

A PEER-REVIEWED ARTICLE

## Certain non-AIDS-defining cancers higher in HIV population

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Although the incidence of AIDS-defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical carcinoma\*) has decreased with the use of antiretroviral therapy, non-AIDS-defining cancers have increased in HIV-infected patients, as suggested by numerous studies.<sup>1, 2, 3, 4, 5</sup>

These malignancies have increased as has the proportion of mortality associated with non-AIDS-defining malignancies in HIV-infected patients.<sup>6</sup> In fact, cancer prevalence ranges from 7% to 15% as cause of mortality in the HIV population.<sup>7</sup> These conditions appear to have an earlier onset and worse prognosis in HIV-infected patients than in the general cancer population.<sup>6</sup> Initial data reports from the Interim LSU Public Hospital HIV Outpatient Program (HOP) clinic in New Orleans indicate the frequency of these conditions at around 10% of the total HIV-population (unpublished data). This correlates with data from a very recent 20-year cohort study where it was found that 10% of the HIV-infected population developed cancer.<sup>8,29</sup>

Some studies have shown that HIV increases susceptibility to such cancers through the direct effects of the virus (genetic instability and increased susceptibility to carcinogens, for instance) and long-term immunosuppression.<sup>6, 8</sup> Other possible contributors to the increased prevalence of non-AIDS-defining cancers are greater prevalence of co-infection with viruses that have etiologic roles in cancer and endothelial cell abnormalities including the elaboration of angiogenic factors that could serve to facilitate tumor growth.<sup>6</sup>

Several studies have shown that among the different non-AIDS-defining cancers, solid tumors and hematologic malignancies may be more prevalent in HIV-infected patients.<sup>6</sup> A recent review found that the incidence of anal carcinoma, Hodgkin lymphoma, liver cancer, lung cancer, melanoma, oropharyngeal carcinoma, leukemia, colorectal cancer, and renal cancer are greater than in the general population.<sup>9</sup>

It has also been suggested that neither CD4 cell count at the time of diagnosis nor CD4 cell count nadir was predictive of non-AIDS-associated malignancy.<sup>6</sup> Viral load has also been studied and its influence does not appear to be significant in relation to prevalence of non-AIDS cancers.<sup>6</sup> On the other hand, other reviews have showed that there might be a role for CD4 cell count nadir.<sup>8, 10</sup>

Current studies suggest that patients with HIV-associated non-AIDS-defining cancers, particularly those with robust CD4 counts, should be treated with similar approaches to their HIV-negative counterparts.<sup>8</sup> As discussed below, information on this topic is scarce.<sup>8</sup>

HAART therapy appears to be a protective factor against the appearance of certain non-AIDS-defining cancers (other than Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical carcinoma).<sup>6,8,11</sup> Based on these results, some authors have suggested that, in view of the fact that newer antiretroviral regimens have more favorable toxicity and better resistance profiles than prior regimens, initiating therapy at higher CD4 cell counts may be a better option for adjuvant treatment in HIV-infected patients with non-AIDS-defining cancers.<sup>10</sup>

### **Epidemiology**

A number of reports indicate that certain types of non-AIDS-defining cancers are higher among HIV-infected persons than among the general population.<sup>9, 12</sup> The incidence of non-AIDS-defining cancers has increased significantly over the past 10 years and has now surpassed that of AIDS-defining cancers in HIV-infected patients.<sup>13</sup> Several malignant conditions, including Hodgkin lymphoma, anal cancer, soft tissue cancer, and multiple myeloma have been found in increased numbers in HIV-infected patients.<sup>12</sup> Other reports also indicate that anal carcinoma, head and neck carcinoma, testicular cancer, cancer of lung, colon, skin (basal cell skin carcinoma, squamous cell carcinoma, cell skin carcinoma, and melanoma) have increased in HIV-infected patients.<sup>1, 11</sup> Some authors also point out that other malignancies, such as prostate, breast, and bladder cancer, appear to be decreased in the HIV-infected community,<sup>6</sup> even though other reports indicate that these neoplasms appear increased in HIV-infected patients.<sup>8</sup> More information is needed in relation to the epidemiology of certain types of malignancies.<sup>8</sup> (See Table 1, page 16.)

### **Pathogenesis and risk factors**

Many factors are involved in the pathogenesis of non-AIDS-defining cancers. HIV-related defects in cell-mediated immunity could lead to an increased risk of malignancy via decreased tumor surveillance and

suppression of oncogenic viruses.<sup>8</sup>

Greater prevalence of coinfection with viruses that have etiologic roles in cancer has been related to an increased frequency of cancers in HIV-infected populations. These include human herpesvirus 8 (primary effusion lymphoma, Kaposi sarcoma, Castleman disease), human papilloma virus (cervical, anal, penile, and possibly head and neck cancers), Epstein-Barr virus (Hodgkin disease, non-Hodgkin lymphoma, primary central nervous system lymphoma, leiomyosarcoma) and hepatitis B and C.<sup>13, 25</sup>

Among environmental factors and behaviors, tobacco and alcohol use have been linked to an increased number of cases of cancer in HIV-infected patients.<sup>13</sup>

Other reports indicate that the oncogenic role of HIV is controversial.<sup>14</sup> In the case of lung cancer *in vitro* studies have shown that the *tat* (transactivator of transcription) gene product from HIV can increase the expression of the proto-oncogenes *c-myc*, *c-fos* and *c-jun* and downregulate the tumor suppression gene *p53* in lung adenocarcinoma cell lines.<sup>14</sup> It is difficult to determine the role of chronic immunodepression in the risk of lung cancer among HIV-infected patients.<sup>13, 27</sup> In a published clinical review on lung cancer, Lavole *et al* found that HIV-seropositive patients did not seem to be severely immunodepressed. A recent study has shown that in the post-HAART period, the degree of immunodepression was less severe and the risk of lung cancer was nonetheless higher in this period.<sup>13, 27</sup> Therefore it appears that the presence of immunosuppression does not fully explain the behavior of certain lung cancers in HIV-infected patients.

The role of a possible increase in genomic instability in the higher risk of lung cancer among HIV-infected patients has also been suggested by a study of 16 polymorphic markers on eight chromosome arms frequently deleted in lung cancer.<sup>13, 27</sup> This study points out that microsatellite instability was six times more frequent in the HIV-infected patients.<sup>13, 27</sup>

It is also interesting that some authors have noted the interaction between HIV virus and other potential oncogenic viruses.<sup>15, 16</sup> One article mentioned that in the case of anal carcinoma, although the interaction effect of HPV on HIV is not fully understood at the cellular level, a direct interaction occurs between the two viruses, with the HIV favoring the activation of the E6 and E7 genes of the HPV, increasing the expression of their oncoproteins.<sup>16</sup>

In the case of Hodgkin disease, one of the most common non-AIDS-defining cancers, an association with Epstein-Barr virus (EBV) has been described.<sup>10</sup> It has also been suggested that this connection may help explain the aggressive clinical nature and histological characteristics (mixed cellularity and lymphocyte depletion subtype) seen in this type of cancer in HIV-infected patients. Indeed, EBV is postulated to induce oncogenesis via the production of an oncoprotein, LMP-1, that is released when the virus infects lymphocytes.<sup>10</sup>

HIV-infected patients with gastrointestinal malignancies are also overrepresented. Some authors have shown that smooth muscle tumors (leiomyomas, leiomyosarcomas) are disproportionately represented in patients with AIDS.<sup>17</sup> These tumors have been linked to Epstein-Barr virus (EBV).<sup>17</sup> Certain rare tumors, such as gastric adenocarcinoma, have also been reported to possibly be more frequent in HIV-infected patients and the link between oncogenic viruses and HIV needs to be elucidated.<sup>18</sup> This same principle, a suspected link between HIV and oncogenic virus, may apply to colon cancer.<sup>19</sup> In relation to hepatocellular carcinoma, it is well known that coinfection with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) is associated with increased HCV replication and a more rapid progression to severe liver disease, including the development of cirrhosis and hepatocellular carcinoma.

\* 20, 23

Certain skin cancers occur with increased frequency or altered course in patients with HIV. Malignant melanomas and squamous cell carcinomas are examples of cutaneous malignancies that have a more aggressive course in patients with HIV. Others, such as basal cell carcinoma, appear more frequently in this population but do not seem to be more aggressive.<sup>21</sup> A prolonged immunosuppressive state may be the main cause for the increased frequency seen in HIV-infected patients.<sup>21, 26</sup> Some nonmelanomatous skin cancers are associated with certain cutaneous HPV types.<sup>23</sup>

Renal cell carcinoma, the most common form of kidney cancer arising from the renal tubule in adults, also appears to be slightly increased in the HIV-infected population.<sup>22</sup> In these cases, prolonged immunosuppression has been proposed as the mechanism responsible for the increased frequency of this type of cancer.<sup>22, 26</sup>

A study from Kenya showed that squamous cell carcinoma of head and neck is one of the most common head and neck malignant neoplasms and it seems to be more common in younger HIV-infected groups than in the non-HIV group of patients.<sup>24</sup> This study also mentions that tobacco and alcohol use, human papilloma virus (HPV) infection, immunodeficiency, and possibly genetic changes may be significant risk factors.<sup>24</sup>

In contrast to some studies, a meta-analysis suggested that immune deficiency may be the culprit for the increased risk of cancer in HIV-populations.<sup>26</sup> In this study, two populations with immune deficiencies were studied (transplant and HIV-infected patients). The authors found similarities in the frequency of certain

cancers (20 of 28 cancers studied) though some differences were also noted. The authors concluded that immunodepression was the only common factor in relation to the increased frequency of cancers.<sup>26</sup> (See Table 2, page 16.)

A recent retrospective analysis of a multicenter, prospective natural history study, including 4498 HIV-infected US military beneficiaries, indicated that age and race were the most common risk factors for the development of certain non-AIDS-defining cancers.<sup>29</sup> This study analyzed data over two decades and divided the frequency of cancers into pre-HAART and post-HAART eras. The authors found that age and white race (skin cancers) were the most associated risk factors for cancer. This could mean that a higher frequency of non-AIDS-defining cancers would be found in aging HIV-infected populations. One of the few studies of cancer risk in elderly persons with HIV/AIDS showed that the profile of cancer risk in elderly persons generally resembled that in younger adults with AIDS. This study analyzed AIDS data from 1981 to 1996 and found 1142 cases of cancer out of 8828 elderly patients with AIDS.<sup>30</sup>

### **Influence of CD4 cell count, viral load, and HAART**

It has been established that the severity of immunosuppression is predictive of death from both AIDS and non-AIDS-defining malignancies in HIV-infected patients.<sup>31, 32 33</sup> It is also known that a poor initial CD4 cell count recovery, despite effective antiretroviral therapy, results in longer time spent at low CD4 cell count, thereby increasing the risk for a broad category of HIV-related morbidity and mortality conditions.<sup>34</sup>

The majority of non-AIDS-defining cancers appear with CD4 cell counts above 200. This situation suggests that a potential “quality immune response” alteration might be responsible for the activation of certain mechanisms that encourage oncogenesis.

Plasma HIV viral load is an important reflection of immune status. In fact, plasma HIV viral load at the time of seroconversion is correlated strongly with the risk of immunosuppressive complications and may be a better predictor of immunodepression than CD4 cell counts. High HIV-viral loads lead to greater levels of viral protein, to direct interactions with cell-cycle control, and to greater degree of type-2 cytokine predominance and impaired local immunity.<sup>35</sup>

In a study from a hybrid hematology/oncology and HIV practice, it was found that a substantial portion of patients died from non-AIDS-defining cancers despite non-detectable viral loads and reasonably well-preserved immune function.<sup>7</sup>

Highly active antiretroviral therapy (HAART) has helped to decrease the incidence of AIDS-related malignancies, but as has been mentioned above, the non-AIDS-defining cancer frequencies have not been affected.<sup>23</sup> A very recent study indicated that HAART does not have a significant impact on non-AIDS-defining cancers.<sup>29</sup> A controversial report suggests that HAART could be a factor in the development of Hodgkin lymphoma. This study, which analyzed the frequency of non-AIDS-defining malignancies before and after the introduction of HAART, found that Hodgkin lymphoma was much more common in HIV-infected persons relative to the general population, regardless of sex, the study period (before or after HAART), and the transmission group (among men). Therefore, the authors conclude that the potential role of HAART on the development of Hodgkin lymphoma cannot be excluded.<sup>32</sup> Recent reports have indicated that there is a three-fold higher risk of Hodgkin disease in HIV-infected patients who receive antiretroviral therapy compared to HIV-infected patients who are not on antiretrovirals.<sup>31</sup> Therefore, the potential role of antiretrovirals in the development/perpetuation of Hodgkin disease has been suggested.<sup>32</sup>

### **Treatment**

Data on the ideal management of AIDS and non-AIDS-defining cancers are not optimal. Current studies suggest that patients with HIV-associated malignancies could be treated using approaches similar to those for their counterparts in the general population.<sup>36</sup> The clinical management of malignancies in HIV-infected patients is evolving and factors such as feasibility and toxicity, including drug-drug interactions as a result of the combination of HAART and chemotherapy, are also important to take into consideration. Most of the strategies now recommend continuing HAART during cancer treatments.<sup>36,5</sup> Hematopoietic growth factors are often useful in preventing chemotherapy-related complications. The use of these factors has still not been studied in HIV-populations. Some reports indicate that the majority of patients with non-AIDS-defining cancers have a two-year survival of more than 50%.<sup>6</sup>

In a study of HIV-infected patients with Hodgkin disease, where 59 patients were treated simultaneously with chemotherapy and HAART, complete remission was achieved in 81% of patients and the three-year disease-free survival was 68%.<sup>37</sup> Another study found that HIV-infected patients with Hodgkin disease who responded to antiretroviral therapy, or who had an HIV RNA level below 500 copies/ml, had an overall survival rate of 89% at

two years, compared with 44% for those who did not respond.<sup>37</sup>

Data on the toxicity and efficacy of chemotherapy, in the setting of lung cancer in HIV-infected patients, are rare and imprecise. While surgery is the treatment of choice for localized disease, HIV-infected patients are often poor surgical candidates.<sup>8</sup> In the case of nonmelanomatous skin cancers, the experts recommend that HIV-infected patients be treated as their HIV-negative counterparts would be.<sup>8</sup>

A very interesting experience has been reported with prostate cancer in HIV-infected patients.<sup>38</sup> These patients were treated with prostatectomy, brachytherapy, external beam radiotherapy and/or hormonal treatment with good results. On this report the HIV-1 protease inhibitor nelfinavir induced growth arrest and apoptosis of human prostate cancer cells, suggesting that this drug might be useful for the treatment of individuals with prostate cancer.<sup>38</sup>

Although available evidence suggests that HIV-infected cancer patients should receive at least the same intensity of cancer therapy as non-HIV-infected patients, much remains to be learned about every facet of treatment and management of patients with non-AIDS-defining cancers.<sup>13</sup> The efficacy of standard chemotherapy regimens used in non-HIV-patients has not been well studied in HIV-infected populations. The toxicities experienced by HIV-infected patients could be more severe and threatening.<sup>13</sup> The potential interactions between cancer chemotherapy and antiretroviral regimens are numerous and not yet well studied. Reports from the AIDS Malignancy Consortium are currently examining the potential role of intensification of cancer therapy.<sup>13</sup> The issue of higher relapse rate of certain non-AIDS-defining cancers in HIV-populations (anal carcinoma, Hodgkin disease, and lung cancer) has also been mentioned and further studies have been recommended.<sup>13</sup>

Even though there is no consensus about the use and role of HAART in non-AIDS-defining cancers, some authors have recommended and advocated the possibility of starting antiretroviral therapy earlier than the commonly practiced guidelines for certain types of cancers.<sup>10</sup> This is based on the fact that the delay in treatment in certain types of cancer, such as anal carcinoma, might contribute to the development of anal intraepithelial lesions that are not reversible even after HAART has been started.<sup>37</sup>

In relation to prevention measures, a high index of suspicion for cancer must be maintained in HIV-infected patients. Preventative measures such as yearly cervical and anal Papanicolaou testing, gynecologic examinations, high-resolution anoscopy, yearly breast examinations, and prostate examinations should be performed. In patients with chronic hepatitis B and C, imaging of the liver and alpha-fetoprotein measurements should be performed periodically. Sunscreen use and avoidance of overexposure to sunlight should be stressed, given the observed increase in skin cancers.<sup>13</sup> A very aggressive smoking cessation policy should be established. The role of HPV vaccines in the prevention of certain HPV-related non-AIDS-defining cancers is still to be determined.<sup>39, 40</sup>

### **Future research**

More studies are needed to assess risk and associated factors for non-AIDS-defining cancers. The frequency of these conditions needs to be accurately determined to direct efforts for decreasing prevalence.

Effective screening and treatment options need to be established. It is crucial that we get a better understanding of the interactions among chemotherapy, HAART, and other medications used by HIV-infected patients. The role of more aggressive chemotherapy regimens and earlier-start HAART therapy in patients who have non-AIDS-defining cancers needs to be clarified. Whether the same chemotherapy regimens could be applied with success in HIV-infected populations is still debatable. The role of a higher relapse rate in HIV-infected patients needs to be verified with inclusion of HIV-infected patients in clinical trials.

As we progress in our study of the frequency of non-AIDS defining malignancies, prevention will be an important tool against these problems. The creation of integrated oncology/infectious diseases working groups for clinical and research purposes is one possible approach to this problem. Another avenue for exploration could be the formulation of particular guidelines for these populations. When it comes to aging HIV-infected populations, these suggestions may be even more important as these patients may be at a higher risk of developing these malignancies. More research into these issues is needed in order to prepare for what could be a new epidemic. ♦

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<b>Table 1: Comparison of standardized incidence rates for non-AIDS-defining malignancies between HIV-infected patients and general population</b>		
<b>Malignancy</b>	<b>HIV-infected patients (standardized incidence rate per 100,000 person years; 2000-2003)</b>	<b>General population (standardized incidence rate per 100,000 person years; 2000-2003)</b>
Anal carcinoma	78.2	1.3
Colorectal cancer	66.2	21.1
Hodgkin lymphoma	64.4	3.6
Liver cancer	35.4	4.7
Lung cancer	84.9	23.4
Melanoma	37.5	9.9
Oropharyngeal cancer	36.9	11.7

Source: Patel P, Hanson D, Sullivan P, Novak R, Moorman A, Tong T, Holmberg S, Brooks J. Incidence and Types of Cancer among HIV-infected Persons Compared with the General Population in the United States, 1992-2003. *Annals of Internal Medicine*. Volume 148, Number 10.

<b>Table 2: Standardized incidence ratios of malignancies increased in both HIV/AIDS and transplant patients</b>		
<b>Malignancy</b>	<b>HIV/AIDS (n=444,172) standardized incidence ratio</b>	<b>Transplant (n=31,977) standardized incidence ratio</b>
Lung cancer	2.72 (1.91-3.87)	2.18 (1.85-2.57)
Kidney cancer	1.50 (1.23-1.83)	6.78 (5.69-8.08)
Myeloma	2.71 (2.13-3.44)	3.12 (2.13-4.57)
Leukemia	3.20 (2.51-3.44)	2.38 (1.77-3.79)
Melanoma	1.24 (1.04-1.48)	2.34 (1.98-2.77)

Source: Grulich AE, Van Leeuwen MT, Folster M, Vajdic CM. Incidence of cancer in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *The Lancet*, Vol 370, July 7, 2007