Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naïve patients

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Objective: To evaluate the frequency of discontinuation of the first highly active antiretroviral regimen (HAART) and the factors predictive of discontinuing for toxicity and failure in a population-based cohort of HIV-positive individuals in Italy, naïve from antiretrovirals at enrolment.

Methods: The study population consisted of individuals who initiated HAART and had at least one follow-up visit. The primary end-points were discontinuation of any component of HAART for drug toxicity and discontinuation for failure. Survival analyses were performed to identify predictive factors for reaching the two end-points.

Results: Eight hundred and sixty-two individuals initiated HAART; in 727 of them (84.3%) this consisted of two nucleoside reverse transcriptase inhibitors (NRTI) and one protease inhibitor (PI). Over a median follow-up of 45 weeks, 312 patients (36.2%) discontinued therapy: 182 (21.1%) discontinued due to toxicity, 44 (5.1%) due to failure. The probability of discontinuing HAART at 1 year was 25.5% [95% confidence interval (CI), 21.9–28.9] due to toxicity and 7.6% (95% CI, 4.9–10.3) due to failure. Independent factors associated with discontinuation for toxicity were: gender [relative hazard (RH) = 0.51; 95% CI, 0.32–0.80 for men versus women], type of treatment (indinavir-containing regimens, RH = 1.94; 95% CI, 1.10–3.41 and ritonavir-containing regimens, RH = 3.83; 95% CI, 2.09–7.03 versus hard-gell saquinavir) and time spent on treatment (RH = 0.89; 95% CI, 0.80–0.98 for each additional month). Discontinuation due to failure was independently associated with the most recent HIV-RNA (RH = 3.20; 95% CI, 1.74–5.88 for $\log_{10}$ copies/ml higher), and with type of treatment (indinavir-containing regimens, RH = 0.21; 95% CI, 0.06–0.78 and ritonavir-containing regimens, RH = 0.23; 95% CI, 0.04–1.26 versus hard-gell saquinavir).

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Conclusions: If the current HAART regimen caused no toxicity, less than 10% of naïve patients discontinue their first HAART regimen because of failure after 1 year from starting therapy.

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Introduction

Highly active antiretroviral therapy (HAART) is effective both in reducing plasma viral load and in prolonging AIDS-free survival, as demonstrated by various clinical trials [1–4]. Since HAART was introduced in clinical practice, AIDS-related events, hospitalizations and deaths have decreased in various clinical settings [5–7].

However, HAART has two main drawbacks: toxicity and low compliance. Although the frequency and the effects of toxicity have been assessed in clinical trials [2–4], they have not been thoroughly evaluated in clinical settings. Low compliance, which is often a consequence of persistent side effects, may lead to suboptimal therapy or to therapy discontinuation and ultimately to treatment failure [8].

According to population-based studies on HAART conducted among unselected pre-treated patients, virological failure occurs in almost 50% of patients after 6–12 months of therapy [9,10], and within 8 months approximately 25% of patients discontinue the initial HAART regimen due to failure, toxicity or non-compliance [11,12]. Van Roon *et al.* [13] studied the incidence of discontinuation of HAART and its determinants in a clinical cohort of mixed drug-naïve and -experienced patients who mainly started saquinavir-containing regimens. They found that 25% of patients discontinued HAART by 1 year from starting therapy. Main predictors of discontinuing HAART were baseline CD4 cell count and being naïve at the time of starting HAART. However, none of these studies have investigated the determinants of discontinuation of HAART according to the reason for discontinuing (collected from clinicians in real time) in an observational cohort of antiretroviral-naïve patients starting their first HAART regimen.

Although an increasing number of new drugs have been licensed in the last few years, when treatment fails, the clinical options are limited by the existence of cross-resistance among drugs of the same class; options are also limited in cases of toxicity, since various types of toxicity are generally common to several antiretroviral drugs [14].

Based on these considerations, we decided to determine the frequency of discontinuation of the first HAART regimen and to study the factors associated with discontinuation because of toxicity or failure in a population of HIV-positive antiretroviral-naïve patients starting their first HAART regimen in Italy.

Study population and methods

The study population was that of the Italian Cohort of Antiretroviral-Naïve Patients (I.CO.N.A.) study which between March 1997 and 31 May 1999 has recruited 3586 patients from 65 infectious disease wards in Italy [15]. All patients must be antiretroviral-naïve at the time of enrolment, regardless of the reason for which they had never been treated. The present study only analysed those patients who, once enrolled in the I.CO.N.A. study, began an antiretroviral regimen with at least three antiretroviral drugs (i.e., HAART) and who underwent at least one follow-up visit after starting therapy. Data from all patients of the I.CO.N.A. study are registered in a data-base running via internet [16] which includes demographic, immunological, virological, clinical and therapeutic parameters. All patients are assumed to receive the recommended doses of antiretroviral drugs. All events are registered in the data-base over the follow-up (i.e., all CD4 cell count and HIV RNA measurements, clinical events, changes in therapy or prophylactic treatment, hospitalizations, and death); in their absence, a follow-up visit is scheduled at least every 6 months. When a patient discontinues therapy, regardless of whether or not he/she switches to another regimen, clinicians are asked to report the reason for discontinuing. A coded computer form is provided in which reasons for discontinuing are categorized as follows: immunological failure, virological failure, clinical failure, toxicity based on laboratory data, gastrointestinal intolerance, hypersensitivity, other side effects/symptoms, lack of compliance, patient's decision, changes in international guidelines, clinical contraindications, and 'other reasons'. The clinician is asked to choose only one of these reasons.

Statistical analysis

Standard survival analysis by means of Kaplan–Meier estimates and Cox proportional hazards model was

performed. Kaplan–Meier plots have been used to describe the probability of discontinuing HAART by a certain time from starting therapy and the Cox model to determine the predictors of discontinuing HAART. We considered two primary end-points for this analysis: (i) discontinuing HAART for reasons associated with drug-intolerance (i.e., toxicity based on laboratory data, gastrointestinal intolerance, hypersensitivity, other side effects/symptoms) and (ii) discontinuing HAART for clinical decisions associated with poor virological/immunological response or clinical outcome. The date of discontinuation was defined as the first time one of the drugs in the specific combination was terminated; the reason for discontinuing this drug was defined as the reason associated with discontinuing the prescribed treatment combination. 'Time zero' of the analysis was the date of starting HAART. When we investigated the association between 'time spent on treatment' and the defined end-points, time zero was the date of first clinical follow-up.

Thus survival time was the time since the first clinical follow-up and patients were not considered to be at risk of discontinuing until this time was greater or equal to the time of initiating HAART. This was done so 'time on treatment' did not coincide with the survival time and could be included in the model as a covariate. Follow-up times of patients who never discontinued HAART were censored at their last clinical visit; this was done because, although discontinuation should be reported between clinical visits, some delay in reporting such information generally occurs. For the same reason, patients with no clinical visits after the date of starting therapy were excluded from the analysis. Follow-up times of patients who discontinued HAART for reasons other than the end-points of interest were censored at the time of discontinuation under the assumption that the probability of discontinuing for toxicity was totally unrelated to that of discontinuing for failure. This assumption was checked by repeating the analysis with end-point toxicity only on patients whose viral load at the time of discontinuing was below 500 copies/ml. A fixed covariate was fitted for baseline CD4 cell count and HIV-RNA, whereas to investigate whether the most recent value of these markers was affecting the probability of discontinuation of HAART, a time-updated covariate was included in the model. To control for the potential confounding effect of infectious disease ward a stratified proportional hazards model has been fitted. When investigating the determinants of discontinuation of HAART only 717 patients who started two nucleoside reverse transcriptase inhibitors (NRTI) and one of the following protease inhibitors: indinavir, ritonavir or hard-gell saquinavir were included in the analysis.

Results

A total of 862 patients were included in this analysis. The baseline characteristics of the patients are shown in Table 1. Of this total, 632 (73.3%) patients were males, 349 (40.5%) were intravenous drug users, 183 (21.2%) were infected by the homosexual route, 273 (31.7%) by the heterosexual route and 57 (6.6%) by other or unknown routes. Most patients (68.5%) were asymptomatic, i.e. in group A of the US Centers for Disease Control and Prevention (CDC) [17]. Median CD4+ cell count at HAART initiation was 309×10^6 cells/l (range, 1–1294), median HIV-RNA was 4.78 $\log_{10}$ copies/ml (range, 2.75–6.74). Clinical markers have been measured approximately every 3 months: 28 patients (3.2%) had one measurement, 102 (11.8%) had two measurements, 164 (19.0%) had three measurements and 568 (65.9%) had four or more measurements. A total of 727 (83.9%) patients initiated two NRTI plus one protease inhibitor (PI), 15 (1.7%) initiated three NRTI, 33 (3.8%) initiated two NRTI plus one non-nucleoside reverse transcriptase inhibitor (NNRTI), four (0.5%) initiated three other drugs and 83 (9.6%) initiated four or more drugs. Zidovudine and lamivudine were the most used NRTI (82.1 and 66.2% of patients, respectively), stavudine was started by 23.7% of patients and didanosine by 21.3%. Among the

Table 1. Baseline characteristics of 862 patients initiating HAART.

Baseline characteristics	n (%)[a]
Gender	
Men	632 (73.3)
Age (years)	
median (range)	34 (19–79)
HIV Modality	
IVDU	349 (40.5)
Homosexuals	183 (21.2)
Heterosexuals	273 (31.7)
Other	57 (6.6)
CD4 cell count (cells $\times 10^6$/l)	
median (range)	309 (1–1294)
HIV-RNA (log 10 copies/ml)	
median (range)	4.78 (2.75–6.74)
CDC category	
A	590 (68.5)
B	166 (19.3)
C	106 (12.3)
Initial regimen	
Three NRTI	15 (1.7)
Two NRTI + PI	727 (84.3)
on saquinavir	213 (29.3)
on ritonavir	110 (8.7)
on indinavir	394 (54.2)
on nelfinavir	10 (1.4)
Two NRTI + NNRTI	33 (3.8)
Three other	4 (0.5)
⩾ four drugs	83 (9.6)

[a]Data are n (%) unless stated otherwise. IVDU, intravenous drug users; CDC, Centers for Disease Control and Prevention; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors.

727 patients starting two NRTI and one PI, indinavir was used in 394 patients (54.2%), hard-gell saquinavir in 213 (29.3%), ritonavir in 110 (15.1%) and nelfinavir in 10 (1.4%). Among the 33 patients starting two NRTI and one NNRTI, nevirapine was the most commonly used (30 patients, 90.9%), efavirenz was used in two patients and delavirdine in one patient. The most frequent combination was zidovudine + lamivudine + indinavir (274 patients; 37.7%).

Over a median follow-up of 45 weeks (range, 1–102), a total of 312 (36.2%) patients discontinued their initial HAART regimen: 182 (21.1%) discontinued because of toxicity, 44 (5.1%) discontinued because of failure, 61 (7.1%) because of non-adherence and 25 (2.9%) for other reasons. Specific causes of discontinuation within this broad classification are shown on Table 2. The main types of toxicity were gastrointestinal intolerance and general side effects/symptoms which accounted for 26.3 and 18.9% of the total discontinuations.

Regarding the reasons for discontinuation for failure, viral load (4.2%), rather than CD4 cell count (0.6%), was the most common reason that clinicians decided to discontinue the prescribed treatment; discontinuation due to clinical failure was also infrequent (0.3%).

The time to discontinuation varied according to the reason of discontinuation. Discontinuations because of toxicity occurred earlier (median = 84 days) than discontinuations due to failure (median = 270 days). Discontinuations because of gastrointestinal intolerance and general side effects/symptoms occurred after a median of 66 and 87 days, respectively. Patients who discontinued HAART because of virological failure did so after a median of 273 days.

The probability of discontinuation because of toxicity and because of failure by a certain time from starting HAART were estimated using Kaplan–Meier analysis (Fig. 1). After 1 year from starting HAART, 25.5% of patients [95% confidence interval (CI), 21.9–28.9] discontinued the initial HAART treatment because of

Table 2. Main causes of discontinuation of the first antiretroviral regimen in 862 patients who initiated HAART.

Cause of discontinuation	n (%)
Toxicity	
Laboratory	31 (3.6)
Side effects/symptoms	59 (6.8)
Hypersensitive reactions	9 (1.0)
Gastrointestinal intolerance	82 (9.5)
Lypodystrophy	1 (0.1)
Total	182 (21.1)
Failure	
Virological	36 (4.2)
Immunological	5 (0.6)
Clinical	3 (0.3)
Total	44 (5.1)
Non-adherence	
Non-adherence	19 (2.2)
Patient's decision	42 (4.9)
Total	61 (7.1)
Other	
Guidelines adequacy	1 (0.1)
Clinical contraindications	5 (0.6)
Other	19 (2.2)
Total	25 (2.9)
Total number discontinuing	312 (36.2)

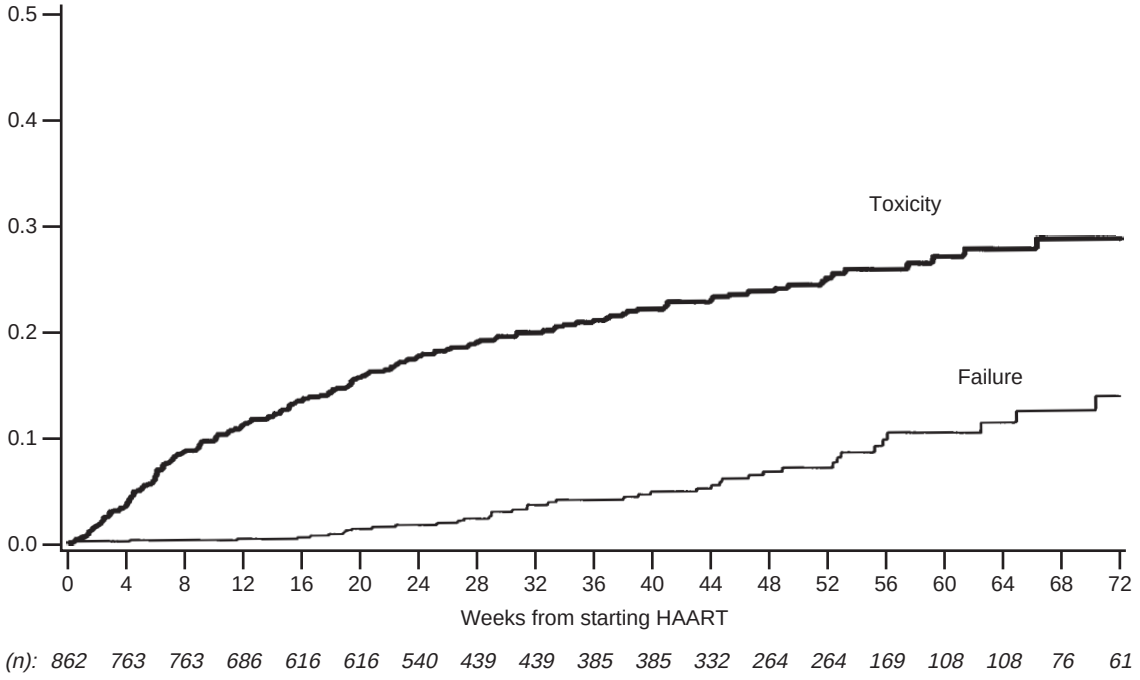

Fig. 1. Kaplan–Meier estimates of time to discontinuation because of toxicity or because of failure (all patients).

toxicity, whereas 7.6% (95% CI, 4.9–10.3) of patients discontinued because of failure.

Figure 2 shows the probability of discontinuing because of toxicity according to the protease inhibitor started within the group of patients who started two NRTI and one protease inhibitor. It is clear from this plot that discontinuations because of toxicity in patients receiving ritonavir-containing regimens occurred earlier and more frequently compared with patients on indinavir- and saquinavir-containing regimens (log-rank $P = 0.0001$).

Crude and adjusted relative hazards for therapy discontinuation due to toxicity and to failure, from fitting a Cox regression model stratified for clinical centre, are shown in Table 3. Age, weight, presence of markers for hepatitis B virus co-infection and hepatitis C virus co-infection, baseline CD4 cell count, baseline HIV-RNA, CDC classification, modality of HIV transmission failed to show any significant association with the probability of discontinuing treatment, whatever the reason (data not shown). By contrast, gender, time spent on treatment, and type of regimen started were independently associated with the probability of discontinuing HAART because of toxicity. Specifically, men were 57% less likely than women to discontinue for toxicity [relative hazard (RH) = 0.43; 95% CI, 0.28–0.66; $P = 0.0002$] for a given HIV transmission route, CD4 cell count and viral load (most recent value), time since treatment was started, and type of treatment. Results were similar after further adjusting for patients' weight at the time of receiving HAART (data not shown). Patients given indinavir- and ritonavir-containing regimens were more likely to discontinue HAART for toxicity than patients given saquinavir-containing regimens (RH = 1.63; 95% CI, 0.96–2.77; $P = 0.07$ for indinavir and RH = 3.66; 95% CI, 2.07–6.47; $P = 0.0001$ for ritonavir versus saquinavir). Time spent on treatment was also an important predictor of discontinuing for toxicity, the probability of discontinuation decreasing with longer periods of treatment (RH = 0.92 per additional month spent on treatment, 95% CI, 0.85–1.00; $P = 0.05$). Results were similar when the analyses were repeated including only patients who had a viral load below 500 copies/ml at the time of discontinuation (data not shown).

Type of treatment and the most recent HIV-RNA showed a significant independent association with the probability of discontinuing HAART for failure. Regimens containing indinavir were associated with a reduced probability of discontinuing because of failure in comparison with saquinavir-containing regimens, for a given viral load and CD4 cell count, CDC stage classification, and HIV transmission route (RH = 0.24; 95% CI, 0.08–0.73; $P = 0.01$). The comparison with ritonavir-containing regimens was marginally non-significant (RH = 0.20; 95% CI, 0.03–1.16; $P = 0.07$). Interestingly, higher CD4 cell count were associated with a decreased probability of discontinuing HAART because of failure in the univariate analysis but this association was no longer significant after controlling for the other covariates considered.

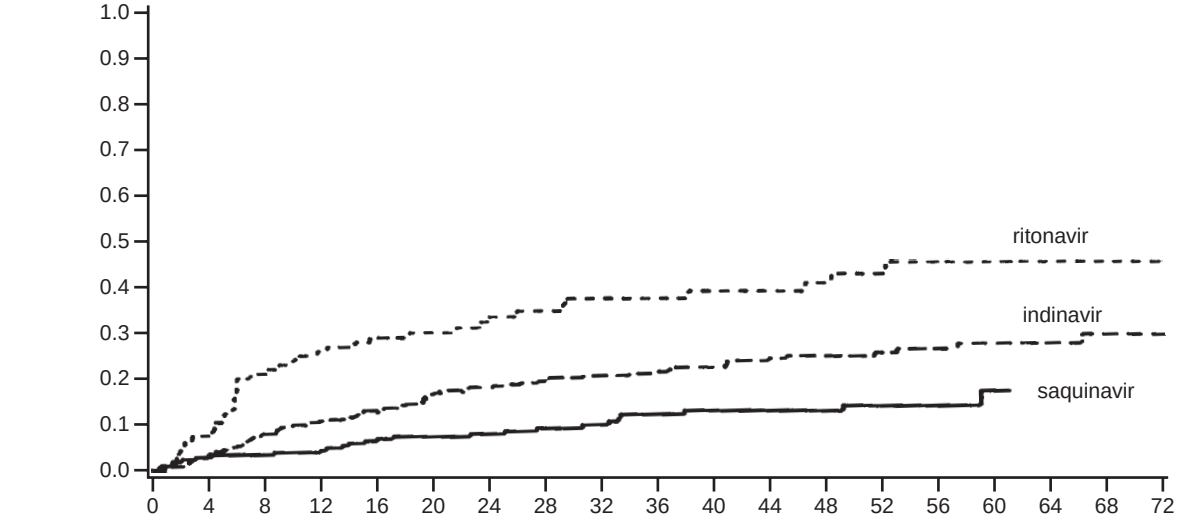

Fig. 2. Kaplan–Meier estimates of time to discontinuation because of toxicity according to the protease inhibitor started (only 717 patients who started two nucleoside reverse transcriptase inhibitors + saquinavir, ritonavir or indinavir).

Table 3. Crude and adjusted relative hazards (RH) for therapy discontinuation of the first HAART regimen due to toxicity and failure in 717 patients who started two nucleoside reverse transcriptase inhibitors + saquinavir, ritonavir or indinavir.

Characteristic	Crude RH (95% CI) *P*-value	Adjusted RH (95% CI) *P*-value
Discontinuation due to toxicity (n = 154/717)		
Gender		
Women	1.00	1.00
Men	0.44 (0.30–0.64) $P = 0.0001$	0.43 (0.28–0.66) $P = 0.0002$
HIV modality		
IVDU	1.00	1.00
Homosexuals	0.58 (0.35–0.97) $P = 0.04$	0.70 (0.41–1.19) $P = 0.19$
Heterosexuals	1.09 (0.72–1.65) $P = 0.68$	0.82 (0.52–1.29) $P = 0.40$
Other	1.02 (0.48–2.19) $P = 0.95$	1.50 (0.48–2.29) $P = 0.90$
Most recent CD4 cell count (50% cells/μl higher)	0.89 (0.77–1.02) $P = 0.09$	0.99 (0.84–1.16) $P = 0.86$
Most recent HIV RNA (log copies/ml higher)	1.24 (1.03–1.49) $P = 0.02$	1.21 (0.99–1.49) $P = 0.07$
Treatment		
Saquinavir-containing	1.00	1.00
Indinavir-containing	1.68 (1.00–2.81) $P = 0.05$	1.63 (0.96–2.77) $P = 0.07$
Ritonavir-containing	3.58 (2.04–6.28) $P = 0.0001$	3.66 (2.07–6.47) $P = 0.0001$
Time spent on treatment (month longer)	1.11 (1.05–1.18) $P = 0.0008$	0.92 (0.85–1.00) $P = 0.05$
Discontinuation due to failure (n = 37/717)		
CDC category		
A	1.00	1.00
B	1.50 (0.56–4.02) $P = 0.42$	2.15 (0.56–8.34) $P = 0.27$
C	2.90 (1.10–7.65) $P = 0.03$	1.80 (0.38–8.40) $P = 0.46$
HIV modality		
IVDU	1.00	1.00
Homosexuals	2.06 (0.69–6.15) $P = 0.19$	1.32 (0.36–4.81) $P = 0.67$
Heterosexuals	2.60 (1.05–6.45) $P = 0.04$	1.68 (0.47–5.97) $P = 0.42$
Other	1.29 (0.31–5.45) $P = 0.73$	0.44 (0.06–3.49) $P = 0.43$
Most recent CD4 cell count (50% cells/μl higher)	0.69 (0.54–0.87) $P = 0.002$	0.83 (0.56–1.25) $P = 0.38$
Most recent HIV RNA) (log copies/ml higher	2.84 (1.92–4.18) $P = 0.0001$	2.81 (1.62–4.86) $P = 0.0002$
Treatment		
Saquinavir-containing	1.00	1.00
Indinavir-containing	0.19 (0.07–0.49) $P = 0.0007$	0.24 (0.08–0.73) $P = 0.01$
Ritonavir-containing	0.26 (0.06–1.21) $P = 0.08$	0.20 (0.03–1.16) $P = 0.07$

CI, confidence interval; IVDU, intravenous drug users; CDC, Centers for Disease Control and Prevention.

Discussion

The I.CO.N.A. study [15] provides unique data for estimating the proportion of HIV-positive antiretroviral naïve patients who discontinue their first HAART treatment and for identifying characteristics associated with discontinuation in routine clinical practice. Moreover, the 'real-life' allocation to different HAART regimens and the high proportion of women allow the association between type of regimen and gender and the risk of therapy discontinuation to be evaluated.

With respect to the specific treatment regimens, it must be considered that the I.CO.N.A. cohort still mainly consists of patients recruited in 1997, the year in which protease inhibitors became available in Italy and in

which HAART began to be recommended as the first regimen for compliant patients [18].

To date, discontinuation has not been addressed as a primary end-point in clinical trials, which generally evaluate treatment efficacy with an intention-to-treat approach, considering drop-outs as failures, and consequently penalize more aggressive, more toxic combinations. Nevertheless, the results of different clinical trials seem to indicate that the frequency of discontinuations due to toxicity depends on the trial, on the duration of follow-up, and on the tested combination. Among patients receiving indinavir, 1-4% have been reported to discontinue for toxicity, with no differences when compared with double combinations, in studies with follow-up periods ranging from 38 to 100 weeks [1,3]. In the trial by Cameron *et al.* [2], over a median of 29 weeks, a higher proportion of patients receiving ritonavir discontinued for toxicity compared to those receiving less potent regimens (21 versus 8%). In another study, approximately 5% of patients receiving hard-gell saquinavir discontinued for toxicity over a median of 24 weeks, with no differences with double combination therapy [4].

A key result of this observational study is that 36% of the 862 patients studied discontinued their first antiretroviral regimen in a median follow-up of 45 weeks, a proportion for the most part higher than those reported in clinical trials. Overall, toxicity, which mainly occurred within the first 3 months, was implicated in about 58% (182 of 312) of the discontinuations, whereas failure, occurring later, was implicated only in about 14% (44 of 312). The more frequent and earlier occurrence of discontinuations for toxicity were expected, since long-term toxicity, especially that believed to be associated with protease inhibitors [19], could not be evaluated because of the relatively brief follow-up period. These results are remarkably similar to those of a clinical survey conducted in a large clinic in the UK [12]. The Kaplan–Meier estimates of time to discontinuation due to failure, since patients' follow-up were censored if they discontinued for other reasons, can be interpreted as the proportion of patients who discontinue their first regimen in an ideal world where these drugs had no toxic effects. Thus, interestingly, less than 10% of antiretroviral-naïve patients would discontinue their first HAART regimen because of failure by 1 year from starting therapy if they could perfectly tolerate their regimen (Fig. 1).

Although it is well known that patients are more strictly observed in clinical trials than in general practice, the discrepancies are greater than expected. However, large hospital-based cohorts such as ours provide a better source for estimating the rate of therapy discontinuation, in that they are more representative of patients seen in routine clinical practice. Furthermore, previous studies conducted among observational cohorts of HIV-infected patients have reported higher rates of discontinuation and failure than those observed in clinical trials [9–12]. However, none of these studies examined the determinants of discontinuation of HAART according to the reason in a population of previously antiretroviral-naïve patients.

Non-adherence was a cause of therapy discontinuation in approximately 7% of cases. This rate is lower than the rates observed in other cohorts of unselected patients and in controlled clinical trials [20,21]. Given that we only considered those cases of non-adherence that were related to drug-taking behaviour, the true prevalence of erratic adherence may have been underestimated. This estimate, in fact, could have been higher if detected by adequate tools, such as self-reporting or objective measurements. It is also conceivable that patients initiating a first HAART treatment may be more likely to adhere than patients with a history of heavy treatment, and that clinicians, in a setting where medical care is free of charge, may correctly identify those patients at risk of low adherence and assign them to a non-PI regimen. Finally, since our study did not include any measures for confirming compliance, some of the discontinuations primarily due to non-compliance may have been classified as virological failure, due to co-existing rebound in viral load, or other reasons.

Another important finding of this paper is that women were twice as likely as men, in the adjusted analysis, to discontinue HAART due to toxicity. Clinical trials are generally performed on men and thus do not address this issue; an observational study similar to the present one showed that women were more likely to be excluded from the analysis of viral load because they discontinued double combination regimens or HAART more frequently than men [22]. Discontinuation due to toxicity was associated with the specific treatment combination started. Both indinavir- and ritonavir-containing regimens were associated with a higher risk of toxicity events compared with saquinavir-containing regimens. In particular toxicity events appeared to occur earlier and more frequently in patients who received ritonavir (Fig. 2). In the multivariable Cox model, the risk of discontinuation for toxicity was more than three times higher for patients given ritonavir and about 60% higher for patients given indinavir, in comparison with patients given saquinavir. However, since patients were not randomly allocated to the different regimens, these findings need to be interpreted with caution [23,24]. Nonetheless, ritonavir is known to be poorly tolerated, particularly as a result of gastrointestinal problems, and this may lead to poor compliance [11]. In mid-1998 ritonavir tablets were no longer available and patients on ritonavir-containing regimens were switched to the syrup formulation of

ritonavir. The well-known bad taste of the syrup may have increased the chance of discontinuing these regimens because of non-adherence (e.g. patients' decision) but we controlled for this in the analysis by censoring follow-up times at the time of discontinuations for reasons other than the end-points of interest. Results are more difficult to interpret for indinavir, which, as already mentioned, is generally associated with a very low rate of severe adverse events; however, the association was marginally non-significant ($P = 0.07$). The first months of treatment are crucial, as the risk of discontinuing because of toxicity decreases by 8% with each month on therapy. Again, it must be emphasized that this study, due to the short follow-up, currently lacks the power to evaluate chronic long-term toxicity. Surprisingly, even if patients with a high CD4 cell count are generally believed to tolerate drugs better than those with a low CD4 cell count, neither baseline nor most recent CD4 cell count showed a statistically significant association with discontinuing for toxicity.

The relatively good clinical conditions of the cohort at baseline (68% of patients in CDC stage A) and the short follow-up can explain the low rate of discontinuations due to clinical failure (less than 1%) over a median 45-week period of therapy. As expected, virological failure was the most common cause of therapy failure. In the multivariable Cox model, indinavir-containing regimens were associated with a reduced risk of discontinuation due to failure compared with saquinavir-containing regimens, which is consistent with the results of clinical trials and other similar observational studies [1,3,11,12]. Again, these results need to be taken with caution since it is not a randomized comparison. However, the low bioavailability of hard-gell saquinavir is well known as it has now been replaced by the soft-gell formulation. The result that the most recent HIV-RNA is predictive of discontinuation due to failure is not surprising and provides evidence that the classification of the reason of discontinuation given by the clinicians is reliable. The baseline HIV RNA level showed no statistical association with the outcome. This in contrast with the results of other studies showing that initial viral load at the time of starting therapy increases the chance of incomplete virological suppression upon initiation of HAART [9,10,25]. However in these studies a quantitative measure (such as, for example, viral load $\leqslant 500$ copies/ml) was used to define the endpoint of the analysis. Furthermore, only 44 patients discontinued HAART because of failure and it is possible that the association with baseline viral load was not significant simply because of a lack of statistical power. Similarly, in the multivariate analysis, baseline CD4 cell count was not associated with the probability of discontinuing HAART because of failure, which is apparently inconsistent with the results of other studies that investigated the value of CD4 cell count in predicting virological response [10,25]. However, the univariate analysis carried strong evidence for an association, patients with higher CD4 cell count being at a lower chance of discontinuing due to failure.

Some aspects of the statistical analysis performed need to be discussed before interpreting the results and drawing final conclusions. First, survival analyses were conducted under the assumption that the probability of discontinuation for toxicity is completely unrelated to the probability of discontinuing for failure. Obviously, this assumption may not be entirely valid, and the results could be affected by a bias due to informative censoring [26]. However, the analysis for studying the factors associated with discontinuing for toxicity was repeated, including only patients who had a viral load below 500 copies/ml at the time of discontinuation; this analysis provided very similar results (data not shown), suggesting that, if this bias exists, it is probably small. A possible limitation of the study is that I.CO.N.A. includes patients from 65 different infectious diseases wards, and the way in which the individual wards determined the single reason for discontinuation in cases of concomitant reasons may have varied. However, this bias has been partially corrected by close central monitoring of all data; moreover, the potential confounding effect of the individual wards has been controlled for in the analyses.

In conclusion, patients receiving indinavir- and ritonavir-containing HAART regimens, were at lower chance of discontinuing HAART because of failure but also at higher risk of discontinuing because of toxicity compared with those receiving hard-gell saquinavir. Continuation of initial HAART regimen in antiretroviral-naïve patients is crucial for maintaining long-term viral suppression. Recent international guidelines because of the problems of intolerance and toxicity associated with PI-containing regimens indicate HAART regimens including two NRTI and one NNRTI as a viable alternative [27]. However, the lack of long-term data on NNRTI and clinical end-points makes PI-containing regimes the safer choice at present and continued monitoring of toxicity in patients (especially women) receiving indinavir- and ritonavir-containing HAART regimes recommended. If the current HAART regimen caused no toxicity, less than 10% of naïve patients discontinue their initial treatment because of failure after 1 year from starting therapy.

References

1. 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.
2. Cameron DW, Hearth-Chiozzi, Danner S, *et al.* **Randomized**

placebo-controlled trial of ritonavir in advanced HIV-1 disease. *Lancet* 1998, **351**:543–549.
3. 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.
4. 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.
5. Palella FJ, Delaney KM, Moorman AC, *et al.* **Declining morbidity and mortality among patients with advanced human immunodeficiency virus syndrome.** *N Engl J Med* 1998, **338**:853–860.
6. 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.
7. Mocroft A, Vella S, Benfield TL, *et al.* **Changing patterns of mortality across Europe in patients infected with HIV-1.** *Lancet* 1998, **352**:1725–1730.
8. Vanhove GF, Schapiro JM, Winters MA, Merigan TC, Blaschke TF. **Patient compliance and drug failure in protease inhibitor monotherapy.** *JAMA* 1996, **276**:1955–1956.
9. 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.
10. Mocroft A, Gill MJ, Davidson W, *et al.* **Predictors of a viral response and subsequent virological treatment failiure in patients with HIV starting a protease inhibitor.** *AIDS* 1998, **12**:2161–2167.
11. d'Arminio Monforte A, Testa L, Adorni F, *et al.* **Clinical outcome and predictive factors of failure of highly active antiretroviral therapy in antiretroviral-experienced patients in advanced stages of HIV-1 infection.** *AIDS* 1998, **12**:1631–1637.
12. Youle M, Sawyer W, for the HIV Health Economics Collaboration. **Reasons for discontinuation of antiretroviral treatment: a clinical survey.** *AIDS* 1998, **12**:P186.
13. Van Roon EN, Verzijl JM, Juttmann JR, *et al.* **Incidence of discontinuation of highly active antiretroviral therapy (HAART) and its determinants.** *J Acquir Immune Defic Syndr* 1999; **20**:290–294.
14. Anon. **Guidelines for the use of antiretroviral agents in HIV infected adults and adolescents.** *Ann Intern Med* 1998, **128**:1079–1100.
15. d'Arminio Monforte A, Pezzotti P, Arici C, *et al.* **Determinants of initiation of antiretroviral therapy (ART) in an italian cohort of HIV-positive patients naïve from antiretrovirals (I.CO.N.A. Study).** *AIDS* 1998, **12**:P99.
16. Database can be found at HYPERLINK http://www.icona.org
17. Anon. **1993 Revised Classification System for HIV infection and Expanded Surveillance Case Definition for AIDS among adolescents and adults.** *MMWR* 1992, **41**:19–23.
18. 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.
19. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. **Visceral fat accumulation associated with use of indinavir.** *Lancet* 1998, **351**:871–875.
20. Kastrissios H, Suarez J-R, Katzenstein D, Girard P, Sheiner LB, Blaschke TF. **Characterizing patterns of drug-taking behaviour with a multiple drug regimen in an AIDS clinical trial.** *AIDS* 1998, **12**:2295–2303.
21. Eldred LJ, Wu AW, Chaisson RE, Moore RD. **Adherence to antiretroviral and pneumocystis prophylaxis in AIDS disease.** *J Acquir Immune Defic Syndr* 1998, **18**:117–125.
22. Hogg RS, Rhone SA, Yip B, *et al.* **Antiviral effect of double and triple drug combinations amongst HIV-infected adults: lessons from the implementation of viral load-driven antiretroviral therapy.** *AIDS* 1998, **12**:279–284.
23. Phillips AN. **Role of cohort studies.** Presented at *12th World AIDS Conference,* Geneva, June 28–July 3 1998.
24. Feinstein A. **The role of observational studies in the evaluation of therapy.** Stat Med 1984, **3**:341–345.
25. Staszveski S, Miller V, Sabin CA, *et al.* **Virological response to protease inhibitor therapy in an HIV clinic cohort.** *AIDS* 1999 (in press).
26. Hoover DR, Peng Y, Saah AJ, Detels RR, Day RS, Phair JP. **Using multiple decrement models to estimate risk and morbidity from specific AIDS illnesses. Multicentre AIDS Cohort Study (MACS).** *Stat Med* 1996, **15**:2307–2321.
27. Carpenter CCJ, Fischl MA, Hammer SM, *et al.* **Antiretroviral therapy for HIV infection in 1998. Updated recommendations of the International AIDS Society-USA Panel.** *JAMA* 1998, **280**: 78–86.

Appendix

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