

Impact of occasional short interruptions of HAART on the progression of HIV infection: results from a cohort study

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Objectives and design: To investigate the clinical consequences of occasional and short (≤ 3 months) treatment interruptions in patients having initiated highly active antiretroviral therapy (HAART). Data from the prospective Swiss HIV Cohort Study were used.

Methods: Four different endpoints [death, Centers for Disease Control and Prevention (CDC) stages B and C, and CD4 cell count increase $\geq 50 \times 10^6/l$] were studied in relation to the number of interruptions that occurred. In order to focus on short interruptions exclusively, observations of patients with a treatment interruption of > 3 months were censored. The CD4 cell count and viraemia were treated as time-dependent variables because of the importance of these factors when an interruption occurs.

Results: Between 1 January 1996 and 31 October 2000, 4720 Swiss HIV Cohort Study participants initiated HAART, which was interrupted at least once by 1299 participants. The main reasons for the interruptions were social factors. Interruptions did not increase significantly the risk of HIV-associated morbidity and mortality, except for a marginally increased risk for a CDC stage C event after the first interruption. The first interruption decreased significantly the likelihood of increasing the CD4 cell count. Subsequent interruptions had no further significant effect. High CD4 cell count and low viraemia, assessed as baseline and as longitudinal variables, were associated with a decreased risk of clinical progression.

Conclusions: Occasional treatment interruptions of < 3 months neither worsen nor improve disease outcome on an average term (3–4 years). Our results suggest that interruptions might be non-risky, particularly when viraemia is low and CD4 cell count is high. These results require confirmation. © 2002 Lippincott Williams & Wilkins

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Introduction

Multiple clinical trials and observational studies have demonstrated the efficacy of highly active antiretroviral

therapy (HAART) in decreasing HIV-related morbidity and mortality [1–3]. However, the potential of such complex therapy is impaired by poor adherence and intolerance leading to treatment interruptions [4–7].

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(see also pp. 787–789)

Treatment interruptions may have adverse consequences and several trials indicated that the discontinuation of one of the drugs of a triple-drug combination leads to viral rebound [8–16]. However, the impact of short interruptions (< 3 months) occurring outside of clinical trial settings (i.e., occasional) has not yet been documented in the literature.

We have designed this study to investigate the clinical consequences of occasional and short treatment interruptions in patients having initiated HAART. The specific objectives of this research were: to describe participants of the Swiss HIV Cohort Study (SHCS) who discontinued HAART and to compare them to participants who never interrupted treatment; to assess the duration and timing of HAART interruptions; and to compare the clinical outcome and the evolution of the CD4 cell count of patients with and without interruptions.

Until 1999, treatments and treatment interruptions were recorded in the SHCS on a monthly basis. For this reason the shortest interruptions documented were of 1 month. Because the main question asked by this study concerns the existence of a difference in the clinical progression of patients who experienced interruptions after initiating HAART compared with those who never interrupted treatment, treatment changes without interruptions were not considered.

Methods

The Swiss HIV Cohort Study

The SHCS enrolls patients with HIV infection aged 16 years or older, independently of disease stage and degree of immunodeficiency [17]. Prospective enrolment started in 1988. Approximately 73% of all patients with reported AIDS in Switzerland participate in the SHCS [18]. Patients are followed in seven clinical centres (Basel, Bern, Geneva, Lausanne, Lugano, St. Gallen, and Zurich). Information is collected at registration and at follow-up visits at 6 month intervals, and includes additional CD4 cell count and HIV-1 RNA determinations from routine interim consultations. The follow-up questionnaire includes a detailed history of HIV-associated diseases, defined as category B or C clinical conditions of the 1993 revised Centers for Disease Control and Prevention (CDC) classification system for HIV infection [19], type and dates of starting and discontinuing antiretroviral medication.

Eligibility and definitions

In this study, HAART was defined as a combination treatment with at least three antiretroviral drugs, including at least one protease inhibitor (PI). This definition included patients receiving saquinavir hard

gel capsules as the only PI. Patients receiving efavirenz or nevirapine with a combination of at least two other antiretroviral drugs were also considered as receiving HAART. Eligible patients were those who started HAART between 1 January 1996 and 31 October 2000, thus allowing sufficient follow-up. Information available up to May 2001 was included.

A treatment interruption was defined as the absence of any antiretroviral drug during at least 1 month in a patient who was previously receiving HAART. The end of the interruption was defined as the time when the patient was treated again, even if it was not with HAART. Interruptions lasting between 1 and 3 months were considered. For patients with interruptions of > 3 months' duration, the observation was censored at the end of the third month of interruption.

Patients with and without treatment interruptions were compared in terms of mortality, the occurrence of the first CDC stage B and C clinical events, the first occurrence of an increase of $\geq 50 \times 10^6$ CD4 lymphocytes/l for patients with a baseline CD4 cell count $< 500 \times 10^6$ /l. Therefore, the number of patients included in each comparison varied according to which endpoint was studied. [As not all of the relapses are registered in our database, we restricted the analysis to the first occurrence of a clinical event B or C. Therefore, only patients in stage A (versus A and B) at initiation of HAART were considered for the analysis of endpoint 'B event' (versus 'C event')].

Data from patients enrolled in studies of structured treatment interruptions were discarded.

Statistical analysis

Statistical comparisons were conducted using the Cox time-dependent proportional hazards regression model. We also compared groups of patients, using Wilcoxon Mann-Whitney and Chi-squared non-parametric tests. The beginning of the follow-up was defined as the time of initiation of HAART. Interruptions were treated as time-dependent variables. This point is very important as the risk is likely to change after an interruption, particularly before and after the first interruption. It would be incorrect to consider interruptions as a baseline characteristic, as before the occurrence of the first interruption patients with and without interruptions are expected to be at the same risk.

Each interruption was modelled by a discrete variable taking the value 0 before its occurrence and 1 thereafter. Therefore, the coefficient associated with the first interruption measured the long-term impact of this interruption, whereas the coefficients of the subsequent interruptions measured the additional risk. To deter-

mine the cumulative impact of several interruptions, one has to sum the coefficients associated with these interruptions. Using discrete variables taking the value 1 only during the interruption would be meaningless, particularly with the Cox model which considers only the set of time points where events occur.

The CD4 cell count, as well as the viraemia, were also treated as time-dependent variables as the risk is likely to be more related to current values of these factors than to baseline values. However, to assess both the cross-sectional effect of baseline values and the longitudinal effect of current values, we used the baseline values as the first regressor and the difference between baseline values and current values as the second regressor. Considering only baseline values or only current values would result in a biased estimation, if cross-sectional and longitudinal effects were different [20]. However, baseline values of the CD4 cell count were retained for the endpoint increase of CD4 cell count of $\geq 50 \times 10^6$ cells/l to prevent the updated values from masking the effect of interruptions.

To focus on the impact of short interruptions exclusively, the follow-up of patients was censored when an interruption of > 3 months occurred, and death cases after more than 3 months of treatment cessation were not considered as in this case the death could be attributed to the long interruption, which is not the focus of our study. Also, as the treatment is generally stopped sometime before death, patients who at the end of their follow-up had stopped their treatment for < 3 months before dying were not considered to have had an interruption.

To determine the CD4 cell count and \log_{10} viraemia for each patient in the 'risk group' at each time point an event occurred, we made a linear interpolation between two consecutive measurements. To determine CD4 cell count and viraemia at the initiation of HAART, we considered the first available measurement within 45 days of the initiation.

Variables included and tested in the multivariate proportional hazards model were patient's age, sex, transmission category [men who have sex with men (MSM), heterosexual, injecting drug users (IDU)], duration of HIV infection (determined on the base of the seroconversion date if available and if not the date of first positive test, and if also not available the registration date), CDC stage at initiation of HAART, current values of viraemia and CD4 cell count as well as baseline values, prior antiretroviral treatment, and the occurrence of interruptions. Variables were selected manually according to *P*-value and confounding was assessed. When a variable was not a confounder and was not statistically significant (at the level of 5%), it was removed. For categorical variables, categories were

merged when they were not statistically significant, to gain power.

Schönfeld residuals were used to assess the proportionality assumption, and Martingale, deviance and Cox–Snell residuals were used to assess the overall goodness of fit as well as the functional form for the covariables and the possible outliers [21–23].

Statistical analysis was conducted using the STATA 7 statistical package.

Results

Between 1 January 1996 and 31 October 2000, 4720 SHCS participants initiated HAART and were, therefore, eligible for this study. A total of 1299 patients interrupted their treatment once or more, 174 twice or more, 36 three times or more, 10 four times or more and three interrupted treatments five times. Therefore, the total number of short interruptions observed was 1522. The number of long interruptions, of which the first 3 months before censoring contributed to this amount, was 927. After the remaining 595 short interruptions the treatment was started again. Characteristics of the participants are presented in Table 1.

The entire population was considered only for the endpoint death, whereas for the other endpoints the relevant subpopulations were considered (see Table 2). As far as the endpoint death is concerned, there were 1299 (27.5%) patients who interrupted their treatment at least once and 3421 patients who did not interrupt. When the first occurrence of a CDC stage B event was considered, 524 (25%) patients had at least one interruption and 1572 never interrupted, whereas for the CDC stage C event 954 (27%) patients interrupted at least once and 2583 did not interrupt. When a CD4 cell count increase of $> 50 \times 10^6$ cells/l was considered, 1000 (27.5%) patients had at least one interruption and 2636 never interrupted.

The median time since start of HAART to the first interruption was 335 days [interquartile range (IQR), 126–699], and between the first and the second interruption 213 days (IQR, 108–396), between the second and the third 157 days (IQR, 98–235), between the third and the fourth 179 days (IQR, 69–276) and between the fourth and the fifth 120 days (IQR, 36–169). The overall median duration of the 1522 interruptions was 93 days (IQR, 61–93), whereas it was 93 days for the first (IQR, 61–93), 93 days for the second (IQR, 61–93), 64 days for the third (IQR, 31–93), 89 days for the fourth (IQR, 45–93), and 93 days for the fifth (IQR, 93–93).

Table 1. Baseline characteristics of patients beginning highly active antiretroviral treatment according to the number of treatment interruptions. Swiss HIV Cohort Study, 1996–2000.

	No interruption	One interruption	Two interruptions	Three or more interruptions	Total
All patients [n (%)]	3421 (72.5)	1125 (23.8)	138 (2.9)	36 (0.8)	4720
Sex [n (%)]					
Female	928 (27.1)	376 (33.4)	52 (37.7)	11 (30.6)	1367 (29.0)
Male	2493 (72.9)	749 (66.6)	86 (62.3)	25 (69.4)	3353 (71.0)
Mean age (years)	38.5	36.6	36.6	37.8	38.0
Pre-treatment [n (%)]					
Yes	1641 (48.0)	602 (53.5)	107 (77.5)	24 (66.7)	2374 (50.3)
No	1780 (52.0)	523 (46.5)	31 (22.5)	12 (33.3)	2346 (49.7)
HIV acquisition [n (%)]					
Men who have sex with men	1291 (37.7)	299 (26.6)	36 (26.1)	10 (27.8)	1636 (34.7)
Heterosexual	1145 (33.5)	338 (30.0)	35 (25.4)	7 (19.4)	1525 (32.3)
Injecting drug users	857 (25.1)	454 (40.4)	60 (43.5)	18 (50.0)	1389 (29.4)
Unknown	128 (3.7)	34 (3.0)	7 (5.1)	1 (2.8)	170 (3.6)
CDC stage [n (%)]					
A	1572 (46.0)	484 (43.0)	34 (24.6)	6 (16.7)	2096 (44.4)
B	1011 (29.6)	363 (32.3)	50 (36.2)	17 (47.2)	1441 (30.5)
C	838 (24.5)	278 (24.7)	54 (39.1)	13 (36.1)	1183 (25.1)
Median estimated duration of HIV infection (years)	2.1	3.2	4.8	4.0	2.4
Median CD4 cell count ($\times 10^6$ cells/l)	200	200	130	104	199
Median log ₁₀ viral load (copies/ml)	4.5	4.6	4.7	4.4	4.5

The reason for the interruption was documented for 802 cases. Seven percent of the interruptions were attributable to a treatment failure, 30% to drug intolerance and 63% were classified as 'other'. These proportions remained the same for short and long interruptions considered separately.

We compared the baseline clinical and social characteristics of the patients who had short interruptions (1299/4720 = 27.5%) with those who did not interrupt (bivariate analysis). Patients with and without interruptions were comparable in terms of baseline CD4 cell count, but those with interruptions had higher baseline viraemia ($P < 0.01$). Patients with interruptions had been infected for a longer time ($P < 0.01$), were younger ($P < 0.01$), were more likely to be female

($P < 0.01$), had a shorter follow-up ($P < 0.01$) (median follow-up length of 639 versus 1095 days, albeit 1156 versus 1095 without censoring), were more likely to belong to the IDU group ($P < 0.01$), were more frequently pretreated (56 versus 48%; $P < 0.01$), were less well educated ($P < 0.01$), were in a higher CDC stage ($P < 0.01$), had been treated with a greater total number of distinct drugs ($P < 0.01$), both before ($P < 0.01$) and during HAART ($P < 0.01$), were more likely to have initiated HAART with saquinavir or ritonavir, and less likely with nelfinavir ($P < 0.01$).

Looking for predictive factors of the interruptions, we regressed in a Cox model the time to the first interruption on the following covariables: CD4 cell count and viraemia at baseline, age, sex, estimated HIV

Table 2. Number of patients eligible for each endpoint, events and interruptions selected for the analysis. Swiss HIV Cohort Study, 1996–2000.

Endpoint	Death	First B event ^a	First C event ^b	$> 50 \times 10^6$ CD4 cells/l ^c
Patients (n)	4720	2096	3537	3636
Events [n (%)]	173 (3.7)	329 (15.7)	219 (6.2)	3184 (87.6)
Interruptions (n)				
1	1299	524	954	1000
2	174	40	107	149
3	36	6	23	30
4	10	2	6	8
5	3	–	2	3
Total	1522	572	1092	1190

^aOnly patients in CDC stage A at start of HAART were evaluable for progression to CDC stage B or C. ^bOnly patients in CDC stage A or B at start of HAART were evaluable for progression to CDC stage C. ^cIncrease in CD4 cells from the start of HAART until the end of the follow-up period.

duration, pretreatment, transmission category, CDC stage and the PI used when initiating HAART. We found that a high baseline \log_{10} viraemia [hazard ratio (HR), 1.2; $P < 0.01$], high baseline CD4 cell count (HR, 1.07 per 100×10^6 cells/l; $P < 0.01$), injecting drug use (HR, 2.0; $P < 0.01$) and low education (HR, 1.7; $P < 0.01$) were associated with a higher probability of having treatment interruptions. On the other hand, older patients interrupted less frequently than young ones (HR, 0.96 per 5 years; $P = 0.05$).

Distributions (box plots) of the CD4 cell count and viraemia at baseline values and within 45 days preceding each of the interruptions are given in Fig. 1. The CD4 cell counts were clearly higher and viraemia lower at the first interruption compared to baseline values. These differences tended to fade with subsequent interruptions.

Results of the estimation of the HR are presented in Table 3 and Fig. 2. The hazard ratio for endpoint death was slightly greater than 1 for the first interruption, whereas for the second it was less than one. Both coefficients were statistically not significant. Factors associated with an increased risk of death were age, IDU and viraemia. The baseline and longitudinal effect of viraemia were the same. On the other hand, a high CD4 cell count and a low CDC stage at the initiation of HAART were associated with a better prognosis. The longitudinal effect of the CD4 was stronger than the baseline effect. The impact of a third interruption on survival could not be assessed, because there were too few events.

The risk of developing a type B event was not affected

by interruptions. It was, however, higher for patients who injected drugs and for patients with a high viraemia, and lower the CD4 cell counts. The longitudinal effect of the CD4 cell count was smaller than the baseline effect, as was the case for the viraemia.

As far as type C events are concerned, the first interruption slightly increased the risk of progression, as well as did age and pretreatment. As expected, the risk increased with lower CD4 cell count and higher viraemia. Longitudinal and baseline effects for the CD4 cell count were the same, whereas the longitudinal effect of viraemia was lower than the baseline effect.

The first interruption was significantly associated with a lower probability to increase the CD4 cell count, as was pretreatment, age, male sex, injecting drug use and the duration of HIV infection. On the other hand, a low CDC stage (A or B) at baseline and a high viraemia were associated with greater probability to increase the CD4 cell count. The longitudinal effect of viraemia was lower than the baseline effect.

Discussion

We used the database of the SHCS, a large prospective cohort, to assess the predictive value of occasional and short interruptions of HAART on mortality, clinical CDC events B and C, and CD4 cell count increase (by at least 50×10^6 cells/l). We believe that the issue of occasional treatment interruptions will become more and more relevant in the future, particularly for patients

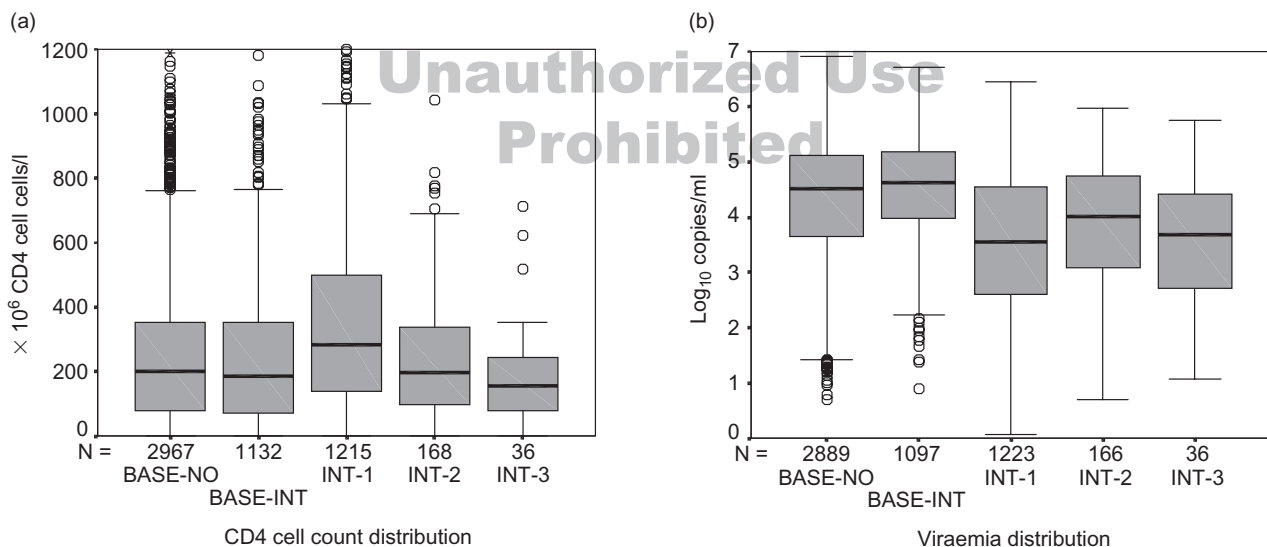


Fig. 1. CD4 cell count (a) and viraemia (b) distributions at baseline and within 45 days preceding each of the interruptions. BASE-NO, baseline values of patients without interruption; BASE-INT, baseline values of patients with interruptions; INT-1-3, values at the first, second and third interruption.

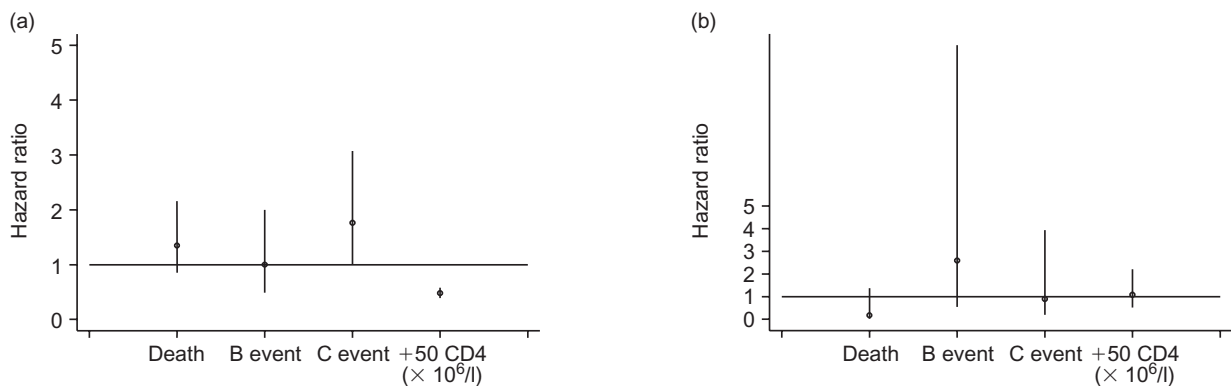
Table 3. Hazard ratios (95% confidence interval) associated with short treatment interruptions^a, Swiss HIV Cohort study, 1996–2000.

Risk factor	Hazard ratio ^b Death	Hazard ratio B event	Hazard ratio C event	Hazard ratio > 50 × 10 ⁶ CD4 cells/l
Interruptions				
No	1	1	1	1
First	1.35 (0.85–2.16)	1.00 (0.49–2.00)	1.76 (1.00–3.07)	0.48 (0.39–0.58)
Second	0.18 (0.02–1.37)	2.59 (0.55–12.09)	0.89 (0.20–3.93)	1.07 (0.52–2.21)
Third	–	–	–	2.61 (0.32–21.0)
Age (per 5 years increase)	1.16 (1.06–1.26)	n.s.	1.09 (1.01–1.18)	0.97 (0.95–0.99)
Sex				
Female	1	1	1	1
Male	n.s.	n.s.	n.s.	0.85 (0.77–0.93)
Pre-treatment ^c				
No	1	1	1	1
Yes	n.s.	n.s.	1.13 (1.01–1.25)	0.89 (0.82–0.97)
HIV acquisition				
Men who have sex with men	1	1	1	1
Heterosexual	n.s.	n.s.	n.s.	0.90 (0.82–1.00)
Injecting drug user	1.76 (1.22–2.53)	1.52 (1.15–2.02)	n.s.	0.72 (0.65–0.80)
CDC stage ^d				
A	0.31 (0.18–0.51)	1	1	1.17 (1.05–1.29)
B	0.40 (0.27–0.59)	–	n.s.	1.10 (1.00–1.21)
C	1	–	–	1
Estimated duration of HIV infection (per 5 years)	n.s.	n.s.	n.s.	0.96 (0.91–1.01)
CD4 cell count (per 100 × 10 ⁶ /l)				
Baseline effect	0.75 (0.66–0.85)	0.67 (0.61–0.74)	0.63 (0.56–0.72)	0.99 (0.96–1.02)
Longitudinal effect	0.49 (0.42–0.58)	0.87 (0.75–1.01)	0.63 (0.56–0.72)	–
Viral load (per log ₁₀ copies/ml)				
Baseline effect	1.09 (0.96–1.23)	1.79 (1.52–2.11)	2.02 (1.63–2.51)	1.20 (1.15–1.25)
Longitudinal effect	1.09 (0.96–1.23)	1.39 (1.19–1.61)	1.57 (1.35–1.84)	1.08 (1.04–1.11)

^aMultivariate Cox proportional hazard model with time dependent variables. For each endpoint, only variables with a risk ratio estimate have been retained in the final model. ^bCo-variables statistically not significant are indicated by n.s. except for the CD4 and viraemia. For categorical variables 1 denotes the reference category. Categories that were statistically not significantly different from the reference category have been merged and are also indicated by n.s. ^cWith antiretroviral drugs. ^dCDC, Centers for Disease Control and Prevention.

with a well controlled viraemia and who are being treated almost chronically. Several studies [8–16] have demonstrated that treatment interruptions are associated with viral rebounds and a CD4 cell count decrease. As this phenomenon is likely to be more emphasized the longer the treatment interruption, we considered only short interruptions lasting between 1 and 3 months.

We found (see Table 3 and Fig. 2) that interruptions of HAART did not significantly increase the risk of HIV-associated morbidity and mortality, except for a statistically marginally increased risk for a CDC stage C event after the first interruption (n = 1125). Subsequent interruptions (n = 174) had no significant clinical effects anymore. These results indicate that from a

**Fig. 2.** Hazard ratios for the first (a) and second (b) therapy interruptions.

clinical point of view, short interruptions do not bear a high risk of clinical progression, neither do they improve the later clinical course.

Not surprisingly, we observed a significant impairment of the HAART-induced recovery of CD4 cell count as an effect of the first interruption. A decline in CD4 cell count was also reported in patients who interrupted treatment due to viral failure [15,16]. On the other hand, the negative effect on the CD4 cell count course was no more visible in patients undergoing two or more interruptions. The most likely explanation for this may be the smaller number of patients with this characteristic. However, several treatment interruptions might also have another biological effect, possibly allowing the immune system to react differently to a repeated viral challenge.

We also investigated the characteristics of patients who discontinued HAART, as well as the timing of the interruptions. The time until the first interruption was generally longer than between successive treatment interruptions. We found that the risk factors associated with treatment interruptions were: being an IDU, young, pretreated, poorly educated, having a high CDC stage, and having high baseline viraemia. The majority of interruptions were attributable either to intolerance or to some other reason, but not to treatment failure. Therefore, it seems that in most cases the treatment interruption was attributable to social factors, and not to treatment inefficiency.

To control for potential confounders, we included the following covariables in our models, in addition to the discrete variables for the interruptions: age, sex, pre-treatment, HIV acquisition mode (MSM, heterosexual and injecting drug use), CDC stage at baseline, the estimated duration of HIV infection, the CD4 cell count and viraemia. Estimations considering only baseline values of the CD4 cell count and viraemia, neglecting the longitudinal effect, resulted in a HR for the first interruption significantly greater than 1 for both the endpoints 'death' (HR, 1.73; IQR, 1.08–2.77) and 'CDC stage C event' (HR, 2.83; IQR, 1.62–4.96), showing a substantial bias when compared with the results of the model considering both the cross-sectional and the longitudinal effects (Table 3). The bias was, however, less important for the other endpoints.

All things considered, the higher the viraemia, the lower the CD4 cell count, the older the patient, and the longer the duration of HIV, the worse the prognosis. Injecting drug use and pretreatment were also associated with a higher risk of clinical progression. Patients in a low CDC stage at baseline had a better prognosis. Concerning the endpoint ' $> 50 \times 10^6$ CD4 cells/l', females seemed to have a better prognosis than

males, which is difficult to explain and might be attributable to an overestimated risk for injecting drug use, as there are more IDU among females (38%) than males (28%).

We observed that the longitudinal effect of the CD4 cell count on the risk of death was stronger than the cross-sectional effect of the baseline value, which was expected as the current values of the CD4 cell count at each interruption are clearly more closely related to the momentary immunodeficiency and risk of subsequent clinical events than the baseline value. Concerning viraemia we observed the opposite phenomenon: the longitudinal effect was generally dampened in comparison with the baseline effect. The reason might be attributable to the potency of HAART to increase the CD4 cell count above the baseline level and reduce the risk of events, particularly when the viraemia rises above the detection limit.

We did not find any significant interactions, particularly between the interruptions and the variable 'pre-treatment'. The model's goodness of fit analysis showed some lack of fit concerning the events taking place either very early or late. This lack of fit is probably common for such studies and should not invalidate our results and conclusions.

There are, however, several limitations to our study. First of all, the reasons for the treatment interruptions could be assessed only in half of the cases and our classification for these reasons is not fine enough, as the majority of the interruptions were classified as 'other'. As treatment failure and intolerance were documented prospectively, this category represents mainly patient's wish, frequently related to the pill burden, fear of side-effects, and the patient's perception that treatment was too complicated [7]. Second, we could not estimate our models separately to assess the stability of the results, when taking into account the reasons for the interruptions. Third, the median follow-up time (846 days; IQR, 348–1318) was probably too short to determine the emergence of resistances, possibly induced by the interruptions. Fourth, with our data we were able to assess the impact of the first two interruptions only, and of the third for the endpoint ' $> 50 \times 10^6$ CD4 cells/l', as the number of observed events was large enough only for the latter endpoint.

With this study we could not assess all potential risks of treatment interruptions. For example, we could not consider the higher risk of sexual transmission of HIV, attributable to viral rebound during the interruption.

Several studies have shown that almost absolute adherence is necessary for optimal virologic suppression [24]. Short-term viraemia, however, may not have a major impact on clinical efficacy, as demonstrated by our

study and the recent observation that intermittent viraemia was not associated with full virologic failure [25]. Treatment interruptions may also promote the emergence of viral resistance, particularly if not all drugs of the regimen are stopped at the same time. After treatment interruption in the presence of resistant virus, however, resistance even partially regressed [16] and fear of selection of new resistances does not seem justified. We assessed short, complete interruptions of therapy, but not periods of partial compliance. It may be that compared to prolonged partial compliance, complete interruptions are less risky, because periods with suboptimal drug concentrations are short.

Our analysis indicates that treatment interruptions of 1–3 months do not seem to have an overall deleterious effect, particularly if the CD4 cell count is high and the viraemia is low. This result is somehow reassuring as drug intolerances, treatment failures, and the wish for 'drug holidays' are likely to increase in the future, with longer duration of treatment. We are aware of the potential danger of the results we are presenting, as interrupting an antiretroviral treatment is a very attractive temptation for the patient. However, as potential biases can never be excluded in observational studies, our results should be confirmed by other researches, and we recommend extreme caution when deciding to interrupt an antiretroviral treatment.

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Appendix

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