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ORIGINAL RESEARCH

Delayed diagnosis of HIV infection and late initiation of antiretroviral therapy in the Swiss HIV Cohort Study

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Objectives

To investigate delayed HIV diagnosis and late initiation of antiretroviral therapy (ART) in the Swiss HIV Cohort Study.

Methods

Two sub-populations were included: 1915 patients with HIV diagnosis from 1998 to 2007 and within 3 months of cohort registration (group A), and 1730 treatment-naïve patients with CD4 $\geq$ 200 cells/μL before their second cohort visit (group B). In group A, predictors for low initial CD4 cell counts were examined with a median regression. In group B, we studied predictors for CD4 $<$ 200 cells/μL without ART despite cohort follow-up.

Results

Median initial CD4 cell count in group A was 331 cells/μL; 31% and 10% were $<$200 and $<$50 cells/μL, respectively. Risk factors for low CD4 count were age and non-White race. Homosexual transmission, intravenous drug use and living alone were protective. In group B, 30% initiated ART with CD4 $\geq$ 200 cells/μL; 18% and 2% dropped to CD4 $<$200 and $<$50 cells/μL without ART, respectively. Sub-Saharan origin was associated with lower probability of CD4 $<$200 cells/μL without ART during follow-up. Median CD4 count at ART initiation was 207 and 253 cells/μL in groups A and B, respectively.

Conclusions

CD4 $<$ 200 cells/μL and, particularly, CD4 $<$ 50 cells/μL before starting ART are predominantly caused by late presentation. Earlier HIV diagnosis is paramount.

Keywords: cohort study, late ART initiation, late HIV diagnosis, late presentation

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Introduction

HIV-1 infection without antiretroviral therapy (ART) in the vast majority of infected individuals progressively destroys the immune system leading to opportunistic diseases and death. A CD4 cell count below 200/μL represents the threshold where the risk for clinical symptoms and AIDS-defining illnesses starts to increase substantially. Current management of HIV infection therefore aims to prevent opportunistic diseases by starting ART before CD4 cell counts decline below this critical level. Early presentation of HIV-infected patients for HIV care is thus paramount. Importantly, recent guidelines indicate the trend to start ART at even higher CD4 T-cell levels [1,2].

Late HIV diagnosis and presentation to HIV care is a common problem leading to significant HIV-related

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morbidity and mortality, even when ART is started promptly [3–19]. In a recent survey from England and Wales of 10 503 heterosexually infected individuals with a new HIV diagnosis and a CD4 cell count at the time of HIV diagnosis, 42% were diagnosed with a CD4 cell count $<200/\mu L$. The investigators estimated that earlier HIV diagnosis would have reduced short-term mortality, i.e. within 1 year of diagnosis, by 56% – corresponding to 249 fewer deaths [9]. Approximately 15% of patients in high-income countries start ART with CD4 T-cells below 50/μL compared to 31% in developing countries [20].

The goal of the present study, performed in the context of the Swiss HIV Cohort Study (SHCS), was to investigate delayed diagnosis of HIV infection, the extent of late initiation of ART despite cohort follow-up and time to ART uptake after dropping to CD4 <200 cells/μL.

Patients and methods

The SHCS (www.shcs.ch) prospectively enrols HIV-infected adults (over the age of 16 years) seen at all five university clinics and two Cantonal hospitals in Switzerland. Clinical data are collected according to a standardized protocol at registration and follow-up visits every 6 months. Laboratory data are transferred electronically from the centre laboratories to the SHCS data centre at follow-up or routine visits. For the present study, we used the SHCS database extract of July 2007.

Study population

To study delayed diagnosis of HIV infection and subsequent time to ART uptake, we concentrate on patients with a short time phase between a newly positive HIV test and entry into the SHCS. We therefore included all 1915 patients registered in the SHCS since 1 January 1998 with their first positive HIV test within 3 months of the cohort registration visit (group A). All but five of the 1915 patients were HIV-1 infected. Patients who registered in the SHCS more than 3 months after their first positive test were excluded because only incomplete data prior to inclusion into the SHCS were available. Not all of these patients enter the cohort while ART-naïve and reasons for inclusion in the SHCS with a long delay after a positive HIV test are diverse, which complicates interpretation. We also excluded patients registered during the early ART period (1996–1997) to obtain a more homogeneous population in regard to ART [21]. Patients were classified as late or very late presenting if their first available (single) CD4 cell count was <200 or <50 cells/μL, respectively.

In a second analysis, we studied late ART initiation – defined as a CD4 cell count <200 cells/μL prior to initiation of therapy – for patients who were already followed up in the SHCS (group B). For this analysis, we included all patients in the SHCS who were ART-naïve up to their second follow-up visit and had no prior CD4 cell count <200 cells/μL. Patients registered prior to 1998 were additionally required to be ART-naïve without a prior CD4 cell count <200 cells/μL until their second cohort visit after 1 January 1998. Note that patient groups A and B are not mutually exclusive: patients in group A with high initial CD4 cell counts were also contained in group B.

Evaluation of late diagnosis of HIV infection

We used a multiple median regression [22] to model the median initial CD4 cell count as a linear function of the following pre-defined covariates: age, gender, race (White *vs.* other), sub-Saharan African origin, infection through homosexual contact, current intravenous (IV) drug substitution programme or IV drug use, basic education (completed 9 years of mandatory schooling or less *vs.* higher), current psychiatric treatment, living alone and calendar year of cohort registration. Median regression estimates the median of the dependent variable (i.e. the initial CD4 cell count), conditional on the values of the covariates. This is similar to least-squares linear regression, which estimates the mean of the dependent variable. Consequently, the coefficients of a median regression output can be interpreted like ordinary regression coefficients. As an example, a coefficient of -63 cells/μL for the covariate age (by $+10$ years) indicates that the median initial CD4 cell count is estimated to decrease by -63 cells/μL if age is increased by 10 years. We preferred the median regression to gain better interpretability and robustness in the results.

As a sensitivity analysis, we modelled whether the patient was diagnosed late with a logistic regression model using the same covariates. We also assessed whether patients with a prior negative test differed in their initial CD4 cell count from other patients.

In a second step, we summarized the time from HIV diagnosis to ART initiation with Kaplan–Meier curves stratified by initial CD4 cell count and modelled it for patients with an initial CD4 cell count <200 cells/μL with a Cox regression using the initial CD4 cell count and the covariates specified earlier as explanatory variables.

Evaluation of late ART initiation during regular SHCS follow-up

We compared patients who initiated ART with a CD4 cell count ≥ 200 cells/μL to patients who dropped below 200 cells/μL while ART-naïve and those without low CD4

cell count or ART initiation with a logit model for multinomial responses. The same covariates as specified earlier were used and time-dependent covariates (e.g. current psychiatric treatment) were evaluated at the date of the cohort registration visit or the first cohort visit after 1 January 1998 for patients registered prior to 1998. For patients dropping to CD4 <200 cells/μL (or <50 cells/μL) while treatment-naïve, the time from this CD4 cell count to ART initiation was also described with Kaplan–Meier curves and Cox regression analysis as described earlier.

Treatment of missing values and other statistical considerations

For patients indicating no HIV test prior to the cohort registration, we imputed the date of the first positive HIV test by the earliest of the cohort registration date, the date of the first available CD4 count and the date of ART initiation. The covariate 'living alone' was only introduced in the SHCS in April 2000. For patients with missing information at baseline for this covariate, we took the information from the first follow-up visit where information was available. After this process, the variable was still missing in 7% and 4% of patients in the two analysis populations, respectively. Moreover, CD4 cell count at baseline was missing in four (0.2%) patients in group B. Because of the low rate of missing data, we used a single random imputation to complete the datasets.

All reported confidence intervals (CIs) are two-sided 95% CIs. Analyses were performed with SAS 9.1 (SAS Institute, Cary, NC, USA) and R version 2.5.1 (R Foundation for Statistical Computing, Vienna, Austria) [23]. The contributed R packages Mice [24] and Quantreg were used for imputation of missing values and median regression, respectively.

Results

Patient characteristics

A total of 5222 patients had been registered in the SHCS since 1998. To investigate delayed diagnosis of HIV infection, we identified 1915 (37%) of these patients whose first positive HIV test was recorded within 90 days prior to the registration visit or indicated that there hadn't been any earlier HIV tests (group A). Baseline characteristics of these patients are summarized in Table 1. We excluded 3307 patients who entered the SHCS later than 90 days after their HIV diagnosis; 1749 of the excluded patients were ART pre-treated. Included patients were more likely to be male (71% *vs.* 66%) and less likely to be active IV drug users or in an IV drug substitution programme (7% *vs.* 15%) than the other patients.

To investigate late initiation of ART despite cohort follow-up – our second research question – we identified 1730 patients who were treatment-naïve with CD4 cell counts ≥ 200 cells/μL until their second cohort visit (group B). Baseline characteristics of these patients are also summarized in Table 1.

Initial CD4 cell counts for patients registered in the SHCS within 90 days of diagnosis of HIV infection

The first CD4 cell counts were recorded a median of 17 days (quartiles 6–34 days) after the first positive HIV test. Median initial CD4 cell count was 331 cells/μL; 596 (31%) and 201 (10%) of patients had an initial CD4 cell count <200 or <50 cells/μL, respectively. Only 18 additional patients subsequently dropped to CD4 levels <50 cells/μL prior to initiation of ART therapy (Table 1).

Prognostic factors for the initial CD4 cell count estimated with the multiple median regression model are displayed in Table 2. Age significantly affects the initial CD4 cell count ($P<0.001$) and the median initial CD4 cell count was estimated to be 63 cells/μL lower if age was increased by 10 years. Similarly, the median initial CD4 cell count was 111 and 89 cells/μL lower in non-White patients and in patients of sub-Saharan origin, respectively (both $P<0.001$). In contrast, homosexual men and participants in drug programmes or with active IV drug use had significantly higher initial CD4 cell counts of $+55$ cells/μL ($P=0.003$) and $+123$ cells/μL ($P<0.001$), respectively. Living alone was also an independent predictor of higher initial CD4 cell counts ($+29$ cells/μL, $P=0.04$). Modelling the effect of age with a more flexible spline function instead confirmed the linear effect of age over the entire age range

Patients with a prior negative HIV test had a significantly higher initial median CD4 cell count than those without (405 *vs.* 216 cells/μL, $P<0.001$). A prior negative HIV test was not included as a covariate in the multiple regression model because it was correlated strongly with other covariates: for instance, homosexual men and drug users were more likely to have a prior negative test. A logistic regression analysis for late HIV diagnosis (i.e. initial CD4 cell count <200 cells/μL) identified the same predictors, confirming the median regression analysis. In addition, we found slightly lower rates of late diagnosis with increasing year of registration [odds ratio (OR) = 0.96 per + 1 year, CI 0.93–1.00] and female gender (OR = 0.75, CI 0.58–0.98). Women had a similar median CD4 cell count compared to heterosexual men (310 *vs.* 293 cells/μL) but were less likely to have very low CD4 cell counts (<50 cells/μL; 9% *vs.* 15%).

Table 1 Baseline characteristics of 1915 patients registered within 90 days of HIV diagnosis (group A) and of 1730 patients who were treatment-naïve with CD4 cell counts $\geq$200 cells/μL until their second cohort visit after 1998 (group B)

Characteristic*	Group A ($n = 1915$)	Group B ($n = 1730$)
Female gender	561 (29%)	550 (32%)
Age (years) – median (quartiles)	36 (30–43)	35 (30–41)
Ethnicity		
White	1430 (75%)	1395 (81%)
Black	350 (18%)	202 (12%)
Asian	85 (4%)	46 (3%)
Other or unknown	50 (3%)	87 (5%)
Sub-Saharan country of origin	316 (17%)	178 (10%)
Most likely source of HIV infection		
Heterosexual	960 (50%)	678 (39%)
Homosexual	711 (37%)	608 (35%)
IV drug use	145 (8%)	388 (22%)
Other or unknown	99 (5%)	56 (3%)
Earlier documented negative HIV tests	1040 (54%)	964 (56%)
In IV drug substitution programme or active IV drug use†	138 (7%)	324 (19%)
Basic education ($\leq$9 years of mandatory schooling)	523 (27%)	514 (30%)
Receiving psychiatric treatment	115 (6%)	152 (9%)
Living alone	755 (42%)	733 (44%)
Calendar year of registration in the SHCS – median (quartiles)	2002 (1999–2005)	2001 (1998–2004)
First recorded CD4 count (cells/μL) – median (quartiles)	331 (156–535)	540 (400–720)
$<$ 50 cells/μL	201 (10%)	–
50–199 cells/μL	395 (21%)	–
Status		
Reached CD4 $<$ 50 cells/μL while ART-naïve	219 (11%)	26 (2%)
Reached CD4 50–199 cells/μL while ART-naïve	505 (26%)	279 (16%)
Initiated ART with CD4 $\geq$ 200 cells/μL	716 (37%)	514 (30%)
No ART initiation and CD4 $\geq$ 200 cells/μL	475 (25%)	911 (53%)
Number of patients initiating ART (at any time)	1413 (74%)	774 (45%)
CD4 count (cells/μL) at ART initiation – median (quartiles)	207 (101–337)	253 (192–336)

*Determined at baseline, i.e. date of cohort registration (left column) or the later of the cohort registration date and the first cohort visit after 1 January 1998 (right column).
†Only 23/138 and 46/324 patients were not in an IV drug substitution programme.
IV, intravenous; SHCS, Swiss HIV Cohort Study.

Table 2 Prognostic factors for initial CD4 cell count (cells/μL) in 1915 patients registered within 90 days of HIV diagnosis (group A)

	Coefficient	CI	*P*-value
Intercept*	282.60	(249.77, 315.44)	$<$0.001
Age (by + 10 years)	− 63.15	(− 75.80, − 50.50)	$<$0.001
Female gender	23.39	(− 11.25, 58.02)	0.19
Non-White race (but not sub-Saharan origin)	− 111.42	(− 153.78, − 69.07)	$<$0.001
Sub-Saharan origin	− 89.04	(− 127.94, − 50.14)	$<$0.001
Homosexual transmission	54.73	(19.13, 90.32)	0.003
In IV drug substitution programme or active IV drug use	122.73	(57.22, 188.23)	$<$0.001
Basic education	− 12.13	(− 45.25, 20.98)	0.47
Receiving psychiatric treatment	47.51	(− 25.33, 120.35)	0.20
Living alone	28.93	(0.89, 56.97)	0.04
Calendar year of registration in the SHCS (+ 1 year)	3.67	(− 0.92, 8.26)	0.12

*Intercept corresponds to a 40-year-old male patients registered in 2000 with none of the characteristics described by the categorical covariates.
Results based on multiple median regression.
CI, 95% confidence interval; IV, intravenous; SHCS, Swiss HIV Cohort Study.

Outcomes and time to ART initiation for patients registered in the SHCS within 90 days of HIV diagnosis

Clinical outcomes of the 1915 patients are summarized in Table 3. The incidence of Centers for Disease Control (CDC) B and C events within 90 days of HIV diagnosis and overall mortality differed significantly between the groups of patients with first CD4 $<$ 50, 50–199 and $\geq$ 200 cells/μL, respectively. Of the 104 patients with a *Pneumocystis jiroveci* pneumonia, 76 (73%) presented with the infection or developed it within 7 days of HIV diagnosis.

Table 3 Clinical outcomes in 1915 patients registered within 90 days of HIV diagnosis (group A)

	Patients with first CD4 < 50 cells/μL ($n = 201$)	Patients with first CD4 50–199 cells/μL ($n = 395$)	Patients with first CD4 ≥ 200 cells/μL ($n = 1319$)
CDC B and C events before or within 90 days after diagnosis of HIV infection			
CDC B and C events*	177 (88%)	196 (50%)	156 (12%)
CDC C events*	132 (66%)	101 (36%)	50 (4%)
CDC B and C events before or within 90 days after diagnosis of HIV infection with an overall incidence > 5%			
*Candida stomatitis**	106 (53%)	74 (19%)	35 (3%)
Pneumocystis jiroveci pneumonia*	69 (34%)	30 (8%)	5 (0.4%)
Deaths during follow-up			
Number of deaths	19 (9%)	30 (8%)	42 (3%)
Total follow-up duration (patient-years)	823	1654	5026
Death rate per 100 patient-years of follow-up (95% confidence interval)†	2.31 (1.27–3.35)	1.81 (1.16–2.46)	0.84 (0.58–1.09)

*χ^2 test for comparisons between the three groups: $P < 0.001$.
†Log-rank test for comparison between the three groups: $P < 0.001$.
CDC, Centers for Disease Control.

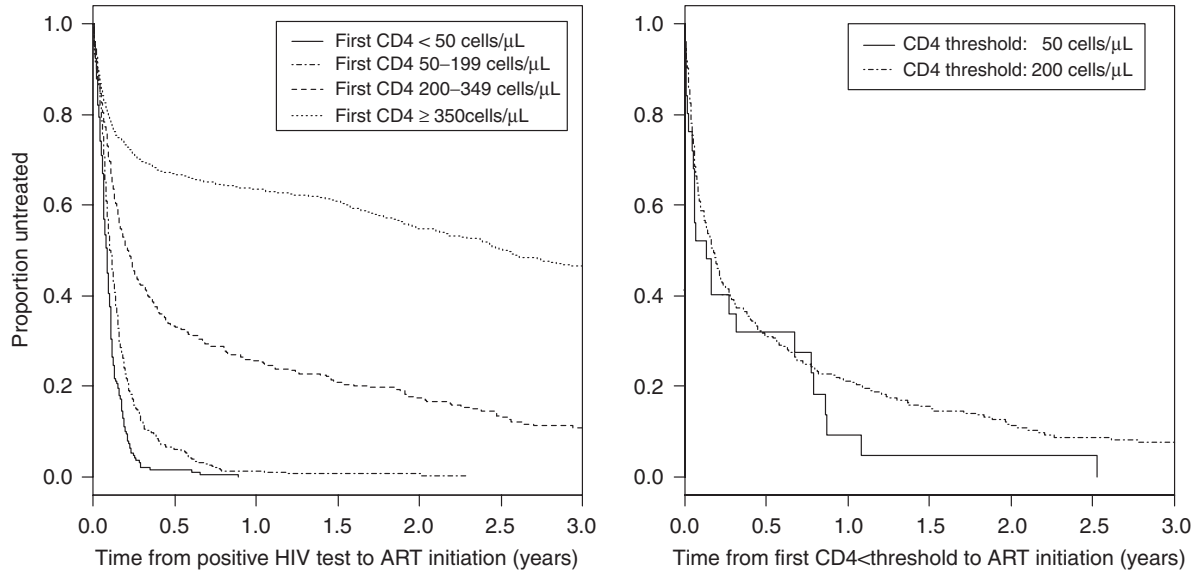

Fig. 1 (a) Time from HIV diagnosis to antiretroviral therapy (ART) initiation for 1915 patients registered within 90 days of their positive HIV test (group A). (b) Time from first CD4 below threshold to ART initiation for 1730 patients who were naïve with CD4 cell counts ≥ 200 cells/μL until their second cohort visit after 1998 (group B). Twenty-six and 305 of the 1730 patients' CD4 counts dropped below 50 and 200 cells/μL, respectively.

ART was initiated in 1413 (74%) patients. Median CD4 cell count at ART initiation was 207 cells/μL. Time from HIV diagnosis to ART initiation, stratified by initial CD4 cell count, is displayed in Fig. 1a. Median time to ART initiation was 30 days and 37 days in patients with initial CD4 < 50 cells/μL and CD4 count of 50–199 cells/μL, respectively; 98% (CI 96–100%) and 94% (CI 91–96%), respectively, were treated within 6 months. In a multiple Cox regression analysis of patients with initial CD4 < 200 cells/μL, homosexual transmission was associated with more timely initiation of ART [hazard ratio (HR) = 1.26, CI 1.01–1.56] whereas higher initial CD4 cell count (HR = 0.63 per + 100 cells/μL, CI 0.54–0.72) and drug programmes or active IV drug use (HR = 0.54, CI 0.31–0.91) were associated with later ART initiation.

Evaluation of late ART initiation during SHCS follow-up

Of the 1730 patients who were ART-naïve with CD4 counts ≥ 200 cells/μL until their second cohort visit, 514 (30%) initiated ART with CD4 ≥ 200 cells/μL; 305 (18%) had a CD4 < 200 cells/μL while ART-naïve (26 of them had a CD4

Table 4 Multinomial logit regression for the 1730 patients who were treatment-naïve with CD4 cell counts ≥ 200 cells/μL until their second cohort visit (group B)

	No ART initiation and no CD4 < 200 cells/μL compared to ART initiation with CD4 ≥ 200 cells/μL			CD4 < 200 cells/μL while ART-naïve compared to ART initiation with CD4 ≥ 200 cells/μL		
	OR	**CI**	***P*-value**	**OR**	**CI**	***P*-value**
Age (by + 10 years)	0.83	(0.73, 0.94)	0.004	1.00	(0.85, 1.17)	0.95
Female gender	0.82	(0.61, 1.10)	0.18	0.85	(0.59, 1.23)	0.39
Non-White race (but not sub-Saharan origin)	1.27	(0.85, 1.91)	0.25	0.71	(0.42. 1.23)	0.23
Sub-Saharan origin	0.85	(0.56, 1.28)	0.42	0.34	(0.18, 0.65)	0.001
Homosexual transmission	0.91	(0.66, 1.26)	0.57	0.73	(0.49, 1.08)	0.12
In IV drug substitution programme or active IV drug use	1.05	(0.74, 1.49)	0.79	1.19	(0.79, 1.79)	0.39
Basic education	0.99	(0.75, 1.29)	0.92	1.09	(0.78, 1.52)	0.61
Receiving psychiatric treatment	1.01	(0.66, 1.56)	0.94	0.97	(0.55, 1.69)	0.91
Living alone	1.16	(0.91, 1.49)	0.23	1.27	(0.94, 1.71)	0.12
Year of baseline visit*	1.32	(1.26, 1.38)	< 0.001	0.96	(0.90, 1.02)	0.15
CD4 count at baseline visit (by + 100 cells/μL)	1.32	(1.26, 1.38)	< 0.001	0.78	(0.71, 0.85)	< 0.001

*Baseline refers to the date of cohort registration or of the first cohort visit after 1 January 1998 (for patients registered prior to 1998).
The regression models the probability of initiating antiretroviral therapy (ART) with a CD4 cell count ≥ 200 cells/μL compared to neither initiating ART nor dropping to CD4 < 200 cells/μL and dropping to CD4 < 200 cells/μL while naïve, respectively.
CI, 95% confidence interval; IV, intravenous; OR, odds ratio (conditional on falling in either of the two categories).

< 50 cells/μL); 911 (53%) neither initiated ART nor had low CD4 cell values (i.e. < 200 cells/μL). In the 26 patients dropping to CD4 < 50 cells/μL while ART-naïve, the median time from the previously recorded CD4 value was 359 days (quartiles 147–951 days), indicating that a majority of these patients had missed physician visits. For 12 of them, this low CD4 cell count was also the first measurement < 200 cells/μL; no other distinctive pattern of this patient group could be identified. A total of 774 (45%) patients initiated treatment; the median CD4 count at ART initiation was 253 cells/μL (Table 1).

Results of the multinomial logistic model for being ART-naïve with CD4 ≥ 200 cells/μL or dropping to CD4 < 200 cells/μL while naïve compared to the baseline category of starting ART with a CD4 ≥ 200 cells/μL are displayed in Table 4. Not surprisingly, patients who neither initiated ART nor dropped to CD4 < 200 cells/μL were younger with higher CD4 cell count at baseline and less follow-up (i.e. later calendar year of baseline visit). Patients with a higher CD4 cell count at baseline (OR = 0.78 by 100 cells/μL higher, CI 0.71–0.85) and those of sub-Saharan origin (OR = 0.34, CI 0.18–0.65) had a lower risk of dropping to CD4 < 200 cells/μL while ART-naïve than others. Indeed, only 15 (8%) of the 178 included patients from sub-Saharan origin dropped to CD4 < 200 cells/μL while naïve and none dropped to CD4 < 50 cells/μL.

Median time from first CD4 < 200 cells/μL to ART initiation in 305 patients was 63 days; 69% (CI 64–74%) were treated within 6 months. In the 26 patients who were ART-naïve until CD4 < 50 cells/μL, median time from that CD4 count until ART initiation was 49 days; 68% (CI 50–85%) were treated within 6 months (Fig. 1b). Twenty-four of the 26 patients initiated ART, one patient died from HIV-related causes without ART initiation and one patient dropped to CD4 < 50 cells/μL in April 2007 and had not yet initiated ART.

The value of the first CD4 cell count below 200 cells/μL independently predicted the time to ART initiation (HR = 0.73 per + 100 cells/μL, CI 0.55–0.98) and so did the calendar year of the drop below 200 cells/μL (HR = 1.13 per + 1 calendar year, CI 1.05–1.20). All other clinical and psychosocial covariates were non-significant, although there were trends that active drug users and patients in IV drug substitution programmes (HR = 0.76, CI 0.54–1.07, $P = 0.11$) as well as women (HR = 0.78, CI 0.57–1.06, $P = 0.11$) took a longer time to initiate ART.

Discussion

In this analysis of a large prospective cohort we investigated late diagnosis of HIV infection and subsequent ART initiation in 1915 patients who entered the SHCS since 1998, all within 3 months of their HIV diagnosis (group A). We further studied late ART initiation during SHCS follow-up in 1730 patients who were treatment-naïve with CD4 cell counts ≥ 200 cells/μL up to their second cohort visit (group B). The principal findings of our study demonstrate that: (i) a considerable number of individuals – 10% and 31% of the study population, respectively – had a CD4 cell count < 50 and < 200 cells/μL at HIV diagnosis; (ii) death rates differed significantly according to initial CD4 cell counts; (iii) low CD4 cell counts at ART initiation and,

particularly, very low CD4 cell counts (<50 cells/μL) without prior ART are predominantly caused by late presentation or missed cohort visits; and (iv) the first CD4 cell count below 200 cells/μL independently predicted the time to ART initiation in both group A and group B.

The substantial rate of patients with low CD4 cell count at diagnosis is in line with data from other countries. For instance, Girardi *et al.* [4] report 24–43% of patients with CD4 < 200 cells/μL at diagnosis in industrialised countries. Homosexual transmission, being in an IV drug substitution programme or active IV drug use and living alone were independently associated with higher initial CD4 cell counts whereas greater age, non-White race and sub-Saharan origin were associated with lower CD4 cell counts. We also found that homosexual men and drug users were more likely to have a prior negative HIV test, which suggests that these patients are more risk-aware and many of them undergo regular HIV testing. The majority of these risk factors confirm results from other studies in different countries [6–9,11–14,16–19]. No previous study investigated the association of living alone. Similarly to homosexual men and IV drug users, patients living alone may have higher risk awareness than patients in a stable partnership, leading to more frequent testing and earlier diagnosis of HIV. In contrast, once HIV is diagnosed, results from the SHCS indicate that a stable partnership is associated with slower progression to AIDS or death in patients receiving highly active antiretroviral therapy (HAART) [25].

A substantial percentage of patients in group A (28%) had a CDC B or C event within 90 days of their first HIV diagnosis. The further follow-up demonstrates again that mortality differed significantly according to initial CD4 cell count. Our results confirm earlier large studies where CD4 cell counts at ART initiation were shown to be the dominant risk factor for progression to AIDS or death [26] but that even late initiation of ART at CD4 < 50 cells/μL still carries quite a good prognosis [19].

This study shows that the drop to low CD4 cell counts before ART initiation is predominantly caused by late presentation or missed cohort visits. This is evidenced by the considerably lower CD4 cell counts at ART initiation in group A compared to group B (median 207 *vs.* 253 cells/μL; lower quartile 101 *vs.* 192 cells/μL). In patients with timely inclusion in the SHCS (i.e. group B), only 26 of 1730 patients did not start ART before their CD4 cell counts dropped below 50 cells/μL during an observation period of almost 10 years. This confirms that the quality of care and the motivation of patients followed in the SHCS are excellent.

In group B patients, we identified a lower CD4 cell count at baseline as a risk factor for dropping to CD4 <200 cells/μL prior to ART initiation. Patients with lower CD4 at baseline (e.g. 220 cells/μL) might be at a higher risk of dropping below 200 cells/μL at a subsequent visit than those with a higher initial CD4 cell count (e.g. 330 cells/μL). Patients of sub-Saharan origin were at higher risk of late HIV diagnosis, but if they entered the SHCS with CD4 > 200 cells/μL they were more likely to initiate ART at higher CD4 cell counts. It could be that these patients, if not diagnosed late, are more likely to follow clinicians' advice to initiate ART. None of the other clinical and psychosocial covariates significantly influenced whether patients dropped to CD4 <200 cells/μL prior to ART initiation or not, suggesting that the care of patients is quite uniform over the entire population.

Our study indicates that patients entering a large prospective cohort with low CD4 counts (<200 cells/μL) commenced ART promptly: median time to ART initiation was 35 days. In comparison, Sabin *et al.* [19] reported a median time to ART uptake of 22 days in 99 patients initiating ART who presented for care for the first time with CD4 < 50 cells/μL. The time from first CD4 < 200 cells/μL during cohort follow-up to ART initiation was slightly longer: it lasted a median of 63 days. This could be partially the result of a selection effect, i.e. an over-representation of patients reluctant to initiate ART despite declining CD4 counts in patient group B. In addition, time from HIV diagnosis to ART initiation could be biased low because patients who initiate ART immediately after HIV diagnosis could be more likely to join the SHCS. We found that time to ART initiation for patients with CD4 at HIV diagnosis <200 cells/μL was significantly shorter in homosexual men but delayed in patients in IV drug substitution programmes and active IV drug users. However, neither of these covariates was significant for time to ART initiation in patients reaching CD4 < 200 cells/μL under regular follow-up in the SHCS, although there was a trend for IV drug users to take longer ($P = 0.11$). This trend may demonstrate that ART is more difficult to initiate in IV drug users, particularly when illicit drug use is ongoing [27].

The main strength of our study is the complementary analysis of reasons for late HIV diagnosis and of risk factor for late ART initiation despite follow-up in the SHCS, which provides a comprehensive picture of the extent of late ART initiation. The additional investigation of time to ART uptake following low CD4 cell counts and associated risk factors are additional strengths.

However, there are also important limitations. Patients who entered the cohort within 3 months of their first positive HIV test differed from patients entering the SHCS at a later stage. For example, they were more likely to be male and less likely to be active IV drug users or in an IV

drug substitution programme, limiting the generalizability of our results on late HIV diagnosis to the entire cohort. An additional weakness is that we cannot distinguish whether patients initiate ART late during follow-up through their own choice or the physician's choice. Finally, while it is excellent news that no more than 26 of the 1730 patients did not start ART before their CD4 cell counts dropped below 50 cells/μL, the low number of patients (26) results in low power of finding predictive factors for identifying this critical patient sub-group.

In conclusion, our study demonstrates that even in a country with unlimited access to healthcare a considerable number of individuals are diagnosed late in their HIV course. In Switzerland, late presentation of HIV is the main reason for the substantial number of patients initiating ART at low CD4 cell counts. The same may hold for other countries in Europe and North America, where the median CD4 at start of ART is low [28]. In view of the marked differences in mortality when comparing late-presenting individuals to those presenting earlier, our results argue in favour of expanded HIV testing [29–31]. These arguments are complemented by our results, which demonstrate that in individuals with timely HIV diagnosis ART is initiated promptly before a further drop of CD4 T-cells. Our results thus strongly support the importance of initiatives like the recent pan-European conference (*HIV in Europe 2007*), which aims to identify political, structural, clinical and social barriers to achieving optimal testing and counselling as well as earlier care for HIV/AIDS.

Evidence is growing that starting ART earlier – at a CD4 count >350 cells/μL – may be associated with better outcomes of HIV- and non-HIV-related conditions such as cancer and hepatitis C virus infection. The efficacy, convenience and tolerability of ART have made substantial progress in recent years; therefore, earlier diagnosis of HIV infection and a stringent follow-up of late presenters are paramount.

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