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Original article

Efficacy and safety of combination therapy with delavirdine and zidovudine: a European/Australian phase II trial

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Abstract

The objective of the study was to investigate the safety and antiviral effect of three delavirdine dose regimens or placebo in combination with zidovudine in patients who were already taking zidovudine. Eighty-nine symptomatic HIV-1 seropositive individuals with CD4$^+$ cell counts between 50 and 350 cells/μl were included in this trial The influence of combination therapy on viral susceptibility to both zidovudine and delavirdine was investigated. Death or the occurrence, or re-occurrence of an AIDS-defining illness was considered as a clinical endpoint. The addition of delavirdine to the antiretroviral treatment regimen resulted in a significant, but transient, reduction in virus load, as determined by quantitative RNA measurements. CD4$^+$ cell count did not change significantly. Susceptibility to zidovudine remained unchanged after 12 weeks of combination therapy, while 70% of the patients demonstrated a substantial decrease ($>$ 10-fold) in sensitivity to delavirdine. Two patients suffered from an AIDS-defining disease during the study. No deaths occurred. Generally, the drug appeared to be safe. Skin rash was the most frequently observed adverse event (52%). In most patients the rash either resolved spontaneously or was treated successfully with

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a short course of antihistamines. The definite place of the compound in the management of HIV disease, in particular when given in combination with other antiretroviral agents, remains to be further explored.

Keywords: Delavirdine; HIV; Zidovudine

1. Introduction

Delavirdine, a bisheteroarylpiperazine (BHAP), is a non-nucleoside reverse transcriptase inhibitor (NNRTI) [1,2]. Several non-nucleoside inhibitors have been described including the pyridinone derivatives, TIBO-compounds, a-APA derivatives, nevirapine and BHAPs [3–7]. NNRTIs are antiretroviral compounds that are structurally unrelated but have a common mechanism for inhibition of HIV-1 reverse transcriptase (RT). All NNRTIs bind to a hydrophobic pocket in the RT at a site distinct from the nucleotide-binding site but close to the residues of the polymerase catalytic site [8–11], leading to a significant slowing of the rate of polymerization catalyzed by the enzyme. Inhibition of RT interferes with the conversion of viral RNA to proviral DNA and its integration into host-cell DNA [12]. Antiretroviral therapy that interferes with the function of this enzyme has been shown to improve the prognosis of the HIV infection and delay the progression of clinical disease [13]. NNRTIs will probably have low toxicity because of their extraordinary specificity for HIV-1 RT [6]. NNRTIs are generally well tolerated, but mild skin rash is a frequently observed side effect [14–16].

Nowadays, there is consensus that the optimal first-line treatment of HIV infection consists of combination therapy with at least three antiretroviral agents [17]. At the time this study was performed, the exact place of NNRTIs in such combination regimens was not yet defined. Several studies have shown a beneficial effect of NNRTIs in combination with nucleoside RT inhibitors (NRTIs) because the development of NNRTI resistance is delayed [18] and the antiviral efficacy is higher due to synergism [3,19–22]. Monotherapy with any antiretroviral agent is considered obsolete nowadays, and this is also true for NNRTIs. In fact, studies have shown that there is a rapid development or selection of resistant virus variants during NNRTI monotherapy [23–25].

While resistance to NNRTIs caused by substitutions at amino acids 103 and 181, confers cross-resistance to all NNRTIs, delavirdine remains active against these mutant strains with a 50% inhibitory concentration (IC_{50}) of 3 mM [26]. Further, delavirdine increases the susceptibility to other antiretroviral agents, both NNRTIs and NRTIs. For example, a proline-to-leucine substitution at amino acid number 236 causes an approximately 70-fold increase in the IC_{50} of delavirdine, but increases the susceptibility to nevirapine, TIBO, and L-697,661 by 7–10-fold [26,27]. A tyrosine-to-cysteine substitution in Y181C increases the IC_{50} of all NNRTIs, but suppresses the development of resistance to zidovudine (approximately 35-fold reduction in IC_{50}) [28]. Mutant virus isolates harbouring a K103N, P236L, or Y181C substitution are reported to develop following delavirdine monotherapy [29].

Taking these findings into consideration, we hypothesized that the combination of delavirdine and zidovudine would increase the efficacy of zidovudine in individuals already receiving zidovudine. We designed a prospective study to compare the antiviral effect, safety, and effect on the development of drug resistance of delavirdine–zidovudine combination therapy with the effect of continued zidovudine monotherapy in symptomatic HIV-1 infected individuals.

2. Patients and methods

2.1. Study design

The study was designed as a multi-centre, double-blind, placebo-controlled trial. The patients were enrolled at 15 centres (three Australian and 12 European). Between October 1993 and July 1994, 89 patients were randomized to one of the four treatment arms (three arms with delavirdine, one arm with placebo). As the optimal daily dose of delavirdine was not yet defined when we started the study, we used two dose regimens, i.e. 200 and 400 mg tds delavirdine. Further, in order to investigate its effect on the incidence of skin rash, we also used a third, escalating-dose regimen, i.e. delavirdine 150 mg/day for 7 days, followed by 600 mg/day for 7 days and, then 1200 mg/day for the duration of the study (i.e. 24 weeks). Subjects who were initially randomized to placebo received delavirdine (300 mg tid) after 12 weeks. All patients had been taking zidovudine for at least 8 weeks before the study; six patients were taking zidovudine and zalcitabine. Treatment with either zidovudine (200 mg tds) or zidovudine/zalcitabine (200 + 0.75 mg tds) was continued during the study. The clinical endpoints of the study were death, occurrence of a new AIDS-defining illness, or recurrence of a previously existing AIDS-defining illness. Patients who were withdrawn from the study due to skin rash were asked to participate in a rechal-

lenge protocol with delavirdine in an escalating-dose regimen in order to investigate whether such a regimen could induce tolerance to the drug at the original dose. The protocol and the informed consent forms were approved by the medical ethics committee of each participating hospital. All patients gave written informed consent. The study was conducted in agreement with the declaration of Helsinki and its revisions [30].

2.2. Drug supply

Film-coated tablets containing either 50 or 100 mg delavirdine mesylate (Rescriptor®) and matching placebo were manufactured and supplied by the Upjohn, Kalamazoo, MI. Zidovudine and zalcitabine were obtained from commercial sources.

2.3. Patients

Individuals were eligible for the study if: (i) they were older than 16 years of age; (ii) had symptomatic HIV-1 infection; (iii) had one screening CD4 count >50 and $<350/\mu l$ within 3 months of the start of the study; (iv) had been taking zidovudine or zidovudine/zalcitabine for at least 8 weeks before the study and; (v) had acceptable results for laboratory investigations (abnormalities $\leq$ grade I on ACTG toxicity scale). Patients were excluded if they: (i) had any NNRTI experience; (ii) were on nucleoside therapy for more than 12 months; (iii) were hypersensitive to piperazine-type drugs; (iv) had participated in trials with investigational antiretroviral medications within 90 days of entering the study; (v) were concomitantly taking terfenadine or ketoconazole; (vi) were using 'hard drugs', or; (vii) were pregnant or lactating.

2.4. Clinical and laboratory evaluation

At the screening visit, the patient's medical history was taken and a physical examination and an ECG were performed. Blood was drawn for complete haematological screening, blood chemistry, and CD4 cell counting. Urine analysis, including screening for drug abuse, was performed. After enrollment, the participants were seen weekly for the first month and monthly thereafter. At each visit clinical and safety (haematology and serum biochemistry) assessments were done. Blood samples for pharmacokinetic analyses were taken every week for the first 4 weeks and at week 12. The ECG was monitored at baseline and at week 4. CD4 lymphocyte counts were determined at baseline and at weeks 2, 4, 8, 12, and 24. In the European centres, samples for quantitative determination of HIV-1 RNA were taken every visit for the first 12 weeks and at week 24. Further, at selected sites (Bichat-Claude Bernard Hospital, Paris, France; University Hospital, Utrecht, the Netherlands; Slotervaart Ziekenhuis, Amsterdam, the Netherlands) the viral susceptibility to the drugs was tested at baseline and after 12 weeks of therapy. The patients who originally received placebo and then delavirdine were assessed in the same way from the start of the active drug phase (week 12).

2.5. Laboratory methods

2.5.1. Quantitative HIV-1 RNA determination

Plasma HIV-1 RNA was quantified using the NASBA QT assay (Organon Teknika, Turnhout, Belgium), according to the instructions of the manufacturer. A detailed description of the method is published elsewhere [31,32].

2.5.2. Drug susceptibility assay

Peripheral blood mononuclear cells (PBMC) from the Dutch and the French patients were collected at baseline and at week 12 and were stored frozen in liquid nitrogen. Virus stocks were obtained by cocultivation at the end of the study. These procedures were performed according to the ACTG/Department of Defense consensus protocol [33].

2.5.3. Pharmacokinetics

Plasma concentrations of delavirdine mesylate (U-90152) and its *N*-deisopropyl metabolite (U-96183) were measured in heparinized plasma samples by Pharma Bio-Research (Zuidlaren, the Netherlands), using a validated, sensitive, and specific isocratic HPLC method.

2.6. Statistical Analysis

The median or mean change in surrogate markers from the prestudy value are presented for each of the delavirdine dose groups and placebo. Changes from baseline were tested at the 0.02 level, using a Wilcoxon signed-rank test. To test differences in effect between the treatment groups a Kruskal–Wallis rank sum test was used at the 0.05 level; when necessary, a pairwise comparison, using a Mann–Whitney rank sum test, was performed. Phenotypic resistance was examined and compared qualitively among the treatment groups. Data collected after a patient was rechallenged were not included in the analysis of surrogate markers. The development of new clinical features by patients in each dose group was compared qualitatively.

3. Results

3.1. Study population

Eighty-nine patients participated in the study: 23 were randomized to delavirdine 600 mg/day; 23 to delavirdine 1200 mg/day; 19 to the delavirdine escalating dosage regimen, and; 24 to placebo. After 12 weeks, the 24 patients in the placebo group were offered delavirdine at a dose of 900 mg/day: 20 patients started delavirdine, two patients had been withdrawn because of medical events, and two patients withdrew from the study in week 12 for personal reasons. Table 1 shows the entry characteristics of the study groups. The four treatment groups were comparable with respect to age, weight, baseline CD4 cell count and RNA load, and the percentage of patients with an AIDS-defining diagnosis at entry. The placebo-treated group contained more women than the other three treatment groups. The mean time patients had been taking zidovudine before the start of the trial varied between 5.0 months in the highest dose group and 8.1 months in the escalating-dose group.

3.2. CD4 cell count

Fig. 1 shows the median change in CD4 cell count in the four treatment groups. Although there was a slight initial increase in CD4 cell counts in the 600 and 1200 mg dosage groups, this was only transient and did not reach statistical significance when compared with CD4 cell counts of the placebo group. Changing from placebo to delavirdine 900 mg/day at week 12 did not affect the number of CD4 cells.

3.3. Quantitative HIV-1 RNA determination

In all treatment groups the circulating plasma viral load decreased significantly (Fig. 2) with P-values of < 0.001 at week 2. The maximum decrease was seen within 3 weeks of therapy and was 0.86 log in the 1200 mg dose group, 0.55 log in the 600 mg dose group, and 0.38 log in the dose escalating group. In the 1200 mg group, plasma RNA levels remained below baseline throughout the 24-week study period; however, at week 24 this reduction was no longer statistically significant. In the other dose groups RNA levels had returned to baseline values by week 8. In the placebo-treated group continuation with zidovudine monotherapy did not result in any change in RNA load, however, the addition of delavirdine at week 12 resulted in a decrease (0.83 log) in virus load after 1 week of combination therapy. After 3 weeks viral load had returned to baseline and remained stable for the rest of the study.

3.4. Drug susceptibility

Drug susceptibility was tested in a limited number of patients (Dutch and French patients, $n = 24$) at baseline and week 12. Delavirdine susceptibility changed significantly within the first 12 weeks of delavirdine therapy (Table 2). The median IC_{50} of delavirdine in the 600 mg group increased from 0.02 to 0.50 mM and in the 1200 mg group from 0.02 to 3.00 mM. In the dose-escalating group the IC_{50} changed from 0.03 to 0.25 mM. As expected, the susceptibility to delavirdine of placebo-treated patients remained unchanged. The IC_{50} values for zidovudine varied at baseline, probably because at entry the patients had beeen taking the drug for different times. The patients in the dose-escalating group had

Table 1
Entry characteristics of the treatment groups

Characteristic	600 mg	1200 mg	150 > 1200 mg	Placebo
Number (male female)	23 (21/2)	23 (21/2)	19 (16/3)	24 (16/8)
Mean age (years)	40	36	41	35
Range	(23–63)	(25–50)	(23–62)	(21–65)
Mean weight (kg)	68.9	71.1	70.4	67.9
Range	(48.0–86.0)	(50.0–101.6)	(49.0–96.2)	(52.0–97.5)
Mean months of prior antiviral therapy	6.4	5.0	8.1	6.1
Range	3.2–11.8	2.3–11.9	1.8–11.9	3.5–11.7
Number of patients with additional zalcitabine therapy prior to entry	2	1	1	2
Number of patients with AIDS defining diagnosis before entry	8	6	7	9
$CD4^+$ cell count (cells/ml)				
Mean	193	167	202	172
Median	152	195	183	160
Range	30–336	28–528	13–435	34–311
RNA load (log copies/ml)				
Mean	4.52	4.74	4.68	4.46
Median	4.38	4.53	4.66	4.50
Range	3.88–5.61	3.60–5.56	3.60–5.38	3.60–5.76

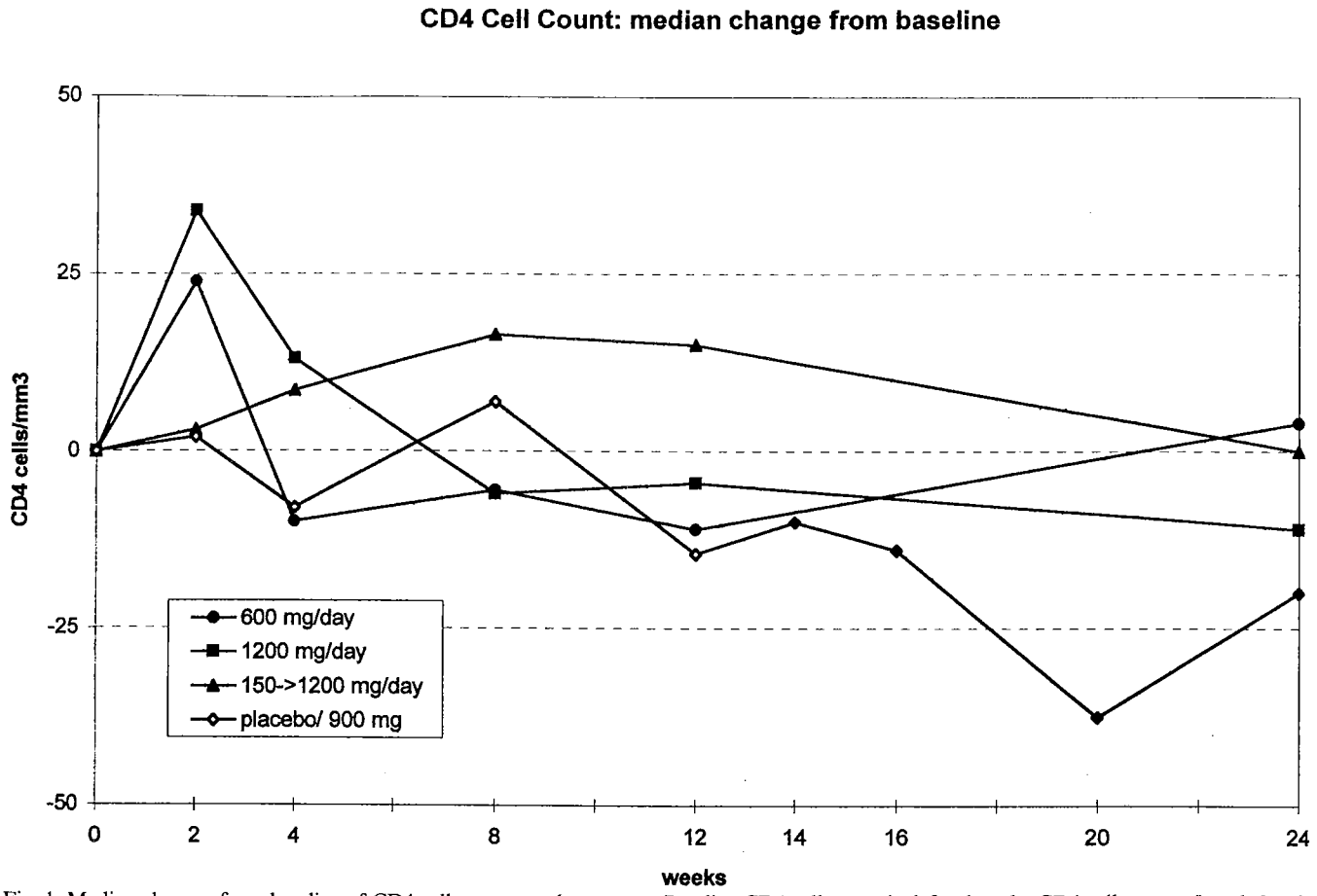

Fig. 1. Median changes from baseline of CD4 cell count per dose group. Baseline CD4 cell count is defined as the CD4 cell count of week 0 only. Patients receiving placebo during the first 12 weeks of the study were switched to delavirdine 900 mg/day at week 12. All patients received zidovudine or zidovudine/zalcitabine (zidovudine 600 mg/day, zalcitabine 2.25 mg/day) in combination with one of the dosages of delavirdine or placebo.

a median IC_{50} for zidovudine of 0.22 mM, compared with IC_{50} values of 0.03 mM and 0.07 mM in the 600 mg and 1200 mg dose groups, respectively, at baseline. Minor changes in median zidovudine sensitivity were observed during the first 12 weeks of the study, with the rise in IC_{50} in the 600 mg dose group from 0.03 to 0.13 μM being the most notable change. In two patients zidovudine resistance was suppressed. One patient treated with 1200 mg delavirdine per day had a baseline zidovudine IC_{50} of 0.85 μM and became 10-fold more sensitive to zidovudine at week 12. In the other patient, who was in the dose-escalating group, the IC_{50} decreased from 0.65 μM at baseline to 0.01 μM after 12 weeks. Both patients had been taking zidovudine for about 6 months before the start of the study.

3.5. Pharmacokinetics

Plasma delavirdine concentrations showed a large inter-subject variation (data not shown) and did not increase in proportion to the increasing dose administered. The concentration ratio of the metabolite U-96183 to delavirdine changed as the dose of delavirdine increased The lowest mean trough concentrations (C_{min}) of plasma delavirdine were found in the 600 mg dose group (1.8 mM) and the highest concentrations (C_{max}) were found in the 1200 mg dose group (33.1 mM). In the 1200 mg dose group, two patients failed to reach a steady state. Therefore, in order to avoid the risk of drug accumulation, the 900 mg dose was considered to be the optimal dose of delavirdine at that time. There was no relationship between C_{max} or C_{min} versus the antiviral effect.

3.6. Clinical efficacy, safety and tolerability

Of the 89 patients enrolled, 50 completed the study. Table 3 presents an overview of the incidence of adverse events and clinical endpoints, and reasons for withdrawal from the study. Thirty-nine patients withdrew, 35 of whom were receiving delavirdine and four of whom were receiving placebo. Among the patients who withdrew, 23 withdrew within the first 12 weeks of the study. The rate of withdrawal was similar in the

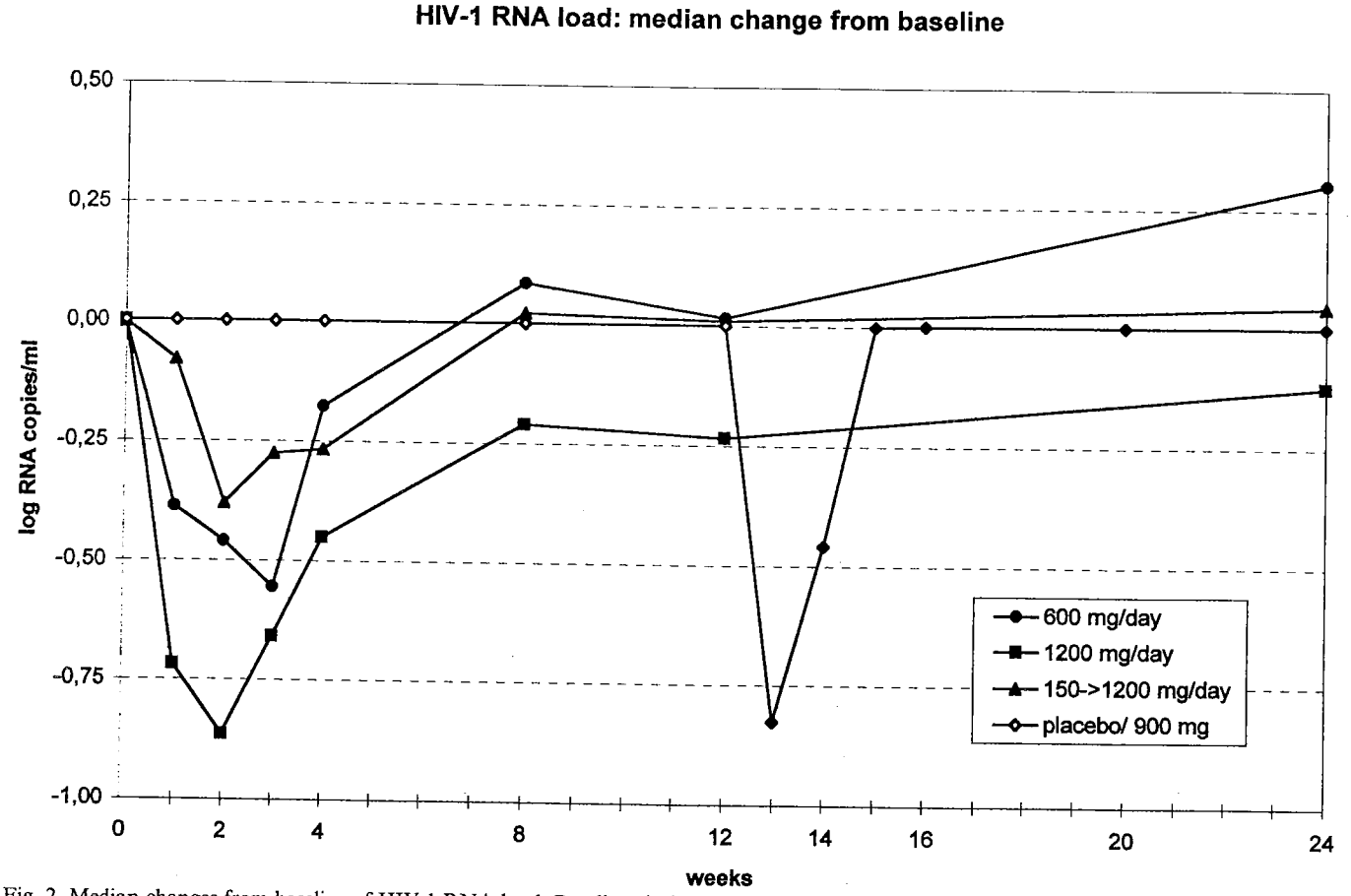

Fig. 2. Median changes from baseline of HIV-1 RNA load. Baseline viral load was defined as log number of RNA copies of week 0 only. Patients receiving placebo during the first 12 weeks of the study were switched to delavirdine 900 mg/day at week 12. All patients received zidovudine or zidovudine zalcitabine (zidovudine 600 mg/day, zalcitabine 2.25 mg/day) in combination with one of the dosages of delavirdine or placebo.

delavirdine treatment groups and was not dose related. The most frequent reason for withdrawal was the occurrence of a non-serious medical event, which was mostly skin rash. Skin rash was reported by 45 patients, one of whom received placebo. Skin rash was sometimes accompanied by fever, headache, and myalgia. Among the 85 delavirdine-treated patients, 18 (21%) withdrew because of skin rash. In the other 26 patients (31%), the skin rash disappeared either spontaneously or after a short treatment with an antihistamine. The maculopapular skin rash typically appeared within the first 2 weeks of dosing in all patients, except one. In that particular patient the skin rash occurred after 19 weeks of treatment with delavirdine. As this patient used concomitant medication, the role of delavirdine in the induction of the skin rash could not be confirmed. Eleven of the 18 patients who withdrew because of the skin rash were rechallenged with delavirdine. In 80% of them, the skin rash reappeared within 2 days, and consequently treatment with delavirdine was stopped definitively. Other medical reasons for withdrawal included gastrointestinal complaints ($n = 1$), hepatitis B ($n = 1$), grade III/IV elevated liver enzyme values ($n = 2$), grade III neutropenia and/or thrombocytopenia ($n = 2$), and bacterial pneumonia ($n = 1$). All patients recovered from the adverse events after discontinuation of delavirdine (or adequate therapy in the case of the pneumonia). Other medical events reported, not leading to discontinuation, were headache, fatigue, gastrointestinal discomfort, and myalgia.

Table 2
Median susceptibility (IC_{50}) of the clinical isolates for delavirdine and zidovudine at baseline (i.e., zidovudine monotherapy) and after 12 weeks of the combination therapy with zidovudine and delavirdine (600 mg, 1200 mg, escalating dose from 150 to 1200 mg) or continuation of zidovudine monotherapy (delavirdine placebo)

Dose group (daily dosage mg)	Delavirdine IC_{50} (μM)		Zidovudine IC_{50} (μM)	
	Baseline	Week 12	Baseline	Week 12
600	0.02	0.50	0.03	0.13
200	0.02	3.00	0.07	0.03
150>1200	0.03	0.25	0.22	0.28
Placebo	0.03	0.01	0.04	0.02

Table 3
Incidence of adverse events[a], clinical endpoints and dropouts

Event	Zidovudine monotherapy (n = 24)	Delavirdine/zidovudine (n = 85)[b]
Skin rash	1 (*1*)[c]	44 (*18*)
Gastro–intestinal complaints	1 (*1*)	1 (*1*)
Hepatitis B		1 (*1*)
Liver enzyme elevation		2 (*2*)
Neutropenia and/or-thrombocytopenia		2 (*2*)
Bacterial pneumonia		1 (*1*)
Clinical endpoint		2 (*2*)
Withdrawal, personal request	2 (*2*)	8 (*8*)
Total number	4 (*4*)	61 (*35*)

[a] Only those events that led to discontinuation are mentioned.
[b] This figure includes 65 patients who were randomized to one of the delavirdine arms of the study plus 20 patients treated with placebo initially who received delavirdine after 12 weeks.
[c] The bold and italic printed figure between brackets indicates the number of patients in whom the occurrence of the events resulted in withdrawal from the study.

Two patients (one in the 600 mg group and one in the dose-escalating group) reached a clinical endpoint during the study. In these, the diagnosis of a new AIDS-defining event was made, i.e. non-Hodgkin's lymphoma and *Pneumocystis carinii* pneumonia. There were no deaths during the study.

4. Discussion

The results of this trial demonstrate that addition of delavirdine to treatment with zidovudine resulted in a significant reduction of viral burden. This beneficial effect was most pronounced during the first 4–8 weeks of the study. With the highest dose of delavirdine, i.e. 1200 mg daily, the effect was prolonged but was no longer significant at the end of the study. The transient antiviral effect of the drug is consistent with the emergence of a delavirdine-resistant virus population within 12 weeks of treatment.

When this study was started, one of the interesting research questions was whether delavirdine could suppress pre-existing viral resistance to zidovudine in zidovudine experienced patients. Our results do not provide evidence for this action of delavirdine. In particular, the IC_{50} values for the dose-escalating group showed that susceptibility to zidovudine was not improved by the additional treatment with delavirdine. The same was true for the other delavirdine groups. However, in comparison with patients randomized to the dose-escalating group, these patients had been taking zidovudine for a shorter time before the study started. Consequently, the viral susceptibility to zidovudine was still relatively good. In two patients, however, there was a considerable (re)sensitization to zidovudine with strongly decreased IC_{50} values within 12 weeks of combination therapy. Whether this change in zidovudine susceptibility was caused by the emergence of a Y181C mutation induced by therapy with delavirdine [28] remains to be investigated.

Delavirdine appeared to be safe and well tolerated. Mild laboratory abnormalities were found, but all variables returned to normal after discontinuation of the drug. The most relevant adverse event associated with delavirdine was skin rash, with an overall incidence of 52%. However, in two-thirds of these events treatment could be continued with or without the temporary addition of antihistamines. Skin rash is a common side effect noted in clinical trials with HIV-positive subjects. The underlying mechanism is unknown but the incidence of skin rash seems to be higher in patients with lower CD4 cell counts [34,35]. In trimethoprim-sulphamethoxazole (TMP-SMZ)-treated patients, it has been postulated that the reaction is a consequence of accumulation of hydroxylamine metabolites of the drug because of a relative glutathione deficiency in HIV-infected individuals [36]. Given that the mesylate salt of delavirdine contains a sulphone moiety, such a mechanism could also be plausible for delavirdine. Patients affected by skin rash while taking TMP-SMZ, have also been treated successfully by the addition of antihistamines [37,38]. Our experience with successful continued administration of delavirdine is in agreement with those reports.

Delavirdine has been recently licensed in the U.S. and Australia, and it is expected that approval will soon follow in Europe. Preliminary reports of the results of large clinical trials have been presented during conferences [39], and final publications will be appearing shortly. The current study demonstrates that delavirdine is a good candidate for combination therapy with nucleoside analogues. The antiviral effect was most favorable in the highest dose group, i.e. 1200 mg/day. This is in line with the current dose recommendation, i.e. 400 mg three times daily. The clinical use of the drug is limited by the development of resistance quite soon after the start of treatment. It would appear, on the basis of currently available knowledge about optimal viral suppression [17], that treatment with one NNRTI, like delavirdine, and one NRTI, like zidovudine, is not adequate. It is expected that the antiviral capacity of the delavirdine will be more pronounced when given in combination with either two NRTIs or one NRTI plus one protease inhibitor. Indeed, preliminary data from an interim analysis (at 32 weeks) of a study comparing triple therapy with delavirdine, zidovudine, and lamivudine with double therapy with

either zidovudine/lamivudine or zidovudine/delavirdine, show a significantly better antiviral response in the triple therapy arm [Pharmacia and Upjohn, data not yet published]. However, data for a longer follow-up of efficacy and safety in such triple combinations are not yet available. Therefore, the definite place of the compound in the management of HIV disease remains to be further explored.

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