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INVITED COMMENTARY

An Appraisal of Non-AIDS-Defining Cancers

In recent years, more and more persons infected with HIV in the United States have developed non-AIDS-defining cancers (NADCs) despite consistent and successful HAART. This phenomenon cannot be ascribed to simply an age effect, ie, that more persons infected with HIV live longer and consequently reach an age where the risk for spontaneous cancers increases exponentially. This is not true. In the most extensive analysis to my knowledge yet undertaken, Simard et al dem-

onstrate that HIV confers an increased cancer risk independent of other factors, including age. Notably, their study calculates cancer risk for the 1996-2006 period. Since this is the time of widespread available triple therapy, it is unlikely that the trends they have documented will change appreciably because of better HAART or better HAART adherence alone. The NADCs are here to stay.

The most dramatically increased incidences are for the NADCs linked to human cancer viruses, just as is the case

with the “classic” AIDS-defining cancers, KS, cervical cancer, and many NHLs, which are linked, respectively, to KS-associated herpesvirus, HPV, and Epstein-Barr virus. Perhaps then in today’s NADCs we are seeing a second wave of immune-controlled cancers that break through the residual immune system that exists in patients undergoing HAART. Alternatively, the exposure risks for infectious agents in general differ among people at high risk for acquiring HIV infection and the general population.

A quarter of all subjects studied by Simard et al acquired HIV by IDU and so likely also acquired hepatitis C virus (HCV) or other blood-borne viruses. This exposure may explain the increased risk for liver cancer in this population and raises the issue of liver transplantation as a treatment technique for HCV- and/or HIV-infected patients. Although follow-up data are necessarily limited, HIV infection per se does not seem to confer an increased risk of solid organ transplant failure. However, the debate is ongoing whether HIV infection and/or HAART drugs are associated with increased HCV re-emergence and mortality.¹⁻³ This association, if it exists, conflicts with the theoretical argument that HAART may have off-target inhibitory effects on HCV replication and that immunosuppressive drugs, such as rapamycin, can inhibit HIV persistence.

Anal cancer stands out among NADCs in the HAART era, with a SIR of approximately 30. The most recent assessment by the WHO [World Health Organization] International Agency for Research on Cancer⁴ also concluded that there is sufficient evidence in humans to call anal cancer HIV (and of course HPV) associated. Should we classify anal cancer as an AIDS-defining cancer in the post-HAART era?

Incidence of Hodgkin disease (HD) has also increased significantly in the HAART era, with a SIR of 12.0 (95% CI, 9.7-14.0) for people in years 6 to 10 after AIDS onset. There is conflicting evidence whether this increase is driven by the higher CD4 count found in people with HIV undergoing HAART, which somehow may fuel disease development.^{5,6} The discrepancy between studies may be owing to methodologic issues or, more likely, to differential pathology. Hodgkin disease occurs in many subclasses associated with different SIRs at 6 to 10 years after AIDS onset (eg, SIR, 6.2 [95% CI, 4.4-8.5] for nodular sclerosis HD and SIR, 17 [95% CI, 12-23] for mixed cellularity HD.) As the subclass composition of HD differs among different populations, so does the HIV-attributable risk to develop HD.

Other cancers show lower SIRs, given that even in this large cohort the incidences of individual NADCs are generally low. Nevertheless, the risks are significant. Lung cancer is a case in point. The incidence of lung cancer is increased in persons infected with HIV, with a SIR of 3.0 (95% CI, 2.8-3.3) at years 3 to 5 and 2.6 (95% CI, 2.3-2.9) at years 6 to 10 after AIDS onset. However, it has not been possible epidemiologically to separate the risk for lung cancer conferred by smoking in persons infected with HIV from the risk conferred by HIV infec-

tion itself. Therefore, lung cancer cannot be called HIV associated at this time.

More work is needed, particularly toward accounting for and defining the relative risks for rarer NADCs. For instance, Merkel cell carcinoma incidence is dramatically increased in persons infected with HIV,⁷ but the total number of cases worldwide is so low that a reliable SIR will probably never be calculated. Simard et al conclude that when the dramatic increase in incidences of anal cancer and Hodgkin disease were excluded, the change in incidence of NADCs between the pre-HAART and HAART era was no longer apparent.

Even in the HAART era, 10 times more people in the United States die of the 4 classic AIDS-defining cancers than die of any 1 of the 3 most frequent NADCs (lung cancer, prostate cancer, or HD). In the case of KS, approximately one-third of patients now develop KS without a detectable HIV load and with nearly normal CD4 counts.^{8,9} This suggests that mere T-cell numbers do not fully explain cancer risk in the HAART era. We might need to look at the immune system functionally as well as in terms of immune repertoire.

Finally, the most important question remains unanswered: Is there a pathophysiologic difference between the cancers (AIDS-defining cancers and NADCs) that develop in HIV-infected persons with long-term HAART drug exposure and the cancers of those who have not experienced HIV infection and HAART? And if there is a difference, how can we exploit it to develop better therapies?

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