Infection
DOI 10.1007/s15010-010-0070-8

CLINICAL AND EPIDEMIOLOGICAL STUDY

Impact of earlier HAART initiation on the immune status and clinical course of treated patients on the basis of cohort data of the German Competence Network for HIV/AIDS

A. Plettenberg · N. H. Brockmeyer · B. Haastert · C. Michalik · S. Dupke · K. Schewe · M. Rausch · M. Hower · A. Ulmer · E. Wolf · T. Lorenzen · G. Arendt · K. Jansen · the Competence Network for HIV/AIDS

Received: 28 June 2010 / Accepted: 30 November 2010

Abstract
Purpose Hitherto, studies on highly active antiretroviral therapy (HAART) initiation have shown partly inconsistent results. Our study investigated the clinical course and course of immune status after HAART initiation at CD4-cell-count/μl of treated patients between 250 and 349 (group 1), compared to 350–449 (group 2), on the basis of the cohort of the Competence Network for HIV/AIDS (KompNet cohort).
Methods Patients had to be HAART-naïve. Medication had to start at the earliest in 1996, being at least triple combination therapy. The primary endpoints of death, first AIDS-defining illness and first drop of CD4-cell-count/μl below 200 were evaluated as censored event times between the initiation of HAART (t_0) and the date of the first event/date of last observation. Probabilities of event-free intervals since t_0 were calculated by Kaplan–Meier estimation, compared by logrank tests. The results were adjusted for confounders using Cox regression. Additionally, incidences were estimated.
Results A total of 822 patients met the inclusion criteria (group 1: 526, group 2: 296), covering 4,133 patient years (py) overall. In group 1, 0.64 death cases/100 py were found, with the corresponding vale being 0.17 in group 2. In group 1, 1.38 AIDS-defining events/100 py occurred, whereas it was 0.78 in group 2. In group 1, 2.64 events of first drop of CD4-cell-count/μl below 200 occurred per 100 py, compared to 0.77 in group 2. Kaplan–Meier estimations showed borderline significant differences regarding death ($p = 0.063$), no differences regarding first

A. Plettenberg · T. Lorenzen
Ifi-Institute, Hamburg, Germany

N. H. Brockmeyer · K. Jansen (✉)
Competence Network for HIV/AIDS, Bochum, Germany
e-mail: klaus.jansen@klinikum-bochum.de

N. H. Brockmeyer
Clinic for Dermatology, Venerology and Allergology,
St. Josef-Hospital, Ruhr University, Bochum, Germany

B. Haastert
mediStatistica, Neuenrade, Germany

C. Michalik
Clinical Trial Centre, University Cologne, Cologne, Germany

S. Dupke
Clinical Centre, Driesener Straße, Berlin, Germany

K. Schewe
Infektionsmedizinisches Centrum Hamburg (ICH),
Hamburg, Germany

M. Rausch
Clinical Centre Fuggerstraße, Berlin, Germany

M. Hower
City Clinic, Dortmund, Germany

A. Ulmer
Clinical Centre Ulmer/Frietsch/Mueller, Stuttgart, Germany

E. Wolf
MVZ Karlsplatz, HIV Research and Clinical Centre, Munich,
Germany

G. Arendt
University Clinic, Dusseldorf, Germany

Published online: 11 January 2011

AIDS-defining illness ($p = 0.148$) and distinct differences regarding the first drop of CD4-cell-count/µl below 200 ($p = 0.0004$).

Conclusions The results gave a strong hint for a therapy initiation at higher CD4-cell-count/µl regarding the outcome of death in treated patients. A distinct benefit was shown regarding the first decline of CD4-cell-count/µl below 200.

Keywords HIV/AIDS · Cohort study · HAART initiation · CD4-cell-count · Clinical course of HIV

Introduction

Despite 14 years of experience with highly active antiretroviral therapy (HAART) in HIV/AIDS patients, the optimal time to start the treatment is still unknown. Decisions on the start of HAART have to balance therapy benefits regarding morbidity and mortality against therapy risks in terms of toxicity, development of resistance and loss of quality of life, on the basis of current medical evidence.

Only preliminary data coming from large randomised clinical trials regarding this topic are disposable till today [1, 2]. They suggest the CD4-cell-count as a prognostic factor and as a decision marker for therapy commencement. Following these arguments, two recent studies showed a benefit of an earlier treatment initiation using extensive cohort data. Kitahata et al. [3] demonstrated an advantage in survival between patients starting HAART immediately or deferred in the two different CD4 cell strata of above 500 cells/µl and between 351 and 500 cells. Sterne et al. [4] found a benefit of treatment initiation on the basis of a CD4-cell-count/µl between 351 and 450 cells, compared to between 251 and 350 cells, in terms of death and developing AIDS. Additional studies gave evidence towards an earlier treatment initiation, highlighting different aspects of this topic [5–18].

Major guidelines for developed countries were adjusted accounting for the described findings, but not in a consistent way till today [19, 20]. However, despite all of the study results, there is multiple discussion about the evidence of surrogate markers: besides CD4-cell-count/µl at treatment initiation as a prognostic factor, other indicators are discussed, such as HIV-RNA, haemoglobin [21], co-infections [22], patient-related factors and other treatment conditions [23–28].

Hence, therapy planning proceeds as a multifactorial process, but the timing of HAART initiation on the basis of CD4-cell-count/µl remains of high importance, so further data analyses of cohorts are warranted regarding that topic.

From the clinical point of view, it is not only of special interest to compare groups of patients having a CD4-cell-count/µl above or below a specific limit such as 200 or 350 at treatment initiation, but to analyse differences looking at treatment initiation between patient groups being highly frequent and relevant in daily medical routine. Therefore, the aim of this study was to compare specific differences in clinical outcomes between two patient groups: the first with the start of initial therapy having a CD4-cell-count/µl between 250 and 349 cells, and the second having a CD4-cell-count/µl between 350 and 449 cells.

The published studies used different methodological approaches and different primary outcomes, and the need for additional analyses of cohort data was stated. We, therefore, analysed the data of the patient cohort of the German Competence Network for HIV/AIDS (KompNet cohort) with respect to this question. Considering the results of Ledergerber et al. [29], a special aim of our study was to evaluate the impact of CD4-cell-count/µl at the start of HAART initiation on the first decline of CD4-cell-count/µl below 200 in treated patients, in addition to the investigation of the main outcomes of death and AIDS.

Methods

Using complementary methodological approaches, the presented study analyses the therapy initiation data of the patient cohort of the German Competence Network for HIV/AIDS. It comprises a broad range of retrospective and prospective clinical, epidemiological and sociodemographic data of more than 15,000 treated patients. This cohort is considered as representative for the population of treated patients in Germany; basic epidemiological, clinical and treatment characteristics of the cohort have been described in detail recently [30, 31].

Primary question

The primary question of the study was to compare immunological and clinical outcomes of treated patients in Germany starting initial HAART with a CD4-cell-count/µl between 250 and 349 (group 1) versus 350 and 449 (group 2). The primary outcomes were time to death, time to developing a first AIDS-defining event (AIDS) or time to first drop of CD4-cell-count/µl below 200. The date of HAART initiation (t_0) was defined as the baseline. The analyses were made on the basis of two populations: firstly, the population of all eligible patients (Table 1), and, secondly, a subpopulation of patients remaining on HAART for at least 3 years.

Table 1 Patient selection: number of eligible patients, inclusion criteria and number of excluded patients

No. of selected patients (*n*)	Inclusion criteria	No. of excluded patients (*n*)
15,804	Basis population	–
15,804	At least 1 CD4-cell-count/µl documented	243
15,561	Observation period ≥3 months	1,212
14,349	Start of HAART since 1996	2,874
11,475	HAART-naïvity at the start of documentation	7,753
3,722	CD4-cell-count/µl <450 at the start of HAART	1,085
2,637	Minimum observation period of 3 months following the start of HAART	125
2,512	Exclusion of patients having AIDS, CD4-cell-count/µl below 200 or myocardial infarction before the start of HAART	1,248
1,264	Start of HAART having CD4-cell-count/µl ≥250	326
938	Initial therapy: at least triple combination therapy	116
822	Study population	

Selection of study population

The consecutive inclusion criteria for selection of the study population are described in Table 1. Each study patient was observed at least 3 months (91 days) before t_0 and at least 3 months afterwards. All patients being observed for at least 3 years after t_0 were selected as a subpopulation.

Statistical methods

The baseline characteristics of both groups were compared statistically using Fisher's exact test, the *t*-test or Wilcoxon's rank sum test. The primary outcomes time from the start of HAART to death, AIDS or first drop of CD4-cell-count/µl below 200 were described at first by incidences per person year and 95% confidence intervals (CIs) assuming Poisson distributions. The primary outcomes were evaluated as possibly censored event times between t_0 and the date of the first event, or the last observation if no event was documented. Time-dependent probabilities of event-free intervals since the start of HAART were estimated by Kaplan–Meier curves for both groups. The corresponding risks were compared between both groups using the logrank test [32]. HIV duration (years) and calendar year of the start of HAART (≥2005 vs. <2005)[1] were considered as possible confounders at the baseline. To adjust for bias from these confounders, Cox regression models were fitted as secondary analyses [24]. In multiple models, a group indicator and both confounders were included as covariables. Hazard ratios and 95% CIs were estimated. Because of the inclusion criteria of the study, all patients dying in the first 3 months after HAART initiation were excluded. To compare all three outcomes on the same time scale, the initial time was chosen as the HAART initiation. The risk of death during the first 3 months after HAART initiation in the whole population was considered to be low. The course of CD4-cell-count/µl was described graphically based on quarterly mean values per patient as a secondary outcome.

In a secondary analysis, the subpopulation of patients who were on HAART for at least 3 years was considered. The 3-year incidence of a first AIDS-defining illness or first drop of CD4-cell-count/µl below 200 was evaluated for both groups and compared by Fisher's exact test. Furthermore, the time course of CD4-cell-count/µl was presented graphically in the 3-year interval.

All statistical tests were two-sided at a significance level of 5%. All analyses were performed by SAS for Windows, version 9.2 TS2M0 (SAS Institute, Inc., Cary, NC, USA).

Data management

The first documented HAART was considered as the initial HAART of the patients in the study population; to ensure plausibility, patients had to be HAART-naïve. The CD4-cell-count/µl at the start of HAART was the last CD4-cell-count/µl within 56 days before t_0. If a patient had no value available in this time interval, then they were excluded from the study population. The first and the last observation date of the patient were the first and the last date of a documented CD4-cell-count/µl or virus load, or the last follow-up of the patient; courses of CD4-cell-count/µl were checked for plausibility. HIV duration at t_0 was estimated by the duration from the documented date of the first positive HIV test, if available, and before the first CD4-

[1] Central clinical and therapy related data of patients regarding the time before enrolment into the cohort are documented retrospectively [3]. Due to the high proportion of data documented retrospectively before 2005, the calendar year of the start of HAART (<2005 vs. ≥2005) was considered as a confounder to adjust for potential influences of different modes of data documentation (retrospective vs. prospective).

cell-count/µl, or the date of the first documented CD4-cell-count/µl otherwise.

Results

Description of study population

Following the eligibility criteria of the study, the study population consisted of 822 patients (Table 1), covering 4,133 patient years overall. Study group 1 (patients having CD4-cell-count/µl between 250 and 349 at t_0) comprised 526 patients, and study group 2 (CD4-cell-count/µl between 350 and 449 at t_0) contained 296 patients (Table 2).

Besides differences in the mean CD4-cell-count/µl between the groups due to the study definition, there were only slight differences regarding each patient's baseline characteristics, which were partly statistically significant (Table 2).

The sociodemographic and clinical baseline characteristics of the subpopulation of patients having a follow-up duration of at least 3 years ($n = 379$) were almost equal to the overall study population, except for longer documentation periods, as defined by the inclusion criteria of this subpopulation.[2] According to analysis criteria, the observed duration after t_0 was exactly 3 years for each patient, and events apart from death were only counted within that period. Fewer patients (16%) started HAART after 2004 (Table 2).

Incidence and probability of clinical events

Regarding the overall population, 0.64 cases of death per 100 patient years (95% CI 0.29–0.98) were found in group 1 of the overall population compared to 0.17 (95% CI 0–0.40) in group 2 (Table 3). Four patients died due to an AIDS-defining illness (one Burkitt lymphoma, one progressive Kaposi sarcoma and two septicaemia), seven deaths occurred from other causes (one cerebral haemorrhage, one Sigma carcinoma, two bronchial carcinoma, one metastasised sarcoma, one liver failure and one suicide), and in four cases, the reasons of death were unknown.

In group 1 of the overall population, 1.38 (95% CI 0.86–1.90) AIDS-defining events occurred per 100 patient years versus 0.78 (95% CI 0.27–1.29) events per 100 patient years in group 2. Regarding the first decline of CD4-cell-count/µl below 200 copies, 2.64 (95% CI 1.91–3.38) events per 100 patient years were seen in group 1, compared to 0.77 (95% CI 0.27–1.28) events per 100 patient years in group 2.

Concerning the subpopulation of patients being under observation for at least 3 years[3] and counting the events within the first 3 years after t_0, AIDS incidences were 1.59 events per 100 patient years (95% CI 0.65–2.53) for group 1 and 0.48 events per 100 patient years (95% CI 0.00–1.15) for group 2, respectively. Regarding the first decline of CD4-cell-count/µl below 200, 2.64 events per 100 patient years (95% CI 1.42–3.86) occurred in group 1 and 0.96 events per 100 patient years (95% CI 0.02–1.90) occurred in group 2.

The survival analysis as to death events showed a borderline significant difference in survival after the start of HAART between both groups (Fig. 1a, logrank test: $p = 0.063$). Up to 11 years after the initiation of HAART, there were more than ten patients at risk in each group. The estimated 10-year probability for survival was 94% (95% CI 90–98%) in group 1 and 97% (95% CI 92–100%) in group 2. A Cox regression model was fitted for the target variable "time to death", adjusted for the duration of HIV infection and the start of HAART after 2004. The hazard ratio (group 2 vs. group 1) was 0.273 (95% CI 0.062–1.213, $p = 0.088$). Furthermore, in this model, HAART starting after 2004 was a significant risk factor (hazard ratio 4.676 and 95% CI 1.017–21.502, $p = 0.048$). The duration of HIV infection was not significant as a risk factor.

For staying free of AIDS-defining events after t_0, another analysis did not show a significant difference between the groups (Fig. 1b, logrank test: $p = 0.148$). Up to 11 years after the start of HAART, there were more than ten patients at risk in each group. The estimated probability for AIDS-free survival remained on a high level, over 90%, 10 years after HAART initiation (estimated probabilities after 10 years with 95% CIs for group 1: 91% [87–95%] and group 2: 90% [83–97%]). The Cox regression model fitted for the target variable "time to develop the first AIDS-defining event" was similarly adjusted as for the overall survival. The hazard ratio (group 2 vs. 1) was 0.587 (95% CI 0.276–1.250, $p = 0.167$). Both confounders were non-significant as risk factors.

Regarding the event of a first decline of CD4-cell-count/µl below 200, the probability differed statistically significantly between the study groups (Fig. 1c, logrank test: $p = 0.0004$). Up to 11 years after the start of HAART, there were more than ten patients at risk in each group. The probability of not dropping below 200 c/µl remained above

[2] The percentage of quarters with a documented CD4-cell-count/µl measurement is lower for the subpopulation with an observation time ≥3 years than in all patients. For the analysis shown in Table 3, a fixed datum reference of 12 quarters was used as a basis for the analyses due to the observation period of at least 3 years. Because not every patient had a CD4-cell-count/µl measurement just in the 12 quarter, the named percentage is lower.

[3] It was not reasonable to calculate the incidences of death for this subpopulation due to the inclusion criteria of this group (observation period at least 3 years) and due to seven cases of death within the first 3 years.

Table 2 Baseline characteristics of eligible patients, overall population ($n = 822$) and subpopulation with observation time ≥3 years ($n = 379$), by study groups

	Overall study population		Tests
	Group 1 (CD4 250–349; $n = 526$)	Group 2 (CD4 350–449; $n = 296$)	
Women (n, %)	64 (12)	46 (16)	Fisher's test: $p = 0.054$
Age at t_0 (years)			t-test: $p = 0.708$
Mean ± SD	39.4 ± 9.8	39.7 ± 10.1	
Range	14.1–73.3	17.8–67.4	
CDC at t_0 (n, %)			Fisher's test: $p = 0.019$ (including missing)
A	249 (47)	134 (45)	
B	183 (35)	127 (43)	
C	0 (0)	0 (0)	
No. missing (%)	94 (18)	35 (12)	
HIV duration at t_0 (years)			t-test: $p = 0.024$
Mean ± SD	2.9 ± 3.6	3.6 ± 4.5	
Range	0.0–21.3	0.0–22.5	
CD4-cell-count/μl at t_0			Test meaningless
Mean ± SD	293 ± 29	395 ± 28	
Range	250–349	350–449	
Start of HAART ≥2005 (n, %)	303 (58)	172 (58)	Fisher's test: $p = 0.941$
Duration from t_0 to end of documentation (years)			Wilcoxon test: $p = 0.947$
Sum	2,034	1,184	
Mean ± SD	3.9 ± 3.1	4.0 ± 3.4	
Range	0.3–13.4	0.3–12.9	
Observed quarters with CD4 measurements (%)			t-test: $p = 0.459$
Mean + SD	65 ± 23	64 ± 24	
Range	8–100	6–100	
Duration of documentation overall (years)			Wilcoxon test: $p = 0.446$
Mean ± SD	5.1 ± 3.2	4.9 ± 3.2	
Range	0.5–16.9	0.4–12.9	
Duration of documentation at t_0 (years)			Wilcoxon test: $p = 0.042$
Mean ± SD	1.2 ± 1.7	0.9 ± 1.4	
Range	0.0–11.0	0.0–11.2	

	Subpopulation having observation time ≥3 years		Tests
	Group 1 (CD4 250–349; $n = 239$)	Group 2 (CD4 350–449; $n = 140$)	
Women (n, %)	24 (10)	20 (14)	Fisher's test: $p = 0.151$
Age at t_0 (years)			t-test: $p = 0.306$
Mean ± SD	39.4 ± 10.4	38.3 ± 9.9	
Range	14.1–73.3	17.8–67.4	
CDC at t_0			Fisher's test: $p = 0.019$
A	80 (33)	46 (33)	
B	85 (36)	67 (48)	
C	0 (0)	0 (0)	
No. missing (%)	74 (31)	27 (19)	
HIV duration at t_0 (years)			t-test: $p = 0.995$
Mean ± SD	2.5 ± 3.7	2.5 ± 3.6	
Range	0.0–19.0	0.0–17.6	

Table 2 continued

	Subpopulation having observation time ≥3 years		Tests
	Group 1 (CD4 250–349; $n = 239$)	Group 2 (CD4 350–449; $n = 140$)	
CD4-cell-count/µl at t_0			Test meaningless
Mean ± SD	295 ± 30	393 ± 28	
Range	250–349	350–449	
Start of HAART ≥2005 (n, %)	38 (16)	22 (16)	Fisher's test: $p = 1.000$
Duration from t_0 to end of documentation (years)			Wilcoxon test: $p = 0.436$
Mean ± SD	6.6 ± 2.6	6.9 ± 2.8	
Range	3.0–13.4	3.0–12.9	
Observed quarters with CD4 measurements in 3 years (%)			t-test: $p = 0.435$
Mean ± SD	45 ± 26	43 ± 26	
Range	0–100	0–100	
Duration of documentation overall			Wilcoxon test: $p = 0.600$
Mean ± SD	7.4 ± 2.9	7.5 ± 2.6	
Range	3.1–16.9	3.2–12.9	
Duration of documentation at t_0 (years)			Wilcoxon test: $p = 0.414$
Mean ± SD	0.8 ± 1.5	0.6 ± 1.1	
Range	0.0–10.1	0.0–7.5	

90% for study group 2, but declined to below 80% in study group 1 (estimated probabilities after 10 years with 95% CIs: group 1: 80% [95% CI 73–87%] and group 2: 94% [95% CI 90–98%]).

The Cox -regression model, adjusted in the same way as above, demonstrated a hazard ratio (group 2 vs. group 1) of 0.302 (95% CI 0.149–0.616, $p = 0.001$).

Additional analyses of patients being under follow-up for at least 3 years did not show any significant differences regarding the frequency of the outcome parameters at the time point 3 years after the start of HAART.

The trend curves of the CD4-cell-count/µl after t_0 showed a distinct increase in both study groups within the first 2 years (Fig. 2a). A descriptive comparison showed higher mean values for study group 2 compared to group 1 within the first 3 years. Regarding both populations, the numbers of patients with data of CD4-cell-count/µl in the respective quarters declined over time.

CD4 values after the start of HAART in the subpopulation that were under observation for at least 3 years remained clearly separated over time (Fig. 2b). The curves of both study groups increased almost steadily, rising more slowly after the first year.

Discussion

Our study analysed data from the KompNet cohort with regards to the clinical outcome of two groups of patients with CD4-cell-count/µl strata between 250 to 349 and 350 to 449. These ranges have been selected because of the ongoing discussion about the optimal timing of HAART initiation stressing potential differences in the clinical course of these two groups in Germany and further afield.

Experts agree that a HAART initiation with CD4-cell-count/µl below 200 is associated with a worse prognosis in comparison to treatment initiation at a higher CD4-cell-count/µl [26, 33]. Current guidelines accommodate this point by recommending that therapy start at an earlier CD4-cell-count/µl. In detail, patients with less than 350 CD4-cell-count/µl should be started with HAART regardless of any additional conditions, and treatment should be considered from 350 to 500 CD4-cell-count/µl in special cases [19, 20].

The clinical benefit of therapy initiation at a CD4-cell-count/µl above 350 has recently been especially investigated [2–4]. The published studies described a two-thirds elevated risk of death if HAART is deferred in patients with a CD4-cell-count/µl between 350 and 500, and an overall risk of death or AIDS-defining events 28% higher in patients with a CD4-cell-count/µl in the range 251–350 compared to patients in the range 351–450. Our study also investigated this clinically highly relevant group of patients with a CD4-cell-count/µl in the range 250–449 at therapy commencement. It focussed on the overall rates of death, AIDS-defining conditions and, additionally, on the time to the first drop of CD4-cell-count/µl below 200, despite HAART being suggested as an independent predictor for disease progression and death, respectively [29].

Table 3 Frequency of outcome parameters, by study groups; complete study population ($n = 822$) and subpopulation with observation time ≥3 years ($n = 379$)

	Complete study population		Tests[a]
	Group 1 (CD4 250–349; $n = 526$)	Group 2 (CD4 350–449; $n = 296$)	
No. of deaths	13	2	–
No. of AIDS events	27	9	–
No. of cases with first decline of CD4-cell-count/µl below 200	50	9	–
	Subpopulation with observation time ≥3 years[c]		
	Group 1 (CD4 250–349; $n = 239$)	Group 2 (CD4 350–449; $n = 140$)	
No. of deaths	5	2	–[b]
No. of AIDS events 3 years after t_0	11	2	Fisher's test: $p = 0.144$
No. of cases with first decline of CD4-cell-count/µl below 200 within 3 years after t_0	18	4	Fisher's test: $p = 0.070$

[a] No tests of significance were calculated as to the frequency of events regarding the complete study population, because of the unfixed time period that was analysed for this group. The concerning tests were calculated instead in the scope of the Kaplan–Meier analyses for this group. Regarding the subpopulation with observation time ≥3 years, tests of significance as to the frequency of events could be calculated due to the fixed time period of analysis

[b] Test meaningless (by definition, all non-survivors in this group died after 3 years)

[c] In group 1, six of 13 non-survivors died within 3 years. Two of the remaining seven 3-year survivors were observed for less than 3 years because there was a gap between the last follow-up visit and the date of death. In group 2, both non-survivors survived for over 3 years

Fig. 1 Kaplan–Meier analysis regarding death (**a**), developing an AIDS-defining event for the first time (**b**) and the first decline of CD4-cell-count/µl below 200 (**c**), by study group (group 1: CD4 250–349, group 2: CD4 350–449; $n = 822$)

Due to our use of very strict inclusion criteria for defining the study population, e.g. the specifically confirmed HAART-naïvety before the start of HAART

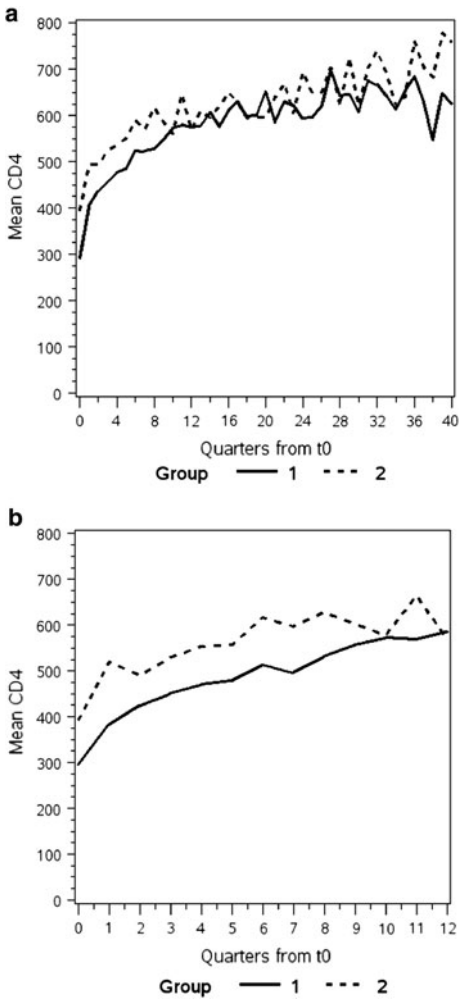

Fig. 2 Mean CD4-cell-count/µl over time for the overall population (**a**) and subpopulation under observation ≥3 years (interval of 3 years) (**b**), by study group (group 1: CD4 250–349, group 2: CD4 350–449; $n = 822$)

documentation in our cohort and the further complex selection process, the eligible study population resulted in a reduction of the number of patients, as is usual for many cohort analyses.

Based on all of the complementary methodological approaches used, we found a better outcome of patients starting their initial HAART with higher CD4-cell-count/µl in terms of death, first AIDS-defining event and first decline below 200. The adjusted hazard ratios of patients with CD4-cell-count/µl in the range 250–349 versus 350–449 showed a tendency according to death and developing an AIDS-defining event ($p = 0.088$ and $p = 0.167$, respectively), and a clear significance for the first drop of CD4-cell-count/µl below 200 with an adjusted hazard ratio of 0.302.

Considering the study of Ledergerber et al. [29], our results suggest, for the first time, evidence for the latest therapy initiation at a CD4-cell-count/µl of 350 regarding a possible decline of CD4-cell-count/µl below 200, to avoid poor clinical course in patients having constantly detectable viral load.

The statistically not significant but remarkable difference between the outcomes death and AIDS-defining event in our evaluation is not contradictory considering the causes of death. Only about a third of all deaths with known cause were due to an AIDS-defining illness; two-thirds were due to other reasons, with a high impact of carcinomas. These findings confirmed the results of some recently published studies [3, 34–36].

Our results are derived from an explorative analysis of cohort data, having some typical limitations. In general, bias from known or unknown confounders cannot be excluded and can only be partly adjusted. Causal inferences cannot be concluded. In this study, we analysed patients that started HAART within a range of CD4-cell-count/µl between 250 and 449. Patients who fulfilled that criterion but stayed therapy-naïve were excluded from the analysis. These patients might benefit from a later commencement of HAART, due to less cumulative side-effects and drug toxicity. In consequence, our results cannot be interpreted as a comparison of therapy strategies starting HAART depending on the actual CD4-cell-count/µl in general, but for the highly relevant patient groups in daily clinical practice.

Regarding patients starting therapy with a lower CD4-cell-count/µl, a lead time bias, meaning patients remain stable for longer before starting HAART, seems not to be probable due to the longer period between the first positive HIV test and the start of initial therapy in the other patient group. Consequently, adjustment for this confounder did not change the results. The significantly higher duration of HIV infection at t_0 in group 2 could be an indication for the slower disease progression in that group. Because the difference between groups 1 and 2 was not very large, we do not assume an influence of this fact on the study results.

Hence, our results indicating a benefit of an earlier start of HAART in the most relevant group of patients to treat regarding the German situation might contribute to move on the discussion about international guidelines for HAART initiation in HIV-positive patients.

Generated hypotheses from the discussion process should be investigated and, if possible, confirmed by controlled clinical trials. Additionally, the kind and frequency of typical complications during the course of disease, as well as of special phenomena such as the immune reconstitution inflammatory syndrome (IRIS) under HAART should be evaluated.

Acknowledgments Firstly, we thank all of the patients participating in our cohort for providing their data and biomaterials to the study.

We are grateful for all the work and dedication of the documentation officers and of the heads of our documenting sites. We thank the Ruhr University Bochum for the financial and structural encouragement. We thank the Federal Ministry of Education and Research especially for its ongoing financial and ideal support since 2002 (grant no. BMBF-01 KI 0501). The following documenting sites currently contribute data to the basis module of the KompNet cohort: Gemeinschaftspraxis Driesener Straße, Berlin; Gemeinschaftspraxis Mehringdamm, Berlin; Gemeinschaftspraxis Turmstraße, Berlin; Gemeinschaftspraxis Fuggerstraße, Berlin; Praxiszentrum Kaiserdamm, Berlin; Universitätsklinikum Benjamin Franklin, Charité, Berlin; Dermatologische Klinik, Ruhr Universität, Bochum; Klinikum, Dortmund; Universitätsklinikum, Düsseldorf; Medizinische Klinik 3, Universitätsklinikum, Erlangen; Klinik für Dermatologie, Universität Essen; HIVCENTER, Universitätsklinikum, Frankfurt; Ifi-Institut, Hamburg; Infektionsmedizinisches Centrum Hamburg (ICH), Hamburg; Medizinische Hochschule, Hannover; Praxis Georgstraße, Hannover; Gemeinschaftspraxis, Kriegsstraße, Karlsruhe; Städtisches Krankenhaus Kemperhof, Koblenz; Praxis Hohenstaufenring, Köln; Gemeinschaftspraxis Isartorplatz, München; MVZ Karlsplatz, HIV Research and Clinical Centre, München; Praxisgemeinschaft Franz Joseph-Straße, München; Klinikum, Osnabrück; Gemeinschaftspraxis Ulmer/Frietsch/Müller, Stuttgart.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Emery S, Neuhaus JA, Phillips AN, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. J Infect Dis. 2008;197:1133–44.
2. Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med. 2006;355:2283–96.
3. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009;360(18):1815–26.
4. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet. 2009;373(9672):1352–63.
5. Ahdieh-Grant L, Yamashita TE, Phair JP, et al. When to initiate highly active antiretroviral therapy: a cohort approach. Am J Epidemiol. 2003;157:738–46.
6. Anastos K, Barrón Y, Miotti P, et al. Risk of progression to AIDS and death in women infected with HIV-1 initiating highly active antiretroviral treatment at different stages of disease. Arch Intern Med. 2002;162:1973–80.
7. Hughes MD, Ribaudo HR. The search for data on when to start treatment for HIV infection. J Infect Dis. 2008;197:1084–6.
8. Opravil M, Ledergerber B, Furrer H, et al. Clinical efficacy of early initiation of HAART in patients with asymptomatic HIV infection and CD4 cell count >350 × 10(6)/l. AIDS. 2002; 16:1371–81.
9. Palella FJ Jr, Deloria-Knoll M, Chmiel JS, et al. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. Ann Intern Med. 2003;138:620–6.
10. Sterling TR, Chaisson RE, Moore RD. HIV-1 RNA, CD4 T-lymphocytes, and clinical response to highly active antiretroviral therapy. AIDS. 2001;15:2251–7.
11. Sterling TR, Chaisson RE, Moore RD. Initiation of highly active antiretroviral therapy at CD4+ T lymphocyte counts of >350 cells/mm^3: disease progression, treatment durability, and drug toxicity. Clin Infect Dis. 2003;36:812–5.
12. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS ONE. 2009;4(5):e5575.
13. Grant P, Zolopa A. Initiation of antiretroviral therapy in the hospitalized patient with an acute AIDS-related opportunistic infection and other conditions: no time to lose. Curr HIV/AIDS Rep. 2009;6(2):63–7.
14. Phillips AN, Gazzard B, Gilson R, et al. Rate of AIDS diseases or death in HIV-infected antiretroviral therapy-naive individuals with high CD4 cell count. AIDS. 2007;21(13):1717–21.
15. May MT, Sterne JA, Costagliola D, et al. HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: a collaborative analysis. Lancet. 2006;368(9534):451–8.
16. Bonnet F, Thiébaut R, Chêne G, et al. Determinants of clinical progression in antiretroviral-naive HIV-infected patients starting highly active antiretroviral therapy. Aquitaine Cohort, France, 1996–2002. HIV Med. 2005;6(3):198–205.
17. Chêne G, Sterne JA, May M, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. Lancet. 2003; 362(9385):679–86.
18. Jacobson LP, Li R, Phair J, et al. Evaluation of the effectiveness of highly active antiretroviral therapy in persons with human immunodeficiency virus using biomarker-based equivalence of disease progression. Am J Epidemiol. 2002;155(8):760–70.
19. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society USA—Panel. JAMA. 2010;304(3):321–33.
20. Clumeck N, Dedes N, Pozniak A, et al. Clinical management and treatment of HIV infected adults in Europe. EACS Guidelines Version 5.2. Available online at: http://www.europeanaidsclinicalsociety.org/guidelines.asp. Accessed 16 September 2010.
21. Lau B, Gange SJ, Kirk GD, et al. Evaluation of human immunodeficiency virus biomarkers: inferences from interval and clinical cohort studies. Epidemiology. 2009;20(5):664–72.
22. Jaén A, Esteve A, Miró JM, et al. Determinants of HIV progression and assessment of the optimal time to initiate highly active antiretroviral therapy: PISCIS Cohort (Spain). J Acquir Immune Defic Syndr. 2008;47(2):212–20.
23. Stöhr W, Dunn D, Porter K, et al. CD4 cell count and initiation of antiretroviral therapy: trends in seven UK centres, 1997–2003. HIV Med. 2007;8(3):135–41.
24. May M, Sterne JA, Sabin C, et al. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. AIDS. 2007;21(9):1185–97.
25. Ho C, Lee S, Wong Kh, et al. Setting a minimum threshold CD4 count for initiation of highly active antiretroviral therapy in HIV-infected patients. HIV Med. 2007;8(3):181–5.
26. Lapadula G, Torti C, Maggiolo F, et al. Predictors of clinical progression among HIV-1-positive patients starting HAART with CD4+ T-cell counts > or = 200 cells/mm^3. Antivir Ther. 2007;12(6):941–7.
27. Locadia M, van Grieken RA, Prins JM, et al. Patients' preferences regarding the timing of highly active antiretroviral therapy initiation for chronic asymptomatic HIV-1 infection. Antivir Ther. 2006;11(3):335–41.
28. Fardet L, Mary-Krause M, Heard I, et al. Influence of gender and HIV transmission group on initial highly active antiretroviral therapy prescription and treatment response. HIV Med. 2006;7(8):520–9.

29. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. Lancet. 2004;364(9428):51–62.
30. Jansen K, Michalik C, Hahn M; Competence Network for HIV/AIDS, et al. The Patient Cohort of the German Competence Network For HIV/AIDS (KompNet): a profile. Eur J Med Res. 2009;14(10):323–31.
31. Jansen K, Brockmeyer NH, Hahn M; Competence Network for HIV/AIDS, et al. Epidemiological composition, clinical and treatment characteristics of the patient cohort of the German Competence Network for HIV/AIDS. Eur J Med Res. 2009; 14(10):415–25.
32. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: Wiley; 1980. p. 21–38.
33. Kaplan JE, Hanson DL, Cohn DL, et al. When to begin highly active antiretroviral therapy? Evidence supporting initiation of therapy at CD4+ lymphocyte counts <350 cells/microL. Clin Infect Dis. 2003;37(7):951–8.
34. Palella F, Armon C, Buchacz K, et al. CD4 at HAART initiation predicts long-term CD4 responses and mortality from AIDS and non-AIDS causes in the HIV Outpatient Study (HOPS). In: Proceedings of the 17th Annual Canadian Conference on HIV/AIDS Research, Saskatoon, Canada, May 2010. San Francisco, CA: CROI; 2010. Abstract 983.
35. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies. Clin Infect Dis. 2010;50(10):1387–96.
36. HIV-CAUSAL Collaboration. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. AIDS. 2010;24(1):123–37.