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## HIV infection, aging, and immune function: implications for cancer risk and prevention

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### Abstract

**Purpose of review**—Combination antiretroviral therapy (ART) has turned HIV infection into a complex chronic disease. This article documents cancer risk among HIV-infected persons, reviews immune system effects of HIV infection in relation to cancer risk, discusses implications for cancer prevention, and suggests future research directions.

**Recent findings**—There has been a shift in the cancer spectrum from AIDS-defining cancers (ADC) to non-ADC, although the burden of ADC remains high. Although a high prevalence of non-HIV cancer risk factors among HIV-infected persons contributes to cancer risk, substantial evidence has accumulated in favor of an independent association between HIV-induced immunodeficiency and elevated risk of many specific cancer types, most of viral cause, although further work is needed to disentangle immunodeficiency and smoking effects for lung cancer, and immunodeficiency and hepatitis virus effects for liver cancer. Relationships between cancer risk and two other immune system hallmarks of HIV infection, chronic inflammation, and immune dysfunction/senescence, remain poorly understood.

**Summary**—Early, sustained ART is a crucial component of cancer prevention. Continued epidemiologic monitoring is needed to detect possible effects on cancer risk of specific ART classes or medications, long-term exposure to systemic inflammation or immune dysfunction, or earlier or more effective ART.

### Keywords

aging; cancer; HIV; immune system; inflammation

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### Conflicts of interest

There are no conflicts of interest.

## INTRODUCTION

Combination antiretroviral therapy (ART), introduced in the mid-1990s, has turned HIV infection into a complex chronic disease [1]. Consequently, more people are living with HIV [2] to older ages (Fig. 1) [3,4]; by 2015, more than half of people living with HIV/AIDS (PLWHA) in the USA will be more than 50 years of age [5]. In this article, we document cancer risk among PLWHA in high-income countries, review immune system effects of HIV infection in relation to cancer risk, discuss implications for cancer prevention, and suggest future research directions.

## EPIDEMIOLOGY OF CANCER IN PEOPLE LIVING WITH HIV/AIDS

In the ART era, the spectrum of cancer diagnoses among PLWHA has shifted from AIDS-defining cancers (ADC), primarily Kaposi sarcoma and non-Hodgkin lymphoma, to non-AIDS-defining cancers (NADC). We explore this shift in detail in Table 1 [6–8,9<sup>■</sup>, 10,11,12<sup>■</sup>,13,14<sup>■</sup>,15–17,18<sup>■</sup>], which presents, by cancer type, the estimated number of incident cancer diagnoses among PLWHA in the USA in 2001–2005, and how this number changed from 1991–1995 to 2001–2005 [18<sup>■</sup>]. In Table 1, we also present, by cancer type, relative risk estimates for PLWHA compared with the general population or an uninfected comparison group [6–8,9<sup>■</sup>,10,11,12<sup>■</sup>,13,14<sup>■</sup>,15–17]. To create this table, we relied heavily on two important studies by Shiels *et al.* [6,18<sup>■</sup>].

The decrease in ADC diagnoses was driven by the sharp decline in Kaposi sarcoma and non-Hodgkin lymphoma incidence rates since the early 1990s [11,12<sup>■</sup>,18<sup>■</sup>,19<sup>■</sup>,20–22], corresponding with the introduction of ART. Nevertheless, even in 2001–2005, non-Hodgkin lymphoma accounted for 24% and Kaposi sarcoma accounted for 15% of cancer diagnoses (Table 1). In the ART era, relative risk (RR) estimates range from 55 to 1584 for Kaposi sarcoma and from 6.5 to 17 for non-Hodgkin lymphoma [7,8,9<sup>■</sup>,10,11,12<sup>■</sup>].

The increase in NADC diagnoses was driven by the aging of the HIV-infected population (as well as by the increasing number of PLWHA) [18<sup>■</sup>]. Because incidence rates for most types of cancer increase exponentially with age [23], the number of diagnoses for these cancer types increased simply because PLWHA are aging. Thus, between 1991–1995 and 2001–2005, NADC diagnoses tripled even though the overall age-standardized, sex-standardized and race-standardized NADC incidence rate declined by about 13% among PLWHA [18<sup>■</sup>]. In 2001–2005, the five leading NADC diagnosed among PLWHA were cancers of the lung and anus, Hodgkin lymphoma, and cancers of the prostate and liver (Table 1) [18<sup>■</sup>].

Cancer types with a known or suspected viral cause had elevated RRs (Table 1) [6,24,25]. In contrast, with the notable exception of lung cancer and some other smoking-related cancers, RRs for most nonviral-related epithelial cancers were null or below null (prostate, breast). In spite of their low RRs, cancers of the prostate and breast were among the cancer types with the greatest rise in crude incidence (Table 1), due to their high baseline risks and strong associations with age.

The elevated risk for a given cancer type in PLWHA may be caused by immune system effects of HIV infection, by high prevalence of non-HIV cancer risk factors, or by combined immune system and non-HIV risk factor effects. The high prevalence of infection from human papillomavirus (HPV) [26–28], hepatitis C virus (HCV) [29], hepatitis B virus (HBV) [29], and Kaposi sarcoma-associated herpesvirus [30], as well as of smoking [31] and alcohol consumption [32], are well documented. Here, we focus on immune system effects of HIV infection, including progress in disentangling immune system effects from non-HIV risk factor effects.

## IMMUNE SYSTEM AND CANCER

The immune system protects against cancer by clearing or suppressing oncogenic virus infections and through general cancer immunosurveillance, a process in which innate and adaptive immunity interact to recognize and destroy cancer cells [33]. Thus, immunosuppressive conditions, including inherited immunodeficiency disorders, post-transplant immunosuppression, and HIV infection, are associated with increased risk of specific cancer types, most prominently lymphomas or other cancers caused by viruses [34].

Chronic immune activation and inflammation, through stimulation of cell proliferation, generation of genotoxic reactive oxygen and nitrogen species, production of procarcinogenic cytokines and growth factors, and possibly other mechanisms, also promote cancer development [35,36]. Such chronic inflammation is typically localized to a specific tissue and may be caused by viruses (e.g., HCV or HBV and liver cancer), other infectious agents (e.g., *Helicobacter pylori* and gastric cancer), autoimmune disorders (e.g., inflammatory bowel disease and colorectal cancer), or toxic exposures (e.g., inflammation caused by smoking or other irritants and lung cancer) [35,36,37].

## IMMUNE SYSTEM EFFECTS OF HIV INFECTION

The three immune system hallmarks of HIV infection are immunodeficiency, chronic immune activation/inflammation, and immune dysfunction/senescence. HIV infection is characterized by a paradoxical coexistence of immunodeficiency, driven by infection and depletion of CD4 cells, and systemic chronic activation of both the innate and adaptive immune systems with resultant chronic inflammation [38,39,40]. Mechanisms underlying chronic immune activation appear to include the immune response to HIV infection itself, direct HIV gene product activation of lymphocytes and macrophages and production of proinflammatory cytokines, immunodeficiency-induced reactivation and replication of other viruses, particularly cytomegalovirus and Epstein–Barr virus, and translocation of intestinal bacterial flora across the gut wall precipitated by massive depletion of CD4 cells in the intestinal mucosa [38,39,40].

Chronic immune activation leads to progressive exhaustion of immune resources associated with thymic involution, impaired hematopoiesis, lymphatic tissue fibrosis, sustained T-cell turnover and apoptosis, decline in T-cell renewal, a deficit of naive T cells, and an excess of differentiated, functionally defective memory T cells with shortened telomeres and limited diversity [38,40,41]. This immune dysfunction mimics the process of aging-associated immunosenescence [38,40,41], which has been postulated to be causally related to the increased cancer risk associated with aging [42,43].

Immune activation and inflammation may persist in persons on ART, albeit at lower levels than among untreated patients [39,41,44]. Thus, inflammatory markers, including interleukin 6 (IL-6), C-reactive protein (CRP), and D-dimer, remain elevated among persons on ART [41,44,45,46], although a recent study comparing demographically similar HIV-infected and uninfected veterans of similar comorbidity status found elevated IL-6 and D-dimer only among HIV-infected veterans with HIV RNA 500 copies/ml or more or CD4 cell count less than 200 cells/ $\mu$ l, and found elevated soluble CD14 (a biomarker of monocyte activation) only among HIV-infected veterans with CD4 cell count less than 200 cells/ $\mu$ l [47]. Cellular immune dysfunction markers, including low CD4 and CD8 naive : memory cell ratios, low activated CD8 cell percentage, and low CD4 : CD8 cell ratio, also persist in patients on ART, especially those who initiated ART at lower CD4 counts and older patients [44,48,49].

## HIV IMMUNE EFFECTS AND CANCER RISK

A recent meta-analysis of studies of cancer risk among PLWHA compared with the general population found the standardized incidence ratio (SIR) for all NADC combined to be 3.7 among persons with AIDS, but only 1.2 among HIV-infected persons without AIDS [6], implicating more profound immune system defects in NADC risk. This result is consistent with any of the three immune system hallmarks of HIV infection contributing to elevated cancer risk. However, to date, research has focused on the role of immunodeficiency, with substantial evidence accumulating in favor of an association with elevated risk of a number of specific cancer types, independent of non-HIV risk factors.

The most compelling evidence comes from a seminal meta-analysis in which the pattern of cancer risk was similar between PLWHA and organ transplant patients [24]. Both populations exhibited elevated SIRs for all cancer types known or suspected to be of viral cause, as well as cancers of the lung, stomach, and kidney, melanoma, multiple myeloma, and leukemia. These populations probably share few cancer risk factors apart from immunodeficiency, the main immune system defect they have in common. However, it should be noted that although immunosuppressive therapy for transplant recipients is not associated with immune activation, a recent study suggested that long-term immunosuppressive therapy leads to T-cell senescence [50].

Additional compelling evidence for an effect of immunodeficiency is provided by the well established strong, inverse relationships between CD4 count and risk for Kaposi sarcoma and non-Hodgkin lymphoma, respectively [21,22,51,52]. Early studies were inconsistent regarding the relationship between CD4 count and NADC risk, probably due to use of insensitive, static CD4 measures, such as CD4 count at AIDS diagnosis. However, recent studies have noted inverse associations between current (i.e., time updated) CD4 count and risk of NADC (grouped) [53,54<sup>■</sup>,55<sup>■</sup>,56<sup>■</sup>,57,58], virus-related NADC (grouped) and nonvirus-related epithelial NADC (grouped) [56<sup>■</sup>], Hodgkin lymphoma [9<sup>■</sup>,56<sup>■</sup>,59<sup>■</sup>,60], melanoma [9<sup>■</sup>], and anal [9<sup>■</sup>,56<sup>■</sup>], lung, [9<sup>■</sup>,56<sup>■</sup>,60], cervical [60], oral cavity/pharynx [9<sup>■</sup>], liver [9<sup>■</sup>,60,61,62<sup>■</sup>], and colorectal cancers [9<sup>■</sup>]. Two studies found no association with NADC (grouped) [63,64<sup>■</sup>].

A key outstanding question is whether current immunodeficiency versus duration of immunodeficiency is more closely associated with increased cancer risk. One study found longer exposure to CD4 cell count less than 200 cells/ $\mu$ l, but not lower current CD4, to be independently associated with increased NADC (grouped) risk [64<sup>■</sup>]. A second study found that lower current CD4 count was a better predictor of elevated risk for Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, and cancers of the lung, liver and cervix than longer exposure to CD4 cell count less than 200, 350, or 500 cells/ $\mu$ l, whereas longer exposure to CD4 cell count less than 200 cells/ $\mu$ l was the best predictor of elevated anal cancer risk [60]. A third study found lower current CD4 count, but not longer exposure to CD4 cell count less than 350 cells/ $\mu$ l, to be associated with increased NADC (grouped) risk [57], whereas a fourth found lower current CD4 count, but not longer exposure to CD4 cell count less than 200 cells/ $\mu$ l, to be associated with increased NADC (grouped) and ADC (grouped) risk, respectively [58]. A fifth study found longer and current exposure to CD4 cell count less than 500 cells/ $\mu$ l to be an equally good predictor of increased NADC (grouped) risk [53]. Finally, a study found that current, but not longer, exposure to CD4 cell count less than 500 cells/ $\mu$ l was associated with increased liver cancer risk [62<sup>■</sup>]. For some cancer types, particularly Hodgkin lymphoma [59<sup>■</sup>], low current CD4 count may be the result of preclinical disease, as opposed to the cause of disease.

The relationships between CD4 count and risk of specific NADC are generally weaker and more subtle than the relationships for ADC [9<sup>■</sup>,52,53,55<sup>■</sup>,58,60]. Furthermore, because CD4 count and markers of inflammation and immune dysfunction are intercorrelated, it is possible that CD4 count is a marker of risk, but not the sole mediator of risk. In general, the association between lower CD4 count and increased NADC risk has been found to be independent of time-updated HIV RNA level [53,57,58,59<sup>■</sup>,60,64<sup>■</sup>], a rough proxy for immune activation. However, higher current HIV RNA level was found to be independently associated with increased risk of non-Hodgkin lymphoma [53,60] and Kaposi sarcoma [60] and longer exposure to high HIV RNA was observed to be independently associated with increased risk of non-Hodgkin lymphoma [53] and anal cancer [60].

The association between lower CD4 count and risk of NADC (grouped) appears to be independent of non-HIV risk factors, persisting after adjustment for smoking, alcohol abuse, HBV coinfection, and/or HCV coinfection [53,54<sup>■</sup>,56<sup>■</sup>,58,64<sup>■</sup>], with the caveat that adjustment was often imperfect due to missing data for adjustment variables.

The weight of evidence also suggests that the inverse association between CD4 count and risk of HPV-related cancers is mostly independent of non-HIV risk factors. As mentioned above, associations have been observed between lower current CD4 count and increased risk of several HPV-related cancers (anal, cervical, oral cavity/pharynx). In addition, lower CD4 count at AIDS onset [65] or at baseline [13], longer duration of low CD4 count [60,64<sup>■</sup>], and lower nadir CD4 [66] were found to be associated with increased anal cancer risk. HIV adversely impacts the natural history of HPV infection, including increased HPV cervical viral load and persistence [26], which are inversely associated with CD4 count [26], as is prevalence of precancerous cervical [26] and anal lesions [67]. The anal cancer incidence rate among PLWHA rose between the pre-ART and early ART eras [13,18<sup>■</sup>,65,66], perhaps because longer survival allowed enough time for progression of precancerous lesions to invasive cancer [65], but appears to have plateaued in the later ART era [13,18<sup>■</sup>]. Longer duration of HIV infection was observed to be associated with increased anal cancer risk [66]. We should note that for oral cavity/pharynx cancer, in one study the elevated risk among PLWHA compared with uninfected persons was no longer significant after adjusting for smoking and alcohol/drug abuse [9<sup>■</sup>].

The relationships between HIV infection/lower CD4 count and lung and liver cancer risk are less clear. For lung cancer, in most [14<sup>■</sup>,15,16,68–70], but not all [9<sup>■</sup>], comparisons, incidence in PLWHA compared with uninfected persons remained elevated after adjusting for smoking. In addition, in three studies, the inverse association between current CD4 count and lung cancer risk among PLWHA persisted after adjustment for smoking [9<sup>■</sup>,56<sup>■</sup>,60]. However, no association between CD4 count and lung cancer risk, smoking adjusted or not, was observed in four other studies [64<sup>■</sup>,68,69,71<sup>■</sup>]. Immunodeficiency-induced recurrent pneumonia and the associated inflammation may contribute to lung carcinogenesis in HIV-infected persons [72].

With respect to liver cancer, HIV accelerates the natural history of HCV [73,74] and HBV [75] infection. In some studies, the inverse association between current CD4 count and liver cancer risk persisted after adjustment for alcohol abuse/dependence [9<sup>■</sup>] and hepatitis coinfection [60,62<sup>■</sup>]. However, other studies found no increased risk of liver cancer in HIV-infected compared with uninfected veterans after adjusting for HCV infection and alcohol abuse/dependence [76], no difference in liver cancer incidence between HIV/HCV-coinfected versus HCV-monoinfected patients [77], and no association between duration of exposure to low CD4 count and liver cancer risk [64<sup>■</sup>].

## CANCER PREVENTION

The two pillars of cancer prevention among PLWHA are restoration of immune function and reduction in the prevalence of non-HIV cancer risk factors. Here, we focus on immune function.

### Early and uninterrupted antiretroviral therapy

Department of Health and Human Services guidelines recommend ART initiation for all PLWHA regardless of CD4 count, but with a lower strength of recommendation for patients with CD4 cell count more than 500 cells/ $\mu$ l [78]. Guidelines are mainly based on large observational cohort studies that found early ART initiation to reduce risk of death and/or AIDS [78]. Specific cancer types, individual or grouped, have not yet been analyzed as separate endpoints in such studies. Our working hypothesis is that early ART initiation directly reduces the risk of a number of specific cancer types.

For these benefits to be realized, early entry of PLWHA into medical care is essential. However, in the USA, one-fifth of PLWHA are unaware of their infection and one-third develop AIDS within a year of their diagnosis [2]; in North America in 2007, more than half had CD4 cell count 350 cells/ $\mu$ l or less at first presentation to medical care [79]. In the USA, during 2003–2009, entry into medical care after diagnosis was delayed for 28% of PLWHA [80].

With these shortcomings, it should not be surprising that the ADC burden among PLWHA, closely linked to CD4 count, remains unacceptably high, and that the standardized incidence rate for all NADC combined declined only about 13% between 1991–1995 and 2001–2005 [18]. Public health efforts to facilitate early diagnosis of HIV infection, linkage to and retention in care, and adherence to ART – all cornerstones of the US National HIV/AIDS Strategy [81] – are crucial in reducing the cancer burden among PLWHA.

### Improved antiretroviral therapy

ART does not fully restore immunologic health, especially when it is initiated late [78,82,83]. Normal CD4 counts are often not achieved with long-term therapy [82,83], and chronic inflammation and immune dysfunction persist. This suggests the need for improved ART regimens [40,83].

Evidence from in-vitro and in-vivo model systems indicates that antiretroviral agents may have antitumor activity independent of their antiviral effect [84], including protease inhibitors [85], nucleoside reverse transcriptase inhibitors (NRTIs) [86–88], and non-NRTIs [89]. There is also concern that some antiretroviral agents may increase cancer risk, including NRTIs [90,91] and CCR5 antagonists [92]. The NRTI zidovudine has been classified as possibly carcinogenic in humans [90]. Epidemiologic data are limited, although in two studies ART class was unrelated to overall NADC risk [54,93].

## RESEARCH DIRECTIONS

Although the evidence is substantial that HIV-induced immunodeficiency, as measured by CD4 count, is independently associated with elevated risk of specific cancer types, most of viral cause, relationships between HIV-induced chronic inflammation and immune dysfunction/senescence and cancer risk remain poorly understood. Research challenges to understanding these relationships, which are likely to differ across cancer types, include intercorrelation among immunodeficiency, inflammation, and immune dysfunction biomarkers, as well as achieving sufficient sample size for all but the most common cancer

types. A limitation of much previous research has been the need to use grouped cancer categories to attain reasonable statistical power.

With respect to immunodeficiency, we do not yet understand the role of duration of low CD4 count versus current CD4 count, latency, the shape of dose–response relationships, or reversibility of effects. Inflammation and immune dysfunction bio-markers are beginning to be studied in relation to mortality and other outcomes, but not yet in relation to cancer risk. In PLWHA, higher levels of the inflammatory markers IL-6, CRP, and D-dimer have been found to be strongly associated with increased mortality risk, independent of CD4 count [44<sup>■</sup>,94]; higher levels of D-dimer were found to be independently associated with elevated cardiovascular disease risk [95]; and higher levels of soluble tumor necrosis factor receptor-1, an inflammation marker, and soluble CD27 and soluble CD40 ligand, both immune activation markers, were found to be independently associated with increased risk of the composite outcome of ADC or death [96<sup>■</sup>]. In the later study, ADC was not evaluated separately as an outcome. There is a wealth of soluble and cellular biomarkers of inflammation and immune dysfunction awaiting to be studied in relation to risk of specific cancer types among PLWHA [44<sup>■</sup>].

Further research also is needed to determine whether specific ART classes or medications are associated with cancer risk. It is particularly important to identify medications that might increase cancer risk because of the lifelong commitment to ART. Finding that an ART medication is associated with reduced risk of a specific cancer type could inform treatment decisions. For example, if a medication specifically protected against anal cancer, its use might be preferred for patients with persistent anal HPV infection.

Finally, many carcinogenic processes have latency periods of decades. Given that we are less than 2 decades into the ART era, additional cancer types associated with increased risk may emerge. Of particular concern is the possibility that long-term exposure to HIV-induced systemic inflammation (or immune dysfunction) may eventually lead to increased risk for common epithelial cancers (e.g., colorectal, breast, prostate) for which inflammation is already known or suspected to be an etiologic factor [35,97–99]. On a more optimistic note, earlier and more effective ART on a population level may result in reduced incidence of cancer types that currently exhibit elevated incidence among PLWHA. For these reasons, epidemiologic monitoring of cancer incidence among PLWHA should continue.

## CONCLUSION

ART and the aging of PLWHA have resulted in a shift in the cancer spectrum from ADC to NADC, although the burden of ADC remains high. HIV effects on the immune system and a high prevalence of non-HIV cancer risk factors contribute independently to elevated risk of many cancer types, most of viral cause. Although HIV-induced immunodeficiency is the main immune system factor implicated in the elevated cancer risk, research is needed on the roles of chronic inflammation and immune dysfunction. Research also is needed on the long-term cancer effects of ART and specific ART classes and medications. Finally, epidemiologic monitoring of long-term trends in cancer incidence among HIV-infected persons should continue.

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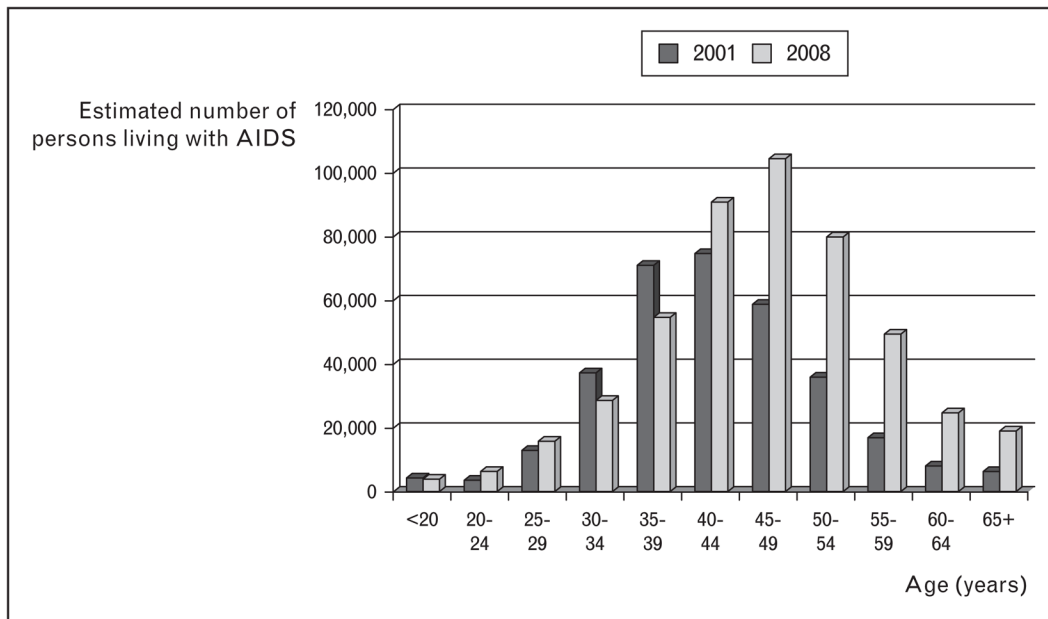
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**KEY POINTS**

- The spectrum of cancer diagnoses among HIV-infected persons has shifted from ADC to NADC, although the burden of ADC remains high.
- Although a high prevalence of non-HIV cancer risk factors, including oncogenic virus infection and smoking, contributes to cancer risk, substantial evidence has accumulated in favor of an independent association between HIV-induced immunodeficiency and elevated risk of many specific cancer types, most of viral cause.
- Relationships between cancer risk and the other two immune system hallmarks of HIV infection, chronic inflammation and immune dysfunction/senescence, remain poorly understood.
- Early, sustained ART is a crucial component of cancer prevention.
- Continued epidemiologic monitoring is needed to detect possible effects on cancer risk of specific ART classes or medications, long-term exposure to systemic inflammation or immune dysfunction, or earlier or more effective ART.



**FIGURE 1.** Age distribution of persons living with AIDS, USA, 2001 and 2008. We show persons living with AIDS because data were available for all 50 states and the District of Columbia for both 2001 and 2008. For persons living with HIV (with or without an AIDS diagnosis), data were available for 40 states in 2008, but only 33 states in 2001, such that the 2 years were not strictly comparable. Adapted with permission from [3] and [4].



**Table 1**

Estimated number of incident cancer cases among persons living with HIV in 2001–2005 in the USA, ratio of incident cases in 2001–2005 compared with 1991–1995, and relative risk among persons living with HIV compared with uninfected persons, by cancer type

Cancer category	Cancer type	Estimated number of cases (%) in 2001–2005 <sup>e</sup>	Relative risk (95% confidence interval)	
			2001–2005/1991–1995 <sup>b</sup>	Meta-analysis [6] <sup>c</sup> Recent additional studies <sup>d</sup>
Kaposi sarcoma-associated herpes virus	Kaposi sarcoma	3827 (15.3)	0.18	– 55 (9.1–2244) [7]; 112 (95–133) [8]; 197 (139–279) [9 <sup>¶</sup> ]; 210 (100–442) [10]; 790 (640–980) [11]; 1584 (1486–1687) [12 <sup>¶</sup> ]
Epstein-Barr virus	Non-Hodgkin lymphoma	5968 (23.9)	0.47	– 6.5 (5.4–7.7) [11]; 8.0 (6.8–9.4) [10]; 11 (4.2–37) [7]; 15 (14–16) [12 <sup>¶</sup> ]; 16 (13–19) [9 <sup>¶</sup> ]; 17 (14–20) [8]
	Hodgkin lymphoma	1143 (4.6)	2.1	11 (8.8–15) 4.9 (3.6–6.6) [10]; 11 (10–13) [12 <sup>¶</sup> ]; 20 (13–31) [9 <sup>¶</sup> ]
Human papillomavirus	Cervix	530 (2.1)	1.6	– 2.9 (1.8–4.4) [11]; 5 (4.0–6.2) [12 <sup>¶</sup> ]; 10 (6.5–16) [8]
	Anus	1885 (7.6)	7.6	28 (21–35) 15 (10–22) [10]; 19 (2.6–823) [7]; 20 (6.6–42) (non-MSM men) [13]; 25 (9.1–48) (women) [13]; 32 (29–36) [12 <sup>¶</sup> ]; 61 (37–101) [9 <sup>¶</sup> ]; 79 (58–102) (MSM) [13]
	Vulva and vagina	124 (0.5)	8.3	6.7 (3.9–11) [12 <sup>¶</sup> ]
	Penis	75 (0.3)	4.9	5.0 (2.5–8.9) [12 <sup>¶</sup> ]
	Oral cavity and pharynx	677 (2.7)	2.8	1.9 (1.4–2.6) (oropharynx); 2.0 (1.1–3.6) (head and neck); 2.2 (1.0–4.7) (lip, oral and pharynx); 4.1 (2.1–7.9) (nasopharynx)
Human papillomavirus suspected	Larynx	415 (1.7)	4.5	1.5 (1.1–2.0) 3.0 (2.3–3.7) [12 <sup>¶</sup> ]
	Esophagus	328 (1.3)	6.2	1.5 (0.99–2.3) 1.4 (0.9–2.0) [12 <sup>¶</sup> ]
	Eye	–	–	– 3.1 (1.6–5.9)
	Nonmelanoma skin <sup>e</sup>	–	–	– 3.5 (1.8–6.8)
Hepatitis B/C virus	Liver	780 (3.1)	5.0	5.6 (4.0–7.7) 2.6 (1.7–4.0) [9 <sup>¶</sup> ]; 2.8 (2.2–3.5) [10]; 4.4 (3.6–5.2) [12 <sup>¶</sup> ]
<i>Helicobacter pylori</i> -related	Stomach	190 (0.8)	2.4	1.7 (1.2–2.5) 1.2 (0.8–1.7) [12 <sup>¶</sup> ]

Cancer category	Cancer type	Estimated number of cases (%) in 2001–2005 <sup>a</sup>	Relative risk (95% confidence interval)		
			2001–2005/1991–1995 <sup>b</sup>	Meta-analysis [6] <sup>c</sup>	Recent additional studies <sup>d</sup>
Common epithelial	Lung	2630 (10.5)	2.2	2.6 (2.1–3.1)	1.7 (1.5–2.0) [14 <sup>†</sup> ]; 1.8 (1.4–2.4) [9 <sup>††</sup> ]; 2.0 (0.92–4.2) [15]; 2.4 (1.6–3.5) [16]; 2.6 (2.4–2.8) [12 <sup>†</sup> ]; 3.4 (0.49–148) [17]; 6.0 (0.47–321) [7]
	Colorectal	687 (2.8)	4.1	0.81 (0.48–1.4) (colon); 1.1 (0.69–1.7) (colorectal); 1.5 (0.54–4.2) (rectum)	0.9 (0.6–1.3) [9 <sup>††</sup> ]; 0.9 (0.8–1.1) [12 <sup>†</sup> ]
	Female breast	613 (2.5)	9.4	0.74 (0.56–0.97)	0.7 (0.5–0.8) [12 <sup>†</sup> ]
	Prostate	1171 (4.7)	8.7	0.69 (0.55–0.86)	0.5 (0.5–0.6) [12 <sup>†</sup> ]; 0.8 (0.6–0.9) [9 <sup>††</sup> ]; 1.0 (0.9–1.1) [10]; 1.1 (0.44–2.5) [7]
	Ovary	46 (0.2)	2.8	1.4 (0.78–2.4)	1.0 (0.5–1.9) [12 <sup>†</sup> ]
	Pancreas	344 (1.4)	7.5	1.0 (0.74–1.4)	1.0 (0.7–1.4) [12 <sup>†</sup> ]
	Uterine corpus	96 (0.4)	6.7	1.5 (0.68–3.4)	0.5 (0.2–1.0) [12 <sup>†</sup> ]
	Bladder	97 (0.4)	2.3	1.1 (0.72–1.7)	0.9 (0.6–1.3) [12 <sup>†</sup> ]
	Kidney	358 (1.4)	3.2	1.7 (1.3–2.2)	0.7 (0.5–1.0) [12 <sup>†</sup> ]
	Other				
	Melanoma	319 (1.3)	3.5	1.2 (0.88–1.6)	1.1 (0.8–1.4) [12 <sup>†</sup> ]; 1.7 (1.3–2.3) [10]; 1.8 (1.3–2.6) [9 <sup>††</sup> ]; 1.9 (0.25–12) [7]
	Soft tissue	129 (0.5)	3.4	–	1.4 (0.9–2.2) [12 <sup>†</sup> ]
	Testis	128 (0.5)	0.92	1.4 (1.1–1.9)	0.7 (0.5–1.1) [12 <sup>†</sup> ]
	Brain	73 (0.3)	1.4	1.8 (1.2–2.7)	0.6 (0.3–1.0) [12 <sup>†</sup> ]
	Thyroid	145 (0.6)	4.2	1.1 (0.56–2.3)	0.7 (0.4–1.0) [12 <sup>†</sup> ]
	Myeloma	251 (1.0)	2.5	2.6 (1.5–4.5)	0.7 (0.4–1.1) [12 <sup>†</sup> ]
	Leukemia	215 (0.9)	1.9	2.6 (1.9–3.5)	1.7 (0.8–3.3) (lymphocytic) [12 <sup>†</sup> ]; 2.1 (1.5–2.9) (myeloid/monocytic) [12 <sup>†</sup> ]
AIDS-defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma, cervical cancer)	All	10 325 (41.4)	0.30	–	–
Non-AIDS-defining cancers	All	14 036 (56.3)	3.2	2.0 (1.8–2.2)	1.6 (1.5–1.7) [10]; 1.6 (1.6–1.7) [12 <sup>†</sup> ]
Total		24 944			

<sup>a</sup> Adapted with permission from [18<sup>†††</sup>]. For each non-AIDS-defining cancer (NADC), we applied the Shields *et al.* estimates for persons living with AIDS or HIV only in 34 US states in 2004–2007 to their estimates for persons living with AIDS in the USA as a whole in 2001–2005 to obtain extrapolated estimates for all persons living with HIV (with or without an AIDS diagnosis) in the USA in 2001–2005.

Note the caveat that these extrapolations rely on the assumption that HIV patients in the 34 states are representative of HIV patients in the entire USA with respect to cancer risk. It was not necessary to perform this extrapolation for AIDS-defining cancers (ADC) because these only occur among AIDS patients by definition. Percentages of all ADC and all NADC add to 97.7% because 2.3% of cancer were 'poorly specified malignancies' and could not be classified as ADC or NADC. Some rare NADC are not listed in the table.

<sup>b</sup> Adapted with permission from [18]. Ratio of the number of new cancer diagnoses among persons living with AIDS in 2001–2005 compared with 1991–1995. This ratio is restricted to persons living with AIDS. Note that this ratio reflects both changes in the crude cancer incidence rates and the increase in the size of the population living with AIDS between 1991–1995 and 2001–2005.

<sup>c</sup> Adapted with permission from [6]. This meta-analysis calculated NADC-type-specific summary standardized incidence ratios across 18 studies of persons living with HIV/AIDS compared with the general population. The studies spanned the pre-ART and ART eras and included persons living with AIDS and HIV only.

<sup>d</sup> Restricted to recent studies, not included in the Shiels *et al.* [6] meta-analysis, with data from the ART era. The relative risks presented in the table were adjusted for demographic variables, but not for non-HIV risk factors such as smoking. Relative risks are comparisons between an HIV-infected population and the general population or an HIV-uninfected comparison group.

<sup>e</sup> This result should be interpreted with caution as it may reflect ascertainment of rare nonmelanoma skin cancers, as opposed to the common basal cell and squamous cell carcinomas, which are often not ascertained by cancer registries. Furthermore, Kaposi sarcoma can be misclassified as nonmelanoma skin cancer.