

Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment

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Background: Abacavir sulfate/lamivudine (ABC/3TC) and tenofovir DF/emtricitabine (TDF/FTC) are widely used nucleoside reverse transcriptase inhibitors for initial HIV-1 treatment. This is the first completed, randomized clinical trial to directly compare the efficacy, safety, and tolerability of these agents, each in combination with lopinavir/ritonavir in antiretroviral-naive patients.

Methods: Six hundred and eighty-eight antiretroviral-naive, HIV-1-infected patients were randomized in this double-blind, placebo-matched, multicenter, noninferiority study to receive a once-daily regimen of either ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg, both with lopinavir/ritonavir 800 mg/200 mg. Primary endpoints were the proportion of patients with HIV-1 RNA below 50 copies/ml at week 48 (missing = failure, switch included analysis) and the proportion of patients experiencing adverse events over 96 weeks.

Results: At week 48, 68% in the ABC/3TC group vs. 67% in the TDF/FTC group achieved an HIV-1 RNA below 50 copies/ml (intent-to-treat exposed missing = failure, 95% confidence interval on the difference -6.63 to 7.40, $P=0.913$), demonstrating the noninferiority of ABC/3TC to TDF/FTC at week 48. Noninferiority of the two regimens was sustained at week 96 (60% vs. 58%, respectively, 95% confidence interval -5.41 to 9.32, $P=0.603$). In addition, efficacy of both regimens was similar in patients with baseline HIV-1 RNA $\geq 100\,000$ copies/ml or CD4⁺ cell counts below 50 cells/ μ l. Median CD4⁺ recovery (ABC/3TC vs. TDF/FTC, cells/ μ l) was +250 vs. +247 by week 96. Premature study discontinuation due to adverse events occurred in 6% of patients in both groups. Protocol-defined virologic failure occurred in 14% of patients in both groups.

Conclusion: Both ABC/3TC and TDF/FTC provided comparable antiviral efficacy, safety, and tolerability when each was combined with lopinavir/ritonavir in treatment-naive patients.

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AIDS 2009, **23**:000–000

Keywords: abacavir, antiretroviral therapy, emtricitabine, lamivudine, lopinavir, ritonavir, tenofovir

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Received: 18 February 2009; revised: 6 April 2009; accepted: 9 April 2009.

DOI:10.1097/QAD.0b013e32832cbcc2

Introduction

Triple combination highly active antiretroviral therapy containing a protease inhibitor with two nucleoside reverse transcriptase inhibitors (NRTIs) has resulted in dramatic decreases in HIV-1-related morbidity and mortality and is currently considered a standard of care regimen for initial treatment of HIV-1-infected patients [1–4].

No large, randomized clinical trials have been completed to date comparing the two most commonly prescribed, once daily, dual-nucleoside backbones, abacavir sulfate/lamivudine (ABC/3TC) and tenofovir DF/emtricitabine (TDF/FTC), in treatment-naïve patients. The HEAT (HIV Study with Epzicom And Truvada) study was conducted to compare the efficacy and safety of ABC/3TC with TDF/FTC, each in combination with once-daily lopinavir/ritonavir (LPV/r) over 96 weeks.

Methods

Participants

HEAT was a randomized (1 : 1), double-blind, placebo-matched, noninferiority study comparing two once-daily regimens containing a fixed dose combination nucleoside, ritonavir-boosted protease inhibitor, and placebo for the comparator nucleoside. Antiretroviral therapy (ART)-naïve, HIV-1-infected patients, at least 18 years old with plasma HIV-1 RNA ≥ 1000 copies/ml (c/ml) and any CD4⁺ cell count were recruited from the United States and Puerto Rico. Prospective screening of patients for the *HLA-B*5701* allele was not performed. Patients were excluded for the following but not limited to medical conditions compromising patient safety, use of prohibited medications, protocol-specified abnormal laboratory values, and estimated Cockcroft–Gault creatinine clearance below 50 ml/min. Patients were stratified at study entry by screening HIV-1 RNA (<100 000 or $\geq 100 000$ c/ml). The study was approved by ethics review boards at each participating center and conducted in accordance with *Good Clinical Practice*. All patients provided their written informed consent.

Design and interventions

Each participant was randomly assigned to receive ABC/3TC (600 mg/300 mg, Epzicom or Kivexa; Glaxo-SmithKline, Ware, UK) and TDF/FTC placebo or TDF/FTC (300 mg/200 mg, Truvada; Gilead Sciences, Foster City, California, USA) and ABC/3TC placebo, each with open-label LPV/r (800 mg/200 mg, Kaletra; Abbott Laboratories, Abbott Park, Illinois, USA) for 96 weeks. Placebo for ABC/3TC resembled the appearance and weight of the commercial tablet. The TDF/FTC tablet was blinded by overencapsulating both the TDF/FTC placebo and active tablets with tightly

fitted, opaque, soft gelatin capsules. Due to a formulation change in LPV/r shortly after study initiation, all patients received LPV/r six capsules daily (q.d.) from baseline to week 48 followed by four tablets q.d. from weeks 48 to 96. Unblinding of the NRTI was allowed only for patients' safety. Patients who experienced proximal renal tubule dysfunction (PRTD) or a suspected hypersensitivity reaction (HSR) to ABC were allowed to remain in the study after discontinuation of their blinded NRTI and substitution to any approved NRTI other than ABC or TDF. In the event of gastrointestinal intolerance to q.d. LPV/r, patients were allowed to receive LPV/r twice daily (b.i.d.). In cases of treatment-limiting intolerance to LPV/r, patients were permitted to substitute any other approved protease inhibitor and continue in the study; no other antiretroviral substitutions were allowed. Patients with confirmed virologic failure were permitted to continue their randomized regimen only after consultation with the investigator and sponsor.

Procedures and assessments

Patients were evaluated at screening, baseline (day 1), and at weeks 2, 6, 12, 18, 24, 32, 40, 48, 60, 72, 84, and 96, or withdrawal. At each visit, samples for HIV-1 RNA, CD4⁺/CD8⁺ lymphocyte subsets, clinical chemistries, hematology, and urinalysis were collected and analyzed. At baseline, Centers for Disease Control and Prevention classification, hepatitis B and C serology and β -human chorionic gonadotropin (wherever appropriate) were assessed. Herpes simplex virus 2 (HSV-2) serology was assessed at week 48 or later. Plasma HIV-1 RNA concentrations were measured by the Roche Cobas Amplicor HIV-1 Monitor or Ultrasensitive Monitor Test (Roche Diagnostic Systems, Branchburg, New Jersey, USA). Adverse events, concurrent medications, and HIV-associated conditions were assessed at each visit. Adverse events were graded using the 2004 Division of AIDS toxicity grading scale. All suspected ABC HSRs were reported as serious adverse events (SAEs). A sample for viral genotypic and phenotypic analysis was stored at baseline and at all subsequent visits. Viral genotypes and phenotypes were performed at Monogram Biosciences Inc. (South San Francisco, California, USA) on patients meeting protocol-defined virologic failure criteria. Genotypic mutations were defined according to International AIDS Society (IAS)-USA guidelines (August/September 2007) [5]. All other laboratory tests were performed centrally by Quest Diagnostics (Van Nuys, California, USA).

Outcome measures

The primary efficacy endpoint was the proportion of patients with HIV-1 RNA below 50 c/ml at 48 weeks (missing = failure, M = F) and the primary safety endpoint was the incidence of adverse events over 96 weeks. Secondary endpoints included the proportion with HIV-1 RNA below 400 c/ml, change in HIV-1 RNA and CD4⁺ cell counts, time to virologic failure, time to loss of

virologic response (TLOVR), development of genotypic and phenotypic resistance at virologic failure, rate of blinded NRTI discontinuation due to suspected ABC HSR or PRTD, and fasting lipid measures. Virologic failure was defined as either failure to achieve HIV-1 RNA below 200 c/ml or confirmed rebound to ≥ 200 c/ml after reduction to below 50 c/ml by week 24. After week 24, virologic failure was defined as a confirmed HIV-1 RNA rebound to ≥ 200 c/ml.

Statistical analysis

Success was defined as the proportion of patients that achieved an HIV-1 RNA below 50 c/ml. Assuming a 65% success rate in each group at week 48, a targeted sample size of 680 patients (340 patients per arm) provided 90% power (one sided, $\alpha = 0.025$) to establish noninferiority of ABC/3TC to TDF/FTC each in combination with LPV/r. Noninferiority was defined as the lower bound of the two-sided 95% confidence interval (CI) on the treatment difference (ABC/3TC – TDF/FTC) being above –12%.

The primary population for efficacy analyses was the intent-to-treat exposed (ITT-E) population, which included all randomized patients exposed to at least one dose of study medication. In the M is equal to F analysis, all available data were included and missing data were considered failures. Additional analyses for the proportion of patients achieving HIV-1 RNA levels below the lower limits of detection (< 50 and < 400 c/ml) included the Food and Drug Administration-defined TLOVR, observed, and missing/discontinuation is equal to failure (MD = F).

According to the TLOVR algorithm, responders were patients with confirmed viral load below 50 (400) c/ml on two consecutive occasions who had not yet met any nonresponder criterion. Nonresponders were patients who never achieved confirmed viral load below 50 (400) c/ml on two consecutive occasions, prematurely discontinued study and study medication for any reason, had confirmed rebound to ≥ 50 (400) c/ml or had an unconfirmed viral load of ≥ 50 (400) c/ml on their final study visit. The ITT-E observed analysis included all observed data. In the ITT-E, MD is equal to F analysis, patients with missing data or data collected after switching or discontinuation of randomized study medication were considered failures.

For the primary efficacy analysis and the corresponding sensitivity analyses, the treatment response rates (RR) in each group were stratified by the baseline HIV-1 RNA ($< 100\,000$ or $\geq 100\,000$ c/ml) using Mantel–Haenszel weights.

The primary safety population included all randomized patients who consumed at least one dose of study drug and were analyzed by the actual treatment received.

Results

Patient disposition and baseline characteristics

During the recruitment period (July 2005 through June 2006), 694 patients from 78 centers were randomized (Fig. 1). Six patients were randomized but discontinued study prior to receiving any study medication and thus were excluded from the ITT-E population. In total, 66% (455/688) of the ITT-E population completed the 96-week study.

Baseline demographics and characteristics were similar between treatment groups (Fig. 1). The median baseline HIV-1 RNA was $4.9 \log_{10}$ c/ml and median CD4⁺ cell count was 202 cells/ μ l. Notably, 43% of the population had HIV-1 RNA $\geq 100\,000$ c/ml and 19% had a CD4⁺ cell count below 50 cells/ μ l at baseline.

Efficacy results

In the primary efficacy analysis, 68% of patients in the ABC/3TC vs. 67% in TDF/FTC group achieved an HIV-1 RNA below 50 c/ml at week 48 based on stratified response rate using an ITT-E, M is equal to F analysis (95% CI on the treatment difference –6.63 to 7.40), thus establishing the noninferiority of ABC/3TC to TDF/FTC. Sensitivity analyses (ABC/3TC vs. TDF/FTC) using TLOVR (63% vs. 61%), MD is equal to F (64% vs. 62%), and observed analyses of the ITT-E population (84% vs. 87%) demonstrated consistent results at 48 weeks. At week 96, the noninferiority of ABC/3TC to TDF/FTC was maintained as 60% vs. 58% of patients achieved an HIV-1 RNA below 50 c/ml (ITT-E, M = F) (Fig. 2).

Treatment responses by baseline HIV-1 RNA strata were similar between groups at weeks 48 and 96 (Fig. 3). Among patients (ABC/3TC vs. TDF/FTC) with baseline HIV-1 RNA $\geq 100\,000$ c/ml, 63% vs. 65% achieved an HIV-1 RNA below 50 c/ml at week 48 and 56% vs. 58% maintained this endpoint at week 96 using the ITT-E, M is equal to F analysis. Among patients (ABC/3TC vs. TDF/FTC) with baseline HIV-1 RNA below 100 000 c/ml, 71% vs. 69% were below 50 c/ml at week 48 and 63% vs. 58% remained below 50 c/ml at week 96.

At week 96, median CD4⁺ cell count increased by 250 cells/ μ l from baseline in the ABC/3TC group [interquartile range (IQR) = 148–358] and by 247 cells/ μ l in the TDF/FTC group (IQR = 149–359). Median CD4⁺ cell counts at week 96 in the ABC/3TC and TDF/FTC groups were 466 and 445 cells/ μ l, respectively.

Through week 96, 14% of patients in the ABC/3TC vs. 14% in TDF/FTC group met the protocol definition of virologic failure while on study treatment. The median time to protocol-defined virologic failure in the ITT-E population could not be estimated by the Kaplan–Meier method due to the small number of patients with virologic failure.

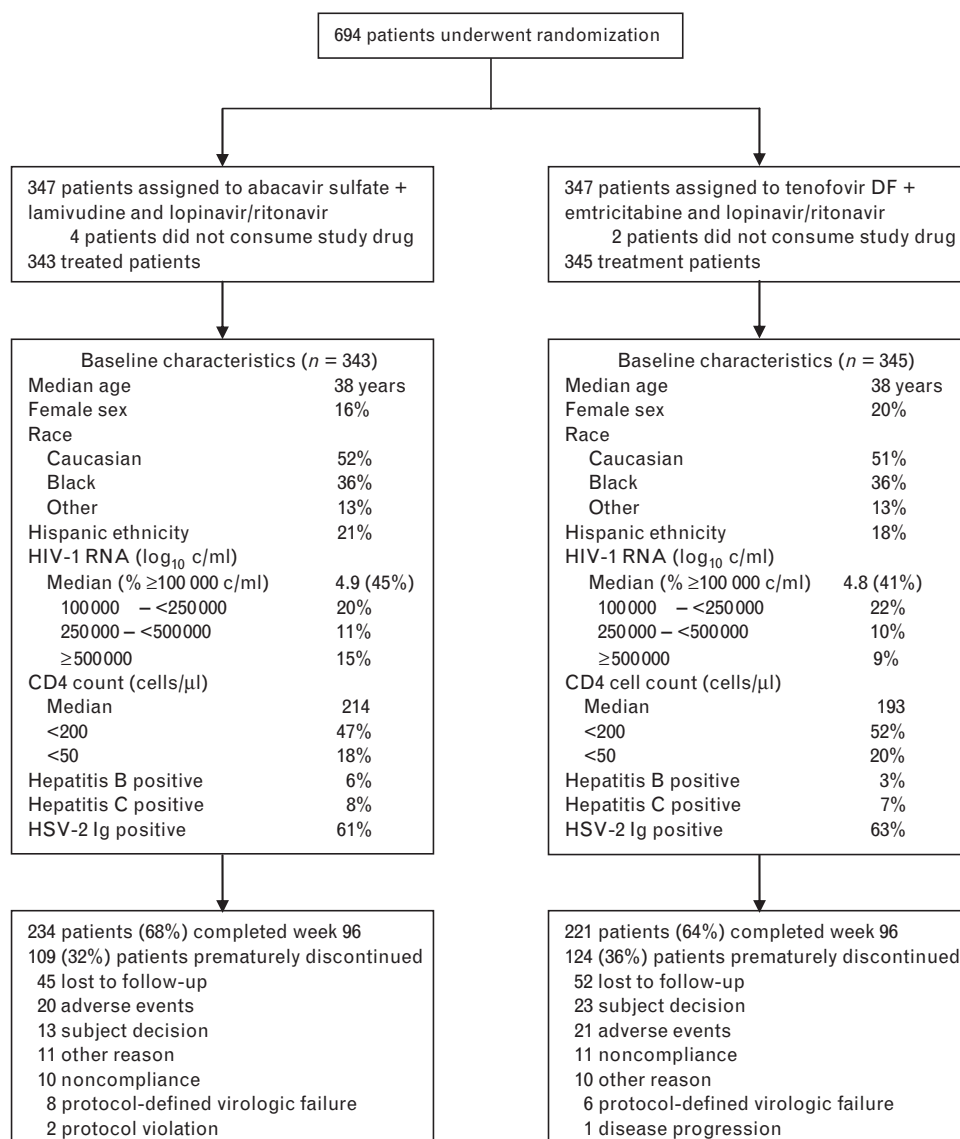


Fig. 1. Patient disposition and characteristics. Each patient self-identified race and ethnicity separately.

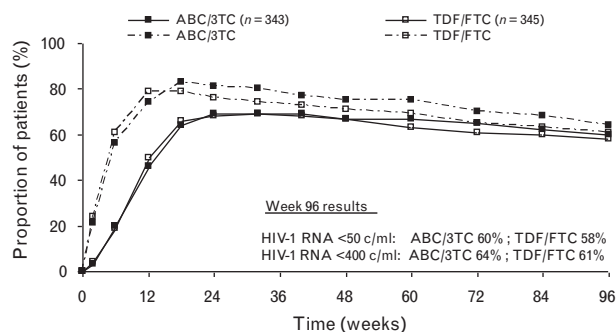


Fig. 2. Proportion of patients with HIV-1 RNA <50 and <400 copies/ml. Proportion of patients with HIV-1 RNA below 50 c/ml (solid line) and below 400 c/ml (dashed line); ITT-E, intent-to-treat exposed; M = F, missing = failure.

Drug-associated resistance as defined by the IAS-USA resistance guidelines was assessed for the 97 patients (14%) with protocol-defined virologic failure (ABC/3TC, 49; TDF/FTC, 48). Eighty-six of these patients had paired baseline and on-treatment samples for genotypic and phenotypic analysis; 40 out of 86 (47%) patients had virus with treatment-emergent mutations. Twenty-eight of 86 (33%) patients had virus with acquired NRTI-associated mutations (ABC/3TC, 11; TDF/FTC, 17); the most common substitution occurred at codon 184, (ABC/3TC, 11; TDF/FTC, 17). Eighteen of 86 (21%) patients acquired minor protease inhibitor-associated mutations (ABC/3TC, 11; TDF/FTC, 7). One patient receiving ABC/3TC acquired primary protease inhibitor resistance. This patient had a documented re-exposure to HIV from a partner who was heavily ART experienced,

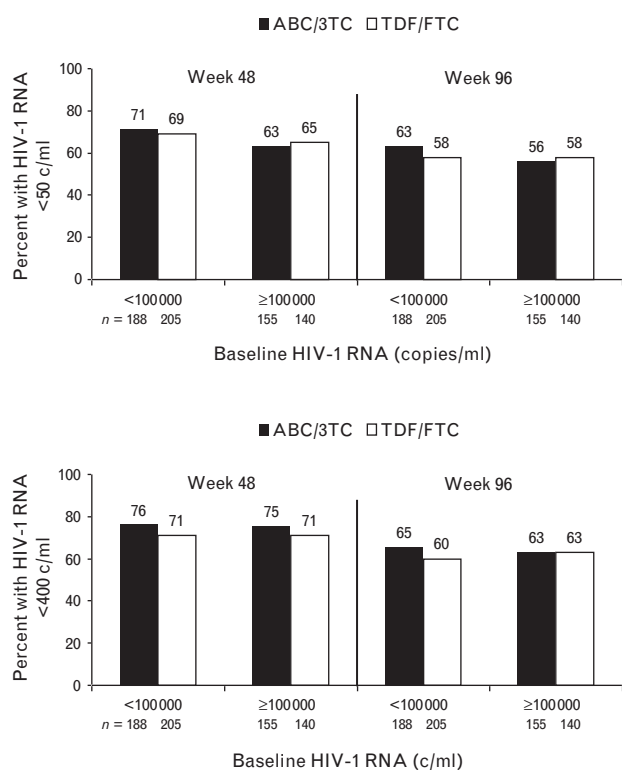


Fig. 3. HIV-1 RNA <50 and <400 copies/ml by baseline viral load (missing = failure). Proportion of patients with HIV-1 RNA below 50 c/ml (top) and below 400 c/ml (bottom), both stratified by baseline HIV-1 RNA.

prior to the virologic failure timepoint. Phenotypic results confirmed these genotypic findings.

Safety results

The safety population was composed of 688 patients (ABC/3TC, 343; TDF/FTC, 345). Median exposure to all study medications was 96 weeks (range 0.1–110 weeks). The proportion of grade 2–4 adverse events was similar between treatment groups over 96 weeks; 80% for each group, and 50% vs. 46% (ABC/3TC vs. TDF/FTC) were considered drug related (Table 1). The most common drug-related grade 2–4 adverse events was diarrhea occurring in 19% of patients in each group; the proportion of grade 3–4 adverse events was similar between groups through week 96; 30% vs. 28% (ABC/3TC vs. TDF/FTC), and 15% were considered drug-related by the investigator in each group. SAEs (exclusive of ABC HSR) were reported in 9% of patients receiving ABC/3TC and 12% of patients receiving TDF/FTC through 96 weeks. Drug-related SAEs occurred in 5% vs. 3% of patients, respectively, the most common of which was suspected ABC HSR (4% ABC/3TC, <1% TDF/FTC) (Table 1). A similar proportion of patients in both groups changed their LPV/r dosing from once daily to b.i.d. due to gastrointestinal intolerance [ABC/3TC, 59 (17%), TDF/FTC, 51 (15%)].

Study withdrawals due to an adverse event were similar between groups [ABC/3TC, 19 (6%), TDF/FTC, 22 (6%)]; events that occurred in more than one patient per group included suspected ABC HSR [2 vs. 0 (<1%)], renal failure [0 vs. 2 (<1%)], diarrhea [1 (<1%) vs. 2 (<1%)], vomiting [1 (<1%) vs. 2 (<1%)], nausea [0 vs. 2 (<1%)], hyperlipidemia [2 (<1%) vs. 1 (<1%)], increased triglycerides [3 (<1%) vs. 2 (<1%)], increased aspartate aminotransferase [2 (<1%) vs. 1 (<1%)], and mycobacterium–avium complex infection [0 vs. 2 (<1%)]. The most common adverse events that led to study withdrawals were related to lipid abnormalities in the ABC/3TC group and gastrointestinal abnormalities in the TDF/FTC group.

Suspected ABC HSR occurred in 17 patients [ABC/3TC, 14 (4%), TDF/FTC, 3 (<1%)], the majority of which were grade 1 or 2 (11/17); five patients were grade 3 (four in ABC/3TC, one in TDF/FTC), no grade 4 ABC HSR was reported (Table 1). One case of ABC HSR in the ABC/3TC arm was graded as ‘not applicable’ by the investigator. Patients with suspected ABC HSR were required to discontinue randomized NRTI; however, study discontinuations due to suspected ABC HSR were rare (<1%). A post-hoc, retrospective analysis of 13 of 17 patients (12 ABC/3TC, one TDF/FTC) with suspected ABC HSR and consent for pharmacogenetic testing showed that seven of 12 (58%) patients receiving ABC/3TC and zero of one patient receiving TDF/FTC were positive for the *HLA-B*5701* allele.

At the last on-treatment study visit, minor changes in glomerular filtration rate (GFR) estimated by either the abbreviated four-variable modification of diet in renal disease (MDRD) equation or Cockcroft–Gault creatinine clearance equations were observed in both treatment arms (Table 2). Progression to a more advanced chronic kidney disease (CKD) stage occurred in 31 of 324 (10%) patients in the ABC/3TC arm vs. 49 of 328 (15%) patients in the TDF/FTC arm at the last on-treatment visit; four in the ABC/3TC arm and 11 in the TDF/FTC arm progressed to stage 3 CKD (eGFR <60 ml/min/1.73 m²). No patient in either treatment arm progressed to stage 4 CKD (eGFR <30 ml/min/1.73 m²). PRTD was assessed for all patients and defined as a confirmed rise in serum creatinine of at least 0.5 mg/dl from baseline and serum phosphate below 2 mg/dl or either of the above accompanied by any two of the following: proteinuria (≥100 mg/dl), glycosuria (≥250 g/dl), low serum potassium (<3 mEq/l), or low serum bicarbonate (<19 mEq/l). Five patients (1%) developed PRTD over 96 weeks in the TDF/FTC group vs. none receiving ABC/3TC. Four men (two whites, one African–American, and one Other race) and one Japanese female patient experienced PRTD at a mean duration of 30 weeks into therapy (range 6–61 weeks). Two patients had confounding risk factors at baseline; one patient was receiving trimethoprim–sulfamethoxazole concurrently

Table 1. Most common drug-related adverse events in at least 5% of patients in any group and all serious adverse events reported by investigators.

Drug-related adverse events	ABC/3TC <i>n</i> = 343 (%)		TDF/FTC <i>n</i> = 345 (%)	
	Grade 2–4	Grade 3–4	Grade 2–4	Grade 3–4
Patients with any drug-related adverse events	171 (50%)	50 (15%)	157 (46%)	52 (15%)
Diarrhea	19%	2%	19%	1%
Nausea	8%	0	6%	<1%
Increased triglycerides	6%	2%	6%	3%
Increased cholesterol	7%	1%	4%	1%
Decreased GFR	5%	2%	5%	2%
Suspected ABC HSR ^{a,b}	3%	1%	<1%	<1%

Drug-related SAEs (fatal + nonfatal)	ABC/3TC <i>n</i> = 343 <i>n</i> (%)	TDF/FTC <i>n</i> = 345 <i>n</i> (%)
Patients with any drug-related serious adverse events	18 (5)	10 (3)
Suspected ABC HSR	14 (4)	3 (<1)
Immune reconstitution syndrome	2 (<1)	0
Anemia	1 (<1)	1 (<1)
Renal failure	0	2 (<1)
Hepatotoxicity ^c	1 (<1)	0
Sepsis	0	1 (<1)
Decreased creatinine renal clearance	0	1 (<1)
Pulmonary embolism ^{d,e}	1 (<1)	2 (<1)
Deep vein thrombosis ^e	0	1 (<1)

ABC/3TC, abacavir sulfate/lamivudine; GFR, glomerular filtration rate; HSR, hypersensitivity reaction; SAEs, serious adverse events; TDF/FTC, tenofovir DF/emtricitabine.

^aProspective *HLA-B*5701* screening was not performed in this study.

^bSuspected ABC HSR is included for completeness in this table. However, two cases of suspected ABC HSR were recorded as grade 1 and not applicable, respectively, by the study investigator are excluded in this table.

^cPatient was coinfecting with hepatitis B.

^dPulmonary embolism was considered a serious adverse event, regardless of whether it was reported as serious by the investigator. Included are one patient on ABC/3TC reported to have a serious, nondrug-related grade 2 event and two patients on TDF/FTC (one reported to be a serious and drug-related grade 4 event, and the other reported as a nonserious, nondrug-related grade 4 event).

^eOne patient in the TDF/FTC group had both pulmonary embolism and deep vein thrombosis, which were judged by the investigator as treatment-related; additional follow-up by medical monitor could not determine if proposed causality was associated with timing of events or other mechanism.

Eight patients died during the study, none were judged by investigators as drug related (one ABC/3TC, head trauma following a fall; seven TDF/FTC, pneumonia, gastrointestinal hemorrhage, cardiopulmonary failure after larynx surgery, disseminated mycobacterium infection, exacerbation of chronic obstructive pulmonary disease and respiratory failure, progressive multifocal leukoencephalopathy, and AIDS in a patient with heavy ethanol use and depression).

and one patient was coinfecting with hepatitis C. The mean age of these patients was 46 years (range 35–60 years) with a median baseline eGFR (MDRD) of 83 ml/min/1.73 m² (range 61–177). Of the five patients, two switched to another nucleoside backbone, four recovered from the event, but recovery status was unknown for one patient who discontinued study prematurely. Only two patients who developed PRTD completed the study, reasons for early discontinuation in the other three patients included patient's decision to withdraw, adverse events, and loss to follow-up.

Treatment-emergent elevations in serum aminotransferases were more common in patients with evidence of coinfection with hepatitis B, C, or both. Grade 3/4 ALT elevations were observed in less than 1% (3/295 in ABC/3TC and 2/306 in TDF/FTC) of patients without coinfection compared with 9% (5/45 in ABC/3TC and 2/33 in TDF/FTC) of patients coinfecting with hepatitis B, C, or both in both treatment groups.

Both groups showed similar changes from baseline in fasting lipid values at week 96 (Table 2). Elevations in

cholesterol and triglycerides were seen in both groups; however, the total cholesterol:high-density lipoprotein (HDL) ratio was essentially unchanged. One hundred and twenty-one patients (18%) received one or more lipid-lowering medication(s) during the study: 20% in the ABC/3TC and 15% in the TDF/FTC group. Eighteen patients (11 in ABC/3TC and seven in TDF/FTC) were receiving lipid-lowering medications prior to study participation and continued the medications in the study.

Cardiovascular and biomarker results

Six patients had a cardiovascular event during this study (2, ABC/3TC; 4, TDF/FTC); none were considered related to study drug. Two events occurred in two separate patients receiving ABC/3TC, chest pain in a patient with history of angina and hypertension and transient ischemic attack (TIA) in another patient with a history of hypertension and hypertriglyceridemia. Four events occurred in four separate patients receiving TDF/FTC; cardiac arrest following a cocaine overdose, severe aggravated heart failure with congestive heart failure precipitated by worsening renal insufficiency, cerebrovascular accident in a patient with history of smoking, and

Table 2. Laboratory parameters of interest.

Median (mg/dl)	ABC/3TC n = 343			TDF/FTC n = 345				
	Number tested (baseline, week 96)	Baseline	Week 96	Median Δ	Number tested (baseline, week 96)	Baseline	Week 96	Median Δ
Lipids								
Total cholesterol:	278, 204	4.41 (1.70–40)	4.07 (1.72–18.25)	–0.27	286, 187	4.45 (1.81–89)	4 (2.04–12.13)	–0.44
HDL ratio								
Total cholesterol	279, 205	158 (71–264)	202 (106–334)	36	286, 188	159 (59–297)	186 (97–297)	28
HDL-cholesterol	278, 204	36 (3–80)	47 (8–137)	10	286, 189	35 (2–93)	47 (8–96)	12
LDL-cholesterol	261 186	93 (4–197)	107 (10–222)	9	270, 172	92 (0–221)	94 (42–201)	8
Triglycerides	279, 205	122 (34–1153)	187 (54–1209)	54	286 188	134 (40–968)	180 (53–1191)	42
Non-HDL-cholesterol ^a	278, 204	123 (37–227)	150 (63–297)	25	286, 188	123 (39–239)	140 (71–258)	18
Metabolic								
Glucose	343, 236	90 (46–286)	90 (28–383)	–1	344, 219	89 (61–576)	89 (47–266)	1
Insulin (μU/ml)	323, 228	10 (1–158)	8 (1–438)	–1	330, 213	10 (1–95)	7 (1–204)	–2
Renal								
MDRD GFR (ml/min/1.73 ^b)	339, 325	88 (36–208)	93 ^b (36–180)	0 ^c	340, 333	87 (44–177)	88 ^b (30–176)	0
C–G GFR (ml/min)	339, 325	103 (35–281)	112 ^b (46–292)	7 ^c	340, 333	100 (45–211)	103 ^b (35–282)	4
Biomarkers								
sVCAM-1 (ng/ml)	241, 211	–49	–51		228, 202	–48	–50	
IL-6 (pg/ml)	220, 192	–26	–19		220, 197	–23	–25	
hs-CRP (mg/l)	235, 205	–12	–5		224, 199	–20	–17	

Median (range) values for fasting lipids, metabolic parameters, GFR, and biomarkers. ABC/3TC, abacavir sulfate/lamivudine; GFR, glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; HSR, hypersensitivity reaction; IL-6, interleukin 6; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease; SAEs, serious adverse events; sVCAM-1, soluble vascular cellular adhesion molecule-1; TDF/FTC, tenofovir DF/emtricitabine.

^aNon-HDL-cholesterol was calculated by subtracting HDL-cholesterol from total cholesterol.

^bValue was obtained at week 96 or at last observation while patient was still on randomized treatment.

^cMedian change at week 96 or at last observation while patient was still on randomized treatment.

TIA in a patient with history of hypertension and hypertriglyceridemia. Additionally, one patient with a history of hypertension and 30 years of smoking reported a nonserious cardiovascular event of peripheral vascular disease in the ABC/3TC group.

A post-hoc exploratory analysis was undertaken to assess three markers of inflammation, high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and soluble vascular cellular adhesion molecule-1 (sVCAM-1). Data from patients with matched samples at baseline and either week 48 or 96 were analyzed to determine changes from baseline. The percentage change (ABC/3TC vs. TDF/FTC) in biomarker geometric mean concentrations from baseline to week 48 was (−12% vs. −20%, hs-CRP), (−26% vs. −23%, IL-6), and (−49% vs. −48%, sVCAM-1) and from baseline to week 96 was (−5% vs. −17%, hs-CRP), (−19% vs. −25%, IL-6), and (−51% vs. −50%, sVCAM-1). Decreases were noted at each postbaseline timepoint for all three markers and the declines between treatment groups for all assessments were not significantly different (Table 2).

Discussion

This was the first large, randomized comparison of the only two once-daily dual-nucleoside combinations for initial HIV-1 therapy, each in combination with LPV/r. ABC/3TC was noninferior to TDF/FTC and no differences in potency or immunologic response between groups in the overall population or by baseline viral load strata (< or $\geq 100\,000$ c/ml) was observed through 96 weeks.

The 63% response rate in the ABC/3TC arm with entry viral load $\geq 100\,000$ c/ml was consistent with the 59–69% response rate of similar patients who achieved an HIV-1 RNA below 50 c/ml at 48 weeks using a M is equal to F analysis when ABC + 3TC was combined with either efavirenz (EFV) or a boosted protease inhibitor [6–9]. A lower treatment response rate or increased time to reach undetectable viral load is not unexpected in patients with baseline viral load of $\geq 100\,000$ vs. below 100 000 c/ml. In two recent studies of boosted protease inhibitors, a lower virologic response was observed among TDF/FTC-treated patients with baseline viral load of $\geq 100\,000$ c/ml [10,11].

Direct head-to-head comparisons of ABC/3TC with TDF/FTC are limited. The ongoing AIDS Clinical Trials Group study, A5202, compares ABC/3TC and TDF/FTC with either atazanavir/ritonavir (ATV/r) or EFV. The high viral load cohort ($\geq 100\,000$ c/ml at screening) from this study was unblinded based on a recommendation from the data safety monitoring board noting a shorter time to virologic failure in those patients taking ABC/3TC [12]. The A5202 study differed from the

HEAT study in several ways, including use of ATV/r or EFV as the third agent, virologic failure definition, primary endpoint, and management of adverse events; the impact of these differences on the results is unknown.

Recently, results of four smaller, nonrandomized studies comparing ABC/3TC or TDF/FTC-based therapy with other boosted protease inhibitors or nonnucleosides in previously ART-naïve or experienced patients were presented. Study populations were stratified by baseline HIV-1 RNA (<100 000 or $\geq 100\,000$ c/ml) and no difference in virologic response to HIV-1 RNA below 50 c/ml at week 24 or 48 were reported [13–16]. Suspected ABC HSR was relatively uncommon (4%) compared to previous studies in which prospective *HLA-B*5701* screening was not performed [28,29]. In the Atazanavir Ritonavir Induction-Simplification with Epzicom Study (ARIES), prospective use of *HLA-B*5701* screening identified patients at highest risk of experiencing an ABC HSR and demonstrated that the rate of HSR could be decreased by using prospective testing. In the HEAT study, prospective *HLA-B*5701* screening may have lowered the incidence of ABC HSR in the ABC/3TC group from 4% to less than 1% [17].

Both regimens in this study were well tolerated with similar rates of treatment discontinuation. Gastrointestinal disturbances were more common with TDF/FTC; lipid abnormalities were more common with ABC/3TC. Although the non-HDL ratio remained below five for both treatment groups, a greater increase in total cholesterol, triglycerides, and low-density lipoprotein were observed among patients receiving ABC/3TC.

PRTD was reported in a small number of patients in the TDF/FTC group through 96 weeks, consistent with recent case reports [18–23] of tubulopathy, including Fanconi syndrome in the literature. Two patients with acute renal failure were discontinued from the TDF/FTC arm. At the last on treatment visit, 11 vs. four patients in the TDF vs. ABC arms, respectively, progressed to stage 3 CKD. Most of these patients had confounding factors such as pre-existing systemic or renal disease.

Because of the unexpected finding from observational cohort studies [24,25] of increased myocardial infarction and cardiovascular disease (CVD) risk among patients starting ABC-containing regimens, we reviewed all cardiovascular events that occurred in the HEAT study. Few cardiovascular events were reported and none were judged by investigators as being related to the study drug. Additionally, all were confounded by concurrent medical conditions, risk factors for CVD, or both. Although information was not available to calculate cardiac risk for patients in the trial, a retrospective analysis of three inflammatory markers (hs-CRP, IL-6, and sVCAM-1) associated with cardiovascular risk was conducted, demonstrating similar declines in both groups. These

results do not support a hypothesis of increased cardiovascular risk mediated through increases in inflammatory markers for either ABC/3TC or TDF/FTC.

Similar rates of protocol-defined virologic failure were observed between treatment groups. Treatment-emergent drug resistance was assessed for 86 of 97 patients, with protocol-defined virologic failure and available data during the course of the study. The rate of NRTI-acquired resistance detected in the ABC/3TC treatment group is consistent with previous studies of comparable treatment regimens, but the rate of acquired NRTI resistance detected in the TDF/FTC treatment group was higher than reported in previous studies using TDF/FTC with boosted PIs [6,26,27].

The results of the HEAT study demonstrate that ABC/3TC and TDF/FTC, each in combination with LPV/r, are highly effective initial regimens regardless of baseline viral load or CD4⁺ cell count. Long-term virologic, immunologic, safety, tolerability, and antiretroviral resistance for ABC/3TC were similar to those with TDF/FTC over 96 weeks. In this study, both ABC/3TC and TDF/FTC proved to be effective and well tolerated backbones for initial ART.

Acknowledgements

The study was sponsored by GlaxoSmithKline (GSK). The authors would like to thank the patients, study investigators, study coordinators, and GSK study-monitoring group for their contributions to this study. We also thank Abbott Laboratories for providing Kaletra at a reduced price. We also thank the GlaxoSmithKline study team members: A. Cameron, J. Warren, S. Gooding, M. Moore, Qiming Liao, B. Wine, E. Blackmon, R. Torres, G. Lingashastry, C. Stainsby, N. Curristin, P. Gupta, M. Daniel, C. Stone, C. Craig, S. Chriscoe, J. Bond, C. Brothers, M. Gartland, J. Heilman, and C. Hill-Zabala.

HEAT study Investigators: K. Abriola, T. Adeyemi, B. Akil, S. Ambardar, J. Bellizzi, N. Bellos, D. Berger, G. Blick, M. Borucki, F. Bredeek, C. Brinson, W. Burman, A. Burnside, J. Cade, B. Casanas, G. Coodley, P. Cook, R. Corales, M. Cuenca, R. Dretler, J. Duggan, R. Elion, M. Fischl, F. Garcia, E. Godofsky, S. Green, R. Greenberg, S. Hall, A. Huang, R. Jones, P. Kadlecik, P.N. Kumar, P. Lackey, S. Lalla-Reddy, A. LaMarca, C. Lucasti, M. Markowitz, C. Mayer, C. McDonald, D. McDonough, A. Mestre, A. Mills, M. Mogyros, J. Morales, R. Myers, R. Nahass, C. Newman, R. Novak, J. Parada, D. Parks, D. Pitrak, M. Ramgopal, G. Richmond, S. Roberts, A. Rodriguez, J. Rodriguez, P. Salvato, L. Santiago, K. Sathasivam, S. Schneider, R. Schwartz, R. Scott, A. Scribner, G. Sepulveda-Arzola, G. Simon, S.

Sisneros, J. Slim, L. Sloan, M. Thompson, G. Townsend, M. Van den Berg-Wolf, T. Vanig, V. Vega, J. Wade, C. Walworth, W. Weinberg, M. Weinert, B. Young, and C. Zurawski.

Kimberly Y. Smith has served as a speaker and advisor and received honoraria from the following companies: GlaxoSmithKline, Abbott, Bristol-Myers-Squibb, Gilead, Merck, Tibotec, Pfizer, and Boehringer Ingelheim. Derek Fine has served as a speaker and advisor and has received honoraria from GlaxoSmithKline. Nicholas Bellos has served as a speaker, advisor, and has received research support from GlaxoSmithKline, Abbott, and Tibotec. Louis Sloan has served as a speaker for Merck, Pfizer, and Schering Plough. Philip Lackey has no financial or potential conflicts of interest to disclose. Princy N. Kumar has served as a speaker, and received research support from GlaxoSmithKline and Merck. Parul Patel, Denise H. Sutherland-Phillips, Cindy Vavro, Linda Yau, Paul Wannamaker, and Mark S. Shaefer are all employees of GlaxoSmithKline.

The sponsor developed the study design with input from prospective investigators and analyzed the data. Substantial contributions to study conception, design, analysis, and interpretation of the data were made by K.Y.S., D.F., P.P., L.Y., C.V., D.S.P., M.S.S., and P.W. Substantial contributions to acquisition of data and critical review of the manuscript were made by N.B., L.S., P.L., and P.N.K.. All authors had full access to the data and vouch for the accuracy and completeness of the data and analyses. The manuscript was written and approved by all of the authors, each of whom contributed to drafts and revisions.

The ClinicalTrials.gov registration number for the HEAT study (EPZ104057) was NCT00244712.

Data in this article were previously presented in part at the 15th Conference on Retroviruses and Opportunistic Infections in February 2008 (48-week data) and at the 17th International AIDS Conference in August 2008 (96-week data).

References

1. Crum NF, Riffenburgh RH, Wegner S, Agan BK, Tasker SA, Spooner KM, *et al.* **Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre, early, and late HAART (highly active antiretroviral therapy) eras.** *J Acquir Immune Defic Syndr* 2006; **41**:194–200.
2. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, *et al.* **Decline in the AIDS and death rates in the EuroSIDA study: an observational study.** *Lancet* 2003; **362**:22–29.
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services; 2008. pp. 1–139. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. [Accessed 1 December 2008].

4. Hammer SM, Eron JJ, Reiss P, Schooley RT, Thompson MA, Walmsley S, *et al.* **Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel.** *JAMA* 2008; **300**:555–570.
5. Hirsch MS, Gunthard HF, Schapiro JM, Brun-Vezinet F, Clotet B, Hammer SM, *et al.* **Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel.** *Clin Infect Dis* 2008; **47**:266–285.
6. Eron JJ, Yeni P, Gathe J Jr, Estrada V, DeJesus E, Staszewski S, *et al.* **The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised noninferiority trial.** *Lancet* 2006; **386**:476–482.
7. Gallant JE, Rodriguez AE, Weinberg WG, Young B, Berger DS, Lim ML, *et al.* **Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects.** *J Infect Dis* 2005; **192**:1921–1930.
8. Markowitz M, Hill-Zabala C, Lang J, DeJesus E, Liao Q, Lanier ER, *et al.* **Induction with abacavir/lamivudine/zidovudine plus efavirenz for 48 weeks followed by 48-week maintenance with abacavir/lamivudine/zidovudine alone in antiretroviral-naive HIV-1-infected patients.** *J Acquir Immune Defic Syndr* 2005; **39**:257–264.
9. Moyle GJ, DeJesus E, Cahn P, Castillo SA, Zhao H, Gordon DN, *et al.* **Abacavir once or twice daily combined with once-daily lamivudine and efavirenz for the treatment of antiretroviral-naive HIV-1-infected adults: results of the ziagen once daily in Antiretroviral Combination Study.** *J Acquir Immune Defic Syndr* 2005; **38**:417–425.
10. Ortiz R, DeJesus E, Khanlou H, Voronin E, van Lunzen J, Andrade-Villanueva J, *et al.* **Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48.** *AIDS* 2008; **22**:1389–1397.
11. Molina JM, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, *et al.* **Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study.** *Lancet* 2008; **372**:646–655.
12. Sax P, Tierney C, Collier A, Fischl M, Godfrey C, Jahed N, *et al.* **ACTG 5202: shorter time to virologic failure (VF) with abacavir/lamivudine (ABC/3TC) than tenofovir/emtricitabine (TDF/FTC) as part of combination therapy in treatment-naive subjects with screening HIV RNA $\geq 100,000$ c/ml** [abstract #THAB0303]. *17th International AIDS Conference*; Mexico City, Mexico; 2008.
13. Wolf E, Trein A, Schmidt W, Baumgarten A, Jaeger H, Stellbrink HJ. **Similar virological response rates for ART-naive subjects starting KVV + LPV/r or TVD + LPV/r: data from the prospective observational STAR cohort** [abstract #P7]. *9th International Congress on Drug Therapy in HIV Infection*; Glasgow, Scotland; 2008.
14. Eccleston KJ, Bambumba A, Babu CS, Ahmed S, Lee V. **Efficacy and safety of tenofovir/emtricitabine compared to abacavir/lamivudine in HIV-1 infected patients in clinical setting: the TEAL study** [abstract #P79]. *9th International Congress on Drug Therapy in HIV Infection*; Glasgow, Scotland; 2008.
15. Daniels RH, Gazzard BG, Holmes P, Scourfield A, Bower M, Nelson M. **Comparing the efficacy of Truvada and Kivexa combination therapy in HAART-naive individuals with different viral loads** [abstract #P14]. *9th International Congress on Drug Therapy in HIV Infection*; Glasgow, Scotland; 2008.
16. Das S, Arumainayagam J, Kumari B, Chandramani S, Riddell L, Ghanem M. **The TOKEN study: safety and efficacy of Truvada or Kivexa in combination with efavirenz in treatment-naive predominantly black African HIV patients** [abstract #P15]. *9th International Congress on Drug Therapy in HIV Infection*; Glasgow, Scotland; 2008.
17. Young B, Squires K, Patel P, DeJesus E, Bellos N, Berger D. **First large, multicenter, open-label study utilizing HLA-BM5701 screening for abacavir hypersensitivity in North America.** *AIDS* 2008; **22**:1673–1681.
18. Verhelst D, Monge M, Meynard J, Fouqueray B, Mougenot B, Girard PM, *et al.* **Fanconi syndrome and renal failure induced by tenofovir: a first case report.** *Am J Kidney Dis* 2002; **40**:1331–1333.
19. Karras A, Lafaurie M, Furco A, Bourgarit A, Droz D, Sereni D, *et al.* **Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome and nephrogenic diabetes insipidus.** *Clin Infect Dis* 2003; **36**:1070–1073.
20. Zimmerman A, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. **Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions.** *Clin Infect Dis* 2006; **42**:283–290.
21. Guest J, Rimland D, Patterson B, Desilva K. **Tenofovir-induced nephrotoxicity in the first year of therapy** [abstract #778]. *13th Conference on Retroviruses and Opportunistic Infections*; Denver, Colorado; 2006.
22. Heffelfinger J, Hanson D, Voetsch A, McNaghten A, Sullivan P. **Renal impairment associated with the use of tenofovir** [abstract #779]. *13th Conference on Retroviruses and Opportunistic Infections*; Denver, Colorado; 2006.
23. Kapitsinou PP, Ansari N. **Acute renal failure in an AIDS patient on tenofovir: a case report.** *J Med Case Reports* 2008; **2**:94.
24. Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, *et al.* **Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study.** *Lancet* 2008; **371**:1417–1426.
25. Lundgren JD, Neuhaus J, Babiker A, Cooper D, Duprez D, El-Sadr W, *et al.*, for the SMART/INSIGHT and the D:A:D Study groups. **Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients.** *AIDS* 2008; **22**:F17–F24.
26. Molina JM, Podsadecki TJ, Johnson MA, Wilkin A, Domingo P, Myers R, *et al.* **A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks.** *AIDS Res Hum Retroviruses* 2007; **23**:1505–1514.
27. Gathe J, da Silva BA, Cohen DE, Loutfy MR, Podzamczar D, Rubio R, *et al.* **A once-daily lopinavir/ritonavir-based regimen is noninferior to twice-daily dosing and results in similar safety and tolerability in antiretroviral-naive subjects through 48 weeks.** *J Acquir Immune Defic Syndr* 2009; **50**:474–481.
28. Epzicom package insert, GlaxoSmithKline, March 2009.
29. DeJesus E, Herrera G, Teofilo E, Gerstoff J, Buendia CB, Brand JD, *et al.* **Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults.** *Clin Infect Dis* 2004; **39**:1038–1046.