# Second Malignancies

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The incidence and spectrum of neoplasms among persons infected with HIV have risen with the increasing survival in the era of combined antiretroviral therapy (cART) [1, 2] and have contributed as a significant cause of death in this population [2, 3]. The specific neoplasms developed include anal cancer, liver cancer, lung cancer, head and neck carcinomas, and carcinomas of the skin, including penile and vulvar/vaginal cancer, among others.

Epidemiologic studies have shown that these neoplasms occur with higher frequency than in non-HIV-infected persons and, in general, tend to occur in patients who are younger than their HIV-negative counterparts. On the other hand, these cancers tend to show atypical pathology (e.g., poorly differentiated neoplasms and high tumor grade) and have a more aggressive behavior (e.g., higher probability of local progression and metastasis), resulting in poorer response to therapy and outcome [2].

In addition to a true increased prevalence of these tumors in HIV-infected patients, other factors can explain the higher frequency observed in recent times.

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There may be the greater screening of some groups (e.g., Papanicolaou test for anal cancer), more frequent detection of incidental lesions during controls of HIV infection and treatment, and longevity in the presence of chronic immunodeficiency. In this regard, the role of a low CD4+ cell count in the development of AIDS-defining cancers is well established. Other contributing factors may include the increased aging of the HIV-infected population, certain lifestyle habits (e.g., sexual behavior) and increased exposure to carcinogens (e.g., tobacco and alcohol), and coinfection with oncogenic viruses (e.g., human papillomavirus, Epstein-Barr virus, hepatitis C virus, hepatitis B virus), among others [2–4]. No association has been demonstrated between long-term exposure to antiretroviral agents and occurrence of malignancies [5]. Some studies on structured antiretroviral treatment interruptions have resulted in an increase of AIDS-defining and non-AIDS-defining cancers, but this finding needs further evaluation. Finally, long-term follow-up should be performed in patients cured of AIDS-defining cancers (e.g., lymphomas), in whom the development of second cancers is not infrequent [6, 7].

The timing of cancer diagnoses among patients initiating cART is different for AIDS-defining and non-AIDS-defining neoplasms. While the former cancers decrease over time, the incidence of the latter group increases especially when CD4+ cell counts remain low after 12 months of cART. These results indicate the crucial importance of early HIV diagnosis followed by prompt cART initiation along with aggressive cancer screening and prevention efforts throughout the course of HIV care.

Clinicians should attempt to adhere to standard screening recommendations established for the non-HIV-infected population [8] and should promote risk-reduction behaviors (e.g., safe sexual practices and smoking cessation, among others). Further research is needed for additional cancer-specific screening (e.g., screening for human papillomavirus in the squamous epithelium of the oral cavity and anus).

The management of non-AIDS-defining cancers is challenging for several reasons [9]. Tumor staging may be affected by the presence of reactive lymphadenopathy or other imaging abnormalities unrelated to cancer. On the other hand, the comorbidities associated with the HIV infection may result in a poor performance status. Prophylaxis against opportunistic infections and hematopoietic growth factor support are often needed [10–12]. Finally, the combination of cytotoxic chemotherapy with antiretrovirals may result in additive cytotoxicity or other drug-drug interactions that may further enhance immunosuppression [13]. Nonetheless, the general recommendation is to treat HIV-infected patients with cancer with the same strategies employed in noninfected patients, whenever possible.

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