Clinical implications of immune recovery during antiretroviral treatment for HIV infection
Kesselring, A.M.

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Chapter 4
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 Wit4,6

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 NADM 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-
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-naive 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. Immune deficiency 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 monotherapy 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 (78%) 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; 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 ≥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 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/mm³ (IQR) | 150 (155–240) |
| Prior monotherapy/dual therapy with NRTI | 2240 (20) |
| Country of origin | Europe/United States/Australia 7250 (63) |
| Other | 4209 (37) |
| HIV transmission category | 6003 (52) |
| MSM | 6003 (52) |
| Heterosexual sex | 3958 (35) |
| Intravenous drug user | 541 (5) |
| Other | 957 (8) |
| HBV status | 10116 (88) |
| Negative | 10116 (88) |
| Positive | 531 (5) |
| Unknown | 812 (7) |
| HCV status | 9401 (82) |
| Negative | 561 (5) |
| Positive | 1497 (13) |
| Unknown | 797 (7) |
| Alcohol abuse | 6552 (57) |
| Tobacco use | 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...
A median duration of follow-up of 5.5 years (interquartile range was available for 8508 patients (74%), of whom 6552 (57%) had based on detection of HCV RNA. Information on tobacco use (5%). Sixty-eight percent of HCV infection diagnoses were Of the total number, 20% had received mono or dual treatment nucleoside reverse-transcriptase inhibitor. Additionally, the latest CD4 cell counts below certain thresholds (CD4 cell count at start cART, AIDS prior to CDC-C prior to start cART 3079 (27) Age, median years (IQR) 38 (32–45) 300 (180–468) 360 (235–558) Lagged prior to diagnosis, median cells/mm³ (IQR) 377 (250–540) 320 (236–467) 400 (267–560) cART* Prior to diagnosis 208 (90) 93 (92) 115 (89) Lagged prior to diagnosis 205 (89%) 89 (88) 116 (89) Undetectable viremia <400 cps/mL* Prior to diagnosis 175 (78) 74 (73) 101 (78) Lagged prior to diagnosis 169 (75) 70 (71) 99 (79) Hepatitis coinfection prior to cART initiation* 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.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>All malignancies (n = 231)</th>
<th>Infection related (n = 101)</th>
<th>Not infection related (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, median years (IQR)</td>
<td>49 (43–55)</td>
<td>49 (43–55)</td>
<td>50 (43–59)</td>
</tr>
<tr>
<td>Male sex</td>
<td>199 (86)</td>
<td>89 (88)</td>
<td>110 (85)</td>
</tr>
<tr>
<td>Monotherapy/dual-therapy with NRTI prior to cART</td>
<td>89 (39%)</td>
<td>40 (40)</td>
<td>49 (38)</td>
</tr>
<tr>
<td>AIDS prior to cART</td>
<td>89 (39%)</td>
<td>46 (46)</td>
<td>43 (33)</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>15 (6)</td>
<td>9 (9)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>CD4+ cell count, median cells/mm³ (IQR)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>340 (210–540)</td>
<td>300 (180–468)</td>
<td>360 (235–558)</td>
</tr>
<tr>
<td>Lagged prior to diagnosis, median cells/mm³ (IQR)</td>
<td>377 (250–540)</td>
<td>320 (236–467)</td>
<td>400 (267–560)</td>
</tr>
<tr>
<td>cART* Prior to diagnosis</td>
<td>208 (90)</td>
<td>93 (92)</td>
<td>115 (89)</td>
</tr>
<tr>
<td>Lagged prior to diagnosis</td>
<td>205 (89%)</td>
<td>89 (88)</td>
<td>116 (89)</td>
</tr>
<tr>
<td>Undetectable viremia &lt;400 cps/mL* Prior to diagnosis</td>
<td>175 (78)</td>
<td>74 (73)</td>
<td>101 (78)</td>
</tr>
<tr>
<td>Lagged prior to diagnosis</td>
<td>169 (75)</td>
<td>70 (71)</td>
<td>99 (79)</td>
</tr>
<tr>
<td>Hepatitis coinfection prior to cART initiation*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV positive</td>
<td>17 (8)</td>
<td>11 (12)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>HBV status unknown</td>
<td>16 (7)</td>
<td>6 (6)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>HCV positive</td>
<td>14 (7)</td>
<td>9 (10)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>HCV, status unknown</td>
<td>27 (12)</td>
<td>13 (13)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Tobacco use ever</td>
<td>145 (63)</td>
<td>63 (63)</td>
<td>82 (63)</td>
</tr>
<tr>
<td>Unknown</td>
<td>50 (22)</td>
<td>22 (22)</td>
<td>28 (22)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>23 (10)</td>
<td>10 (10)</td>
<td>13 (10)</td>
</tr>
</tbody>
</table>

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.

identified as unrelated to infection were lung cancer (44 cases), hematological cancer (n=17), prostate cancer (n=16), breast cancer (n=13), and colon cancer (n=10), as well as 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 coinfected with HBV, 3 were coinfected with HCV, 3 were not coinfected, 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). HBV 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
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/mm$^3$, 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 initiation of 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/mm$^3$, 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/mm$^3$ 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/mm$^3$ and, to a lesser extent, time with a CD4+ cell count of 200–350 cells/mm$^3$ was an independent predictor of non–AIDS-related malignancies. 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/mm$^3$. Impaired CD4+ cell restoration because of suboptimal

**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.
Immunodeficiency and non-AIDS defining malignancies

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.

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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