Articles

Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study

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Summary

Background The efficacy of highly active antiretroviral therapy (HAART) in suppression of HIV-1 is well documented. We investigated virological and clinical outcomes of HAART in routine practice.

Methods We analysed prospective data from the Swiss HIV Cohort Study on suppression of viral load and progression to AIDS or death in 2674 outpatients (median age 36 years, 27·3% women) who started HAART in 1995–98. Viral rebound was defined as two consecutive HIV-1-RNA measurements of more than 400 copies/mL. We analysed separately outcomes in patients with a history of antiretroviral treatment and in treatment-naïve patients.

Findings An estimated 90·7% of treatment-naïve patients reached undetectable viral load (<400 copies/mL) by 12 months. Among pretreated patients, estimates ranged from 70·3% treated with one new drug to 78·7% on three new drugs. 2 years after reaching undetectable concentrations, an estimated 20·1% of treatment-naïve patients and 35·7–40·1% of pretreated patients had viral rebound. At 30 months, an estimated 6·6% (95% CI 4·6–8·6) of patients who had maintained undetectable concentrations, 9·0% (5·5–12·5) who had viral rebound, and 20·1% (15·3–24·9) who had never reached undetectable concentrations developed AIDS or died. Compared with patients who maintained undetectable viral load, the adjusted relative hazard of AIDS or death was 1·00 (0·66–1·55) for patients with viral rebound, and 2·40 (1·72–3·33) for patients who failed to reach undetectable concentrations.

Interpretation The rate of virological failure of HAART was high among these patients, but the probability of clinical progression was low even in patients with viral rebound.

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Introduction

Highly active antiretroviral therapy (HAART) is currently the most important component of the treatment of HIV-1 infection. At present, HAART generally consists of one protease inhibitor combined with at least two nucleoside analogue reverse-transcriptase inhibitors. The efficacy of HAART in suppression of plasma HIV-1 RNA to undetectable concentrations has been documented in clinical trials.[1–3] The virological and immunological success rates reported from such trials may not, however, be generalisable to the whole population of HIV-1-infected patients.[4] Furthermore, new opportunistic diseases or death are rarely used as endpoints in trials of HAART. It is widely accepted that plasma viral loads and CD4 cell counts reflect clinical efficacy, and virological and immunological responses are therefore used as surrogate endpoints. Viral load and CD4 counts are, however, imperfect surrogate markers that do not capture effects due to toxic effects or mediated through other causal pathways.[5,6]

In the absence of trials assessing clinical endpoints, observational data are the only source of information relating new treatment regimens to the risk of serious clinical disease. Studies in the USA[7] and Europe[8,9] have documented a substantial decrease in the risk of new opportunistic infections and of mortality after HAART was introduced. These studies have not, however, related virological responses to clinical progression.

We analysed the database of the national Swiss HIV Cohort Study to assess virological and immunological responses to HAART in routine care and to relate these findings to clinical disease progression.

Methods

Patients

The Swiss HIV Cohort Study is a prospective cohort study with continuing enrolment of HIV-1-infected patients aged 16 years or older.[8,10] Patients are followed up in one of seven outpatient clinics. Enrolment is independent of disease stage or degree of immunosuppression and information is collected according to standardised criteria at registration and follow-up visits every 6 months. Comparisons with the national AIDS registry have shown that the cohort includes 70% of patients with AIDS.[10] CD4 lymphocyte count is measured with flow cytometry, and HIV-1 RNA (viral load) with the Amplicor test (Roche Diagnostics, Basle, Switzerland; level of detection 400 copies/mL). Additional viral load and CD4 count values

Characteristic	Number of patients (n=2674)
Demographic	
Median (range) age (years)	36 (17–82)
Male/female	1944 (72·7%)/730 (27·3%)
Transmission category	
Homosexual men	983 (36·8%)
Injecting drug users	799 (29·9%)
Heterosexual contact	789 (29·5%)
Other	103 (3·8%)
Clinical stage	
A	1097 (41·0%)
B	888 (33·2%)
C	689 (25·8%)
History of antiretroviral treatment	1517 (56·7%)
Median (range) viral load (log_{10} copies/mL)	4·49 (2·60–6·88)
Median (range) CD4 cell count (cells/μL)	192 (0–1439)
Initiation of HAART	
Reverse-transcriptase-inhibitor experienced	
3 new drugs	433 (16·2%)
2 new drugs	603 (22·5%)
1 new drug	481 (18·0%)
Treatment naïve	1157 (43·3%)
Protease inhibitor used	
Indinavir	1169 (43·7%)
Nelfinavir	553 (20·7%)
Ritonavir	529 (19·8%)
Saquinavir* and ritonavir	222 (8·3%)
Saquinavir*	172 (6·4%)
Other protease-inhibitor combinations	29 (1·1%)

*Hard-gel capsules.

Table 1: **Characteristics at start of HAART**

from routine consultations are also recorded. HAART, defined as combinations including at least three drugs, with at least one protease inhibitor, was gradually introduced in Switzerland from 1995 onwards. Clinical stage is defined according to the 1993 classification system for HIV-1 infection.[11] We included all participants of the Swiss HIV Cohort Study who started HAART between Sept 1, 1995, and Nov 30, 1998, who had a CD4 count and viral-load measurement within 3 months before starting HAART, and at least one follow-up visit more than 1 month after HAART was started. The database included information up to Dec 31, 1998.

Endpoints

We studied responses of viral load and CD4 count. Virological response was defined as suppression of viral load to less than the detection limit, and CD4-cell response as an increase of at least 50 cells/μL. In the analysis we used the date of the first measurement meeting the definition. Among participants who reached viral load of less than the level of detection, viral rebound was defined as two consecutive measurements of more than 400 copies/mL. We used the date of the first of the two measurements in our analysis. Our main clinical endpoints were progression to a new AIDS-defining event or death.

Statistical analysis

We used Kaplan-Meier life-tables and Cox's regression for time-to-event analyses. For initial viral and CD4 responses and clinical endpoints we measured time from the start of HAART. Time to viral rebound was measured from the date of the first undetectable viral load, and viral response to a second regimen from the date of changing treatment. We measured time to the date these endpoints occurred or the date of the most recent follow-up visit. We examined viral response to the initial treatment regimen in a separate Cox's model and censored time when the treatment was modified to study the predictors of viral response to the initial regimen.

We calculated the rate of new clinical AIDS events and mortality by dividing the number of patients developing the event by the number of person-years at risk. We used Poisson's distribution to calculate CIs for rates. The proportion of patients with undetectable viral load in each quarter up to 30

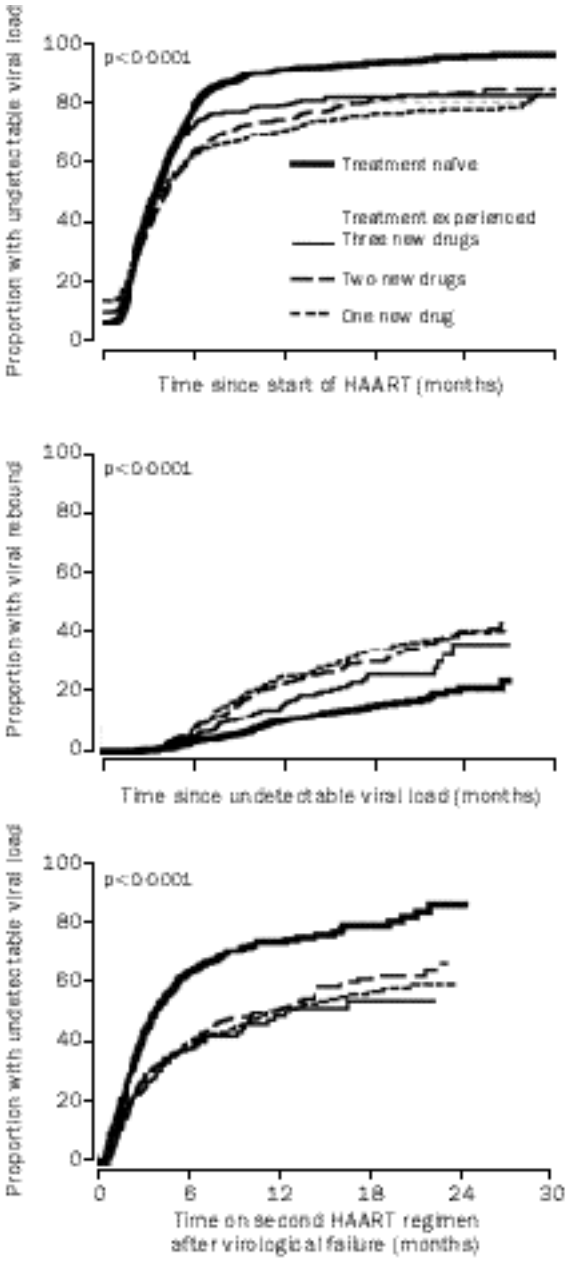

Figure 1: **Kaplan-Meier curves of probability of reaching undetectable viral load (top), of viral rebound (middle), and of reaching undetectable viral load on second HAART regimen after virological failure (bottom) by initial regimen**

months after starting HAART was calculated by dividing the number of patients with undetectable viral load by the total number of patients followed up in that quarter. Finally, we defined two historical comparison groups of cohort participants who started antiretroviral treatment in 1987–92 (monotherapy) and those who started in 1993–96 (monotherapy or dual therapy). We matched historical patients to HAART patients for baseline CD4 count within four strata (<50 cells/μL, 50–99 cells/μL, 100–199 cells/μL, and ⩾200 cells/μL). For each current patient on HAART we randomly selected two historical patients whose baseline CD4 count was in the same CD4 stratum.

We used SAS (version 6.12) and Stata software (version 6.0) for analyses. Results are presented as Kaplan-Meier estimates of the probability of patients reaching an endpoint, relative hazards, or rates per 100 person-years, with 95% CIs. Statistical and graphical tests showed that the proportional hazards assumption was not violated.

	Relative hazard (95% CI)	p
Initiation of HAART		<0·0001
Reverse-transcriptase-inhibitor experienced		
3 new drugs	0·82 (0·70–0·94)	
2 new drugs	0·79 (0·69–0·91)	
1 new drug	0·65 (0·55–0·77)	
Treatment naïve	1·0*	
Protease inhibitor used		<0·0001
Saquinavir† hard-gel capsules *vs* other	0·31 (0·22–0·44)	
Clinical stage		0·009
A	1·0*	
B	0·93 (0·83–1·06)	
C	0·80 (0·69–0·93)	
Viral load (copies per mL)/1 $\log_{10}$ increase	0·75 (0·71–0·80)	<0·0001
CD4 lymphocyte count per 100 cells/μL increase	1·04 (1·01–1·07)	0·007
Age (years)/10-year increase	0·99 (0·94–1·05)	0·69
Calendar period (1997–98 *vs* 1995–96)	1·31 (1·17–1·48)	<0·0001

*Reference. †As only protease inhibitor.
Results from Cox's regression analysis; estimates adjusted for all variables listed.

Table 2: **Probability of reaching undetectable viral load with initial treatment regimen**

Results

Patients

Between September, 1995, and November, 1998, 3451 (65·1%) of 5298 patients followed up in the Swiss HIV Cohort study had started HAART. We excluded 252 (7·3%) patients who did not have at least one follow-up visit after HAART was started, and 525 (15·2%) with missing viral load or CD4 count at baseline. The analyses were based on 2674 (77·5%) patients (table 1). Included and excluded patients did not differ significantly for age, sex, transmission group, or clinical stage at baseline. History of antiretroviral treatment was less frequent among excluded patients (52·4 *vs* 56·7%). Patients were followed up for a total of 3626 patient-years. The median number of viral-load measurements and CD4 counts per year was 4·6 and 4·3, respectively. 40 patients (1·5%) were lost to follow-up because they moved abroad or withdrew consent, and 97 patients (3·6%) had not been seen in the past year. Patients lost to follow-up were similar to patients with regular follow-up for clinical stage, CD4 count, and viral load at baseline.

Virological responses

Kaplan-Meier plots showed a steep increase in the estimated probability of patients reaching undetectable concentrations by 12 months (figure 1). Overall, the rate of undetectable viral load at 12 months was 81·2% (95% CI 79·7–82·7). Among treatment-naïve patients, an estimated 90·7% achieved undetectable concentrations by 12 months compared with 78·7% of pretreated patients who received three new drugs, 74·0% of those on two new drugs, and 70·3% of those on one new drug ($p<0·0001$). Use of saquinavir as the only protease inhibitor in the initial HAART combination, clinical stage C, and high viral load were associated with a decrease in probability of reaching undetectable viral load. By contrast, higher CD4 count and more recent start of HAART were associated with an increased probability of reaching undetectable viral load (table 2).

Among the 2232 (83·5%) patients who reached undetectable viral load during follow-up, the probability of a viral rebound 2 years after reaching undetectable concentrations was 20·1% for treatment-naïve patients and 35·7–40·1% for pretreated patients (figure 1).

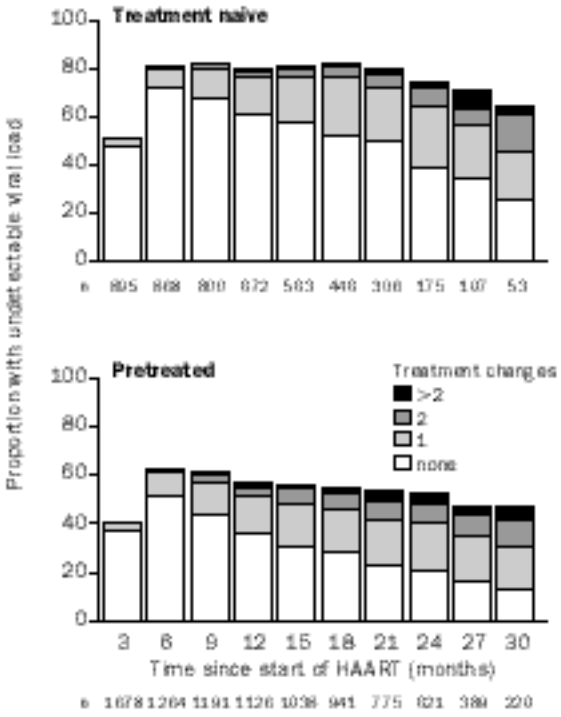

Figure 2: **Quarterly prevalence of undetectable viral load up to 30 months**
Shaded bars=number of changes made to initial regimen.

Treatment was changed at least once in 1402 (52·4%) patients. The estimated probabilities of treatment change at 12 months were 79·3% for saquinavir, 60·8% for ritonavir, 45·2% for indinavir, 40·6% for saquinavir and ritonavir, and 30·5% for nelfinavir. Among 964 patients with detectable HIV-1 RNA at the time of treatment change, the probability of reaching undetectable viral load was 57·1% (95% CI 53·7–60·6) at 12 months after treatment change (figure 1). Compared with the initial

	Number of patients	Median number of cells gained (IQR)
All patients	2323	76 (19–153)
Initiation of HAART		
Reverse-transcriptase-inhibitor experienced		
3 new drugs	376	80·5 (20·0 to 161·0)
2 new drugs	520	66·5 (16·0 to 132·5)
1 new drug	419	50 (−3 to 113)
Treatment naïve	1008	94 (30 to 184)
Clinical stage		
A	952	97 (18·5 to 195·0)
B	765	67 (18 to 133)
C	606	65·5 (20·0 to 123·0)
Baseline CD4 cell count (cells/μL)		
0–50	439	66 (34 to 109)
51–100	300	79·5 (31·5 to 141·5)
101–200	468	80 (21 to 156)
201–500	905	85 (9 to 179)
>500	211	54 (−50 to 225)
Baseline viral load ($\log_{10}$ copies/mL)		
>5	688	94 (40 to 160)
>4–5	875	78 (21 to 162)
>3–4	475	61 (7 to 144)
≤3	285	44 (−14 to 117)
6-month viral load*		
Undetectable	1525	90 (28 to 167)
Detectable	755	54 (3 to 115)

Analysis based on 2323 patients with CD4 cell count at 6 months. *Missing in 43 patients.

Table 3: **Number of CD4 cells gained within first 6 months of treatment**

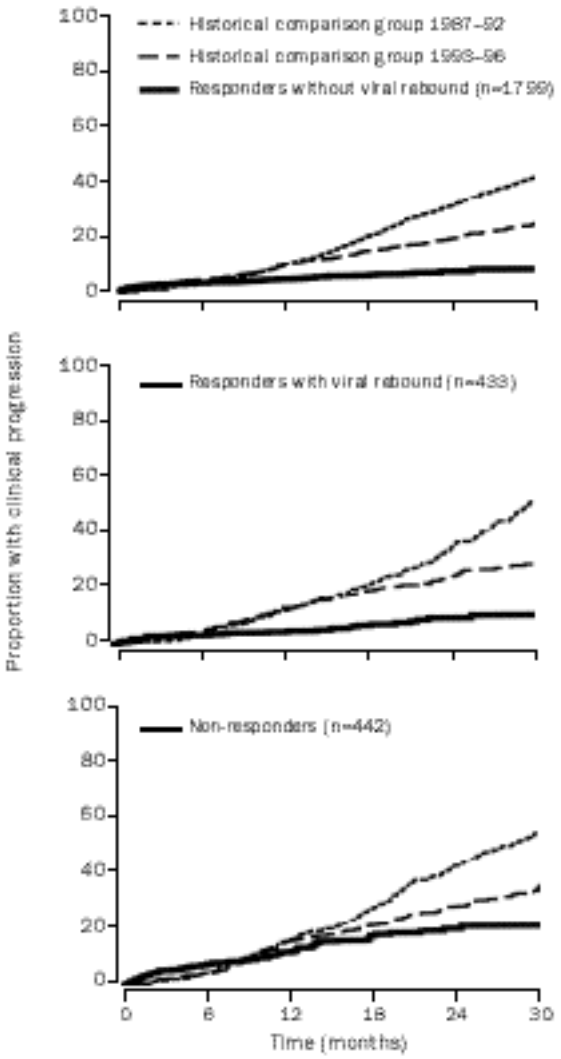

Figure 3: **Kaplan-Meier curves of the probability of developing a new clinical AIDS event or death among patients with sustained undetectable viral load (top), with initially undetectable viral load followed by viral rebound (middle), and in patients who never reached undetectable viral load (bottom) in current patients on HAART and matched historical groups**

response, the Kaplan-Meier curves show a flatter increase in the estimated proportion of patients reaching undetectable concentrations. Among treatment-naïve patients, an estimated 73·9% reached undetectable HIV-1-RNA concentrations by 12 months after treatment change. The corresponding proportions for pretreated patients ranged from 48·6% to 51·3%.

Among treatment-naïve patients, the prevalence of undetectable viral load decreased from 81·5% in the second quarter to 66·0% at 30 months (figure 2). Among pretreated patients, the corresponding proportions were 62·7% and 47·7%. This decrease was associated with a high rate of treatment change. At 30 months, only 40·0% of treatment-naïve and 30·5% of pretreated patients with undetectable viral load were still on their initial regimen.

CD4 responses

In Cox's regression, gains of at least 50 CD4 cells/μL were associated with the initial HAART regimen ($p<0·0001$), the clinical stage at baseline ($p=0·0003$), viral load at baseline ($p<0·0001$) and whether undetectable concentrations were reached ($p=0·002$). Absolute CD4-cell gains according to these factors are shown in table 3.

Clinical progression

Overall, 141 patients experienced a new clinical AIDS event after starting HAART and 46 patients died of an HIV-1-related cause. The incidence of new AIDS events was 4·0 (3·4–4·8) and mortality was 1·3 (0·9–1·7) per 100 person-years. At 30 months, estimated probabilities of disease progression were 6·6% (4·6–8·6) for patients who achieved and maintained undetectable viral loads, 9·0% (5·5–12·5) for patients who achieved undetectable concentrations but had a viral rebound, and 20·1% (15·3–24·9) for patients who never achieved undetectable concentrations ($p=0·001$, figure 3). This finding was confirmed in Cox's regression models adjusted for CD4 count and age at baseline. Compared with patients who reached and maintained undetectable concentrations, the relative hazard was 1·00 (0·66–1·55) for patients with viral rebound and 2·40 (1·72–3·33) for patients who failed to reach undetectable concentrations. There was no effect for the choice of the protease inhibitor or pretreatment.

Historical groups and current HAART patients were closely matched for CD4 counts, with differences in median count at baseline ranging from 1 cell/μL to 6 cells/μL. Among historical patients, 25·1% were in clinical stage C compared with 25·8% among patients on HAART ($p=0·57$). Kaplan-Meier estimates of disease progression or death were consistently higher in historical groups than current groups, even when compared with patients who never reached undetectable HIV-1 RNA on HAART (figure 3).

Discussion

HAART led to suppression of viral replication in a substantial proportion of patients, but our results were less favourable than those from randomised trials.[1,3,12] Gulick and colleagues[3] showed that initial treatment with a triple-combination therapy, including a protease inhibitor, led to sustained suppression of viral load in pretreated patients. At 100 weeks, viral load continued to be undetectable in 78% of patients. Conversely, we found that 20–30% of pretreated patients never reached undetectable concentrations of HIV-1 RNA and that there were high rates of viral rebound among those who did. Viral rebound or adverse effects led to modifications of treatment regimens in many patients. Despite the limited success of HAART, however, to sustain suppression of HIV-1 replication, the probability of clinical progression was substantially lower than in previous years. This finding is explained by an important rise in CD4 count, which is maintained despite detectable virus.[13]

In more-developed countries, HAART has substantially decreased the morbidity and mortality of HIV-1-infected patients.[7,9,14,15] In our study, the incidence of new clinical AIDS events was 4·2 per 100 person-years from September, 1995, to December, 1998. During the same period, mortality from HIV-1-related causes was 1·3 per 100 person-years. Our results therefore show an important further decline of HIV-1-associated morbidity and mortality in patients treated

with HAART compared with data from the Swiss study[8] and other cohorts.[7,9,14] In the dual-therapy era, mortality among patients of a comparable Canadian cohort was around ten per 100 patient-years.[14] In a study covering the introduction of protease inhibitors, Palella and colleagues[7] also reported a mortality rate of about ten per 100 patient-years, but the analysis was based on patients with more advanced disease and most, but not all, patients received a protease inhibitor. Mocroft and colleagues,[9] for the EuroSIDA Study Group, reported death rates of between 2·2 and 6·5 per 100 patient-years among patients on protease inhibitors.

We found an increased risk of clinical progression among patients who never reached undetectable viral load, with an estimated 20·1% progressing to a new AIDS event or death by 30 months. Even in this group, however, clinical progression was substantially less than that for patients in the historical monotherapy and dual-therapy groups. Among patients who initially achieved undetectable viral load, progression was rare and patients who had sustained suppression and patients who experienced a viral rebound during follow-up did not differ. With use of second-line treatments, clinical progression could thus be prevented in most of the patients who achieved undetectable concentrations but who later developed a viral rebound.

Several factors predicted the probability of reaching undetectable viral load with the initial treatment regimen, including baseline viral load, clinical stage, and CD4 count. Our results confirm those from previous smaller studies.[4,16–18] Clinical stage and CD4 count were independent predictors, with more advanced disease associated with less favourable virological response. Immunological response was related to virological response and to baseline viral load. Patients with undetectable viral load at 6 months and, unexpectedly, patients with a higher baseline viral load gained more CD4 cells after HAART was started. The decrease in HIV-1 RNA therefore seems to lead to a more pronounced rise in CD4 cells if viral load was high initially. Patients who had previously been treated with reverse-transcriptase inhibitors were less likely to achieve viral suppression. Sequential initiation of antiretroviral drugs impairs virological efficacy, probably because of failure to overcome drug-resistant mutations.[19] In the study by Gulick and colleagues,[3] patients pretreated with zidovudine who were randomised to treatment with a combination of two reverse-transcriptase inhibitors, with a protease inhibitor added 24 weeks later, showed high rates of viral rebound (70% at 100 weeks). Our results underscore the importance of changing as many drugs as possible when modifying a HAART regimen.

Patients starting on a regimen including saquinavir hard-gel capsules as the only protease inhibitor were less likely to reach undetectable viral load and less likely to experience a substantial increase in CD4 lymphocytes. Direct comparisons of the efficacy of drugs in observational studies must be interpreted with caution.[20,21] In Switzerland, different protease inhibitors became available at different times, against a background of changing treatment policies, changing characteristics of patients eligible for HAART, and accumulating experience of treating physicians. In our study, however, the inferior performance of saquinavir hard-gel capsules remained after control for relevant differences in baseline characteristics and calendar year. Furthermore, our findings are in line with the results from clinical trials and observational studies of smaller groups of patients[4,16,17] and can be plausibly explained by the inferior bioavailability of saquinavir in hard-gel formulation.[22]

The crucial question of whether to "hit" the virus early and hard before immunodeficiency develops, or whether to wait until the clinical benefits of treatment clearly outweigh toxic effects and effects on quality of life[23,24] remains unresolved. Pathophysiological arguments have been proposed in support of both positions.[25,26] By current standards,[27,28] the virus was hit late in most patients in our study. The viral-load assay we used was insensitive and undetectable viral load cannot, therefore, be equated with complete suppression of viral replication. Important clinical benefits were nevertheless seen, and sustained suppression was not required for these benefits to be realised. Opportunistic diseases and deaths, however, occurred mainly in patients with virological responses below optimum. Earlier and more effective HAART, by ensuring better virological responses, might have prevented those complications.

In prospective cohort studies, follow-up patterns may be informative of disease progression. For example, patients with slow progression of disease may avoid outpatient visits and, therefore, contribute less complete information, or may allow themselves to be lost to follow-up. This "walking well" phenomenon may lead to high estimates of clinical progression. Conversely, if patients with more severe disease are more likely to leave the study, the bias will act in the opposite direction. Bias owing to informative censoring is unlikely to have been a difficulty in our study because 95% of patients had been seen in the past year, and those who had not been seen had similar characteristics at baseline. We did time-to-event analyses, although the time was strictly not known for laboratory endpoints. For example, we used the date of first measurement of undetectable HIV-1 RNA as a proxy for the date at which undetectable viral load was reached. We did, however, obtain similar results by logistic regression, which does not require information on the time the endpoint occurred (data not shown).

In conclusion, the rate of virological failure of HAART regimens was higher than that reported in randomised controlled trials, and a second regimen was therefore required in many patients. Despite this limited virological success, however, clinical progression and mortality remained low for more than 2 years. Virological and immunological responses should be assessed before HAART is taken to be failing and the regimen is modified, especially because the number of available treatment options is limited. Controlled trials are required to define the optimum time of starting HAART and the best therapeutic strategies after virological, immunological, or clinical treatment failure.

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Contributors
All authors contributed to overall study design and coordination. B Ledergerber and M Egger conceived the study and did the statistical

analyses. All authors contributed to the text of the first draft of the manuscript. M Egger, B Ledergerber, and R Weber wrote the final version of the paper.

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