

# Efavirenz versus Boosted Atazanavir or Zidovudine and Abacavir in Antiretroviral Treatment–Naive, HIV-Infected Subjects: Week 48 Data from the Altair Study

Rebekah L. Puls,<sup>1</sup> Preeyaporn Srasuebkul,<sup>1</sup> Kathy Petoumenos,<sup>1</sup> Christoph Boesecke,<sup>1</sup> Chris Duncombe,<sup>3</sup> Waldo H. Belloso,<sup>4</sup> Jean-Michel Molina,<sup>5</sup> Lin Li,<sup>6</sup> Anchalee Avihingsanon,<sup>3</sup> Brian Gazzard,<sup>7</sup> David A. Cooper,<sup>1,2</sup> and Sean Emery<sup>1</sup> for the Altair Study Group<sup>a</sup>

<sup>1</sup>Coogee Campus, Coogee, and <sup>2</sup>St Vincent's Centre for Applied Medical Research, Darlinghurst, National Centre in HIV Epidemiology and Clinical Research, Faculty of Medicine, University of New South Wales, Australia; <sup>3</sup>HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand; <sup>4</sup>Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; <sup>5</sup>Department of Infectious Diseases, Saint Louis Hôpital, Paris, France; <sup>6</sup>Infectious Diseases Research Centre, Tan Tock Seng Hospital, Singapore; and <sup>7</sup>Department of HIV/GUM Medicine, St. Stephen's Centre, Chelsea and Westminster Hospital, London, United Kingdom

**Background.** Antiretroviral therapy is complicated by drug interactions and contraindications. Novel regimens are needed.

**Methods.** This open label study randomly assigned treatment-naive, human immunodeficiency virus (HIV)–infected subjects to receive tenofovir-emtricitabine with efavirenz (Arm I), with ritonavir-boosted atazanavir (Arm II), or with zidovudine/abacavir (Arm III). Pair-wise comparisons of differences in time-weighted mean change from baseline plasma HIV-RNA to week 48 formed the primary analysis. Treatment arms were noninferior if the upper limit of the 95% confidence interval (CI) was  $<0.5 \log_{10}$  copies/mL. Secondary objectives included virologic, immunologic and safety end points.

**Results.** The intention-to-treat population comprised 322 patients (Arm I,  $n = 114$ ; Arm II,  $n = 105$ ; and Arm III,  $n = 103$ ). Noninferiority for the primary end point was established. Analysis for superiority showed that Arm III was significantly less potent than Arm I ( $-0.20 \log_{10}$  copies/mL; 95% CI,  $-0.39$  to  $-0.01 \log_{10}$  copies/mL;  $P = .038$ ). The proportions of patients on each of Arm I (95%) and Arm II (96%) with  $<200$  copies/mL were not different ( $P = .75$ ), but the percentage of patients in Arm III with  $<200$  copies/mL (82%) was significantly lower ( $P = .005$ ). CD4+ cell counts did not differ. Serious adverse events were more frequent in Arm III ( $n = 30$ ) than in Arm I or Arm II ( $n = 15$  for each;  $P = .062$ ).

**Conclusions.** A novel quadruple nucleo(t)side combination demonstrated significantly less suppression of HIV replication, compared with the suppression demonstrated by standard antiretroviral therapy regimens, although it did meet the predetermined formal definition of noninferiority. Secondary analyses indicated statistically inferior virologic and safety performance. Efavirenz and ritonavir-boosted atazanavir arms were equivalent in viral suppression and safety.

The success of long-term treatment with combination antiretroviral therapy (ART) is increasingly intertwined with safety and tolerability issues. Healthcare providers

and patients prefer simple regimens that support long-term compliance and preserve future treatment options. Currently recommended first-line therapy is 2 nucleo(t)side analog reverse-transcriptase inhibitors (NtRTIs) with either a nonnucleoside reverse-transcriptase inhibitor, a ritonavir-boosted protease inhibitor, or raltegravir, an integrase inhibitor [1].

Received 13 April 2010; accepted 28 June 2010; electronically published 24 August 2010.

Reprints or correspondence: Rebekah L. Puls, National Centre in HIV Epidemiology and Clinical Research, Faculty of Medicine, University of New South Wales, 45 Beach St, Coogee, New South Wales, Australia, 2034 (rpuls@ncheer.unsw.edu.au).

**Clinical Infectious Diseases** 2010;51(7):855–864

© 2010 by the Infectious Diseases Society of America. All rights reserved.  
1058-4838/2010/5107-0016\$15.00

DOI: 10.1096/656363

The views expressed in this publication do not necessarily represent the position of the Australian government.

Presented in part: 5th International AIDS Society Conference, Cape Town, South Africa, July 2009 (abstract LBPE09).

<sup>a</sup> Members of the study group are listed at the end of the text.

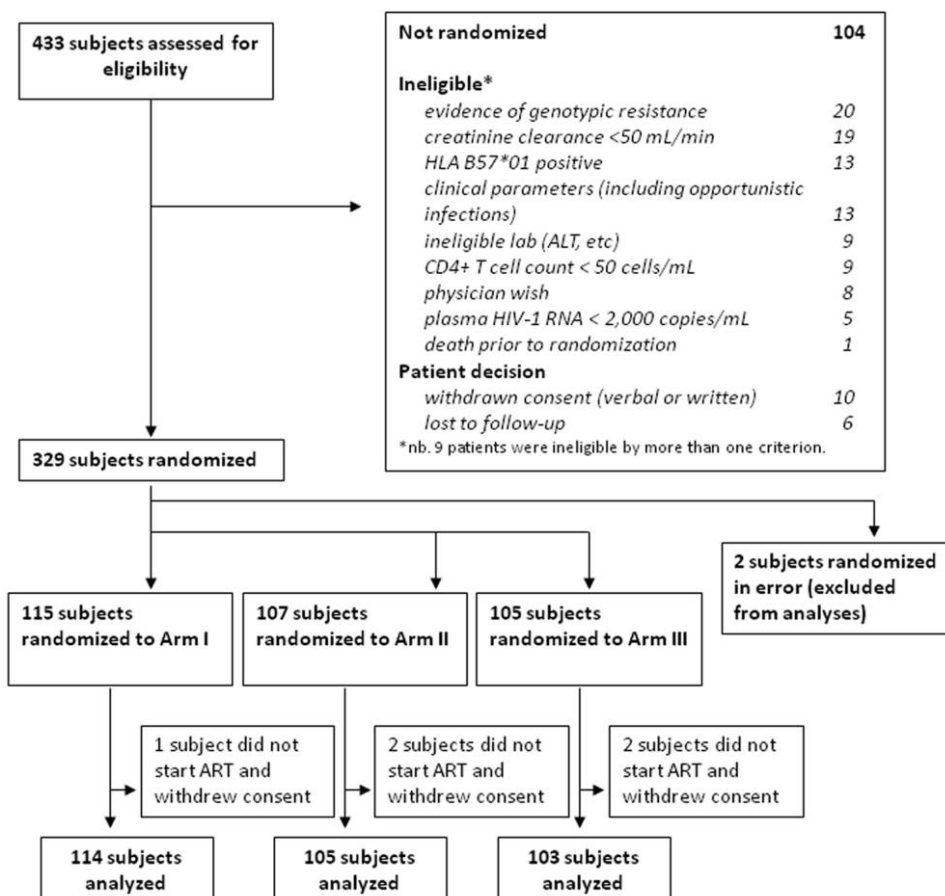


Figure 1. Participant disposition.

These recommendations are troublesome for a number of patients: those requiring tuberculosis treatment [2–8] or opiate replacement [9] and pregnant women [10–12]. This is particularly true for countries in the developing world. Regimens comprising NtRTIs alone are attractive because they are not cautioned in these settings. Such class-sparing regimens may achieve maximal virologic suppression and thus may prevent resistance development, particularly where limited options for constructing sequential regimens exist.

Lower levels of antiretroviral potency and association with rapid selection of human immunodeficiency virus (HIV) drug resistance were indicated in clinical studies assessing triple NtRTI therapy in naive patients [13–17]. In pilot studies including regimens containing tenofovir (TDF), adequate virologic efficacy and safety resulted in renewed interest in NtRTI regimens of combination ART [18–20], but concerns remain. Although potent antiretroviral activity was demonstrated, responses to triple NtRTIs were less sustained, compared with the responses of more traditional combination ART [19, 21]. A randomized study of quadruple NtRTIs demonstrated comparable virologic suppression with an efavirenz (EFV)–containing comparator [21]. By including zidovudine (ZDV) in a

TDF-containing regimen, the study team reasoned that K65R mutation selection would be inhibited [22–24]. Although not powered for conventional end points, the authors believed that observed virologic responses warranted evaluation of similar regimens in a larger randomized study.

The Altair protocol evaluated quadruple NtRTIs in a randomized, open-label, clinical trial that recruited treatment-naive adult HIV-infected patients. We hypothesized that TDF–emtricitabine (FTC) combined with ritonavir-boosted atazanavir (r/ATV) or combined with ZDV plus abacavir (ABC) would offer noninferior antiretroviral efficacy over 48 weeks, compared with TDF-FTC combined with EFV. This study also compared EFV and r/ATV with TDF-FTC.

## METHODS

**Study design.** Altair was a randomized, open-label, clinical study at 36 sites [25]. Eligible volunteers were healthy, ART-naive, adult HIV-infected patients with CD4+ cell counts >50 cells/ $\mu$ L and plasma HIV-1 RNA >2000 copies/mL. Patients were required to have laboratory parameters within protocol-specified ranges, creatinine clearance of  $\geq$ 70 mL/min (Cock-

**Table 1. Selected Baseline Characteristics by Treatment Arm**

Characteristic	Arm I EFV/TDF-FTC (n = 114)	Arm II r/ATV/TDF-FTC (n = 105)	Arm III ZDV/ABC/TDF-FTC (n = 103)	Total (n = 322)
Age, mean ± SD, years	37.3 ± 9.0	36.7 ± 8.5	35.8 ± 10.1	36.6 ± 9.2
Female sex	24 (21)	30 (29)	22 (21)	76 (24)
CDC stage A or B	108 (95)	101 (96)	100 (97)	309 (96)
Race or ethnicity				
Asian	35 (31)	37 (35)	35 (34)	107 (33)
White	46 (40)	43 (41)	35 (34)	124 (38)
Hispanic and/or Latino	24 (21)	20 (19)	25 (24)	69 (21)
MSM transmission	60 (53)	53 (50)	54 (52)	167 (52)
HIV-RNA, mean ± SD, log <sub>10</sub> copies/mL	4.67 ± 0.63	4.77 ± 0.58	4.64 ± 0.68	4.69 ± 0.63
HIV-RNA copies/mL				
<50,000	47 (41)	37 (35)	47 (46)	131 (41)
50,000–200,000	56 (49)	57 (54)	46 (45)	159 (49)
>200,000	11 (9.7)	11 (10)	10 (9.7)	32 (9.9)
CD4+ cell count, mean ± SD, cells/μL	227 ± 95	235 ± 114	226 ± 136	229 ± 115

**Note.** Data are no. (%) of patients unless otherwise indicated. ABC, abacavir; CDC, Centers for Disease Control and Prevention; EFV, efavirenz; FTC, emtricitabine; HIV, human immunodeficiency virus; MSM, men who have sex with men; r/ATV, ritonavir-boosted atazanavir; SD, standard deviation; TDF, tenofovir; ZDV, zidovudine.

croft-Gault), and no evidence of HIV-drug resistance [26]. Patients were excluded if they were HLA-B\*5701–positive, were pregnant and/or breastfeeding, used prohibited substances, had serious infection or illness requiring intervention, or had known renal insufficiency, obstructive liver disease, intractable diarrhea, cardiomyopathy, or substantial cardiovascular disease.

The study protocol was approved by local ethics committees and, where appropriate, national regulatory authorities. Written informed consent was obtained from each participant.

**Hypothesis.** We hypothesized that in treatment-naïve HIV-infected subjects, either r/ATV (Arm II) or 250 mg or 300 mg twice daily ZDV plus 600 mg once daily ABC (Arm III), combined with TDF-FTC, would offer noninferior antiretroviral efficacy over 48 weeks, compared with 600 mg once daily EFV (Arm I) combined with TDF-FTC, as assessed by change from baseline plasma HIV-1 RNA viral load.

**Randomization and study drugs.** Patients were randomly assigned in equal proportions to 1 of 3 regimens. Randomization was stratified for clinical site and plasma HIV-RNA <100,000 or ≥100,000 copies/mL at baseline.

TDF-FTC was presented as the fixed dose combination (Truvada). In Arms I and II, study drugs were administered orally once daily, whereas in Arm III, ZDV was taken in 2 equal doses ~12 hours apart.

**Follow-up visits.** Patients were followed up at weeks 0, 4, 12, 24, 36, and 48 for physical examination, adverse events collection, clinical biochemistry, hematology, T cell subsets, and plasma HIV-RNA quantification. At weeks 0 and 48, assessment of quality of life (SF-12 questionnaire); assessment of stress, anxiety, and depression (DASS-21 questionnaire) [27]; and

timed gait tests were performed [28]. Ten-year Framingham risk was calculated [29]. Seven-day adherence to therapy was assessed at weeks 4 and 48 by the Community Programs for Clinical Research on AIDS Antiretroviral Medication Self-Report Form [30].

During follow-up, some patients changed their randomly assigned regimen because of treatment-limiting toxicities. The protocol recommendations to preserve “in strategy” compositions of the regimens were as follows: change EFV to nevirapine (Arm I); change r/ATV to another boosted protease inhibitor (Arm II), and change ZDV to stavudine (Arm III).

HIV drug genotypic resistance testing [26] was performed on virus isolates at baseline and virologic failure (defined by 2 consecutive measures of HIV-RNA >400 copies/mL after confirmed HIV-RNA ≤400 copies/mL in the on-treatment population or failure to achieve HIV-RNA ≤400 copies/mL). Regimen failure (virologic, immunologic, or clinical) was managed per local guidelines.

**Data monitoring.** An independent Data and Safety Monitoring Board reviewed virology and safety data when all recruited subjects completed 24 weeks on study.

**Statistical considerations.** The primary end point was time-weighted area under the curve (TWAUC) mean change from baseline plasma HIV-RNA to week 48 by treatment arm. There were no post hoc analyses performed on data generated. Analyses of proportions of patients with plasma HIV-RNA were performed using 3 cut-offs (<50 copies/mL, <200 copies/mL, and <400 copies/mL). The plasma HIV-RNA threshold (200 copies/mL) was selected as our principal measure to address concerns about the validity of a <50 copy/mL threshold [31].

**Table 2. Cessation or Modification of Randomly Assigned Treatment over 48 Weeks of Study**

Period	Arm I EFV/TDF-FTC (n = 114)	Arm II r/ATV/TDF-FTC (n = 105)	Arm III ZDV/ABC/TDF-FTC (n = 103)
Weeks 0–4	3	0	3
Weeks 4–24	2	2	13
Weeks 24–48	2	4	5
Total, no. (%) of patients	7 (6.1)	6 (5.7)	21 (20.4)

**Note.** Data are no. of patients stopping or changing from randomized treatment by various weeks on study, unless otherwise indicated. Within-strategy changes are not included. ABC, abacavir; EFV, efavirenz; FTC, emtricitabine; r/ATV, ritonavir-boosted atazanavir; TDF, tenofovir; ZDV, zidovudine.

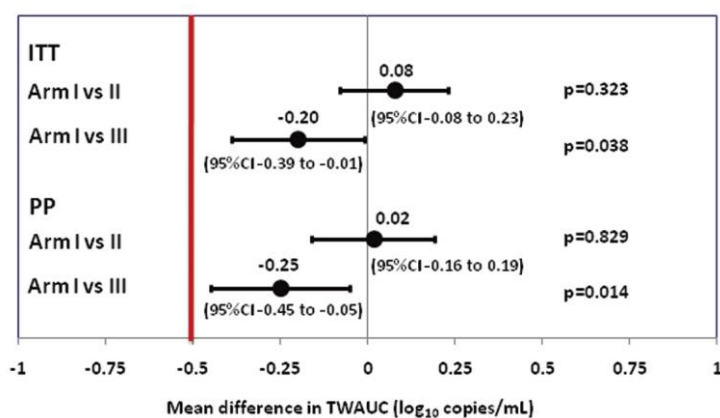
**Sample size.** Between-patient variability of time-weighted change in plasma HIV-RNA was assumed to correspond to a standard deviation (SD) of 1.0 log<sub>10</sub>. At a significance level of .05, this would give a 90% chance that the 2-sided 95% confidence interval (CI) has an upper limit below 0.5 log<sub>10</sub>. The recruitment objective was 100 patients per arm, including 15 additional patients per arm to provide for losses to follow-up.

**Statistical analyses.** The TWAUC mean change from baseline HIV-RNA to week 48 was calculated for each patient as the area under the curve change from baseline to each follow-up HIV-RNA measure, averaged over the patient's total duration of follow-up. Noninferiority was demonstrated if the upper limit of the 95% CI for the difference in TWAUC between arms was at most 0.5 log<sub>10</sub> [32]. Comparison of time-weighted change between treatments was determined by calculating difference between means, the corresponding 95% CIs, and *t* test-derived *P* values. There were 2 pair-wise comparisons of the primary end point: Arm I versus Arm II and Arm I versus Arm III. A third pair-wise comparison, between Arm II and Arm III, was also conducted. The intention-to-treat (ITT) popula-

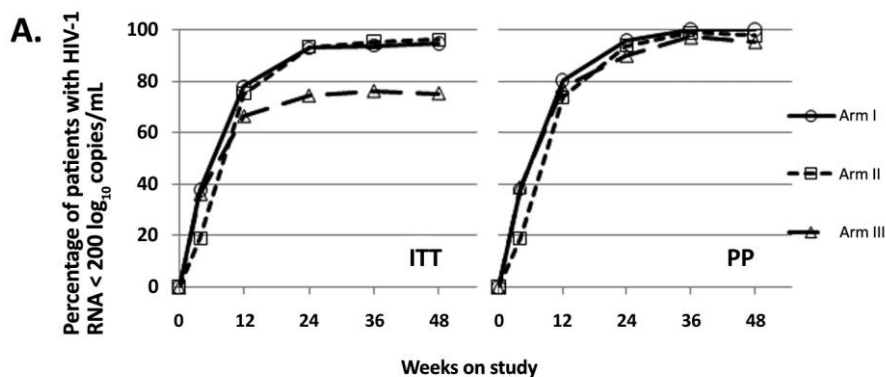
tion was defined as randomly assigned participants who received ≥1 study medication dose and ≥1 follow-up visit. There was no extrapolation of data for the primary end point.

Additional per protocol (PP) analyses were conducted; the population was defined as all participants included in the ITT analysis, censored at the time randomly assigned therapy was stopped. Patient data were not censored if the change to randomized therapy was consistent with the preservation of strategy. For continuous secondary end points, mean change from baseline to week 48 was calculated; both ITT (last observation carried forward) and PP analyses were conducted. *t* tests to compare groups and the Wilcoxon test for data not normally distributed were used. Differences in proportions were assessed using  $\chi^2$  statistics, 95% CIs, and *P* values. For time-to-event end points, hazard ratios (HRs) for comparison of event rates and baseline predictors of virologic failure were assessed using Cox regression methods.

Simple, direct 2-sample comparisons of randomly assigned treatment groups with a 2-sided  $\alpha$  of .05, unadjusted for base-



**Figure 2.** Graph showing primary end point of mean difference in time-weighted area under the curve (TWAUC) mean change from baseline plasma human immunodeficiency virus–RNA to week 48. Pair-wise analysis was performed on the intention-to-treat (ITT) and per protocol (PP) populations for Arm II (ritonavir-boosted atazanavir/tenofovir-emtricitabine) and Arm III (zidovudine/abacavir/tenofovir-emtricitabine), compared with Arm I (efavirenz/tenofovir-emtricitabine). The 95% confidence interval (CI) and *P* value for each pair-wise comparison are listed.



HIV-1 RNA threshold		Arm I EFV/TDF-FTC N(%)	Arm II r/ATV/TDF-FTC N(%)	Arm III ZDV/ABC/TDF-FTC N(%)	P Arms I vs II	P Arms I vs III
>50 copies/mL <sup>a</sup>	ITT	97 (90%)	93 (92%)	75 (76%)	0.446	0.017
	PP	82 (93%)	81 (93%)	60 (94%)	0.755	0.367
>200 copies/mL	ITT	108 (95%)	101 (96%)	85 (82%)	0.750	0.005
	PP	93 (100%)	89 (98%)	64 (96%)	0.243	0.077
>400 copies/mL	ITT	109 (95%)	102 (97%)	85 (82%)	0.723	0.002
	PP	93 (93%)	89 (98%)	64 (96%)	0.243	0.072

<sup>a</sup> 14 patients at one site excluded due to lower limit of detection of HIV-RNA viral load assay of 80 copies/mL

**Figure 3.** A, Percentage of patients with plasma human immunodeficiency virus (HIV)-RNA <200 log<sub>10</sub> copies/mL to week 48. B, Percentage of patients with plasma HIV-RNA less than threshold plasma viral load at week 48. ABC, abacavir; EFV, efavirenz; FTC, emtricitabine; ITT, intention-to-treat population; PP, per protocol population; r/ATV, ritonavir-boosted atazanavir; TDF, tenofovir; ZDV, zidovudine.

line covariates, were used. No adjustment was made for multiple comparisons.

**Safety analyses.** Data on all-grade adverse events were collected. Sites evaluated events for severity, relativity to randomized therapy, and classification as symptomatic of immune reconstitution inflammatory syndrome (IRIS) [33]. The number of patients with all-grade adverse events was summarized by randomly assigned treatment group and severity.

**Ancillary analyses.** One preplanned subgroup analysis was performed. Outcomes of primary and key secondary efficacy end points were compared in strata defined by baseline plasma HIV-RNA <100,000 or ≥100,000 copies/mL. Interaction between strata and treatment was assessed using linear regression.

## RESULTS

**Recruitment, baseline characteristics, and disposition.** Beginning March 2007, 433 patients were screened, of whom 88

were ineligible, mostly because of CD4+ cell count and/or HIV-RNA ineligibility (8.3% of those screened), genotypic HIV-drug resistance (4.6%), low creatinine clearance (4.4%), HLA-B\*5701 positivity (3.0%), and physician wish (1.8%). Sixteen patients withdrew consent or were lost to follow-up before random assignment. Of 329 patients randomly assigned, 2 volunteers were randomly assigned in error, both before withdrawing consent (Figure 1). The ITT population comprised 322 patients.

Baseline data were similar across treatment arms (Table 1). Mean plasma HIV-RNA was 4.69 log<sub>10</sub> copies/mL, and mean CD4+ cell count was 229 cells/μL (41.3% of patients had ≤200 cells/μL). The Framingham score was 4.2 (3.6); nine patients in each arm scored between 10 and 20, and 2 patients (Arm I) had an estimated 10-year cardiovascular disease risk >20%.

There were 2 deaths (accidental electrocution and autoimmune hemolytic anemia; both in Arm I), and 2 patients were lost to follow-up (0.62% of the population for analysis). Nine

**Table 3. Human Immunodeficiency Virus Drug Genotypic Resistance Testing at Virologic Failure**

Patient	Arm	RT inhibitor mutations	Protease inhibitor mutations
1	I	K103KN	None
2	I	None	None
3	I	M184I	L10V
4	II	M184V, M184I	None
5	II	None	None
6	II	None	None
7	III	None	None
8	III	None	I62V, L63P, M36I
9	III	None	V77I
10	III	M184V, T215F, V118I, V75M	None
11	III	None	None
12	III	None	M36I, L63V
13	III	K65R	I13V, I15V, I62V, L10I

**Note.** RT, reverse transcriptase.

patients withdrew consent by week 48, when 309 patients (Arm I,  $n = 111$ ; Arm II,  $n = 104$ ; and Arm III,  $n = 94$ ) remained in follow-up. The rate of missed visits was 0.27%.

**Exposure to randomized treatment and patient-reported adherence.** By week 48, there were 34 patients (10.6%) who had stopped or had changed randomized treatment to an alternative strategy (Table 2). Cessation and/or modifications of ART were due to rash ( $n = 3$ ) and neurological symptoms ( $n = 3$ ) in Arm I; jaundice ( $n = 5$ ) in Arm II; and gastrointestinal disorders ( $n = 17$ ) and anemia ( $n = 7$ ) in Arm III. No discontinuations were attributed to TDF-FTC. One patient switched from Arm I and another stopped Arm III for clinical reasons. ATV was reduced to 200 mg once daily in 7 patients following elevated bilirubin levels.

At week 48, 96.6% of patients who were receiving Arm I reported 100% adherence over the previous week, compared with 95.2% of those receiving Arm II and 87.7% of those receiving Arm III. There were no significant treatment differences in patients who reported 100% adherence at week 4 (Arm I vs

Arm II,  $P > .99$ ; Arm I vs Arm III,  $P = .153$ ) or at week 48 (Arm I vs Arm II,  $P = .714$ ; Arm I vs Arm III,  $P = .054$ ).

**Primary outcome.** For the ITT population, mean reductions in TWAUC were 2.59 logs for Arm I, 2.67 logs for Arm II, and 2.39 logs for Arm III. For differences in mean TWAUC in plasma HIV-RNA, Arm II and Arm III were noninferior to Arm I for both ITT and PP populations (Figure 2).

**Secondary outcomes.** Having established noninferiority for our primary end point, we then conducted a range of supportive secondary analyses. In the ITT population, there was no significant difference in mean TWAUC between Arm I and Arm II ( $P = .323$ ). Arm III was significantly inferior to Arm I by this measure ( $P = .038$ ). Arm II showed statistically significantly greater TWAUC, compared with Arm III, with a difference in mean TWAUC of  $-0.28$  (95% CI,  $-0.46$  to  $-0.10$ ;  $P = .003$ ) (ITT) and  $-0.27$  (95% CI,  $-0.46$  to  $-0.08$ ;  $P = .007$ ) (PP).

Compared with the corresponding percentage in Arm I, the percentage of Arm III patients with  $<200$  copies/mL plasma HIV-RNA by ITT at 48 weeks was significantly lower ( $P = .005$ ) (Figure 3), whereas that of Arm II was not significantly different from that of Arm I ( $P = .750$ ). In the PP population, there were no significant differences between treatments.

There were no differences in time to plasma HIV-RNA  $<200$  copies/mL for either Arm II ( $n = 105$ ) or Arm III ( $n = 97$ ), compared with Arm I ( $n = 111$ ) (Arm I vs Arm II HR, 0.86; 95% CI, 0.66–1.13; and Arm I vs Arm III HR, 0.95; 95% CI, 0.72–1.24).

In the ITT population with confirmed HIV-RNA  $<200$  copies/mL, 17 patients in Arm III rebounded to  $>200$  copies/mL. This occurred at a significantly greater rate in Arm III, compared with the rate in Arm I ( $n = 6$ ) (HR, 3.30; 95% CI, 1.03–8.37;  $P = .012$ ), although the rate in Arm II ( $n = 5$ ) was not significantly different from the rate in Arm I (HR, 0.88; 95% CI, 0.27–2.89;  $P = .840$ ). Results were consistent for other HIV-RNA thresholds and the PP population.

**Immunology.** The mean change from baseline CD4+ cell

**Table 4. Data on Adverse Events over 48 Weeks of Study, by Randomly Assigned Treatment Arm**

Variable	Arm I EFV/TDF-FTC ( $n = 114$ )	Arm II r/ATV/TDF-FTC ( $n = 105$ )	Arm III ZDV/ABC/TDF-FTC ( $n = 103$ )
No. of adverse events	495	409	485
No. of patients experiencing an adverse event	99	95	91
No. of adverse events $\geq$ grade 3	25	35	32
No. of serious adverse events	15	15 <sup>a</sup>	30 <sup>b</sup>
No. of patients with $\geq 1$ serious adverse event	14	8	12

**Note.** Numbers represent total values over 48-week study. ABC, abacavir; EFV, efavirenz; FTC, emtricitabine; r/ATV, ritonavir-boosted atazanavir; TDF, tenofovir; ZDV, zidovudine.

<sup>a</sup> Pair-wise analysis of no. of serious adverse events by randomized treatment arm, Arm I vs Arm II,  $P = .922$ .

<sup>b</sup> Pair-wise analysis of no. of serious adverse events by randomized treatment arm, Arm I vs III,  $P = .062$ .

count in Arm I was 187 cells/ $\mu$ L; this was not significantly different from that of Arm II (192 cells/ $\mu$ L;  $P = .814$ ) or that of Arm III (163 cells/ $\mu$ L;  $P = .217$ ).

**HIV drug resistance testing.** Virologic failure (defined in the Methods) occurred in 4 patients in Arm I, 4 patients in Arm II, and 11 patients in Arm III. Virus isolates were available for characterization of HIV-drug resistance from 13 of these patients (Table 3); 5 contained  $\geq 1$  reverse transcriptase inhibitor mutation. Protease inhibitor mutations were found in 5 virus isolates. Of note, virus isolated from 1 Arm III patient had developed K65R mutation, in combination with multiple protease inhibitor mutations. Virus from an additional Arm III patient contained multiple NtRTI mutations.

**Ancillary analyses.** Subgroup analyses demonstrated that significant differences between arms were not explained by baseline HIV-RNA. In univariate and multivariate Cox regression analysis, randomization to Arm III was the only predictor of virologic failure, HIV-RNA  $>200$  copies/mL, and cessation of randomized treatment or clinical failure and/or death. Patients who never achieved viral suppression were censored at randomization.

**Other health outcomes analyses.** There were no significant differences between treatment arms in quality of life; stress, anxiety, and depression score; or timed gait test result from week 0 to week 48 in both ITT and PP populations (data not shown).

**Safety.** There were no significant differences in number or severity of adverse events between treatments (Table 4). The most common events were infections and infestations (Arm I and Arm II) and gastrointestinal disorders (Arm III). There were no serious non-AIDS events. The number of serious adverse events in Arm III ( $n = 30$ ) was twice that of either Arm I or Arm II ( $n = 15$  for each) ( $P = .062$ ). However, serious adverse events were experienced by similar numbers of patients in Arm I (14) and Arm III (12). There were no serious adverse events attributable to TDF-FTC or r/ATV, although 2 were directly attributed by investigators to EFV (rash) and 2 to ZDV (anemia).

Overall, 52 diagnoses of presumed IRIS were reported in 41 (12.7%) of the participants (14 events in Arm I, 17 events in Arm II, and 21 events in Arm III), with nonspecific skin ailments being most common. Among participants with IRIS, mean CD4+ cell count  $\pm$  SD at randomization was  $186 \pm 99$  cells/ $\mu$ L, lower than in those not experiencing IRIS ( $236 \pm 102$  cells/ $\mu$ L). There were no significant differences between treatment groups with regard to IRIS (Arm I vs Arm II,  $P = .467$ ; Arm I vs Arm III,  $P = .163$ ). The median time from ART initiation to first IRIS was shorter in Arm III (30 days; interquartile range [IQR], 16–162 days), compared with the corresponding times in Arm I (95 days; IQR, 79–242 days) and Arm II (69 days; IQR, 25–164 days).

## DISCUSSION

Selection of combination ART must be guided by robust evidence, with treatment guidelines being the cornerstone of these decisions. Such guidelines currently recommend regimens that are difficult in certain populations. The Altair study was designed with these patients in mind.

The predefined primary end point demonstrated that Arm III was noninferior to Arm I, although inferior to Arm I by a range of secondary efficacy measures. By ITT, the percentage of patients at week 48 with HIV-RNA  $<200$  copies/mL was significantly lower in patients receiving Arm III (82%), compared with the corresponding percentage of patients receiving EFV-containing treatment (95%). Interestingly, this was not consistent for the PP population. The lower virologic response in Arm III may have been driven by higher treatment discontinuations arising from ZDV-related adverse events by 48 weeks.

When combined with TDF-FTC, r/ATV performed well, comparable with other investigations [34]. For most end points, Arm II performed significantly better than Arm III, although pairwise comparisons between the 2 arms were not routine. Altair was one of the first direct comparisons of EFV versus r/ATV as accompaniment to TDF-FTC in naive patients. Although our study had a relatively small sample size, the data are of real interest to clinicians faced with making daily decisions for naive patients. Recent data from the AIDS Clinical Trial Group 5202 showed similar outcomes at 96 weeks [35]. Long term follow-up will allow examination of differential outcomes arising from choice of first-line therapy.

In Altair, the proportion of Arm III patients with HIV-RNA  $<50$  copies/mL was comparable with other TDF-containing quadruple NtRTI regimens [21, 36, 37], as well as with other first-line regimens [38, 39]. Quadruple NtRTIs in Altair performed better than previously [21], perhaps because Altair was conducted in a larger and more diverse patient population.

Approximately 3 times as many patients switched from Arm III, compared with the number who switched from standard regimens. These patients were HLA-B\*5701-negative; therefore, there was no ABC hypersensitivity. Although no difference was reported in adherence between treatments, reduced Arm III adherence may have been missed, because most changes occurred between weeks 4 and 24. For those able to tolerate Arm III and to remain in the PP population for analysis, there was no significant difference, compared with Arm I, for any primary or secondary analyses.

Although not significantly different in time to HIV-RNA  $<200$  copies/mL, patients on Arm III were 3 times more likely to rebound virologically. Therefore, although acting with similar potency at least initially, Arm III performed poorly in sustaining virologic suppression. There was no evidence that baseline HIV-RNA or CD4+ cell count influenced virologic suppression, and

the only predictor of virologic failure was randomization to Arm III.

NtRTI mutations were observed in virus from patients for whom Arm III failed. Of concern is the K65R mutation that should have been prevented, given the inclusion of ZDV [21, 36, 37]. This patient was known to be only partially adherent for several months because of gastrointestinal complications before switching to EFV/lamivudine/ZDV at 28 weeks. Thereafter, the patient maintained HIV-RNA <50 copies/mL to week 96.

The choice of primary end point warrants discussion. To show noninferiority in a 2-arm trial with a viral load end point would have required ~300 patients per arm, beyond our capacity at the time of study design. The TWAUC end point had certain advantages, capturing differences in rate of decrease in plasma HIV-RNA as well as virologic breakthrough. It also handled missing values easily and transparently. Finally, because it quantitatively combines detectable with undetectable viral loads over the entire follow-up period, it was thought to be a more powerful end point. From our viewpoint, showing that mean TWAUC between 2 arms was within 0.5 log<sub>10</sub>copies/mL would provide evidence about the overall similarity of 2 regimens.

At 48 weeks, the Altair Protocol Steering Committee reached a consensus position that resulted in guidance to investigators to change the regimen for Arm III patients to either EFV- or r/ATV-containing regimens. This change was implemented promptly, even in patients responding well to treatment. To examine whether quadruple NtRTIs are associated with poorer responses to subsequent regimens, a follow-up visit at week 144 has been scheduled to include HIV-RNA level, CD4+ cell count, and safety outcomes.

In combination with TDF-FTC, both r/ATV and ZDV/ABC were noninferior by the primary end point to EFV, although ZDV/ABC was significantly inferior by most secondary efficacy measures. The lack of substantive difference between arms containing EFV or r/ATV further indicated overall poor performance of quadruple NtRTIs. Furthermore, safety and tolerability appeared in most analyses to weigh against Arm III. We do not recommend ZDV/ABC/TDF-FTC for use in HIV-infected patients commencing first-line therapy when options for more conventional regimens are accessible. Of note, Arm III did result in levels of suppression of virus replication similar to those of the DART Study [19, 20]. In some instances when more conventional regimens are not available, for example as salvage regimens in treatment-experienced patients [40–42], such quadruple NtRTI approaches may have potential warranting further investigation.

## ALTAIR STUDY GROUP

**Protocol Steering Committee.** Waldo H. Belloso, David Cooper (cochair), Sean Emery, Brian Gazzard (cochair), Chien-Ching Hung, Heiko Jessen, Adeeba Kamarulazaman, Lin Li, Patrick Li, Marcelo Losso, Juan Sierra-Madero, Patrick Mallon, Byron Mason, Jean-Michel Molina, Kathy Petoumenos, Praphan Phanuphak, Shimon Pollack, Rebekah Puls, James Rooney, Sharon Walmsley, Alan Winston, Marcelo Wolff.

**Altair Study Team (Sydney and Buenos Aires).** Sean Emery, Rebekah L Puls, Christoph Boesecke, Jaime Lazovski, Kathy Petoumenos, Marina Delfino, Fraser Drummond, Maria Ariaga, Carlo Dazo, Hila Haskelberg, Preeyaporn Srasuebkul, Kymme Courtney-Vega, Maja Berilazic, Aurelio Vulcao, Kate Merlin.

**Site investigators and staff.** Argentina: Waldo H. Belloso, Jorge Benetucci, Victor Bittar, Arnaldo Casiro, Jorge Corral, Daniel David, Hector Laplume, Marcelo Losso, Sergio Lupo, Betina Angel, Ana Crinejo, Lucia Daciuk, Claudia Elias, Marisa Sanchez, Graciela Guaragna, Cristina Miglioranza, Stella Maris Oliva, Liliana Trape; Australia: Jonathan Anderson, David A Cooper, Nicholas Doong, Dominic Dwyer, Martyn French, Jennifer Hoy, Pam Konecny, Richard Moore, John Quin, Sarah Pett, Tim Read, Jessica Rotty, Alan Street, Robyn Dever, Sian Edwards, Claire Forsdyke, Elissa Giddings, Jeff Hudson, Helen Kent, Karen Macrae, Catherine Magill, Sally Newell, Richard Norris, Maggie Piper, Janine Roney, Julie Silvers, Jenny Skett; Canada: John Gill, Marianne Harris, Julio Montaner, Sharon Walmsley, Brenda Beckthold, Adri d'Aquila, Natalie Jahnke; Chile: Rebeca Northland, Marcelo Wolff, Gladys Allendes; France: Jean-Michel Molina, Samuel Ferret; Germany: Heiko Jessen, Arne Jessen, Pavel Khaykin, Christoph Stephan, Kathleen Mantsch, Carmen Zedlack; Hong Kong: Patrick Li, Man Po Lee, Chan Sze-Nga, Chung Wai Yee; Ireland: Patrick Mallon, Jackie Breiden, Eileen O'Connor; Israel: Shimon Pollack, Eynat Kedem, Rina Shpilman; Malaysia: Adeeba Kamarulazaman, Margaret Tan; Mexico: Juan Sierra-Madero, Rosa Brena, Areli Ortiz; Singapore: Lin Li, Evelyn Chia; Taiwan: Chien-Ching Hung, Wen Chun Liu; Thailand: Anchalee Avihingsanon, Chris Duncombe, Praphan Phanuphak, Kanitta Pussadee; and United Kingdom: Brian Gazzard, Laura Waters, Alan Winston, Christopher Collister, Chris Higgs, Ken Legg.

## Acknowledgments

We extend our grateful thanks to all the participants, and we thank Gilead Sciences for providing the fixed dose combination of TDF-FTC as well as research funding.

**Financial support.** The Australian Government Department of Health and Ageing; Gilead Sciences (unrestricted grant).

**Manuscript preparation.** This was an investigator-driven study, although representatives of Gilead Sciences reviewed the manuscript before submission.

**Potential conflicts of interest.** J.-M.M. has received honoraria and con-

sulting fees from GlaxoSmithKline, Abbott, Gilead, Tibotec, Pfizer, and Bristol-Myers Squibb. B.G. has received research grants and/or honoraria from Gilead Sciences, Bristol-Myers Squibb, GlaxoSmithKline, and Merck. D.A.C. has received honoraria, consultancies, and/or research grants from, or has been an investigator in clinical trials sponsored by, Abbott, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, and Merck Sharp and Dohme. S.E. has received honoraria, consultancies, and research grants from, or has been an investigator in clinical trials sponsored by, Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Chiron-Novartis, Gilead Sciences, GlaxoSmithKline, Merck Sharp and Dohme, Roche, Tibotec, and Virax Immunotherapeutics. All other authors: no conflict.

## References

- United States Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>. Published 1 December 2009. Accessed 29 July 2010.
- López-Cortés LF, Ruiz-Valderas R, Viciano P, et al. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet* **2002**; *41*:681–690.
- Patel A, Patel K, Patel J, Shah N, Patel B, Rani S. Safety and antiretroviral effectiveness of concomitant use of rifampicin and efavirenz for antiretroviral-naïve patients in India who are coinfecting with tuberculosis and HIV-1. *J Acquir Immune Defic Syndr* **2004**; *37*:1166–1169.
- Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS* **2006**; *20*:131–132.
- Brennan-Benson P, Lyus R, Harrison T, Pakianathan M, Macallan D. Pharmacokinetic interactions between efavirenz and rifampicin in the treatment of HIV and tuberculosis: one size does not fit all. *AIDS* **2005**; *19*:1541–1543.
- Friedland G, Khoo S, Jack C, Lalloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. *J Antimicrob Chemother* **2006**; *58*:1299–1302.
- Sathia L, Obiorah I, Taylor G, et al. Concomitant use of nonnucleoside analogue reverse-transcriptase inhibitors and rifampicin in TB/HIV type 1–coinfecting patients. *AIDS Res Hum Retroviruses* **2008**; *24*:897–901.
- Boulle A, Van Cutsem G, Cohen K, et al. Outcomes of nevirapine and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA* **2008**; *300*:530–539.
- Clarke SM, Mulcahy FM, Tjia J, et al. The pharmacokinetics of methadone in HIV-positive patients receiving the nonnucleoside reverse-transcriptase inhibitor efavirenz. *Br J Clin Pharmacol* **2001**; *51*:213–217.
- Jungmann EM, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? *Sex Transm Infect* **2001**; *77*:441–443.
- Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS* **2002**; *16*:299–300.
- De Santis M, Carducci B, De Santis L, Cavaliere AF, Straface G. Periconceptual exposure to efavirenz and neural tube defects. *Arch Intern Med* **2002**; *162*:355.
- 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.
- Gallant JE, Rodriguez AE, Weinberg WG, et al; for the ESS30009 Study. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naïve subjects. *J Infect Dis* **2005**; *192*:1921–1930.
- Gulick RM, Ribaldo HJ, Shikuma CM, et al. Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection: a randomized controlled trial. *JAMA* **2006**; *296*(7):769–781.
- Gulick R, Ribaldo H, Shikuma C, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* **2004**; *350*:1850–1861.
- Mauss S, Milinkovic A, Hoffmann C, et al. Low rate of treatment failure on antiretroviral therapy with tenofovir, lamivudine and zidovudine. *AIDS* **2005**; *19*:101–103.
- Rey D, Krebs M, Partisani M, et al. Virologic response of zidovudine, lamivudine, and tenofovir disoproxil fumarate combination in antiretroviral-naïve HIV-1-infected patients. *J Acquir Immune Defic Syndr* **2006**; *43*:530–534.
- 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.
- DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised noninferiority trial. *Lancet* **2010**; *375*:123–131.
- Moyle G, Higgs C, Teague C, et al. An open-label randomised comparative pilot study of a single-class quadruple therapy regimen versus a 2-class triple therapy regimen for persons initiating antiretroviral therapy. *Antivir Ther* **2006**; *11*:73–78.
- 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.
- Parikh UM, Koontz DL, Chu CK, Schinazi RF, Mellors JW. In vitro activity of structurally diverse nucleoside analogs against human immunodeficiency virus type 1 with the K65R mutation in reverse transcriptase. *Antimicrob Agents Chemother* **2005**; *49*:1139–1144.
- White KL, Chen JM, Feng JY, et al. The K65R reverse transcriptase mutation in HIV-1 reverses the excision phenotype of zidovudine resistance mutations. *Antivir Ther* **2006**; *11*:155–163.
- United States National Institutes of Health. ALTAIR—alternative antiretroviral strategies: a comparison of three initial regimens. <http://clinicaltrials.gov/ct2/show/NCT00335322>. Published 8 June 2006. Updated 24 November 2009. Accessed 30 July 2010.
- Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1. *Top HIV Med* **2008**; *16*:138–145.
- Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large nonclinical sample. *Br J Clin Psychol* **2005**; *44*:227–239.
- Brew B. HIV neurology. Contemporary Neurology Series. New York: Oxford University Press. **2001**.
- Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* **1998**; *97*:1837–47.
- Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG Adherence Instruments. *AIDS Care* **2000**; *12*:255–266.
- Ribaldo H, Lennox J, Currier J, et al. Virologic failure end point definition in clinical trials: is using HIV-1 RNA threshold <200 copies/mL better than <50 copies/mL? an analysis of ACTG studies. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections. **2009**. Abstract 580.
- French M, Amin J, Roth N, et al; for the OzCombo 2 investigators. Randomized, open-label, comparative trial to evaluate the efficacy and safety of three antiretroviral drug combinations including two nucleoside analogues and nevirapine for previously untreated HIV-1 infection: the OzCombo 2 study. *HIV Clin Trials* **2002**; *3*:177–185.
- French MA. Disorders of immune reconstitution in patients with HIV infection responding to antiretroviral therapy. *Curr HIV/AIDS Rep* **2007**; *4*:16–21.
- Molina JM, Andrade-Villanueva J, Echevarria J, et al; for the CASTLE Study Team. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48

- week efficacy and safety results of the CASTLE study. *Lancet* **2008**; 372:646–655.
35. Daar E, Tierney C, Fischl M, et al; for the ACTGA5202 Study Team. ACTG 5202: final results of ABC/3TC or TDF/FTC with either EFV or ATV/r in treatment-naive HIV-infected patients. In: Program and abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. **2010**. Abstract 59LB.
  36. Elion R, Cohen C, deJesus E, et al; for the COL40263 Study Team. Once-daily abacavir/lamivudine/zidovudine plus tenofovir for the treatment of HIV-1 infection in antiretroviral-naive subjects: a 48-week pilot study. *HIV Clin Trials* **2006**; 7:324–333.
  37. Ferrer E, Gatell JM, Sanchez P, et al. Zidovudine/lamivudine/abacavir plus tenofovir in HIV-infected naive patients: a 96-week prospective one-arm pilot study. *AIDS Res Hum Retroviruses* **2008**; 24:931–934.
  38. Eron J Jr, Yeni P, Gathe J Jr, et al; for the KLEAN Study Team. 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 randomized noninferiority trial. *Lancet* **2006**; 368:476–482.
  39. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir, emtricitabine and efavirenz vs zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* **2006**; 354:251–260.
  40. Llibre JM, Bonjoch A, Iribarren J, et al; for the HIV Conference Call Study Group. Targeting only reverse transcriptase with zidovudine/lamivudine/abacavir plus tenofovir in HIV-1-infected patients with multidrug-resistant virus: a multicentre pilot study. *HIV Med* **2008**; 9: 508–513.
  41. Stephan C, Dauer B, Khaykin P, et al. Quadruple nucleos(t)ide reverse-transcriptase inhibitors-only regimen of tenofovir plus zidovudine/lamivudine/abacavir in heavily pretreated HIV-1 infected patients: salvage therapy or backbone only? *Curr HIV Res* **2009**; 7:320–326.
  42. Stürmer M, Staszewski S, Doerr HW. Quadruple nucleoside therapy with zidovudine, lamivudine, abacavir and tenofovir in the treatment of HIV. *Antivir Ther* **2007**; 12:695–703.