Chapter 4

A randomized controlled trial of single-class maintenance therapy with abacavir/lamivudine/zidovudine after standard triple antiretroviral induction therapy: final 96-week results from the FREE study

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ABSTRACT

Objectives: The aim of the study was to test the antiviral efficacy of a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen, with potential beneficial metabolic effects, as maintenance therapy after induction with dual NRTI and a boosted protease inhibitor (PI).

Methods: An open-label, noninferiority study was carried out. Antiretroviral therapy (ART)-naïve patients with CD4+ T-cell count ≤350 cells/µl and HIV-1 RNA >30,000 copies/ml (n=207) were treated with zidovudine/lamivudine and lopinavir/ritonavir. After achieving HIV-1 RNA <50 copies/ml on two consecutive occasions between weeks 12 and 24 after baseline, 120 patients (baseline: median HIV-1 RNA 5.19 $\log_{10}$ copies/ml, median CD4+ T-cell count 180 cells/µl), were randomized to abacavir/lamivudine/zidovudine (ABC/3TC/ZDV) (n=61) or to continue PI-based ART (n=59).

Results: For the proportions of patients (intention-to-treat, missing=failure) with HIV-1 RNA <400 copies/ml (PI group, 66%; ABC/3TC/ZDV group, 71%) and <50 copies/ml (PI group, 63%; ABC/3TC/ZDV group, 62%) at 96 weeks, switching to ABC/3TC/ZDV was noninferior compared to continuing the PI regimen; the difference in failure rate (ABC/3TC/ZDV minus PI) was –4.4 percentage points [95% confidence interval (CI) –21.0 to +12.3 percentage points] and +0.4 percentage points (95% CI –16.9 to +17.7 percentage points), respectively. In the per-protocol analysis, the difference in virologic failure for HIV-1 RNA >400 copies/ml (0 of 39 patients in the PI group and two of 45 patients in the NRTI group) and for HIV-1 RNA >50 copies/ml (two of 39 and three of 45 patients, respectively) was +4.4 percentage points (95% CI: -2.1 to +11.0) and +1.5 percentage points (95% CI –8.6 to +11.7 percentage points), respectively, also showing noninferiority. Serum lipids significantly improved in the NRTI-group, but not in the PI arm.

Conclusions: A single-class NRTI regimen after successful induction with standard ART had similar antiviral efficacy compared to continuation of a PI-based regimen at 96 weeks after baseline, with improved serum lipids.

INTRODUCTION

Combination antiretroviral therapy (cART) only consisting of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) is not recommended as first-line treatment for HIV infections [1].

Antiretroviral regimens frequently have to be adjusted because of toxicity, drug-drug interactions or pregnancy. Our hypothesis was that a triple-NRTI regimen can be used safely as a maintenance regimen after successful virologic suppression with a standard cART. This study was initiated at a time when preferred regimens were still complex with a high pill burden and with more concerns about toxicity, resulting in, for example, lipodystrophy.

Initial studies addressing a switch to triple NRTIs included patients that had not been ART-naïve from the start, resulting in suboptimal responses [2-6]. Subsequent studies exploring the induction-maintenance concept in ART-naïve patients demonstrated noninferiority for triple-NRTI regimens compared with two-class triple- (or quadruple) cART [7-11]. Some of these studies were not entirely prospective [7,10], or did not have a comparative design for the maintenance phase [12]. Other studies showed treatment failures because of drug intolerance [9,11,12].

Here we describe the final results of a randomized, prospective, 96-week study in ART-naïve patients using protease inhibitor (PI)-based triple cART as induction therapy, followed by maintenance with abacavir/lamivudine/zidovudine (ABC/3TC/ZDV) in those who reached an undetectable plasma HIV-1 RNA level (<50 copies/ml). Our objective was to evaluate noninferiority of ABC/3TC/ZDV compared with continued cART with lopinavir /ritonavir (LPV/r). We were also interested in the metabolic effects of the switch. Interim results at week 48 showed that virologic success rates with the triple-NRTI regimen and the PI-based cART regimen were similar [13].

METHODS

Study population

ART-naïve adults with a CD4+ T-cell count ≤350 cells/µl and an HIV-1 RNA level ≥30,000 copies/ml at screening were eligible for inclusion in the study. Exclusion criteria included diabetes mellitus, being treated for dyslipidemia, or predefined laboratory abnormalities. Female patients were excluded if they were pregnant or breast-feeding.

Study design and study sites

FREE (to become free of PI-related problems, such as toxicity, pill burden) is an investigator-initiated, randomized, open-label, 96-week study conducted at 10 sites in the Netherlands and one site in Belgium. During the induction phase, patients were treated with one fixed-dose tablet of lamivudine

150 mg/zidovudine 300 mg (Combivir; GlaxoSmithKline, Zeist, The Netherlands, and Genval, Belgium) twice daily and with three capsules lopinavir 133 mg/ritonavir 33 mg (Kaletra; Abbott, Hoofddorp, The Netherlands and Louvain-La-Neuve, Belgium) twice daily. In 2005, the capsules were replaced by tablets 200/50 mg, taken as two tablets twice-daily.

Patients with HIV-1 RNA levels <50 copies/ml between weeks 12 and 24, measured on two consecutive visits, were eligible for randomization in the maintenance phase.

Patients were randomly allocated on a 1:1 basis either to continue 3TC/ZDV and LPV/r or to switch to one fixed-dose tablet of ABC 300 mg/3TC 150 mg/ZDV 300 mg (Trizivir; GlaxoSmithKline, Zeist, the Netherlands, and Louvain-La-Neuve, Belgium) twice daily. Randomization was based on computer-generated randomization lists stratified by baseline HIV-1 RNA levels (stratum 1: 30,000-100,000, stratum 2: 100,000-1,000,000 and stratum 3: >1,000,000 copies/ml). Randomly permuted blocks of size four were used. There was no predetermined restriction on the number of patients randomized per stratum. Actual randomization of a patient took place within two weeks after week 12, week 18, or week 24, depending on when viral load undetectability was reached in the patient on two consecutive visits. Patients were allocated by stratum according to the method of sequentially numbered and opaque sealed envelopes to be opened by a designated person. For each patient becoming eligible in a certain stratum, the designated person was asked to open the next envelope in that stratum. Open envelopes were stored during the study. Each randomization number could only be allocated once to an eligible patient.

Screening and on-study evaluations included a clinical assessment and laboratory evaluations: plasma HIV-1 RNA, CD4+ T-cell count, hematology and clinical chemistry tests, including lipid profiles. Blood was taken while fasting only at screening; no food restriction was imposed at follow-up visits. At the time at which this study started, routine genotyping for the human leucocyte antigen (HLA)-B*5701 allele was not available. The presence of this allele was identified as a risk factor for development of the abacavir hypersensitivity reaction [14]. On-study evaluations included clinic visits at baseline and at weeks 4, 8, 12, 18, 24 for the induction phase; and at weeks 30 (only for patients switched to ABC/3TC/ZDV at week 26), 36, 48, 60, 72, 84 and 96 for the maintenance phase. HIV-1 RNA was assessed locally at each visit using the Roche Ultra Sensitive Assay with a lower limit of detection of 50 copies/ml. Virologic failure was defined as plasma HIV-1 RNA >400 copies/ml on two consecutive occasions or HIV-1 RNA >1000 copies/ml at any one time point after randomization. Treatment failure was defined as a composite of virologic failure and withdrawal from the study in the maintenance phase for any reason.

The purpose of the study was to show noninferiority of switching to ABC/3TC/ZDV as compared with continuation of the PI by a margin of >20 percentage points.

End points

The primary end point of the study was antiviral efficacy determined by comparing the proportion of patients with plasma HIV-1 RNA of <400 copies/ml at week 96 for the intention-to-treat (ITT) population, including all randomized patients, missing equals failure (M=F). Secondary end points included:

1) antiviral efficacy, determined using the proportion of patients with plasma HIV-1 RNA of <50 copies/ml at week 96 for the ITT population (M=F);
2) time to virologic failure defined as HIV-1 RNA >400 copies/ml in the per-protocol population (i.e. the participants actually receiving the study treatment after randomization and not withdrawn because of reasons other than virologic failure before week 96);
3) time to virologic failure defined similarly, with the 400 copies/ml cut-off point replaced by 50 copies /ml;
4) time to treatment failure (HIV-1 RNA >400 and >50 copies/ml);
5) absolute and cumulative CD4+ T-cell count changes compared to baseline;
6) safety and tolerability.

Other secondary end points were changes in adherence, treatment satisfaction and quality of life, measured by using self-reported questionnaires. Results for these outcomes have been reported separately [15].

Sample size

With an expected antiviral efficacy of 80% at week 96 and a noninferiority margin of 20 percentage points, 50 randomized evaluable subjects per group were needed to show noninferiority with 80% power, using a test size of 0.05 (one-sided).

Statistical analyses

The proportion of subjects with virologic failure was compared between the two groups using a 95% confidence interval (CI) for the difference in proportions between the two treatment groups in the ITT analysis (primary end point) and in the per-protocol analysis. Time to virologic failure was analyzed using the Kaplan-Meier method. The exact log-rank test was used to test the hypothesis of equal time-to-failure distributions in the two treatment groups. Subjects who developed a virologic failure (according to either definition) reached their end point during the trial earlier than week 96.

The proportion of subjects with total treatment failure was compared between the two groups using a 95% CI for the difference in proportions in the per-protocol analysis.

Changes in the absolute numbers of CD4+ T cells during the randomization phase were analyzed using linear mixed modelling. All patients with at least one CD4 measurement were included in the analysis.

Missing CD4-values in patients with an incomplete series of CD4-measurements were appropriately dealt with by the restricted maximum likelihood estimation method used in linear mixed modelling.

Lipids were analyzed after log-transformation using linear mixed modelling for the two study phases separately: induction phase (phase 1) and maintenance trial phase (phase 2). Phase 1 ran from screening to week 12. For phase 2 analyses the time of randomization was considered a fixed starting time, although it was not a fixed moment in time as subjects were randomized at week 12, 18 or 24 from the start of study (phase 1) . In the model adjustment was made for fasting (yes/no).

Statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Ethics

The protocol was approved by the Institutional Review Boards of all the hospitals involved. All participants gave consent after written information had been given, in accordance with national and international legislation, as well as the declaration of Helsinki.

The protocol (with revisions and updates) was registered at Clinicaltrials.com; Registration Identifier Number: NCT00405925.

RESULTS

Patients and treatment

A total of 241 patients were assessed for eligibility between March 2003 and August 2007 (the last visit for the last patient occurred on 17 June 2009), 207 patients were enrolled in the induction phase. The findings at baseline of the patients are given in Table 1.

Patients were predominantly white (79%). Eighty-seven patients (36%) did not reach the maintenance phase (Figure 1) primarily because they did not achieve virologic suppression before week 18 (47 patients), or because of side effects (22 patients). Of baseline variables, only HIV-1 RNA level and CD4+ T-cell count differed significantly between the patients who did not reach the maintenance phase ('dropouts'; median HIV-1 RNA 5.41 $\log_{10}$ copies/ml) and the randomized patients (median HIV-1 RNA 5.06 log10copies/ml; *P*=0.004). Median CD4+ T-cell count was 160 cells/µl in the dropouts and 200 cells/µl in the randomized group (*P*=0.027). A total of 120 patients were eligible for randomization in the maintenance phase. Fifty-nine patients were randomized to continue the PI-based regimen, and 61 were switched to ABC/3TC/ZDV. There were no significant differences at baseline in CD4+ T-cell count (*P*=0.15) or HIV-1 RNA level (*P*=0.084) between the groups at randomization. Of these 120 patients, nine did not start with the allocated treatment: five patients randomized in the PI arm, and four in the ABC/3TC/ZDV arm (Figure 1).

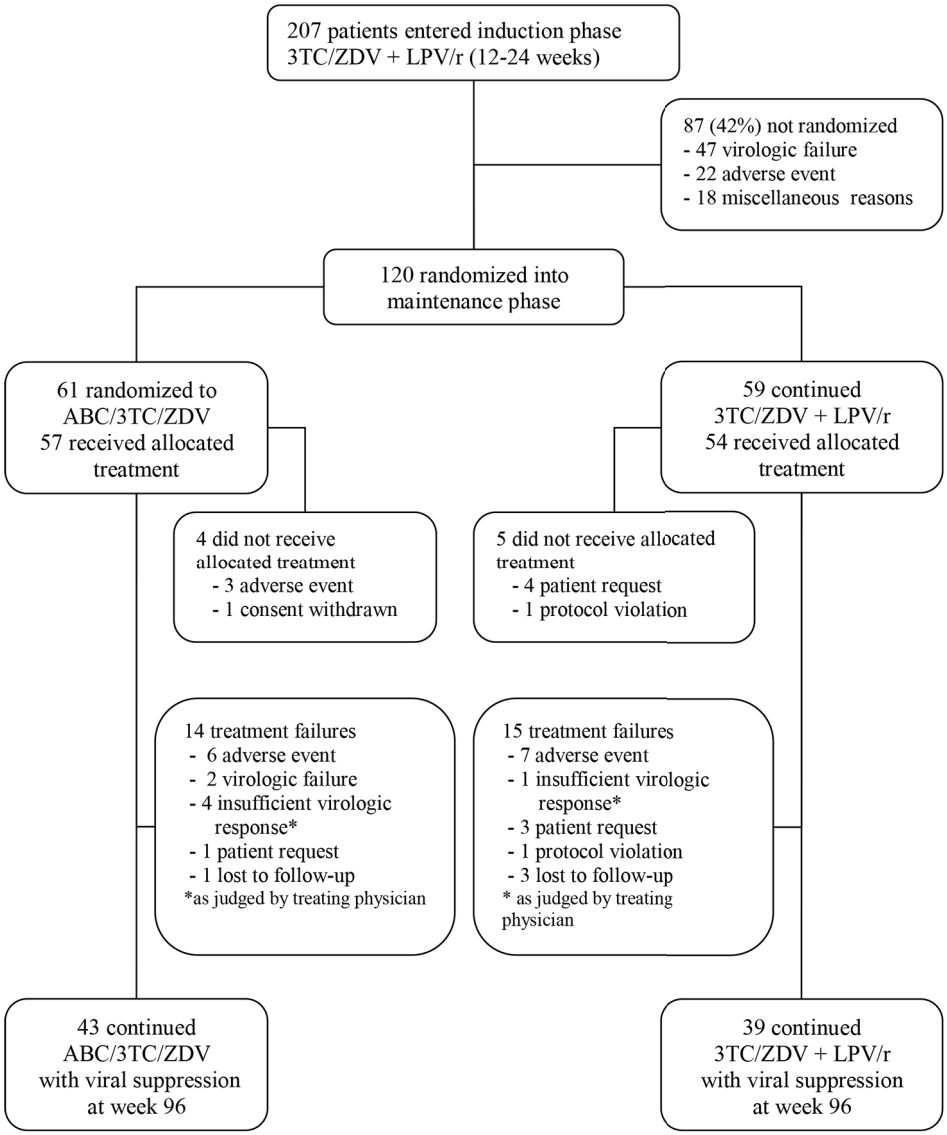

Figure 1. Enrollment and outcomes. ABC=abacavir; 3TC=lamivudine; LPV/r=lopinavir/ritonavir; ZDV=zidovudine.

Virologic efficacy

Intention-to-treat analysis

At 96 weeks, 39 (66%) of the 59 patients continuing the PI regimen and 43 (71%) of the 61 patients receiving ABC/3TC/ZDV had HIV-1 RNA <400 copies/ml (primary end point). With a difference in failure rate (ABC/3TC/ZDV minus PI) of –4.4 percentage points (95% CI: –21.0 to +12.3) this established

ABC/3TC/ZDV as noninferior to continued PI treatment, with the upper limit of the CI not exceeding the noninferiority boundary of 20 percentage points. For HIV-1 RNA <50 copies/ml, the proportion of patients was 37 of 59 (63%) in the PI arm and 38 of 61 (62 %) in the ABC/3TC/ZDV arm, also showing noninferiority with a difference in failure rate of +0.4 percentage points (95% CI: –16.9 to +17.7).

Table 1. Characteristics of the Study Participants at Baseline and at Randomization

	Induction phase	Maintenance phase	
	3TC/ZDV+LPV/r	**3TC/ZDV+LPV/r**	**ABC/3TC/ZDV**
Patients			
Total, n	207	59	61
Median age, years (range)	39.7 (19.4-78.1)	40.3 (24.7-62.0)	43.1 (21.9-68.6)
Male gender, n (%)	181 (87%)	52 (88%)	50 (82%)
HIV-1 RNA at baseline			
Median, $\log_{10}$ copies/ml (range)	5.19 (2.97-7.45)	5.03 (4.17-6.61)	5.07 (2.97-6.18)
≥100000 copies/ml, n (%)	115 (60%)	29 (49%)	33 (54%)
CD4+ T cells/µl at baseline			
Median (range)	180 (10-440)	207 (10-370)	195 (10-347)
<50, n (%)	31 (15%)	6 (11%)	9 (16%)
>50-<200, n (%)	73 (35%)	18 (34%)	20 (35%)
CD4+ T cells/µl at randomization			
Median (range)	NA	407 (110-700)	370 (80-800)

3TC=lamivudine; ABC=abacavir; LPV/r= lopinavir/ritonavir; ZDV=zidovudine; NA=not applicable.

Per-protocol analysis

The number of subjects withdrawn before week 96 without virologic failure was 36 (20 in the PI group, 16 in the ABC/3TC/ZDV group). Of these 36 subjects, nine subjects withdrew immediately after randomization and had contributed no follow-up information during the trial (see *Patients and treatment*). The remaining 27 subjects (15 in the PI group, 12 in the ABC/3TC/ZDV group) withdrew during the maintenance phase. The number of subjects for the per-protocol analysis for virologic failure was 84 (39 in the PI group, 45 in the ABC/3TC/ZDV group). The proportion of subjects with virologic failure with HIV-1 RNA >400 copies/ml (according to the predefined criteria) in the ABC/3TC/ZDV group (two of 45) was 4.4 percentage points higher (95% CI: -2.1 to +11.0) than that in the PI group (none of 39). For virologic failure with HIV-1 RNA >50 copies/ml, the proportion in the ABC/3TC/ZDV group (three of 45) was 1.5 percentage points higher (95 % CI: -8.6 to +11.7) than that in the PI group (two of 39). For either virologic failure type, the upper limit of the CI did not exceed the noninferiority boundary of 20 percentage points. The Kaplan-Meier curves comparing the failure-free probabilities between the two treatment arms are shown in Figure 2. The distribution of time to virologic failure with HIV-1 RNA >400 copies/ml during the trial did not differ significantly between the two groups

(exact log-rank test *P*=0.33). Also for the distribution of time to virologic failure with HIV-1 RNA >50 copies/ml, no significant difference between the two groups was seen (exact log-rank test *P*=0.64). For a difference in the distribution of time to virologic failure between the two arms, no noninferiority boundary was defined in the protocol.

When virologic failure was defined as HIV-1 RNA >400 copies/mL, the proportion of patients with total treatment failure in the ABC/3TC/ZDV group (14 of 57) was 3.2 percentage points lower (95 % CI: -19.6 to +13.1) than that in the group on standard PI treatment (15 of 54). When virologic failure was defined as HIV-1 RNA >50 copies/ml, the proportion of patients with total treatment failure in the ABC/3TC/ZDV group (15 of 57) was 5.2 percentage points lower (95% CI: –22.0 to +11.7) than that in the group on standard PI treatment (17 of 54). For either treatment failure type, the upper limit of the CI did not pass the noninferiority boundary of 20 percentage points.

Intermittent low-level viremia (HIV-1 RNA >50 and <400 copies/ml) occurred in 10 patients in the PI arm and in 14 patients in the ABC/3TC/ZDV arm (*P*=0.78). In seven patients in the PI arm this occurred once, in two it occurred on two occasions and in one it occurred three times. In the ABC/3TC/ZDV arm this occurred once in 11 patients and three times in 3 patients. The distribution of low-level viremia among the different HIV-1 RNA strata at baseline is shown in Table 2.

Immunologic outcome

After randomization, the number of CD4+ T cells continued to increase. At week 96, the raw mean CD4+ T-cell count was 490 cells/µl (standard deviation [SD] 157) for the 40 patients in the PI group and 439 cells/µl (SD 204) for the 43 patients in the ABC/3TC/ZDV group (*P*=0.20). For the PI group, the mean increase in CD4+ T-cell count was 156 cells/µl (95% CI: 121-190), for the ABC/3TC/ZDV group the mean increase was 95 cells/µl (95% CI: 52-139) according to this crude analysis (*P*=0.033). Using a more sophisticated analysis employing linear mixed modelling using all repeated CD4+ T-cell measurements and more appropriately dealing with missing values, the difference was no longer significant. All 120 patients had at least one valid measurement of CD4+ T-cell count and were included in the linear mixed modelling analysis. In the PI group, the mean increase was 182 cells/µl (95% CI: 103-261) and in the ABC/3TC/ZDV group, the mean increase was 132 cells/µl (95% CI: 72-193) in the ABC/3TC/ZDV group, with a mean difference of 50 cells/µl (95% CI: -50 to + 150; *P*=0.33).

Adverse events and metabolic effects

Adverse events leading to discontinuation of study drugs occurred in seven patients in the PI arm and in six patients in the ABC/3TC/ZDV arm (Figure 1). In the PI arm, five patients stopped because of lipodystrophy or dyslipidemia; one patient developed Hodgkin's lymphoma. In the ABC/3TC/ZDV arm there were two patients with a possible hypersensitivity reaction to ABC, one patient with grade 3 anemia on ZDV, and one patient with grade 2 myopathy on ZDV. There were no myocardial infarctions in either group.

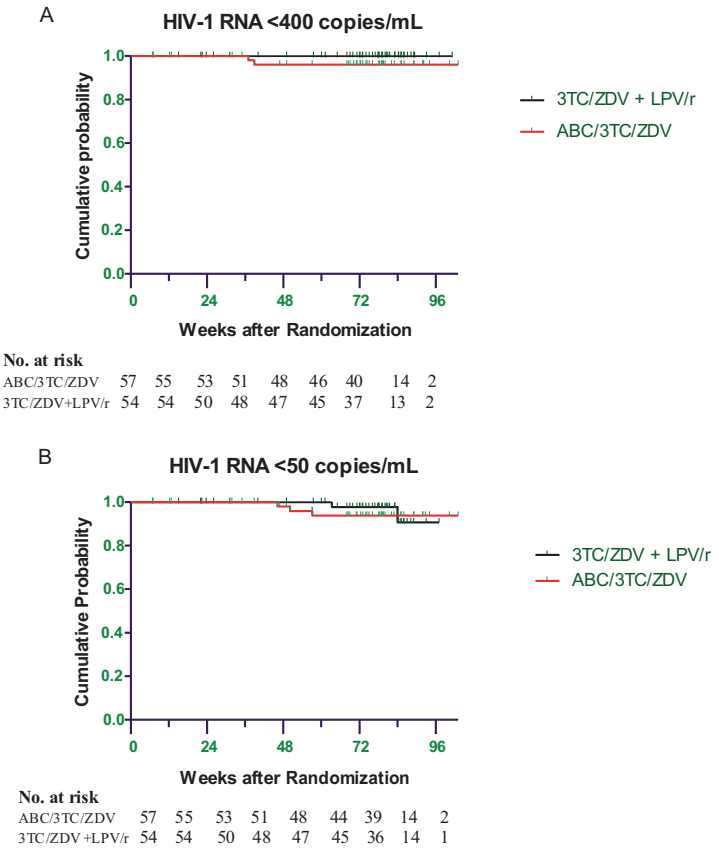

Figure 2. Kaplan-Meier estimates of time virologic failure with HIV-1 RNA <400 copies/ml (Panel A) and HIV-1 RNA <50 copies/ml (Panel B). ABC=abacavir; 3TC=lamivudine; LPV/r=lopinavir/ritonavir; ZDV=zidovudine.

Table 2. Patients with Intermittent Low-Level Viremia (HIV-1 RNA >50 and <400 copies/ml) and Patients with HIV-1 RNA >400 copies/ml (Including Virological Failures) According to Baseline HIV-1 RNA Stratum

HIV-1 RNA at baseline *copies/ml*	**Viremia** *copies/ml*	**3TC/ZDV+LPV/r** *No. of patients (%)*	**ABC/3TC/ZDV** *No. of patients (%)*
<100,000	>50-<400	2 (8)	5 (19)
	>400	0	0
>100,000-<1,000,000	>50-<400	6 (24)	6 (22)
	>400	0	2 (7)
>1,000,000	>50-<400	1 (50)	1 (33)
	>400	0	0
Unknown	>50-<400	0	0
	>400	1 (25	0

ABC=abacavir; 3TC=lamivudine; LPV/r=lopinavir/ritonavir; ZDV=zidovudine.

At week 12 after baseline, total cholesterol values had increased by 21 % *P*<0.0005), low-density lipoprotein (LDL) cholesterol by 11% (*P*<0.0005) , high-density lipoprotein (HDL) cholesterol by 22% (*P*<0.0005) and triglyceride levels by 56% (*P*<0.0005). During the maintenance phase, total cholesterol was significantly higher in the PI group than in the ABC/3TC/ZDV group: 19% at week 96 (*P*<0.0005). Although LDL cholesterol was always higher in the PI group than in the ABC/3TC/ZDV group at the different time points, this difference was not statistically significant at week 96. HDL cholesterol values were also insignificantly higher in the PI group. Triglyceride values were significantly higher in the PI group, with a difference of 54% (*P*<0.0005) at week 96. In the ABC/3TC/ZDV arm all lipid values decreased compared with levels at randomization. Values were only significantly lower for total cholesterol (9.8%; *P*=0.007) and triglycerides (31%; *P*=0.001) for nonfasting subjects at week 96 (Figure 3).

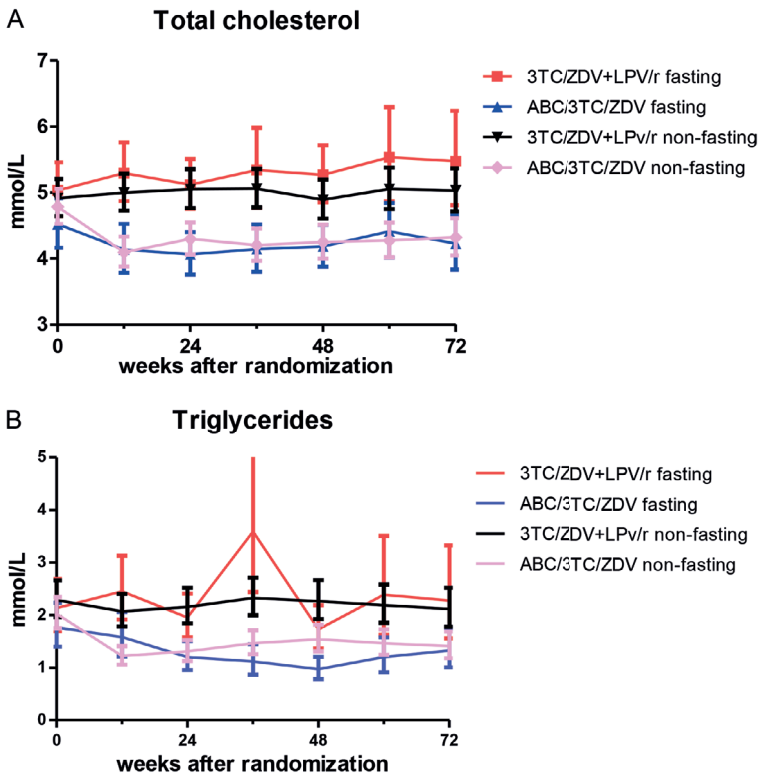

Figure 3. Geometric mean values (95% CI) of total cholesterol (A) and triglyerides (B) during maintenance phase. ABC=abacavir; 3TC=lamivudine; LPV/r=lopinavir/ritonavir; ZDV=zidovudine.

DISCUSSION

This study shows that maintenance therapy with ABC/3TC/ZDV was noninferior to continuation of cART with LPV/r, for virologic outcome HIV-1 RNA >400 and >50 copies/ml for the treatment duration studied, provided that successful viral suppression was achieved with the cART induction regimen. Also in terms of total treatment outcome, the antiviral efficacy of ABC/3TC/ZDV was noninferior to that of the PI-based treatment.

This is the first prospective trial looking at ABC/3TC/ZDV maintenance after a 3-drug two-class induction regimen and the only trial comparing the triple-NRTI regimen with a boosted PI regimen. Two other prospective trials compared ABC/3TC/ZDV as maintenance therapy to a continued 4-drug two-class induction regimen with ABC/3TC/ZDV plus the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV) [9,11]. Here noninferiority was also shown with HIV-1 RNA <50 in 79% of patients in the quadruple arm and 77% in the ABC/3TC/ZDV arm (ITT; M = F; P = 0.7) [11], and 75% and 74%, point estimate of the difference 1% (95% CI: –13 to +14%) [9].

There have been trials in the past that also showed noninferiority of maintenance therapy with triple-NRTI regimens in antiretroviral-naïve patients at the start of their treatment [7,10,16-18]. However, these trials were not completely prospective from the beginning of the cART, and the various PIs used in these studies were predominantly unboosted.

The results of our trial are in line with the conclusions of a recently published Cochrane review of the use of abacavir-based triple-NRTI regimens for maintenance therapy after successful induction therapy with a PI-based regimen [19]. This showed an overall failure rate comparable to that of continuing the PI regimen or to switching to an NNRTI.

There are some caveats with our approach. Patients with higher initial viral loads (strata 2 and 3; HIV-1 RNA >100,000 copies/ml) tended to have less beneficial responses. Both patients with virologic failure in the ABC/3TC/ZDV arm occurred in stratum 2. In both groups we saw patients with intermittent low-level viremia, which also tended to occur more in the patients with higher initial viral loads. Regimens with a boosted PI have a high genetic barrier. The concern with triple-NRTI regimens is that resistance-associated mutations in the presence of viral rebound might be acquired [20]. Our results are consistent with the results of other trials at that time. A comparison between three regimens for ART-naïve patients showed virologic failure in as many as 20-35% and regimen failure in 55-65% after two years [21]. Nowadays the response rate is higher, but because of changes in guidelines, the CD4+ T-cell counts of included patients are higher and HIV-1 RNA levels lower at baseline [22].

In addition, this study has some shortcomings. First, the sample size was limited, as it was based on a noninferiority boundary of 20 percentage points for the difference in proportion of virologic failure.

With a larger sample size a smaller noninferiority boundary would have been detectable. The sample size was also limited because only patients who had HIV-1 RNA < 50 copies/mL by week 18 (or earlier) were eligible for randomization, causing a high dropout rate of patients in the induction phase. Second, the definition of virologic failure with the threshold for HIV-1 RNA of 400 copies/ml, the accepted limit of detection at the time the study was initiated, would now be considered too high. A sample size based on noninferiority for the time to virologic failure defined as HIV-1 RNA >50 copies/ml and HIV-1 RNA <50 copies/ml at 96 weeks as primary outcome would now be considered more appropriate. There was no parametric noninferiority limit defined in the protocol for the difference in the distribution of time to virologic failure. In this study, however, these distributions did not appear to be significantly different between the treatment arms. In analyzing the results of this noninferiority study intention-to-treat as well as per-protocol analyses were performed. Both types of analyses showed noninferiority of ABC/3TC/ZDV to PI. In the protocol (created in 2002) only an intention-to-treat analysis was prescribed. Later, it became generally recognized that an intention-to-treat analysis is too liberal for a noninferiority study as it favors a zero difference result between the treatment arms. That is the reason why per-protocol analyses were also performed [23].

With the current wealth of treatment options, one might wonder whether NRTI-only regimens should still be considered for use. cART only consisting of ABC/3TC/ZDV is generally not recommended as first-line treatment because of suboptimal virologic activity [1]. However, a recent Cochrane review of the use of ABC/3TC/ZDV for initial treatment of HIV infection concluded that this regimen might still be useful, especially in patients with pre-existing hyperlipidemia and those not tolerating ritonavir [24]. The combination of ABC/3TC/ZDV is also considered an acceptable alternative by the World Health Organization (WHO) in selected situations where standard cART is contraindicated or unavailable [25].

In special circumstances, triple-NRTI regimens are potentially advantageous because they have a low pill burden, are well tolerated, have fewer drug interactions, have no dietary restrictions, are available in alternative formulations [26], have a class-sparing effect, and have low costs. Moreover, triple-NRTI regimens can be used successfully in women of child-bearing age and during lactation [27,28]. Some of these advantages can be particularly important for less affluent populations and low-income countries. In addition, most NRTIs, especially ZDV and ABC, are drugs with a good central nervous system penetration, and a high central nervous system penetration-effectiveness (CPE) score as proposed by the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study group [29]. Furthermore, in our study we showed improvement in lipid profiles, especially with regard to total cholesterol and triglycerides. These beneficial metabolic effects have been shown in other induction-maintenance studies both in the treatment-experienced groups [2,4-6] and in antiretroviral-naïve groups [9-11,17]. Because of the increased incidence of cardiovascular disease found for cumulative exposure to PIs [30], these effects on dyslipidemia are an additional advantage. However, thymidine analogue NRTIs are associated with lipoatrophy and reduced insulin sensitivity, whether or not

combined with PIs [14,31,32]. In contrast, ABC or tenofovir disoproxil fumarate are much less associated with lipodystrophy [33,34]. Current exposure to ABC has been associated with an increased risk of myocardial infarction in two large observational cohort studies[35, 36]. Other studies did not confirm these findings [37-39]. Moreover, two recent meta-analyses of randomized, controlled trials indicate that ABC does not have a significant association with myocardial infarction[40,41].

Although NRTI-only regimens are no longer preferred regimens, this study shows that we can safely fall back on an NRTI-only regimen in special circumstances in patients with adequately suppressed HIV replication. Compared with continuing standard cART, such a switch also offers metabolic advantages.

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