Once-Daily Abacavir/Lamivudine/Zidovudine plus Tenofovir for the Treatment of HIV-1 Infection in Antiretroviral-Naïve Subjects: A 48-Week Pilot Study

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Purpose: To assess the safety and efficacy of a 4-drug, 3-tablet, once-daily (qd) regimen consisting of abacavir/lamivudine/zidovudine (ABC/3TC/ZDV; 2 tablets) and tenofovir (TDF) in antiretroviral-naïve patients with plasma HIV-1 RNA ≥30,000 copies/mL at 48 weeks. **Method:** All participants received ABC/3TC/ZDV (300/150/300 mg) and TDF (300 mg) qd in this pilot, open-label, multicenter study. Intent-to-treat (ITT) analyses were conducted to evaluate virologic and immunologic efficacy. **Results:** Of the 123 participants enrolled, 52 (42%) prematurely discontinued study for adverse events (14), were lost to follow-up (13), had virologic nonresponse (12), and withdrew for other reasons (13). At week 48, by ITT missing=failure analysis, 41% (51/123) and 51% (63/123) of participants had plasma HIV-1 RNA <50 copies/mL and <400 copies/mL, respectively; by ITT-observed analysis, 75% (51/68) and 93% (63/68) had plasma HIV-1 RNA <50 copies/mL and <400 copies/mL, respectively; 11% (14/123) met virologic nonresponse criteria. Median week 48 change in CD4+ cell count from baseline was +127 cells/mm^3. Median week 48 changes from baseline for fasting lipids were as follows: cholesterol (–9 mg/dL), HDL (+1 mg/dL), LDL (–9 mg/dL), and triglycerides (–4 mg/dL). **Conclusion:** A high rate of premature discontinuations contributed to the overall suboptimal virologic response to ABC/3TC/ZDV+TDF qd; however, the regimen was not associated with high rates of virologic failure previously observed with TDF+ABC/3TC. **Key words:** *abacavir/lamivudine/zidovudine, tenofovir, once-daily dosing*

Although many antiretroviral regimens exist for initial treatment of HIV-1 infection, the effectiveness of these regimens may be limited by difficulty with adherence, side effects, toxicity, and drug interactions as well as concomitant disease and comorbidities. Therefore, identifying the simplest regimen that would suppress viral activity and have the fewest drug interactions remains an important treatment goal. In contrast to protease inhibitor (PI)- or nonnucleoside reverse transcriptase (NNRTI)-containing regimens, all-NRTI regimens are simple, are relatively free of drug interactions, may potentially be dosed once daily, and would be class-sparing, preserving NNRTIs and PIs for future use.

Initial triple-NRTI studies of abacavir (ABC) + lamivudine (3TC) + zidovudine (ZDV) given twice daily (bid) had comparable efficacy to the standard of care and potential resistance benefits.[1] In CNA3005, the triple-NRTI regimen was shown to be equivalent to the indinavir regimen overall (both arms had 51% of patients with plasma HIV-1 RNA <400 copies/mL at 48 weeks), but the ABC+3TC+ZDV arm was not as efficacious for patients with baseline viral loads >100,000 copies/mL. Fifty-one percent of patients who received indinavir had HIV-1 RNA <50 copies/

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mL at 48 weeks versus 31% of patients in the ABC+3TC+ZDV arm. These differences in higher viral load suggest that there may be decreased potency in a three-drug NRTI regimen.

In a meta-analysis of virologic failures from four clinical trials, among participants who received therapies containing ABC and ZDV, the K65R and L74V mutations were seen in <2% of participants.[2] In contrast, among participants who received ABC without ZDV, the K65R mutation was observed in approximately 10% of these participants. These results suggested that the presence of ZDV may delay emergence of K65R, a resistance-conferring RT mutation that is associated with reduced susceptibility to all currently approved nucleosides/nucleotides with the exception of ZDV.[3]

We therefore conducted a pilot study of a quadruple-NRTI regimen consisting of a fixed dose combination (FDC) of ABC/3TC/ZDV (TZV; Trizivir®) and a fourth NRTI, tenofovir disoproxil fumarate (300 mg) (TDF; Viread®), in antiretroviral-naïve individuals with high baseline HIV-1 RNA (≥30,000 copies/mL) to be administered once daily (qd). Although the ABC/3TC/ZDV FDC was not approved for once-daily dosing, clinical studies have demonstrated equivalent or noninferior virologic efficacy for once-daily and twice-daily dosing of ABC[4] and 3TC.[5] At the time the present study was initiated, a proof-of-concept study provided supporting evidence of antiviral activity of once-daily ZDV.[6] The study showed that ZDV 600 mg qd had antiviral activity, although it was less pronounced than that seen with ZDV 300 mg bid (0.6 $\log_{10}$ copies/mL vs. 0.9 $\log_{10}$ copies/mL after 14 days of dosing). Based on this evidence, we postulated that the combination of ABC/3TC/ZDV with TDF might (a) augment antiviral potency of the regimen, and (b) confer additional resistance benefit since viruses containing the M184V mutation have shown hypersusceptibility to TDF in vitro.[3,7]

METHOD

Study Population

Antiretroviral-naïve male and female participants ≥18 and ≤65 years of age with HIV-1 documented by ELISA and confirmed by Western blot, positive HIV-1 blood culture, positive serum antigen, or plasma viremia were eligible for inclusion into this study. Participants had to provide written informed consent, have an entry plasma HIV RNA ≥30,000 copies/mL (Roche Amplicor® HIV-1 Monitor™ kit; Roche Diagnostic Systems, Inc., Branchburg, New Jersey, USA) within 21 days prior to study enrollment, and not have an AIDS-defining illness within 30 days of screening. Women able to conceive were required to have a negative serum pregnancy test at screening and to use adequate birth control during the study. The study was approved by the institutional review boards for each site, and all participants provided written informed consent.

Study Design

This was a nonrandomized, single-arm, open-label, observational study conducted at 11 centers in the United States. Participants received the co-formulated FDC ABC/3TC/ZDV (300/150/300 mg, Trizivir®; GlaxoSmithKline, North Carolina, USA) (2 tablets qd) + TDF (300 mg, Viread®; Gilead Sciences, California, USA) (1 tablet qd) for 48 weeks. Participants who met confirmed virologic nonresponse, defined as two consecutive viral load assessments ≥400 copies/mL at week 24 or later, were required to discontinue the study.

Following reports of a high number of virologic failures (49%, 63%) in participants receiving ABC/3TC+TDF in two studies,[8,9] an unplanned interim analysis was performed for this study. Although our analysis did not demonstrate that there was a high rate of virologic failures,[10] the original study protocol was amended to allow participants to switch therapy as an additional safety measure. Participants were allowed to replace TDF with lopinavir/ritonavir (400/100 mg co-formulation: 3 capsules twice daily [bid], with food) if they met any of the following protocol-defined switch criteria: ≥1 $\log_{10}$ copies/mL increase in plasma HIV-1 RNA above nadir between week 8 and week 24 (virologic rebound); plasma HIV-1 RNA ≥400 copies/mL at week 24 or later (virologic nonresponse); plasma HIV-1 RNA between 50 and 400 copies/mL at week 16 or later (incomplete virologic response). All plasma HIV-1 RNA levels had to be confirmed by a second measurement 2 to 4 weeks after the first measurement.

Assessments

Plasma samples were assayed for HIV-1 RNA

using the Roche Amplicor HIV-1 Monitor™ ultrasensitive assay, version 1.0 (lower limit of detection: 50 copies/mL) and standard assay (lower limit of detection: 400 copies/mL). Blood counts included CD4+ and CD8+ subset analyses. Plasma HIV-1 RNA concentration, CD4+ and CD8+ cell counts, hematology, and clinical chemistry were performed at screening, on day 1, and at weeks 4, 8, 16, 24, 32, 40, and 48. An additional plasma HIV-1 RNA measurement was taken at week 2. Blood samples were analyzed for fasting glucose, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides at weeks 8, 24, and 48. Safety was measured by clinical and laboratory evaluations. The severity of adverse events and laboratory abnormalities was graded according to the AIDS Clinical Trials Group (ACTG) toxicity scale.[11] All laboratory tests were performed centrally by Quest Diagnostics (Van Nuys, California, USA).

Peripheral blood mononuclear cells (PBMCs) were collected on day 1 (baseline) and week 48 to assess changes in mitochondrial DNA copy number.[12] Mitochondrial DNA analyses were assessed at GlaxoSmithKline (Research Triangle Park, North Carolina, USA). HIV-1 genotyping and phenotyping were performed on baseline samples from all participants at GlaxoSmithKline (Research Triangle Park, North Carolina, USA) while for virologic failures, HIV-1 genotyping and phenotyping were performed for samples up through the time of confirmed virologic nonresponse and at the time of study withdrawal by Virco (Michelen, Belgium). Self-reported adherence was assessed by the Patient Medication Adherence Questionnaire (PMAQ-3W): perfect adherence to each study drug/regimen was measured by the responses to the four questions in Part 2 of PMAQ-3W.

Statistical Analysis

The intent-to-treat (ITT) population was the primary population used for all efficacy analyses and was defined to include all enrolled participants in the study. The planned primary endpoint for the study was the proportion of participants with HIV-1 RNA <50 copies/mL by week 24, evaluated using the ITT population observed (ITT Obs) rate. The ITT Obs rate includes only observed assessments in the calculation of the rate; missing assessments are not imputed and are not included in the calculation of the rate. The ITT missing equals failure (M=F) rate imputes failures for missing assessments. The proportion of participants who achieved <400 copies/mL and <50 copies/mL in plasma HIV-1 RNA at week 48 were estimated. The baseline, week 48 PBMC levels, and week 48 change in PBMC levels from baseline were also summarized. Safety summaries were performed on the safety population, which consisted of all participants who had taken at least one dose of study drug. The number and percent of participants who had grades 3 and 4 adverse events or laboratory toxicities were summarized. In addition, the measured and change from baseline values were summarized for fasting lipids, including total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and glucose.

A planned interim analysis was performed at week 24.[13]

RESULTS

Baseline Characteristics and Patient Accountability

A total of 123 participants were enrolled from July 2002 to August 2004. The demographics and baseline characteristics of study participants are shown in **Table 1**. Seventy-one subjects (58%) completed 48 weeks of therapy, and 52 (42%) withdrew from the study prematurely (**Table 2**). Of the 14 withdrawals due to adverse events, 8 cases were due to suspected hypersensitivity reaction (HSR) to ABC. One patient switched from TDF to lopinavir/ritonavir treatment after meeting the protocol-defined criteria for switching from the study treatment. One participant died of Kaposi's sarcoma during the study. Of the 52 premature discontinuations, approximately half of the discontinuations were judged to be unrelated to study drugs, including lost to follow-up, consent withdrawal, protocol violations, and other reasons. Protocol violations included noncompliance and being off study medications for prolonged periods. Three participants prematurely discontinued for other reasons, including lack of efficacy, incarceration, and relocation to another state.

Plasma HIV RNA

At week 48, the proportion of participants who achieved a plasma HIV-1 RNA level of <50 copies/

Table 1. Subject demographics and baseline characteristics

Characteristic	Measure
Sex, *n* (%)	
Female	21 (17)
Male	102 (83)
Age, median years (range)	38 (20–57)
Race, *n* (%)	
Black	50 (41)
Hispanic	16 (13)
White	57 (46)
CDC classification, *n* (%)	
A or asymptomatic	91 (74)
B or symptomatic	20 (16)
C or AIDS-defining illness	12 (10)
HIV risk factor, *n* (%)	
Homosexual contact	79 (64)
Heterosexual contact	40 (33)
Injectable drug use	6 (5)
Occupational exposure	2 (2)
Transfusion	2 (2)
Other	1 (<1)
Baseline HIV RNA, median $\log_{10}$ copies/mL (range)	5.08 (4.08–6.53)
<100,000 copies/mL, *n* (%)	51 (41)
≥100,000 copies/mL, *n* (%)	72 (59)
Baseline CD4+, median cells/mm^3 (range)	222 (20–857)
Baseline CD8+, median cells/mm^3 (range)	727 (105–2822)
Baseline fasting lipid profile, median mg/dL (range)	
Cholesterol (total), *n* = 109	162 (63–270)
HDL cholesterol, *n* = 108	38 (13–78)
LDL cholesterol, *n* = 108	96 (12–187)
Triglycerides, *n* = 109	109 (43–323)

Table 2. Subject accountability: premature study discontinuations

Primary reason for discontinuation[a]	*n* (%)
Adverse event:	14 (27)
suspected abacavir hypersensitivity reaction (8)	
nausea/vomiting (1)	
nausea/vomiting/headache (1)	
cancer (1)	
mood swings (1)	
abnormal liver function test (1)	
positive syphilis test (1)	
Lost to follow-up	13 (25)
Virologic nonresponse	12 (23)
Consent withdrawn	5 (10)
Protocol violation	5 (10)
Other	3 (6)

[a]A total of 52 subjects (42%) prematurely discontinued the study.

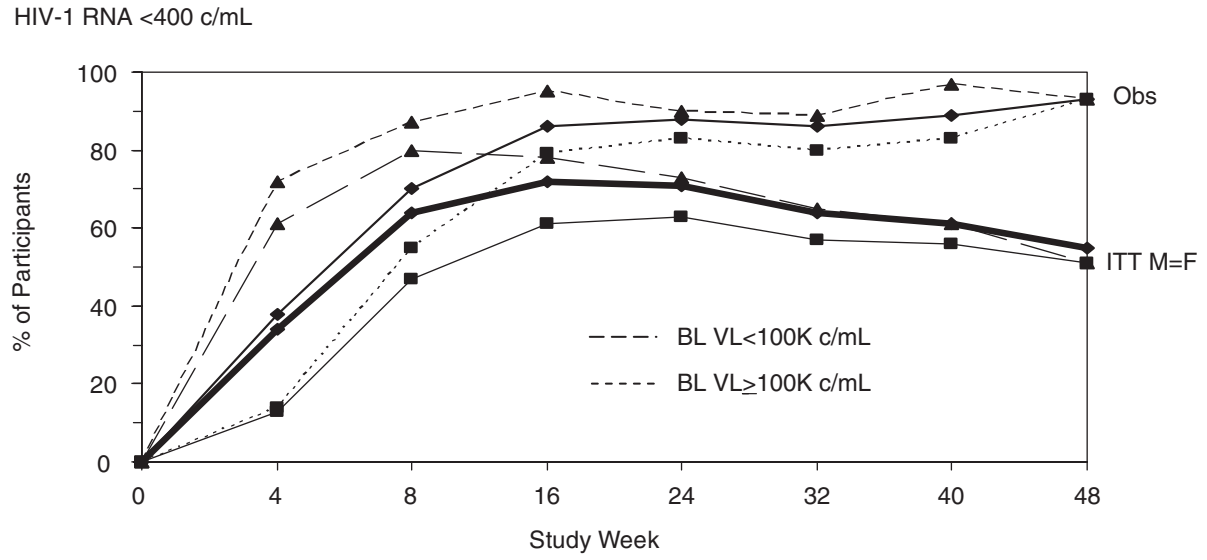
mL was 41% (51/123; ITT: M=F) and 75% (51/68; ITT: Obs) (see **Figure 1A**). The proportion of participants with plasma HIV-1 RNA level of <400 copies/mL was 51% (63/123; ITT: M=F) and 93% (63/68; ITT: Obs) (see **Figure 1B**). When participants were stratified by baseline HIV-1 RNA, a lower proportion of participants achieved virologic suppression among those with high baseline HIV-1 RNA (≥100,000 copies/mL) compared with those with low baseline HIV-1 RNA (<100,000 copies/mL) (**Figures 1A** and **1B**). Overall, 14 participants (11%) met virologic nonresponse criteria; of these, 12 (86%) had baseline plasma HIV-1 RNA ≥100,000 copies/mL, consistent with the lower virologic response rates among those with high baseline HIV-1 RNA.

CD4+ and CD8+ cell counts

By week 48, the CD4+ cell count increased with a median of 127 cells/mm^3 (range, –173 to 515; n = 67). The CD8+ cell count decreased by a median of 109 cells/mm^3 (range, –1586 to 813; n = 67).

Safety

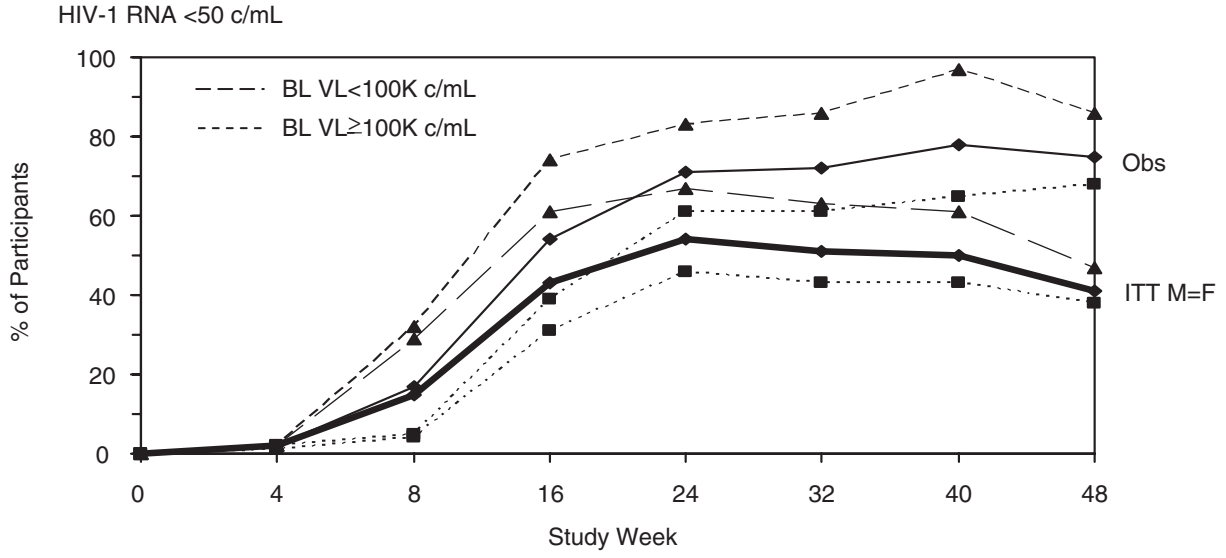
Suspected ABC HSR was reported in eight (6.5%) participants: three females and five males (three whites, two Hispanics, three blacks). All eight cases occurred within the first 3 weeks of



n

Obs all =	123	107	109	98	95	88	80	68
VL < 100K =	51	43	47	42	41	37	32	28
VL ≥ 100K =	72	64	62	56	54	51	48	40

(**A**)



n

Obs all =	123	105	106	95	91	81	75	64
VL < 100K =	51	43	47	42	41	37	32	28
VL ≥ 100K =	72	64	62	56	54	51	48	40

(**B**)

Figure 1. Proportion of participants achieving plasma HIV-1 RNA (**A**) <400 copies/mL and (**B**) <50 copies/mL by week 48 according to an intent-to-treat (ITT) analyses: missing = failure (M=F) and observed (Obs). Results are also stratified by baseline (BL) viral load (VL) ≥100,000 copies/mL or <100,000 copies/mL.

study drug administration, and all cases resolved without sequelae upon discontinuation of drug. Fifteen percent (18/123) of participants experienced a grade 3 or 4 adverse event. The most common grade 3 or 4 adverse events (occurring in ≥2% of participants) were drug hypersensitivity (4%; *n* = 5) and nausea (2%; *n* = 2).

Treatment-emergent grade 3 or 4 laboratory toxicities were reported in 11% (14/123) of participants. The most common grade 3 or 4 laboratory abnormalities (occurring in ≥2% of participants) were increases in serum lipase (3%, 4/122), alanine aminotransferase (2%, 3/122), aspartate aminotransferase (2%, 2/122), and gamma glutamyl transferase (GGT) (2%, 2/122) and decreases in white blood cell count (2%, 2/121) and platelets (2%, 2/121). The majority of patients in this study (97%; 119/123) did not experience disease progression.

Fasting Lipids

Median changes from baseline in fasting lipid values through week 48 are shown in **Figure 2**. The median decrease from baseline in total cholesterol and LDL cholesterol concentrations was 9 mg/dL (each). The median decrease from baseline in triglycerides was 3.5 mg/dL. A small increase from baseline was noted in HDL cholesterol (1 mg/dL).

Mitochondrial DNA Level

Of the 54 participants who had the mitochondrial DNA measured at baseline, 16 had a second measurement at week 48. A median change of 0.02 was noted in the mitochondrial DNA concentration for these 16 participants: 291 copies/cell (baseline) and 285 copies/cell (week 48).

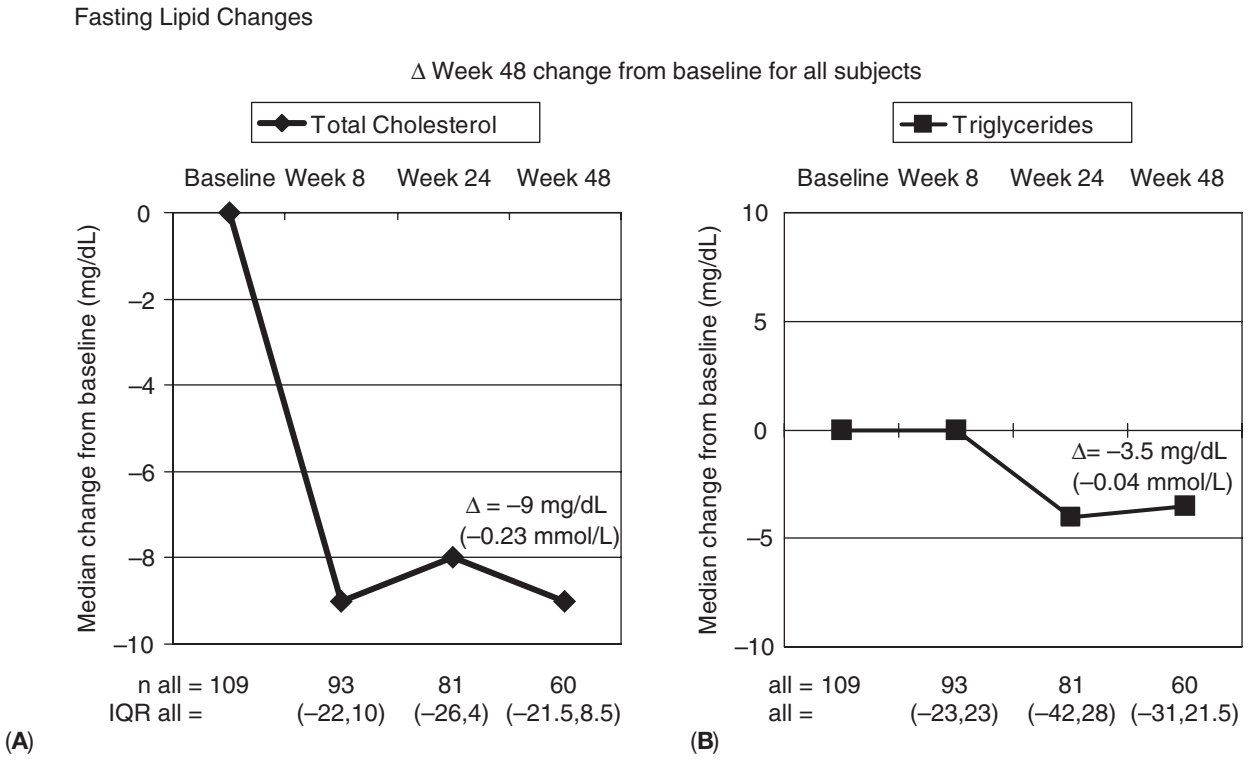
Adherence

Adherence to each study drug/regimen was assessed by the four questions in Part 2 of PMAQ-3W. A "no" answer to all four questions was considered "perfect" adherence to the study drug or regimen. Perfect adherence to the combination ABC/3TC/ZDV+TDF regimen was reported in 71% of participants (81/113). Of the virologic nonresponders, only about half (8/14) reported being perfectly adherent at weeks 4, 24, and 48 by PMAQ-3W part 2.

DISCUSSION

This single-arm pilot study demonstrated that a high rate of premature discontinuations contributed to the overall low virologic suppression rates to once-daily ABC/3TC/ZDV+TDF; however, the regimen was not associated with high rates of virologic failure previously observed with TDF+ABC/3TC. For those participants who remained on study, once-daily regimen ABC/3TC/ZDV+TDF had antiviral efficacy and a favorable lipid profile. At 48 weeks, 51% and 93% of participants achieved sustained plasma HIV-1 RNA concentrations of <400 copies/mL (ITT: M=F and ITT: Obs analyses, respectively). The proportions of participants with <50 plasma HIV-1 RNA copies/mL at 48 weeks were lower but equally disparate for the two types of analyses (41% and 75% for ITT: M=F and ITT: Obs analyses, respectively). The disparity in virologic response rates by the different ITT analyses reflects the high rate of discontinuations in this study due to multiple factors, most of which were judged unrelated to study drugs.

The results from this study indicate that, despite ZDV being dosed once-daily, the ABC/3TC/ZDV+TDF regimen was not associated with early virologic nonresponse or high rates of virologic failure previously observed with the TDF+ABC/3TC regimen in other studies. In the present study, virologic nonresponse was noted in 11% (14/123) of participants over the 48-week study period. An earlier unplanned interim analysis showed that 8 of 88 participants (15%) with at least 8 weeks of HIV-1 RNA data had met protocol-defined virologic nonresponse, including 7 with baseline HIV-1 RNA ≥100,000 copies/mL but only 1 with baseline HIV-1 RNA <100,000 copies/mL.[10] These results are in contrast to those reported for three studies involving the TDF+ABC+3TC qd combination.[14–16] Two studies were prematurely interrupted when virologic failure criteria were met in 63% (12/17) of participants[14] and in 49% (50/102) of participants.[16] In the study by Landman et al.,[15] 33% (12/36) participants had virologic failure at week 24. Suboptimal results were also reported for the combinations of TDF+ddI+3TC,[17] ABC+ddI+d4T,[18,19] or ABC+ddI+3TC.[20] In the DART study, which is a large, randomized study evaluating first-line therapy of ZDV/3TC (Combivir®) and TDF in patients with high baseline HIV-1 RNA and ad-



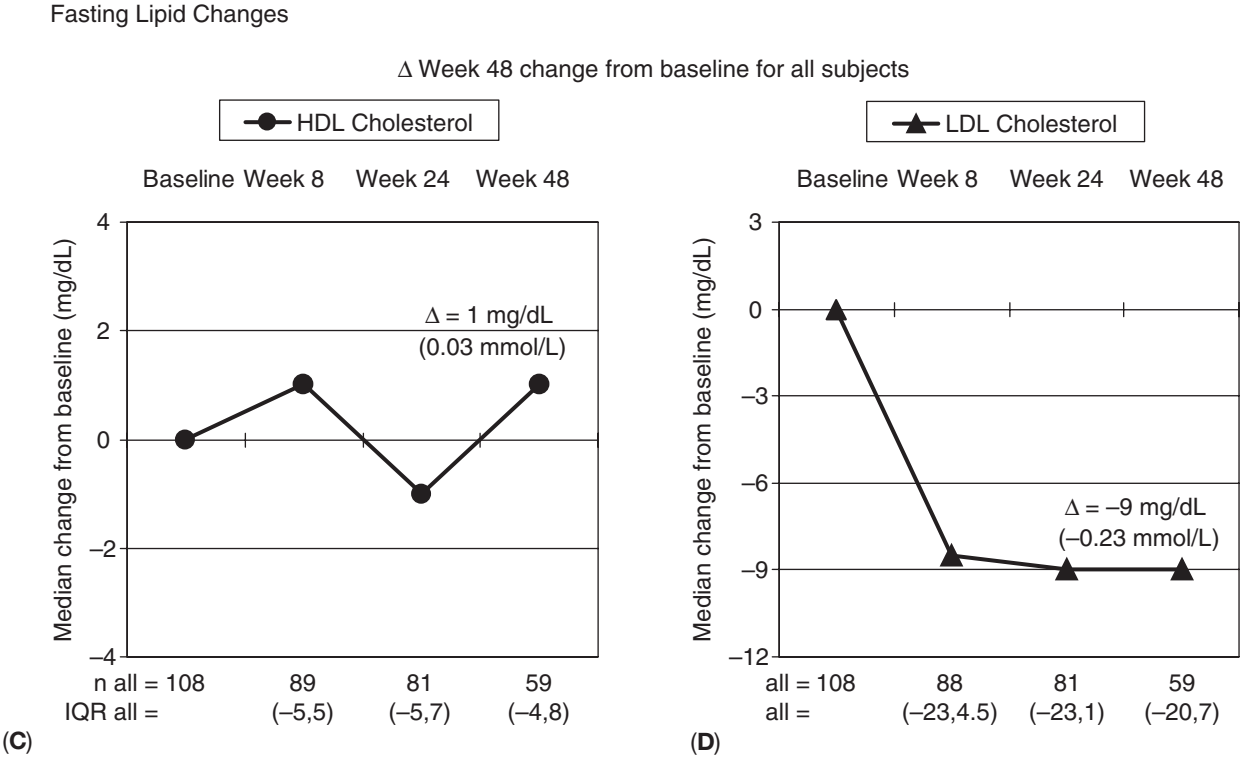


Figure 2. Median change from baseline in fasting lipid parameters with interquartile range by sex for: (**A**) total cholesterol, (**B**) triglycerides, (**C**) HDL cholesterol, and (**D**) LDL cholesterol. Δ = week 48 change from baseline for all participants. IQR = interquartile range; HDL = high density lipoprotein (HDL) cholesterol; LDL = low density lipoprotein (LDL) cholesterol.

vanced disease, 55% (165/300) of participants had HIV-1 RNA <50 copies/mL and 65% (196/300) had HIV-1 RNA < 400 copies/mL by ITT M=F analysis at 48 weeks.[21] These findings, along with the resistance data reported for our study,[22] suggest that resistance development occurs by a different pathway for ABC/3TC/ZDV+TDF compared with that for TDF+ABC/3TC, resulting in a lower incidence of virologic failure. Our findings also suggest that the clinical utility of the beneficial interaction between ZDV and TDF should be explored in future investigations. The use of ZDV and TDF in initial therapy is limited by the greater efficacy benefit seen with twice-daily therapies and the widespread adoption of once-daily therapies. However, second-line regimens with TDF combined with ZDV may be a useful model to evaluate this interaction as a means of prolonging both TDF activity and utilizing the additional antiviral benefit of ZDV.

The safety and activity of a quadruple-NRTI regimen consisting of ABC/3TC/ZDV and TDF have been evaluated in a number of small studies. In a study by Moyle and colleagues in antiretroviral-naïve participants,[23] a higher 48-week virologic response rate was reported in their randomized study of ABC/3TC/ZDV bid plus TDF qd than the present study: 67% (38/57) and 97% (55/57) of participants achieved plasma HIV-1 RNA <50 copies/mL (ITT: M=F and ITT: as treated, respectively). The difference in response rates between the two studies may be due to differences in dosing schedules of ABC/3TC/ZDV used for the two studies. In ACTG 5095, among participants who were originally randomized to ABC/3TC/ZDV and had HIV-1 RNA <200 copies/mL, among those who intensified treatment with TDF, 22% (19/85) of participants reached protocol-defined treatment failure at 72 weeks.[24] ABC/3TC/ZDV+TDF has also been evaluated in antiretroviral-naïve participants by retrospective analysis[25] and in treatment-experienced participants by both retrospective and prospective analyses.[26–28] In the Greiger-Zanlungo analysis, 88% (22/25) of participants with baseline HIV-1 RNA of 4.7 $\log_{10}$ copies/mL and baseline CD4 of 331 cells/mL had HIV-1 RNA <50 copies/mL after 16 months on treatment.

In this study, no unexpected or clinically significant toxicities emerged with the use of ABC/3TC/ZDV+TDF. However, adverse events accounted for 27% (14/52) of all study discontinuations. Of the 14 participants who withdrew from the study because of adverse events, approximately half withdrew due to suspected ABC HSR (8/14, or 57%). Although suspected ABC HSR was the most common reason for study discontinuation (15% or 8/52), the overall ABC HSR rate (8/123, or 6.5%) is comparable to that observed in clinical studies of ABC given once or twice daily.[4,5,29,30] A minority of adverse events or toxicities reported may be attributable to ZDV (≤2%, 3/123).

One of the more interesting results in this study was the modest improvement in fasting serum lipid concentrations, as evidenced by the decrease from baseline values in total cholesterol, LDL cholesterol, and triglycerides. HDL cholesterol was slightly elevated from baseline. These findings compare favorably with those reported for participants treated with ABC/3TC/ZDV for 96 weeks in a prospective randomized study of hyperlipidemia in antiretroviral-naïve individuals[31] as well as those reported for participants treated with TDF+3TC+efavirenz for 144 weeks[32] or with TDF+emitracitabine+efavirenz for 48 weeks.[33] Results from A5095 indicated that among those on ABC/3TC/ZDV there were minimal to no short-term changes in lipid or glucose parameters over 24 weeks, whereas a moderate increase in triglycerides and a slight increase in LDL cholesterol were observed over 72 weeks among those in whom TDF was added.[34]

Toxicities associated with the long-term use of NRTIs may be caused by the inhibition of mitochondrial DNA synthesis and depletion, resulting in cellular and tissue-specific toxicity.[35,36] No evidence of mitochondrial toxicity was seen in the present study as mitochondrial DNA levels were essentially unchanged.

CONCLUSION

The high rate of premature study discontinuations contributed to the overall low virologic response rates observed with the once-daily ABC/3TC/ZDV+TDF regimen; however, the regimen was not associated with the high rates of virologic failure previously observed with TDF+ABC/3TC. For those participants who remained on study, the once-daily regimen of ABC/3TC/ZDV+TDF provided good antiviral efficacy and a favorable lipid profile. The broader utility of this regimen for initial therapy merits additional study given the need for all-NRTI regimens for

certain patient groups where NNRTIs and PIs cannot be conveniently used. ABC/3TC/ZDV+TDF is an attractive class-sparing regimen for several reasons: it has a low pill burden (total of three tablets daily), can be dosed without regard to food, has few drug interactions, and may be associated with a favorable lipid profile after 48 weeks of treatment. ABC/3TC/ZDV+TDF may be an especially attractive therapeutic option for HIV-infected patients with psychiatric conditions or hepatitis B or hepatitis C coinfection and for those being treated with rifampin-based tuberculosis regimens or methadone. Thus, a fully powered study of ABC/3TC/ZDV given twice daily in combination with TDF once daily is warranted to establish the role of this quadruple-NRTI regimen as initial therapy in antiretroviral-naïve patients.

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REFERENCES

1. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: a randomized equivalence trial. *JAMA.* 2001;285:1155–1163.
2. Ait-Khaled M, Lanier R, Richards N, et al. Zidovudine appears to prevent selection of K65R and L74V mutations normally selected by abacavir mono- or combination therapies not containing zidovudine [Abstract 129]. *Antivir Ther*. 2002;7:S107.
3. Wainberg MA, Miller MD, Quan Y, et al. In vitro selection and characterization of HIV-1 with reduced susceptibility to PMPA. *Antivir Ther.* 1999; 4:87–94.
4. Moyle GJ, DeJesus E, Cahn P, et al. Abacavir once or twice daily combined with once-daily lamivudine and efavirenz for the treatment of antiretroviral-naïve HIV-infected adults. *J Acquir Immune Defic Syndr*. 2005;38:417–425.
5. DeJesus E, McCarty D, Farthing CF, et al. Once-daily versus twice-daily lamivudine, in combination with zidovudine and efavirenz, for the treatment of antiretroviral-naive adults with HIV infection: a randomized equivalence trial. *Clin Infect Dis.* 2004;39:411–418.
6. Ruane PJ, Richmond GJ, DeJesus et al. Pharmacodynamic effects of zidovudine 600 mg once/day versus 300 mg twice/day in therapy-naïve patients infected with human immunodeficiency virus. *Pharmacotherapy*. 2004;24:307–312.
7. Miller MD, Anton KE, Mulato AS, et al. Human immunodeficiency virus type 1 expressing the lamivudine-associated M184V mutation in reverse transcriptase shows increased susceptibility to adefovir and decreased replication capability in vitro. *J Infect Dis*. 1999 179:92–100.
8. Gallant JE, Rodriguez AE, Weinberg W, et al. Early nonresponse to tenofovir DF (TDF) + abacavir (ABC) and lamivudine (3TC) in a randomized trial compared to efavirenz (EFV) + ABC + 3TC: ESS30009 unplanned interim analysis. In: Program and abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; September 14–17, 2003; San Diego, CA. Abstract H-1722a.
9. Farthing C, Khanlou H, Yeh V. Early virologic failure in a pilot study evaluating the efficacy of abacavir, lamivudine, and tenofovir in treatment-naïve HIV-infected patients. *Antivir Ther.* 2003;8(suppl 1):Abstract 43.
10. Elion R, Cohen C, DeJesus E, et al. COL40263: resistance and efficacy of once-daily Trizivir and tenofovir DF in antiretroviral naïve subjects. In: 11th Conference on Retroviruses & Opportunistic Infections; February 8–11, 2004; San Francisco, CA. Abstract M-138.
11. Regulatory Compliance Center. *Division of AIDS (DAIDS) Table of Grading Severity of Adult Adverse Experiences.* Betheseda, MD: National Institute of Allergy and Infectious Diseases; August 1992.
12. Paulsen DM, Hill BJ, Hernandez J, McComsey G, Ross LL. Quantification of mitochondrial DNA in human cells using

real-time PCR with fluorogenic reporters. In: Abstracts of the XIV International Conference on AIDS; July 2002; Barcelona. Abstract B4509.
13. DeJesus E, Elion R, Cohen C, et al. Week 24 analysis of once-daily (QD) Trizivir (TZV) and tenofovir DF (TDF) in antiretroviral-naïve subjects (COL40263). In: Program and abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 30–November 2, 2004; Washington, DC. Abstract H-456.
14. Khanlou H, Yeh V, Guyer B, Farthing C. Early virologic failure in a pilot study evaluating the efficacy of therapy containing once-daily abacavir, lamivudine, and tenofovir DF in treatment-naïve HIV-infected patients. *AIDS Patient Care STDS.* 2005;19(3):135–140.
15. Landman R, Descamps D, Peytavin G, et al. Early virologic failure and rescue therapy of tenofovir, abacavir, and lamivudine for initial therapy of HIV-1 infection: TONUS study. *HIV Clin Trials.* 2005;6:291–305.
16. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naïve subjects. *J Infect Dis.* 2005;192:1921–1930.
17. Jemsek J, Hutcherson P, Harper E. Poor virologic responses and early emergence of resistance in treatment naive, HIV-infected patients receiving a once daily triple nucleoside regimen of didanosine, lamivudine, and tenofovir DF. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections. February 8–11 2004; San Francisco, CA. Abstract 51
18. Roge BT, Katzenstein TL, Obel N, et al. K65R with and without S68: a new resistance profile in vivo detected in most patients failing abacavir, didanosine and stavudine. *Antivir Ther.* 2003,8:173–182.
19. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS.* 2003,17:2045–2052.
20. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS.* 2003,17:987–999.
21. DART Virology Group and Trial Team. Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa. *AIDS.* 2006;20:1391–1399.
22. Elion R, Ha B, DeJesus E, Cohen C, et al. Selection of HIV reverse transcriptase (RT) thymidine analogue mutations (TAMS) rather then K65R is the preferred route of resistance seen in patients with virologic failure (VF) on once-daily (QD) Trizivir (TZV) and tenofovir (TDF). In: Program and abstracts of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy; December 16–19, 2005; Washington, DC. Abstract H-1068.
23. Moyle G, Higgs C, Teague A, et al. An open-label, randomized comparative pilot study of a single-class quadruple therapy regimen versus a 2-class triple therapy regimen for individuals initiating antiretroviral therapy. *Antivir Ther.* 2006;11:73–78.
24. Gulick R, Lalama C, Shikuma C, et al. Randomized intensification of a triple nucleoside regimen with efavirenz or tenofovir in ACTG 5095. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 4–8, 2006; Denver, CO. Abstract 519.
25. Greiger-Zanlungo M, Rubin, M, Blick, D, Garton, T. Quadruple nucleoside reverse transcriptase inhibitor (NRTI) therapy with Trizivir® (TZV) and Viread® (TDF) in HAART-naive and -experienced HIV/AIDS patients. In: Program and abstracts of the 15th International AIDS Conference; July 11–16, 2004; Bangkok, Thailand. Abstract TuPeB4513.
26. Dauer B, Carlebach A, Stuermer M, et al. Virologic response to tenofovir DF (TDF) plus Trizivir (TZV) therapy in heavily ART-experienced, HIV+ patients: 24 week results. In: Program and abstracts of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy; December 16–19, 2005; Washington, DC. Abstract H-520.
27. Rodriguez A, Hill-Zababla C, Sloan L, et al. Patients experiencing early virologic failure on a protease inhibitor- or nonnucleoside reverse transcriptase inhibitor-based initial regimen containing a thymidine analogue and lamivudine can be successfully treated with a quadruple-nucleoside regimen. *J Acquir Immune Defic Syndr.* 2006;41:127–129.
28. Latham V, Stebbing J, Mandalia S, et al. Adherence to trizivir and tenofovir as a simplified salvage regimen is associated with suppression of viraemia and a decreased cholesterol. *J Antimicrob Chemother.* 2005;56:186–189.
29. Berenguer J, Perez-Elias MJ, Bellon JM, et al. Effectiveness and safety of abacavir, lamivudine, and zidovudine in antiretroviral-naïve HIV-infected patients: results from a large multicenter observational cohort. *J Acquir Immune Defic Syndr.* 2006;41:154–159.
30. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naïve HIV-1-infected patients. *J Acquir Immune Defic Syndr.* 2004;35:22–32.
31. Kumar P, Rodriguez-French A, Thompson M, et al. A prospective, 96-week study of the impact of Trizivir, Combivir/nelfinavir, and lamivudine/stavudine/ nelfinavir on lipids, metabolic parameters and efficacy in antiretroviral-naive patients: effect of sex and ethnicity. *HIV Med.* 2006;7:85–98.
32. Gallant JE, Staszewski S, DeJesus E, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3 year randomized trial. *JAMA.* 2004;292:191–201.
33. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med.* 2006;354:251–260.
34. Shikuma C, Yang Y, Meyer WA, et al. Metabolic analyses within A5095: effect of efavirenz against an all nucleoside/nucleotide background. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5–8, 2006; Denver, CO. Abstract N-166.
35. Nolan D, Hammond E, Martin A, et al. Mitochondrial DNA depletion and morphologic changes in adipocytes associated with nucleoside reverse transcriptase inhibitor therapy. *AIDS.* 2003;17:1329–1338.
36. Nolan D, Hammond E, James I, McKinnon E, Mallal S. Contribution of nucleoside-analogue reverse transcriptase inhibitor therapy to lipoatrophy from the population to the cellular level. *Antivir Ther.* 2003;8:617–626.