Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome and Cancer: Past, Present, and Future

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From the beginning of the human immunodeficiency virus (HIV) epidemic in 1981, it has been apparent that people infected with this virus have an elevated risk for certain cancers, most notably Kaposi sarcoma (KS) and non-Hodgkin lymphoma. Indeed, it was the explosive outbreak of KS among young homosexual men in New York City and California that signaled the onset of the epidemic. HIV induces clinical disease, the acquired immunodeficiency syndrome (AIDS), by causing progressive depletion of $CD4^+$ T lymphocytes, the linchpin of the cell-mediated immune system. Only since 1996 have we had effective HIV/AIDS treatment, in the form of highly active antiretroviral therapy (HAART), that can markedly suppress the replication of HIV, partially restore immunity, reduce morbidity, and extend life *(1)*.

The HIV epidemic has taught us a great deal about many things, cancer not least of all. Chang et al. *(2)* discovered a gamma herpesvirus, human herpesvirus 8 (HHV8), to be the long sought cause of KS. Knowles et al. *(3)* identified a novel, rare non-Hodgkin lymphoma subtype, now termed primary effusion lymphoma. Cesarman et al. *(4)* showed that primary effusion lymphoma tumors always contain and are probably caused by HHV8, perhaps assisted by the other human gamma herpesvirus, Epstein Barr virus (EBV).

Use of HAART may alter the spectrum of AIDS malignancies and afford new insights on cancer etiology. This was considered by the Swiss HIV Cohort Study (SHCS), as reported by Clifford and colleagues in this issue of the Journal *(5)*. Their findings support the basic tenet that HIV-induced immunosuppression is responsible for the profound excess of KS and non-Hodgkin lymphoma among HIV-infected persons. Risk for KS and non-Hodgkin lymphoma increased steadily as $CD4^+$ cell counts declined. Risk was higher in persons with AIDS than in persons with less severe immunosuppression, and HAART greatly reduced risk for these cancers. These observations confirm results from prior studies *(6–8)*.

Nonetheless, clarifying how immunity and EBV are involved in the etiology of lymphoma, including Hodgkin lymphoma as well as non-Hodgkin lymphoma, continues to be difficult. Among persons with AIDS, the excess risk for non-Hodgkin lymphoma varies by histology, with increases ranging from 14-fold for low-grade lymphoma to 630-fold for high-grade immunoblastic lymphoma *(9)*. The incidence of central nervous system lymphoma in persons with AIDS is elevated approximately 3600-fold compared with that in the general population *(10)*. The SHCS study found that non-Hodgkin lymphoma incidence decreased approximately 76% with use of HAART *(5)*. Other studies have been less encouraging. In the EuroSIDA study, the incidence of AIDS-defining conditions overall declined 73% with HAART, but non-Hodgkin lymphoma declined only 40% *(11)*. A meta-analysis of 11 studies estimated that AIDS-non-Hodgkin lymphoma incidence fell 42% during the HAART era compared with the pre-HAART era *(8)*. The picture may also be somewhat nuanced, with varying reductions for different non-Hodgkin lymphoma subtypes. In the meta-analysis *(8)*, the estimated decline was greatest (58%) for central nervous system lymphoma, intermediate (43%) for immunoblastic lymphoma, and essentially zero for Burkitt lymphoma.

The picture is more confusing for Hodgkin lymphoma. Hodgkin lymphoma incidence in persons with HIV/AIDS is elevated about 12-fold compared with that in the general population and is especially high for mixed cellularity (increased 18-fold) and lymphocytic depletion (35-fold) subtypes

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(12). Nearly all Hodgkin lymphoma tumors in persons with HIV/AIDS are EBV-positive *(13)*. However, the relationship between Hodgkin lymphoma incidence and $CD4^+$ cell count is not clear-cut *(5,7)*, and the meta-analysis found only a statistically nonsignificant decline in the HAART era *(8)*. More surprisingly, the current SHCS study actually found a threefold higher risk of Hodgkin lymphoma in HIV-infected persons treated with HAART than in those not treated *(5)*. Indeed, among HAART-treated individuals, the relative risk compared with the general population appeared higher for Hodgkin lymphoma than for non-Hodgkin lymphoma. However, the SHCS study had only 18 cases of Hodgkin lymphoma, and these relative risk estimates did not differ statistically significantly. Thus, although Hodgkin lymphoma and non-Hodgkin lymphoma are related to EBV and the risk for these malignancies increases with depressed or disordered immunity, major pieces of the puzzle are missing.

In addition to insights on cancer etiology, the HIV epidemic presents important cancer prevention issues. People living with HIV/AIDS in the United States and in Europe have disproportionately high rates of tobacco smoking, hepatitis B and C infections, and human papillomavirus infection, which are the primary causes of cancers of the lung; liver; and cervix, anus, and other anogenital sites, respectively. As a result, incidence of these cancers is increased among people with HIV/AIDS, but a role for immunodeficiency has been difficult to establish. The current SHCS study corroborates the increased risk for these cancers and the lack of association with $CD4^+$ cell count or AIDS onset *(7,14,15)*. More importantly, the SHCS found no obvious positive or negative effect of HAART on the risk of these malignancies *(5)*. Still, the small number of these cancers in the SHCS study prevents strong conclusions, and the questions of whether, at what stage, and how immunosuppression might contribute to these cancers remain somewhat unresolved. In any event, as HAART prolongs the lives of HIV-infected persons, it stands to reason that the cumulative incidence of these cancers will rise. There will be a continuing need for effective programs targeted to people with HIV/AIDS to reduce smoking, screen for and treat cervical and anal lesions, and treat chronic hepatitis infections.

Life expectancy for those receiving HAART has been measured in years but may extend for decades. As HIV-infected persons age, there will be an increasing incidence of cancers of the colon, breast, and prostate. The etiology of these and other age-related cancers is complex and poorly understood, but they mostly arise through a series of genetic mutations acquired over a lifetime *(16,17)*. The absence of increased risk for these cancers in people with HIV in the SHCS study and others *(5,12,18,19)* is reassuring and implies that immune surveillance does not play a role in eliminating the genetically damaged cells that represent the precursors of these cancers. Nonetheless, there has been little opportunity for epidemiologic investigation of these cancers in persons with HIV/AIDS, and the picture may change with time.

As we embark on the third decade of the HIV epidemic and approach a decade of the availability of HAART, the size of the HIV/AIDS population is increasing, and their long-term cancer risks are undefined. In the SHCS, risk for KS and non-Hodgkin lymphoma continued to be at least 20-fold higher among HAART-treated individuals compared with that for the general population *(5)*. It is unknown whether these "breakthrough" cancers arise solely among individuals in whom HAART has obviously failed or whether other mechanisms are involved. Also unknown are the types and magnitude of cancer risk after 10–20 years with partial immune reconstitution with HAART. Under some models, aging and prolonged mild immunosuppression could interact, particularly in the setting of known cancer risk factors, to magnify the incidence of tumors currently deemed unrelated to AIDS. Finally, as the HIV epidemic continues to spread across Africa and Asia, a spectrum of other cancers could arise. Controlling the epidemic and ameliorating the suffering of persons living with HIV/AIDS are more urgent than ever. Continued study of cancer in people with HIV/AIDS will redound to give us clues about cancer etiology to the benefit of all.

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