

Immunodeficiency as a Risk Factor for Non-AIDS-Defining Malignancies in HIV-1-Infected Patients Receiving Combination Antiretroviral Therapy

Anouk Kesselring,¹ Luuk Gras,¹ Colette Smit,¹ Gitte van Twillert,² Annelies Verbon,³ Frank de Wolf,¹ Peter Reiss,^{4,5} and Ferdinand Wit^{4,5}

¹HIV Monitoring Foundation, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; ²Department of Internal Medicine, Medical Center, Alkmaar; ³Department of Internal Medicine, Erasmus Medical Center, Rotterdam; ⁴Center for Poverty-Related Communicable Diseases, Amsterdam, the Netherlands; and ⁵Department of Internal Medicine, Subdivision Infectious Diseases Tropical Medicine and AIDS, Amsterdam Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Background. The aim of this study was to investigate the association between immunodeficiency, viremia, and non-AIDS-defining malignancies (NADM).

Methods. Patients starting combination antiretroviral therapy (cART) as of 1 January 1996 were selected from the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. In Cox models, risk factors for NADM were investigated. These included age, sex, transmission route, smoking, alcohol abuse, prior AIDS diagnosis, duration of exposure to cART, and estimated duration of human immunodeficiency virus infection. CD4⁺ cell count and viral load (VL) were considered as time-updated variables and as measures of cumulative exposure to CD4⁺ cell counts of <200, <350, or <500 cells/mm³ and detectable VL >50, >400, and >1000 copies/mL, respectively.

Results. In a cohort of 11,459 patients, 236 NADMs were diagnosed; 102 were caused by infection, and 134 were attributable to other causes. Median CD4⁺ cell count at NADM diagnosis was 340 cells/mm³ (range, 210–540 cells/mm³). Median time to first NADM after starting cART was 5.0 years (range, 2.2–8.2 years). In multivariate models, cumulative exposure to CD4⁺ cell counts <200 cells/mm³ remained significant (hazard ratio [HR], 1.12; range, 1.03–1.22) for each additional year of exposure. In stratified analyses, cumulative exposure to CD4⁺ cell counts <200 cells/mm³ was associated with malignancies possibly caused by infection (HR, 1.16; range, 1.03–1.31) but was not associated with other types of cancers. No significant effect of viremia was seen in either type of cancer.

Conclusions. Cumulative exposure to CD4⁺ cell counts <200 cells/mm³ during cART was associated with an increased risk of infection-related non-AIDS-defining malignancies.

Since the introduction of combination antiretroviral therapy (cART), the incidence of AIDS-defining infections and malignancies has decreased markedly [1–3]. Conversely, the incidence and proportion of deaths

related to non-AIDS-related malignancies and other non-AIDS events are increasing among patients with human immunodeficiency virus type 1 (HIV-1) infection in industrialized nations in the cART era. Both increased life expectancy [4] and the reduction of competing causes of death are contributing to the increased incidence in non-AIDS-related malignancies [5, 6]. In addition, patients with HIV infection may have increased rates of high-risk behaviors, such as tobacco use [1], that contribute to cancer development. Limited data are available about the relationship of immunodeficiency, viremia, and exposure to (specific) antiretroviral agents to the risk for non-AIDS-related malignancies [7–9]. The use of nonnucleoside reverse-

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Correspondence: Anouk Kesselring, MD, HIV Monitoring Foundation, Academic Medical Center, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands (a.m.kesselring@amc.uva.nl).

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transcriptase inhibitors (NNRTIs) has been linked to an increased incidence of non-AIDS-defining malignancies (in particular, Hodgkin lymphoma) [10]. In contrast, protease inhibitors (PIs) can affect important cellular and tissue processes, and they thereby can potentially reduce the risk of Kaposi sarcoma and some types of non-Hodgkin lymphomas [11].

Furthermore, HIV itself may play a role in the onset of cancer, either by a direct oncogenic effect (eg, by the HIV *tat* gene) [12] or as a consequence of immune suppression. Uncontrolled HIV viremia has been linked to a greater risk of both AIDS-defining and non-AIDS-defining diseases [13–16]. Although the incidence of AIDS-defining cancers, notably Kaposi's sarcoma, non-Hodgkin lymphoma, and invasive cervical carcinoma, has decreased markedly in the cART era as a result of improved immune function in patients with HIV infection [3], the relationship between immune status and the incidence of non-AIDS-defining malignancies may be different when considering particular types of cancer [17–20]. Furthermore, chronic viral coinfections, such as infections due to hepatitis B and C virus, Epstein-Barr virus, and human papillomavirus, are prevalent in HIV-1-infected patients and may contribute to the development of cancer [21–23]. Malignancies that develop in immunodeficient patients are often associated with chronic viral coinfection [17, 18].

The aim of our study was to further explore the role of cART, immunodeficiency, and HIV viremia in the treated HIV-infected population as risk factors for non-AIDS-defining malignancies, while adjusting for traditional risk factors.

METHODS

Data Collection

The observational AIDS Therapy Evaluation in the Netherlands (ATHENA) follows HIV-positive patients who are registered in 1 of the 25 designated treatment centers in the Netherlands. Clinical data for patients who have decided not to opt out is anonymously recorded in a central database that is maintained by Stichting HIV Monitoring [24]. The ATHENA database includes information on patient demographic characteristics, immunological and virological parameters, detailed treatment data, data on adverse events, and AIDS-defining and selected non-AIDS-defining clinical events. Alcohol abuse (>28 glasses per week for men and >21 glasses per week for women) was recorded when reported by the treating physician. Information on the patients' tobacco use (having a history of smoking, no amount specified) was collected from the ATHENA cohort for those who were also participating in the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study [25, first and second enrollment]. Additionally, since 1 January 2008, detailed

data on tobacco and alcohol use has been prospectively collected for all new patients entered into ATHENA.

Definitions

cART was defined as the concomitant use of a PI or NNRTI plus 2 nucleoside/tide reverse-transcriptase inhibitors (NRTIs). Chronic hepatitis B virus (HBV) infection was defined by test results positive for the presence of HBV surface antigen. Chronic hepatitis C virus (HCV) infection was defined by test results positive for the presence of HCV RNA or, if HCV RNA was missing, by the presence of HCV-positive antibodies. Sensitivity analyses were performed defining HCV infection present in those with plasma samples positive for HCV RNA, regardless of HCV-negative antibody status. Cancers defined as possibly related to an infectious agent were anal, vulvar, laryngeal, and esophageal cancers (associated with human papillomavirus, although this is still a controversial issue); hepatocellular carcinoma (associated with HBV or HCV); Hodgkin lymphoma (associated with Epstein-Barr virus); and gastric cancer (associated with *Helicobacter pylori*) [18]. No biomarkers to detect Epstein-Barr virus, human papillomavirus, or *H. pylori* for validation of these associations were available in our database.

Study Population

The study included treatment-naïve and HIV-1-infected patients with prior mono or dual exposure to NRTIs who were >16 years of age and had started cART after 1 January 1996. Follow-up was started at cART initiation and ended at the date of the last available CD4+ cell count or HIV RNA measurement after the start of cART or 1 February 2009, whichever occurred first.

Case Finding

Non-AIDS-defining malignancies that occurred after the initiation of cART were considered as endpoints. Although pathology reports are not routinely collected in ATHENA, histological confirmation of malignancies is part of the standard clinical practice in the Netherlands. AIDS-defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer), precancerous stages of non-AIDS-defining malignancies, basal-cell carcinoma, and squamous-cell carcinoma of the skin were not included in the data analyses, according to the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study protocol for collecting non-AIDS-defining malignancies [26].

Statistical Analysis

Cox proportional hazards models were used to investigate time to diagnosis of a first non-AIDS-defining malignancy. CD4+ cell counts and HIV RNA measurements were time-updated every 3 months. If CD4+ cell counts or HIV RNA measure-

ments were missing, the previous observation was carried forward.

Potential confounders that were investigated in the models were sex, region of origin, mode of HIV acquisition, nadir CD4+ cell count, CD4+ cell count at start cART, AIDS prior to starting cART, alcohol abuse, having a history of smoking, estimated duration of HIV infection prior to the start of cART, and chronic HBV/HCV coinfection. Age and exposure to cART were included in the models as time-updated variables. Exposure to cART was modeled as the cumulative exposure to PIs, NNRTIs, and NRTIs. Immunodeficiency was taken into account as the latest CD4+ cell count and as cumulative exposure to CD4+ cell counts below certain thresholds (<200, <350, and <500 cells/mm³). Additionally, the latest CD4+ cell count was recorded with a 6-month lag time to be certain that the observed count was measured prior to diagnosis and prior to subsequent treatment of a malignancy to rule out immunosuppressive effects of chemotherapy or radiation therapy [27] and to rule out secondary immunodeficiency due to a malignancy in the period prior to diagnosis [28]. Viremia was similarly investigated as the latest viral load noted with a 6-month lag time and as cumulative time of viremia >50, >400, and >1000 copies/mL. Paired Student *t* tests were used to investigate changes in CD4+ cell count in the months before the diagnosis of a non-AIDS-defining malignancy in patients with a non-AIDS-related malignancy. All analyses were performed with SAS, version 9.1 (SAS Institute).

RESULTS

Patient Characteristics

In total, 11,459 patients were selected, most of whom were men who have sex with men (MSM) and were from Western Europe. Of the total number, 20% had received mono or dual treatment prior to cART, and 27% had received a diagnosis of AIDS prior to cART initiation. Rates of chronic HBV and HCV infection were low (5% and 6%, respectively), and only a small proportion of patients were infected through intravenous drug use (5%). Sixty-eight percent of HCV infection diagnoses were based on detection of HCV RNA. Information on tobacco use was available for 8508 patients (74%), of whom 6552 (57%) had ever smoked. Alcohol abuse was reported in 7% of patients (Table 1). Follow-up time was 67,179 person-years (PY), with a median duration of follow-up of 5.5 years (interquartile range [IQR], 2.2–8.3 years). The median time duration of cART was 4.8 years (IQR, 1.9–8.2 years). Patients with HIV-1 RNA levels \geq 400 copies/mL contributed one-fifth (13,971 PY) of the total follow-up time.

Although the majority of patients had suppressed viral loads (76%; Table 2), CD4+ cell counts decreased significantly in the 6 months prior to diagnosis (patients overall, 29 cells/mm³

Table 1. Characteristics of 11,459 Patients Infected with Human Immunodeficiency Virus (HIV) at the Start of Combination Antiretroviral Therapy (cART) in the Netherlands

Variable	Patients (n= 11459)
Male sex	8816 (77)
Age, median years (IQR)	38 (32–45)
CDC-C prior to start cART	3079 (27)
HIV RNA load at start cART, median log ₁₀ copies/mL (IQR)	4.9 (4.3–5.3)
CD4+ cell count at the start cART, median cells/mm ³ (IQR)	150 (55–240)
Prior monotherapy/dual therapy with NRTI	2240 (20)
Country of origin	
Europe/United States/Australia	7250 (63)
Other	4209 (37)
HIV transmission category	
MSM	6003 (52)
Heterosexual sex	3958 (35)
Intravenous drug user	541 (5)
Other	957 (8)
HBV status ^a	
Negative	10116 (88)
Positive	531 (5)
Unknown	812 (7)
HCV status ^b	
Negative	9401 (82)
Positive	561 (5)
Unknown	1497 (13)
Alcohol abuse	797 (7)
Tobacco use	
Ever	6552 (57)
Never	1956 (17)
Missing	2951 (26)

NOTE. Data are no. (%) of patients, unless otherwise indicated. CDC-C, Centers for Disease Control C event; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; MSM, men who have sex with men; NRTI, nucleoside reverse-transcriptase inhibitor.

^a Chronic hepatitis B virus infection was defined as test results positive for hepatitis B surface antigen.

^b Chronic hepatitis C virus infection was defined as plasma samples positive for HCV RNA or HCV-positive antibodies in case HCV RNA data were missing; 68% of diagnoses of hepatitis C were based on the presence of HCV RNA in plasma samples.

[*P* = .03]; patients with viral suppression, 36 cells/mm³ [*P* = .02]).

Non-AIDS-Related Malignancies

Of 11,459 patients, 231 received a diagnosis during follow-up. A total of 236 non-AIDS-defining malignancies were diagnosed; 102 (43%) of these cancers were potentially related to an infectious cause, and 134 (57%) were not related to infection. Of the 102 patients with cancer that had a possible infectious cause, 37 had anal cancer, 21 had laryngeal cancer, 16 had hepatocellular cancer, 20 had Hodgkin's lymphoma, 3 had esophageal cancer, 1 had gastric cancer, and 4 had vulvar cancer. Cancers

Table 2. Characteristics of Human Immunodeficiency Virus Type 1 (HIV-1)-Infected Patients with a Diagnosis of Non-AIDS-Related Malignancy in the Netherlands

Variable	All malignancies (<i>n</i> = 231)	Infection related (<i>n</i> = 101)	Not infection related (<i>n</i> = 130)
Age at diagnosis, median years (IQR)	49(43–55)	49 (43–55)	50 (43–59)
Male sex	199 (86)	89 (88)	110 (85)
Monotherapy/dual-therapy with NRTI prior to cART	89 (39%)	40 (40)	49 (38)
AIDS prior to cART	89 (39%)	46 (46)	43 (33)
Intravenous drug use	15 (6)	9 (9)	6 (5)
CD4+ cell count, median cells/mm ³ (IQR) ^a			
At diagnosis	340 (210–540)	300 (180–468)	360 (235–558)
Lagged prior to diagnosis, median cells/mm ³ (IQR)	377 (250–540)	320 (236–467)	400 (267–560)
cART ^a			
Prior to diagnosis	208 (90)	93 (92)	115 (89)
Lagged prior to diagnosis	205 (89%)	89 (88)	116 (89)
Undetectable viremia <400 cps/mL ^a			
Prior to diagnosis	175 (76)	74 (73)	101 (78)
Lagged prior to diagnosis	169 (75)	70 (71)	99 (79)
Hepatitis coinfection prior to cART initiation ^b			
HBV positive	17 (8)	11 (12)	6 (5)
HBV status unknown	16 (7)	6 (6)	10 (8)
HCV positive	14 (7)	9 (10)	5 (4)
HCV, status unknown	27 (12)	13 (13)	14 (11)
Tobacco use			
Ever	145 (63)	63 (63)	82 (63)
Unknown	50 (22)	22 (22)	28 (22)
Alcohol abuse	23 (10)	10 (10)	13 (10)

NOTE. Data are no. (%) of patients, unless otherwise indicated. cART, combination antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NRTI, nucleoside reverse-transcriptase inhibitor.

^a At first diagnosis of a non-AIDS-defining malignancy after cART initiation.

^b Chronic HCV infection was defined as plasma samples positive for HCV RNA or detection of HCV-positive antibodies in cases in which HCV RNA data were missing. Chronic HBV infection was defined as test results positive for hepatitis B surface antigen.

identified as unrelated to infection were lung cancer (44 cases), pancreatic cancer (5), renal cancer (4), bladder cancer (6), testicular cancer (8), cerebral cancer (not including primary central nervous system lymphoma) (3), bone cancer (1), and melanoma (7).

Of the patients who received a diagnosis of a non-AIDS-defining malignancy after starting cART, 39% had prior experience with mono or dual therapy. Only 2 patients had received a previous diagnosis of a non-AIDS-defining malignancy (hepatocellular carcinoma) prior to starting cART, and in both patients, the malignancy after starting cART (in both cases, Hodgkin lymphoma) was not a recurrence.

A sample of 105 cancer diagnoses were checked for the availability of pathology reports. Clinical diagnosis was based on pathology reports in 92 patients, on findings of radiologic examinations in 8, and on laboratory markers of disease in 1.

Risk Factors for Individual Non-AIDS-Defining Malignancies

The majority of patients with an anal carcinoma (*n* = 37) were men (*n* = 35), and 27 were MSM = . In multivariate models,

we found that a longer exposure to CD4+ cell counts <200 cells/mm³ (hazard ratio [HR], 1.52 for every additional year of infection; 95% confidence interval [CI], 1.24–1.87) and between 200–350 cells/mm³ (HR, 1.29; 95% CI, 1.02–1.62) was significantly associated with anal cancer. Other risk factors were older age (HR for each 10-year increase, 1.35; 95% CI, 0.99–1.83), Western origin (HR, 3.98; 95% CI, 1.07–14.70), and receipt of an AIDS diagnosis prior to starting cART (HR, 2.02; 95% CI, 1.06–3.83).

All patients with a liver-related carcinoma were male (*n* = 16), and 8 were coinfectd with HBV, 3 were coinfectd with HCV, 3 were not coinfectd, and the HBV/HCV infection status was unknown for 2 patients. In multivariate models, risk factors were age (HR, 2.06; 95% CI, 1.32–3.23), alcohol abuse (HR, 4.0; 95% CI, 1.12–14.30), and HBV coinfection (HR, 26.6; 95% CI, 9.7–72.99). HCV coinfection was not significantly associated with liver-related malignancies, nor was cumulative exposure to low CD4+ cell counts. Risk factors for lung cancer were age (HR per each additional decade, 2.0; 95% CI, 1.61–2.50) and smoking (HR, 7.34; 95% CI, 0.96–55.90). No association was

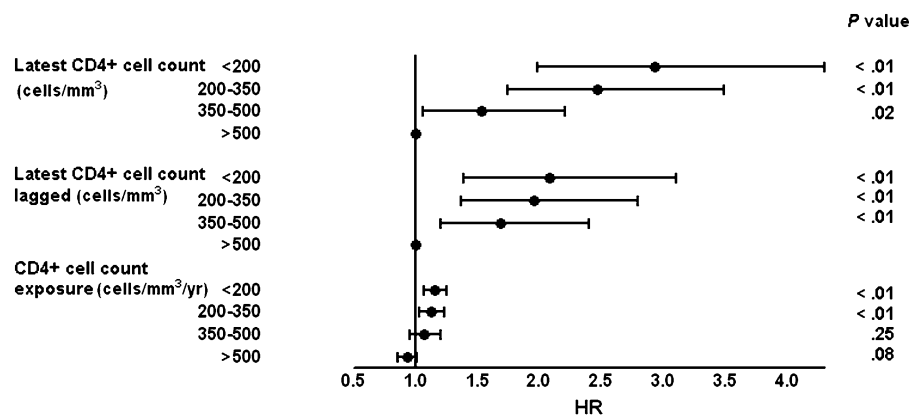


Figure 1. Association of different measures of immunodeficiency with non-AIDS-defining malignancies in human immunodeficiency virus type 1 (HIV-1)-infected patients in the Netherlands. Univariate models are shown that have not been adjusted for other potential risk factors. HR, hazard ratio.

found between lung cancer and cumulative exposure to low CD4+ cell counts.

Risk Factors for Non-AIDS-Defining Malignancies

In univariate Cox regression models, the latest CD4+ cell count, latest CD4+ cell count with a 6-month lag, time, cumulative exposure to low CD4+ cell counts, and lower nadir CD4+ cell count (HR per cell/mm³, 0.13; 95% CI, 0.04–0.40) were each associated with non-AIDS-defining malignancies (Figure 1). The CD4+ cell count and viral load at the start of cART, latest viral load, and cumulative exposure to viremia <50, 50–400, and >1000 copies/mL were not found to be predictors for non-AIDS-related malignancies. Cumulative exposure to individual cART regimens was not significantly associated with increased risk for non-AIDS-defining malignancies.

All multivariate models were adjusted for age, prior AIDS diagnosis, sex, region of origin, cumulative exposure to cART, cumulative exposure to immunodeficiency and viremia, estimated duration of HIV infection prior to cART, chronic HBV/HCV infection, smoking, and alcohol abuse.

In multivariate Cox regression models, a longer exposure to CD4+ cell counts <200 cells and, to a lesser extent, a range between 200 and 350 cells/mm³, were associated with a higher risk of non-AIDS-defining malignancies (HR for every additional year, 1.12 [95% CI, 1.03–1.22] and 1.08 [95% CI, 0.99–1.18], respectively). A longer exposure to detectable viremia was not significantly associated with non-AIDS-defining cancers (HR, 1.03; 95% CI, 0.99–1.06), and neither were the latest viral load or latest CD4+ cell count (at diagnosis and with a 6-month lag time).

Additional significant risk factors for non-AIDS-defining malignancies were chronic HBV infection (HR, 1.77; 95% CI, 1.08–2.91), older age per each additional decade (HR, 1.79; 95% CI, 1.57–2.04), prior AIDS diagnosis (HR, 1.35; 95% CI, 1.02–1.77), and being of Western origin (HR, 1.69; 95% CI, 1.16–2.45) (Figure 2).

In multivariate adjusted analyses where non-AIDS-defining malignancies were stratified according to whether the cause was possibly related to infection, a longer exposure to CD4+ cell counts <200 cells/mm³ was significantly associated with cancer possibly caused by infection (HR for every additional year of infection, 1.16; 95% CI, 1.03–1.31), but this association was not seen in other types of cancers (HR, 1.07; 95% CI, 0.95–1.21). No significant effect of viremia was seen in either group of cancers (Figure 3), but older age was associated with both types of cancers. Chronic HBV infection and receipt of an AIDS diagnosis prior to starting cART predicted a risk of cancers related to infection (independent of the CD4+ cell count), which was driven by hepatocellular carcinoma. In sensitivity analyses in which patients with hepatocellular carcinoma without HBV/HCV coinfection were excluded from the infection-related group, the effect of immunodeficiency and other risk factors remained unchanged. Because there is no consensus about the relationship between human papilloma virus infection and esophageal cancers, we repeated the analysis excluding the esophageal cancers from the infection-related cancers and found similar results (data not shown).

DISCUSSION

Findings

In patients in whom HIV infection is well suppressed with cART, their time spent with a CD4+ cell count <200 cells/mm³ and, to a lesser extent, time with a CD4+ cell count of 200–350 cells/mm³ was an independent predictor of non-AIDS-defining malignancy. This effect of immunodeficiency was driven by non-AIDS-defining cancer that was possibly caused by an infection and accounted for an increased risk of 16% per each additional year exposed to CD4+ cell counts <200 cells/mm³. Impaired CD4+ cell restoration because of suboptimal

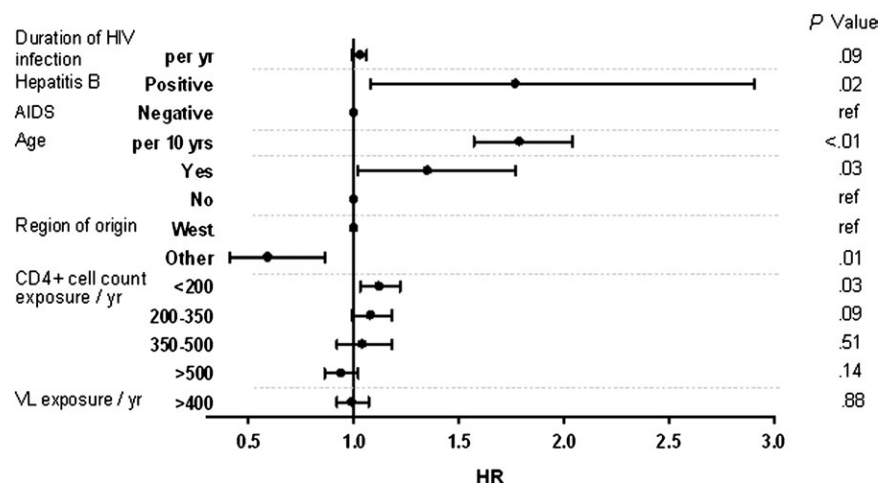


Figure 2. Risk factors for non-AIDS-defining malignancies in human immunodeficiency virus type 1 (HIV-1)-infected patients receiving combination antiretroviral therapy (cART) in the Netherlands. A multivariate Cox regression model is shown, adjusted for age, prior AIDS, sex, region of origin, cumulative exposure to cART, cumulative exposure to immunodeficiency and viremia, estimated duration of HIV-1 infection prior to initiation of cART, coinfections, smoking, and alcohol abuse. CD4+ cell exposure is expressed in cells/mm³ per year; viral load exposure is expressed in copies/mL per year. HR, hazard ratio; VL, viral load; yrs, years.

treatment regimens before the start of cART could contribute to a longer duration of immunodeficiency and, therefore, to an increased risk of malignancies in such patients.

Immunodeficiency appears to play a role in AIDS-defining malignancies, as well as in certain non-AIDS-defining malignancies [17–20, 29, 30]. The risk of these malignancies is increased in immunocompromised patients, possibly because of decreased immune surveillance for oncogenic (viral) infections, as well as for the presence of cancerous or precancerous cells themselves [31]. The cancer types that are increased in frequency in HIV-1-infected patients are similar to those most frequently

seen in immunosuppressed recipients of organ transplants [18]. However, immunosuppressed HIV-1-infected patients are apparently not at an increased risk for the development of some of the most common cancers, such as those of the breast, prostate, or colon, although several studies that controlled for tobacco use have found an association of HIV-1 infection with lung cancer [32, 33]. Many of the cancers that occur at increased rates in HIV-1-infected patients in the cART era are those with a known or suspected infectious cause [17, 18], which suggests that concomitant infection with oncogenic viruses and other pathogens may be associated with a greater risk for these types of

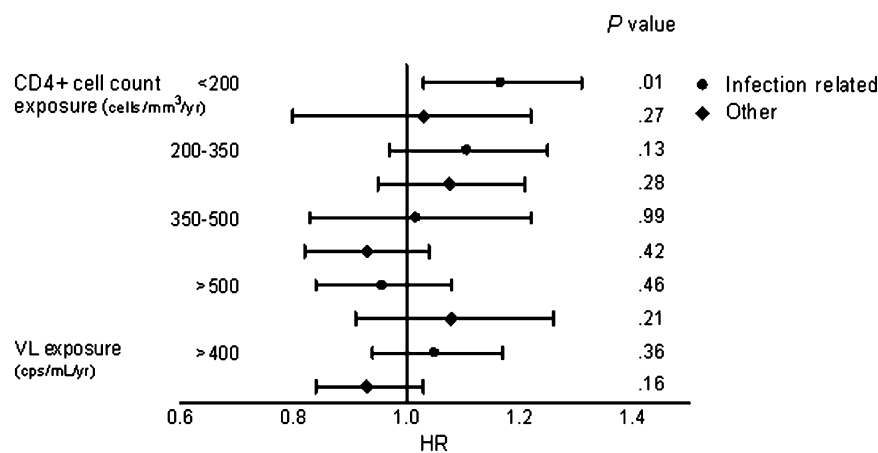


Figure 3. Effect of immunodeficiency on malignancies due to infection-related causes and other causes in human immunodeficiency virus type 1 (HIV-1)-infected patients receiving combination antiretroviral therapy (cART) in the Netherlands. Multivariate Cox regression models, adjusted for age, prior AIDS, sex, region of origin, cumulative exposure to cART, cumulative exposure to immunodeficiency and viremia, estimated duration of HIV-1 infection prior to cART initiation, coinfections, smoking, and alcohol abuse. CD4+ cell exposure is expressed in cells/mm³ per year; viral load exposure is expressed in copies/mL per year. cps, copies; HR, hazard ratio; VL, viral load; yrs, years.

cancer. Immunodeficiency has been associated with increased persistence, reactivation, and progression of some of these infections [34–36].

Measures of Immunodeficiency

Our findings complement other studies that have reported the most-recently measured CD4+ cell count as a predictor for fatal and nonfatal non-AIDS-defining malignancies [9, 19, 37]. In sensitivity analyses in our cohort, the latest CD4+ cell count was indeed strongly associated with non-AIDS-defining malignancies; however, cumulative exposure to lower CD4+ cell counts proved to be a more accurate measure of immunodeficiency. Additionally, in our study, we observed a slight but significant decrease in CD4+ cell count before the diagnosis of a non-AIDS-defining malignancy. This was also observed when including only those patients with undetectable viral loads, which makes the possibility of a lack of adherence being a contributory factor a less probable explanation. Similarly, a decrease in peripheral blood CD4+ cell counts was observed in patients with a diagnosis of Hodgkin's disease in a large cohort collaboration [38]. It is likely that, before the diagnosis of a malignancy, a variety of immunologic abnormalities are already present, and the cancer induces alterations in normal immune responses, thus escaping immune recognition and destruction [28, 39, 40]. This suggests that a low current CD4+ cell count could be both a cause and an effect of the cancer, resulting in an overestimation of the importance of the most-recently measured CD4+ cell count as a predictor for non-AIDS-defining malignancies.

Context and Limitations

Lifestyle factors, such as smoking [32], may contribute to the higher cancer incidence among HIV-infected persons and should be adequately controlled for in analyses [41]. In many cohort studies, detailed information regarding smoking is not available or is incomplete. In our study, information on having a history of tobacco use was available for 74% of patients. Because tobacco use is a major risk factor for some (predominantly non-infection-related) malignancies, the absence of complete information regarding smoking history may have confounded our results, particularly in analyses based on non-infection-related malignancies. It is possible that our study may not have been sufficiently powered to identify any effect of viremia on the risk for non-AIDS-defining malignancies, because HIV-1 viral load was undetectable during most of the follow-up period in the majority of patients. Accordingly, the power for detecting differences among cART regimens in the effect on the onset of non-AIDS-related malignancies was limited. Types of non-AIDS-defining cancers were relatively heterogeneous and, because many types of non-AIDS-defining malignancies are relatively uncommon, larger studies are needed to be able to conduct analyses of risk for individual types of cancer. Because

there is no formal link to a national cancer registry, it is possible that some diagnoses of relatively minor malignancies (such as basal cell carcinoma) are not collected in our database, although it is most likely that serious malignancies were recorded in patient records. The vast majority of diagnoses of malignancies in the Netherlands are histopathologically confirmed. In cases in which pathology reports were missing, histopathological confirmation of diagnosis was most likely done in a hospital other than hospital in which the patient received care for the HIV-1 infection.

Conclusion and Recommendations

In HIV-1-infected patients receiving cART, cumulative exposure to a greater degree of cellular immunodeficiency was found to be an independent predictor for infection-related non-AIDS-defining malignancies. Factors that remain important to consider when assessing cancer risk in HIV-infected patients, apart from immunodeficiency, are higher age; concomitant chronic infection with oncogenic viruses, such as HBV or HCV, Epstein-Barr virus, and human papilloma viruses; smoking; and alcohol abuse. Current guidelines recommend starting cART at CD4+ cell counts which are higher than the levels of immunodeficiency that we found to be associated with an increased risk of developing malignancies, which might help in preventing malignancies in such patients. Screening for anal human papilloma virus infections and premalignant lesions, counseling patients to quit smoking, and vaccinating against HBV could further reduce the incidence of non-AIDS-defining malignancies in the HIV-1-infected population treated with cART.

ATHENA Cohort Study

The following clinical sites participate in the ATHENA cohort study: Medical Center, Alkmaar; Onze Lieve Vrouwe Gasthuis, Amsterdam; Prinsengracht Hospital, Amsterdam; Slotervaart Hospital, Amsterdam; Medical Center, Jan van Goyen Kliniek, Amsterdam; Medical Center, Vrije Universiteit, Amsterdam; Academic Medical Center, Amsterdam; Hospital Rijnstate, Arnhem; Medical Center Haaglanden, the Hague; Hospital Leyenburg, the Hague; Catharina Hospital, Eindhoven; Medisch Spectrum Twente, Enschede; University Hospital, Groningen; Kennemer Gasthuis, Haarlem; Medical Center, Leeuwarden; University Medical Center, Leiden; University Hospital, Maastricht; University Medical Center St Radboud, Nijmegen; Erasmus University Medical Center, Rotterdam; St Elisabeth Hospital, Tilburg; University Medical Center, Utrecht; and Hospital Walcheren, Vlissingen.

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All other authors: No reported conflicts.

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 in the Acknowledgements section.

References

- Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* **2005**; 97:425–432.
- Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994–98: the EuroSIDA study. *Lancet* **2000**; 356:291–296.
- Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst* **2000**; 92:1823–1830.
- Lima VD, Hogg RS, Harrigan PR, et al. Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. *AIDS* **2007**; 21:685–692.
- Bonnet F, Burty C, Lewden C, et al. Changes in cancer mortality among HIV-infected patients: the Mortalite 2005 Survey. *Clin Infect Dis* **2009**; 48:633–639.
- Marin B, Thiebaut R, Bucher HC, et al. Non–AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. *AIDS* **2009**; 23:1743–1753.
- Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. *Ann Intern Med* **2008**; 148:728–736.
- Prosperi MC, Cozzi-Lepri A, Castagna A, et al. Incidence of malignancies in HIV-infected patients and prognostic role of current CD4 cell count: evidence from a large Italian cohort study. *Clin Infect Dis* **2010**; 50:1316–1321.
- Bruyand M, Thiebaut R, Lawson-Ayayi S, et al. Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. *Clin Infect Dis* **2009**; 49:1109–1116.
- Powles T, Robinson D, Stebbing J, et al. Highly active antiretroviral therapy and the incidence of non–AIDS-defining cancers in people with HIV infection. *J Clin Oncol* **2009**; 27:884–890.
- Sgadari C, Monini P, Barillari G, Ensoli B. Use of HIV protease inhibitors to block Kaposi's sarcoma and tumour growth. *Lancet Oncol* **2003**; 4:537–547.
- De FG, Bellan C, Lazzi S, et al. Interaction between HIV-1 Tat and pRb2/p130: a possible mechanism in the pathogenesis of AIDS-related neoplasms. *Oncogene* **2003**; 22:6214–6219.
- Ferry T, Raffi F, Collin-Filleul F, et al. Uncontrolled viral replication as a risk factor for non-AIDS severe clinical events in HIV-infected patients on long-term antiretroviral therapy: APROCO/COPILOTE (ANRS CO8) cohort study. *J Acquir Immune Defic Syndr* **2009**; 51:407–415.
- Zoufaly A, Stellbrink HJ, Heiden MA, et al. Cumulative HIV viremia during highly active antiretroviral therapy is a strong predictor of AIDS-related lymphoma. *J Infect Dis* **2009**; 200:79–87.
- El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* **2006**; 355:2283–2296.
- Silverberg MJ, Neuhaus J, Bower M, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. *AIDS* **2007**; 21:1957–1963.
- Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* **2001**; 285:1736–1745.
- Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* **2007**; 370:59–67.
- Monforte A, Abrams D, Pradier C, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS* **2008**; 22:2143–2153.
- Incidence and risk factors of HIV-related non-Hodgkin's lymphoma in the era of combination antiretroviral therapy: a European multicohort study. *Antivir Ther* **2009**; 14:1065–1074.
- Forslund O, Iftner T, Andersson K, et al. Cutaneous human papillomaviruses found in sun-exposed skin: eta-papillomavirus species 2 predominates in squamous cell carcinoma. *J Infect Dis* **2007**; 196:876–883.
- Clifford GM, Rickenbach M, Polesel J, et al. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. *AIDS* **2008**; 22:2135–2141.
- Wong HL, Breen EC, Pfeiffer RM, et al. Cytokine signaling pathway polymorphisms and AIDS-related non-Hodgkin lymphoma risk in the multicenter AIDS cohort study. *AIDS* **2010**; 24:1025–1033.
- Gras L, Van Sighem A, Smit C, Zaheri S, de Wolf F. Monitoring of human immunodeficiency virus (HIV) infection in the Netherlands. 8 A.D. Jan 1.
- <http://www.cphiv.dk/DAD/About/tabid/106/Default.aspx>. Accessed 24 March 2011.
- <http://www.cphiv.dk/Portals/0/files/Cancer%20Version%201.1.pdf>. Accessed 24 March 2011.
- Anderson RE, Warner NL. Ionizing radiation and the immune response. *Adv Immunol* **1976**; 24:215–335.
- Kavanaugh DY, Carbone DP. Immunologic dysfunction in cancer. *Hematol Oncol Clin North Am* **1996**; 10:927–951.
- Silverberg MJ, Abrams DI. AIDS-defining and non-AIDS-defining malignancies: cancer occurrence in the antiretroviral therapy era. *Curr Opin Oncol* **2007**; 19:446–451.
- Grulich AE. Cancer: the effects of HIV and antiretroviral therapy, and implications for early antiretroviral therapy initiation. *Curr Opin HIV AIDS* **2009**; 4:183–187.
- Burnet FM. Immunological surveillance in neoplasia. *Transplant Rev* **1971**; 7:3–25.
- Kirk GD, Merlo C, O'Driscoll P, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis* **2007**; 45:103–110.
- Bower M, Powles T, Nelson M, et al. HIV-related lung cancer in the era of highly active antiretroviral therapy. *AIDS* **2003**; 17:371–375.
- Strickler HD, Burk RD, Fazzari M, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. *J Natl Cancer Inst* **2005**; 97:577–586.
- Colin JF, Cazals-Hatem D, Liorot MA, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology* **1999**; 29:1306–1310.
- Ling PD, Vilchez RA, Keitel WA, et al. Epstein-Barr virus DNA loads in adult human immunodeficiency virus type 1-infected patients receiving highly active antiretroviral therapy. *Clin Infect Dis* **2003**; 37:1244–1249.
- Guiguet M, Boue F, Cadranet J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol* **2009**; 10:1152–1159.
- Egger M. Cause or consequence? Peripheral CD4 cell counts and Hodgkin's disease in patients on cART **2010**.
- Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* **2002**; 3:991–998.
- Swann JB, Smyth MJ. Immune surveillance of tumors. *J Clin Invest* **2007**; 117:1137–1146.
- Giordano TP, Kramer JR. Does HIV infection independently increase the incidence of lung cancer? *Clin Infect Dis* **2005**; 40:490–491.