

# Malignancies in HIV/AIDS: from epidemiology to therapeutic challenges

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The incidence of AIDS-defining cancers (ADCs) – Kaposi sarcoma, primary central nervous system lymphoma, non-Hodgkin lymphoma, and cervical cancer – although on the decline since shortly after the introduction of HAART, has continued to be greater even in treated HIV-infected persons than in the general population. Although the survival of newly infected people living with HIV/AIDS now rivals that of the general population, morbidity and mortality associated with non-AIDS-defining cancers (NADCs) such as lung, liver, anal, and melanoma are significant and also continue to rise. Increasing age (i.e. longevity) is the greatest risk factor for NADCs, but longevity alone is not sufficient to fully explain these trends in cancer epidemiology. In this review, we briefly review the epidemiology and etiology of cancers seen in HIV/AIDS, and in this context, discuss preclinical research and broad treatment considerations. Investigation of these considerations provides insight into why malignancies continue to be a major problem in the current era of HIV/AIDS care.

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## Introduction

In late 1995, the first generation of HIV protease inhibitors became commercially available. Within a few months, clinicians were combining these novel drugs with nucleoside and nonnucleoside reverse transcriptase inhibitors. The beneficial effects of what soon became known as HAART were immediate and profound. In just a few years, the number of cases of newly diagnosed AIDS, AIDS-related deaths, and AIDS-defining cancers (ADCs), had decreased by greater than 70% [1–3]. However, even as AIDS-related mortality has continued

to decline, the rate of new HIV infections has remained constant [4–6]. Consequently, the number of people living with HIV/AIDS (PLWHA) has increased by a factor of four [4–6]. Although HAART affords PLWHA a longer life expectancy, it also leaves them increasingly vulnerable to the same array of cancers associated with aging that are seen in the general population [7–12]. These non-AIDS-defining cancers (NADCs) include those associated with viral infections [e.g. anal (human papillomavirus, HPV), liver (hepatitis C virus – HCV and hepatitis B virus – HBV), head and neck (HPV)] and those not associated with viral infections (e.g. lung and

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melanoma). In industrial nations, the number of cases of NADCs now equals or exceeds the number of cases of ADCs, and NADCs are a leading cause of mortality for PLWHA [3,7–10,13–16]. Age and immune status, however, are insufficient to fully explain these trends in cancer risk. For PLWHA, even those with normal CD4<sup>+</sup> T-cell counts, the risk for many NADCs remains greater than for their age-matched HIV-seronegative counterparts [8–10,13,14]. Furthermore, compared with the general population, PLWHA present with more aggressive and advanced disease at the time of cancer diagnosis [17–20]. These changes in cancer epidemiology are not well understood. We include preclinical research findings and discuss the epidemiology and etiology of both NADCs and ADCs. We also briefly examine cancer treatment in the context of HAART-chemotherapy interactions.

## Epidemiology

### AIDS-defining cancers

In 1982, the United States Center for Disease Control and Prevention expanded the case definition of AIDS to include HIV-infected individuals diagnosed with Kaposi sarcoma and primary central nervous system lymphoma (PCNSL) [2]. Cervical cancer and intermediate-grade and high-grade forms of non-Hodgkin lymphoma (NHL) were added to the list of ADCs shortly thereafter [2]. The risk of cancer in PLWHA can be defined by the standard incidence ratio (SIR) [21]. For malignancies associated with HIV infection, the SIR compares the rate of cancers in the HIV/AIDS population to the number expected in the general population at any given time [2,7–10,22,23]. In the HAART era, the SIR has decreased for all ADCs, with the exception of invasive cervical carcinoma [2,7–10,22,23]. However, the risk for each of the ADCs remains above that of the general population (Table 1) [2,7–10,22,23].

Prior to the emergence of HIV, Kaposi sarcoma was a rare disorder. Between 1987 and 1993, Kaposi sarcoma incidence increased 66-fold from 0.5 to 33 patients per 100 000 patient-years in PLWHA [1]. During this period, NHL incidence increased by a more modest three-fold. Based on the complex epidemiology and histologic interpretation of lymphomas, nine subtypes were defined by the WHO as associated with HIV infection (Table 2) [24–28]. Among these nine, all are considered ADCs except low-grade lymphomas, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), and Hodgkin lymphoma [2,21,24]. The most common AIDS-defining NHLs are of B-cell origin, present with advanced stage disease, and follow an aggressive clinical course [29]. These AIDS-defining NHLs include PCNSL, Burkitt's lymphoma, diffuse large B-cell lymphoma (DLBCL), plasmablastic lymphoma,

**Table 1. Standard incidence ratios for common AIDS-defining and non-AIDS-defining cancers in the early and later HAART era and in the context of tumor-associated oncogenic viruses.**

HIV-associated malignancies	SIR pre-HAART (1990–1995)	SIR early-HAART era (1996–2002)
<b>ADCs</b>		
Kaposi sarcoma	22 100	3640
PCNSL	5000	>1020
Burkitt's lymphoma	52	49
DLBCL	64	29.6
All NHLs	79	22.6
Cervical carcinoma	4.2	5.3
<b>NADCs</b>		
Hodgkin lymphoma	8.1	14
Anal carcinoma	18.3	33
Lung carcinoma	2.5	2.2–6.6
Head and neck carcinoma	1.2	1–4
Prostate cancer	N/A	4
Hepatocellular carcinoma	19	7–35
Melanoma	N/A	3
All NADCs	1.8	1.7–2

ADCs, AIDS-defining cancers; DLBCL, diffuse large B-cell lymphoma; EBV Epstein–Barr virus; HPV, human papillomavirus; N/A, not available; NADCs, non-AIDS-defining cancers; NHL, non-Hodgkin lymphoma; PCNSL, primary central nervous system lymphoma; SIR, standard incidence ratio.

and primary effusion lymphoma (PEL) [24,29]. In the pre-HAART era, DLBCL and PCNSL were the most common NHLs in PLWHA, presenting with an incidence of 453 and 233 cases per 100 000 patient-years, respectively [23,29]. Between 2001 and 2007, the most common AIDS-defining NHL remained DLBCL, although its incidence had decreased to 120 cases per 100 000 patient-years [23]. During this same period, and with an incidence of 32 cases per 100 000 patient-years, Burkitt's lymphoma supplanted PCNSL as the second most common AIDS-defining NHL [23].

Together, Kaposi sarcoma and NHL accounted for 99% of all ADCs in the pre-HAART era [1]. From 1991–1995 to 2001–2005 when ART was introduced, the number of Kaposi sarcoma cases declined by 84% and the number of NHL cases declined by 54%. During this same interval, the incidence of all ADCs decreased by 70% [1,3]. In the HAART era, however, ADCs continue to be a major problem. Between 2001 and 2005, more than 2000 cases per year were diagnosed in the United States, and these malignancies currently account for 15–19% of all deaths in PLWHA [14,16]. One of the most important risk factors for NHL and Kaposi sarcoma is immune suppression as reflected by the CD4<sup>+</sup> T-cell count [7,30,31]. In retrospective analyses, the SIR for NHL increased from 35.8 to 145 and for Kaposi sarcoma from 76 to 571 when the CD4<sup>+</sup> T-cell count decreased from 500 to less than 100 cells/ $\mu$ l. In contrast, the incidence of Burkitt's lymphoma increased from 9.6 to 30.7 per 100 000 person-years as the CD4<sup>+</sup> T-cell count increased from less than 50 to greater than 250 cells/ $\mu$ l [25–27]. This paradoxical observation is further discussed in the Etiology section below.

**Table 2. WHO classification of lymphoid malignancies associated with HIV infection.**

Lymphoma type	Comments
Burkitt's lymphoma, Burkitt's-like lymphoma	Presents with a higher CD4 <sup>+</sup> T-cell count; 100% associated with cMYC translocation
Diffuse large B-cell lymphoma	Centroblastic 30% EBV [25,26]
Centroblastic immunoblastic (associated with PCNSL)	Immunoblastic 90% EBV and associated with primary CNS lymphoma [25,26]
Extranodal MALT lymphoma	Non-AIDS-defining cancer; rare
Peripheral T-cell lymphoma	Rare
Primary effusion/body cavity lymphoma	Rare; presents in patients in the late stages of HIV; associated 100% with HHV-8 and EBV [25,27]
Plasmablastic lymphoma of the oral cavity	Rare; associated with HHV-8 50% and EBV 50% [26]
Polymorphic B-cell lymphoma (PTLD-like)	Rare
Hodgkin lymphoma	Non-AIDS-defining lymphoma; may present in patients with elevated CD4 <sup>+</sup> T-cell count; EBV 80–100% [28]

DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; HHV-8, human herpesvirus 8; MALT, marginal zone lymphoma of mucosa-associated lymphoid tissue; PCNSL, primary central nervous system lymphoma; PTLD, posttransplant lymphoproliferative disorder.

### Non-AIDS-defining cancers

In the United States, NADC incidence increased greater than three-fold, from 3193 to 10 059 cases when comparing the intervals 1991–1995 and 2001–2005 [3]. In resource-rich countries in the pre-HAART era, NADCs accounted for approximately 8–38% of all HIV malignancies [3,32,33]. In the HAART era, this number has increased to 50–58% [3,13,22,32–35]. Depending on the malignancy, the SIR for most NADCs ranges from 2 to 35 (Table 1) [13,23,32–39]. The most important risk factors for NADCs are advancing age and the length of time one has been infected with HIV [7,13,40]. Additional important factors that impact NADC incidence are exposure to cigarette smoke and oncogenic viruses [39,41–43]. Less clear risk factors include a low CD4<sup>+</sup> T-cell count and the use of anti-HIV therapy [7,22,44,45]. In a multivariate analysis, two risk factors for NADCs emerge: a CD4<sup>+</sup> cell count less than 200 cells/ $\mu$ l and the use of HAART [10]. However, the link between low CD4<sup>+</sup> T-cell count and NADCs is conflicting and is disease-dependent and time-dependent. The SIR for anal cancer increases from 22 to 68 when the CD4<sup>+</sup> T-cell count remains less than 200 cells/ $\mu$ l for more than 5 years compared to 2 years [43]. In contrast, the SIR for Hodgkin lymphoma increases from 5 to 14 as the CD4<sup>+</sup> T-cell count rises from 50 to 200 cells/ $\mu$ l [3,36,39]. When PLWHA are compared to recipients of solid organ transplants, both populations have similar risks for Kaposi sarcoma and NHL as well as certain NADCs including Hodgkin lymphoma, anal, liver, and lung cancer [44]. In the case of lung cancer, even when correcting for cigarette smoking, the incidence remains greater in PLWHA than in the general population, although no correlation between low CD4<sup>+</sup> T-cell count and lung cancer risk has been identified [41,42].

The role of HAART as a possible contributor to malignancy has not been validated by all studies [13,46,47]. NADCs are prevalent among long-term surviving HIV-infected patients not requiring therapy or in developing countries without access to therapy [48].

Therefore, HAART may be a risk factor due to its ability to increase longevity rather than its direct carcinogenic or anticarcinogenic potential. Of interest, statins (like HAART) have, through alternative modes of action, anti-inflammatory properties that reduce immune activation. In a recent retrospective analysis, they were associated with a 57% decrease in NADCs [49]. Additional studies are needed to better understand the role of chronic inflammation as a mediator of cancer risk.

The effects of both NADCs and ADCs are profound and 26–30% of PLWHA will die from these malignancies [14,15]. In the United States, more than 4000 new cases of cancer are diagnosed in PLWHA each year [3]. The median age of PLWHA in the United States now exceeds 50 years. Developing robust strategies to screen this group for preventable cancers will become increasingly important. Unfortunately, standard guidelines for cancer screening in this group do not exist. More research and algorithms are needed to improve cancer detection rates while also examining behaviors that can influence risk factors for cancer such as unsafe sex, heavy alcohol consumption, and cigarette smoking [50,51].

### Etiology

The etiological factors that contribute to both ADCs and NADCs are multifactorial and an entire review could be devoted to this topic alone. Thus, we describe the major factors that may be most relevant to malignancies in HIV/AIDS, including those that have been less described or previously not recognized. Further, as these factors are well represented across the spectrum of lymphomas, we focus on AIDS-defining NHLs and HIV-associated Hodgkin lymphoma as models of these factors.

PLWHA are susceptible to infection by oncogenic viruses. Kaposi sarcoma-associated herpes virus (KSHV)

or human herpes virus 8 (HHV-8), Epstein–Barr virus (EBV), HPV, and HBV and HCV are implicated in various ADCs and NADCs and are more prevalent in PLWHA (Table 3) [25–27,52,53] than the general population [25,26,28,52,54–56]. These viruses can alter mechanisms of apoptosis and cell cycle regulation, activate oncogenes, and inhibit tumor suppressor genes [53,57–62]. Viruses associated with ADCs and NADCs can also express micro-ribonucleic acids (miRNAs), which are small noncoding RNAs that act as negative regulators of protein synthesis by covalently binding to single-stranded mRNA [63–66]. HHV-8, HPV, and EBV together express over 40 miRNAs that play varied roles in promoting cancer [64,66–68]. EBV-expressed miRNAs include MiR-BHRF1-1, which inhibits the tumor suppressor gene p53 and miR-BART1, which activates BCL-2, an antiapoptotic protein [59,66–69]. HIV, although clearly not a direct oncogenic virus, has also been implicated in inhibiting the p53 tumor suppressor gene, altering cell cycle regulation, and activating proto-oncogenes that can lead to cellular transformation [57,62].

In terms of lymphoma, EBV and HHV-8 are the most common viruses associated with AIDS-defining NHLs and HIV-associated Hodgkin lymphoma (Table 3) [25,26,28,70,71]. Forty percent of Burkitt's lymphomas and as many as 80–100% of immunoblastic B-cell lymphomas, Hodgkin lymphomas, and PCNSLs are linked to EBV infection in the HIV/AIDS setting [25,26,28]. PEL, a rare lymphoma subtype with a peculiar tropism for involving serous cavities, is most often associated with both HHV-8 and EBV [25,26,28]. Chronic antigenic stimulation of B cells and macrophages induced by EBV, HIV, and HHV-8 elicits cytokine and

growth factor release, which promote B-cell proliferation and the outgrowth of a monoclonal B-cell population [71,72]. In addition, AIDS-defining NHLs are often associated with characteristic molecular abnormalities. For Burkitt's lymphoma and Burkitt's-like lymphomas, this includes a translocation of the cMYC gene with the immunoglobulin heavy and light chains [73,74]. In addition, the tumor suppressor genes p53 and BCL-6 are mutated in 30% or more of DLBCL and Burkitt's lymphoma cases. Both of these genes, if mutated or overexpressed, contribute to lymphoma genesis by preventing cell cycle regulation, inhibiting B-cell apoptosis (via p53 mutation), and preventing B-cell terminal differentiation (via BCL-6 overexpression) [73,74]. The extent to which overexpression of various proteins, translocation of important genes, and oncogene activation by various viruses play in this intricate process of lymphoma genesis remains an area of active investigation.

For PLWHA, those with the lowest CD4<sup>+</sup> cell counts are at greatest risk for DLBCL, although in the HAART era, the absolute CD4<sup>+</sup> cell count at diagnosis is greater than in the pre-HAART era. In contrast, patients with Burkitt's lymphoma and Hodgkin lymphoma are usually diagnosed with somewhat higher CD4<sup>+</sup> T-cell counts [28,36,75]. CD4<sup>+</sup> T cells modulate B cells and antibody production directed at extracellular organisms, and cell-mediated responses, which involve CD8<sup>+</sup> T-cell defense against intercellular organisms [76–81]. HIV can readily infect these CD4<sup>+</sup> T cells and without HAART, they are destined to be depleted [76,79]. CD4<sup>+</sup> T cells produce cytokines that help regulate B-cell and T-cell responses [76,79]. In addition to immune regulation, these cytokines can also influence B-cell and T-cell survival [79]. This effect could account for the disruption (in patients with chronic HIV infection) of germinal centers, the areas in the lymph nodes and lymphoid tissues where B cells proliferate, differentiate, class switch, and augment antibody production in response to infection [77,80,81]. The B cells that reside in the germinal centers but are not exposed to CD4<sup>+</sup> T-cell survival signals (due to elimination of CD4<sup>+</sup> T cells by HIV) are destined to undergo premature apoptosis [76–79,81]. Burkitt's lymphoma is a cancer derived from germinal center B cells. If the germinal center is not present or disrupted (e.g. due to lack of CD4<sup>+</sup> T cells), then Burkitt's lymphoma may not develop. This might help explain the paradox of why Burkitt's lymphoma incidence increases as the CD4<sup>+</sup> T-cell count rises [33].

The cancer cell associated with Hodgkin lymphoma, the Hodgkin Reed Sternberg (hRS) cell, is also of B-cell origin [82]. Studies of both primary Hodgkin lymphoma cultures and hRS cell lines reveal that these cells secrete some of the same cytokines produced by CD4<sup>+</sup> T cells, including interleukin-5 (IL-5), IL-10, IL-12, and IL-13 [78,83–89]. These interleukins not only affect B-cell, T-cell, and eosinophil-cell activation, proliferation, and

**Table 3. Common AIDS-defining and non-AIDS-defining and tumor-associated oncogenic viruses.**

HIV-associated malignancies	Associated oncogenic virus
Kaposi sarcoma	100% HHV-8 [53]
PCNSL	100% EBV [26]
Burkitt's lymphoma	20–40% EBV [26]
DLBCL	Centroblastic 30% EBV [26] Immunoblastic 90% EBV [26]
PEL	100% HHV-8 [27] 100% EBV [25,27]
Plasmablastic	50% HHV-8 [25,26] 50% EBV [25,26]
Cervical	100% HPV [53]
Hodgkin lymphoma	80–100% EBV [25,26]
Anal carcinoma	100% HPV [52]
Head and neck carcinoma	HPV [53] EBV [53]
Hepatocellular Carcinoma	HBV [53] HCV [53]

DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-8, human herpesvirus 8; HPV, human papillomavirus; NADC, non-AIDS-defining cancer; NHL, non-Hodgkin lymphoma; PCNSL, primary central nervous system lymphoma; PEL, primary effusion lymphoma.

survival, but also act as trophic factors promoting hRS cell survival via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signal transduction pathway [85,87,88]. The hRS cell also secretes chemokines that attract CD4<sup>+</sup> T cells to their 'microenvironment,' which further augments hRS survival [72,78, 83,84,86].

How oncogenic viruses, HIV, and CD4<sup>+</sup> T-cell lymphocytes interact to promote these malignancies remains an area of active investigation. As discussed above, without these signals, as is the situation in AIDS, the microenvironment may be inadequate to support the genesis of malignancies. Another explanation may be that CD4<sup>+</sup> T-cell counts may not sufficiently indicate malignancy potential at the time of cancer diagnosis, as by the time that CD4<sup>+</sup> T-cell counts drop, the cancer has been developing for some time undetected. Some studies, instead, have linked the nadir CD4<sup>+</sup> T-cell count to future pro-malignancy potential [9,10]. Finally, total CD4<sup>+</sup> T-cell counts (nadir or at the time of cancer diagnosis) alone may not adequately provide an indication of the potential of certain CD4<sup>+</sup> T-cell subsets in helping or regulating antitumor responses. In HIV/AIDS particularly, CD4<sup>+</sup> T cells have important dual impact on both anti-HIV and antitumor responses. First, CD4<sup>+</sup> T cells are important providers of CD8<sup>+</sup> T-cell help and, in their absence, long-term CD8<sup>+</sup> T-cell responses require alternative forms of costimulation [90–92]. Second, CD4<sup>+</sup> T cells are a prime target and reservoir of HIV infection. A growing number of CD4<sup>+</sup> T-cell subsets have been recognized with roles ranging from regulation (inhibition) to propagation of immune responses based on their cytokine profile, transcription factor requirements, and immune regulatory functions [79,93–103]. Although the role of traditional subsets of CD4<sup>+</sup> T cells [T helper type 1 (Th1), Th2, and regulator T (Treg) cells] has been investigated, little to no basic science or clinical information exists regarding novel subsets [Th9, Th17, Th22, natural (nTreg), inducible Treg, IL-35-producing (Tr35) and IL-35-inducible Treg (iT35), and cytotoxic CD4<sup>+</sup> T cells] in HIV/AIDS and/or in the context of malignancies in HIV/AIDS. In addition, although total CD4<sup>+</sup> T-cell counts are used as a marker of disease progression or treatment efficacy (as CD4<sup>+</sup> T-cell counts recover with HAART), it is unknown whether all subsets recover proportionately, or whether certain subsets or proportions of subsets leave HIV/AIDS patients resistant to infection but more susceptible to malignancies.

Lifestyle choices also clearly impact cancer risk. Cigarette smoking is common in the HIV population. Greater than 50% of PLWHA smoke compared to just 18% of the United States general population older than 18 years of age [104,105]. PLWHA who smoke are at higher risk for ADCs and NADCs, including those that involve the lung, esophagus, kidney, bladder, head and neck, breast, and

cervix [104,106,107]. The correlation between smoking and colon and hepatocellular cancer is not as strong [107]. Alcohol addiction is also more common in PLWHA. Cancer mortality is three times higher in patients who smoke than in nonsmokers [108]. In addition, when assessing all causes of death, AIDS-related and non-AIDS-related mortality rates are five times higher in PLWHA who smoke compared with those who do not [109]. In the United States, rates of heavy alcohol consumption among PLWHA are twice as great as they are in the general population [106]. Alcohol consumption is also associated with cancers of the mouth, esophagus, pharynx, larynx, and liver [110].

Differences in exposure to oncogenic viruses, CD4<sup>+</sup> T-cell recovery, and lifestyle may strongly influence the incidence of certain cancers in PLWHA, but why such individuals are often diagnosed with more advanced stage tumors than the general population requires further study [29,42,43]. Disparities in healthcare and how PLWHA access medical care, as well as the higher incidence of AIDS and cancer in minority populations, are additional important points when considering the incidence of various cancers in PLWHA [111–113].

## Treatment

In the HAART era, HIV-infected patients are increasingly offered chemotherapy options for malignancies that were once restricted to nonimmunosuppressed patients with cancer or cancer patients who were HIV seronegative. Safer, more convenient, and better tolerated HAART options, improved supportive care strategies, and incremental refinements in cancer treatments have all contributed to improvements in overall survival (OS) and a decrease in therapy-associated toxicity in select HIV-cancer groups. From the pre-HAART to the HAART era, the OS for patients with Hodgkin lymphoma improved from 45% at 2 years to 76–81% at 5 years [114–116]. Similarly, DLBCL OS improved from just 8 months in the pre-HAART era to a current 5-year OS of 60–80% [117–120]. HIV-infected patients with anal carcinoma now have similar treatment-associated toxicities, including risk of colostomy, and OS compared to their non-HIV-infected counterparts [121,122]. While the specific treatments for each cancer type are outside the scope of this review, here we focus on the interactions of HIV medications and chemotherapeutic agents and briefly assess immunotherapeutic options.

Many chemotherapeutic drugs and HIV medications are metabolized through the cytochrome p450 (CYP) enzyme system of the liver. HAART can augment or inhibit the clearance of chemotherapy agents by the upregulation or inhibition of the CYP system (Table 4)

**Table 4. Interactions between chemotherapeutics and antiretroviral agents.**

Chemotherapeutic agents	P450 system responsible for metabolism	Antiretroviral inhibitor <sup>a</sup>	Antiretroviral inducer <sup>b</sup>	Associated cancers (being treated)
Vinblastine Vincristine	CYP 3A4	Delavirdine, Ritonavir, Amprenavir, Atazanavir, Indinavir Lopinavir Nelfinavir, Saquinavir	Nivarapine Efavirenz	Hodgkin lymphoma ALL, NHL
Paclitaxel Docetaxol Etoposide	CYP 2C8 CYP 3A4 CYP 3A4 CYP 2E1	Same as above	Nivarapine Efavirenz	KS, breast, lung, cervical NHL, lung
Ifosphamide Cyclophosphamide	CYP 3A4 CYP 2C9 CYP 2B6 CYP 2E1	Efavirenz Amprenavir	Nivarapine Efavirenz	NHL, lung, breast, sarcoma
Dacarbazine	CYP 2E1	Ritonavir		Hodgkin lymphoma

ALL, acute lymphocytic leukemia; CYP, cytochrome P450; KS, Kaposi sarcoma; NHL, non-Hodgkin lymphoma.

<sup>a</sup>Inhibitors increase the concentration of the active metabolite.

<sup>b</sup>Inducers decrease the concentration of the active metabolite.

[123–127]. This can lead to either increased chemotherapy-associated toxicity or a decrease in treatment efficacy [123–125,128]. In addition, several HIV medications and chemotherapy agents have overlapping toxicities [124–129] (Table 5). Zidovudine can cause myelosuppression in 8% of treated patients, didanosine and stavudine can cause peripheral neuropathy, and HIV protease inhibitors can cause nausea and vomiting. Nucleotide analogues can contribute to nephrotoxicity, whereas protease inhibitors and nonnucleoside reverse transcriptase inhibitors can cause hepatotoxicity [123–125]. Such known side-effects and their frequencies need to be considered when combining HAART with specific chemotherapy agents that have a high risk of cytopenias, nephrotoxicity, peripheral

neuropathy, hepatotoxicity, and unwanted gastrointestinal side-effects.

The HIV protease inhibitor ritonavir is a particularly potent inhibitor of the CYP system. Its effect on CYP3A4 leads to diminished clearance of vinca alkaloids, taxanes, and alkylating agents [124,125,127]. Consequently, ritonavir is associated with increased toxicity when combined with vincristine-based and even more so when combined with vinblastine-based chemotherapies (used to treat NHL and Hodgkin lymphoma, respectively) [130–132]. Ritonavir should be avoided during vinblastine-based Hodgkin lymphoma treatment as the rates of febrile neutropenia, neuropathy, and neutropenia are considerably elevated when these agents are combined

**Table 5. Major overlapping toxicities observed with HIV medications and chemotherapy.**

Chemotherapy agent	Adverse events	HIV medication/class
Common with most chemotherapeutic classes. [i.e. anthracyclines, taxanes vinca alkaloids, platinum alkylating agents, camptothecins, etoposide, and antimetabolites (methotrexate and 5FU)]	Myelosuppression	Zidovudine
All taxanes; all vinca alkaloids; oxaliplatin; bortezomib	Neuropathy (motor and/or peripheral)	Didanosine; stavudine
Cisplatin Carboplatin	Nephrotoxicity	Tenofovir Indinavir
Common with most chemotherapeutic classes.	Nausea/vomiting	Protease inhibitors; zidovudine
Vinca alkaloids Common with most chemotherapeutic classes. (Chemotherapeutic agents that can be administered without any dose reductions in the setting of liver toxicity include cisplatin, gemcitabine, and bleomycin) [128]	Constipation Hepatotoxicity	Protease inhibitors; nucleoside and nonnucleoside reverse transcriptase inhibitors
Irinotecan Topotecan Fluorouracil	Diarrhea	Nelfinavir Lopinavir

[130–132]. Fluconazole is also associated with increased toxicity (e.g. neutropenia and neuropathy) when combined with the vinca alkaloids through a similar mechanism, as it too inhibits the CYP3A4 system [132]. Thus, care should be taken to identify chemotherapy-HAART interactions as well as HAART interactions with other medications that are used to treat or to prevent opportunistic infections or to mitigate chemotherapy side-effects, including antiemetic agents. In light of these complicated interactions, we recommend treating cancer patients in consultation with infectious disease specialists and pharmacists who are aware of potential and complicated drug–drug interactions, and if possible, with hematologist/oncologists who have special expertise in the treatment of patients with HIV and cancer.

When chemotherapy and HAART are given concomitantly during NHL treatment, CD4<sup>+</sup> cell counts typically decline by greater than 50% [133]. These values usually return to normal at 6 months to 1 year after therapy [133]. For anal cancer patients who receive pelvic radiation, the CD4<sup>+</sup> T-cell count may fall even more severely and may not readily recover to pretreatment values [134]. Pelvic radiation is myelosuppressive as the major source of bone marrow is also radiated. In addition, scatter of radiation may also affect the gut, which is also an important compartment for CD4<sup>+</sup> T cells [129,135,136]. For HIV patients with malignancies, we recommend that *Pneumocystis jiroveci* prophylaxis be initiated regardless of the CD4<sup>+</sup> T-cell count at the time of chemotherapy initiation. Prophylactic medications to minimize the risk of other opportunistic infections, including thrush and herpes simplex virus, are also warranted during treatment [134]. Granulocyte colony-stimulating agents to minimize the effects of chemotherapy-induced neutropenia and antibiotic prophylaxis to further reduce infectious complications are also routinely implemented during the treatment of HIV/AIDS-related lymphomas and other cancers on a risk-assessment basis [114,117,119,120].

In theory, all patients with HIV/AIDS-related malignancies, for whom HAART would be prescribed in the absence of cancer, should be maintained on HAART during chemotherapy. Reasons for HAART discontinuation during treatment include concerns of drug interactions with chemotherapy and poor patient adherence because of nausea or vomiting. Due to HAART-chemotherapy interactions, investigators from the National Cancer Institute (NCI) have examined the discontinuation of HIV therapy during a short 4–6-month treatment period for AIDS-related lymphomas [117,119]. As anticipated, the HIV viral load increased and the CD4<sup>+</sup> T-cell count declined, but once HIV therapy was reinitiated at the completion of chemotherapy, both improved over the following 6–12 months [117,119]. At 5 years, the OS was 68% and appears comparable to results that have been reported

when HIV-infected patients with AIDS-related lymphomas were treated with concurrent chemotherapy and HAART. In the absence of head-to-head comparisons, offering to continue HAART or to hold HAART until systemic chemotherapy is completed are both reasonable options [117,119,120].

The chimeric anti-CD20 monoclonal antibody rituximab offers substantial benefit when used with combination chemotherapy for treatment of CD20<sup>+</sup> aggressive B-cell lymphomas [137]. The role of rituximab in the treatment of AIDS-associated lymphomas has been more controversial based on findings from two studies, which linked rituximab with a significant risk of infection complications [109,137]. The first study was a phase 3 trial of The AIDS Malignancy Consortium (AMC) comparing the chemotherapy regimen cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with CHOP along with rituximab (CHOP-R) in the treatment of aggressive AIDS-defining lymphomas [109]. In this trial, the rituximab arm was associated with a modest benefit in efficacy, but patients who received monoclonal therapy had a significantly higher incidence of treatment-related infectious deaths (14 versus 2%;  $P=0.027$ ) [109]. This finding was particularly true for those patients who went into treatment with CD4<sup>+</sup> T-cell counts less than 50 cells/ $\mu$ l. A second study was a retrospective analysis of three phase 2 trials of cyclophosphamide, doxorubicin, etoposide, and rituximab (CDE-R) that also showed an 8% elevation in treatment-related infectious deaths [137]. More recently, studies of CHOP-R for the treatment of AIDS-associated lymphomas demonstrated few infectious complications and a 2-year OS rate of 75%. In one recent study of 52 evaluated patients, only one death was due to infection [138].

Three subsequent phase 2 studies for AIDS-associated lymphomas, one by the AMC and two by the NCI also confirmed the safety and efficacy of rituximab [117,119,120]. Based on these results, rituximab is now typically combined with chemotherapy, and should not be withheld for patients with CD4<sup>+</sup> T-cell counts less than 50 cells/ $\mu$ l. Caution should be exercised when treating patients with severe immunosuppression however, as these patients have an elevated risk for infection. Studies by the AMC are now being undertaken to evaluate immunotherapy for HIV-associated Hodgkin lymphoma. Brentuximab vedotin, is an antibody–drug conjugate, which specifically binds to the hRS cell receptor, CD30, thus initiating targeted tumor death. Remarkably, 32% of non-HIV-infected patients with refractory Hodgkin lymphoma, who participated in a phase 2 study of brentuximab vedotin as a single agent, achieved a complete response (CR), with an overall response rate (ORR) of 73% [139].

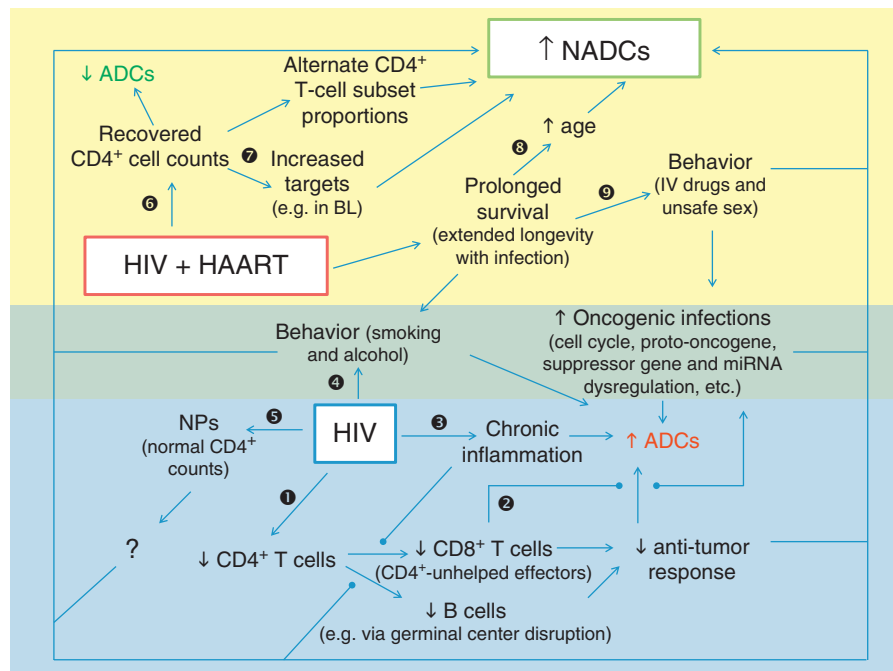
Recently, other modes of immunomodulation have emerged as successful mainstream therapies for cancer.

Among these, sipuleucel-T (which utilizes loading of patient dendritic cells with prostate tumor antigens fused with an immunomodulatory factor granulocyte macrophage colony-stimulating factor [GM-CSF]) and ipilimumab (which blocks T-cell inhibitory surface protein CTLA-4) are FDA-approved for use in the treatment of castration-resistant prostate cancer and melanoma, respectively [140,141]. The major direct or indirect end result of these immunotherapies and others in late-stage clinical trials [including stimulation with IL-2 and blockade of program cell death protein 1 (PD-1)] is likely the rescue of CD8<sup>+</sup> T cells. Based on the critical role of CD8<sup>+</sup> T cells in both viral infection and cancer, and the dual dysfunction of CD8<sup>+</sup> T-cell responses against both HIV and malignancies, consideration should be given to

the use of similar immunotherapy for treatment of malignancies in HIV/AIDS.

## Conclusion

More than 30 years after cases of HIV/AIDS were finally globally recognized and more than 55 years since the first proven case of HIV infection [142], HIV/AIDS continues to be a deadly epidemic. Despite medical, social, and political interventions, the number of people living with HIV (approximately 34.0 million as of 2011), the number of people newly infected each year with HIV (2.5 million in 2011), and the number of people dying of



**Fig. 1. Summary of AIDS-defining cancer and non-AIDS-defining cancer etiology in the context of HIV and HAART.** Colored panels comprise concepts that are closely related: lower blue panel includes concepts related most closely to HIV infection (HIV), upper yellow panel indicates concepts related most closely to HAART treatment in HIV (HIV + HAART), and middle green panel indicates concepts related to both HIV and HIV + HAART. ADCs, AIDS-defining cancers; BL, Burkitt's lymphoma; i.v., intravenous; NADCs, non-AIDS-defining cancers; NPs, nonprogressors. Summary of ADC and NADC etiology in the context of HIV and HAART. ① HIV infection results in the depletion of CD4<sup>+</sup> cells leading to ineffective CD4<sup>+</sup>-unhelped CD8<sup>+</sup> T-effector and B cells, which results in decreased antitumor responses and a resultant increase in ADCs. ② Lack of CD4<sup>+</sup> cell help leads to a lack of responses against oncogenic infections, leading to cellular and molecular dysregulation and a resultant increase in ADCs and NADCs. ③ HIV infection results in a state of chronic inflammation leading to a subsequent increase in ADCs and NADCs through mechanisms that are not sufficiently understood. ④ Behaviors increased in HIV/AIDS (e.g. smoking and alcohol overconsumption) lead to an increase in ADCs and NADCs. ⑤ Despite normal CD4<sup>+</sup> cell counts in nonprogressors (NPs; i.e. HIV patients not requiring treatment while maintaining low/undetectable HIV viral loads for extended periods of time), NADCs continue to be increased above the level found in the non-HIV-infected population. ⑥ CD4<sup>+</sup> cell counts recover in HIV patients treated with HAART, and a resultant decrease in ADCs is observed, but ADCs remain increased above the level found in the non-HIV-infected population. ⑦ Despite recovery of total CD4<sup>+</sup> cell counts, the CD4<sup>+</sup> T-cell subset distribution (Th1, Th2, Th9, Th17, Th35, Treg cells, etc.) may not return to normal proportions, and increased numbers of CD4<sup>+</sup> T cells allow for outgrowth of CD4<sup>+</sup>-involved/dependent cancers. ⑧ Increased survival with HAART results in extended longevity in the context of infection leading to increased age (i.e., time for NADC outgrowth). ⑨ Increased survival with HAART results in extended time involving behaviors associated HIV/AIDS (e.g. smoking, alcohol overconsumption, i.v. drug use, and unsafe sex leading to oncogenic infections) and resulting in a subsequent increase in ADCs and NADCs.



**Table 6. General guidelines for the treatment of HIV-associated cancers.**

- Optimal treatment of patients with HIV-associated malignancies includes input from a multidisciplinary team consisting of a pharmacist, an infectious disease specialist, and a hematologist/oncologist.
- HIV medications can inhibit the Cyt p450 system, potentially augmenting toxicities by preventing chemotherapy metabolism (see Table 4 as a guide).
- Multiple overlapping toxicities are seen with HIV medications and chemotherapy agents (see Table 5 as a guide).
- Supportive care medications can also augment chemotherapy toxicities (i.e. azole antifungals and vincristine).
- Avoid the use of ritonavir when combined with vinblastine in the setting of Hodgkin's lymphoma.
- Rituximab offers substantial benefit when used with combination chemotherapy for treatment of CD20 aggressive B-cell lymphomas. Rituximab should not be withheld for patients with CD4<sup>+</sup> cell counts less than 50 cells/ $\mu$ l. But care should be taken, as patients with low CD4<sup>+</sup> T-cell counts are more prone to infectious complications.
- CD4<sup>+</sup> T-cell counts can decrease during chemotherapy and/or in the setting of pelvic radiation. Thus, prophylaxis during therapy for opportunistic infections is often warranted despite a normal CD4<sup>+</sup> T-cell count at therapy onset.
- Granulocyte colony-stimulating agents and antibiotic prophylaxis are strongly encouraged to minimize the effects of chemotherapy-induced neutropenia during the treatment of AIDS-related lymphomas.

HIV (1.7 million people in 2011) continue to increase [5]. Although medical interventions (mainly in the form of HAART) have resulted in a decrease in AIDS-defining diseases (including infections and cancers), longevity of the HIV/AIDS population has also allowed for the emergence of aging-related diseases, including NADCs (Fig. 1). However, age alone cannot explain the rise in NADCs, especially as NADCs present earlier, more often with metastases, and exhibit a more rapidly progressive course even in adequately treated, medication-compliant HIV/AIDS patients [143]. The paucity in basic science, translational, and clinical research toward an understanding of the cause and best course of treatment for malignancies in HIV/AIDS raises the need for further investment of time, effort, and funds in these fields. Enrolling patients into clinical trials who are diagnosed with HIV/AIDS is of utmost importance, as without structured research protocols, questions regarding treatment, pharmacology, cause, and screening will be more difficult to answer. We also recommend a multidisciplinary approach to HIV-cancer care, including a primary care physician, infectious disease specialist, a hematologist/oncologist, and pharmacist all specializing in HIV/AIDS care (Table 6). Current epidemiological and etiological data strongly suggest that HIV/AIDS patients should be under increased surveillance not only for ADCs, but likewise for NADCs, even years earlier than the general population. In addition, earlier or more monitored treatment of oncogenic viruses and avoidance of cancer-associated lifestyles must be considered. The HIV/AIDS population appears to be more susceptible to almost all cancers. Although great strides have been made toward increasing the longevity and survival of patients with HIV/AIDS and of patients with malignancies, new considerations must be made and new actions taken to overcome the challenge of preventing and treating malignancies in HIV/AIDS.

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## Conflicts of interest

There are no conflicts of interest.

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