Clinical outcome and predictive factors of failure of highly active antiretroviral therapy in antiretroviral-experienced patients in advanced stages of HIV-1 infection

Antonella d'Arminio Monforte, Letizia Testa, Fulvio Adorni*, Elisabetta Chiesa, Teresa Bini, G. Carla Moscatelli, Clara Abeli, Stefano Rusconi, Salvatore Sollima, Claudia Balotta, Massimo Musicco*, Massimo Galli and Mauro Moroni

Objective: To verify the effectiveness of highly active antiretroviral therapy (HAART) and to identify any factors predictive of clinical outcome in a clinical setting.

Design: Observational study.

Methods: Treatment failure (i.e., the occurrence of new or recurrent AIDS-defining events, death or any definitive discontinuation) and the course of CD4+ cell counts and HIV RNA copies were evaluated in 250 heavily pretreated HIV-infected patients starting HAART [153 with indinavir (IDV), 55 with ritonavir (RTV), 43 with saquinavir (SQV)]. Univariate and multivariate analyses were performed to identify predictors of worse outcome.

Results: During a median follow-up of 8 months, 75 patients (30%) had treatment failure because of the occurrence of an AIDS-defining event or death (n = 24), inefficacy (n = 24), or severe intolerance (n = 27). Twenty new and six recurrent AIDS-defining events, and nine deaths occurred (six out of 20 AIDS-defining events and two out of nine deaths within 1 month of treatment). CD4+ counts were above 200×10^6/l at AIDS diagnosis in only two patients. None of the SQV patients, 12 (7.8%) of the IDV patients, and 15 (27.3%) of the RTV-treated patients were considered non-compliant. The SQV-containing regimens independently correlated with treatment failure (relative risk, 2.46; 95% confidence interval, 1.20–5.03; versus IDV). Low compliance partially determined outcome in RTV-treated patients; both severe immunodepression and AIDS at baseline were predictive of treatment failure. There was a 10-fold increase in CD4+ cell counts in the patients treated with IDV and RTV; the best virological outcome occurred in IDV-treated patients, with 68.4% of patients showing undetectable HIV RNA copies after 6 months.

Conclusions: HAART was effective in 70% of patients; low compliance and previous AIDS diagnosis represented predictive factors of therapy failure.

AIDS 1998, **12**:1631–1637

Keywords: Highly active antiretroviral therapy, treatment failure, compliance

From the Institute of Infectious and Tropical Diseases, University of Milan, and *CNR-ITBA, Milan, Italy.

Sponsorship: Work supported by grants from National Institute of Health, AIDS Project 50A.0.10.1997.

Requests for reprints to: Antonella d'Arminio Monforte, Institute of Infectious and Tropical Diseases, University of Milan, L. Sacco Hospital, via GB Grassi 74, 20157 Milan, Italy.

Date of receipt: 12 March 1998; revised: 7 May 1998; accepted: 13 May 1998.

Introduction

Highly active antiretroviral therapy (HAART) has radically changed the therapeutic approach towards HIV infection. Regimens containing protease inhibitors have been proved to be effective on clinical and virological parameters in randomized controlled trials involving HIV-positive patients with advanced disease [1–3].

As established by international guidelines [4,5], HAART has now become the standard treatment for HIV infection, and is also second-choice treatment in patients who have previously received nucleoside reverse transcriptase inhibitors (NRTI). A sharp reduction in AIDS-defining events, days of hospitalization and deaths following the introduction of HAART is now a common experience in clinical settings [6,7].

However, some important questions remain to be answered. Because HAART has to be prolonged indefinitely, what is the rate of discontinuation and what are the events impeding the continuation of therapy in a clinical setting? Second, how many patients remain compliant and how does poor compliance affect clinical outcome? Third, is it possible to identify patients with a predictable worse outcome who should be excluded by empirical therapy and considered candidates for resistance-driven therapy or even more aggressive regimens?

The aim of this study was to verify the effectiveness of first HAART regimens and identify factors predictive of clinical outcome in a cohort of highly immunodepressed HIV-infected patients.

Patients and methods

The study included 250 antiretroviral therapy-experienced HIV-1-infected patients treated at our department, who consecutively started HAART between April 1996 and March 31 1997. Because protease inhibitors were registered in Italy in January 1997, all of the patients who initiated HAART before that date (n = 146) entered compassionate use programs. In particular, both the indinavir (IDV) and ritonavir (RTV) compassionate protocols enrolled patients with baseline CD4+ counts $\leq 50 \times 10^6$/l who were unresponsive/intolerant to double NRTI therapy; in these cases, protease inhibitor treatment was randomly assigned. The saquinavir (SQV) compassionate use programme allowed the enrolment of less immunodepressed patients with CD4+ counts $\leq 300 \times 10^6$/l. After January 1997, the choice of protease inhibitor regimen was left to the clinicians' judgement.

Protease inhibitors were associated with two NRTI. The antiretroviral drugs were given at standard doses: zidovudine 300 mg twice daily, didanosine 200 or 100 mg twice daily (depending on whether the patient weighed at least or below 60 kg), zalcitabine 0.75 mg three times daily, stavudine 40 or 30 mg twice daily (depending on whether the patient weighed at least or below 60 kg), lamivudine 150 mg twice daily, IDV 800 mg three times daily, RTV 600 mg twice daily, SQV 600 mg three times daily.

All patients received primary and secondary prophylaxis for opportunistic infections according to international guidelines [8], with the exception of primary prophylaxis for cytomegalovirus (CMV) disease and non-tuberculous mycobacterial (NTM) infection because these were not applied as standard practice at our institution.

At baseline, the following information was collected: age, sex, Centers of Disease Control stage according to the 1993 classification [9], date of initiation of first antiretroviral regimen, number of NRTI substitutions within the previous 6 months (in order to include patients in which a protease inhibitor was added a short time after the change of NRTI). NRTI were always substituted with other NRTI that had never been previously administered.

New or recurrent AIDS-defining events, definitive discontinuations and their causes, non-compliance and death were recorded whenever they occurred. Definitive discontinuations of the initial HAART regimen included the following: (i) side-effects/toxicities; (ii) clinical inefficacy as established by the clinician on the basis of clinical worsening (with or without AIDS-defining events), with or without an increasing viral load or decreasing CD4+ cell count; (iii) the patient's decision. Non-compliance was defined as an intake of less than 70% of the total monthly dose of HAART on admission. Treatment failure was defined as the occurrence of the first event amongst the following: new or recurrent AIDS-defining events, death, any definitive discontinuation of the initial HAART regimen.

CD4+ cell counts (Elite flow cytometer, Coulter Corporation, Miami, Florida, USA) and HIV RNA measurements (branched DNA, Chiron, Inc., Emeryville, California, USA; detection limit, 500 copies/ml) were made at baseline, and then every 3 months. The last date of follow-up for the present analysis was 30 September 1997.

The SPSS software package was used to perform all of the statistical analyses. Categorical variables were compared between groups by means of Pearson's χ^2 test. Mann–Whitney U-test or Kruskal–Wallis non-parametric test was used to compare the distribution of continuous variables between two or three non-related

groups, respectively. In order to identify any factor predictive of treatment failure, univariate and multivariate analysis were performed using Cox's regression model. The factors considered in the analyses were those presumed to influence outcome: sex, age, AIDS, the number of NRTI substitutions, CD4+ cell counts and viral load at baseline, the protease inhibitor regimen given, and treatment compliance.

Results

Between 1 April 1996 and 31 March 1997, 250 patients started a HAART regimen containing IDV (n = 153), RTV (n = 55), or SQV (n = 42). The main baseline characteristics of the three groups are summarized in Table 1. The patients starting SQV-containing regimens had less advanced HIV infection than those in the other two groups, as documented by the clinical, immunological and virological parameters. The RTV-treated patients had lower CD4+ cell counts than those treated with IDV ($P = 0.0001$). The median duration of prior NRTI therapy was 26 months; 90.8% of patients introduced at least one new NRTI within 6 months prior to HAART initiation. The median duration of follow-up was 253 days (228 days for IDV patients, 377 for RTV patients, and 247 for SQV-treated patients; $P = 0.00001$).

The first encountered causes of treatment failure by regimen are shown in Table 2. Treatment failure occurred in 75 patients (30%): 33 on IDV (21.6%), 25 on RTV (45.5%), and 17 on SQV (40.5%; $P = 0.002$) after a median of 86 days (range, 3–383 days; 49 days in IDV patients, 99 days in RTV patients, and 182 days in SQV patients; $P = 0.01$).

Nineteen patients experienced 20 new AIDS-defining events, five experienced six recurrences of previous AIDS-defining events, and nine patients died. Six of the AIDS-defining events and two deaths occurred during the first month of therapy. The following diseases were diagnosed: NTM infection (four cases), Kaposi's sarcoma (three cases), CMV retinitis, progressive multifocal leukoencephalopathy and *Pneumocystis carinii* pneumonia (two cases each), pulmonary tuberculosis, non-Hodgkin's lymphoma, primary brain lymphoma, AIDS dementia complex, brain toxoplasmosis, oesophageal candidiasis and isosporidiasis (one case each). Median CD4+ cell count at AIDS onset was 79×10^6/l (range, 3–203×10^6/l; median, 34×10^6/l in the cases occurring during the first month). In two patients receiving an IDV-containing regimen a new AIDS-defining events occurred while their CD4+ cell counts were above 200×10^6/l. The recurrences of AIDS-defining events were as follows: CMV retinitis (three cases), and NTM infection, brain toxoplasmosis and recurrent bacterial pneumonia (one case each).

Table 1. Baseline characteristics of 250 patients initiating highly active antiretroviral therapy.

		n (%)			
	Total	Indinavir (n = 153)	Ritonavir (n = 55)	Saquinavir (n = 42)	*P*
Age (years)					
< 35	139	81 (52.9)	31 (56.4)	27 (64.3)	
> 35	111	72 (47.1)	24 (43.6)	15 (35.7)	NS
Sex					
Male	182	115 (75.2)	43 (78.2)	24 (57.1)	
Female	68	38 (24.8)	12 (21.8)	18 (42.9)	NS
AIDS					
No	147	82 (53.6)	31 (56.4)	34 (81.0)	
Yes	103	71 (46.4)	24 (43.6)	8 (19)	0.006
CD4+ cell count ($\times 10^6$/l)					
< 50	130	81 (53.3)	44 (80)	5 (11.9)	
50–99	40	29 (19.1)	6 (10.9)	5 (11.9)	
≥ 100	79	42 (27.6)	5 (9.1)	32 (76.2)	0.00001
HIV RNA level (copies/ml)					
< 500–9999	41	22 (14.4)	5 (9.1)	14 (33.3)	
10000–99999	55	34 (22.2)	16 (29.1)	5 (11.9)	
≥ 100000	72	49 (32.0)	19 (34.5)	4 (9.5)	
Undetermined	82	48 (31.4)	15 (27.3)	19 (45.2)	0.0012
Median (range) duration of prior NRTI therapy, months	26	26 (0.5–125)	31 (1–99)	24 (5–76)	NS
NRTI substitutions					
0	23	11 (7.2)	9 (16.4)	3 (7.1)	
1	151	86 (56.2)	40 (72.7)	25 (59.5)	
2	76	56 (36.6)	6 (10.9)	14 (33.3)	0.0062
Median (range) CD4+ cells ($\times 10^6$/l)		40 (1–724)	22 (1–276)	209 (1–882)	0.0014
HIV RNA level (copies/ml)					
Median		88860	93625	6498	0.0001
Range		< 500–1164834	< 500–1012500	< 500–1154834	

NRTI, Nucleoside reverse transcriptase inhibitor.

Table 2. First causes of treatment failure in 75 patients who failed highly active antiretroviral therapy.

Treatment failures	Indinavir (n = 153)	Ritonavir (n = 55)	Saquinavir (n = 42)	Total (n = 250)	*P*
Death	2 (1.3)	1 (1.8)	–	3 (1.2)	NS
AIDS-defining event					
New	13 (8.5)	3 (5.5)	2 (4.8)	18 (4.2)	NS
Recurrent	–	3 (5.5)	–	3 (1.2)	
Discontinuations					
Intolerance	11 (7.2)	13 (23.6)	3 (7.1)	27 (10.8)	< 0.01
Inefficacy	7 (4.6)	5 (9.1)	12 (28.6)	24 (9.6)	< 0.01
Higher HIV RNA level	3	2	6	11	
Lower CD4+ cell counts	–	2	3	5	
Both	–	1	3	4	
Clinical worsening*	4	–	–	4	
Total	33 (21.6)	25 (45.5)	17 (40.5)	75 (30.0)	0.002

*Impossibility to ingest any pill.

Twelve (7.8%) of the IDV patients, 15 (27.3%) of the RTV patients, and none of the SQV-treated patients were considered non-compliant during follow-up ($P = 0.00002$).

A total of 64 patients (25.6%) definitively discontinued their HAART regimen because of inefficacy (27 patients), side-effects/toxicity (30 patients), or their own decision (seven cases, all non-compliant). The main cause of intolerance were gastrointestinal complaints (12 out of 15 on RTV, all three on SQV, and five out of 12 on IDV). Paresthesia caused treatment discontinuation in two cases (one on IDV, one on RTV), and renal colic in one IDV-treated patient. Ten of the 23 patients discontinuing IDV switched to another HAART regimen: seven to RTV, and three to RTV–SQV. Twenty four out of 25 patients discontinuing RTV switched to IDV (17 cases) or added SQV (seven cases). Eleven out of 16 patients discontinuing SQV switched to IDV (nine cases) or added RTV (two cases).

Table 3 shows the crude and adjusted relative risks (RR) of treatment failure by protease inhibitor, clinical stage at inclusion, and baseline CD4+ cell count. The crude risk of a worse prognosis was greater in the RTV than in the IDV group ($P = 0.038$). The variables influencing the crude risk of failure in the RTV-treated patients were CD4+ cell count at inclusion and compliance to treatment. After adjusting for these variables, the risk of clinical failure in RTV-treated patients was not significantly different from that in IDV-treated patients. Taking into account the presence of AIDS and CD4+ cell counts at enrolment, as well as compliance, the SQV-treated patients had a 2.46 higher risk of treatment failure than those treated with IDV ($P = 0.014$).

Treatment failure was observed in 39 (37.9%) out of 103 AIDS patients and 36 (24.5%) out of 147 non-AIDS patients ($P = 0.02$). The crude RR of failure in the patients with AIDS at baseline was significantly higher than that in the non-AIDS patients [RR, 1.65; 95% confidence interval (CI), 1.05–2.60; $P = 0.03$]. In the multivariable model, AIDS patients had a worse prognosis than those without AIDS, even when this difference was not statistically significant (RR, 1.66; 95% CI, 0.99–2.78).

Treatment failure occurred in 47 (36.2%) out of 130 patients with CD4+ cell counts below 50×10^6/l, 12 (30%) out of 40 of those with CD4+ cell counts

Table 3. Crude and adjusted relative risks (RR) of treatment failure.

	Protease inhibitor			Clinical stage		CD4+ cell counts ($\times 10^6$/l)		
	Indinavir (n = 153)	Ritonavir (n = 55)	Saquinavir (n = 42)	Non-AIDS (n = 147)	AIDS (n = 103)	< 50 (n = 130)	50–99 (n = 40)	> 100 (n = 79)
Clinical failure (%)	33 (216)	25 (45.5)	17 (40.5)	33 (24.5)	39 (37.9)	47 (36.2)	12 (30.0)	16 (20.3)
Crude RR	1.0	1.74 (1.03–2.94)	1.69 (0.94–3.03)	1.0	1.65 (1.05–2.60)	1.0	0.97 (0.51–1.83)	0.60 (0.34–1.07)
Adjusted RR								
Sex	1.0	1.75 (1.04–2.97)	1.62 (0.89–2.97)	1.0	1.72 (1.09–2.72)	1.0	0.96 (0.51–1.82)	0.54 (0.30–0.98)
Age	1.0	1.74 (1.03–2.94)	1.72 (0.96–3.11)	1.0	1.65 (1.05–2.59)	1.0	0.97 (0.51–1.83)	0.61 (0.34–1.08)
AIDS	1.0	1.75 (1.04–2.95)	1.91 (1.05–3.46)			1.0	1.07 (0.56–2.03)	0.71 (0.39–1.30)
NRTI substitutions	1.0	1.77 (1.04–3.02)	1.70 (0.94–3.05)	1.0	1.63 (1.03–2.56)	1.0	0.95 (0.50–1.80)	0.61 (0.34–1.08)
CD4+ cell counts	1.0	1.51 (1.88–2.59)	2.72 (1.37–5.40)	1.0	1.50 (0.93–2.44)			
HIV RNA level	1.0	1.80 (1.06–3.04)	1.65 (0.89–3.09)	1.0	1.63 (1.03–2.58)	1.0	1.06 (0.55–2.04)	0.58 (0.31–1.06)
Protease inhibitor				1.0	1.76 (1.11–2.80)	1.0	1.01 (0.53–1.94)	0.42 (0.20–0.85)
Compliance	1.0	1.49 (0.86–2.57)	1.81 (1.00–3.28)	1.0	1.79 (1.13–2.84)	1.0	1.01 (0.53–1.91)	0.68 (0.38–1.22)
Any of the above	1.0	1.51 (0.85–2.69)	2.46 (1.20–5.03)	1.0	1.66 (0.99–2.78)	1.0	1.38 (0.68–2.82)	0.58 (0.26–1.26)

NRTI, Nucleoside reverse transcriptase inhibitor.

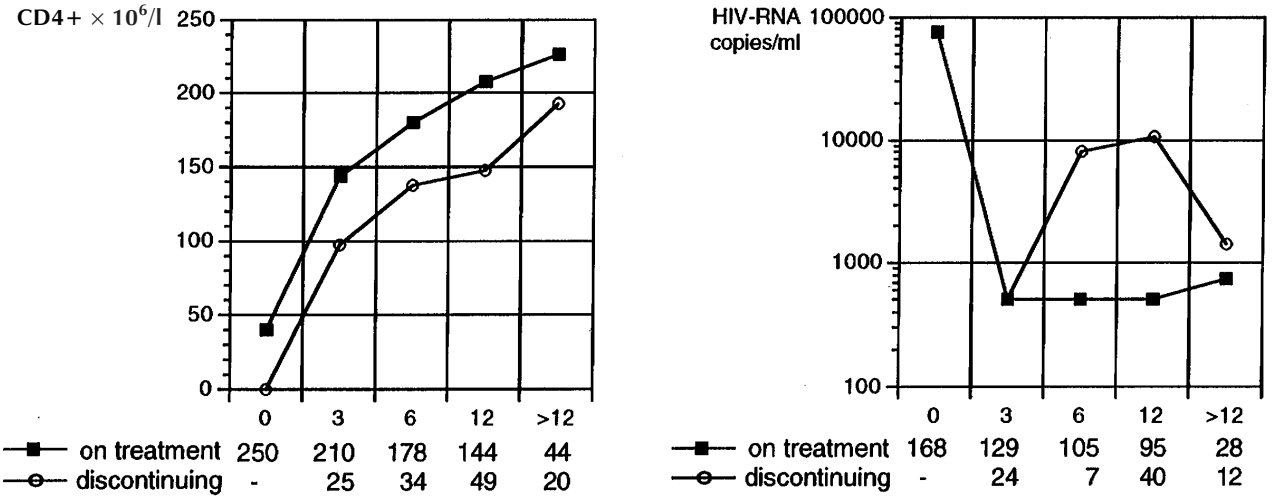

Fig. 1. Median CD4+ cell count (× 10^6/l) and viral load (HIV RNA copies/ml) in patients on treatment and discontinuing their initial highly active antiretroviral therapy regimen.

50–99 × 10^6/l, and in 16 (20.3%) out of 79 of those with CD4+ cell counts ≥ 100 × 10^6/l ($P = 0.015$). There was a trend towards a lower risk of failure in the patients with baseline CD4+ cell counts of ≥ 100 × 10^6/l, and this was confirmed after adjusting for all the variables considered in the analysis. The protease inhibitor regimen given affected the risk of failure in patients with baseline CD4+ cell counts ≥ 100 × 10^6/l (RR, 0.42; 95% CI, 0.20–0.85; versus CD4+ cell counts < 50 × 10^6/l; $P = 0.016$).

The median CD4+ cell counts and HIV RNA copies in patients on treatment and in those discontinuing their initial HAART regimen are shown in Fig. 1. CD4+ cell counts increased sharply and continued to increase even after the 12th month in the patients on treatment. The increase in CD4+ cell counts was lower in patients who discontinued their initial HAART regimen. The median viral load decreased from 74 765 HIV RNA copies/ml to less than 500 copies/ml by month 3 of treatment, and remained undetectable in patients on treatment until month 12 of therapy. On contrast, in patients who discontinued their initial HAART regimen, viral load increased abruptly and median values of 8112 and 10 417 copies/ml were observed after 6 and 12 months, respectively.

Fig. 2 shows the courses of the median CD4+ cell counts and viral load in patients who remained on treatment with each of the three protease inhibitor reg-

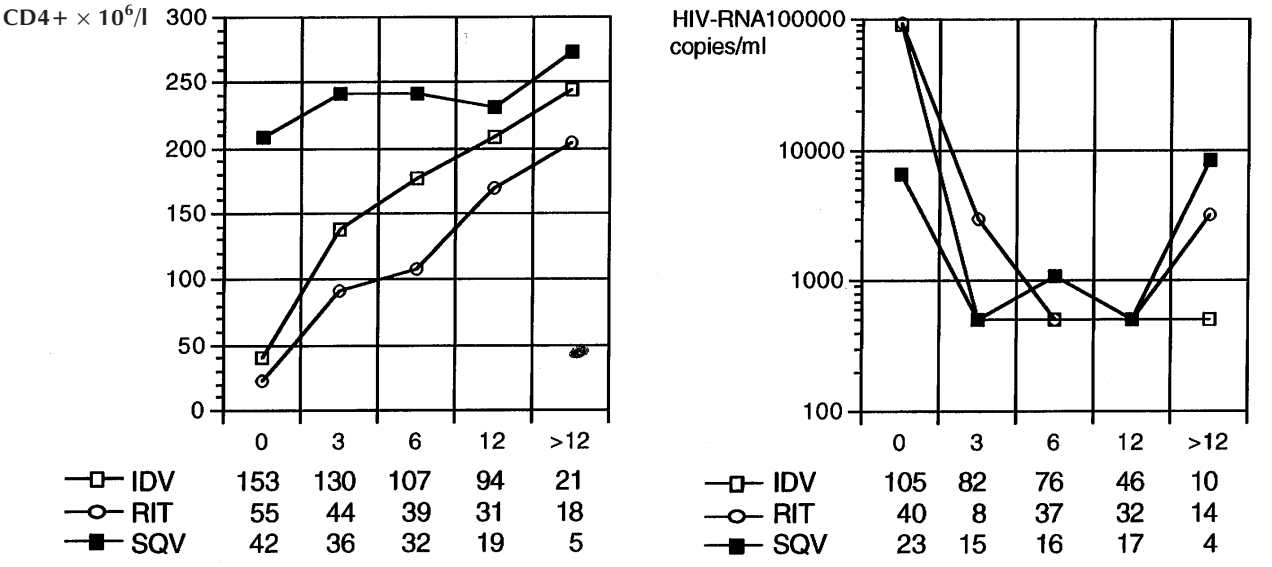

Fig. 2. Median CD4+ cell count (×10^6/l) and viral load (HIV RNA copies/ml) in patients on treatment with the three protease inhibitors regimen. HIV RNA measurements were lacking at the 3-month determination in 30 ritonavir (RIT)-treated patients and at 3- and 6-month determinations in five and two saquinavir (SQV)-treated patients. IDV, Indinavir.

imens. The CD4+ cell counts increased sharply in both IDV- and RTV-treated patients, reaching 10 times the initial values, whereas the increase in median CD4+ cell counts was less than 1.5-fold in patients treated with SQV-containing regimens.

A total of 56.1, 68.4, 60.9 and 80% of patients treated with IDV had undetectable viral load after 3, 6, 12 and > 12 months of therapy, respectively, with median values below detectable limits from 3 months. RTV-treated patients had median values below the detection limit at 6 and 12-month measurements; the proportions of patients with undetectable viral load was 37.5, 54.1, 56.3 and 35.7% after 3, 6, 12 and > 12 months of therapy, respectively. In the SQV-treated patients the viral load varied irregularly during the observation period, with undetectable viral load in 66% of the patients after 3 months, 43.8% after 6 months, 52.9% after 12 months, and 0% over 12 months.

Discussion

The cohort studied included 250 severely immunodepressed antiretroviral-experienced patients consecutively observed in a clinical setting. Before protease inhibitors were registered in Italy, compassionate use programs including RTV and IDV only allowed the inclusion of patients with severe immunodepression. After the registration of the three drugs, the prevalent clinical attitude in our institution was to give SQV-containing regimens mainly to patients with less advanced HIV disease, because the pharmacokinetic data published before 1997 suggested that SQV was less potent than IDV or RTV [10], a view that was further supported by the recommendations of 1997 international guidelines [5]. This explains why the SQV-treated patients presented less advanced baseline clinical, immunological and virological conditions than those treated with RTV or IDV. The duration of follow-up was significantly shorter in the case of IDV-treated patients because more patients were assigned to IDV treatment during 1997 on the basis of clinicians' decision.

Treatment failure occurred in 30% of the patients as a whole. This is not surprising given that the patients were in an advanced stage of disease and had previously received antiretroviral therapies for long periods of time. Over the median follow-up of 8 months, new AIDS-defining events occurred in less than 8% of the patients, with one-third of them occurring within the first month of HAART and probably at least partially due to undiagnosed underlying diseases. Only two AIDS-defining events (primary brain lymphoma and NTM infection) occurred after reaching CD4+ cell counts $\geq 200 \times 10^6$/l, a finding that may be relevant in the planning of prophylaxis for opportunistic diseases in these patients. NTM infections were relatively frequent in our patients, who were not given primary prophylaxis (four cases out of 20 AIDS-defining events), due the low incidence of NTM infections previously reported [11]. Various studies have demonstrated a reduction and changing pattern of CMV disease during HAART [12,13]. In our cohort, all of the cases of both new and recurrent episodes of CMV disease occurred in patients with CD4+ cell counts of less than 100×10^6/l. Bearing in mind the possible drug interactions between regimens for opportunistic infections and protease inhibitors, controlled clinical trials seem to be warranted in order to evaluate the risk–benefit ratio of primary and secondary prophylaxis in patients on HAART with immunological improvement.

One-quarter of the patients definitively discontinued their initial HAART regimen because of inefficacy (11%), severe toxicity (12%), or as result of their own decision (2.8%). Discontinuation due to inefficacy could be decided by the clinical staff even before the occurrence of clinical events, as a decrease in CD4+ cell counts and an increase in viral load were considered sufficient to classify the ongoing treatment as failing, in agreement with 1997 guidelines [5]. Side-effects leading to the discontinuation of HAART principally affected the gastrointestinal tract.

Compliance to therapy represents a major problem for patients receiving HAART [14]. Compliance was observed in all of the patients given SQV, but in only about 60 and 80% of those receiving RTV and IDV, respectively. In this population of patients with advanced HIV disease who were strongly motivated to take therapy, the main reasons for non-compliance were side-effects, and reflect their frequency in the different regimens. To the best of our knowledge, only a few studies have analysed the impact of compliance on HAART outcome [14,15], even though expected compliance to treatments is one of the variables that international guidelines indicate should be taken into account in establishing therapeutic regimens [5].

The results of multivariable analysis indicated that the relatively high risk of failure in RTV-treated patients was dependent on their severe immunodepression and poor treatment compliance. The opposite was true of SQV, with relatively high CD4+ cell counts and good compliance contributing to a good outcome according to univariate analysis, although when we adjusted for these variables, SQV-treated patients were found to have the worst prognosis. It is possible that this worse outcome may be related to the limited bioavailability of the drug in the current formulation [10]. No association between outcome and the number of nucleoside analogues substitutions was found. The small number of patients not changing at least one nucleoside ana-

logue at the initiation of HAART, and also the fact that not all of the patients initiated HAART because of the failure of their ongoing antiretroviral regimen may represent the explanations to these findings. The presence of AIDS at baseline was a predictor of a worse treatment outcome at both univariate and multivariate analysis, regardless of the protease inhibitor regimen, and there was a trend to a worse prognosis in patients with low CD4+ cell counts. These last two findings, which confirm the results of clinical trials [2], argue in favour of the early initiation of HAART in patients with less advanced HIV infection, who can be expected to tolerate the regimens better and to achieve a better outcome.

The curves of the CD4+ cell counts and viral load showed the immunological and virological effects of HAART. As expected, the patients who remained on treatment with the initial regimen had a better immunological and virological response than those who discontinued treatment. It has to be underlined that 70% of the patients who discontinued HAART (45 out of 64) switched to another protease inhibitor-containing regimen, which may explain the increase in median CD4+ cell counts in patients discontinuing their first regimen. It has been demonstrated that even a short period of HAART discontinuation leads to a rebound in viral load [14]; during short-term follow-up, the switch to other protease inhibitor-containing regimens seemed to be capable of controlling viral replication in the majority of the patients belonging to our cohort who failed the first regimen, as demonstrated by the viral load course of patients discontinuing their initial regimen. Looking at the immunological and virological effects of each of the three protease inhibitor-containing regimens, the large rise in CD4+ cell counts observed in the patients given RTV and IDV is in agreement with the results of clinical trials [1,15]; CD4+ cell counts were still increasing after 12 months in patients remaining on therapy. However, the slight rise in CD4+ cell counts in SQV-treated patients was less than expected by the results of randomized controlled trials [3,16]. The decrease in viral load was striking in IDV-treated patients, with median non-detectable levels persisting throughout follow-up. A similar course was observed until 6 months in RTV-treated patients, whereas those treated with SQV experienced a first rebound at 6 months of therapy. Overall, the proportions of patients with undetectable viral load at 6 months were comparable to or slightly higher than those recently reported by a German study [17].

In conclusion, in a clinical setting of heavily pretreated, severely immunodepressed patients, 30% of the patients failed to respond to their initial HAART regimen. Given the poor clinical and immunological conditions of the majority of patients, these findings have to be considered as frankly encouraging. Nevertheless, neither RTV-containing regimens nor the hard-gel SQV-containing regimens can be recommended as first-choice inhibitor regimens in therapy-experienced patients with advanced HIV infection.

References

1. Cameron DW, Heath-Chiozzi M, Danner S, *et al.*: **Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease.** *Lancet* 1997, **351**:543–549.
2. Hammer SM, Kathleen ES, Hughes MD, *et al.*: **A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4+ cell counts of 200 per cubic millimeter or less.** *N Engl J Med* 1997, **337**:725–733.
3. Clumeck N on behalf of the Saquinavir International Phase III Trial (SV 14604) Group: **Clinical benefit of saquinavir (SQV) plus zalcitabine (ddC) plus zidovudine (ZDV) in untreated/minimally treated HIV-infected patients.** 37th *Interscience Conference on Antimicrobial Agents and Chemotherapy*. Toronto, 28 September to 1 October 1997 [abstract LB4].
4. Carpenter CJ, Fischl MA, Hammer SM, *et al.*: **Antiretroviral therapy for HIV infection in 1996. Recommendations of an international panel.** *JAMA* 1996, **276**:146–154.
5. Carpenter CJ, Fischl MA, Hammer SM, *et al.*: **Antiretroviral therapy for HIV infection in 1997. Updated recommendations of the International AIDS Society–USA Panel.** *JAMA* 1997, **277**:1962–1969.
6. Chiasson MA: **Declining AIDS mortality in New York City. New York City Department of Health.** *Bull N Y Acad Med* 1997, **74**:151–152.
7. Mouton Y, Alfandari S, Valette M, *et al.*: **Impact of protease inhibitors on AIDS-defining events and hospitalizations in 10 French AIDS reference centres. Federation National des Centres de Lutte contre le SIDA.** *AIDS* 1997, **11**:F101–F105.
8. USPHS/IDSA Prevention of Opportunistic Infections Working Group: **1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus.** *MMWR* 1997, **46** (RR-12):1–46.
9. Centers for Disease Control: **1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults.** *MMWR* 1992, **41** (RR-17):19–23.
10. Noble S, Faulds D: **Saquinavir. A review of its pharmacology and clinical potential in the management of HIV infection.** *Drugs* 1996, **52**:93–112.
11. d'Arminio Monforte A, Vago L, Gori A, *et al.*: **Clinical diagnosis of mycobacterial diseases versus autopsy findings in 350 patients with AIDS.** *Eur J Clin Microbiol Infect Dis* 1996, **15**:453–458.
12. Jacobson MA, Zegans M, Pavan PR, *et al.*: **Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy.** *Lancet* 1997, **349**:1443–1445.
13. Mallolas J, Arrizabalaga J, Loncà M, *et al.*: **Cytomegalovirus disease in HIV-1-infected patients treated with protease inhibitors.** *AIDS* 1997, **11**:1785–1787.
14. Vanhove GF, Schapiro JM, Winters MA, Merigan TC, Blaschke TF: **Patient compliance and drug failure in protease inhibitor monotherapy.** *JAMA* 1996, **276**:1955–1956.
15. Gulick RM, Mellors JW, Havlir D, *et al.*: **Treatment with indinavir, zidovudine and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy.** *N Engl J Med* 1997, **337**:734–739.
16. Collier AC, Coombs RW, Schoenfeld DA, *et al.*: **Treatment of human immunodeficiency virus infection with saquinavir, zidovudine and zalcitabine.** *N Engl J Med* 1996, **334**:1011–1017.
17. Fatkenheuer G, Theisen A, Roskstroh J, *et al.*: **Virological treatment failure of protease inhibitor therapy in an unselected cohort of HIV-infected patients.** *AIDS* 1997, **11**:F113–F116.