Two years ago, while revisiting the quality and durability of highly active antiretroviral therapy–linked immune reconstitution, I noted that the incidence of certain non–AIDS-defining malignancies associated with sexually transmitted viruses in immunosuppressed persons, including penile, oral, and anal cancers, have continued to increase among HIV-infected persons despite the use of highly active antiretroviral therapy. For example, a large study of anal intraepithelial neoplasia (AIN) among HIV-positive men who have sex with men in San Francisco found that 81% had AIN of any grade, and its prevalence had not been diminished by the use of effective antiretroviral therapy. Similar to Papanicolaou tests for cervical cancer screening, the use of patient-based anal cytological sampling followed by referral of those with abnormal results for anoscopy and treatment of biopsy-proven high-grade AIN is being explored to suppress development of anal cancer in this population. However, the prevalence of other conditions linked to incomplete immune reconstitution and sexually transmitted infections, such as those caused by human papillomavirus, hepatitis B virus (HBV), and hepatitis C virus (HCV), is also rising as persons receiving antiretroviral therapy live longer.

Massive depletion of CD4+ memory T cells occurs within days to weeks after HIV-1 infection, and their absolute numbers and responsivity are not restored by highly active antiretroviral therapy. HIV-infected patients are also in a continual state of T-cell and monocyte activation and cytokine imbalance, which is only partially ameliorated by highly active antiretroviral therapy. These changes, coupled with the persistence of the common coinfecting viruses noted above, might be expected to expand the spectrum of cancers in HIV-infected persons, and they do. The incidence of AIDS-defining cancers, such as Kaposi sarcoma and some non-Hodgkin lymphomas, has declined dramatically following the introduction of highly active antiretroviral therapy, but the impact of antiretroviral therapy on other AIDS-defining cancers, including cervical carcinoma, is less clear. As noted above, several non–AIDS-defining malignancies associated with immune suppression in general have increased significantly despite the use of highly active antiretroviral therapy. HBV and HCV are key factors in the rise in mortality from non–AIDS-defining illnesses, including cancer, among long-term HIV-infected persons. In an observational longitudinal study of 10,937 patients in EuroSIDA, the death rate from liver-related disease was 3.5 per 1000 person-years of follow-up. In those with equivalent CD4 counts, duration of highly active antiretroviral therapy was directly related to increasing incidence of death from hepatic causes. There was a 13% increase in such mortality per year overall (P < .0001), with a 12% increase in deaths per year of highly active antiretroviral therapy for those receiving treatment (P < .02). HBV and HCV status correlated with liver-related deaths, and such patients were more likely to be either hepatitis B surface antigen (HBsAg)-positive (13.6% vs 5.2%) or HCV antibody-positive at recruitment (45.7% vs 16.7%). Analysis of injection drug users as an isolated group did not alter these findings. Potential interactions among HCV or HBV, HIV, and HBsAg are myriad and can be severe, as has been discussed over the years in The AIDS Reader. Early suppression of HIV replication slows the progression of HCV-related liver fibrosis, changes that may relate to HIV-associated defects in cytokine activation and regulation, limiting efficient clearance of HCV and modulating cytokines involved in hepatic inflammation and fibrogenesis. Apart from hepatocellular carcinoma, it recently has been recognized that HCV infection itself confers a 20% to 30% increased risk of non-Hodgkin lymphoma and a 3-fold higher risk of Waldenström macroglobulinemia, in the absence of HIV. Although the magnitude and durability of the anti-HIV effects of highly active antiretroviral therapy in the setting of HCV infection have been questioned, the risk of liver cancer is clearly lower with...
antiretroviral use. The effect of such therapy on other cancers, whether related to or independent of HBV/HCV infection, is far less encouraging.

Screenings of adults in the San Francisco AIDS surveillance registry for 1990-2000 uncovered 482 non–AIDS-defining cancers. Data from this group were matched with those from the California Cancer Registry and were adjusted for age, sex, and race. For the AIDS surveillance registry patients, results indicated significantly increased standardized incidence ratios (SIRs) for anal cancer (SIR, 13.4), oral cavity and pharynx malignancies (SIR, 1.7), prostate cancer (SIR, 1.7), malignant melanoma (SIR, 2.4), and Hodgkin disease (SIR, 2.4). Neither highly active antiretroviral therapy use nor diagnosis during the HAART era had an impact on incidence of these malignancies.

In a related prospective study, the AIDS Link to the Intravenous Experience (of importance because this study did not rely on linkages to cancer registries), HIV infection was accompanied by an increased lung cancer risk (hazard ratio, 3.6) independent of smoking history. Illicit drug use was not associated with this risk, and highly active antiretroviral therapy did not alter its incidence or associated mortality. Indeed, in a recent meta-analysis of 7 studies of patients with HIV/AIDS and 5 studies of transplant recipients, there was a significantly increased incidence of 20 of the 28 types of cancer examined in both populations. In addition to the cancers noted above, they included liver and gastric cancer. This pattern suggests that persistent immune deficiency despite antiretroviral treatment, rather than other cancer risk factors, is responsible for the increase of cancer being reported in persons with HIV/AIDS.

It is a consistent finding among a variety of studies from the resource-rich world that while substantial improvements in survival after the introduction of highly active antiretroviral therapy continue to be demonstrated for all people with AIDS, the magnitude of these changes vary greatly depending on the presence of specific AIDS-defining illnesses as well as non–AIDS-defining hepatic disorders and malignancies. Greater attention must be given to prevention interventions, be they smoking cessation programs, anal cytological sampling, HBV vaccination, or HCV treatment initiatives, if treatment of HIV infection is to be maximally beneficial to all patients.

References:


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