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Editorial

Risk of cancers in HIV infection

Riesgo de cáncer en la infección por VIH

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Cancer is a frequent comorbidity in HIV-infected individuals, and it represents 34% of the causes of death in 2010 in France.¹ Initially, three cancers, known to be virus associated, that is Kaposi's sarcoma (associated with HHV8), non-Hodgkin's lymphoma (associated with EBV in most cases) and cervical cancer (associated with HPV) were added to the list of AIDS-defining conditions because of their association to immunodeficiency.^{2,3} However, non-AIDS defining cancers are also more frequent in HIV infected individuals than in the general population by a factor 2–3 according to the different studies, and the most frequent are Hodgkin lymphoma (associated with EBV), lung, anal (associated with HPV) and liver (associated with HBV or HCV) cancers.^{4–6} In this issue of the journal two articles are published, one on the risk of AIDS defining cancers in Spain in the combined antiretroviral treatment (cART) era,⁷ and the other reviewing what is currently known on the risk on non-AIDS defining cancers in HIV-infected individuals.⁸

In Suárez-García et al., unsurprisingly, the risk of Kaposi sarcoma (KS) and non-Hodgkin lymphomas (NHL including cerebral) was associated with immunodeficiency. After accounting for immunodeficiency and adjusting for viral load, there was a protective effect of being on cART, an effect mediated neither by the impact of treatment on viral load control nor on CD4 cell counts. Similar results were found in the French Hospital Database on HIV infection (FHDH ANRS CO4).⁹ In addition we found that viral load above 4 log 10 copies/mL was associated with an increased risk, while the smaller sample size in the CoRIS-CoRIS MD cohort may have prevented the detection of this risk factor. When only cases diagnosed more than 30 days after enrolment were accounted for, HCV infection was associated with a higher risk of NHL, in line with recent publications.^{10,11}

For non-AIDS defining cancers the relative risk compared with the general population differs widely according to cancer type, being the highest for anal cancer (47) and Hodgkin lymphoma (19) and much smaller for lung cancer (3.5), while the relative risk for liver cancer depends a lot on the frequency of HCV coinfection, in a meta-analysis of studies conducted in the cART era.⁵ Interestingly

the relative risks for breast and prostate cancer, two hormone-dependant cancers, were smaller than one (0.6 for both) in the same meta-analysis. As noted in Valencia Ortega,⁸ low breast cancer risk with HIV have been reported to be specifically linked to CXCR4-using variants of HIV. These variants are thought to exclusively bind to and signal through a receptor commonly expressed on hyperplastic and neoplastic breast duct cells.¹²

The hypothesis of premature ageing associated with HIV infection was raised because age related comorbidities, including non-AIDS defining cancers, occurred at much younger age (10–20 years younger) in patients infected with HIV compared to uninfected individuals.^{13,14} However, when studying age at diagnosis of non-AIDS defining cancers, after adjusting for the difference in age distribution between patients with AIDS and the general population, Shiels et al. showed that the differences in median age at diagnosis were modest and most of them were not significant.¹⁵

Recent papers on the risk of anal cancer in HIV-infected individuals showed an increase risk in the cART era compared to the pre cART era.^{16–18} This is consistent with the finding duration of immunodeficiency is a risk factor for anal cancer and not current level of CD4 cell count.⁹ Palefsky and Holly¹⁹ have proposed that immune suppression would affect earlier stage of intraepithelial neoplasia related to HPV, but have a small role in progression to invasive cancer that might be related to a cumulative effect of genetic changes. The finding that anal cancer was better predicted by the duration of immunodeficiency and of high viral load could be explained by this mechanism. In the cART era patients who have been profoundly immunosuppressed survive longer and the intraepithelial neoplasia, promoted by immunodeficiency, can then develop to cancer, emphasizing that progression of anal intraepithelial neoplasia towards invasive cancer is not easily reversible.

For Hodgkin lymphoma, lung and liver cancers, their risk is also elevated in organ transplant recipients,⁴ and we showed that the level of immunodeficiency is also a risk factor for these cancers, even when accounting for tobacco exposure for lung cancer or for HBV or HCV status for liver cancer.⁹ Lung cancer is the only frequent cancer in HIV-infected patients not known to be associated with viral infection. Several studies have suggested that HIV infection is associated with the risk of lung cancer even after adjusting for cigarette smoking.^{20–22} However, persistent inflammation and activation, commonly described in HIV patients even with

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controlled viral load under cART, have been shown to increase the risk of lung cancer in non-HIV infected individuals.²³

Finally, given the link of the different cancers with immunodeficiency, one may expect a lower risk in treated patients with recovered immunity as evidenced with a CD4 cell count above 500/mm³, except for anal cancer, or who initiate cART with maintained level. There are few studies exploring this hypothesis so far, due to lack of sufficient person-years of follow-up with these two situations. In Silverberg et al., the relative risk in HIV infected patients with current CD4 > 500/mm³, was still highly significant for Kaposi sarcoma (60), Anal cancer (34), Hodgkin lymphoma (13.5), Non-Hodgkin lymphoma (4), but no longer for lung (1.2) and liver cancer (1.0).²⁴ We went a step further and showed that for anal cancer, among patients with CD4 cell counts above 500/mm³ for at least 2 years, the relative risks were 67.5 (95% CI, 41.2–104.3) when the CD4 nadir was less than 200/mm³ for more than 2 years and 24.5 (95% CI, 17.1–34.1) when the CD4 nadir was more than 200/mm³.¹⁷ For AIDS defining cancers, it would also be important to account for viral load and cART, as there are independent risk factors. Further studies are needed to clarify this issue.

In conclusion, as re-emphasized by Valencia Ortega,⁸ cART would be most beneficial to prevent the risk of cancer in HIV infected patients, if it restores or maintains CD4 count above 500/mm³, thereby indicating the need for an earlier diagnosis of HIV infection and an earlier treatment initiation.

References

1. Roussillon C, Henard S, Hardel L, Rosenthal E, Aouba A, Bonnet F, et al. Cause de décès des patients infectés par le VIH en France en 2010: Etude ANRS EN20 Mortalité 2010. *BEH.* 2012;46–47:541–5.
2. Goedert JJ, Côté TR, Virgo P, Scoppa SM, Kingma DW, Gail MH, et al. Spectrum of AIDS-associated malignant disorders. *Lancet.* 1998;351:1833–9.
3. Frisch M, Biggar RJ, Engels EA, Goedert JJ; AIDS-Cancer Match Registry Study Group. Association of cancer with AIDS-related immunosuppression in adults. *JAMA.* 2001;285:1736–45.
4. 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.
5. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. *J Acquir Immune Defic Syndr.* 2009;52:611–22.
6. Spano JP, Costagliola D, Katlama C, Mounier N, Oksenhendler E, Khayat D. AIDS-related malignancies: state of the art and therapeutic challenges. *J Clin Oncol.* 2008;26:4834–42.
7. Suárez-García I, Jarrín I, Iribarren JA, López-Cortés LF, Lacruz-Rodrigo J, Masía M, et al. Incidence and risk factors of AIDS-defining cancers in a cohort of HIV-positive adults: importance of the definition of incident cases. *Enferm Infecc Microbiol Clin.* 2013;31:303–11.
8. Valencia Ortega ME. Tumores no definitorios de sida o el gigante dormido: actualización. *Enferm Infecc Microbiol Clin.* 2013;31:318–26.
9. Guiguet M, Boué F, Cadranet J, Lang JM, Rosenthal E, Costagliola D, on behalf of the Clinical Epidemiology Group of the FHDH-ANRS CO4 cohort. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol.* 2009;10:1152–9.
10. Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. *Cancer Epidemiol Biomarkers Prev.* 2006;15:2078–85.
11. Terrier B, Costagliola D, Prevot S, Chavez H, Missy P, Rince P, et al [Epub ahead of print] Characteristics of B-cell Lymphomas in HIV-HCV coinfecting patients during the combined antiretroviral therapy era. An ANRS CO16 LYMPHOVIR cohort study. *J Acquir Immune Defic Syndr.* 2013. <http://dx.doi.org/10.1097/QAL.0b013e31828a77f0>.
12. Hessel NA, Napolitano LA, Smith D, Lie Y, Levine A, Young M, et al. HIV tropism and decreased risk of breast cancer. *PLoS ONE.* 2010;5:e14349.
13. Bhavan KP, Kampalath VN, Overton ET. The aging of the HIV epidemic. *Curr HIV/AIDS Rep.* 2008;5:150–8.
14. Effros RB, Fletcher CV, Gebo K, Halter JB, Hazzard WR, Horne FM, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clin Infect Dis.* 2008;47:542–53.
15. Shiels MS, Pfeiffer RM, Engels EA. Age at cancer diagnosis among persons with AIDS in the United States. *Arch Intern Med.* 2010;153:452–60.
16. Seaberg EC, Wiley D, Martínez-Maza O, Chmiel JS, Kingsley L, Tang Y, et al. Cancer incidence in the multicenter AIDS Cohort Study before and during the HAART era: 1984 to 2007. *Cancer.* 2010;116:5507–16.
17. Piketty C, Selinger-Leneman H, Bouvier AM, Belot A, Mary-Krause M, Duvivier C, et al. The incidence of HIV-related anal cancer remains elevated despite long-term cART: results from the French Hospital Database on HIV (FHDH-ANRS CO4 cohort). *J Clin Oncol.* 2012;30:4360–6.
18. Franceschi S, Lise M, Clifford GM, Rickenbach M, Levi F, Maspoli M, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: The Swiss HIV Cohort Study. *Br J Cancer.* 2010;103:416–22.
19. Palefsky J, Holly E. Immunosuppression and co-infection with HIV. *J Natl Cancer Inst Monogr.* 2003;31:41–6.
20. Engels EA, Brock MV, Chen J, Hooker CM, Gillison M, Moore RD. Elevated incidence of lung cancer among HIV-infected individuals. *J Clin Oncol.* 2005;24:1383–8.
21. Chaturvedi AK, Pfeiffer RM, Chang L, Goedert JJ, Biggar RJ, Engels EA. Elevated risk of lung cancer among people with AIDS. *AIDS.* 2007;21:207–13.
22. Kirk GD, Merlo C, O'Driscoll P, Mehta SH, Galai N, Vlahov D, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis.* 2007;45:103–10.
23. Pine SR, Mechanic LE, Enewold L, Chaturvedi AK, Katki HA, Zheng YL, et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. *J Natl Cancer Inst.* 2011;103:1112–22.
24. Silverberg MJ, Chao C, Leyden WA, Xu L, Horberg MA, Klein D, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. *Cancer Epidemiol Biomarkers Prev.* 2011;20:2551–9.