the hypersensitivity reaction occurred between 1 and 2 weeks after ABC was initiated. Symptoms related to ABC-related hypersensitivity reaction included skin rash, fever, nausea, and vomiting. In all cases, symptoms resolved on discontinuation of ABC.

Overall, 29 participants (14%; 10, ABC/3TC/ZDV and 19, 3TC/ZDV) experienced at least one severe (grades 3 and 4) laboratory abnormality (Table 3). There was no significant difference between the numbers of abnormal laboratory events between the 2 groups. The most common grades 3 and 4 hematology abnormalities were neutropenia and leukopenia. The most common grades 3 and 4 clinical chemistry abnormalities were elevated amylase and hypernatremia.

DISCUSSION

The present study is the first phase III pediatric clinical trial conducted concurrently with clinical trials in adults to contribute toward the accelerated approval of a new antiretroviral agent. Virologic, immunologic, and clinical results over the 48 weeks of this study indicate that the addition of ABC to 3TC/ZDV provided increased antiviral activity over that provided by 3TC/ZDV. However, as expected, in antiretroviral therapy-experienced participants, many of whom had received previous therapy with ZDV with or without 3TC, the degree of viral suppression provided by the ABC/3TC/ZDV regimen was modest, while improvement in immune response was moderate. Clinical adverse events were generally similar between treatment groups, with the exception of nausea/vomiting and cough, which occurred more frequently among participants receiving ABC/3TC/ZDV. Grade 3 or 4 laboratory abnormalities occurred infrequently, and there was no evidence of unexpected laboratory abnormalities with ABC.

The present study was designed at a time when little was known about the HIV-1 RNA response in children and, in addition, protease inhibitors had not yet been approved for use in children. The selection of $CD4^+$ percentage >15% as an inclusion criterion and plasma HIV-1 RNA <10 000 copies/mL as the primary endpoint was based in part on the findings of 2 studies. A study by Mofenson et al[26] demonstrated that a high plasma HIV-1 RNA level (>100 000 copies/mL) and a $CD4^+$ cell percentage of <15% were associated with high risk of disease progression and mortality of 81%. Results from another study (ACTG 152) showed that in children 30 months of age and older, the risk for disease progression increased when plasma HIV-1 RNA levels exceeded 10 000 to 20 000 copies/mL.[27] Thus, a plasma HIV-1 RNA of <10 000 copies/mL was selected as the primary endpoint to demonstrate efficacy because it would likely distinguish antiviral activity over and above what could be achieved by existing therapy and indicate a clinical benefit. Furthermore, at the time our study was initiated, there were no data available on the expected proportion of children achieving plasma HIV-1 RNA of ≤400 copies/mL using available treatments.

In this study, statistical analyses were adjusted to account for ~20% of the participants with baseline plasma HIV-1 RNA ≤10 000 copies. Baseline HIV-1 RNA was not originally planned as a covariate because such a significant proportion of children were not expected to enroll in the study with HIV-1 RNA ≤10 000 copies/mL. Without controlling for baseline HIV-1 RNA, the switch=failure analysis did not indicate a significant difference between treatment groups in the proportion of participants with HIV-1 RNA ≤10 000 copies/mL (P = .14). However, with so many participants enrolled into the study with HIV-1 RNA already below the analysis threshold level, controlling for this covariate was required.

The subgroup analyses of virologic results by baseline HIV-1 RNA yielded findings consistent with previous observations.[26–28] As expected, most participants (~80%) who had plasma HIV-1 RNA ≤10 000 copies/mL at baseline continued to remain below this level by week 48. However, for participants with baseline plasma HIV-1 RNA >10 000 copies/mL, <30% (by switch=failure analysis) achieved viral suppression to below 10 000 copies/mL on randomized therapy. Correspondingly, few participants in both strata achieved plasma HIV-1 RNA ≤400 copies/mL by week 48. The long duration of previous

NRTI therapy likely resulted in multidrug-resistant virus and, therefore, the difficulty in reducing plasma HIV-1 RNA to ≤400 copies/mL. Results could be improved by combining ABC with other new antiretroviral agents of different classes.

At week 48, the virologic and immunologic results observed with the dual NRTI regimen in our study are generally consistent with those reported in other studies of therapy-experienced children. In NRTI-experienced children, median plasma HIV-1 RNA reductions of ~.2 to .5 $\log_{10}$ copies/mL and median increases in $CD4^+$ cell counts of 25 to 73 cells/mm^3 have been reported with dual NRTI regimens.[10,11] In contrast, in treatment-naïve pediatric populations, median plasma HIV-1 RNA reductions of .7 to 1 $\log_{10}$ copies/mL and median increases in $CD4^+$ cell counts of 70 to 100 cells/mm^3 have been reported with dual NRTI regimens.[6,7]

Participants in the ABC/3TC/ZDV group achieved moderate increases in median $CD4^+$ cell counts from baseline, while virologic and immunologic responses observed are consistent with data from studies in adults. Early results in treatment-experienced adults indicate that the addition of ABC to dual NRTI regimens resulted in median plasma HIV-1 RNA reductions of .44 $\log_{10}$ copies/mL and increases in CD4 cell counts of 30 cells/mm^3 by week 16. [30] In contrast, in antiretroviral naïve adults, ABC monotherapy resulted in median plasma HIV-1 RNA reductions of ≥1.5 $\log_{10}$ copies/mL[31] and combination antiretroviral therapy with ABC reduced plasma HIV-1 RNA levels by up to 2.8 $\log_{10}$ copies/mL.[32–34] Because improvement in immune response is associated with better clinical prognosis and a lower risk of disease progression,[26] further study is needed to determine whether the observed immune response can be maintained long-term.

Our results from the open-label period of the study indicate that the addition of a new NRTI in children who are heavily nucleoside-experienced did not result in maximal suppression of viral replication to undetectable levels. An improved response was observed among those participants who added ABC plus other antiretroviral agents. As evidenced by the ITT switch-included analysis, the response rate for the 3TC/ZDV group was comparable to that of the of the ABC/3TC/ZDV group at week 48, indicating that an appropriate use of ABC in this population would be as an alternative nucleoside analog in salvage regimens. The potency of ABC, as demonstrated in other studies[31–34] and as indicated by the additional viral suppression achieved in the present study, suggest that ABC can be combined successfully with protease inhibitors and other antiretroviral agents in a salvage regimen.

Our study showed that both treatment regimens provided generally comparable improvements in age-adjusted *z* scores for height, weight, and head circumference. Previous studies have shown that changes in growth parameters can be correlated with clinical outcome.[35,36] A study by McKinney et al[7] reported that combination therapy with 3TC/ZDV significantly improved weight for age and length for age *z* scores, compared with those achieved by ddI monotherapy in treatment-naïve children who were <3 years of age. Although our analyses were not stratified by age, it is unlikely that a treatment effect will be detected in this therapy-experienced population.

The ABC/3TC/ZDV and 3TC/ZDV regimens were generally well-tolerated, with <10% of participants in each treatment group experiencing a treatment-limiting adverse event. The adverse event most frequently associated with ABC/3TC/ZDV was nausea/vomiting, which was generally transient in nature and did not lead to discontinuation of the study drug. The frequency of ABC-related hypersensitivity reaction in this study was 3%, consistent with the incidence reported in other studies.[31,33] Incidences of grades 3 and 4 hepatic, hematologic, pancreatic, and renal toxicities occurred infrequently among participants treated with ABC/3TC/ZDV and were no higher than incidences observed among participants treated with 3TC/ZDV. These tolerability/safety findings are in agreement with those reported previously in other clinical trials that have evaluated ABC/3TC/ZDV[31,33,34] or 3TC/ZDV.[5,37,38]

CONCLUSION

The results of this study indicate that, for children previously treated with NRTIs, ABC in combination with 3TC/ZDV provided increased antiviral activity. Although this combination regimen was inadequate for achieving viral suppression to undetectable levels, the results of this study indicate that ABC would be an effective component of other triple-combination therapies. Our findings also support treatment guidelines indicating that children who have been on antiretroviral therapy and are failing should have the option to receive triple-therapy regimens with at least 2 new drugs. The results of this study add to current knowledge that ABC is a potent NRTI with a favorable efficacy profile, is safe and generally well-tolerated, and will contribute to HIV-1 suppression when used in combination with other antiretroviral drugs.

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