HAL
archives-ouvertes.fr

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, Rodolphe Thiébaut, Sylvie Lawson-Ayayi, Pierre Joly, Annie-Jeanne Sasco, Patrick Mercié, Jean Luc Pellegrin, Didier Neau, François Dabis, Philippe Morlat, et al.

▶ **To cite this version:**

Mathias Bruyand, Rodolphe Thiébaut, Sylvie Lawson-Ayayi, Pierre Joly, Annie-Jeanne Sasco, 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.: Malignancy, HIV and immune deficiency. Clinical Infectious Diseases, Oxford University Press (OUP), 2009, 49 (7), pp.1109-16. <10.1086/605594>. <inserm-00391182>

HAL Id: inserm-00391182
http://www.hal.inserm.fr/inserm-00391182

Submitted on 3 Sep 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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-Ayayi [1 2], Pierre Joly [1], Annie-Jeanne Sasco [1], Patrick Mercié [1 2 3], Jean Luc Pellegrin [2 3], Didier Neau [1 2 3], François Dabis [1 2], Philippe Morlat [1 2 3], Geneviève Chêne [1 2], Fabrice Bonnet [1 2 3 *]

[1] Centre épidémiologie et biostatistique INSERM : U897 , Université Victor Segalen - Bordeaux II , FR

[2] COREVIH, Coordination Régionale de la lutte contre l'infection due au VIH CHU Bordeaux , 33076 Bordeaux,FR

[3] Service de médecine interne et maladies infectieuses CHU Bordeaux , Groupe hospitalier Saint-André , 1, rue Jean burguet 33000 Bordeaux,FR

* Correspondence should be adressed to: Fabrice Bonnet <fabrice.bonnet@chu-bordeaux.fr >

Abstract

Background

HIV-infected patients are at higher risk of malignancies. Besides 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 AIDS-defining and non-AIDS-defining malignancies.

Methods

Patients consecutively enrolled in the hospital based ANRS CO3 Aquitaine Cohort were included if their follow-up was >3 months between 1998 and 2006. Multivariate modelling used an extended Cox proportional hazards models for time-dependent covariates and delayed entry.

Results

The 4,194 patients included developed 251 first malignancies during 22,389 person-years. A higher incidence of AIDS-defining malignancies (107 cases) was independently associated with: (i) both longer and current exposures to plasma HIV RNA >500 copies/ml: Hazard ratio [HR]=1.27 per year; p<0.001 and HR=3.30; p<0.001, respectively, and (ii) both longer and current exposure to CD4+ count<200/mm^3 : HR=1.36 per year; p<0.001 and HR=6.33; p<0.001, respectively. A higher incidence of non-AIDS-defining malignancies (144 cases) was independently associated with longer and current exposure to CD4+ count<500/mm^3 (HR=1.13 per year; p=0.01 and HR=2.07; p<0.001, respectively), and male gender (HR=1.69; p=0.02) but not plasma HIV RNA (p=0.49 and p=0.10 for cumulative and current exposures).

Conclusions

Uncontrolled plasma HIV RNA was independently associated with a higher likelihood of developing AIDS-defining malignancies, while immunosuppression was associated with a higher risk of developing any types of malignancies. Antiretroviral treatment should aim at reaching and maintaining a CD4+ count >500/mm^3 to prevent the occurrence of malignancy, this should be integrated to malignancy prevention policies.

MESH Keywords Adult ; CD4 Lymphocyte Count ; Cohort Studies ; Female ; Follow-Up Studies ; HIV Infections ; complications ; immunology ; Humans ; Incidence ; Male ; Middle Aged ; Models, Statistical ; Multivariate Analysis ; Neoplasms ; epidemiology ; RNA, Viral ; blood ; Viral Load

Author Keywords HIV ; malignancy ; risk ; immunodeficiency ; CD4+ count

Introduction

The association between HIV infection and the occurrence of certain types of malignancies has been established for a long time [1]. Due to their high incidence rates among HIV-infected patients, Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and invasive cervical cancer are considered as AIDS-defining malignancies [2]. Their high incidence may be explained by cellular immunosuppression and chronic infection with oncogenic viruses [1 , 3]. Since 1996, the substantial improvement in survival 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 is two to three times higher than within the general population and malignancies, whether AIDS-defining or not, have become the most frequent cause of death in HIV-infected patients [6 –8]. Such an increase in the proportion of deaths due to malignancies may be explained by prolonged survival,

overall ageing of the HIV-infected population and a decreasing mortality related to opportunistic infections [9 –13]. The high prevalence of traditional risk factors for malignancies, such as tobacco or alcohol consumption, 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, as exposure to immunodeficiency or uncontrolled plasma HIV RNA viral load can be considered as cumulative over the time or 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 immuno-virological 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 between January 1st , 1998 and December 31st , 2006 within the ANRS CO3 Aquitaine Cohort, a prospective hospital-based cohort of HIV-1-infected patients under routine clinical management, in South-Western France, were used [23]. This cohort was initiated in 1987 at the Bordeaux University hospital and in four other public hospitals by the Groupe d'Epidémiologie Clinique du Sida en Aquitaine (GECSA). All adults who are in- or out-patients of the participating hospital wards, with HIV-1 infection confirmed by Western blot testing and having given informed consent, are eligible in the cohort. Patients included in this analysis had (i) at least three months of follow-up, (ii) at least two visits reported during the study period and (iii) at least one plasma HIV RNA and CD4+ cell count measurements documented during the study period. All morbid events are collected using the International Classification of Diseases 10th revision codes. The codes corresponding to malignancies were extracted from the database to identify the cases. Malignancies diagnosed before January 1st , 1998, or during the first three months of follow-up in the Aquitaine Cohort were considered as 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 two pre-defined thresholds; latest available CD4+ cell count; time spent with plasma HIV RNA above two pre-defined thresholds; latest available plasma HIV RNA measurement; duration of cART exposure and latest cART prescription. We considered 200 CD4+/mm^3 as a marker of severe immunosuppression and 500 CD4+/mm^3 as a marker of immune restoration [24]. We used 500 copies/mL as the lowest threshold of plasma HIV RNA that could be detected throughout the 10-year study period. We also considered the threshold of 10,000 copies/mL as a high level of HIV replication. To estimate the time spent with plasma HIV RNA above 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 value was missing at a recorded follow-up clinic visit, it was 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 one was >6 months. cART was defined as a regimen including at least three antiretroviral drugs.

Statistical analysis

Proportional hazards regression models with delayed entry were used to estimate the association between time-updated variables, gender, and the risk of occurrence of a first new diagnosis of malignancy for a given patient during the study period. Age was the baseline time as, in such a Cox model, we assume that the risk of malignancy is strongly age dependent. 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 after January 1st , 1998. In these survival analyses, the risk of malignancy is estimated as a function of ageing and age is not included as a variable in the models [25 , 26]. Patients without a diagnosis of malignancy and still alive on December 31st , 2006 were right-censored at the date of their 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 considered separately AIDS-defining malignancies and non-AIDS-defining malignancies, while robustness analyses considered KS and NHL.

In the models taking into account the latest measurement, plasma HIV RNA and CD4+ cell count were considered as binary variables (higher or lower than the threshold considered), and cART was considered as prescribed or not. All adjusted models considered the following variables: CD4+ cell count lower than the threshold pre-specified in the model (duration of exposure or latest measurement), plasma HIV RNA higher than the threshold considered in the model (duration of exposure or latest measurement), cART exposure (duration of exposure or last prescription) and gender. In addition to the latest values of plasma HIV RNA and CD4+ cell count, representing the current exposure, we calculated a cumulative exposure to clinically relevant cut-offs of these markers as 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 are studied in separate models since they are highly correlated. The models were compared with the Akaike criterion (AIC), the lower the better fit.

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 while the hazard of non-AIDS-defining malignancies was estimated. As a history of malignancy was an exclusion criterion, no prevalent cases were included.

Due to incomplete data regarding traditional risk factors for non-AIDS malignancies (tobacco consumption, HBV and HCV infections), they were not considered in the analyses performed on the entire dataset. Hence, a robustness analysis adjusted for these risk factors, considering them as fixed-effect variables, was conducted on patients with available data concerning tobacco consumption, HBV and HCV infections. SAS software (version 9.1, SAS® Institute, Cary, NC) was used to perform the analyses.

Results

During the study period 4,828 patients were followed-up in the ANRS CO3 Aquitaine Cohort, 324 of them 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 4,194 eligible patients, accounting for 22,389 person-years (py), 251 first new diagnosis of malignancy were validated through histological (111 cases) or medical reports (140 cases). The cohort was predominantly male (72%), the 144 non-AIDS-defining malignancies and the 107 AIDS-defining malignancies were experienced by 83% and 78% men. The incidence rates of AIDS-defining malignancies were 5.2 cases per 1,000 py (95% Confidence Interval [CI]: 4.1 – 6.4) in men and 3.6 cases per 1,000 py (95% CI: 2.1 – 5.1) in women. The incidence rates of non-AIDS-defining malignancies were 7.5 cases per 1,000 py (95% CI: 6.1 – 8.8) in men and 3.8 cases per 1,000 py (95% CI: 2.3 – 5.3) 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, 5,033 concerned patients affected by a malignancy. At least two plasma HIV RNA and CD4 measuremens were reported among 4,145 patients (240 malignancies) and 4,155 patients (241 malignancies), respectively.

AIDS-defining malignancies

Both CD4+ <200 cells/mm^3 and plasma HIV RNA viral load >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, while current exposure to cART and gender were not related to the hazard of AIDS-defining malignancy (table 2).

Sixty-one cases of NHL were diagnosed over the study period among the 4,194 patients included, accounting for 57% of all diagnoses of AIDS-defining malignancies. Current exposure to both plasma HIV RNA viral load >500 copies/mL and CD4+ <200 cells/mm^3 was independently associated with a higher hazard of NHL: Hazard Ratio (HR) = 3.02 (95% CI: 1.65 – 5.52; p <0.001) and HR = 5.12 (95% CI: 3.01 – 8.70; p <0.001), respectively.

Considering the cumulative exposure, each year spent with plasma HIV RNA viral load >500 copies/mL and CD4+ <200 cells/mm^3 was independently associated with a higher risk of NHL: HR = 1.34 (95% CI: 1.19–1.51; p <0.001) and HR = 1.31 (95% CI: 1.12 – 1.53; p <0.001), 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 viral load >10,000 copies/mL was associated with a higher hazard of NHL (HR = 1.59; 95% CI: 1.38 – 1.83; p <0.001), while each year spent with a CD4+ <200 cells/mm^3 and each year of cART exposure tended to be associated with a higher risk (HR = 1.18; p = 0.057) and a lower risk of NHL (HR = 0.88; p = 0.052), respectively. Thirty-nine cases of KS were reported among the 4,194 patients, accounting for 36% of the AIDS-defining malignancies diagnosed. Multivariable analyses considering cumulative exposure showed that each year spent with CD4+ <200 cells/mm^3 was associated with a higher hazard of KS (HR=1.55, 95% CI: 1.24–1.93; p <0.001), whereas remaining with a plasma HIV RNA viral load >500 copies/mL did not affect the KS hazard (p=0.22). Female gender was associated with a lower incidence of KS (HR = 0.13; 95% CI: 0.03–0.53; p=0.005).

Non-AIDS-defining malignancies

A CD4+ cell count <500 cells/mm^3 was independently associated with a higher hazard of non-AIDS-defining malignancy, whatever the exposure considered (table 3). Plasma HIV RNA and cART were not associated with the risk of non-AIDS-defining malignancy, whatever the model considered, while female gender was related to a lower hazard (table 3). Analyses using higher thresholds for plasma HIV RNA and considering the cumulative exposure led to similar results (data not shown). In analyses considering lower thresholds for CD4+ cell count, each year spent with CD4+ <200 cells/mm^3 was independently associated with a higher risk of non-AIDS-defining malignancy (HR = 1.16, 95% CI: 1.04–1.30; p = 0.01).

Adjustment for other risk factors of malignancy

Among 3,210 patients with available data regarding tobacco consumption and HBV or HCV co-infection status, 113 non-AIDS-defining malignancies occurred.

The thresholds considered were 500 copies/mL for plasma HIV RNA and 500 cells/mm^3 for CD4+. The results of these analyses adjusted for gender, CD4+ cell count, HIV RNA, cART, tobacco consumption, HBV and HCV co-infections are presented considering two durations of cART exposure because of an interaction between the durations with CD4+ <500 cells/mm^3 and cART exposure (p = 0.02). A longer exposure to CD4+ cell count <500 cells/mm^3 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 = 0.007) in patients who remained free of cART. This association no longer existed among cART treated patients (p = 0.12 after 4 years of cART exposure).

Moreover, our results were not affected by robustness analysis considering the transmission group, whatever the type of malignancy considered.

Comparison between cumulative and current exposure

The difference in AIC between the model taking into account the current exposure to latest measurement compared to the model considering the cumulative exposure (tables 2 and 3) could be considered as 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 viral load were associated with a higher hazard 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 is a key factor to prevent NHL occurrence, at all stages of immune deficiency. HIV replication, through activation of the immune system, could be independently 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, immune deficiency and viral replication and one may speculate that the absence of 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 malignancy might be due to immune reconstitution rather than control of viral replication per se. In other hand, both longer and current exposure to uncontrolled plasma HIV RNA and immunosuppression were associated with a higher risk of AIDS-defining malignancy, underlining that the best possible control of HIV infection 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 when compared with the general population but none of them 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, chronically exposed 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, following a prescription of cART, the risk of malignancy may decrease when the CD4+ cell count rises above 500 cells/mm^3 . Our results regarding cumulative exposure to CD4+ <500 cells/mm^3 conveys important additional results, since they suggest that patients with longstanding immunodeficiency experience a higher rate of malignancy compared to patients without immunodeficiency. This could help to target a high risk population to implement prevention and screening policies.

Based on Akaike criterion, our analysis does not indicate a particular advantage of cumulative exposure to low CD4+ cells in comparison to the latest CD4+ cell count for both AIDS-defining and non-AIDS-defining malignancies. However, the consistent finding of a raised risk of AIDS and non-AIDS-defining malignancies associated with cumulative time spent below CD4+ < 200/mm^3 or 500/mm^3 provides a stronger argument that HIV infected patients may benefit from early initiation of antiretroviral treatment to decrease the risk of AIDS and non-AIDS-defining malignancies.

Burgi et al found that the use of cART was protective for malignancies, [33] and the D:A:D cohort collaboration found that the incidence of fatal non-AIDS 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 further studies including more patients should specifically address this issue. However, our results show that early control of HIV replication and maintenance of high levels of CD4+ cell count are associated with lower risk of malignancies.

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

Due to incomplete data regarding the risk factors for non-AIDS-defining malignancies (tobacco consumption, HBV or HCV infections), 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 estimating the risk of non-AIDS-defining malignancy in a large subgroup of patients free of missing values concerning these data. The association between immunosuppression and the occurrence of specific non-AIDS-defining malignancies could not be explored in this study. We acknowledge that 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 exposure to uncontrolled plasma HIV-RNA 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, whether AIDS-defining or not. Considering the global ageing 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 aim at reaching and maintaining not only an undetectable plasma HIV RNA, but also a CD4+ cell count higher than 500 cells/mm^3 to prevent the occurrence of malignancy, AIDS-defining or not. In HIV infected population, this should be integrated to malignancy prevention policies.

Ackowledgements:

Sponsorship:

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).

Appendix
Composition of the GECSA

The Groupe d'Epidemiologie Clinique du Sida en Aquitaine (GECSA) steering the ANRS CO3

Aquitaine Cohort is organized as follows:

Epidemiology, Methodology

M. Bruyand, G. Chêne, F. Dabis (Principal Investigator), S. Lawson-Ayayi, R. Thiébaut.

Infectious diseases, Internal Medicine

M. Bonarek, F. Bonnal, F. Bonnet, N. Bernard, O. Caubet, L. Caunègre, C. Cazanave, J. Ceccaldi, FA Dauchy, M. Pillot-Debelleix, C. De La Taille, S. De Witte, M. Dupon, P. Duffau, H. Dutronc, S. Farbos, Y. Gerard, C. Greib, D. Lacoste, S. Lafarie, E. Lazaro, P. Loste, D. Malvy, P. Mercié, P. Morlat, D. Neau, A. Ochoa, JL. Pellegrin, T. Pistone, JM. Ragnaud, MC. Receveur, S. Tchamgoué, MA. Vandenhende, JF. Viallard.

Immunology, Virology, Pharmacology, Pharmacovigilance

Immunology: P. Blanco, JF. Moreau, I. Pellegrin. Virology: H. Fleury, ME. Lafon, B. Masquelier.

Pharmacology: D. Breilh. Pharmacovigilance: G. Miremont-Salamé.

Data collection

MJ. Blaizeau, M. Decoin, S. Delveaux, C. D'Ivernois, C. Hannapier, V. Jauvin, O. Leleux, B. Uwamaliya-Nziyumvira.

Data management

S. Geffard, G. Palmer, D. Touchard.

Scientific committee

M. Dupon, M. Longy-Boursier, P. Morlat, JL. Pellegrin, JM. Ragnaud and F. Dabis.*

Footnotes:

These results were presented in part at the 15th Conference on retroviruses and opportunistic infections (Hynes Convention center, Boston, MA, US, February 3-6, 2008), abstract 15.

Conflict of interest: M Bruyand: no conflict R Thiébaut: no conflict S Lawson-Ayayi: no conflict P Joly: no conflict A.J Sasco: no conflict P Mercié: no conflict JL Pellegrin: no conflict D Neau: no conflict F Dabis: no conflict P Morlat: no conflict G Chêne: no conflict F Bonnet: no conflict

References:

- 1 . Silverberg MJ , Abrams DI . AIDS-defining and non-AIDS-defining malignancies: cancer occurrence in the antiretroviral therapy era . Curr Opin Oncol . 2007 ; 19 : 446 - 51
- 2 . 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults . MMWR Recomm Rep . 1992 ; 41 : 1 - 19
- 3 . Chang Y , Cesarman E , Pessin MS . Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma . Science . 1994 ; 266 : 1865 - 9
- 4 . Bonnet F , Chêne G , Thiebaut R . Trends and determinants of severe morbidity in HIV infected patients: the ANRS CO3 Aquitaine cohort, 2000–2004 . HIV Med . 2007 ; 8 : 547 - 54
- 5 . Lewden C , Salmon D , Morlat P . Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS . Int J Epidemiol . 2005 ; 34 : 121 - 30
- 6 . Sackoff JE , Hanna DB , Pfeiffer MR , Torian LV . Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City . Ann Intern Med . 2006 ; 145 : 397 - 406
- 7 . Bonnet F , Lewden C , May T . Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy . Cancer . 2004 ; 101 : 317 - 24
- 8 . Lewden C , May T , Rosenthal E . Changes in causes of death among adults infected by HIV between 2000 and 2005: The “Mortalite 2000 and 2005” surveys (ANRS EN19 and Mortavic) . J Acquir Immune Defic Syndr . 2008 ; 48 : 590 - 8
- 9 . Clifford GM , Polesel J , Rickenbach M . Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy . J Natl Cancer Inst . 2005 ; 97 : 425 - 32
- 10 . Bonnet F , Balestre E , Thiebaut R . Factors associated with the occurrence of AIDS-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: Aquitaine Cohort, France . Clin Infect Dis . 2006 ; 42 : 411 - 7
- 11 . Engels EA , Pfeiffer RM , Goedert JJ . Trends in cancer risk among people with AIDS in the United States 1980–2002 . Aids . 2006 ; 20 : 1645 - 54
- 12 . Herida M , Mary-Krause M , Kaphan R . Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients . J Clin Oncol . 2003 ; 21 : 3447 - 53
- 13 . Bonnet F , Burty C , Lewden C . Changes in cancer mortality among HIV-infected patients: the Mortalite 2005 Survey . Clin Infect Dis . 2009 ; 48 : 633 - 9
- 14 . Benard A , Tessier JF , Rambeloarisoa J . HIV infection and tobacco smoking behaviour: prospects for prevention? ANRS CO3 Aquitaine Cohort, 2002 . Int J Tuberc Lung Dis . 2006 ; 10 : 378 - 83
- 15 . Friis-Moller N , Weber R , Reiss P . Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study . Aids . 2003 ; 17 : 1179 - 93
- 16 . Puoti M , Bruno R , Soriano V . Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome . Aids . 2004 ; 18 : 2285 - 93
- 17 . Clifford GM , Rickenbach M , Polesel J . Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma . AIDS . 2008 ; 22 : 2135 - 41
- 18 . Mack KD , Wei R , Herndier B . HIV insertional cis-activation of the protooncogene c-fes in AIDS lymphogenesis . J Acquir Immune Defic Syndr Hum Retrovirol . 1997 ; 14 : A44 - (abstract)
- 19 . el-Solh A , Kumar NM , Nair MP , Schwartz SA , Lwebuga-Mukasa JS . An RGD containing peptide from HIV-1 Tat-(65–80) modulates protooncogene expression in human bronchoalveolar carcinoma cell line, A549 . Immunol Invest . 1997 ; 26 : 351 - 70
- 20 . Marsh JW , Herndier B , Tsuzuki A . Cytokine expression in large cell lymphoma associated with acquired immunodeficiency syndrome . J Interferon Cytokine Res . 1995 ; 15 : 261 - 8
- 21 . Ott M , Emiliani S , Van Lint C . Immune hyperactivation of HIV-1-infected T cells mediated by Tat and the CD28 pathway . Science . 1997 ; 275 : 1481 - 5
- 22 . Hajjar M , Lacoste D , Brossard G . Non-Acquired Immune Deficiency Syndrome-Defining Malignancies in a Hospital-Based Cohort of Human Immunodeficiency Virus-Infected Patients: Bordeaux, France, 1985–1991 . J Natl Cancer Inst . 1992 ; 84 : 1593 - 5
- 23 . Thiebaut R , Morlat P , Jacqmin-Gadda H . Clinical progression of HIV-1 infection according to the viral response during the first year of antiretroviral treatment . AIDS . 2000 ; 14 : 971 - 8
- 24 . Lewden C , Chene G , Morlat P . HIV-infected adults with a CD4 cell count greater than 500 cells/mm3 on long-term combination antiretroviral therapy reach same mortality rates as the general population . J Acquir Immune Defic Syndr . 2007 ; 46 : 72 - 7
- 25 . Commenges D , Letenneur L , Joly P . Re: “Serum transferrin saturation, stroke incidence, and mortality in women and men. The NHANES I Epidemiologic Followup Study” . Am J Epidemiol . 1997 ; 146 : 683 - 4
- 26 . Breslow NE , Day NE . Statistical methods in cancer research. Volume II--The design and analysis of cohort studies . IARC Sci Publ . 1987 ; 1 - 406
- 27 . Commenges D , Sarrayeh A , Letenneur L , Guedj J , Bar-Hen A . Estimating a difference of Kulback-Leibler risks using a normalized difference of AIC . Annals of Applied Statistics . 2008 ; 2 : 1123 - 42
- 28 . Deeks SG , Kitchen CMR , Liu L . Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell changes independent of viral load . Blood . 2004 ; 104 : 942 - 7
- 29 . 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
- 30 . Frisch M , Biggar R , Engels E , Goedert J . Association of cancer with AIDS-related immunosuppression in adults . JAMA . 2001 ; 285 : 1736 - 45
- 31 . Vajdic CM , McDonald SP , McCredie MR . Cancer incidence before and after kidney transplantation . Jama . 2006 ; 296 : 2823 - 31
- 32 . Serraino D , Piselli P , Busnach G . Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern Europe . Eur J Cancer . 2007 ; 43 : 2117 - 23
- 33 . Burgi A , Brodine S , Wegner S . Incidence and risk factors for the occurrence of non-AIDS-defining cancers among human immunodeficiency virus-infected individuals . Cancer . 2005 ; 104 : 1505 - 11
- 34 . d'Arminio Monforte A . Malignancy-related deaths among HIV-infected patients . Clin Infect Dis . 2009 ; 48 : 640 - 1
- 35 . Remontet L , Esteve J , Bouvier AM . Cancer incidence and mortality in France over the period 1978–2000 . Rev Epidemiol Sante Publique . 2003 ; 51 : 3 - 30

Table 1

Characteristics of the 251 new cases of malignancy (ANRS CO3 Aquitaine Cohort, 1998–2006)

	All (n = 251)			
	Non-AIDS-defining (n = 144)		AIDS-defining (n = 107)	
Type of malignancy	**n**		**n**	
Non-Hodgkin's lymphoma	-		61	
Kaposi's sarcoma	-		39	
Cervix carcinoma	-		7	
Bronchopulmonary	30		-	
Skin malignancy (melanoma)	20 (4)		-	
Hodgkin's disease	18		-	
Hepatocarcinoma	16		-	
Anal malignancy	14		-	
Other hemopathies	6		-	
Other solid tumors	40		-	
Characteristics (continuous variables)	Median	IQR	Median	IQR
Age at malignancy diagnosis (years)	46.7	41.3–54.9	41.3	35.4–47.5
Duration of follow-up in the study period (years)	4.2	1.9–6.2	3.1	1.2–4.9
Time since first HIV positive test (years)	12.5	8.4–15.9	10.0	4.4–14.1
Nadir of plasma HIV RNA viral load during the study period (Log copies/ml)	1.7	1.7–2.7	3.0	1.8–4.0
Plasma HIV RNA viral load value at the time of malignancy diagnosis (Log copies/ml)	2.7	1.7–3.8	4.5	2.7–5.2
Duration of follow-up with plasma HIV RNA viral load ≤ 500 copies/ml (years)	1.5	0.3–3.5	0.0	0.0–0.7
Nadir of CD4+ cell count during the study period (cells/mm^3)	186	93–296	129	21–281
CD4+ cell count value at the time of malignancy diagnosis (cells/mm^3)	341	178–488	198	52–390
Duration of cART use during the study period (years)	2.9	0.7–5.3	1.6	0.5–3.5
Characteristics (categorical variables)	%		%	
Gender (men)	83		78	
Intra venous drug users	25		25	

NOTE. IQR, Inter Quartile Range

Table 2

Determinants of a first AIDS-defining malignancy, multivariate analyses including either cumulative exposure to viro-immunological markers or latest measurements (ANRS CO3 Aquitaine Cohort, 1998–2006; N = 4194; 107 cases)

Cumulative exposure[a,b]				Latest measurement[a,b]			
Variables	**HR**	**95% CI**	**p**	**Variables**	**HR**	**95% CI**	**p**
CD4+ <200 cells/mm^3 (per additional year of exposure)	1.36	[1.21 – 1.54]	<0.001	CD4+ <200 cells/mm^3 (yes vs no)	6.33	[4.25 – 9.41]	<0.001
Plasma HIV RNA >500 copies/mL (per additional year of exposure)	1.27	[1.15 – 1.40]	<0.001	Plasma HIV RNA >500 copies/mL (yes vs no)	3.30	[2.07 – 5.25]	<0.001
cART exposure (per additional year)	0.82	[0.74 – 0.91]	<0.001	cART (yes vs no)	0.93	[0.61 – 1.43]	0.74
Gender (women vs men)	0.69	[0.43 – 1.10]	0.11	Gender (w vs m)	0.75	[0.47 – 1.19]	0.22

NOTE. HR, Hazard Ratio for the association between a given variable and hazard of AIDS-defining malignancy
CI, Confidence Interval

a Adjusted for other variables: CD4+ <200, plasma HIV RNA >500, cART exposure and gender

b Akaike criterion (AIC) for cumulative exposure = 1325.3, AIC for latest measurement = 1251.4

Table 3

Determinants of a first non-AIDS-defining malignancy, multivariate analyses including either cumulative exposure to viro-immunological markers or latest measurements (ANRS CO3 Aquitaine Cohort, 1998–2006; N = 4194; 144 cases)

Cumulative exposure[a,b]				Latest measurement[a,b]			
Variables	**HR**	**95% CI**	**p**	**Variables**	**HR**	**95% CI**	**p**
CD4+ <500 cells/mm^3 (per additional year of exposure)	1.13	[1.03 – 1.24]	0.01	CD4+ <500 cells/mm^3 (yes vs no)	2.07	[1.41 – 3.05]	<0.001
Plasma HIV RNA >500 copies/mL (per additional year of exposure)	1.03	[0.94 – 1.13]	0.49	Plasma HIV RNA >500 copies/mL (yes vs no)	1.34	[0.94 – 1.91]	0.10
cART exposure (per additional year)	0.99	[0.91 – 1.08]	0.87	cART exposure (yes vs no)	1.04	[0.70 – 1.54]	0.85
Gender (women vs men)	0.59	[0.38 – 0.92]	0.02	Gender (w vs m)	0.60	[0.39 – 0.94]	0.02

NOTE.HR: Hazard Ratio for the association between a given variable and hazard of non-AIDS-defining malignancy
CI: Confidence Interval

a Adjusted for other variables: CD4+ <500, plasma HIV RNA >500, cART exposure and gender

b Akaike criterion (AIC) for cumulative exposure = 1725.4, AIC for latest measurement = 1717.8