HIV infection and cancer in the era of highly active antiretroviral therapy (Review)

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Abstract. The majority of cancers affecting HIV-infected subjects are those established as acquired immunodeficiency syndrome (AIDS)-defining: Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and invasive cervical cancer (ICC). However, other types of cancer, such as Hodgkin's disease (HD), anal cancer, lung cancer and testicular germ cell tumors appear to be more common among HIV-infected subjects compared to the general population. While not classified as AIDS-defining, these malignancies have been referred to as AIDS-associated malignancies. The mechanisms by which depressed immunity could increase the risk for cancer are unclear, except for in KS and most subtypes of NHL, where it is strictly associated with a low CD4 count. Although it remains unclear whether HIV-1 acts directly as an oncogenic agent, it may contribute to the development of malignancies through several mechanisms (e.g., infection by oncogenic viruses, impaired immune surveillance, imbalance between cellular proliferation and differentiation). Studies of the effect of highly active antiretroviral therapy (HAART) on the incidence and progression of HIV/AIDS-associated cancers provided contrasting data. While a significant decrease in the incidence of KS has been observed, HAART has not had a significant impact on NHL incidence, particularly systemic NHL, or on ICC, HD, anal cancers and other non-AIDS-defining cancers. Regardless of whether these cancers are directly related to HIV-induced immunodeficiency, treating cancer in HIV-infected patients remains a challenge because of drug interactions, compounded side effects, and the potential effect of chemotherapy on CD4 count and HIV-1 viral load. A better knowledge of viral mechanisms of immune evasion and manipulation will provide the basis for a better management and treatment of the malignancies associated with chronic viral infections.

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1. Introduction

Cancer is a significant cause of morbidity and mortality in human immunodeficiency virus (HIV)-infected subjects (1). The majority of cancers affecting HIV-infected subjects are those established as acquired immunodeficiency syndrome (AIDS)-defining: Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical cancer. However, other types of cancer also appear to be more common among HIV-infected subjects compared to the general population. While not classified as AIDS-defining, these malignancies are affecting the HIV-infected community greatly and have been referred to as AIDS-associated malignancies (1). The clinical classification of cancers observed in the HIV-infected community is reported in Table I.

The introduction of highly active antiretroviral therapy (HAART) has resulted in decreased mortality and morbidity, improving the quality of life of HIV-infected subjects. However, the widespread use of HAART altered the incidence of cancer or perhaps even increased the prevalence of some types of cancer in the HIV-infected population providing a new intriguing clinical scenery (1).

2. AIDS-defining cancers

Kaposi's sarcoma. In the general population, Kaposi's sarcoma (KS) is a rare, typically indolent cancer that affects older people or those receiving immunosuppressants following an organ transplant. People infected with HIV-1 are 100 to 300 times more likely to develop KS (1-6).

In 1981 the first HIV-associated KS was described in the United States where 35% of AIDS patients were found to present with this rare tumour. It is common in homosexuals with AIDS but rare in other risk groups. The cause of AIDS-associated KS is presently unknown and causes may be

Table I. AIDS-associated cancers: clinical classification (1).

AIDS-defining cancers
Kaposi's sarcoma
Non-Hodgkin's lymphoma
Invasive cervical cancer
Non AIDS-defining cancers
Hodgkin's lymphoma
Anal cancer
Lung cancer
Testicular germ tumors
Other cancers in the HIV-infected community
Skin/lip/tongue cancer
Pharynx/larynx cancer
Penis cancer
Liver cancer
Kidney cancer
Pancreas cancer
Gastrointestinal cancers
Brain and central nervous system cancer
Prostate cancer
Bladder cancer
Vulva/vagina cancer
Breast cancer
Leukemia
Multiple myeloma
Soft tissue sarcomas
Leiomyosarcoma
Angiosarcoma

multiple (5,7). AIDS-associated KS is associated with human herpesvirus-8 (HHV-8), also known as KS-associated herpes virus), although there is no definitive evidence that HHV-8 causes KS (5). The risk and severity of KS increase in the presence of low CD4 count (6) and subjects with an intact immune system tend not to develop KS when infected with HHV-8 (7).

Studies have unequivocally demonstrated a significant decline in the incidence of KS following the introduction of HAART (5,8-10). In the early 1980's, KS was the AIDS-defining illness in approximately 30% of infected individuals; a value which later dropped to 10-15% in the late 1990s (7). The incidence rates for KS are 5 times lower in HIV-infected patients who have received HAART, compared to those who have not (11). In San Francisco, deaths from KS significantly decreased from 15.6% of total AIDS deaths in 1994 to 7.1% in 1998 (12). HAART regimens containing protease inhibitors and non-nucleoside reverse transcriptase inhibitors are equally protective against developing KS (10). Most patients who develop KS while taking HAART show evidence of virologic treatment failure. Importantly, HAART may also have a positive effect on treating established KS, especially in patients without visceral disease (10).

In developing countries where the availability of HAART is scanty an increased incidence of KS has been observed (9). Currently, KS represents one of the most common diseases in the HIV-infected community in Africa with a related high mortality rate for pulmonary involvement (9).

Non-Hodgkin's lymphoma. Compared to the general population the risk of developing a non-Hodgkin's lymphoma (NHL, also referred to as AIDS-associated lymphoma) is significantly increased in the HIV-infected population (from 40 to 400 times, median 150-220 times), depending on the specific study and the type of NHL (1-6,13,14).

NHL encompasses several types of lymphoma, including systemic NHL, primary central nervous system NHL (PCNSL, also referred to as primary brain lymphoma or cerebral lymphoma), and primary effusion lymphoma (PEL) or body cavity-based lymphoma, a rare and aggressive form of NHL (7,13,15). Data also indicate that high-grade lymphoma is more prevalent in the HIV-infected community compared to low-grade lymphoma (7,13,15). The risk of developing NHL, particularly PCNSL, increases with lower CD4 counts, and further progression of HIV infection (6,7).

No definitive conclusions can be drawn regarding the effect of HAART on the incidence of NHL (1,16). Some studies have demonstrated significant decreases in the incidence of NHL following the introduction of HAART, whereby incidence rates decreased by almost 50% (9), and patients receiving HAART experienced a 5-fold decrease in the incidence of NHL compared to treatment-naive patients (11). However, other studies failed to show any significant change, and even suggested modest increases in the incidence of NHL in HIV-infected subjects (12,13). Significant decreases have been reported for immunoblastic lymphoma in some studies (9), but not in others (8). Incidence of AIDS-associated Burkitt's lymphoma has not decreased and one analysis even demonstrated an increase in incidence after the introduction of HAART, but this increase was not statistically significant (9). Studies showed that the incidence of PCNSL decreased considerably following the introduction of HAART (9,11,13). Administration of HAART has also been associated with longer survival in patients suffering from PCNSL (17). The effect of HAART on the incidence of PEL is unknown because of the rarity of the disease (1). Interestingly, patients with systemic NHL who received and responded to HAART were significantly more likely to achieve a complete response, suggesting that a patient's response to HAART may provide insight into their cancer prognosis (14,16,18).

Invasive cervical cancer (ICC). HIV-infected women are approximately 5 to 9 times more likely to have ICC compared to HIV-uninfected women (1,3,6,19) and this cancer accounts for 55% of AIDS-associated malignancies in some settings (20). Human papillomavirus (HPV) is involved in almost all cases of cervical cancer, regardless of HIV status, and is strongly associated with cervical intraepithelial neoplasia (CIN) and squamous intraepithelial lesions (SIL), which are precursors to ICC (21,22). While the relationship between HIV-1 infection and ICC is not definitive, this is not the case for CIN and SIL (1). In contrast to HIV-uninfected women whose low-grade lesions typically resolve without treatment

(23), lesions are more likely to progress and to recur after treatment in HIV-infected women in relation to the state of immunodeficiency (22,24).

Several studies have assessed the impact of HAART on the incidence and progression of precancerous cervical lesions. One large study reported no significant changes in the incidence of ICC when rates were compared during the pre-HAART and post-HAART eras (9). Some studies have shown decreased cytologic progression of these lesions (25,26), while others have reported increased progression or non-conclusive results (21). Moreover, HAART was not associated with decreased prevalence or persistence of HPV infection, but a significant reduction in the incidence of HPV-16 and HPV-18 (oncogenic types of HPV) was detected in HAART-treated women, suggesting that HAART may have an effect on acute HPV infection, but not on advanced infection (1,27).

3. Non-AIDS-defining cancers

Hodgkin's disease. Although Hodgkin's disease (HD) is not considered an AIDS-defining cancer, with contrasting opinions from some researchers (3), HIV-infected subjects are 7.6 to 11.5 times more likely to have HD compared to the general population (1-4,6,13,28). While analyses have routinely demonstrated an increased risk of HD in HIV-infected subjects, a causal link between HIV-1 and HD has not been established and studies assessing the effect of immunosuppression on the incidence of HD are conflicting (1,3,4,6,28).

Few studies have looked at the effect of HAART on the incidence of HD in HIV disease (1). However, those that have assessed this relationship reported no difference in rates either when comparing patients who had received HAART with treatment-naive patients (29) or when comparing HD rates during the pre-HAART and post-HAART eras (9).

Anal cancer. HIV-infected subjects are 30 to 50 times more likely to have anal cancer, with rates as high as 60-fold in HIV-infected men who are bisexual or homosexual (1,30). Anal cancer in HIV-infected subjects is strongly associated with HPV infection (specifically, HPV-16 and HPV-18 in high-grade form) (31) and the presence of precancerous anal lesions, which are referred to as squamous intraepithelial lesions (SIL) and anal intraepithelial neoplasia (AIN) (1,24,32).

Until recently, anal sex was assumed to be the mode of acquisition for anal HPV infection. However, when rates of HPV infection and SILs were compared in HIV-infected men with or without a history of bisexual or homosexual behavior, rates were high even in those men with no history of anal sex who contracted HIV infection through intravenous drug use, suggesting that HPV infection may be acquired through means other than anal intercourse (1,30). Moreover, acccording to a report by Pakefsky *et al* 76% of HIV-infected women and 42% of high-risk HIV-uninfected women tested positive for anal HPV-DNA (33). Presently, it is unclear whether prevalent risk factors, such as anal intercourse, a history of sexually transmitted diseases, or even heavy tobacco use are responsible for the increased incidence of anal cancer in the HIV-infected population (1). It is possible that HIV-induced immunosuppression may facilitate the development of anal cancer in subjects coinfected by HPV, since high-grade and progressive forms of anal cancer have been described in HIV-infected subjects with a low CD4 count (32). However, one study revealed that the incidence was significantly increased even during early HIV infection, suggesting that severe immunosuppression is not necessary for the development of anal cancer in HIV-infected subjects (28).

The possible benefits of HAART on the incidence of anal cancer and anal precancerous lesions have not been conclusively demonstrated (1). Few studies have examined this relationship suggesting that HAART has not decreased the incidence or increased the regression of these lesions (24,32,34). When rates during the pre-HAART and post-HAART eras were compared, no significant change in the incidence of anal cancer was observed (24,34).

Lung cancer. HIV-infected subjects are 2.5 to 7.5 times more likely to develop lung cancer compared to the general population (1-4,6). In several studies lung cancer was the most frequently observed non-AIDS-defining malignancy (6,12,19). Several studies have reported a positive correlation between rates of lung cancer and HIV-induced immunosuppression (3,4). Analyses of risk behavior have reported conflicting data: one study showed that HIV-infected patients with lung cancer smoked twice as many cigarettes as HIV-uninfected patients with lung cancer (35), while another study that compared HIV-infected to HIV-uninfected women with similar smoking histories showed a 2-fold increased incidence in the HIV-infected women (19). Long-term cigarette exposure is typically lower in HIV-infected subjects because they are usually diagnosed with lung cancer at an earlier age (36).

Before the introduction of HAART, rates of lung cancer were low, perhaps on account of early AIDS-related mortality (1). A recent analysis showed an almost 9-fold increase in lung cancer incidence following the introduction of HAART (36). Unfortunately, the outcome of these patients remains poor despite HAART (1).

Testicular germ cell tumors. HIV-infected men are 1.4 to 8.2 times more likely to develop testicular cancer compared to the general population (2-4,6,31,37), although other studies failed to show a significantly increased incidence (28). While no viral oncogene has been implicated in HIV-associated testicular cancer, viruses such as mumps orchitis, HPV, Epstein-Barr virus, and human endogenous retrovirus K10 are associated with testicular cancer in HIV-uninfected men and may be involved in development of testicular cancer also in HIV-infected subjects (37,38), independently of the state of immunodeficiency (3,37).

The effect of HAART on incidence rates has not been analyzed thoroughly, but one report showed no difference in incidence rates when comparing the pre-HAART and post-HAART eras (37).

4. Other malignancies in the HIV-infected community

In addition to the cancers discussed above, the risk of developing several other cancers appears to be slightly increased in HIV-infected subjects: leukemia (3,4,28), pharynx (3,4), pancreas (3), multiple myeloma (2-4,28), esophagus (3,4),

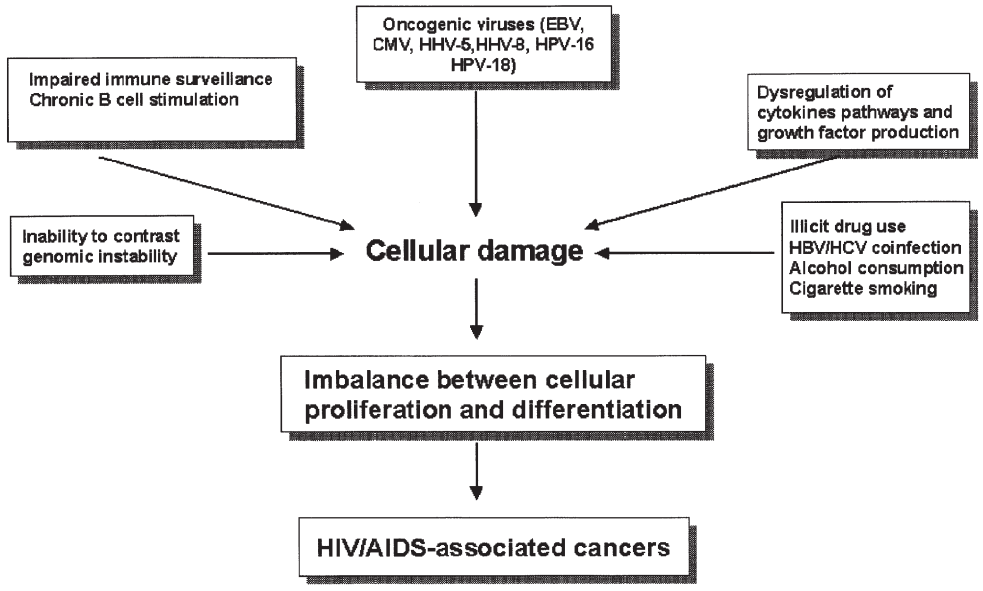

Figure 1. Potential mechanisms implicated in the development of cancer in HIV/AIDS. EBV, Epstein-Barr virus; CMV, cytomegalovirus; HHV, human herpes virus; HPV, human papillomavirus; HBV, hepatitis B virus; HCV, hepatitis C virus.

liver (3,8,28), skin (2-4,31), lip (3,28), kidney (3), penile (3), tongue (4), colorectal (4), vulva/vagina (3), stomach (3,4), brain and central nervous system (2-4), leiomyosarcoma (3,31), larynx (3,4), heart (3), and angiosarcoma (2). The incidence of certain types of cancers, such as prostate (4,4,6), breast (3,6) and bladder cancer (4) appears to be decreased in the HIV-infected community, especially after the introduction of HAART (1), although a small case study reported a non-significant increase in the incidence of prostate cancer in HIV-infected men (39). The rates of breast cancer in men may have increased to some extent, especially in intravenous drug users (3). Further controlled clinical and epidemiological studies are needed to better define the trend of these HIV-associated malignancies after the introduction of HAART.

5. Potential causes of cancer in HIV/AIDS

Although it remains unclear whether HIV-1 acts directly as an oncogenic agent, it may contribute to the development of malignancies through several mechanisms (Fig. 1).

Infection by oncogenic viruses (e.g., cytomegalovirus, Epstein-Barr virus, HHV-5, HHV-8, HPV-16 and HPV-18), impaired immune surveillance, dysregulation of cytokine pathways and growth factor production, chronic B cell stimulation, and imbalance between cellular proliferation and differentiation may all contribute to the development of HIV/AIDS-associated malignancies (1,5-7,12,13). Uncontrolled viral infection may play a significant causative role in many HIV/AIDS-associated cancers according to the immunodeficiency state of the subject (1).

Many HIV-associated malignancies affect sites that are in contact with the outside environment (e.g., cervix, lung, oral cavity, skin, and anus). The increased density of immune cells and coincident elevated concentration of HIV-1 at these sites could lead to local compromised immune defenses and the subsequent development of malignancies at these sites (1,40). Alternatively, risk factors present in the HIV-infected community, including multiple sexual partners, hepatitis B virus/hepatitis C virus coinfection, illicit drug use, increased alcohol consumption and cigarette smoking, could account for the increased rates of these cancers (1). For example, compared to HIV-uninfected patients with cancer, more HIV-infected patients with cancer have a history of cigarette smoking and illicit drug use (35,40).

6. The impact of HAART

Although it may be premature to draw any definitive conclusions, preliminary data suggest that with the exception of KS, HAART has not had a significant impact on cancer incidence in the HIV-infected population (1). Widespread availability of HAART has only occurred within the last decade and many of the malignancies discussed above require several years to develop. Because of HAART's effect on the incidence of KS (5,8-10), one would expect malignancies that are associated with immunosuppression to undergo a significant decline in the incidence following the widespread availability of HAART, especially in developed countries. If immunodeficiency is a key factor in the development of these tumors, the improvement of immunologic functions associated with HAART would slow tumor progression. Unfortunately, this has not been the case (1). For example, evidence suggests that NHL occurs more frequently in immunocompromised patients (6,8,15), but HAART has not had a significant impact on NHL incidence, particularly systemic NHL (8,9,11-13,16).

It has been speculated that the extended survival afforded by HAART, in conjunction with incomplete immune restoration, may increase the incidence of some cancers (1). Prolonged exposure to viral oncogenes, moderate immune suppression, and genomic instability could result in impaired immune surveillance and the subsequent development of tumors (1,32,36,37). Based on this scenery, the incidence of tumors associated with chronic moderate immune suppression would be expected to increase. In fact, the incidence of lung

cancer appears to increase after the introduction of HAART (1,36). Another explanation could be that prior to the introduction of HAART, patients typically died of opportunistic infections or other HIV-associated complications prior to developing a malignancy, some of which take years to develop (1). It is unclear whether HAART will ever provide full immune recovery in HIV-infected subjects, a situation that may be necessary in order to decrease cancer incidence as a whole in this specific population (1). Some researchers speculate that cancer rates, specifically of AIDS-associated lymphoma, will rise in areas with widespread availability to HAART (41), though others disagree (9).

Regardless of whether these cancers are directly related to HIV-induced immunodeficiency, treating cancer in HIV-positive patients remains a challenge because of drug interactions, compounded side effects, and the potential effect of chemotherapy on CD4 count and HIV-1 viral load (1,37,38,42). Moreover, treatment compliance by HIV-infected patients with cancer may be poor, possibly because of the increased responsibility of taking drugs for both diseases with associated increased rate of compounded side effects (1). The question of whether to suspend HAART during chemotherapy depends on several factors, particularly the type and stage of malignancy and the stage of HIV infection (16,43,44). A better knowledge of viral mechanisms of immune evasion and manipulation will provide the basis for a better management and treatment of the malignancies associated with chronic viral infections.

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