

CD4 Decline Is Associated With Increased Risk of Cardiovascular Disease, Cancer, and Death in Virally Suppressed Patients With HIV

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Background. The clinical implications of a considerable CD4 decline despite antiretroviral treatment and viral suppression are unknown. We aimed to test the hypothesis that a major CD4 decline could be a marker of cardiovascular disease or undiagnosed cancer.

Methods. Patients with human immunodeficiency virus (HIV) were followed in the Danish nationwide, population-based cohort study in the period 1995–2010 with quarterly CD4 measurements. Associations between a CD4 decline of $\geq 30\%$ and cardiovascular disease, cancer, and death were analyzed using Poisson regression with date of CD4 decline as a time-updated variable.

Results. We followed 2584 virally suppressed HIV patients for 13 369 person-years (PY; median observation time, 4.7 years). Fifty-six patients developed CD4 decline (incidence rate, 4.2/1000 PY [95% confidence interval {CI}, 3.2–5.4]). CD4 counts dropped from a median of 492 cells/ μL to 240 cells/ μL . CD8, CD3, and total lymphocyte counts dropped concomitantly. No HIV-related factors, apart from treatment with didanosine, were associated with CD4 decline. The risk of cardiovascular disease, cancer, and death increased markedly ≤ 6 months after CD4 decline (incidence rate ratio, 11.7 [95% CI, 3.6–37.4] and 13.7 [95% CI, 4.3–43.6], respectively, and mortality rate ratio 4.3 [95% CI, 1.1–17.6]).

Conclusion. A major decline in CD4 count is associated with a marked increased risk of cardiovascular disease, cancer, and death among virally suppressed HIV patients.

Keywords. HIV; mortality; lymphocyte count; cardiovascular disease; cancer.

In untreated human immunodeficiency virus (HIV) infection, CD4 counts decline by 50–70 cells/ μL per year [1, 2]. After initiation of antiretroviral therapy (ART), CD4 counts usually reach normal range within a few years and continue to increase for 7–10 years [3]. However, during follow-up with stable increase, a small proportion of patients experience a considerable CD4 decline despite ART and viral suppression. With the

exception of being a harbinger for Hodgkin lymphoma [4], the clinical significance of such a decrease is unknown.

A CD4 decline may reflect a selective loss of CD4 cells, which is usually the case when the CD4 decline is HIV-related and concomitant viral rebound is observed [5, 6]. Alternatively, a decline in CD4 count can be caused by factors not related to HIV and is then often a decline in total lymphocyte count with a stable CD4/CD8 ratio.

Lymphocyte counts can decline because of increased destruction or apoptosis, decreased production, external loss, or migration of lymphocytes from blood to tissues. Several viral and bacterial infections as well as systemic autoimmune diseases are associated with low lymphocyte counts [7]. Lymphopenia is often present in patients with unstable angina pectoris, myocardial

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infarction, or heart failure, and low lymphocyte counts predict ischemic events and death among patients with acute coronary syndromes [8–10]. Lymphocytes infiltrate solid, malignant tumors, and low lymphocyte counts prior to chemo- or radiotherapy are associated with an adverse prognosis [11].

In the Danish HIV Cohort study (DHCS), patients have been followed prospectively for >15 years with laboratory monitoring every 3 months, which offers a unique opportunity to study associations between CD4 decline and risk of morbidity and mortality.

We hypothesized that a decline in CD4 count in virally suppressed HIV patients may be a marker of cardiovascular disease or undiagnosed cancer. The aim of the present study was to estimate the risk of cardiovascular disease, cancer, and death associated with CD4 cell decline in absence of causative factors such as HIV viremia, immunosuppressive treatment, chemotherapy, or radiotherapy.

METHODS

In a nationwide, population-based cohort study, we followed HIV patients, who were virally suppressed on ART, with serial CD4 measurements and estimated their risk of cardiovascular disease, cancer, and death. The association between CD4 decline and the risk of these outcomes was analyzed using Poisson regression with date of CD4 decline as an time-updated variable. Drug therapy and illnesses around the time of

CD4 decline were assessed through review of medical files, and data on long-term outcomes were retrieved from nationwide registries.

Data Sources

Data were obtained from DHCS, described in detail elsewhere [12]. Viral loads and CD4 counts were measured with intended intervals of 3 months and extracted electronically from laboratory data files. Lymphocyte and CD8 counts were obtained from review of medical files. Data on dates of migration and deaths were obtained from the Danish Civil Registration System [13]. The Danish National Hospital Registry [14] and the Danish Cancer Registry [15] provided information on dates and diagnoses of cardiovascular disease and cancer. Medical files were reviewed to retrieve data on potential causes of CD4 decline.

Study Population

We included all HIV type 1–infected individuals enrolled in DHCS, who (1) were aged ≥ 16 years at time of HIV diagnosis, (2) had initiated ART and achieved viral suppression (viral load [VL] < 400 copies/mL), (3) had a follow-up period with viral suppression of ≥ 8 months, and (4) during the period with viral suppression had ≥ 5 CD4 counts with an interval of ≥ 2 months between measurements. To avoid immortal time bias, date of the fifth CD4 measurement during viral suppression was used as index date (Figure 1). Individuals diagnosed with cancer

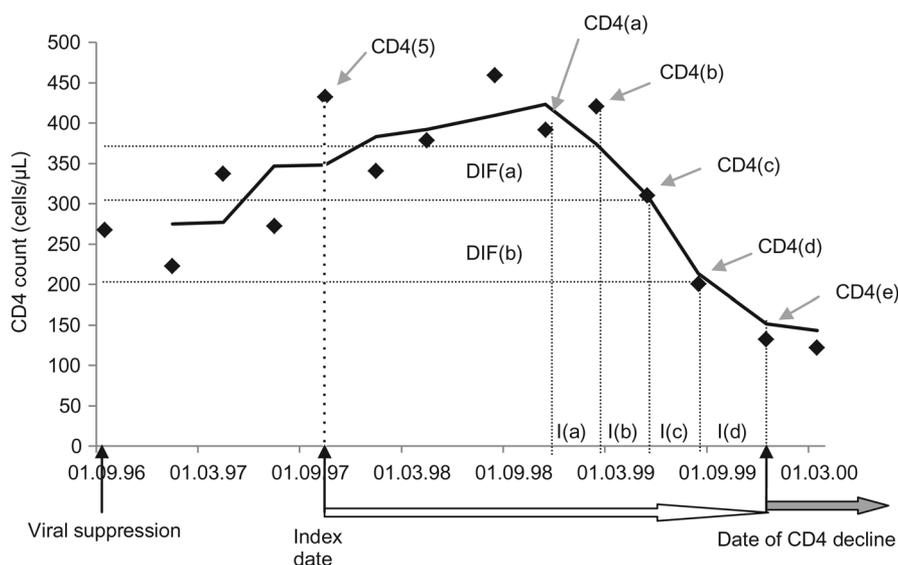


Figure 1. Illustration of the method used to define CD4 decline. The curve represents the moving average; CD4 counts are shown as \blacklozenge . Observation time before and after CD4 decline are marked by \Rightarrow and \Leftarrow , respectively. CD4 decline was defined as 2 consecutive relative CD4 changes of less than or equal to -15% , calculated using the following formula: $\text{relative CD4 change(a)} = (100 \times \text{DIF(a)}/\text{CD4(a)}) / (I(a) + I(b) + I(c))$, where I is the time interval between 2 CD4 measurements and $\text{DIF(a)} = \text{moving average(a)} - \text{moving average(b)}$; $\text{moving average(a)} = (\text{CD4(a)} + \text{CD4(b)} + \text{CD4(c)})/3$; $\text{moving average(b)} = (\text{CD4(b)} + \text{CD4(c)} + \text{CD4(d)})/3$. Abbreviation: DIF, difference between 2 consecutive moving averages.

prior to the index date and those with CD4 decline due to treatment with interferon for hepatitis C virus (HCV) infection were excluded.

CD4 Decline

To minimize the effect of random variations in CD4 counts, moving averages of 3 CD4 counts were analyzed rather than single measurements. Relative differences in CD4 counts by time interval were analyzed. CD4 decline was defined as 2 consecutive declines in moving average of $\geq 15\%$ (Figure 1). Estimates of CD4 decline included 5 single CD4 counts and a time interval of at least 8 months. Date of CD4 decline was defined as the date of the last CD4 measurement in the second of 2 consecutive moving averages with a decline of $\geq 15\%$. In the sensitivity analyses, we changed the definition of CD4 decline to 2 consecutive declines in moving average of $\geq 10\%$.

Outcomes

Outcomes were time to first inpatient admission or outpatient visit with a diagnosis of cardiovascular disease or cancer. Diagnoses were coded according to the *International Classification of Diseases, 10th Revision (ICD-10)*. Cardiovascular disease was defined as ICD-10 codes I20–I25 or I60–I69, and cancer was defined as ICD-10 codes C00–C97.

Statistical Analysis

Time was calculated from index date until date of study outcome, the second of 2 consecutive VL ≥ 400 copies/mL, 1 VL ≥ 4000 copies/mL, 365 days after the last VL or CD4 measurement, emigration, death, or 1 January 2010, whichever came first.

Factors associated with CD4 decline as well as incidence rate ratio (IRR) and mortality rate ratio (MRR) were estimated using Poisson regression analysis with date of CD4 decline included as a time-updated variable. The following variables were included in the model: sex, origin (Danish, African, Asian, or other), route of HIV transmission (homosexual, heterosexual, injection drug use, or other), time from HIV diagnosis to viral suppression, AIDS prior to the period of viral suppression, HCV coinfection (HCV RNA positive/negative), and CD4 count at baseline. Age was included as a time-updated variable with 2-year intervals.

Time of exposure to each antiretroviral drug (ARV) within the study period was calculated, acknowledging treatment switches and discontinuations. The relative risk of CD4 decline during exposure versus nonexposure to individual ARVs was estimated using Poisson regression analyses adjusted for the confounders mentioned above.

The study was approved by the Danish Data Protection Agency. SPSS statistical software, version 15.0 (Norusis; SPSS

Inc, Chicago, Illinois) and Stata, version 8.0 (StataCorp, College Station, Texas), were used for data analysis.

RESULTS

A total of 2584 individuals fulfilled the inclusion criteria (Figure 2) and were followed for a total of 13 389 person-years (PY); the median observation time was 4.7 years (interquartile range [IQR], 1.8–8.2 years). The majority of participants were male (75%), 47% were homosexual, and median age at baseline was 41 years (Table 1). Individuals with CD4 decline during follow-up were similar to those with a stable or increasing CD4 count, apart from a higher proportion of injection drug users and HCV-coinfected persons. The median year of HIV diagnosis was 1994 versus 1997, and the time period from HIV diagnosis to viral suppression and follow-up time was longer among individuals with a CD4 decline. A total of 55 521 CD4 measurements were included in the analyses (median CD4 count, 500 cells/ μL [IQR, 340–700 cells/ μL]).

CD4 Decline

A total of 56 individuals experienced considerable CD4 decline, as defined above (incidence rate [IR], 4.2/1000 PY [95% confidence interval {CI}, 3.2–5.4]). All of these individuals had concomitant decline of lymphocytes and CD3 count, and the CD4/CD8 ratio did not change (Table 2). The median time from viral suppression to CD4 decline was 2.9 years (IQR, 1.5–6.5 years). In the multivariate analysis neither sex, age, origin, route of HIV transmission, year of diagnosis, CD4 at baseline, AIDS at baseline, time from HIV diagnosis to viral suppression, or HCV were associated with risk of CD4 decline.

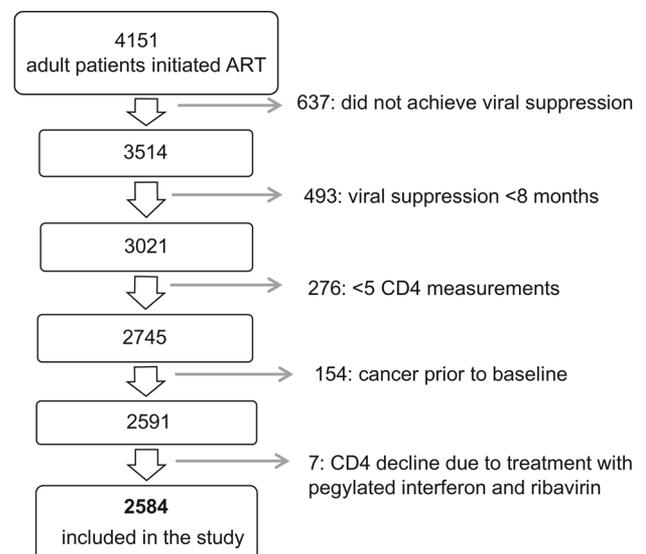


Figure 2. Study profile. Abbreviation: ART, antiretroviral therapy.

Table 1. Characteristics of the Study Population

Characteristic	Total	CD4 Decline	
		No	Yes
No.	2584	2528	56
Total observation time, y	13 369	13 007	362
Observation time, y ^a	4.7 (1.8–8.2)	4.6 (1.7–8.2)	6.8 (3.1–9.4)
No. of CD4 counts ^a	24 (15–33)	24 (15–33)	29 (22–35)
Interval between CD4 counts, d ^a	98 (86–119)	98 (86–119)	95 (84–111)
Male sex	1935 (74.9)	1894 (74.9)	41 (73.2)
Age at baseline, y ^a	41 (34–48)	41 (34–48)	43 (36–49)
Origin			
Danish	1834 (71.0)	1797 (71.1)	37 (66.1)
African	363 (14.0)	356 (14.1)	7 (12.5)
Asian	150 (5.8)	146 (5.8)	4 (7.1)
Other	237 (9.2)	229 (9.1)	8 (14.3)
Route of infection			
Homosexual	1220 (47.2)	1198 (47.4)	22 (39.3)
Heterosexual	1062 (41.1)	1039 (41.1)	23 (41.1)
IDU	170 (6.6)	162 (6.4)	8 (14.3)
Other	132 (5.1)	129 (5.1)	3 (5.4)
Year of HIV diagnosis ^a	1998 (1992–2002)	1998 (1992–2002)	1994 (1989–1999)
Nadir CD4, cells/ μ L ^a	260 (130–402)	260 (130–400)	266 (128–435)
CD4 at baseline, cells/ μ L ^a	298 (180–420)	298 (180–420)	303 (138–431)
AIDS at baseline	540 (20.9)	528 (20.9)	11 (19.6)
Time from HIV diagnosis to viral suppression ^a , mo	29 (5–92)	28 (5–90)	62 (10–117)
HCV RNA positive	224 (8.7)	214 (8.5)	9 (16.1)

Data are presented as No. (%) unless otherwise specified.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use.

^a Median (interquartile range).

Antiretroviral Drugs

Didanosine was the only one of 13 ARVs analyzed to be associated with CD4 decline (IRR, 2.0 [95% CI, 1.0–3.7]; [Supplementary Table 1](#)). Ten patients received a combination of

didanosine and tenofovir at baseline; none of these individuals experienced CD4 decline.

Morbidity

At time of CD4 decline, 2 patients had pulmonary tuberculosis, 1 had syphilis, and 1 had sarcoidosis. No patients developed AIDS after CD4 decline. The risk of cardiovascular disease and cancer was markedly increased ≤ 6 months after CD4 decline (IRR, 11.7, [95% CI, 3.6–37.4] and 13.7 [95% CI, 4.3–43.6], respectively; [Table 3](#)). The incidence per 10 000 PY of Hodgkin lymphoma was 1.5 (95% CI, .4–6.1) before and 98.5 (95% CI, 24.6–394) ≤ 6 months after CD4 decline. Despite relatively high CD4 counts in the study population, IRs of cancers, which have been associated with viral infection and immunodeficiency, were high ([Table 4](#)).

Two of 8 patients diagnosed with cardiovascular disease and 1 of 6 patients diagnosed with cancer after CD4 decline died within the study period. Among the 56 patients with CD4 decline, 34 were alive and had not been diagnosed with cardiovascular disease, cancer, or other illness, which have been

Table 2. CD4, CD8, and CD3 Counts Before and at Date of Meeting the Definition of CD4 Decline

	Before CD4 Decline ^a , Median (IQR)	Date of CD4 Decline, Median (IQR)
CD4 count, cells/ μ L	492 (320–720)	240 (150–350)
CD8 count, cells/ μ L	990 (610–1408)	562 (357–870)
CD4/CD8 ratio	0.5 (0.3–0.7)	0.4 (0.3–0.7)
CD3 count, cells/ μ L	1580 (926–2380)	890 (607–1319)
Lymphocyte count, 10^9 /L	1.8 (1.5–2.7)	1.1 (0.7–1.5)

Abbreviation: IQR, interquartile range.

^a The first CD4 count included in the analysis of CD4 change, eg, the fourth CD4 count prior to meeting the definition of CD4 decline.

Table 3. Cardiovascular Disease, Cancer and Mortality Before and After CD4 Decline

State	CD4 Decline	Events or Deaths, No.	IR/1000 PY (95% CI)	IRR or MRR ^a (95% CI)	
				Unadjusted	Adjusted
Morbidity					
CVD	No./before	112	8.9 (7.4–10.7)	1.0	1.0
	<6 mo after	3	132.3 (42.7–410.3)	14.8 (4.7–46.7)	11.7 (3.6–37.4)
	≥6 mo after	4	26.5 (10.0–70.7)	3.0 (1.1–8.1)	2.7 (1.0–7.5)
Cancer	No./before	87	6.6 (5.4–8.2)	1.0	1.0
	<6 mo after	3	115.8 (37.4–359.1)	17.5 (5.5–55.4)	13.7 (4.3–43.6)
	≥6 mo after	3	17.0 (5.5–52.7)	2.6 (.8–8.1)	2.2 (.7–7.2)
Mortality					
All	No./before	138	10.5 (8.9–12.4)	1.0	1.0
	<6 mo after	2	77.2 (19.3–309)	7.4 (1.8–29.7)	4.3 (1.1–17.6)
	≥6 mo after	7	39.6 (18.9–83.1)	3.8 (1.8–8.1)	1.8 (.8–4.1)
HCV negative ^b	No./before	112	9.2 (7.6–11.1)	1.0	1.0
	<6 mo after	2	92.5 (23.1–397)	10.0 (2.5–40.7)	7.0 (1.7–28.6)
	≥6 mo after	4	31.5 (11.8–84.0)	3.4 (1.3–9.3)	2.6 (1.0–7.2)
Baseline CD4 ≥200 cells/μL	No./before	91	10.1 (8.2–12.4)	1.0	1.0
	<6 mo after	1	62.1 (8.7–441)	6.2 (.9–44.1)	5.5 (.8–39.6)
	≥6 mo after	3	27.6 (8.9–85.6)	2.7 (.9–8.6)	1.6 (.5–5.5)
Baseline CD4 <200 cells/μL	No./before	47	11.3 (8.5–15.1)	1.0	1.0
	<6 mo after	1	102 (14.4–725)	9.0 (1.2–65.3)	3.6 (.5–26.9)
	≥6 mo after	4	58.9 (22.1–157)	5.2 (1.9–14.4)	2.3 (.7–7.1)

Mortality was analyzed in the complete study population and in individuals without hepatitis C and stratified on baseline CD4 count. Analysis was adjusted for sex, origin, route of human immunodeficiency virus (HIV) transmission, time from HIV diagnosis to viral suppression, AIDS prior to the period of viral suppression, hepatitis C, and CD4 count at baseline.

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HCV, hepatitis C virus; IR, incidence rate; IRR, incidence rate ratio; MRR, mortality rate ratio; PY, person-years.

^a IRR for morbidity; MRR for mortality.

^b HCV negative: polymerase chain reaction for hepatitis C RNA negative.

documented to be associated with CD4 decline, at the end of follow-up.

Mortality

Mortality rates were substantially increased ≤6 months after CD4 decline (MRR, 4.3 [95% CI, 1.1–17.6]) and moderately increased thereafter (MRR, 1.8 [95% CI, .8–4.1]; Table 3). The association was stronger among individuals without HCV coinfection (MRR, 7.0 [95% CI, 1.7–28.6] ≤6 months and 2.6 [95% CI, 1.0–7.2] >6 months after CD4 decline). Analysis stratified by baseline CD4 count yielded similar results. Mortality rates were very high (102/1000 PY [95% CI, 14.4–725]) ≤6 months after CD4 decline among individuals with baseline CD4 <200 cells/μL, but MRRs did not differ significantly by baseline CD4 count. Estimates in the unadjusted analysis changed markedly after adjustment for age and route of HIV infection, whereas other confounders included in the analysis only changed the estimates marginally.

Sensitivity Analyses

The exclusion of 4 individuals diagnosed with conditions known to be associated with CD4 decline from the analysis yielded similar results (data not shown). When CD4 decline was defined as 2 consecutive drops in CD4 of 10% instead of 15%, 209 patients met the definition of CD4 decline, which was still associated with increased risk of cardiovascular disease, cancer, and death, but not to the same extent (IRR, 1.8 [95% CI, 1.1–3.0]; 2.3 [95% CI, 1.3–3.8]; and 2.2 [95% CI, 1.4–3.4], respectively). Using the drop in CD4 of 10% 19 patients were diagnosed with cardiovascular disease and 17 with cancer, and 26 died after CD4 decline.

DISCUSSION

We longitudinally followed CD4 trajectories in HIV patients with stable viral suppression over a median period of 4.7 years, and found that a considerable drop in CD4 count, in absence of

Table 4. Cancers Diagnosed During Follow-up

Type of Cancer	No. Before CD4 Decline	After CD4 Decline	Total	IR/10 000 PY (95% CI)
Non-Hodgkin lymphoma	10		10	7.5 (4.0–13.9)
Hodgkin lymphoma	2	2	4	3.0 (1.1–8.0)
Kaposi sarcoma	2		2	1.5 (.4–6.0)
Head and neck	10		10	7.5 (4.0–13.9)
Lung	13	1	14	10.5 (6.2–17.7)
Esophagus	3		3	2.2 (.7–7.0)
Colon/rectum	6		6	4.5 (2.0–10.0)
Anal	12	1	13	9.7 (5.7–16.8)
Hepatocellular carcinoma	3		3	2.2 (.7–7.0)
Cervical	2		2	6.2 (1.6–24.7) ^a
Breast	3	1	4	12.4 (4.6–33.0) ^a
Penis	3		4	4.0 (1.5–10.5) ^b
Prostate	1		1	1.0 (.2–7.0) ^b
Testis	3		3	3.0 (1.0–9.2) ^b
Brain	3		3	2.2 (.7–7.0)
Thyroid		1	1	0.8 (.1–5.3)
Malignant melanoma	3		3	2.2 (.7–7.0)
Other	2		2	1.5 (.4–6.0)
Unknown primary	6		6	4.5 (2.0–10.0)

Abbreviations: CI, confidence interval; IR, incidence rate; PY, person-years.

^aAmong females.

^bAmong males.

immunosuppressive drugs, radiotherapy, or chemotherapy, was associated with marked increased risk of cardiovascular disease, cancer, and death.

There are some limitations of the study. Lymphocyte, CD3, and CD8 counts were not available from electronic laboratory databases and were retrieved from the medical files of the patients with CD4 decline. It was not feasible to retrieve these data for the complete study population. However, patients with CD4 decline had a concomitant drop in lymphocyte, CD3, and CD8 counts and thus the CD4 decline was a reflection of decreasing lymphocyte counts. The small number of endpoints did not allow detailed analysis of different types of cancer. Strengths of the study include the population-based, nationwide design, the almost complete follow-up, and the use of nationwide registries, which leaves few study outcomes undetected. Furthermore, the study of a large cohort with a relatively high morbidity and mortality rate offers a unique opportunity to study the predictive value of changes in CD4 counts. The study population was followed for several years with CD4 counts measured prospectively at 3-month intervals.

In HIV-negative patients with prevalent heart disease, low lymphocyte counts predict risk of ischemic events and

death [10]. We found that among HIV-infected individuals without a prior diagnosis of heart disease, the risk of developing cardiovascular disease increased >10-fold within the first 6 months after CD4 decline. The short time interval suggests that the observed association was not explained by immunodeficiency causing cardiovascular disease, but rather that CD4 decline could be a marker of inflammation or unstable atherosclerotic plaques.

Bohlius et al documented that in HIV patients CD4 counts drop prior to diagnosis of Hodgkin lymphoma [4], but whether this is specific for Hodgkin lymphoma or also occurs in other cancers has not been established. We found a significant decline in CD4 count ≤ 6 months before diagnosis in 2 of 6 patients with Hodgkin lymphoma. There was a high risk of a cancer diagnosis ≤ 6 months after CD4 decline and a nonsignificant increase in risk thereafter, suggesting that the CD4 decline was a consequence and not a cause of cancer. CD4 counts might have dropped because of migration of lymphocytes from blood to malignant tumors, but our data do not indicate that a large drop in CD4 counts is common prior to diagnosis of cancers other than Hodgkin lymphoma.

The prognostic value of CD4 count for risk of death has been studied extensively in HIV patients. Nadir CD4 count, CD4 increase after treatment initiation, and the most recent CD4 count are all independently associated with mortality [16–18]. However, none of these studies have addressed the significance of a sustained major drop in CD4 count. We found an increased risk of death after CD4 decline among virally suppressed individuals. The relative risk of death did not significantly differ by baseline CD4 count, and only 1 death occurring after CD4 decline could be related to an infection (HCV). When excluding individuals with HCV coinfection, who in this cohort are predominantly injection drug users and have high mortality due to accidents, injuries, and drug toxicity/overdose [19], the estimate of the risk associated with CD4 decline was even higher.

Whether our findings can be generalized to HIV-negative individuals is uncertain. On one hand, we did not find any association between CD4 decline and HIV-related factors, apart from exposure to didanosine, a drug now rarely used, which has previously been shown to be associated with CD4 decline [20]. Furthermore, apart from HCV, few patients had infections such as syphilis or tuberculosis, which are common among HIV patients and have been associated with CD4 decline [21, 22]. On the other hand, despite CD4 counts within the normal range, the immune system of well-treated HIV patients may have a reduced capacity to respond to stressors, thus paving the way for lymphopenia.

Risk factors and biomarkers for cardiovascular disease are quite similar between HIV-infected and HIV-negative individuals [23], and the observed association between CD4/

lymphocyte decline and cardiovascular disease could potentially apply to the general population. With respect to cancer, it is less likely that our findings are generalizable to the general population, as the distribution of cancers was different from what is observed in the general population. Both among patients with and without CD4 decline, cancers thought to be related to viral infections such as Epstein-Barr virus, human herpesvirus 8, human papillomavirus, HCV, and hepatitis B virus (eg, lymphoma, Kaposi sarcoma, head and neck cancer, anal cancer, cervical cancer, and hepatocellular carcinoma) were relatively common. Both previous immunodeficiency and behavioral factors may explain the high prevalence of these cancers among HIV-infected individuals.

To our knowledge, the clinical implications of a major CD4 decline among HIV patients have not been studied before, and the optimal definition of CD4 decline as prognostic marker has not been defined. We formulated a definition of CD4 decline to establish objective criteria for the study and chose a strict definition to reduce “noise” due to random variations in CD4 counts. Results of this study need to be confirmed in other cohorts. We performed a sensitivity analysis employing a less strict definition, and when using this definition, we identified a higher number of patients who developed cardiovascular disease and cancer after CD4 decline, but the relative risk associated with CD4 decline decreased.

We conclude that in virally suppressed HIV patients, an unexplained, major decline in CD4 count is associated with a markedly increased risk of cardiovascular disease, cancer, and death. The association between CD4 decline and adverse prognosis may not be specific for HIV-infected individuals, and analysis of changes in total lymphocyte counts may reveal similar associations. This could be explored in other populations in whom regular monitoring of lymphocyte counts is performed.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. All of the authors contributed to the conception and design of the study, as well as to analyses and interpretation of data.

The manuscript was drafted by M. H., J. G., and N. O. and was critically reviewed and subsequently approved by all authors.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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