Mortality and progression to AIDS after starting highly active antiretroviral therapy

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Objectives: To examine survival and progression to AIDS among HIV-infected patients after starting highly active antiretroviral therapy (HAART).

Methods: The study population consisted of 3724 patients from the ATHENA observational cohort who initiated HAART. We considered progression to either an AIDS-defining disease or death, distinguishing HIV-related and non-related (including therapy-related) deaths. A time-dependent multivariate hazards model was fitted to the patient data and 5-year survival probabilities under various therapy scenarios estimated.

Results: A total of 459 patients developed AIDS and 346 died during 12 503 person-years of follow-up. HIV-related mortality decreased from 3.8 to 0.7 per 100 person-years between 1996 and 2000 whereas non-HIV-related mortality did not change (0.4 and 0.9, respectively, $P = 0.25$). For asymptomatic and symptomatic therapy naive patients younger than 50 years with CD4 counts above 10×10^6 and 150×10^6 cells/l, respectively, predicted 5-year survival probabilities were above 90% when HAART was used continuously. This limit was 450×10^6 cells/l when HAART was used during 20 weeks in each 24 week-period of follow-up, and 110×10^6 cells/l when patients delayed initiation of HAART for 1 year after becoming eligible for treatment.

Conclusions: Survival probabilities were high among HIV-infected patients initiating HAART at an early stage of infection. The best therapy strategy is therefore to start HAART at this stage of infection. However, deferring HAART in patients with high CD4 cell counts may be clinically more appropriate given toxicity and adherence problems. The lack of any change in non-HIV-related mortality suggests that toxicity has not yet become a major risk factor for death.

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Introduction

The short term beneficial effect of highly active antiretroviral therapy (HAART) on survival and development of an AIDS-defining illness is well established [1–3]. Not only has the life expectancy of HIV-infected patients increased but also their quality of life has improved [4,5]. In addition the spectrum of causes of mortality is changing as the number of deaths related to opportunistic infections has diminished [6,7].

A significant problem associated with HAART is the adverse effects of drugs which may result in increasing morbidity and a reduced quality of life [4,8,9]. In addition, low adherence to drug regimens may lead to sub-optimal therapy thereby jeopardizing the likelihood of maintaining viral suppression [10–12], which in turn may lead to therapy failure and drug resistance [13,14]. It is therefore currently recommended that antiretroviral treatment is deferred in patients who have high CD4+ T-cell counts or relatively low plasma levels of HIV-RNA or both [15]. Another debated issue is structured therapy interruptions (STI) which, by enhancing HIV-specific immune responses, may contribute to maintaining virologic suppression [16–19].

Several studies have assessed prognostic markers related to progression to death or AIDS. Baseline CD4+ T-cell counts are highly predictive for (AIDS-free) survival in both untreated and treated patients whereas baseline HIV-RNA levels have little additional predictive value in treated patients [20–23]. Increases in CD4+ T-cell counts during treatment with HAART and reaching undetectable levels of viral load are also significantly associated with a better prognosis [22,24,25].

In the present study prognostic markers for survival and progression to AIDS among HIV-infected patients in the ATHENA observational cohort [26] were included in a multivariate hazards model. This model was used to estimate 5-year survival probabilities for patients at initiation of HAART. We know of only one previous study that estimated survival probabilities for patients treated with HAART [27]. These probabilities are important when answering questions regarding life expectancy when patients begin demanding and life-long anti-HIV treatment. In addition, we assessed the effect of HAART taken continuously or discontinuously, which was used as a surrogate marker of therapy success. This allowed us to predict the effect on disease outcome of unstructured treatment interruptions or deferred treatment. Finally we studied the changes in HIV-related and non-related mortality and associated risk factors.

Methods

Study group

Data used in this study were selected from the ATHENA observational cohort [26]. This cohort consists of HIV-infected patients living in The Netherlands (n = 3908 by 31 July 2001) and using highly active antiretroviral therapy (HAART). At the time of inclusion patients were at least 18 years old and gave informed consent to participate. Monitoring of patients was undertaken in 22 hospitals across the country. At each visit data were collected on case report forms and entered into the database on site. Data were then sent to the central database where consistency checks were performed. Source document verification was performed for 10% of the data and mistakes or missing data were reported back to each site and corrected.

Prospective data collection started in May 1998. From patients who started HAART before that time data were collected retrospectively, including those patients who had died before 1 May 1998. Demographic data were collected at entry in ATHENA. Clinical data focused on HIV-1 infection related events according to the Centers of Disease Control definition [28], the therapeutic and prophylactic drugs used to treat opportunistic infections and the combination and dose of the antiretroviral drugs used and their side-effects. In addition, data on plasma HIV-1 RNA concentration and CD4+ and CD8+ T-cell counts were collected.

The start date T_0 of HAART, which in our study defined the start of follow-up, was determined from the data on antiretroviral drug use. HAART was defined as a combination of at least three drugs from at least two classes (nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors). Patients whose HAART regimen was not recorded before closure of the database (31 July 2001) were excluded from this study (n = 166). Therapy interruptions after T_0 were assessed by counting the number of weeks N_{HAART} in which HAART was used in the preceding 24 weeks. In the first 24 weeks after start of the first HAART regimen we assumed a 100% usage of HAART ($N_{\mathrm{HAART}} = 24$). After each period of 24 weeks of follow-up N_{HAART} was adjusted to its most recent value.

CD4+ T-cell counts and HIV-RNA load were measured on average every 12 weeks. Baseline (i.e. at start of HAART) CD4 cell count and viral load were determined by taking the value closest to the start of HAART measured between 24 weeks prior to T_0 and 1 week thereafter for CD4 cell counts and 0 weeks after T_0 for viral load. Disease status at baseline was defined as the most serious CDC-event (category B or

C) in the year prior to T_0 and the first 4 weeks thereafter. Additional information was collected on the transmission route (homosexual sex, heterosexual sex, intravenous drug use and other), gender and age at T_0. Groups of patients were compared using Wilcoxon Mann–Whitney and χ^2 non-parametric tests.

End points in this study were either death or AIDS events occurring as of 4 weeks after start of HAART. A CD4 cell count below 200×10^6 cells/l in isolation was not considered as an AIDS-defining event [27]. Patients who did not die or develop AIDS were censored at 3 months after the last follow-up visit, at the date of closure of the database, or, when analysing progression to AIDS, at the date of death, whichever came first. The period of 3 months corresponded with the median time between two consecutive visits.

Death cases were scored by a panel of three independent physicians (P.R., I.C.G., K.B.) as HIV-related, non-HIV-related (including therapy-related cases) or unknown. This score was based on clinical data at time of death reported by the treating physician and the patient's history of CDC and adverse events. Cases about which the physicians disagreed were discussed by the panel until a consensus score was reached. Mortality was calculated per 100 person-years of follow-up after T_0. Poisson's distribution was used to calculate 95% confidence intervals for rates. Expected death rates were calculated for an age and gender matched group from the general Dutch population [29].

Statistical model

A multivariate hazards model was used to find the set of covariates that best predicted the time from start of HAART to onset of AIDS and death. For each patient the hazard for death or AIDS, $h(t)$, after t years of follow-up after T_0 is modelled as the product of an underlying hazard $h_0(t)$ common to all patients and a function containing patient-specific covariates. In order to estimate the underlying hazard in models with time-dependent covariates we used a discrete-time generalized linear model [30] in which for each patient the follow-up time was split in 3-week intervals, such that the Poisson probability of having two or more events per patient in the same time interval could be neglected. The hazard $h(t_i)$ of dying in time interval i is then given by the expression

$$h(t_i) = h_0(t_i) \exp[\textstyle\sum_j \beta_j(t_i) * \text{covariate}_j(t_i)]$$

where the sum runs over all covariates j with corresponding hazard ratios $\exp[\beta_j(t_i)]$. The survival probability $S(t_i)$ up to time interval i is given by $S(t_i) = \exp[-\mathrm{H}(t_i)]$ with $\mathrm{H}(t_i)$ the cumulative hazard at t_i defined as $\mathrm{H}(t_i) = \sum_{j \leqslant i} h(t_j)$.

Covariates considered for inclusion in the model were disease status at start of HAART, age, gender and transmission route. Antiretroviral pre-treatment before start of HAART was included as a dichotomous covariate indicating whether or not a patient was pre-treated more than 1 year prior to T_0 (no significant difference in disease progression was found between therapy-naive patients and patients pre-treated less than 1 year). N_{HAART} was stratified in three categories: continuous use of HAART ($N_{\mathrm{HAART}} = 24$), not continuous but 16 weeks or more ($16 \leqslant N_{\mathrm{HAART}} < 24$) and less than 16 weeks ($N_{\mathrm{HAART}} < 16$). We also considered baseline CD4 cell count and viral load and a covariate indicating whether a baseline CD4 cell count was available. An analogous covariate for viral load was not included, as it would be severely biased because pre-treated patients were less likely to have a baseline viral load than therapy-naive patients (Table 1). Parameters were estimated by maximizing the partial likelihood. Covariates were excluded from the model via backward elimination if this did not yield a significantly worse model ($P < 0.01$, log-likelihood, χ^2 test). Wald 95% confidence intervals were calculated for the hazard ratios.

Predicted survival probabilities

By extrapolating the model beyond the median follow-up time of the study group we could estimate 5-year survival probabilities after initiation of HAART using the hazards model as described. We estimated survival probabilities assuming various therapy scenarios: (a) continuous HAART ($N_{\mathrm{HAART}} = 24$ always), (b) HAART is interrupted for 4 weeks in each 24-week interval of follow-up (by definition $N_{\mathrm{HAART}} = 24$ in the first 24 weeks after T_0 and $N_{\mathrm{HAART}} = 20$ thereafter), irrespective of the reason and the temporal pattern of the interruptions, and (c) instead of starting HAART at T_0 patients waited for 48 weeks and started continuous HAART thereafter ('deferred HAART', $N_{\mathrm{HAART}} = 24$ in the first 24 weeks of follow-up, 0 in the next 48 weeks, and again 24 thereafter). In this latter scenario T_0 is not the start of HAART but the time by which patients were eligible for treatment. Baseline values for the covariates in the hazards model were still determined at this time to allow a direct comparison between the three scenarios. Bootstrapping methods were used to obtain 95% confidence intervals on S(t) and to test the significance of differences between survival probabilities. A risk calculator based on our model will become available via our website (www.hiv-monitoring.nl).

All statistical analyses were carried out using SAS version 8.00 (SAS Institute, Cary, North Carolins, USA).

Table 1. Characteristics of all therapy-naive and pre-treated patients at start of highly active antiretroviral therapy (HAART) (T_0) and of those initiating HAART in 1996 and 2000/2001.

	Therapy naive			pre-treated		
	All (n = 2112)	1996 (n = 309)	2000/01 (n = 291)	All (n = 1612)	1996 (n = 987)	2000/01 (n = 44)
CDC-C event in the year prior to T_0	535 (25%)	87 (28%)	84 (29%)†	388 (24%)	279 (28%)*	2 (5%)†*
CDC-B event in the year prior to T_0	337 (16%)	46 (15%)	41 (14%)	262 (16%)	173 (18%)	7 (16%)
Pre-treatment longer than 1 year	–	–	–	1078 (67%)	678 (69%)	30 (68%)
Follow-up after T_0 (years), median (IQR)	3.1† (1.9–4.1)	4.7† (4.4–4.9)	0.8 (0.5–1.2)	4.4† (3.2–4.9)	4.8† (4.2–5.0)	0.7 (0.3–1.1)
Male	1793 (85%)	274 (89%)	237 (81%)	1388 (86%)	863 (87%)*	32 (74%)*
Transmission via IVD	99 (5%)†	11 (4%)	11 (4%)†	131 (8%)†	69 (7%)	7 (16%)†
Age (years), median (IQR)	37† (32–45)	37 (33–46)	38 (31–44)	39† (34–46)	39 (34–46)	37 (33–43)
CD4 count ($\times 10^6$ cells/l), median (IQR)	222† (87–370)[a]	210† (90–320)	185† (79–345)	170† (60–300)[a]	130†* (40–250)	280†* (190–410)
Log_{10} RNA (copies/ml), median (IQR)	5.0† (4.5–5.4)[b]	4.9† (4.6–5.5)	5.0† (4.6–5.5)	4.4† (3.4–5.0)[b]	4.5† (3.5–5.1)	4.3† (3.7–4.9)

IQR, interquartile range; IVD, intravenous drug use; CDC, Centers for Disease Control; [a]baseline CD4+ T-cell count available for 1767 (84%) therapy-naive and 1386 (86%) pre-treated patients; [b]baseline HIV-RNA available for 1808 (86%) therapy-naive and 1070 (66%) pre-treated patients; *significantly different ($P < 0.01$) between 1996 and 2000/01 patients; †significantly different ($P < 0.01$) between naive and pre-treated patients.

Results

The number of patients in the ATHENA database that initiated HAART was 3742 of which 18 patients were excluded as their age at start of HAART was unknown. Thus our study contained 3724 patients who received HAART of whom 346 died during follow-up. The total follow-up time was 12 503 person-years. Characteristics of the patients at start of HAART are shown in Table 1. Among the 3708 patients who survived more than 4 weeks 459 patients were diagnosed with AIDS during follow-up. Of the 16 patients who did not survive more than 4 weeks nine died whilst the remaining seven patients were censored.

Development of AIDS

Covariates associated with progression to AIDS are listed in Table 2. The underlying hazard function h_0 was modelled as a constant plus the log-transformed time of follow-up which was significantly associated with a reduced risk of developing AIDS [22]. For pre-treated patients the risk of progression to AIDS was 1.91 times larger than for patients who had no or less than 1 year of previous treatment. Each unit increase in log-transformed baseline CD4 cell count reduced the risk of progression to AIDS by a factor 0.62. Patients without a measured baseline CD4 cell count had a hazard ratio of 3.11 compared to those who had one. Gender, transmission category and viral load and age at baseline were not significantly associated with development of AIDS.

The effect on disease progression of having been diagnosed with AIDS in the year prior to start of HAART was the only one that was found to be dependent on time of follow-up after start of HAART. Compared to patients who were not diagnosed with AIDS before initiation of HAART the hazard ratio was 4.22 in the first half year after T_0 decreasing to 1.83 in the 2.5 years thereafter, while after 3 years following start of HAART the hazard ratio was no longer significant. A Centers of Disease Control (CDC) category-B event in the year prior to start of HAART was not significantly associated with progression to AIDS after start of HAART. Interrupting HAART up to 8 weeks ($16 \leqslant N_{\mathrm{HAART}} < 24$) or more than eight weeks ($N_{\mathrm{HAART}} < 16$) of the preceding 24 weeks was associated with a hazard ratio of 2.03 and 4.94, respectively, compared to continuous treatment with HAART.

Survival

In addition to the covariates associated with progression to AIDS two extra covariates were associated with survival, transmission via intravenous drug use and age at start of HAART (Table 2). In contrast to progression to AIDS, survival was not directly associated with time of follow-up. The hazard ratio of having experi-

Table 2. Effect of baseline variables and N_{HAART} (number of weeks on highly active antiretroviral therapy in each 24-week interval of follow-up) on the risk of progression to AIDS or death.

Endpoint	HR (95% CI) AIDS	HR (95% CI) death
Pre-treatment longer than 1 year		
No	1	1
Yes	1.91 (1.57–2.31)	2.18 (1.75–2.72)
Transmission		
Sexual or other	1	1
IVD	*1.00 (0.70–1.44)	2.36 (1.73–3.21)
Age at T_0 per year	*1.003 (0.993–1.014)	1.034 (1.022–1.047)
CDC-C event in the year prior to T_0†		
No	1	1
Yes: < 0.5 year of follow-up after T_0	4.22 (3.09–5.75)	14.5 (8.84–23.7)
Yes: 0.5–3 years of follow-up after T_0	1.83 (1.41–2.37)	2.39 (1.82–3.15)
Yes: > 3 years of follow-up after T_0	*1.48 (0.85–2.57)	*1.41 (0.91–2.19)
Baseline CD4 cell count measured		
Yes	1	1
No	3.11 (2.17–4.47)	2.67 (1.77–4.02)
Log CD4 ($\times 10^6$ cells/l) per unit increase	0.62 (0.56–0.69)	0.68 (0.61–0.77)
N_{HAART}‡		
24 weeks	1	1
16–23 weeks	2.03 (1.38–2.97)	4.00 (2.81–5.69)
< 16 weeks	4.94 (3.82–6.39)	7.28 (5.65–9.37)

CI, confidence interval; HR, multivariate hazard ratio with respect to the underlying hazard $h_0(t)$ which is given by $\exp[-\alpha_1 - \alpha_2 \log(t)]$ with t time of follow-up since T_0 in years and $\alpha_1 = 8.0$ (95% CI, 7.4–8.5), $\alpha_2 = 0.66$ (95% CI, 0.55–0.78) (endpoint AIDS) and $\alpha_1 = 10.1$ (95% CI, 9.5–10.7), $^*\alpha_2 = 0.10$ (95% CI, −0.07 to 0.26) (endpoint death); IVD, intravenous drug use; †time-dependent hazard ratios; ‡time-dependent covariate; *hazard ratio statistically not significant.

enced a CDC category-C event in the year prior to start of HAART was 14.5 in the first half year after initiation of HAART decreasing to 2.39 in the 2.5 years thereafter. Hazard ratios associated with treatment interruptions were 4.00 ($16 \leqslant N_{HAART} < 24$) and 7.28 ($N_{HAART} < 16$).

Survival probabilities

Estimated 5-year survival probabilities as a function of baseline CD4 cell count and age for therapy-naive patients who are not intravenous drug users are given in Figure 1. Figures 1a and 1b show survival probabilities for patients without and with an AIDS-defining disease, respectively, in the year prior to the start of HAART who use HAART continuously (therapy scenario a). For patients younger than 50 years with CD4 cell counts above 10×10^6 or 150×10^6 cells/l (see Figure 1a and 1b), respectively, the predicted survival probabilities are above 90%. Estimated 5-year survival probabilities for patients without prior AIDS-defining event who interrupt HAART during 4 weeks of each 24-week interval of follow-up (scenario b) are only above 90% when CD4 cell counts at start of treatment are above 450×10^6 cells/l (Figure 1c). When the same group of patients defers HAART for 48 weeks and uses continuous HAART thereafter patients with CD4 counts above 110×10^6 cells/l have a 90% 5-year survival probability (scenario c).

HIV-related and non-related mortality

Of the 346 deaths in our study group HIV-related mortality was scored as the most probable cause of death in 191 (55%) cases whereas in 97 (28%) cases the cause of death was non-HIV-related of which seven (2%) were therapy-related. In 58 (17%) cases the cause of death could not be determined. HIV-related mortality per 100 person-years of follow-up since start of HAART was 3.8 [95% confidence interval (CI), 2.4–5.9] in 1996 and decreased to 0.7 (95% CI, 0.5–1.1) in 2000 ($P < 0.01$) (Fig. 2). Non-HIV-related mortality did not change over time, 0.4 (95% CI, 0.0–1.3) and 0.9 (95% CI, 0.6–1.3), respectively ($P = 0.25$).

Covariates associated with either HIV-related or non-related death are shown in Table 3. No significant association was found between intravenous drug use and HIV-related death while CD4 cell counts at baseline were not associated with non-HIV-related death. Pre-treatment with antiretroviral drugs, a CDC category-C event in the year prior to start of HAART as well as discontinuous use of HAART were associated with an increased risk of HIV-related and non-related death.

Discussion

Our study shows, in accordance with previous findings, that clinical markers associated with a higher survival

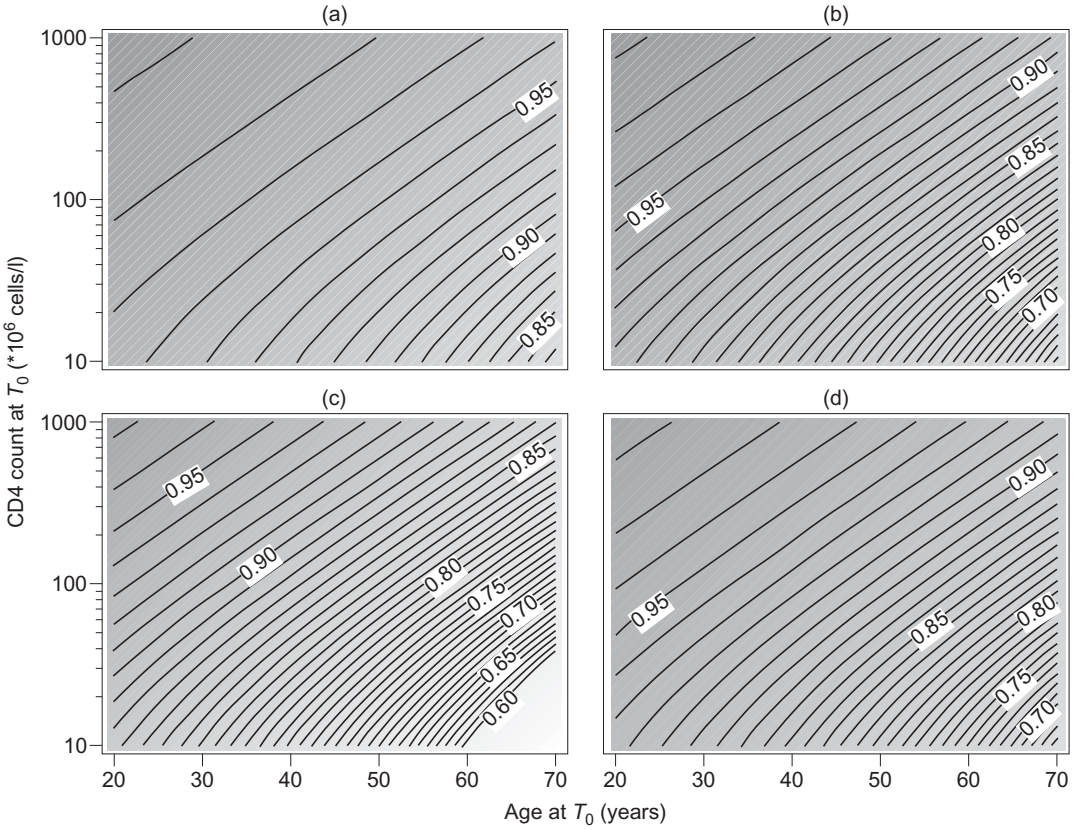

Fig. 1. Five-year survival probabilities as a function of age and CD4+ T-cell counts at baseline for antiretroviral therapy-naive patients who are not intravenous drug users. (a) + (b): patients without (a) or with (b) an AIDS-defining disease prior to start of HAART and using HAART continuously; (c) patients without an AIDS-defining disease prior to start and using HAART during 20 weeks in each 24-week interval of follow-up; (d) patients without an AIDS-defining disease prior to T_0 deferring initiation of HAART for 48 weeks after becoming eligible for treatment and using continuous HAART thereafter.

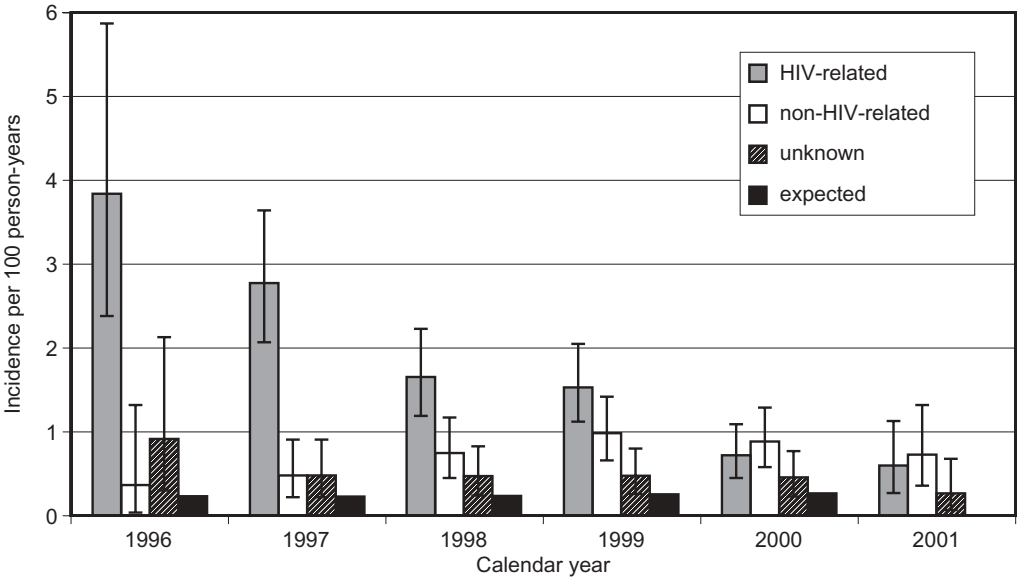

Fig. 2. Incidence of mortality over calendar time with 95% confidence intervals. Grey bars represent HIV-related mortality, white bars represent non-HIV-related deaths and diagonal bars represent unknown death causes. Black bars denote mortality in the age and gender matched general Dutch population (unavailable for 2001).

Table 3. Effect of baseline variables and N_{HAART} (number of weeks on highly active antiretroviral therapy in each 24-week interval of follow-up) on the risk of progression to an HIV-related or non-related death.

Endpoint	HR (95% CI) HIV-related death	HR (95% CI) non-HIV-related death
Pre-treatment longer than 1 year		
No	1	1
Yes	2.29 (1.70–3.08)	1.97 (1.30–2.99)
Transmission		
Sexual or other	1	1
IVD	*1.33 (0.80–2.24)	4.80 (2.94–7.84)
Age at T_0 per year	1.029 (1.012–1.046)	1.048 (1.025–1.072)
CDC-C event in the year prior to T_0†		
No	1	1
Yes: < 0.5 year of follow-up after T_0	18.1 (9.76–33.6)	14.7 (4.49–48.0)
Yes: 0.5–3 year of follow-up after T_0	[a]3.43 (2.36–5.00)	*1.55 (0.85–2.82)
Yes: > 3 years of follow-up after T_0	[a]2.53 (1.43–4.47)	*0.64 (0.25–1.63)
CD4 count measured		
Yes	1	1
No	3.19 (1.77–5.76)	*1.52 (0.73–3.13)
Log CD4 ($\times 10^6$ cells/l) per unit increase	0.61 (0.52–0.72)	*0.90 (0.71–1.13)
N_{HAART}‡		
24 weeks	1	1
16–23 weeks	3.98 (2.40–6.61)	[b]3.20 (2.27–6.03)
< 16 weeks	9.06 (6.33–13.0)	[b]3.63 (2.27–5.80)

CI, confidence interval; HR, multivariate hazard ratio with respect to the underlying hazard $h_0(t)$ which is given by $\exp[-\alpha_1 + \alpha_2 \log(t)]$ with t time of follow-up since T_0 in years and $\alpha_1 = 10.9$ (95% C, 10.1–11.8), *$\alpha_2 = -0.15$ (95% CI, −0.36 to 0.05) (HIV-related deaths) and $\alpha_1 = 11.2$ (95% CI, 10.1–12.4), $\alpha_2 = 0.67$ (95% CI, 0.32–1.02) (non-HIV-related deaths); IVD, intravenous drug use; †time-dependent hazard ratios; ‡time-dependent covariate; *hazard ratio statistically not significant; [a,b]difference between categories not significant.

probability and a slower progression to AIDS are a high baseline CD4+ T-cell count, absence of CDC category-C events before start of HAART and no or limited prior treatment with antiretroviral drugs. Age and intravenous drug use are significant predictors for progression to death but not for development of AIDS. In addition, continuous HAART is associated with slower progression to death and AIDS in comparison with interrupted HAART. The large difference between the AIDS and survival model in parameter values associated with an AIDS-diagnosis in the year prior to initiation of HAART is largely explained by the inclusion of time of follow-up in the first model. To avoid complexity in our model we only included prognostic variables that are measured in routine patient care. Thus our model could easily be applied to other observational cohorts.

In accordance with previous studies [22,23] we did not find a significant association between HIV-RNA levels at start of HAART and subsequent disease progression. Other studies showed that reaching undetectable plasma HIV-RNA levels during HAART is much more strongly related to risk of death and AIDS than pre-HAART RNA levels are [22,24]. In our analyses, however, we did not include viral load during HAART as we aimed to predict survival probabilities at the time of initiating HAART. Furthermore, we did not include haemoglobin and transaminase levels which have been shown to be associated with survival probability [31] since in our data these values were only recorded during follow-up.

By using our model to estimate survival probabilities we found that for young patients starting continuous HAART whilst in a less advanced stage of HIV-infection the 5-year survival probabilities were above 90%. This agrees with the 3-year survival probabilities that were previously found for a similar group of patients and varied between 95.9% and 99.8% [27]. Longer term predictions could be made but since the long-term effects of HAART are still unknown, these predictions cannot be validated with currently available data and might be too optimistic considering the risk of toxicities and resistance.

The effect of treatment on disease outcome is assessed by studying therapy interruptions, which reflect both failure to suppress viral load or to increase CD4 cell counts and toxicity-driven switches. This analysis does not aim at drawing conclusions about the effect of a treatment strategy adopted at start of HAART. The high survival probabilities for patients with high baseline CD4 counts using interrupted HAART confirm that occasional treatment interruptions shorter than 3 months do not increase the risk of death [19]. Our results are also compatible with STI studies which show that short-term disease progression does not change or

may even improve slightly [16–18]. However, therapy interruptions in our cohort are largely unstructured and occur for a longer period of time (median duration 2 months, data not shown) than in previous reports. Moreover, therapy may have been interrupted because of toxicity or therapy failure, the latter two being associated themselves with an increased risk of death and AIDS. Other studies have shown that therapy failure is the reason for about 10% of the therapy interruptions within 1 year after start of HAART, and toxicity for about 30%. This latter percentage increases with each calendar year following the introduction of HAART [26,32,33]. Untangling the pure effect of STI from these other therapy interruptions is difficult in the settings of an observational cohort.

A possible underestimation of the effect of therapy interruptions is caused by patients who die within 24 weeks after initiating HAART as, by construction, therapy interruptions are not counted. We argue, however, that the effect of interruptions on disease progression is not instantaneous but only manifests itself after some time.

The optimum time to initiate HAART in asymptomatic patients is an issue that is hard to resolve [15,27]. The beneficial effect on immune restoration should be balanced against the risk of drug-related toxicities and development of drug resistance [15,34]. Our model could predict survival probabilities for patients who deferred initiation of HAART for 1 year after becoming eligible for treatment, although these predictions were not based on a dedicated study on deferring treatment. We approximated the decrease in CD4 counts in this year by an increased risk of death due to the absence of treatment. This risk is probably overestimated as treatment interruptions in our data were always during HAART. Compared to patients of the same age and CD4 cell count who initiated HAART immediately after becoming eligible for treatment, the difference in survival probabilities was a few percentage points when CD4 cell counts were above 110×10^6 cells/l. Although small, this difference was significant and compatible with previous findings that initiating HAART in patients with CD4 cell counts above 350×10^6 cells/l significantly delayed clinical progression [34].

HIV-related and non-related mortality

From 1996 until 2000 the mortality amongst HIV-infected persons in the ATHENA cohort declined. A similar reduction has been observed in other studies and is largely explained by the introduction of HAART [2,3]. However, part of the decline might be attributed to changes in the infected and treated population during these years, as it shifted towards one in a less advanced stage of HIV-1 infection at the start of HAART with a growing fraction of therapy-naive patients. Mortality rates in 2001 were unreliable as not all follow-up data are available yet.

Non-HIV-related mortality was two to three times higher than in the general population [7]. Part of this excess can be explained by the seven proven and approximately 25 possibly therapy-related causes of death. Moreover, the HIV-infected and treated population is not representative of the general Dutch population, as there are relatively more intravenous drug-users who have a higher risk of dying of non-HIV-related causes.

Although misclassification of causes of death may limit interpretation of the results, the stable incidence of non-HIV-related causes over the years suggests that toxicity has not yet become a major cause of death. This may, however, change in the future when the long-term consequences of HAART become more clearly recognized. Thus, the recognition and careful recording of therapy-related toxicity and deaths remains of utmost importance.

In conclusion, using only covariates known at baseline, we could predict survival probabilities for patients initiating HAART under various therapy scenarios. Our model predicted that using HAART continuously is the best scenario. Deferring HAART for 1 year after becoming eligible for treatment and using continuous HAART thereafter is, according to our model, better than using interrupted HAART. However, absolute differences between 5-year survival probabilities in these three different scenarios were small for asymptomatic patients younger than 50 years with high levels of CD4 cell counts. Considering the risk of toxicities and adherence problems deferring treatment might therefore be acceptable.

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