

Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine

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Background: Highly active antiretroviral therapy containing three nucleoside reverse transcriptase inhibitors has been somewhat successful, but the clinical efficacy is unclear.

Methods: Randomized, controlled, open-label trial of 180 antiretroviral drug-naïve HIV-infected patients allocated to a regimen of abacavir, stavudine and didanosine (A/S/D, $n = 60$), zidovudine and didanosine (Z/D, $n = 60$) or zidovudine, didanosine and zalcitabine (Z/D/C, $n = 60$); the latter two in combination with lamivudine and zalcitabine. The primary endpoint was HIV plasma RNA ≤ 20 copies/ml after 48 weeks.

Results: At baseline, the median CD4 cell count was 161×10^6 cells/l (range, 0–920) and the HIV RNA was 5.0 log₁₀ copies/ml (range, 2.7–6.7). At 48 weeks, 43% in the A/S/D arm had a HIV RNA ≤ 20 copies/ml, compared with 69% in the Z/D arm ($P < 0.01$) and 62% in the Z/D/C arm ($P < 0.05$). In a multivariate analysis, the A/S/D arm had an odds ratio of obtaining a viral load of ≤ 20 copies/ml at week 48 of 0.25 [95% confidence interval (CI) 0.10–0.59] versus Z/D and 0.53 (95% CI, 0.33–0.83) versus Z/D/C. The A/S/D arm had a particularly poor outcome in patients with higher viral load and AIDS at baseline: 63% had to discontinue A/S/D (any drug). Side effects were more frequent in the A/S/D arm and included neuropathy 27%, suspicion of hypersensitivity 12%, and increase in lactate accompanied by systemic symptoms 8%.

Conclusion: The A/S/D regimen had a low efficacy and a high frequency of adverse events and cannot be recommended.

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Introduction

Highly active antiretroviral therapy (HAART) usually contains two nucleoside reverse transcriptase inhibitors

(NRTI) combined with a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) [1,2]. Regimens including three NRTI have shown promise as well, either used after the viral

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replication has been brought under control by other regimens [3,4] or as initial therapy [5]. However, the efficacy of triple-NRTI regimens has been questioned, and they are generally not considered first choice in antiretroviral drug-naïve patients [1,2].

So far, the triple NRTI regimen most thoroughly evaluated has been the combination of lamivudine, zidovudine and abacavir. One of the main reasons for using combination therapy against HIV is to broaden the genetic barrier towards resistance. In this respect the combination mentioned above is far from optimal, as abacavir shares resistance mutations with both lamivudine (M184V) and zidovudine (T215F/Y, M41L as well as other nucleoside excision mutations) [6].

The present study evaluated a triple NRTI regimen including abacavir in combination with stavudine and didanosine (A/S/D). The two potential cross-resistance mutations K65R and L74V, selected for by both abacavir and didanosine, are rarely seen during combination therapy *in vivo* [7,8]. Therefore, it was presumed that there was no major cross-resistance in the A/S/D combination. Abacavir is considered the most potent NRTI and monotherapy with the drug has been associated with a two log decrease in plasma HIV RNA. Furthermore, the drug has a wide genetic barrier. Stavudine and didanosine is a frequently used combination of NRTI, and high-level phenotypic resistance to both drugs is rarely observed [9]. Abacavir does not have overlapping toxicity with the two other drugs, a prerequisite for a clinical successful combination. As an investigator-driven group, we were further stimulated by the lack of interest in the combination from the pharmaceutical industry, which may explain the lack of virological and toxicological data for this combination.

The A/S/D combination was compared with ritonavir/saquinavir (R/S) nelfinavir and nevirapine (N/N) regimens, both also containing two NRTI (zidovudine and lamivudine) [10]. A comparison of the outcome from the two latter regimens in a larger number of patients has been made in a separate report [11].

Methods

Patients

The study was a multicentre study including patients from five centres in Denmark; departments of infectious diseases at Hvidovre Hospital, Rigshospitalet, Odense University Hospital, Aalborg Hospital and Marselisborg Hospital. The patients included in the present analysis were enrolled between January 1999 and January 2001. Eligible were patients aged 18 years or older with documented HIV infection and no prior

antiretroviral therapy. All patients fulfilling these criteria, as well as the criteria for starting antiretroviral therapy, could enroll. During the recruitment period, it was recommended that patients with HIV-related symptoms, CD4 cell counts $< 200-300 \times 10^6$ cells/l or HIV RNA $> 100\,000$ copies/ml were offered antiretroviral therapy. Exclusion criteria were contraindications to any study drugs, ongoing participation in controlled trials, pregnancy and lactation. Fertile women without safe contraception were also excluded. Fifty-six patients were needed in each arm according to the power calculations (superiority study capable of detecting a 25% difference between the arms, with an α value of 0.05 and a β value of 0.20). Furthermore, it was assumed that 60% of the patients in the control arms would obtain HIV RNA levels of < 20 copies/ml at week 48.

The patients were randomized to abacavir 300 mg twice daily, stavudine 40 mg twice daily and didanosine 400 mg once a day (A/S/D) or ritonavir 400 mg, saquinavir 400 mg, zidovudine 300 mg and lamivudine 150 mg all twice daily (R/S; $n = 60$), or nelfinavir 1250 mg, nevirapine 200 mg, zidovudine 300 mg and lamivudine 150 mg all twice daily (N/N; $n = 60$). Stavudine and didanosine doses were reduced to 30 mg twice daily and 250 mg once a day, respectively, in those weighing < 60 kg. Saquinavir was administered as soft gel capsules (Fortovase) and ritonavir administered as capsules. Nevirapine was dosed as 200 mg daily lead-in for the first 2 weeks. The randomization was central, with no stratification, and done in blocks of 10.

The recommendations with respect to drug interactions were as below; otherwise, there were no restrictions with respect to medications. The protocol did not provide rules for second-line treatment: the choice of which was left to the treating physician. Dose reductions were not allowed; the only dose change possible was a change in R/S to 100/1000 mg, which was amended in July 2000.

The patients were seen at weeks 0, 2, 4, 8, 12 and subsequently every 12 weeks. The follow-up for the present study terminated in January 2002 at which time all enrolled patients had passed the window for their week 48 visit.

Demographic data and data for previous AIDS diagnoses were obtained at baseline.

At baseline and at all follow-up visits, CD4 cell counts and plasma HIV RNA were determined. The Ultra Sensitive method (Roche Molecular Systems, Branchburg, New Jersey, USA) was used for HIV RNA analyses. The analyses were performed in real-time with a lower limit of detection of 20 copies/ml.

Along with the surrogate marker measurements, routine clinical and laboratory controls (liver and kidney function test, S-amylase, hematology) were performed. Non-fasting triglycerides, total cholesterol and serum lactate were optional analyses.

All adverse drug reactions and their severity (grade 1–4) were recorded and coded according to World Health Organization guidelines.

Analyses

The A/S/D arm was added as a third arm to an ongoing randomized, open-label study of N/N versus R/S. It was optional for the patients and physician to have the patient randomized to the three-arm version of the study. The N/N versus R/S study recruited for a longer period and was also open to NRTI-experienced patients [11]. The A/S/D arm was compared with the two other PI containing arms one at a time. Overall analyses (comparing all three arms) were not performed. The primary analyses were performed according to the intent-to-treat principle (i.e., all patients were followed until the completion of follow-up and included in the analyses, irrespectively of whether they had or had not discontinued the medication to which they were randomized).

The primary study endpoint was the virological response analysed as the proportions of patients with HIV RNA ≤ 20 copies/ml. In addition, the average area under the curve minus baseline (AAUCMB) was compared for the three arms. The CD4 cell count change was a secondary study endpoint. Finally, the time to undetectable viral loads in the three arms was compared using Kaplan-Meier timetables.

The principle ‘missing values equal failures’ was applied; that is for any patient whose HIV RNA data was missing at a given point in time, the value of HIV RNA was regarded as above the lower limit of detection. The only exception to this was when a patient’s HIV RNA value was missing at some point but was below the lower limit of detection at the time point just before and just after the specific time point. Such missing HIV RNA values were excluded from the analysis but not counted as failures.

In addition to the intent-to-treat analyses, virological response was also assessed for patients remaining on primary allocated medication (as treated analyses). According to the protocol, the time to virological failure was analysed using a viral load cut-off of 400 copies/ml.

During the evaluation of the safety of the regimens, the primary endpoint was the number of patients who discontinued the study drug because of treatment-limit-

ing adverse events. Secondary endpoints were the individual adverse events.

Statistical analyses were performed in the SAS program (SAS, Cary, North Carolina, USA). Non-parametric tests such as Kruskal–Wallis’ test and parametric tests such as the chi-squared or Fisher’s exact test were used if appropriate. Survival analysis was based on time zero being the time of randomization. *P* values were all two sided and values < 0.05 were considered significant.

Results

A total of 180 patients was randomized in the study (Fig. 1). Two patients were randomized by error, as they had prior NRTI experience, and are excluded from the analyses (both were randomized to N/N and had successful outcome). Two patients did not start randomized treatment; they were both included in the analysis. Of the patients analysed, the distribution between the arms was R/S 60, N/N 58 and A/S/D 60. Generally, the arms were balanced with regard to baseline characteristics (Table 1). However, there was a tendency towards a higher CD4 cell count and fewer AIDS cases in the A/S/D arm. At baseline, the median CD4 cell count was 161×10^6 cells/l (range, 0–920) and the median viral load $5.0 \log_{10}$ copies/ml (range, 2.7–6.7). During the 48 weeks, three patients, one from each arm, were lost to follow-up, and five died (R/S 1, N/N 2 and A/S/D 2). Five patients experienced a new AIDS-defining event (R/S 2, N/N 2, A/S/D 1).

Using the intent-to-treat approach, 69% of the patients in the N/N arm had an HIV RNA < 20 copies/ml at week 48 compared with 43% in the A/S/D arm ($P < 0.01$) (Fig. 2). In the R/S arm, 62% had a plasma HIV RNA level < 20 copies/ml ($P < 0.05$ versus A/S/D arm). In the analyses presented above, patients who changed treatment were included according to the arm to which they were randomized. Although not included in the primary protocol, an analysis was also performed in which patients stopping or changing treatment were considered as having virological failure. In that analysis, the A/S/D arm performed inferiorly compared with both other arms, but the difference was not statistically different (data not shown). In an analysis including only patients on randomized treatment, 87, 76 and 59% had < 20 copies/ml at week 48 in the R/S, N/N and A/S/D arms, respectively.

According to the protocol, analyses of the virological response was grouped by those with and without an AIDS diagnosis at baseline, in patients with a viral load below or above 20 000 copies/ml and in those with a CD4 cell count below or above 50×10^6 cells/l at

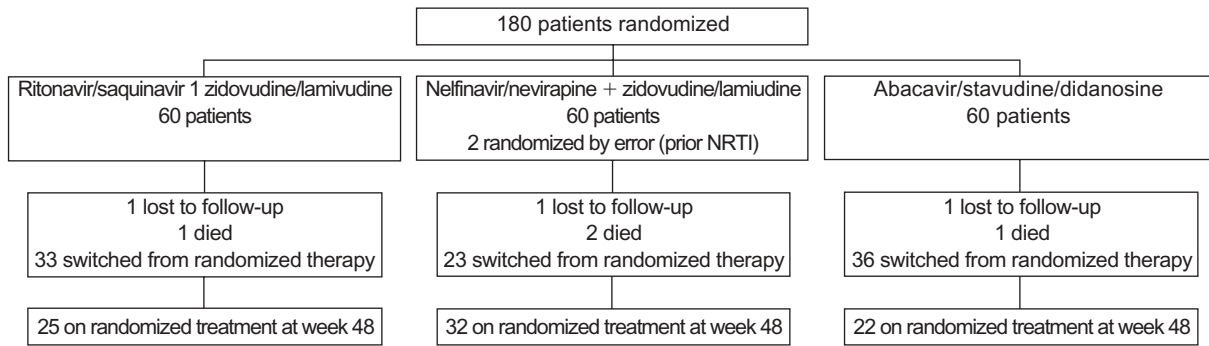


Fig. 1. Patient disposition at week 48. The patients remained under follow-up after premature discontinuation or switch from randomized therapy.

Table 1. Baseline characteristics.

	R/S	N/N	A/S/D
Age [years (range)]	36 (25–62)	36 (26–73)	40 (23–69)
Gender (% female)	23.7	22.8	28.3
Ethnicity (% Caucasian)	78.3	81.0	76.7
HIV transmission group (%)			
Men who have sex with men	40.7	50.9	48.3
Injecting drug user	6.8	7.0	5.0
Heterosexual	44.1	36.8	43.3
AIDS (%)	28.8	22.8	13.3
CD4 cell count [$\times 10^6$ cells/l (range)]	152 (0–570)	144 (0–920)	190 (0–819)
HIV RNA [\log_{10} copies/ml (range)]	5.0 (2.7–6.4)	5.1 (3.4–6.4)	5.0 (3.5–6.3)

R/S, zidovudine/lamivudine with ritonavir/saquinavir; N/N, zidovudine/lamivudine with nelfinavir/nevirapine; A/S/D, abacavir/stavudine/didanosine.

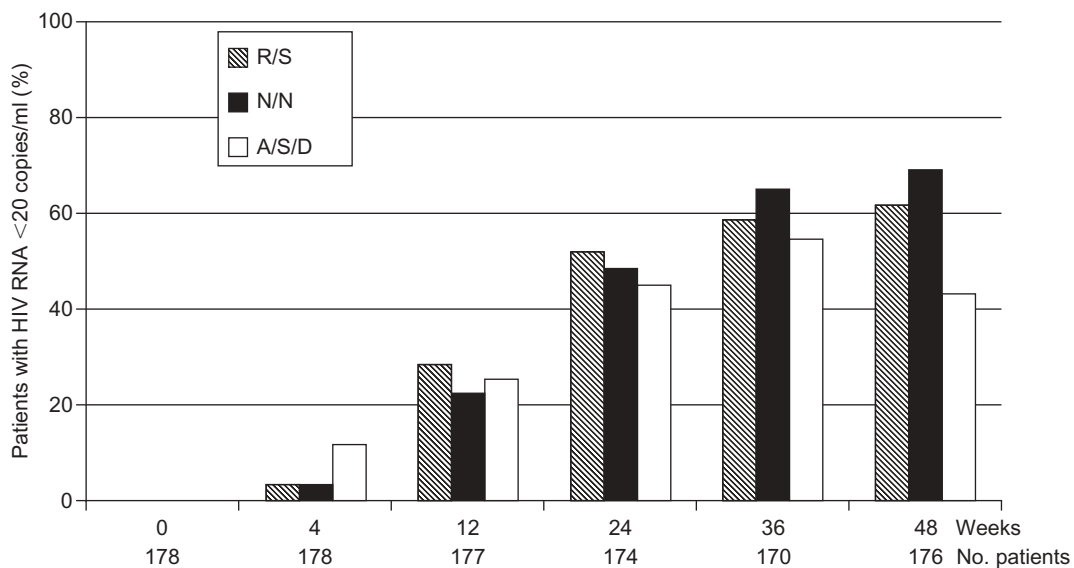


Fig. 2. Proportion of patients with HIV RNA ≤ 20 copies/ml after starting an initial highly active antiretroviral regimen of zidovudine/lamivudine with ritonavir/saquinavir (R/S), zidovudine/lamivudine with nelfinavir/nevirapine (N/N) or abacavir/stavudine/didanosine (A/S/D). Intent-to-treat analysis included patient data after premature switches from randomized therapy with 'missing values equalling failures'. If HIV-RNA was ≤ 20 copies/ml just before and just after a missing measurement, the measurement was excluded from the analysis rather than considered a failure, as reflected in the varying number of patients listed in the figure. The only significant differences were observed at week 48 between N/N and A/S/D ($P < 0.01$) and R/S and A/S/D ($P < 0.05$).

baseline. In the strata of patients with the higher viral load, significantly fewer patients in the A/S/D arm had a viral load ≤ 20 copies/ml at week 48 (Fig. 3). In patients with AIDS at baseline, the A/S/D arm had a very unfavourable outcome, with none of the eight patients reaching a viral load ≤ 20 copies/ml at week 48; a worse outcome in the A/S/D arm was also observed in patients with a low CD4 cell count and a high viral load (Fig. 3).

The unadjusted odds ratio (OR) for obtaining a viral load ≤ 20 copies/ml for the A/S/D arm was 0.69 [95% confidence interval (CI), 0.48–0.99] when compared with the R/S arm and 0.34 (95% CI, 0.16–0.73) when compared with the N/N arm. When adjustment was made for baseline characteristics including a history of an AIDS-defining event, CD4 cell count, HIV RNA, risk group, ethnicity, gender and calendar time of randomization, the A/S/D arm had significantly lower chance of obtaining virological success: OR 0.53 (95% CI, 0.33–0.83) versus R/S and 0.25 (95% CI, 0.10–0.59) versus N/N.

In the AAUCMB analysis, the A/S/D arm performed inferiorly, with an average fall of 2.6 \log_{10} copies/ml in HIV RNA compared with 3.1 \log_{10} copies/ml in the N/N arm ($P < 0.05$) and 3.0 \log_{10} copies/ml in the R/S arm (NS).

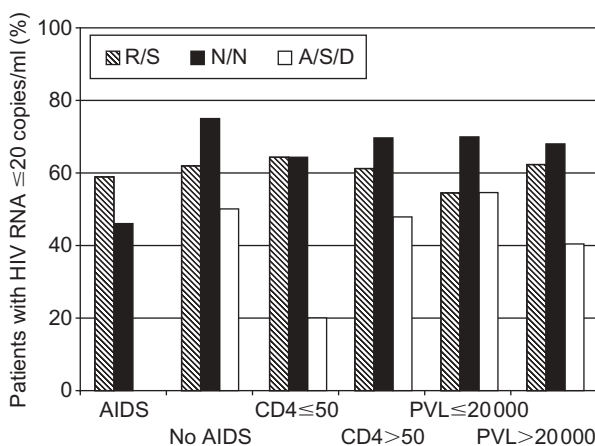


Fig. 3. Proportion of patients with plasma HIV RNA ≤ 20 copies/ml at week 48. The patients are divided according to protocol-defined baseline characteristics. A significant difference ($P < 0.05$) was observed between A/S/D (abacavir/stavudine/didanosine) and N/N (zidovudine/lamivudine with nelfinavir/nevirapine) in all subgroups except the low HIV RNA stratum. The R/S (zidovudine/lamivudine with ritonavir/saquinavir) arm differed significantly from the A/S/D arm among the patients with AIDS at baseline, and in the low CD4 cell count and high HIV RNA strata. CD4 ≤ 50 and > 50 , CD4 cell counts ≤ 50 and $> 50 \times 10^6$ cells/l, respectively; PVL $\leq 20\,000$ and $> 20\,000$, plasma viral loads of $\leq 20\,000$ and $> 20\,000$ copies/ml, respectively.

Similar tendencies for the kinetics of the viral decline were observed, with a median time to viral load ≤ 20 copies/ml of 28, 26 and 30 weeks in the R/S, N/N and A/S/D arms, respectively. Once undetectable, the time to detectable virus did not differ significantly between the groups.

A significant increase in the CD4 cell count at week 48 was observed in all three arms (140, 185 and 140×10^6 cells/l in the R/S, N/N and A/S/D arms, respectively) with no significant differences between the groups.

A substantial proportion of the patients changed treatment during the first 48 weeks (Fig. 4): 63, 58 and 45% of the patients randomized to A/S/D, R/S and N/N arm ($P < 0.05$ versus A/S/D), respectively, changed at least one component in their initial regimen. Furthermore, the number of changed drugs was greater in the A/S/D arm where 42% of those who changed needed to change all three drugs compared with 8% and 29% in the N/N and the R/S arms, respectively. In the N/N and the R/S arms, change of regimen usually occurred within the first 3 months of treatment. In contrast, discontinuation in the A/S/D arm continued over the 48 weeks at an almost constant rate. The drugs discontinued most frequently were didanosine and stavudine in the A/S/D arm and ritonavir and saquinavir in the R/S arm. These four drugs were discontinued in approximately half of the patients exposed. At the other end of the spectrum, lamivudine was only rarely switched. The likelihood that the patients were changed to a PI, boosted PI or efavirenz was equivalent in the three arms. More patients in the A/S/D arm were changed to abacavir, zidovudine and lamivudine (A/S/D 10 versus N/N 3 and R/S 2).

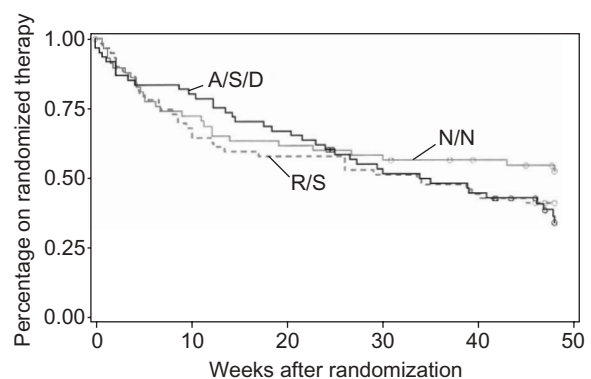


Fig. 4. Discontinuation of randomized treatment for any component of a regimen. Those in the A/S/D arm discontinued randomized treatment significantly more frequent than those in the N/N arm ($P < 0.05$). A/S/D, abacavir/stavudine/didanosine; N/N, zidovudine/lamivudine with nelfinavir/nevirapine; R/S, zidovudine/lamivudine with ritonavir/saquinavir.

By far the most common reason for change in treatment was side effects. Severe adverse events (grade 4), including hospitalizations, occurred in 7%, 12% and 13% of the patients in the R/S, N/N and A/S/D arms, respectively (grade 3–4: 17%, 26% and 28%, respectively); these differences did not reach statistical significance. The type of side effects differed between the three arms. Neuropathy was significantly more frequent in the A/S/D arm, where it was reported in 27% ($P < 0.001$ towards both other arms). The neuropathy was usually reversible after discontinuation of stavudine and didanosine, but one patient who also had motor symptoms remains on gabapentin for sensory neuropathy 2 years after discontinuation. Hypersensitivity towards abacavir was suspected in 12% among the A/S/D patients.

In this arm, a further five patients had to discontinue treatment because of increased lactate associated with clinical symptoms, while none had to do so in the two other arms. The five patients had a plasma lactate level of 3.9 mmol/l (range, 2.6–9.1), which normalized within 1–3 months. In these patients, transaminases were 115 U/l (range, 20–210; upper limit of normal, 50); lactate dehydrogenase was slightly increased in four of the five; amylase was increased in four of the five and they had an average weight loss of 3 kg (range, 0–5). None of the patients had acidosis, and all parameters were normal at baseline and normalized after cessation of didanosine and stavudine treatment. The major symptom reported was abdominal pain, but none of the patients was diagnosed with pancreatitis.

A significant higher level of lactate was observed at week 48 in the A/S/D arm compared with both the other arms (median 1.8 mmol/l versus 1.1 mmol/l N/N ($P < 0.01$) and 1.3 mmol/l R/S; $P < 0.05$; $n = 77$). In addition, the levels of lactate dehydrogenase in serum at 48 weeks were significantly higher in this arm, and the amylase level was significantly higher than in the R/S arm. In the R/S arm, 35% stopped treatment because of gastrointestinal complaints, significantly more than in the A/S/D arm ($P < 0.005$). Rash resulting in drug discontinuation was observed in 8, 7 and 0% in the N/N, A/S/D and R/S arms, respectively.

The non-fasting triglycerides did not differ significantly between the arms, but cholesterol at week 48 was higher in the N/N arm compared with the A/S/D arm (median 5.5 versus 4.8 mmol/l; $P < 0.05$).

Discussion

The present study evaluated a regimen containing three NRTI. Both with respect to efficacy and side effects,

the regimen was unsuccessful compared with two other regimens including drugs from two or three drug classes. This was observed despite the fact that the A/S/D arm had a favourable baseline profile; after adjustment for this, the inferiority of the A/S/D arm became even more evident.

Studies reported so far have given the impression that triple NRTI regimens, such as abacavir, lamivudine and zidovudine [5,12] or lamivudine, stavudine and didanosine [13], are less efficient in controlling viral replication than NNRTI- and PI-containing regimens. When the present study was planned, it was considered that the A/S/D arm was potentially more efficacious than a combination of abacavir, lamivudine and zidovudine. This was because there were no known shared resistance mutations in the abacavir, lamivudine and zidovudine combination. Further, it was assumed that the A/S/D combination was more efficient than a combination of didanosine, stavudine and lamivudine because of the greater genetic barrier provided by abacavir compared with lamivudine. One reason why the regimen failed might be the fact that mutations speeding up the excision of nucleoside analogues (nucleoside excision mutations) have been shown to provide a more cross-class resistance among NRTI than previously indicated [14]. It is clear that cross-class resistance is a threat to a combination only involving that class, as it will tend to diminish the genetic barrier. The increasing number of patients infected with a primary resistant HIV [15] is a potential threat to all regimens, but in particular to the susceptible triple NRTI regimens. At least in a few of the patients included in the present study, this was the cause of failure. Furthermore one of the cross-resistance mutations, K65R, which we assumed avoidable in the A/S/D combination, did in fact appear in 5 patients [16].

The side effects were substantial in the A/S/D arm. Nearly all of the adverse effects in the arm could be related to what is considered mitochondrial toxicity, with neuropathy and elevated lactate being most prominent. A nucleoside combination of didanosine and stavudine has been extensively used in many studies as a backbone to regimens containing an NNRTI [17,18,19] and an NNRTI and with a PI [13]. This combination has also been studied against zidovudine and lamivudine as a backbone for indinavir treatment [20]. In all of these scenarios less than 15% have discontinued therapy because of neuropathy. In a study of neuropathy among patients treated with didanosine and stavudine, the frequency of clinical neuropathy was 12% [21]. In some studies, didanosine has increased stavudine-associated neuropathy [22], and this is even further increased by hydroxyurea [23].

Neuropathy is not an established side effect to treat-

ment with abacavir. Therefore, the high incidence observed in the A/S/D arm is most likely not a simple result of overlapping toxicities. Rather, abacavir might sensitize mitochondria to the damage of the other two NRTI or it might alter the degradation of these drugs either systemically or within the mitochondria.

The increase in lactate observed in the A/S/D arm was to be expected. Stavudine has previously been shown to cause an increase of similar magnitude but of unknown clinical significance [24]. Of far greater concern are the five patients with increased lactate who had to stop treatment because of accompanying symptoms and liver enzyme elevation. This picture is a well-known clinical entity [25] but usually is only seen in 1% of patients taking didanosine plus stavudine. The fact that we observed it in 8% of the patients in the triple NRTI arm (A/S/D) further supports the suggestion that abacavir enhances mitochondrial toxicity.

The control arms were not the ones we would have chosen in 2003; they are complex and at least the R/S arm carries a high risk of adverse events. However, the R/S arm – the reference-arm – has shown similar efficacy compared with traditional HAART [10] and was considered standard of care in Denmark in 1998. The N/N arm was an experimental arm. The rationale was to provide maximal efficacy with minimal toxicity by adding an NNRTI to the PI regimen with least side effects.

The high discontinuation rate of study drugs is of great concern, but there are several explanations for this. First of all, it cannot be ignored that especially the A/S/D and the R/S regimens induced many adverse events, which is reflected in the significantly higher discontinuation rate observed in these regimens compared with the N/N arm. Additional explanations for the discontinuation rate are patients' motivation, which may have waned with the improved survival and absence of deaths among close friends. Further, altered attitudes among health professionals may have affected the discontinuation rate. It has become increasingly clear that poor adherence is the major threat to the success of HAART [26]; unfortunately, prospective assessment of adherence was not made in this trial. Poor adherence is, however, often associated with side effects, and changes in antiviral regimens are, therefore, often encouraged by the experience of side effects by the patient. Adding further to this process is the availability of more convenient regimens. Discontinuation rates seem to be time dependable, as illustrated by a substantially increased discontinuation rate for R/S 400/400 mg over time (O. Kirk, personal communication).

Most importantly, we presume that the high discontinuation rate does not influence the outcome of the

present study. Consequently, a high switch rate would tend to diminish differences between the arms not produce them. The only scenario where a high frequency of switches produces differences between the arms is when the primary regimen influences the choice of the second regimens – and the second regimens have different efficacies. More patients in the A/S/D arm were changed to abacavir, zidovudine and lamivudine, but this was not likely to generate the overall results of the study, as the inferiority of the A/S/D arm also showed up in the on-treatment analysis.

In summary, the evaluated triple NRTI regimen carried many side effects and had a low efficacy. It cannot be recommended for use in drug-naïve patients.

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