Uncontrolled HIV RNA, Immunodeficiency, and Malignancy: Implications for Cancer Control

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(See the article by Bruyand et al, on pages 1109–16.)

In April 2009, *The Lancet Oncology* published the findings of a working group (36 scientists from 16 countries) that met in February 2009 at the International Agency for Research on Cancer (Lyon, France) to reassess the carcinogenicity of the biological agents classified as “carcinogenic to humans” (group 1) [1]. With regard to human immunodeficiency virus (HIV) infection, a clear link has been recognized with several oncogenic viruses, mainly Epstein-Barr virus, Kaposi sarcoma herpes virus, and the human papilloma viruses. The epidemiological and mechanistic evidence accumulated worldwide has been considered sufficient to determine that HIV, through an immunosuppressive indirect action, causes Kaposi sarcoma, non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, and cancers of the cervix, anus, and conjunctiva. The evidence supporting a causal role of HIV was considered limited for cancers of the vulva, vagina, and penis; for nonmelanoma skin cancer; and for hepatocellular carcinoma. However, for other cancer types (namely lung cancer), the evidence was considered insufficient. The main difficulty in assessing the site-specific carcinogenicity of HIV was to disentangle the role of HIV-induced immunosuppression from the role of other well-established risk factors for cancer (eg, smoking and lung cancer; hepatitis C virus infection and liver cancer) that are more frequent among HIV-infected patients than in the sex- and age-corresponding general population. The study by Bruyand et al [2] on French HIV-infected patients in this issue of *Clinical Infectious Diseases* offers a new piece of evidence to shed further light on the topic.

From an epidemiologic viewpoint, the age at which immunosuppression starts and the duration and degree of immunosuppression are key parameters to be considered when investigating the occurrence of cancer in the setting of acquired immunosuppression—whether HIV-related or iatrogenically induced after organ transplantation. In agreement with international standards, the French study used a CD4+ cell count <200 cells/mm³ (or <500 cells/mm³ for non–AIDS-defining cancers) and a plasma HIV load >500 copies/mm³ as markers of severe immunosuppression and of uncontrolled plasma HIV load. The association of severe immunosuppression with cancer risk was separately assessed for AIDS-defining cancers (ie, Kaposi sarcoma, NHL, and cervical cancer) and for non–AIDS-defining cancers. Two aspects of the methodology employed by Bruyand and colleagues were rarely used from previous investigations and are worth noting: (1) the computation of individual time spent with an uncontrolled HIV RNA level or with a low CD4+ cell count, and (2) the adjustment, on an individual basis, for risk factors other than immunosuppression. On the other hand, the presentation of the combined results for all 3 AIDS-defining cancers (in Table 2 in the article) and for all non–AIDS-defining cancers together (in Table 3) may have concealed inconsistent, site-dependent relationships between immunosuppression and cancer occurrence.

With regard to the 3 AIDS-defining cancers, it is well known that HIV-infected patients treated with combination antiretroviral therapy (cART) have a largely reduced risk of developing Kaposi sarcoma or NHL. Conversely, treatment with cART does not influence the risk of cervical cancer in HIV-infected women. Of the 3 AIDS-defining malignancies, NHL are of particular importance, given their persisting negative impact on survival of people with AIDS in the cART era. From this perspective, the findings from the French study—a nearly 30% significantly increased risk for NHL for each year spent with severe immunosuppression and a 15% reduced risk for NHL for each year spent receiving cART—are original and have important implications. In fact,
cART has a crucial role in the prevention of NHL, because Epstein-Barr virus infection and immunosuppression are the only known risk factors for development of such malignancy. Data from Bruyant et al [2] show that diminishing the time spent with severe immunosuppression and increasing the time spent receiving cART are substantial tools for controlling the occurrence of NHL and, thus, for reducing HIV-related mortality.

With the advent of cART, the burden of Kaposi sarcoma on morbidity and mortality of HIV-infected people has substantially diminished, and the French study confirmed the importance of controlling the degree of immunosuppression through maintaining a CD4+ cell count >200 cells/mm3.

Because of prolonged survival and aging, morbidity and mortality in HIV-infected individuals are increasingly influenced by malignancies that would have occurred regardless of HIV infection. In fact, non–AIDS-defining illnesses are among the leading causes of death of people with HIV infection in the cART era (in Italy, the proportion of persons with AIDS who died of a non–AIDS-defining cancer increased from 3.7% in 1999 to 8.7% in 2006), and several efforts are needed to improve prevention and control strategies. Few cancer types account for the vast majority of non–AIDS-defining malignancies, and these were well identified by Bruyand and colleagues (ie, lung cancer, Hodgkin lymphoma, liver cancer, anal cancer, and skin cancers). Data from the literature indicate that the risk of developing some of these cancers (eg, lung cancer and liver cancer) does not seem to be influenced by cART, whereas the association with the degree of immunosuppression—as measured mainly by current CD4+ cell count—has not yet been well defined. For Hodgkin lymphoma, the picture is more complex, because the current CD4+ cell count is influenced by sequestration of lymphocytes at the tumor site in the months preceding the diagnosis of Hodgkin lymphoma—a mechanism that promotes a decrease in the number of circulating CD4+ cells. This observation makes timing of CD4+ cell count determinations, with respect to diagnosis of Hodgkin lymphoma, a key element to consider in the controversial relationship between immunosuppression and this malignancy.

Given the relative small numbers of observed cases for each single cancer type, Bruyand et al [2] choose to combine data for all non–AIDS-defining malignancies. As already noted, this fact may somehow limit the interpretation of study findings, because the assumption of consistency of results across non–AIDS-defining cancers is likely to be weak. Overall, the French study points to an important role for CD4+ cell counts in increasing the risk of non–AIDS–associated malignancies. This elevated risk was observed when both cumulative and current CD4+ cell count <500 cells/mm3 were considered. However, after adjustment for confounding factors (including smoking) in a subgroup of study subjects, the association was statistically significant only in patients who were never treated with cART. It would be interesting to further explore this observation, with particular regard to lung cancer: what is the risk of lung cancer for HIV-infected smokers treated with cART and with a CD4+ cell count that is persistently greater than 500 cells/mm3? Combination of an appropriate antiretroviral regimen with prevention programs—an-tismoking campaigns and screening programs are, in my opinion, the priorities—is the main message of the study by Bruyand and colleagues for the prevention and control of cancer in HIV-infected people in the cART era. This is a message that I totally share.

Acknowledgments
Potential conflicts of interest. D.S.: no conflicts.

References