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

Mathias Bruyand,1,2 Rodolphe Thiébaut,1,2 Sylvie Lawson-Ayayì,1,2 Pierre Joly,1,3 Annie Jeanne Sasco,1,3 Patrick Mercie,1,2 Jean Luc Pellegrin,2,3,4 Didier Neau,1,2,3,4 François Dabis,1,2,3 Philippe Morlat,1,2,3,4 Geneviève Chène,1,2,3 and Fabrice Bonnet,1,2,3,4 for the Groupe d’Épidémiologie Clinique du SIDA en Aquitaine (GECSA)*

1Institut National de la Santé et de la Recherche Médicale (INSERM) U897, 2Centre Hospitalier Universitaire (CHU) de Bordeaux, Coordination Régionale de la Lutte Contre l’Infection due au VIH, 3Université Victor Segalen Bordeaux 2, and 4Services de Médecine Interne et Maladies Infectieuses, CHU de Bordeaux, Bordeaux, France

(See the editorial commentary by Serraino, on pages 1117–8.)

Background. Human immunodeficiency virus (HIV)–infected patients are at higher risk of malignancies. In addition to traditional determinants, a specific deleterious effect of HIV and immunodeficiency is speculated. We aimed at studying the association between immunological and virological characteristics of HIV-infected patients in care and the risk of acquired immunodeficiency syndrome (AIDS)–defining and non–AIDS-defining malignancies.

Methods. Patients consecutively enrolled in the hospital-based Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort were included if the duration of follow-up was >3 months during the period 1998–2006. Multivariate modeling used an extended Cox proportional hazards model for time-dependent covariates and delayed entry.

Results. The 4194 patients included in the study developed 251 first malignancies during 22,389 person-years. A higher incidence of AIDS-defining malignancies (107 cases) was independently associated with (1) both longer and current exposures to a plasma HIV RNA level >500 copies/mL (hazard ratio [HR], 1.27 per year [P<.001] and 3.30 [P<.001], respectively) and (2) both longer and current exposure to a CD4+ cell count <200 cells/mm3 (HR, 1.36 per year [P<.001] and 6.33 [P<.001], respectively). A higher incidence of non–AIDS-defining malignancies (144 cases) was independently associated with longer and current exposure to a CD4+ cell count <500 cells/mm3 (HR, 1.13 per year [P = .01] and 2.07 [P<.001], respectively) and male sex (HR, 1.69; P = .02) but not with plasma HIV RNA level (and for cumulative and current exposures, respectively).

Conclusions. Uncontrolled plasma HIV RNA level was independently associated with a higher likelihood of developing AIDS-defining malignancies, whereas immunosuppression was associated with a higher risk of developing any type of malignancies. Antiretroviral treatment should aim at reaching and maintaining a CD4+ count >500 cells/mm3 to prevent the occurrence of malignancy, this should be integrated to malignancy-prevention policies.
nonsuppression and chronic infection with oncogenic viruses [1, 3]. Since 1996, the substantial improvement in the survival rate after HIV infection related to the increasing use of combination antiretroviral therapy (cART) has been associated with changes in the spectrum of HIV morbidity and mortality [4–6]. Indeed, the incidence of non–AIDS-defining malignancies among people living with HIV infection is 2–3 times higher than that in the general population, and malignancies, whether AIDS-defining or not, have become the most frequent causes of death among HIV-infected patients [6–8]. Such an increase in the proportion of deaths due to malignancies may be explained by prolonged survival, overall aging of the HIV-infected population, and decreasing mortality related to opportunistic infections [9–13]. The high prevalence of traditional risk factors for malignancies, such as tobacco or alcohol consumption and infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), will act as contributing factors [14–16]. In addition, the role of HIV-related immunosuppression as a specific risk factor for non–AIDS-defining malignancies is strongly suspected, and a relationship between the risk of hepatocarcinoma and HIV-related immunosuppression was recently shown [17]. Furthermore, a direct role of HIV in the occurrence of malignancies is suggested [18–22]. Finally, because exposure to immunodeficiency or uncontrolled plasma HIV RNA level can be considered to be cumulative over time or to be current, it remains unclear which type of exposure should be considered in assessing the risk of malignancy. Our objective was to investigate the association between the occurrence of a first malignancy in HIV-infected patients and the immunovirological characteristics observed over time in a large cohort of HIV-infected patients in care, in which malignancies are prospectively recorded.

METHODS

Study population. Data collected during the period 1 January 1998 through 31 December 2006 within the Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort, a prospective hospital-based cohort of HIV type 1–infected patients undergoing routine clinical treatment in southwestern France, were used [23]. This cohort was initiated in 1987 at the Bordeaux University hospital and in 4 other public hospitals by the Groupe d’Épidémiologie Clinique du Sida en Aquitaine (GECSA). All adult in- or outpatients at the participating hospital wards who had HIV-1 infection confirmed by Western blot testing and who had provided informed consent were eligible in the cohort. Patients included in this analysis had (1) at least 3 months of follow-up, (2) at least 2 visits reported during the study period, and (3) at least 1 plasma HIV RNA level and CD4+ cell count measurements documented during the study period. All morbidity events were collected using codes from The International Classification of Diseases, 10th Revision. The codes corresponding to malignancies were extracted from the database to identify the cases. Malignancies diagnosed before 1 January 1998 or during the first 3 months of follow-up in the Aquitaine Cohort were considered to be prevalent cases and were not included in this study.

Risk factors and outcomes. The primary outcome was a confirmed diagnosis of a first malignancy during the follow-up period. All cases were validated through histological reports or source medical files documenting the diagnosis. The following time-updated variables were considered: time spent with a CD4+ cell count less than 2 predefined thresholds, the latest available CD4+ cell count, time spent with a plasma HIV RNA level greater than 2 predefined thresholds, the latest available plasma HIV RNA measurement, duration of cART exposure, and latest cART prescription. We considered a CD4+ cell count <200 cells/mm3 to be a marker of severe immunosuppression and >500 cells/mm3 to be a marker of immune restoration [24]. We used 500 copies/mL as the lowest threshold of plasma HIV RNA level that could be detected throughout the 10-year study period. We also considered the threshold of 10,000 copies/mL to indicate a high level of HIV replication. To estimate the time spent with a plasma HIV RNA level greater than the defined thresholds, we assumed that the value of the measurement reported at a given follow-up visit remained stable until the next follow-up visit. We made the same assumptions to estimate the time spent in each CD4+ cell count category and the duration of cART exposure. When plasma HIV RNA or CD4+ cell count values were missing at a recorded follow-up visit, they were estimated using the last-observation-carried-forward method. Missing values were counted as such when the delay between the last available value and the missing value was >6 months. cART was defined as a regimen including at least 3 antiretroviral drugs.

Statistical analysis. Proportional hazards regression models with delayed entry were used to estimate the association between time-updated variables, sex, and the risk of occurrence of a first new diagnosis of malignancy for a given patient during the study period. We assumed that the risk of malignancy is strongly age dependent, so the date of birth was considered to be the baseline time in the Cox model used. However, this introduces a left truncation problem, and we considered a delayed entry at the date of the follow-up visit reporting the first plasma HIV RNA level after 1 January 1998. In these survival analyses, the risk of malignancy is estimated as a function of aging, and age is not included as a variable in the models [25, 26]. Patients without a diagnosis of malignancy and who were still alive on 31 December 2006 were right-censored at the date of the last follow-up visit. The proportional hazards assumption was checked graphically and by testing interactions between covariates and time for time-updated variables.

The main analyses separately considered AIDS-defining ma-
lignancies and non–AIDS-defining malignancies, whereas robustness analyses considered Kaposi sarcoma and NHL.

In the models that accounted for the latest measurement, plasma HIV RNA level and CD4+ cell count were considered to be binary variables (higher or lower than the threshold considered), and cART was considered to be prescribed or not. All adjusted models considered the following variables: CD4+ cell count less than the threshold that was prespecified in the model (duration of exposure or latest measurement), plasma HIV RNA level greater than the threshold considered in the model (duration of exposure or latest measurement), cART exposure (duration of exposure or last prescription), and sex. In addition to the latest plasma HIV RNA level and CD4+ cell count, representing the current exposure, we calculated a cumulative exposure to clinically relevant cutoffs of these markers, because malignancy usually occurs after a long exposure to potential determinants, and current values might be a consequence rather than a cause of malignancy. Both types of summary statistics were studied in separate models, because they are highly correlated. The models were compared with the Akaike criterion, the lower fit the better.

In all analyses, patients affected by a malignancy that was not included in the outcome definition were right-censored at the time of the diagnosis. This means that the follow-up of patients affected by an AIDS-defining malignancy was right-censored, whereas the hazard of non–AIDS-defining malignancies was estimated. Because a history of malignancy was an exclusion criterion, no prevalent cases were included.

Because of incomplete data regarding traditional risk factors for non–AIDS-defining malignancies (eg, tobacco use and HBV or HCV infection), they were not considered in the analyses performed on the entire dataset. Thus, a robustness analysis adjusted for these risk factors, considering them to be fixed-effect variables, was conducted for patients with available data regarding tobacco use and HBV or HCV infection. SAS software, version 9.1 (SAS Institute) was used to perform the analyses.

RESULTS

During the study period, 4828 patients were observed in the ANRS CO3 Aquitaine Cohort, 324 of whom had a diagnosis of malignancy at study entry and were excluded from the analyses. In addition, 310 patients did not meet the study inclusion criteria. Thus, among 4194 eligible patients, accounting for 36% of the 4194 cases, 2351 first, new diagnoses of malignancy were validated through histological reports (111 cases) or medical records (140 cases). The cohort was predominantly male (72%), and men accounted for 83% of the 144 cases of non–AIDS-defining malignancy and 78% of the 107 cases of AIDS-defining malignancy. The incidences of AIDS-defining malignancies were 5.2 cases per 1000 person-years (95% confidence interval [CI], 4.1–6.4 cases per 1000 person-years) in men and 3.6 cases per 1000 person-years (95% CI, 2.1–5.1 cases per 1000 person-years) in women. The incidences of non–AIDS-defining malignancies were 7.5 cases per 1000 person-years (95% CI, 6.1–8.8 cases per 1000 person-years) in men and 3.8 cases per 1000 person-years (95% CI, 2.3–5.3 cases per 1000 person-years) in women. Table 1 shows the distribution of malignancies and the characteristics of these patients. Among the 97,893 follow-up visits recorded during the study period, 5033 concerned patients affected by a malignancy. At least 2 plasma HIV RNA level and CD4 cell count measurements were reported among 4145 patients (240 malignancies) and 4155 patients (241 malignancies), respectively.

AIDS-defining malignancies. Both a CD4+ cell count <200 cells/mm³ and a plasma HIV RNA level >500 copies/mL were strongly and independently associated with a higher risk of AIDS-defining malignancy, whatever the type of exposure considered (cumulative or current) (Table 2). Each additional year of exposure to cART was associated with a lower risk of AIDS-defining malignancy, whereas current exposure to cART and sex were not related to the hazard of AIDS-defining malignancy (Table 2).

Sixty-one cases of NHL were diagnosed during the study period among the 4194 patients included, accounting for 57% of all diagnoses of AIDS-defining malignancies. Current plasma HIV RNA level >500 copies/mL and CD4+ cell count <200 cells/mm³ were independently associated with a higher hazard of NHL (hazard ratio [HR], 3.02 [95% CI, 1.65–5.52; P < .001] and 5.12 [95% CI, 3.01–8.70; P < .001], respectively). Considering the cumulative exposure, each year spent with a plasma HIV RNA level >500 copies/mL and CD4+ cell count <200 cells/mm³ was independently associated with a higher risk of NHL (HR, 1.34 [95% CI, 1.19–1.51; P < .001] and 1.31 [95% CI, 1.12–1.53; P < .001], respectively), whereas each year of cART exposure was associated with a lower risk of NHL (HR, 0.86; 95% CI, 0.75–0.98).

In another adjusted model, each year spent with a plasma HIV RNA level >10,000 copies/mL was associated with a higher hazard of NHL (HR, 1.59; 95% CI, 1.38–1.83; P < .001), whereas each year spent with a CD4+ cell count <200 cells/mm³ and each year of cART exposure tended to be associated with a higher risk (HR, 1.18; P = .057) and a lower risk of NHL (HR, 0.88; 95% CI, 0.75–0.98).

Thirty-nine cases of Kaposi sarcoma were reported among the 4194 patients, accounting for 36% of the AIDS-defining malignancies diagnosed. Multivariable analyses considering cumulative exposure showed that each year spent with a CD4+ cell count <200 cells/mm³ was associated with a higher hazard of Kaposi sarcoma (HR, 1.55; 95% CI, 1.24–1.93; P < .001), whereas continuing to have a plasma HIV RNA level >500 copies/mL did not affect the Kaposi sarcoma hazard (P =
Table 1. Characteristics of 251 Patients with New Cases of Malignancy, Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort, 1998–2006

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with non–AIDS-defining malignancies (n = 144)</th>
<th>Patients with AIDS-defining malignancies (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of malignancy, no. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>...</td>
<td>61</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>...</td>
<td>39</td>
</tr>
<tr>
<td>Cervix carcinoma</td>
<td>...</td>
<td>7</td>
</tr>
<tr>
<td>Bronchopulmonary</td>
<td>30</td>
<td>...</td>
</tr>
<tr>
<td>Skin malignancy</td>
<td>20</td>
<td>...</td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>18</td>
<td>...</td>
</tr>
<tr>
<td>Hepatocarcinoma</td>
<td>16</td>
<td>...</td>
</tr>
<tr>
<td>Anal malignancy</td>
<td>14</td>
<td>...</td>
</tr>
<tr>
<td>Other hemopathies</td>
<td>6</td>
<td>...</td>
</tr>
<tr>
<td>Other solid tumors</td>
<td>40</td>
<td>...</td>
</tr>
<tr>
<td>Characteristic (continuous variables), median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at malignancy diagnosis, years</td>
<td>46.7 (41.3–54.9)</td>
<td>41.3 (35.4–47.5)</td>
</tr>
<tr>
<td>Duration of follow-up in the study period, years</td>
<td>4.2 (1.9–6.2)</td>
<td>3.1 (1.2–4.9)</td>
</tr>
<tr>
<td>Time since first positive HIV test result, years</td>
<td>12.5 (8.4–15.9)</td>
<td>10.0 (4.4–14.1)</td>
</tr>
<tr>
<td>Plasma HIV RNA level, log copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir during the study period</td>
<td>1.7 (1.7–2.7)</td>
<td>3.0 (1.8–4.0)</td>
</tr>
<tr>
<td>Level at the time of malignancy diagnosis</td>
<td>2.7 (1.7–3.8)</td>
<td>4.5 (2.7–5.2)</td>
</tr>
<tr>
<td>Duration of follow-up with plasma HIV RNA level &lt;500 copies/mL, years</td>
<td>1.5 (0.3–3.5)</td>
<td>0.0 (0.0–0.7)</td>
</tr>
<tr>
<td>CD4+ cell count, cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir during the study period</td>
<td>186 (93–296)</td>
<td>129 (21–281)</td>
</tr>
<tr>
<td>Count at the time of malignancy diagnosis</td>
<td>341 (178–488)</td>
<td>198 (52–390)</td>
</tr>
<tr>
<td>Duration of cART use during the study period, years</td>
<td>2.9 (0.7–5.3)</td>
<td>1.6 (0.5–3.5)</td>
</tr>
<tr>
<td>Characteristic (categorical variables)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of men</td>
<td>83</td>
<td>78</td>
</tr>
<tr>
<td>Percentage of injection drug users</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

**NOTE.** cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range.

* Four of these patients had melanoma.

.22). Female sex was associated with a lower incidence of Kaposi sarcoma (HR, 0.13; 95% CI, 0.03–0.53; P = .005).

**Non–AIDS-defining malignancies.** A CD4+ cell count <500 cells/mm³ was independently associated with a higher hazard of non–AIDS-defining malignancy, whatever the exposure considered (Table 3). Plasma HIV RNA level and cART were not associated with the risk of non–AIDS-defining malignancy, regardless of which model was considered, whereas female sex was related to a lower hazard (Table 3). Analyses that used higher thresholds for plasma HIV RNA level and that considered the cumulative exposure led to similar results (data not shown). In analyses that considered lower thresholds for CD4+ cell count, each year spent with a CD4+ cell count <200 cells/mm³ was independently associated with a higher risk of non–AIDS-defining malignancy (HR, 1.16; 95% CI, 1.04–1.30; P = .01).

**Adjustment for other risk factors of malignancy.** Among 3210 patients with available data regarding tobacco use and HBV or HCV coinfection status, 113 non–AIDS-defining malignancies occurred.

The thresholds considered were 500 copies/mL for plasma HIV RNA level and 500 cells/mm³ for CD4+ cell count. The results of these analyses adjusted for sex, CD4+ cell count, HIV RNA level, cART, tobacco use , and HBV or HCV coinfection are presented considering 2 durations of cART exposure because of an interaction between the durations with a CD4+ cell count <500 cells/mm³ and cART exposure ( P = .02). A longer duration of a CD4+ cell count <500 cells/mm³ remained associated with a higher risk of non–AIDS-defining malignancy (HR, 1.26 per each additional year, 95% CI, 1.07–1.50; P = .007) in patients who continued to not receive cART. This association no longer existed among cART-treated patients ( P = .12 after 4 years of cART exposure).

Moreover, our results were not affected by robustness analysis considering the transmission group, regardless of which type of malignancy was considered.
Comparison between cumulative and current exposure. The difference in Akaike criterion between the model that accounted for current exposure to latest measurement versus the model that considered cumulative exposure (Tables 2 and 3) could be considered negligible in each instance [27].

DISCUSSION

Immunodeficiency is known to be associated with a higher hazard of AIDS-defining malignancy and our results are in accordance with this body of knowledge. Moreover, our study shows that HIV replication, as both current and cumulative exposure to uncontrolled plasma HIV RNA level were associated with a higher hazard of AIDS-defining malignancy, has a major impact on the risk of occurrence of AIDS-defining malignancies, particularly NHL. This suggests that the control of plasma HIV RNA level is a key factor in the prevention of NHL occurrence at all stages of immunodeficiency. HIV replication, through activation of the immune system, could be indepen-

Table 2. Determinants of a First AIDS-Defining Malignancy: Multivariate Analyses Including Either Cumulative Exposure to Viroimmunological Markers or Latest Measurements, Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort, 1998–2006

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cumulative exposure</th>
<th>Latest measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
</tbody>
</table>

CD4+ cell count, <200 cells/mm³
Per additional year of exposure 1.36 (1.21–1.54) <.001
Yes vs no ... 6.33 (4.25–9.41) <.001
Plasma HIV RNA level, >500 copies/mL
Per additional year of exposure 1.27 (1.15–1.40) <.001
Yes vs no ... 3.30 (2.07–5.25) <.001
cART exposure
Per additional year 0.82 (0.74–0.91) <.001
Yes vs no ... 0.93 (0.61–1.43) .74
Female vs male sex 0.69 (0.43–1.10) .11 0.75 (0.47–1.19) .22


<table>
<thead>
<tr>
<th>Variable</th>
<th>Cumulative exposure</th>
<th>Latest measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
</tbody>
</table>

CD4+ cell count, <500 cells/mm³
Per additional year of exposure 1.13 (1.03–1.24) .01
Yes vs no ... 2.07 (1.41–3.05) <.001
Plasma HIV RNA level, >500 copies/mL
Per additional year of exposure 1.03 (0.94–1.13) .49
Yes vs no ... 1.34 (0.94–1.91) .10
cART exposure
Per additional year 0.99 (0.91–1.08) .87
Yes vs no ... 1.04 (0.70–1.54) .85
Female vs male sex 0.59 (0.38–0.92) .02 0.60 (0.39–0.94) .02

NOTE. cART, combination antiretroviral therapy; CI, confidence interval; HR, hazard ratio for the association between a given variable and hazard of AIDS-defining malignancy.

a Adjusted for other variables: CD4+ cell count, <200 cells/mm³; plasma HIV RNA level, >500 copies/mL, exposure to cART; and sex.

b Akaike criterion for cumulative exposure, 1325.3.

Akaike criterion for latest measurement, 1251.4.
ently involved in the occurrence of NHL in patients with high CD4+ cell counts [28]. The fact that exposure to cART was only associated with a lower risk of AIDS-defining malignancy needs to be further explored. However, it is difficult to disentangle the proper effect of cART, immunodeficiency, and viral replication, and one may speculate that the absence of a significant association between cART exposure and non–AIDS-defining malignancy is linked to the absence of association with HIV replication. Thus, the potential benefit of cART for controlling non–AIDS-defining malignancies might be due to immune reconstitution rather than to control of viral replication per se. On the other hand, both longer and current uncontrolled plasma HIV RNA level and immunosuppression were associated with a higher risk of AIDS-defining malignancy, underlining that the best possible control of HIV replication is warranted to prevent AIDS-defining malignancies and especially NHL occurrence.

Several cohort studies have shown a higher risk of non–AIDS-defining malignancy in HIV-infected patients than in the general population, but none of these studies considered the duration of exposure to immunodeficiency [9, 11, 12, 29]. Another large study failed to show any relationship between immunodeficiency at AIDS diagnosis and the risk of malignancy [30]. Our results are consistent with a higher incidence of non–AIDS-defining malignancies observed in solid-organ transplant recipients, who undergo long-term exposure to immunosuppressive therapy, indirectly suggesting that immunodeficiency is independently associated with a higher risk of non–AIDS-defining malignancies in HIV-infected patients [31, 32]. Furthermore, our results regarding the latest CD4+ cell count showed that current immunodeficiency may be involved in the risk of malignancy. This suggests that, after commencement of cART, the risk of malignancy may decrease when the CD4+ cell count rises to >500 cells/mm³. Our results regarding cumulative exposure to CD4 <500 cells/mm² conveys important additional results, because they suggest that patients with long-standing immunodeficiency experience a higher rate of malignancy than do patients without immunodeficiency. This could help to target a high-risk population to implement prevention and screening policies.

On the basis of the Akaike criterion, our analysis does not indicate a particular advantage of cumulative low CD4+ cell counts in comparison to the latest CD4+ cell count for both AIDS-defining and non–AIDS-defining malignancies. However, the consistent finding of an increased risk of AIDS and non–AIDS-defining malignancies associated with cumulative time with a CD4+ cell count <200 cells/mm³ or <500 cells/mm³ provides a stronger argument that HIV-infected patients may benefit from early initiation of antiretroviral treatment to decrease the risk of AIDS and of non–AIDS-defining malignancies.

Burgi et al [33] found that the use of cART was protective for malignancies, and the D:A:D cohort collaboration found that the incidence of fatal non–AIDS-related malignancies was related to exposure to cART [34]. Our main objective was not to estimate the independent effect of cART exposure on the risk of malignancy, and future studies that include more patients should specifically address this issue. However, our results show that early control of HIV replication and maintenance of high CD4+ cell counts are associated with a lower risk of malignancies.

The incidence rate of non–AIDS-defining malignancies was higher among men than among women, as has been commonly observed in the general population in France [35].

Because of incomplete data regarding the risk factors for non–AIDS-defining malignancies (eg, tobacco consumption and HBV or HCV infection), we could not take these risk factors into account in the analyses of the entire cohort. However, these confounding factors were controlled for in analyses that estimated the risk of non–AIDS-defining malignancy in a large subgroup of patients for whom these data were available. The association between immunosuppression and the occurrence of specific non–AIDS-defining malignancies could not be explored in this study. We acknowledge that a larger number of cases is needed to reach larger statistical power to adequately address this issue for each type of non–AIDS-defining malignancy.

Finally, our study showed that an uncontrolled plasma HIV RNA level was associated with a higher risk of AIDS-defining malignancy, regardless of CD4+ cell count and the use of cART. Furthermore, immunodeficiency was associated with a higher risk of malignancy, regardless of whether it was AIDS-defining. Considering the global aging of the HIV-infected population in developed countries, malignancy, which is already one of the main causes of mortality, is likely to become the first clinical and public health challenge in the long-term management of HIV-infected patients.

According to our observations, the objective of cART should be to reach and maintain not only an undetectable plasma HIV RNA level but also a CD4+ cell count >500 cells/mm³, to prevent the occurrence of malignancy, regardless of whether that malignancy is AIDS-defining. In the HIV-infected population, this should be integrated into malignancy-prevention policies.

COMPOSITION OF THE GROUPE D’EPIDEMIOLOGIE CLINIQUE DU SIDA EN AQUITAINE

The Groupe d’Epidemiologie Clinique du Sida en Aquitaine steering the ANRS CO3 Aquitaine Cohort is organized as follows.

Epidemiology and methodology.  M. Bruyand, G. Chêne, F.
Dabis (Principal Investigator), S. Lawson-Ayai, and R. Thiébaut.


Immunology, virology, pharmacology, and pharmacovigilance. P. Blanco, JF. Moreau, and I. Pellegrin (immunology); H. Fleury, M. E. Lafon, and B. Masquelier (virology); D. Breill (pharmacology); and G. Miremont-Salâmé (pharmacovigilance).


Acknowledgments

Financial support. The ANRS CO3 Aquitaine Cohort is supported by a grant from the Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS, France) within the Coordinated Action no. 7 (AC7).

Potential conflicts of interest. All authors: no conflicts.

References