

# Uniform risk of clinical progression despite differences in utilization of highly active antiretroviral therapy: Swiss HIV Cohort Study

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**Objective:** To compare the initiation of highly active antiretroviral therapy (HAART) in HIV-infected patients according to sex, route of HIV acquisition and education, and to assess the impact of differences in utilization on the probability of progression to AIDS.

**Design and setting:** Swiss HIV Cohort Study, a national prospective multi-centre study.

**Participants:** A total of 3342 patients, including 1007 (30%) women. HIV was acquired through injection drug use in 1155 (35%) cases and through sex between men in 1172 (35%). Twenty-eight per cent (957) of participants had attained only the minimum level of schooling. At baseline, the median CD4 cell count was  $269 \times 10^6/l$  cells, median HIV-1 RNA was 4.3 log<sub>10</sub> copies/ml and 2917 (87%) were free of AIDS.

**Methods:** Kaplan–Meier life tables and Cox proportional hazards regression.

**Results:** During 7007 person-years of follow-up 2285 (69%) patients started HAART and 318 (10%) developed a new AIDS event. In multivariable analysis controlling for CD4 cell count, viral load and disease stage at baseline, the probability of starting HAART was lower in injection drug users compared with men who have sex with men, hazard ratio 0.63 (95% confidence intervals 0.56–0.70) and in patients with minimum schooling compared with those with vocational training, hazard ratio 0.82 (0.75–0.91). The risk of progression to AIDS was similar among men and women, patients with a history of injecting drug use, and patients with lower educational attainment in both univariable and multivariable analysis.

**Conclusion:** HIV-infected injecting drug users and those with lower levels of educational attainment start HAART later than other patient groups. The deferred initiation of therapy in these patients does not, however, appear to translate into an increased risk of clinical disease progression. This observation has important implications for treatment policy and the design of future clinical trials.

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**Keywords:** antiretroviral therapy, cohort study, combination therapy, drug users, education, healthcare/economics, health service accessibility, homosexual men, natural history, opportunistic infections, protease inhibitors, Switzerland, viral load, women

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## Introduction

Highly active antiretroviral combination therapy (HAART) for HIV infection was introduced into widespread use in 1996 and is now considered to be the standard of care in developed countries [1,2]. Dramatic reductions in HIV-related morbidity and mortality have been documented after the introduction of these potent drugs in North America and Europe, in men and women [3,4], in injection drug users and those infected through sexual routes of transmission [3,4], and in patients from white and non-white ethnic groups [4]. Despite the existence of clinical guidelines that are based on objective assessments of disease severity [1,2], access to treatment for all groups of affected individuals with HIV infection and other illnesses is not equitable. Sex differences in access to coronary angiography and revascularization procedures for heart disease are well documented [5]. Zidovudine monotherapy has been prescribed less frequently for African Americans [6], women [7], and injection drug users, than for white men infected through sex with men and now injecting drug users [4,8], patients with low levels of education [8] and, in the USA, those without private medical insurance [4] are less likely to receive HAART.

The clinical benefits of HAART have been attributed to recovery of the immune system to restore protection against the opportunistic infections associated with AIDS [9,10]. The optimal time at which HAART should commence is, however, not known. It has been suggested that antiretroviral therapy should 'hit HIV, early and hard' [11] when the viral burden is lower and more homogeneous, and that immune reconstitution is only possible if treatment begins before functional CD4 cell subsets are irretrievably damaged [12]. Others have demonstrated sustained CD4 cell responses even in profoundly immunosuppressed individuals [13]. If the early initiation of HAART is necessary for maximal clinical benefits, then deferred use should be associated with more rapid disease progression. We investigated this hypothesis in a large prospectively followed cohort of HIV-infected individuals in Switzerland, by examining the rate of starting HAART and the impact of differences in rates of initiation on the probability of progression to AIDS according to social and clinical characteristics.

## Materials and methods

The Swiss HIV Cohort Study (SHCS) is an ongoing prospective study, which has been enrolling HIV-infected patients aged 16 years and over since September 1988. The study design and procedures have been described in detail [14]. Patients are followed in one of seven study centres (Basle, Bern, Geneva, Lausanne, Lugano, St Gall and Zurich). Enrolment is

independent of the stage of disease or degree of immunosuppression, and information is collected according to standardized criteria on structured forms at registration and at follow-up visits at 6 monthly intervals. The follow-up questionnaire includes a detailed history of disease associated with HIV and the month of starting and discontinuing drugs. The CD4 positive T lymphocyte count is measured using flow cytometry. HIV-1 RNA (viral load) measurements were introduced in June 1995 using a polymerase chain reaction-based assay (Roche Diagnostics, Basle, Switzerland) with a lower limit of detection of 400 RNA copies per ml.

The current analysis is based on the SHCS database of the end of April 1999, which included data on 10 288 participants, of whom 3468 (59%) had died. All 5509 patients who had at least one viral load measurement and a corresponding CD4 cell count before initiating HAART were eligible. We excluded 198 patients who had not acquired HIV through sexual intercourse or intravenous drug use and 504 patients with missing data on educational level. A further 672 patients did not have at least one follow-up and 793 patients were on HAART before baseline. Therefore, 3342 of eligible patients were included in the analysis, 91 of whom subsequently became lost to follow-up because they moved abroad or withdrew consent.

## Study endpoints and definitions

We examined the probability of starting HAART and progressing to AIDS. AIDS was defined according to clinical stage C of the 1993 revised classification system for HIV infection [15]. HAART was defined as treatment with three or more antiretroviral drugs, including at least one protease inhibitor or at least one non-nucleoside reverse transcriptase inhibitor. Dual therapy was defined as any combination of two antiretroviral drugs, and monotherapy as the use of a single drug. Viral loads recorded as undetectable were assigned a value of 200 RNA copies per ml. Educational attainment was examined in three exclusive ordered categories: minimum schooling included patients who had left school at or below the mandatory minimum leaving age, vocational training included those who had completed mandatory schooling and undertaken an apprenticeship, and university education included those who had completed mandatory schooling and obtained a degree.

## Statistical analysis

The earliest date from which follow-up could commence was the date of the first viral load measurement, so time was measured from this baseline either to the date the endpoint occurred or the date of the last follow-up visit. We calculated Kaplan-Meier probabilities of initiating HAART, stratified by sex, transmission group and educational level at baseline, and compared

survival distributions using log rank tests. Cox proportional hazards models were fitted to examine the individual and combined effects of viral load, CD4 cell count, age, sex, education, transmission group, antiretroviral therapy, and disease stage at baseline on the probability of initiating HAART and of progressing to AIDS. Analyses were conducted using SAS (version 6.12, Cary, NC, USA) and Stata software (version 6.0, College Station, Texas, USA). Results are presented as Kaplan–Meier estimates of the probability of patients reaching an endpoint and relative hazards with 95% confidence intervals. Statistical and graphical tests indicated that the proportional hazards assumption was not violated.

## Results

Baseline characteristics are shown in Table 1. The mean age of participants was 36.7 years and the three major transmission categories were equally represented. At baseline a majority of patients were treated with mono- or dual therapy and four-fifths were free of AIDS. The median CD4 cell count was  $269 \times 10^6/l$  cells and the median viral load was 4.3  $\log_{10}$  RNA copies per ml. The 3342 patients analysed contributed a total of 7007 person-years of follow-up. Most patients (2498, 75%) had their baseline examination in 1995 or 1996.

### Utilization of highly active antiretroviral therapy

A total of 2285 participants started HAART at some stage during follow-up. In 2089 (91%) patients, initial

**Table 1.** Baseline characteristics of 3342 Swiss HIV Cohort Study participants included in the analysis.

Characteristic		
Mean age in years (standard deviation)	36.7	(9)
Sex		
Male	2335	(70)
Female	1007	(30)
Transmission groups		
Men who have sex with men	1172	(35)
Heterosexual intercourse	1015	(30)
Injection drug use	1155	(35)
Education		
Mandatory schooling	957	(28)
Vocational training	1727	(52)
University education	658	(20)
Antiretroviral therapy		
No therapy	775	(34)
Monotherapy	553	(24)
Dual therapy	954	(42)
Clinical disease stage <sup>a</sup>		
CDC stage A	1713	(51)
CDC stage B	1016	(30)
CDC stage C	613	(18)
Median (range) CD4 cells $\times 10^6/l$	269	(2–787)
Median (95% range) $\log_{10}$ RNA copies/ml	4.3	(2.3–5.7)

Results shown as number of patients (percentage of total) unless otherwise stated. <sup>a</sup>Clinical disease stage according to 1993 classification system of the Centers for Disease Control [15].

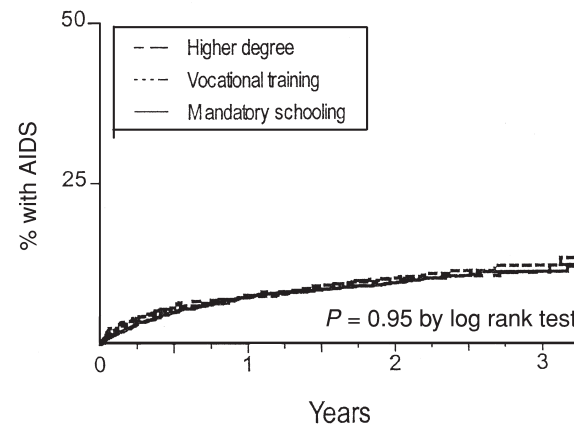
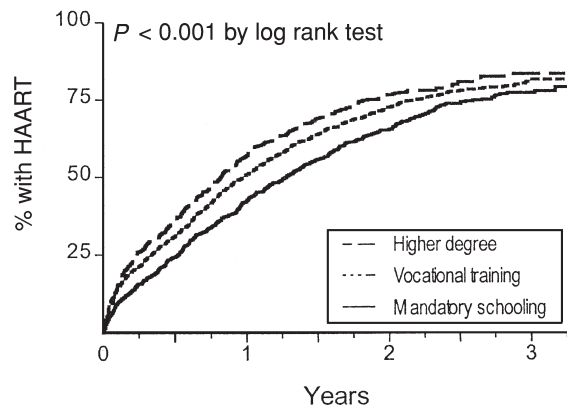
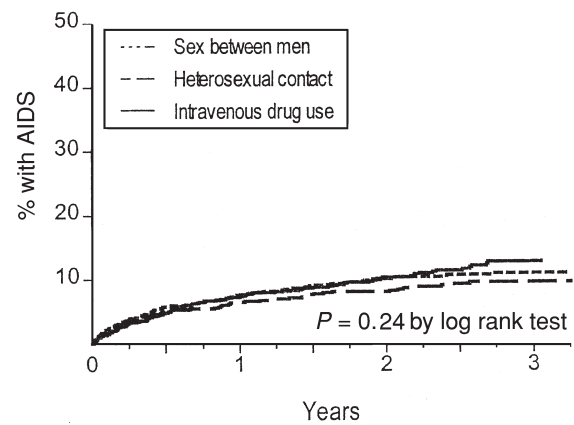
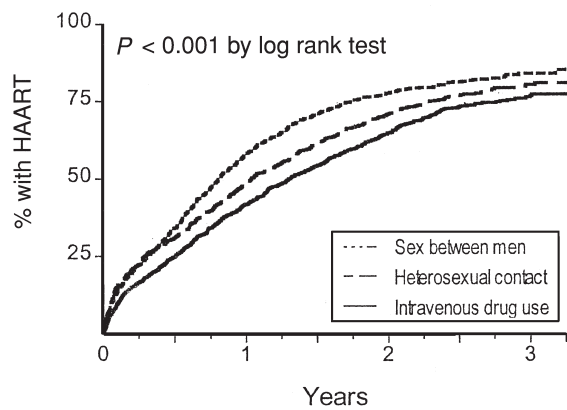
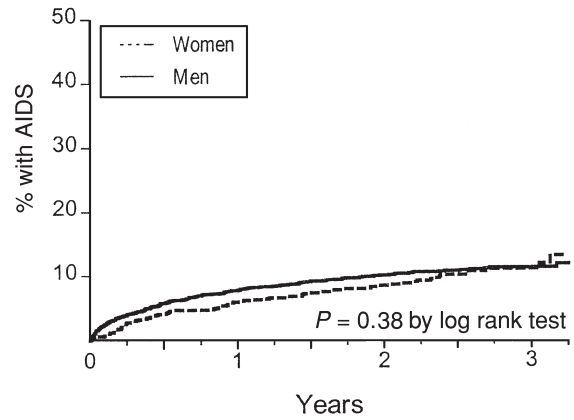
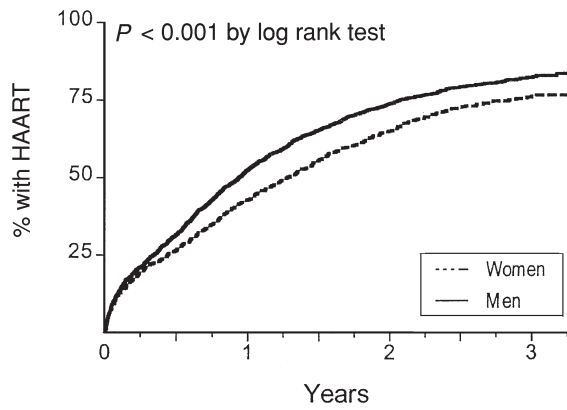
regimens were based on protease inhibitors (saquinavir, zidovudine, didanosine, zalcitabine, stavudine or abacavir). In 70 (3%) patients, regimens included a non-nucleoside reverse transcriptase inhibitor (nevirapine, delavirdine or efavirenz) combined with nucleoside analogues, and in 126 (6%) patients, regimens were based on all three classes of drugs.

Kaplan–Meier estimates of the cumulative probability of starting HAART are shown in Fig. 1. Overall, an estimated 81% (95% confidence intervals 79–82%) of patients had started HAART by 3 years from baseline. Kaplan–Meier curves indicate faster initiation of HAART by men than women, by men infected through sex between men compared with individuals infected through heterosexual intercourse or injection drug use, and by participants with higher compared with lower levels of education. The univariable Cox regression analysis (Table 2) confirms these findings and also shows faster initiation by older patients, those receiving antiretroviral mono- or dual therapy at baseline, and those with more advanced disease. In multivariable analysis, the utilization of HAART was no longer affected by age, sex or clinical stage. However, injection drug users continued to be less likely to start HAART than men who have sex with men (adjusted hazard ratio 0.63, 95% confidence intervals 0.56–0.70), as did patients with minimum schooling compared with those who had completed vocational training (adjusted hazard ratio 0.82, 0.75–0.91). Antiretroviral therapy, low CD4 cell count and higher viral load at baseline were also independent predictors for starting HAART.

### Clinical disease progression

Overall, 318 (10%) participants developed a new AIDS-defining event. Kaplan–Meier curves showed no statistically significant differences ( $P > 0.20$  by log rank test) in progression rates according to sex, route of acquisition of HIV infection or level of educational achievement (Fig. 2). After 3 years of follow-up, an estimated 11% of men who have sex with men had a new AIDS event compared with 13% of injection drug users. Similarly, an estimated 12% of those with minimum schooling and 11% of individuals with a university degree had progressed. Among those with a history of AIDS at baseline, 24% developed an AIDS indicator disease by 3 years, compared with 6% of asymptomatic patients ( $P < 0.001$  by log rank test). In multivariable Cox regression analysis, low CD4 cell count, high viral load and AIDS at baseline were independent predictors of disease progression. Both monotherapy and dual therapy at baseline were significantly associated with slower progression (Table 3).

Kaposi's sarcoma is a relatively early AIDS-defining event seen almost exclusively among men who have



**Fig. 1.** Kaplan–Meier estimates of probability of starting highly active antiretroviral therapy (HAART), stratified by sex, HIV transmission group and level of educational attainment.

**Fig. 2.** Kaplan–Meier estimates of probability of progression to new AIDS-defining illness, stratified by sex, HIV transmission group and level of educational attainment.

sex with men [16], the occurrence of which has been found to explain an increased rate of disease progression in some cohorts [17]. In a sensitivity analysis we calculated regression models excluding Kaposi's sarcoma from our definition of AIDS. After excluding 26

episodes of Kaposi's sarcoma, hazard ratios for progression rates among heterosexuals and infection drug users, compared with men having sex with men, were not materially altered in univariate and multivariable analyses.

**Table 2.** Factors affecting the probability of starting highly active antiretroviral therapy.

Predictor variable	Crude hazard ratio (95% CI)		<i>P</i> *	Adjusted <sup>a</sup> hazard ratio (95% CI)		<i>P</i> *
Age at baseline (per 1 year increase)	1.02	(1.01–1.02)	< 0.001	1.04	(0.00–1.09)	0.16
Sex			< 0.001			0.91
Male	1	(reference)		1	(reference)	
Female	0.77	(0.70–0.85)		0.99	(0.89–1.11)	
Transmission groups			< 0.001			< 0.001
Men who have sex with men	1	(reference)		1	(reference)	
Heterosexuals	0.80	(0.72–0.89)		0.91	(0.81–1.03)	
Injection drug users	0.65	(0.59–0.72)		0.62	(0.56–0.70)	
Education			< 0.001			< 0.001
Mandatory schooling	0.80	(0.72–0.88)		0.82	(0.75–0.91)	
Vocational training	1	(reference)		1	(reference)	
University education	1.19	(1.07–1.33)		1.07	(0.96–1.20)	
Previous therapy						
Monotherapy (yes versus no)	1.10	(0.99–1.23)	0.09	1.0	(0.89–1.13)	0.99
Dual therapy (yes versus no)	1.63	(1.49–1.78)	< 0.001	1.62	(1.47–1.80)	< 0.001
Clinical disease stage			< 0.001			0.06
CDC stage A	1	(reference)		1	(reference)	
CDC stage B	1.42	(1.29–1.56)		1.11	(1.00–1.22)	
CDC stage C	2.30	(2.06–2.57)		1.18	(1.04–1.35)	
CD4 cell count (per 100 × 100 <sup>6</sup> /l cell increase)	0.68	(0.66–0.70)	< 0.001	0.76	(0.73–0.79)	< 0.001
Viral load (per log <sub>10</sub> RNA copies/ml increase)	1.70	(1.63–1.79)	< 0.001	1.52	(1.44–1.60)	< 0.001

Results from Cox regression analyses. \**P* values derived from likelihood ratio tests. <sup>a</sup>Hazard ratios adjusted for all variables in the table.

**Table 3.** Factors affecting the probability of progression to a new AIDS-defining illness.

Predictor variable	Crude hazard ratio (95% CI)		<i>P</i> *	Adjusted <sup>a</sup> hazard ratio (95% CI)		<i>P</i> *
Age at baseline (per 1 year increase)	0.99	(0.88–1.12)	0.90	0.96	(0.83–1.10)	0.55
Sex			0.50			0.96
Male	1	(reference)		1	(reference)	
Female	0.91	(0.72–1.17)		1.01	(0.76–1.34)	
Transmission groups			< 0.001			0.91
Men who have sex with men	1	(reference)		1	(reference)	
Heterosexuals	0.93	(0.70–1.24)		0.94	(0.68–1.34)	
Injection drug users	1.13	(0.88–1.46)		1.0	(0.74–1.35)	
Education			< 0.001			0.90
Mandatory schooling	1.07	(0.83–1.39)		1.04	(0.80–1.36)	
Vocational training	1	(reference)		1	(reference)	
University education	1.02	(0.76–1.37)		0.96	(0.71–1.33)	
Previous therapy						
Monotherapy (yes versus no)	1.51	(1.18–1.94)	0.001	0.74	(0.56–0.99)	0.04
Dual therapy (yes versus no)	0.73	(0.57–0.93)	0.01	0.65	(0.49–0.86)	0.08
Clinical disease stage			< 0.001			0.07
CDC stage A	1	(reference)		1	(reference)	
CDC stage B	1.92	(1.44–2.57)		1.26	(0.92–1.72)	
CDC stage C	4.27	(3.22–5.67)		1.49	(1.06–2.09)	
CD4 cell count (per 100 × 100 <sup>6</sup> /l cell increase)	0.58	(0.55–0.61)	< 0.001	0.67	(0.62–0.73)	< 0.001
Viral load (per log <sub>10</sub> RNA copies/ml increase)	2.80	(2.42–3.24)	< 0.001	1.85	(1.59–2.16)	< 0.001

Results from Cox regression analyses. \**P* values derived from likelihood ratio tests. <sup>a</sup>Hazard ratios adjusted for all variables in the table.

## Discussion

This study of over 3000 HIV-infected individuals followed for up to 3.5 years in the era of triple combination antiretroviral therapy has shown that injection drug users and individuals with low educational levels start HAART later, after taking clinical and laboratory markers of advanced disease into account. Deferring the start of treatment in these patients' groups did not translate into more rapid clinical progression to AIDS. Sex was not associated with progression to AIDS or, after controlling for confounders, with the initiation of therapy.

Explanations for these apparently discordant findings, and their implications, need to be considered in the context of methodological issues and current research.

The SHCS is the largest prevalent cohort of HIV-infected individuals in Europe, with continued enrolment and prolonged follow-up of individuals from all major transmission groups. Observed differences in the utilization of antiretroviral therapy could result from bias in the participation of individuals in the study as a whole, or in those included in the present analysis. Comparisons with the national AIDS registry show that



the SHCS covers 70% of patients with advanced disease in the country [18], and enrolment of people from all major transmission groups into the SHCS has increased in recent years, in line with the availability of HAART. Usage of therapy might differ between groups if the SHCS selectively enrolled injection drug users and less educated people who declined antiretroviral treatment but this is unlikely.

A more likely explanation for the slower rate of starting antiretroviral therapy by SHCS participants with lower levels of educational attainment and those infected through injection drug use is delay in the offer of treatment. In the USA [19] and Canada [20] as well as in the SHCS [8] utilization of HAART by injection drug users has been reported to be lower than expected, particularly among those who are actively injecting [8] or are not enrolled in a rehabilitation programme [19,20]. In a recent survey of SHCS patients not receiving HAART clinicians believed that patients would be unable to adhere to complex antiretroviral regimens in a fifth of cases [8]. Such caution is rational because poor adherence to combination therapy is associated with the emergence of resistant strains of HIV [21–23]. We did not have access to information about adherence for this study.

Progression to first or subsequent AIDS indicator diseases did not appear to be affected by the mode of HIV acquisition or education, despite the observed difference in utilization of therapy. The study may have lacked power to detect modest differences in progression rates, as shown by the confidence intervals around the hazard ratios shown in Table 3. Larger studies with more prolonged follow-up would need to be conducted to exclude such differences. Comparisons of progression rates between groups not randomly allocated to treatment must always be made with caution because of bias and confounding. We may have failed to detect differences in progression rates if patients with higher rates of disease progression started HAART at an earlier stage. Comparison with a group of patients with a better prognosis who started treatment at a later stage may then reduce the size of any observed treatment effects. We included immunological, virological and clinical markers of disease stage at baseline in multivariable regression models, but these may not have fully controlled for differences in progression rates. It is noteworthy, however, that analyses of progression rates in the period before HAART became available failed to show differences between sex and transmission groups [24,25]. Finally, results were similar after the exclusion of Kaposi's sarcoma from our definition of AIDS.

Progression rates could also have been biased if injection drug users and those with less education in the SHCS were less likely to have received mono- and

dual antiretroviral therapy, because HAART has been shown to be more effective in antiretroviral naïve than experienced individuals [24]. In our analyses, uniform progression rates were observed in univariable analyses as well as in multivariable models controlling for the use of monotherapy and dual therapy at baseline.

Discordance in the initiation of therapy and progression of HIV disease was documented in the era of zidovudine monotherapy. In the USA, the Johns Hopkins HIV Clinic Cohort [27] reported that HIV progression rates in 1989 to 1994 were not faster among injection drug users, African Americans and those on low incomes. Poorer utilization of zidovudine monotherapy and prophylaxis against *Pneumocystis carinii* pneumonia had, however, previously been noted among African Americans [6] and drug users in this cohort [28]. The disparity was interpreted in the light of results from randomized studies comparing immediate and deferred policies for the use of zidovudine monotherapy [29]. The limited survival advantage of individuals treated earlier was suggested to have waned, whereas the drug users and African Americans treated later were benefiting at the time that follow-up was censored [27]. The role of viral resistance as a mechanism for treatment failure has since been demonstrated [30,31]. If viral resistance also limits the duration of effectiveness of HAART, then drug users and those with low educational attainment receiving treatment later in this study may, as Chaisson suggested for zidovudine, be continuing to experience the benefits.

The findings from this prospective cohort study emphasize the importance of knowing when to start antiretroviral therapy and the debate among clinicians, scientists [11,12,21,32] and patients [33] continues. In clinical practice, although HAART prolongs survival, it is not a cure and frequently fails to suppress viral replication in the long term [26,34]. There is therefore a trade-off between the clinical benefits of HAART and the complexity of existing regimens, the potential for serious side-effects and the fear of limiting future treatment options [32]. Observational studies are subject to selection bias because the decision to initiate treatment in clinical practice is implicitly influenced by the physician's assessment of prognostic factors, judgments about patients' adherence and patient preference [8]. These factors can only be fully controlled for when treatment allocation is randomized [12,35]. Furthermore, surrogate markers for disease progression do not fully capture the clinical effects of antiretroviral therapy [36], and prolonged follow-up was required to show the long-term equivalence of immediate versus delayed treatment policies. Our apparently contradictory findings on the utilization of therapy and progression of HIV disease in certain groups of patients suggest that after 3.5 years of follow-up, with currently available regimens, deferring HAART may not be

detrimental. Confirmation of these findings in further analyses of observational studies is required, but trials [37] with clinical endpoints and long-term follow-up are needed to answer the question of when to start HAART.

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## Appendix

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