

Simplification with abacavir-based triple nucleoside therapy versus continued protease inhibitor-based highly active antiretroviral therapy in HIV-1-infected patients with undetectable plasma HIV-1 RNA

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Objective: To assess the antiviral efficacy, safety and adherence in patients switched to an abacavir-containing nucleoside reverse transcriptase inhibitor (NRTI) regimen after long-term HIV-1 RNA suppression with a dual NRTI/protease inhibitor (PI) combination.

Methods: In an open-label, multicentre study, patients receiving 2NRTI plus PI for at least 6 months, with a history of undetectable plasma HIV-1 RNA since the initiation of therapy and plasma HIV-1 RNA < 50 copies/ml at screening, were randomly assigned to replace the PI with abacavir (n = 105) or continue the same treatment (n = 106). Clinical assessments included plasma HIV-1 RNA, chemistry, haematology, lymphocyte counts, and adverse event reports. Adherence to treatment was assessed by patient self-report.

Results: A significantly longer time to treatment failure was demonstrated in the abacavir arm compared with the PI arm ($P=0.03$) while treatment failure was experienced by significantly more patients in the PI arm: 24 (23%) versus 12 (12%) ($P=0.03$). Therapy-limiting toxicity led to treatment failure in eight versus 14 cases in the abacavir and PI arms, respectively, whereas virological rebound was the cause in four versus two cases. Significant reductions in cholesterol and non-fasting triglyceride plasma levels at 48 weeks were observed in the abacavir arm ($P<0.001$ and $P=0.035$, respectively). The number of patients reporting no difficulty in taking their therapy showed a marked increase from baseline in the abacavir arm.

Conclusion: The replacement of PI by abacavir in a triple combination regimen following prolonged suppression of plasma HIV-1 RNA provides continued virological suppression, significant improvements in lipid abnormalities and enhanced ease of dosing.

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Introduction

Combination antiretroviral therapy (ART) has proved to be the most effective approach in the treatment of HIV infection. The use of triple therapy combinations that include protease inhibitors (PI) can reduce plasma HIV-1-RNA levels, raise CD4 cell counts and lower the risk of progression to AIDS and death [1,2].

However, not all individuals with HIV infection are able to tolerate long-term therapy with PI-based highly active antiretroviral therapy (HAART). The occurrence of treatment-limiting side-effects, interactions with concomitant medications, and the impact of a high daily pill burden with associated dietary requirements mean that a significant proportion of individuals with HIV-1 infection are unable to remain adherent to such combinations for extended periods of time. In addition, after initial declines in plasma HIV-1-RNA levels, virological failure has been observed in a substantial proportion of clinical trial subjects (18–32%), while results from observational cohort studies suggest that within 8 to 12 months approximately 25% of patients discontinue their initial PI regimen as a result of virological failure, toxicity or adherence issues [3–7].

Recent evidence of long-term effects associated with PI-based HAART has also raised concern. HIV lipodystrophy syndrome was first reported in 1998 and is characterized by peripheral lipoatrophy, central fat accumulation, dyslipidaemia and insulin resistance [8]. In addition to the psychological impact of such morphological changes, increases in cholesterol and triglyceride levels, insulin resistance and diabetes are all well-known major risk factors for cardiovascular complications [9]. Other known toxicities of PI include gastrointestinal disturbances, raised transaminase levels, fatigue, nephrolithiasis and hyperbilirubinaemia [10].

Such issues have resulted in the investigation of simplified, PI-sparing regimens with the potential to maintain virological efficacy while improving quality of life and increasing the likelihood of long-term adherence. Early trials of simplified maintenance, in which a brief induction period with two nucleoside reverse transcriptase inhibitors (NRTI) plus a PI was followed by a maintenance strategy of two NRTI, failed to demonstrate sustained viral suppression [11,12]. Apart from the reduced potency of the maintenance regimen employed in these trials, the duration of viral undetectability before transfer was relatively short (2–3 months) and the level of viral suppression at the time of transfer was in the range of 200–500 HIV-1-RNA copies/ml.

More recent simplified maintenance studies have employed switch regimens with equivalent antiretroviral efficacy to PI-containing HAART, replacing the PI

with non-nucleoside reverse transcriptase inhibitors such as efavirenz and nevirapine [9,13,14]. In addition, inclusion has been limited to individuals with a high level of viral suppression for significant periods of time (6 months to 2 years), and a greater stringency has been applied to the HIV-1-RNA threshold at the time of switch (< 50 copies/ml). The preliminary results of such studies have been promising, demonstrating sustained virological suppression, improvement in quality of life and an amelioration of some of the metabolic abnormalities associated with long-term exposure to PI.

The triple NRTI combination of abacavir, zidovudine and lamivudine has been shown to have antiviral activity comparable to indinavir, zidovudine and lamivudine in ART-naïve patients over 24–48 weeks [5,15]. In individuals with a history of undetectable plasma HIV-1 RNA since the initiation of ART and a high level of viral suppression at study entry, the combination of dual NRTI plus abacavir could be expected to provide sustained suppression comparable to continued treatment with dual NRTI plus a PI.

In a 48 week, randomized, open-label trial we therefore assessed antiviral efficacy, safety, lipid profiles and adherence in patients transferred to an abacavir-based triple NRTI regimen after long-term HIV-1 RNA suppression with a PI plus two NRTI combination.

Methods

Study design and patients

A randomized, open-label, multicentre, 48 week comparative study of the safety and efficacy of 2NRTI plus abacavir (Ziagen, Glaxo Wellcome, Greenford, UK) versus continued 2NRTI plus PI in patients with undetectable plasma HIV-1 RNA (< 50 copies/ml) on 2NRTI plus PI. The primary outcome measure was treatment failure, defined as either virological failure [HIV-1 RNA > 400 copies/ml on two consecutive occasions, as determined by a quantitative reverse transcriptase (RT) polymerase chain reaction assay (Amplicor version 1.5, Roche Diagnostic Systems, Branchburg, NJ, USA)] or premature discontinuation of randomized study treatment. Secondary efficacy outcomes included the change in CD4 cell count from baseline, the proportion of patients with a suppression of plasma HIV-1 RNA to below 50 copies/ml, the development of adverse events, changes in metabolic parameters and treatment adherence.

Patients were recruited from 29 centres in Europe and Canada. The main inclusion criteria were initial treatment with 2NRTI or 2NRTI plus PI, virological undetectability (below the limit of assay quantification) since the initiation of treatment, receipt of current

2NRTI plus PI combination for a minimum of 6 months before screening, and plasma HIV-1-RNA levels of less than 50 copies/ml at the screening visit. All patients provided written informed consent to participate in the study and were randomly assigned to continue their existing treatment or to switch the PI for abacavir (300 mg twice a day) while maintaining their dual nucleoside combination.

Evaluation of patients

Randomization began in October 1998 and ended in June 1999. Demographic characteristics, Centers for Disease Control and Prevention HIV-1 classification and previous ART were documented. After the screening and baseline assessments, patients were followed up at weeks 2, 4, 8, 12, 16, 24, 36 and 48. Routine laboratory monitoring in the non-fasting state was performed at each visit, in addition to clinical assessments determination of lymphocyte subsets (CD4, CD8) and measurement of plasma HIV-1 RNA. Adherence to and difficulty in taking randomized treatment were measured via patient self-report from week 4 onwards using the Treatment Adherence Questionnaire. To ensure that an acceptable virological response was achieved and maintained, patients were allowed to receive alternative HAART upon meeting the protocol-defined switch criterion of plasma HIV-1 RNA greater than 400 copies/ml on two consecutive occasions or experiencing treatment-related adverse events.

Peripheral blood mononuclear cells were collected at baseline, weeks 24 and 48 for the determination of HIV-1-DNA/RNA resistance profiles in patients who experienced virological failure during the study. Total DNA was extracted from peripheral blood mononuclear cells using the QIAGEN DNeasy Tissue Kit (cat. no. 69504) as per the manufacturer's instructions. After amendment of the protocol to allow for the assessment of metabolic status under prolonged NRTI therapy, venous samples for the determination of plasma lactate and anion gap were collected at two time-points (T1 and T2) at least 12 weeks apart after week 16.

Statistical analyses

A sample size of 100 patients in each group was required to provide approximately 90% power to exclude the possibility of the abacavir arm being 15% worse than the PI arm. For efficacy analyses the following populations were used:

- Intent to treat (ITT) exposed: includes patients randomly selected who received at least one dose of randomized study treatment;
- As treated (AT): includes data collected while on randomized treatment only.

The primary population for efficacy analyses was the ITT exposed. ITT exposed principles were applied in two different ways:

- Switch included: data included regardless of whether the patient switched therapy or discontinued from the study;
- Switch = failure: data collected after the patient switched therapy or discontinued from the study regarded as failure.

In all cases the ITT exposed analysis included the missing = failure (M = F) imputation method in which any missing data was counted as a failure.

The safety population was defined as for the ITT-exposed population.

The non-inferiority of the failure rates was assessed using 95% confidence intervals (CI) around the difference in proportions of treatment failure at week 48. The non-inferiority of abacavir to the PI-containing regimen was established when the CI around this difference was greater than -15%, i.e. 2NRTI/abacavir is no worse than 2NRTI/PI. In addition, when the CI excluded zero the Cochran-Mantel-Haenzel test was used to perform a superiority test on the difference between proportions.

Time to treatment failure was estimated using Kaplan-Meier product-limit estimates (presented graphically). The log-rank *P* value was used to assess the difference between the survival curves of the two treatments.

The change from baseline for CD4 cell counts, triglyceride and cholesterol levels was compared using the Wilcoxon rank sum test.

Results

Subject population

A total of 211 patients were enrolled in the study; 106 patients were randomly assigned to remain on their current 2NRTI plus PI regimen and 105 were randomly assigned to continue their current 2NRTI combination and substitute the PI with abacavir. Baseline characteristics were balanced between treatment groups; the percentage of male patients was 87 versus 78 for the abacavir and PI arms, respectively, and median age in years was 38 in each arm (abacavir, range 20-66; PI, range 22-70). Median CD4 cell counts were 504 cells/mm³ (range 72-1565) in the abacavir arm and 507 cells/mm³ (range 67-1457) in the PI. The baseline Centers for Disease Control and Prevention classification was also comparable between treatments; the percentage of patients in the abacavir

group with known category A, B and C classifications, respectively, was 53, 16 and 30, whereas for the PI group these percentages were 55, 21 and 22.

Lipid profiles at baseline showed median triglyceride levels of 1.76 mmol/l (range 0.46–8.93) and 1.64 mmol/l (range 0.45–30.26) in the abacavir and PI arms, respectively, and a median cholesterol level of 5.2 mmol/l (range 2.31–9.45) and 5.3 mmol/l (range 2.21–14.97) in these same groups. Increased lipid values (triglyceride > 2.3 mmol/l and cholesterol > 5.2 mmol/l, respectively) were seen in 49 out of 104 (47%) and 63 out of 104 (61%) patients in the abacavir arm, and in 37 out of 103 (36%) and 68 out of 103 (66%) patients in the PI arm.

The duration and type of pre-study exposure to ART was also comparable between treatment groups: the median time on ART was 20 months in each arm (range 8–53 for abacavir and 7–125 for PI), and the median time on a PI was also 20 months in each arm (range 8–48 for abacavir and 6–41 for PI). Most patients initiated ART with a PI-containing triple combination (90% in the abacavir compared with 87% in the PI arm), whereas only 5 and 8% of patients in abacavir and PI groups, respectively, had received a dual NRTI combination as their first ART. Although entry criteria specified the inclusion of patients who had initiated ART with dual or triple combination therapy, a small number of patients were found to have received zidovudine monotherapy as an initial treatment (4 and 2% of patients in the abacavir and PI arms, respectively).

The NRTI combination being received most frequently at study entry was lamivudine/zidovudine in the form of Combivir or as separate entities (65% of patients in the abacavir arm and 68% in the PI), followed by stavudine/lamivudine (28 and 27%). Other combinations were received by less than 7% of patients in either treatment group. The most frequently used PI at entry was indinavir (received by 69 and 52% of patients in the abacavir and PI arms, respectively), with other PI being received in smaller patient numbers: nelfinavir (12 and 18%), ritonavir (9% in each arm) and saquinavir (4 and 7%). Ritonavir/saquinavir was the only dual PI allowed at the time of randomization; 7 and 14% of patients in the abacavir and PI arms, respectively, were receiving these PI in combination. Indinavir and ritonavir/saquinavir were the only PI showing a slight imbalance in the frequency of use between treatment groups at baseline.

Subject accountability

Four patients (2%) were randomly assigned to a treatment group (one abacavir, three PI) but did not start therapy and were excluded from the ITT-exposed population ($n = 207$). Ninety-three patients (89%) in

the abacavir arm and 80 (75%) in the PI arm completed 48 weeks of randomized treatment. Eleven patients permanently discontinued from the study: seven (3%) withdrew consent or were lost to follow-up (one in the abacavir arm versus six in the PI), three (1%) withdrew from the study as a result of adverse events (abacavir arm), and one (< 1%) was withdrawn because of violation of the protocol (PI arm).

Treatment outcome

The switch to abacavir resulted in a lower incidence of treatment failure over the 48 week study period compared with patients remaining on a PI. In an ITT-exposed analysis of protocol-defined failure, the proportion of patients who met the definition of treatment failure was 12 out of 104 (12%) in the abacavir arm versus 24 out of 103 (23%) in the PI arm. The difference in proportions, 11.8% with a 95% CI (1.54, 21.95), demonstrates statistical significance in favour of the abacavir arm compared with the PI arm ($P = 0.03$). The primary reasons for failure in these arms were: premature discontinuation of randomized treatment as a result of adverse events (eight versus 14); plasma HIV-1-RNA level greater than 400 copies/ml (four versus two); premature discontinuation of randomized treatment for other reasons (zero versus three; the reasons were: patient request; simplification of treatment; and protocol violation), consent withdrawn (zero versus four), and lost to follow-up (zero versus one). Time to treatment failure was significantly longer in the abacavir group compared with the PI group over the 48 week treatment period ($P = 0.03$); Fig. 1.

An analysis of treatment outcome with regard to virological success at week 48 showed that the percentage of patients in the ITT exposed (switch included) population with plasma HIV-1 RNA below the limit of detection was comparable between treatment arms.

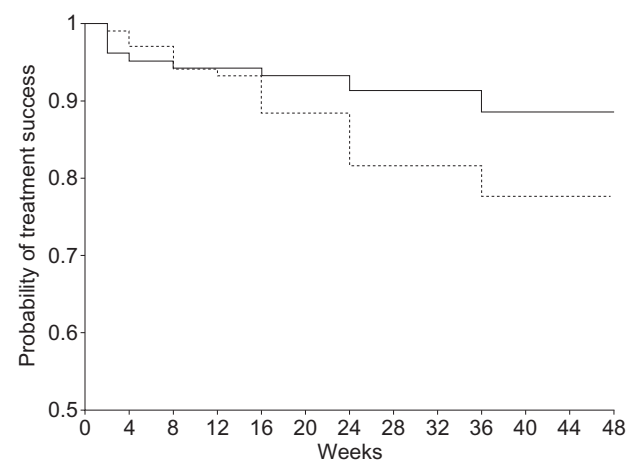


Fig. 1. Time to treatment failure. — Abacavir; - - protease inhibitors.

In the abacavir and PI groups, respectively, 95 out of 104 (91%) and 92 out of 103 (89%) patients had plasma HIV-1 RNA \leq 400 copies/ml, while at the 50 copy or less threshold these proportions were 94 out of 104 (90%) versus 88 out of 103 (85%).

In an ITT-exposed (switch = failure) analysis, including both therapy and study discontinuation as failure, the proportion of patients with plasma HIV-1-RNA levels of 400 copies/ml or less at 48 weeks was 90 out of 104 (87%) in the abacavir arm compared with 76 out of 103 (74%) in the PI arm. At the 50 copy or less threshold these proportions were 89 out of 104 (86%) and 72 out of 103 (70%) in the abacavir and PI arms, respectively.

CD4 cell response

The immunological response at week 48 was similar between treatment groups for both the ITT-exposed and AT populations. CD4 cell counts showed a median increase of 26 cells/mm³ in the abacavir arm compared with 13 cells/mm³ in the PI (ITT-exposed) arm, whereas in the AT population, median gains were 28 and 45 cells/mm³ for the abacavir and PI arms, respectively.

Metabolic profiles

At week 48, a significant reduction in plasma lipid profiles was observed in the abacavir arm for the ITT-exposed population (Fig. 2 and Fig. 3). The median change from baseline for the abacavir and PI arms, respectively, was -0.14 mmol/l versus $+0.04$ mmol/l for triglycerides ($P = 0.035$) and -0.51 mmol/l versus -0.11 mmol/l for cholesterol ($P < 0.001$). Analysis of the AT population showed a similar outcome at week 48: the median change from baseline for triglycerides was -0.16 and $+0.15$ mmol/l in the abacavir and PI arms, respectively, while for cholesterol the median change was -0.59 and -0.02 mmol/l. An adjusted

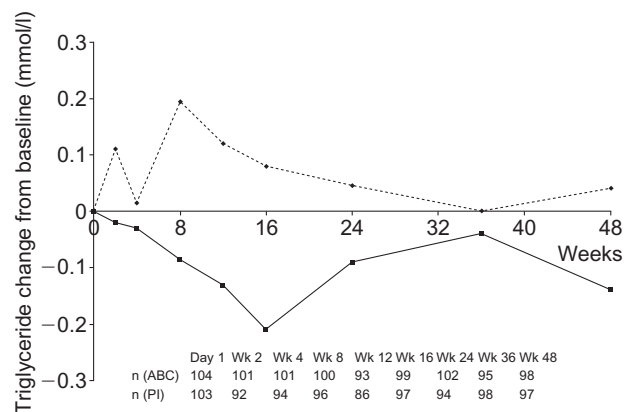


Fig. 2. Median change from baseline in non-fasting triglycerides (intent to treat-exposed). $\text{---}\blacklozenge\text{---}$ Protease inhibitors; $\text{---}\blacksquare\text{---}$ abacavir.

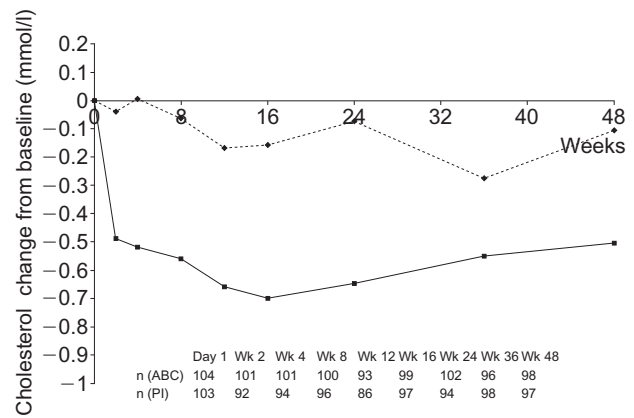


Fig. 3. Median change from baseline in non-fasting cholesterol (intent to treat-exposed). $\text{---}\blacklozenge\text{---}$ Protease inhibitors; $\text{---}\blacksquare\text{---}$ abacavir.

analysis for differences in PI use at baseline showed that there was no impact on the median change from baseline for triglycerides or cholesterol.

The proportion of patients in each arm with elevated plasma lipids at baseline (triglyceride > 2.3 mmol/l, cholesterol > 5.2 mmol/l) decreased by week 48 and showed the greatest reduction in the abacavir group. Increased triglyceride levels in the abacavir arm at baseline had been observed in 49 out of 104 (47%) patients versus 37 out of 103 (36%) in the PI. By week 48, these proportions were 27 out of 104 (26%) and 30 out of 103 (29%). The proportion of patients with increased cholesterol levels at baseline was higher: 63 out of 104 (61%) in the abacavir arm versus 68 out of 103 (66%) in the PI arm. By week 48, however, these proportions had decreased to 31 out of 104 (30%) and 49 out of 103 (48%) in the abacavir and PI groups, respectively, with a larger decrease in the abacavir arm compared with the PI arm ($P = 0.009$).

Median plasma lactate levels were not elevated and did not change over time in either treatment arm. In addition, results were comparable between patients who had simplified to the triple NRTI regimen and those who remained on a PI: T₁ (see Methods) median values for the abacavir and PI arms, respectively, were 1.35 versus 1.40 mmol/l; T₂ values were 1.35 mmol/l for both arms. In addition, few patients had plasma lactate levels indicative of moderate (> 2.0 mmol/l) or severe (> 5.0 mmol/l) lactataemia at either time-point. The proportion of patients with lactate concentrations in the moderate range at T₁ was 14 out of 90 (16%) and 11 out of 80 (14%) for the abacavir and PI arms, respectively; at T₂ these proportions were seven out of 58 (12%) and four out of 49 (8%). Concentrations in the severe range occurred in only two patients (both in the abacavir arm).

Similar results were seen for anion gap, with comparable values at both the first and second measurement between treatment arms and there was no indication of a change over time. T₁ and T₂ results for the abacavir arm were 15.7 and 15.2 mmol/l, respectively, and for the PI arm 15.5 mmol/l at both time-points. These results showed a slight elevation above the reference range for this parameter (< 14 mmol/l = normal).

Resistance

In the six patients who experienced virological failure during the study (plasma HIV-1 RNA > 400 copies/ml on two consecutive occasions), the genotypic resistance profile at baseline and the time of failure was determined. Patterns of resistance, viral load at the time of failure and details of randomized and alternative HAART for these patients are summarized in Table 1.

In five patients, resistance mutations in RT DNA at baseline were not detected, while the only patient with evidence of RT mutations at baseline was found to have received zidovudine monotherapy as initial ART. A single mutation, M184V, was detected in RT DNA at the time of virological rebound in three out of four of the patients on the abacavir arm, while in patients who remained on PI-based therapy new mutations at rebound were not detected.

Three patients switched to alternative HAART following virological rebound. In the abacavir arm, patient 1 received stavudine/didanosine/indinavir/ritonavir at week 22 after a 14 week break from all ART. At week 36, ART was again discontinued, and the plasma HIV-1-RNA measurement at week 48 was 543 956 copies/ml. Patient 3 received nelfinavir in place of abacavir at week 29, followed by a switch to lamivudine/efavirenz/ritonavir/saquinavir at week 44, with the lowest plasma HIV-1-RNA measurement post-rebound being recorded at week 48 (1046 copies/ml). In the PI arm, patient 6 returned to consecutive plasma HIV-1-RNA measurements of less than 50 copies/ml by week 36 under randomized study treatment and switched to Combivir/abacavir at week 40 with no loss of virological control at week 48.

Self-reported adherence in these failing patients (as measured via the Treatment Adherence Questionnaire) was generally high. Patients 2 and 6 reported adherence levels of 70 and 83%, respectively, and the remaining failing patients reported adherence rates of over 97%.

Adverse events

The most frequently reported treatment-related adverse events (those reported by $\geq 5\%$ of subjects in either arm) were nausea, malaise and fatigue, lipodystrophy, and headache. Patients in the abacavir arm experienced a higher incidence of nausea and malaise and fatigue than those who continued their PI-containing regimen

Table 1. Resistance patterns in patients experiencing virological failure.

Patient no.	Week	HIV-1 RNA (c/ml) at time of failure	Mutations at baseline (DNA)	Mutations at rebound (RNA)	Adherence to study regimen (%)		Virological response ^a (c/ml)
					Study regimen	Alternative ART	
Abacavir							
1	4 ^b	475	M41L, T215Y	M41L, M184V, T215Y	97	d4T/ddI/RTV/IDV	543 956
2	8	12 843	Not detected	M184V	70	Stopped ART	39 425
3	16	776	Not detected (plasma)	M184V	97	3TC/EFV/RTV/SQV	1046
4	36	43 200	Not detected	Not detected	99	No change	< 50
Protease inhibitors							
5	8	4478	E35D, L63A, A71V, I93L	E35D, L63A, A71V, I93L	100	No change	7925
6	16	30 619	L101/L, E35D, M36I	E35D, M36I	83	COM/ABC	< 50

ABC, Abacavir; ART, antiretroviral therapy; COM, combivir; ddI, didanosine; d4T, stavudine; EFV, efavirenz; IDV, indinavir; NLF, nelfinavir; RTV, ritonavir; SQV, saquinavir; 3TC, lamivudine.

^aResponse measured at last on-study visit (week 48 for all patients except 2 and 6, in which response measured corresponds to week 36).

^bReceived zidovudine monotherapy as initial ART.

(13/104 versus 5/103; $P = 0.046$ and 9/104 versus 2/103; $P = 0.029$, respectively). The incidence of treatment-related adverse events was not significantly different between treatment groups, although the number of adverse events resulting in the discontinuation of randomized treatment regimens was higher in patients remaining on PI (14 versus 8%, Table 2). There were no differences between treatment arms with regard to grades 3 or 4 laboratory abnormalities or laboratory abnormalities thought to be of clinical significance.

Symptoms of a hypersensitivity reaction were reported in two out of 104 patients (2%) in the abacavir arm. The discontinuation of abacavir resulted in the resolution of symptoms in both cases.

Morbidity and mortality

Two deaths occurred during the study, both of which were patients randomly assigned to the abacavir arm, but neither case was considered to be related to study treatment. One patient permanently discontinued abacavir 6 months after study entry and began nevirapine, nelfinavir and lamivudine. Three and a half weeks after starting these drugs they were discontinued and 5 days later the patient was hospitalized with Stevens–Johnson syndrome. Five days later she developed septic shock from a *Staphylococcus aureus* infection and subsequently died. The second case was a patient who developed haematemesis and melena after treatment of thoracic pain with indomethacin. He developed further bleeding approximately 2 weeks later and died of renal failure.

Treatment adherence

Self-reported adherence at baseline was high in both treatment arms: 90 out of 101 (89%) patients in the abacavir arm and 77 out of 93 (83%) in the PI arm reported taking all doses of their randomized study regimen or missing less than one dose per week. By week 48, this proportion had increased in the abacavir arm compared with a decrease in the PI arm [86/94 (91%) versus 72/95 (76%)]. The percentage of patients reporting that none of the antiretroviral therapies in their randomized regimen were difficult to take increased in both treatment arms compared with baseline,

with a larger increase in the abacavir (40%) versus the PI arm (9%).

Discussion

This study demonstrates that in patients previously well-controlled on PI-based HAART, replacing the PI with abacavir is a generally well-tolerated and effective treatment option. The time to treatment failure over 48 weeks was significantly longer in the simplified abacavir arm compared with the continuation of baseline treatment ($P = 0.03$). In addition, treatment failure was experienced by a higher proportion of patients in the PI group (24/103 versus 12/104), with the disparity in outcome driven largely by an increased number of treatment-limiting adverse events, withdrawals of consent, and a desire for a simplification of treatment in patients remaining on PI-containing therapy.

The use of a potent switch regimen in patients with a high degree of HIV-1 RNA suppression before replacement of the PI addressed the loss of virological control seen in earlier simplification studies [11,12]. In an ITT-exposed (switch included) analysis, treatment outcome in terms of virological success was comparable between study arms, with plasma HIV-1 RNA levels of 400 copies/ml or less at 48 weeks in 95 out of 104 (91%) and 92 out of 103 (89%) patients in the abacavir and PI arms, respectively. A similar HIV-1-RNA response was also seen at the 50 copy or less level [94/104 (90%) in the abacavir arm versus 88/103 (85%) in the PI arm].

This sustained suppression of the plasma viral load is also likely to be dependent upon ART history and the duration of HIV-1 RNA suppression before treatment simplification, making this a therapeutic strategy that may not be as effective in patients who have initiated treatment with sub-optimal ART. A similar study of simplified combination therapy using abacavir/Combivir as the switch regimen [16] showed that treatment with zidovudine as part of a mono or dual NRTI combination prior to the initiation of HAART was a

Table 2. Adverse events resulting in discontinuation of study treatment.

2NRTI/ABC (events = 8)	2NRTI/PI (events = 14)
Suspected ABC hypersensitivity (n = 2)	Lipodystrophy (n = 5)
Cytolytic hepatitis or elevated AST/ALT (n = 2)	Nausea and vomiting (n = 3)
Lactate elevation	Elevated triglyceride and cholesterol levels (n = 2)
Headache, dizziness and pain in jaws	Lactate elevation
Diarrhoea	Worsening renal function
Duodenal ulcer	Nephritis
	Jaundice

ABC, Abacavir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

determinant for virological failure following the switch to simplified therapy. In contrast, patients included in this study were required to have maintained viral suppression following the first initiation of ART. Therefore, although initial treatment with a dual NRTI combination was an acceptable criterion for inclusion, few patients with such a treatment history (13%) were actually included in the study population.

The association between PI therapy and lipid abnormalities has been well-documented [17–19], and the proportion of patients in this study with elevated plasma lipid levels at entry was not unexpected (> 60% of patients in each arm for cholesterol). After the 48 week treatment period, however, the abacavir arm was associated with significant improvements in lipid abnormalities compared with the PI arm, with respect to the median change from baseline for cholesterol and non-fasting triglyceride plasma levels ($P < 0.001$ and $P < 0.04$, respectively). Although the patients in this study population were not assessed for the presence or perception of body shape changes, the reduction in plasma lipid levels following the substitution of PI is a positive outcome for the potential prevention of clinical manifestations of fat redistribution or cardiovascular complications. Furthermore, although the use of non-fasting samples in this study might have diluted some of the difference between treatment arms, it is unlikely to have created one, and one recent study [20] demonstrated good correlation between fasting and non-fasting plasma triglyceride levels. An improvement in lipid profile and insulin sensitivity after the switch to abacavir has been demonstrated in fasting samples from a similar 31 patient comparison: a statistically significant decrease in triglyceride and cholesterol levels was seen as early as 12 weeks after switching, and was sustained over 48 weeks [21]. A post-switch trend of improved cholesterol and insulin sensitivity but not triglyceride levels was also observed in fasting samples from a 34 patient sub-group of this study [22].

An additional assessment of the metabolic impact of randomized therapy was made via the determination of plasma lactate and anion gap, both of which have been reported to be elevated with prolonged exposure to NRTI [23,24]. Although baseline values were not determined (because of the later introduction of these assessments via an amendment of the protocol), the measurement of these parameters on at least two occasions during the study allowed for the detection of differences over time or between treatment arms. Median plasma lactate levels were normal for both arms and did not alter with duration of treatment. In addition, the proportion of patients with hyperlactaemia at any time-point was low, and only one patient in each treatment arm discontinued randomized treatment as a result of elevated plasma lactate. Similarly, measurement of the anion gap showed that

there was little difference in median values over time or between the abacavir and PI arms, although a slight increase above the upper limit of normal (> 14 mmol) was evident at both time-points in each treatment group.

The frequency of mutations in RT RNA after rebound was low, with a single mutation (M184V) detected in three of the four patients who had simplified to abacavir-containing therapy. However, with only six patients meeting the definition of virological failure in this study, and a switch to alternative HAART in just three of these, conclusions regarding the likelihood of successful salvage following rebound are difficult to make. Certainly, the observed association of virological failure in the abacavir arm with the M184V mutation only could reasonably be expected to allow a number of salvage options for therapy.

Treatment was generally well tolerated. Although the incidence of treatment-related adverse events did not significantly differ between arms, randomized treatment was discontinued as a result of an adverse event in a higher number of patients remaining on PI-based HAART compared with those who had switched to abacavir (14 versus eight), including five cases of morphological changes suggestive of lipodystrophy. Although side-effects are a well recognized problem of HAART, and have been shown to contribute to the discontinuation of therapy, the substantial number of patients in this study electing to stop PI treatment because of an adverse event may have been partly due to a negative perception of PI. An open-label trial design has advantages in terms of the assessment of treatment outcome in a 'real-life' setting, but it could also be expected to result in a higher number of premature discontinuations from a therapy viewed as having the potential to cause serious metabolic alterations. The percentage of patients who experienced symptoms of a hypersensitivity reaction (2%) was low in comparison with previous studies [5,25].

As expected in this patient population, with long-term suppression of plasma HIV-1-RNA levels, adherence to pre-study PI-based HAART was high in both treatment arms, and there was little change in the level of adherence over the 48 week treatment period. In terms of difficulty in taking each therapy in the randomized treatment regimen, however, a greater improvement from baseline was seen at 48 weeks for the abacavir arm. Although such a measurement can only be made on a subjective basis, regimen simplicity is an important consideration in the formulation of a therapeutic strategy that at present must be considered to be life-long. Insufficient drug exposure because of sub-optimal adherence is among the major causes of antiretroviral treatment failure, making ease of dosing a key finding of this study.

Conclusion

These data demonstrate that the replacement of PI by abacavir in a triple combination regimen after prolonged suppression of plasma HIV-1 RNA is a generally well-tolerated and successful treatment option in patients who have not received mono or dual ART as part of their treatment history. Such a strategy allows for continued virological suppression, improvements in lipid abnormality profiles and enhanced ease of dosing. In addition, the early detection of virological rebound in individuals receiving simplified abacavir-based HAART may allow a transfer back to PI-containing regimens, saving both the protease and non-nucleoside reverse transcriptase inhibitor classes as future therapy options.

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