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Cancer in People with HIV

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KEYWORDS

- Human immunodeficiency virus-associated cancers
- Human immunodeficiency virus malignancies
- Cancer in people with human immunodeficiency virus
- Acquired immunodeficiency disease defining cancers

KEY POINTS

- Many factors contribute to a continued increased cancer risk among people with HIV (PWH) globally, despite advancements in antiretroviral therapy (ART).
- Behavioral, vaccination, and screening interventions are currently available to reduce cancer risk and should be integrated into routine healthcare, alongside continued research and tailoring to meet the diverse needs of PWH globally.
- PWH diagnosed with cancer can often be treated similarly to people without HIV in the ART era – including with novel cancer therapies and in clinical trials – but unique treatment challenges and opportunities remain among PWH.
- Collaborative multidisciplinary efforts, leveraging implementation science, are critical for continued progress against cancer in PWH, especially in parts of the world with the greatest burden of HIV.

INTRODUCTION

In this review, we provide an overview of the intersection between human immunodeficiency virus (HIV) and cancer. Addressing cancer in the context of HIV requires consideration not only of the specific cancer type but also the broader context. We therefore consider throughout disparities in access to care for people with HIV (PWH), including in low- and middle-income countries (LMICs) where most PWH

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live. We analyze existing evidence to shed light on current clinical management strategies, complications, controversies, and emerging opportunities.

EPIDEMIOLOGY

The Global Human Immunodeficiency Virus Epidemic

In some world regions, the HIV epidemic is largely generalized, while in others the HIV epidemic is more concentrated among specific key populations.[1] These key populations include men who have sex with men (MSM), transgender people, male and female sex workers and their sexual partners, people who inject drugs, incarcerated persons, migrants or refugees, and people of African ancestry. Even within a largely generalized HIV epidemic in sub-Saharan Africa, there are key populations requiring specific attention. These include highly mobile populations (eg, seasonal farm workers, construction workers, long-distance truck drivers, and uniformed forces), people with disabilities, young women (15–24 years), and fishing communities.[2–4] Recognizing these key populations is critical in identifying individuals at higher risk of HIV, and consequently, HIV-associated malignancies. Social, behavioral, and structural factors often act to increase cancer risk for such key populations independent of HIV infection, while also increasing risk for HIV infection, which itself potentiates cancer risk.[5] PWH may also be socially and structurally disadvantaged relative to individuals without HIV, making them susceptible to health disparities across the cancer control continuum. Finally, cancer is now a leading cause of death in PWH as they live longer on antiretroviral therapy (ART).[6,7]

Cancer Risk and Antiretroviral Therapy Among People with Human Immunodeficiency Virus

Early in the global HIV epidemic, it became clear that PWH had a higher risk of developing cancer. By 1993, Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer were included in the surveillance case definition of acquired immunodeficiency syndrome (AIDS).[8] Subsequently, additional cancers were recognized as associated with HIV, including Hodgkin lymphoma, cancers associated with human papillomavirus (HPV), lung cancer, liver cancer, and, in sub-Saharan Africa, conjunctival cancer and squamous cell carcinoma of the skin.[9–11] As noted in **Table 1**, the introduction of ART ushered in a marked decline in some HIV-associated cancers, particularly those most strongly associated with immunodeficiency.[21] Many of these declines have been replicated as ART has been progressively introduced and expanded worldwide, although there are important differences observed across world regions. In particular, high-quality epidemiologic data are often not as readily available to assess trends in LMICs. Finally, risk for some HIV-associated cancers has not been reduced by the introduction of ART, leading to changes in the distribution of specific cancer types among PWH.

Social, Demographic, and Behavioral Risk Transitions Worldwide

In addition to global trends with respect to the HIV epidemic and ART scale-up, and as reflected in **Table 1**, HIV-associated cancer burden is also influenced by broader demographic and socioeconomic changes within and across populations over time.[22] Countries characterized by a low Human Development Index (HDI) have a higher prevalence of infection-related cancers such as cervical, KS, stomach, and liver cancers. Conversely, countries with a high HDI have increased prevalence of cancers associated with reproductive, dietary, and hormonal factors such as female breast, colorectal, and prostate cancers.[23] Therefore, as populations' age and human

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Table 1
Illustrative population-based epidemiologic studies detailing human immunodeficiency virus-associated cancer risk worldwide and across antiretroviral therapy scale-up periods

	Pre-ART			Range	Early ART Scale-up			Range	Late ART Scale-up						Range
Study	Dal Maso et al,[12] 2009	Mbulaiteye et al,[13] 2006	Stein et al,[14] 2008		Clifford et al,[15] 2005	Godbole et[16] 2016	Muchengeti et al,[10] 2023		Dal Maso et al,[12] 2009	Dhokotera et al,[17] 2019	Akarolo-Anthony et al,[18] 2014	Hernandez Ramirez et al,[19] 2017	Tanon et al,[11] 2012	Jaquet et al,[20] 2015	
Countries	Italy	Uganda	South Africa		Switzerland	India	South Africa		Italy	South Africa	Nigeria	USA	Cote d'Ivoire, Benin	Benin, Cote d'Ivoire, Nigeria, Togo	
Study period	1986–1996	1998–2002	1995–2004		1985–2002	1996–2008	1995–2016		1997–2004	2004–2014	2005–2012	1996–2012	2009–2011	2009–2012	
Measure	SIR	SIR	OR		SIR	SIR	OR		SIR	OR	SIR	SIR	OR	OR	
Infection-related Cancers															
Kaposi sarcoma	1792 (1640–1956)	6.4 (4.8–8.4)	47.1 (31.9–69.8)	6.4–1792	192 (170–217)		99.1 (72.6–135.1)	99.1–192	572 (508–641)	134 (111–161)	5.7 (4.1–7.2)	498 (478–519)	62.2 (22.1–175.5)	34.6 (17.3–69.0)	5.7–572
Non-Hodgkin lymphoma	497 (450–546)	6.7 (1.8–17)	5.9 (4.3–8.1)	5.9–479	76.4 (66.5–87.4)	10.6 (5.9–17.5)	11.3 (9.3–13.6)	11.3–76.4	93.4 (83.9–104)	2.7 (2.6–2.9)		11.5 (11.1–11.9)	4.0 (2.0–8.0)	3.6 (1.9–6.8)	2.7–93.4
Cervix	51.0 (23.1–97.3)	2.4 (1.1–4.4)	1.6 (1.3–2.0)	1.6–51.0	8.0 (2.9–17.4)	15.7 (11–22)	2.7 (2.4–3.0)	2.7–15.7	41.5 (28.0–59.3)	1.7 (1.6–1.8)	2.0 (0.4–3.5)	3.24 (2.94–3.56)	7.9 (3.8–16.7)	4.3 (2.2–8.3)	1.7–41.5
Hodgkin lymphoma		5.7 (1.2–17)	1.6 (1.0–2.7)	1.6–5.7	17.3 (10.2–27.4)	7.7 (2.1–19.7)	3.1 (2.4–4.2)	3.1–17.3		1.2 (1.1–1.4)		7.70 (7.20–8.23)	3.0 (0.7–13.3)	3.4 (0.9–13.5)	1.2–7.7
Anogenital (other than cervix)			2.2 (1.4–3.3)	2.2									11.6 (2.9–46.3)	17.7 (6.9–45.2)	11.6–17.7
Vulva and vagina	24.6 (2.3–90.6)			24.6					24.3 (4.6–71.8)						24.3
Vulva							4.8 (3.5–6.4)	4.8		1.9 (1.7–2.2)		9.35 (7.91–11.0)			1.9–9.35
Vagina						25.2 (3.1–91.1)	5.5 (3.0–10.2)	5.5–25.2		0.8 (0.7–1.0)		3.55 (2.30–5.24)			3.55
Penis							5.4 (2.7–10.5)	5.4	12.0 (2.3–35.5)	2.3 (1.8–3.0)		5.33 (4.39–6.40)			2.3–12.0
Anus	35.5 (12.8–77.7)			35.5	33.4 (10.5–78.6)		2.1 (1.4–3.2)	2.1–33.4	44.0 (21.8–78.9)	1.6 (1.3–2.0)	0.3 (0–17.8)	19.1 (18.1–20.0)			1.6–44.0
Merkel cell carcinoma												2.58 (1.24–4.74)			2.58

(*continued on next page*)

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Table 1
(*continued*)

Liver	2.1 (0.4–6.4)			2.1	7.0 (2.2–16.5)	8.1 (3.5–15.9)	0.8 (0.5–1.3)	7.0–8.1	6.4 (3.7–10.5)	0.4 (0.4–0.5)	0.5 (0–5.1)	3.21 (3.02–3.41)	2.7 (1.1–7.7)	2.2 (1.0–5.8)	2.2–6.4
Oral cavity and pharynx					4.1 (2.1–7.4)		1.6 (1.3–1.9)	1.6–4.1		0.5 (0.5–0.6)		1.64 (1.46–1.84)	1.0 (0.2–4.9)	1.6 (0.6–4.4)	0.5–1.64
Other cancer types where role of infection is unknown but for which HIV association is known or postulated															
Squamous cell carcinoma of skin			2.6 (1.4–4.9)	2.6			3.5 (2.5–4.9)	3.5		1.8 (1.6–2.0)			3.4 (0.6–18.3)	5.2 (2.0–14.4)	1.8–5.2
Non-epithelial skin											4.0 (0–8.5)				
Eye Cancer						157 (32–458.2)	18.7 (10.1–34.7)	18.7–157		5.9 (5.1–6.8)	1.5 (0–18.1)				5.9
Conjunctiva		4 (1.5–8.7)		4						21.5 (16.3–28.4)		5.56 (3.44–8.50)			5.6–21.5
Lip							-			2.7 (1.7–4.3)		2.35 (1.43–3.62)			2.35–2.7
Non-melanoma skin	2.1 (1.2–3.3)			2.1	3.2 (2.2–4.5)				1.8 (1.2–2.6)						1.8
Basal cell carcinoma										1.3 (1.1–1.5)					1.3
Melanoma	0.9 (0.2–2.6)				1.1 (0.3–2.8)	6.0 (1.2–17.4)	2.0 (1.2–3.5)	2.0–6.0	0.6 (0.1–1.7)	0.8 (0.6–0.9)		0.86 (0.75–0.98)			0.8–0.86
Lung	2.1 (1.2–3.3)			2.1	3.2 (1.7–5.4)	8.8 (4.8–14.7)	1.2 (0.9–1.4)	3.2–8.8	4.1 (2.9–5.5)	0.5 (0.5–0.6)		1.97 (1.89–2.05)		2.0 (0.4–8.9)	0.5–4.1
Larynx							1.7 (1.3–2.4)	1.7		0.6 (0.5–0.6)		2.11 (1.89–2.05)			0.6–2.11
Myeloma	5.5 (1.0–16.4)				5.5 (0.5–20.4)		1.1 (0.7–1.5)		3.9 (1.0–10.0)	0.6 (0.6–0.7)		0.89 (0.78–1.02)			0.6
Leukemia	4.9 (2.4–8.8)			4.9	1.8 (0.2–6.7)	23.9 (7.8–55.9)	0.7 (0.4–1.3)	23.9	1.1 (0.2–3.3)	0.2 (0.2–0.3)		1.18 (1.00–1.37)	0.8 (0.2–2.4)	0.7 (0.2–2.4)	0.2

Abbreviations: ART, antiretroviral therapy; OR,odds ratio; SIR, standardized incidence ratio. Please see Refs.[10–20]

development improves worldwide, cancer burden among PWH will increasingly include malignancies that are not infection-associated, like breast, colorectal, prostate, and lung cancers, especially in parts of the world with more generalized HIV epidemics.[24,25]

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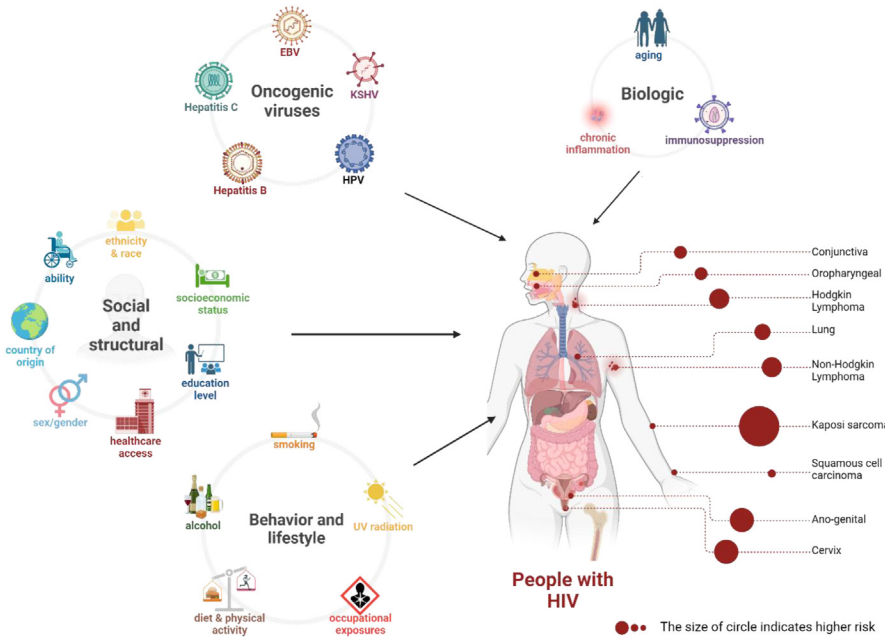


Fig. 1. The complex and intersecting social, structural, behavioral, and lifestyle factors that affect cancer risk for people with HIV. EBV, Epstein-Barr virus; HPV, human papillomavirus; KSHV, Kaposi sarcoma-associated herpesvirus.

PATHOBIOLOGY

The interplay between cancer and HIV is complex and multifactorial as illustrated in Fig. 1, reflecting elements that are unique or related to HIV and others that are related to cancer in the general population and may be exacerbated among PWH.

Oncogenic Infections

Many cancers associated with HIV have an underlying viral infectious cause such as Kaposi sarcoma herpesvirus (KSHV), Epstein-Barr virus (EBV), HPV, and hepatitis B viruses (HBVs) and hepatitis C viruses (HCVs).[26] HIV infection primarily contributes to increased cancer risk by inducing immunosuppression, potentiating oncogenic viruses, and other indirect mechanisms. However, more recent evidence has suggested that HIV-1 itself may be directly carcinogenic, for example, via expression of specific HIV proteins, which induce oxidative stress thereby promoting malignant transformation.[27]

In Table 2, we show a brief timeline of HIV and viral infections associated with cancer. With each subsequent discovery of the association between cancer and oncogenic viral infections, the importance of immunosuppression in viral oncogenesis was confirmed.

Epstein-Barr virus and non-Hodgkin lymphoma

EBV, a gamma-herpesvirus, was the first virus to be causally associated with cancer in humans in 1964. It was initially identified as the causative agent for Burkitt lymphoma, and later as the cause of undifferentiated nasopharyngeal carcinoma and other lymphoma subtypes.[37] EBV is ubiquitous, with approximately 90% of the world's

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Table 2
A brief timeline of human immunodeficiency virus and cancer

1981	Clusters of KS and *Pneumocystis carinii* Pneumonia are identified Among Homosexual Male Residents of California.[28]
1982	HPV is identified as the necessary cause of cervical cancer.[29]
1983	HIV is identified as the cause of AIDS[30]
1984	Baruch Blumberg and Irving Millman develop the HBV vaccine, which reduces risk of liver cancer associated with chronic HBV infection.[31]
1987	The first antiretroviral drug, zidovudine is developed and approved by the US FDA for the treatment of HIV.[32]
1988	Michael Houghton and colleagues discover HCV, which is an important cause of HCC.[33]
1993	Inclusion of KS, NHL, and ICC in the case definition of AIDS by the Centers for Disease Control.[8]
1994	KSHV is discovered.[34]
1996	Highly active ART, typically with three complementary antiviral medicines, is introduced to treat HIV in the US and Europe. HIV-1 is classified as a human carcinogen by the International Agency for Research on Cancer.[26]
1997	EBV is classified as a human carcinogen by the International Agency for Research on Cancer.[26]
1998+	HIV-cancer record linkage studies shed light on the spectrum and risk of cancers in HIV.
1999+	KS and NHL incidence decline in the US and Europe after the introduction of ART. Cancers not classically associated with AIDS emerge and eventually predominate among people with HIV in the US and Europe.
2002	HPV is recognized as a cause of anal, vulvar and oropharyngeal cancers.[35]
2004	ART is introduced into national public health programs in sub-Saharan Africa.
2005+	Cancer becomes a leading cause of death in HIV-infected people in the US and Europe.
2008	Researchers discover Merkel Cell Polyomavirus associated with Merkel cell carcinoma, a rare and aggressive skin cancer.[36]

Abbreviations: ART, antiretroviral therapy; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; ICC, invasive cervical carcinoma; KS, kaposi sarcoma; KSHV, Kaposi sarcoma-associated herpesvirus; NHL, non-Hodgkin lymphoma.

population having latent infection. In PWH, EBV can undergo reactivation, leading to the B-cell proliferation, which can contribute to lymphomagenesis. In part reflecting this, PWH have significantly elevated NHL and Hodgkin lymphoma (HL) risk as shown in **Table 1**.

Kaposi sarcoma herpesvirus and Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease

KSHV is another gamma-herpesvirus also referred to as human herpesvirus 8, first identified in 1994 and found to be causally associated with cancer. Chang and colleagues identified that patients with HIV-associated KS all had KSHV infection.[38] KSHV virus was later identified as the cause of other cancers in PWH, including primary effusion lymphoma,[39] and a form of the lymphoproliferative disorder multicentric Castleman disease.[40]

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Human papillomavirus and cervical, anal, vulvar, vaginal, penile, and head and neck cancer

HPV constitutes the most common sexually transmitted disease, with around 80% of sexually active people being infected sometime in their life.[41] HPV infections are more prevalent and more likely to persist in PWH compared to the general population,[8,42,43] leading to a higher prevalence and incidence of HPV-related cancers among PWH. Cervical cancer was included in the surveillance case definition of AIDS in 1993.[8] A recent metanalysis showed that the risk of cervical cancer is 6 times higher among women with HIV, with most cases occurring in LMICs, especially Sub-Saharan Africa.[44] Despite the advent of ART, nearly all HPV-related cancers are still observed at higher frequency among PWH.[43] In particular, PWH have greater than 20 times increased risk of anal cancer, and HIV-infected MSM have even greater risk (60–80 times greater).[45]

Hepatitis B virus, Hepatitis C virus, and hepatocellular carcinoma

Given common routes of transmission, PWH experience higher incidence of coinfection with HBV and HCV compared to the general population. In the United States (US), estimates indicate chronic HCV prevalence of 26% among PWH versus 0.9% in the general adult population. Similarly, for HBV infection, the prevalence is 5% among PWH versus 0.3% in the general population.[42] That prevalence may vary between 2% and 30% in LMICs.[46] PWH further have increased risk of chronic hepatitis due to compromised immunity, which further elevates the risk of hepatocellular carcinoma (HCC). Data from various cohorts demonstrate recent increases in HCC incidence among PWH in recent years.[47]

Contributing Factors Other than Oncogenic Viruses

Chronic inflammation

Chronic inflammation from HIV infection persistently activates the immune system, leading to cytokine dysregulation that creates a microenvironment that favors oncogenesis.[48] This inflammatory milieu amplifies production of inflammatory mediators such as IL-6 and TNF-alpha, which facilitate angiogenesis and cancer cell survival.[49] In PWH, chronic immune activation is further worsened by infections and toxins (eg, from smoking), which are much more prevalent than in people without HIV (see **Fig. 1**).

Immunosuppression

HIV infection compromises immune surveillance by targeting CD4 cells, allowing cancer cells to evade detection and elimination. This mechanism is likely important even for cancers not clearly associated with oncogenic viruses. An example is squamous cell carcinoma of the skin, for which HIV-related immune suppression might impair immune surveillance of precancerous mutational events triggered by exposure to ultraviolet (UV) light. Reflecting this, the lowest historic CD4 cell count, known as the nadir CD4 cell count, and more prolonged periods of severe immunosuppression correlate with a higher likelihood of developing cancer in PWH.[49] As noted earlier, immunodeficiency also induces reactivation and replication of latent viral infections (eg, cytomegalovirus [CMV], EBV), which can be directly carcinogenic (eg, EBV) or indirectly through chronic activation of the immune system (eg, CMV).[50]

Accelerated aging

Although ART has dramatically increased life expectancy for PWH, HIV infection may also be associated with accelerated aging relative to populations without HIV. This premature aging is driven by persistent immune activation, shortening of telomeres,

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and mitochondrial dysfunction,[48] and potentially contributes to increased risk of age-related cancers.

Direct human immunodeficiency virus effects

There is recent evidence indicating that HIV itself may have direct pro-oncogenic effects through multiple potential mechanisms, involving synergism with other pro-oncogenic viruses, disruption of cell cycle regulation, blockage of tumor suppressor gene function, promotion of chromosome instability through inhibition of telomerase activity, impairment of DNA repair function, induction of tumor angiogenesis, and enhancement of the effects of exogenous carcinogens.[51] Some HIV proteins, including envelope protein gp120, accessory protein negative factor Nef, matrix protein p17, transactivator of transcription Tat, and reverse transcriptase RT may promote malignant transformation, providing increasing support to potential direct carcinogenic effects of HIV.[51]

Effect of antiretroviral therapy

Some studies suggest a potential association between certain ART medicines and increased risk of specific cancers,[52] but such associations are generally not confirmed. ART exposure was not associated with increased risk of non-AIDS defining cancers, except for long-term use of protease inhibitors (PIs), which might be associated with increased anal cancer risk.[52] Interestingly, PIs have anti-angiogenic effect and induce regression of KS in animal models. In clinical practice both non-nucleoside reverse transcriptase inhibitor-based and PI-based regimens are equally effective in reducing incidence of KS.[53] Ongoing studies within the AIDS Malignancy Consortium (AMC) are evaluating the role of PIs for treating KS.

Behavioral and Lifestyle Factors

Tobacco, alcohol, obesity, lack of physical activity, and an unhealthy diet are all known cancer risk factors. Tobacco is responsible for one-fifth of the cancer burden of PWH in the US.[54] Tobacco use is consistently more common among PWH than in the general population worldwide.[42] The synergistic effect of HIV infection and tobacco accentuates the risk of cancer and contributes to the observed higher incidence of lung cancer in PWH. Smoking cessation interventions, therefore, are crucial in cancer prevention among PWH.[55]

Alcohol use disorder and increased alcohol use has been reported among PWH. Alcohol has been related to an increased risk of cancers such as liver and head and neck cancers. It also leads to worse cancer-related outcomes.[56]

Obesity has been reported to be less frequent among PWH in the US.[42] On the contrary, a study in women with HIV in South Africa showed a prevalence of 67.5% of obesity and overweight status.[57] Such regional variations likely reflect not only HIV-related issues, but also dietary and physical activity patterns worldwide. Overweight status and obesity have been increasing across multiple world regions since the advent of ART, in particular with greater use of integrase inhibitors and tenofovir alafenamide (TAF).

Finally, unprotected sexual practices and a higher number of sexual partners contribute to increased risk of oncogenic viral infections, emphasizing the importance of safe sex practices and regular screenings in PWH.

Health Care Disparities

While a comprehensive review of multilevel health care disparities globally is outside the scope of this review, it is important to note that disparities in access to health care services play a role in risk of cancer among PWH. For example, due to complex

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social, economic, and structural factors, PWH may have limited access to cancer screening (eg, cervical, anal) leading to delayed diagnoses and increased cancer morbidity and mortality. Access to timely HIV diagnosis and treatment and vaccines also play a role. Moreover, disparities significantly influence the complex and intersecting social, structural, behavioral, and lifestyle factors that affect cancer risk and outcomes for PWH as shown in **Fig. 1**.

SCREENING AND PREVENTION

Given the increasing lifespan of PWH along with increased cancer risk and burden, optimized cancer screening and prevention for this population has become critical. Considering that the highest burden of HIV is in LMICs, these settings present additional challenges in developing appropriate and cost-effective cancer prevention and screening strategies.

Vaccination and Treatment for Oncogenic Viruses

Vaccination is effective against HBV and HPV infection, and treatment is effective for HBV and HCV even after infection to reduce complications, including liver cirrhosis and cancer. Despite the wide availability of vaccines, there are 300 million people with chronic HBV infection worldwide. The World Health Organization (WHO) hepatitis elimination strategy includes 90% of infants vaccinated for HBV by 2030, 90% of viral hepatitis infections diagnosed, and 80% of viral hepatitis infections treated.[58] Because PWH have higher rates of HBV and HCV infection than individuals without HIV, several guidelines recommend testing of all PWH for HBV and HCV.[59,60] All PWH co-infected with HCV are candidates for curative treatment.[59,60] Direct-acting antiviral HCV regimens in PWH have shown the same efficacy and adverse events profile as in people without HIV. PWH with active HBV should receive an ART regimen that includes emtricitabine (follicular thyroid carcinoma) or lamivudine (3 TC), and tenofovir disoproxil fumarate (TDF) or TAF that are active against HIV and HBV.[59,60] Currently, the fixed dose combination of dolutegravir/TDF/3TC is the most frequent first line regimen used globally. In many LMICs, therefore, routine testing for HBV among PWH is not done since commonly prescribed ART regimens are effective for both HIV and HBV.

Many guidelines, especially from high- and upper-middle income countries, recommend HBV vaccination for PWH.[47,60] WHO recommends HBV vaccination of persons at high risk of HBV infection in older age groups including PWH.[61] Where HBV testing is available, it is recommended in order to identify those who are already immune and therefore, may not need vaccination. Although earlier studies showed a reduced response to HBV vaccination among PWH (35%–70%),[62] longer-term follow-up shows no difference between standard and booster doses.[61] There are currently no clear recommendations for routine booster vaccination among PWH and no information is available regarding lifelong protection in HIV-infected or HIV-exposed infants receiving HBV vaccination.[61]

The high burden of HPV, its persistence, and the elevated risk of HPV-related precancer and cancer among PWH,[42] support the need for targeted vaccination and screening against HPV-associated cancers in this population. Guidelines in high- and upper-middle income countries recommend HPV vaccination before the onset of sexual activity, and it is currently recommended to start vaccination at 11 to 12 years and extending through age 26 years. Catch-up vaccination is advised for all individuals aged 13 to 26 years who have not been vaccinated, and may be offered to older people in selected cases. Despite evidence supporting abbreviated 1-dose and 2-dose vaccination schedules,[63] the current recommendation for PWH is still a 3-dose

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schedule.[64] While the HPV vaccine is generally safe and well-tolerated by PWH,[65] those with lower CD4 counts (<200 cells/ml) and unsuppressed HIV may have lower seropositivity rates compared to those with well-controlled HIV.[66]

Global HPV vaccine uptake varies. Less than 25% to 30% of most LMICs have introduced the vaccine into national immunization schedules, compared to greater than 85% in high-income countries. Notably, there is no specific vaccine recommendation for women with HIV in the global strategy to accelerate the elimination of cervical cancer as a public health problem.[67] Additional challenges in LMIC include HPV vaccination programs being school-based, with HPV vaccination not being routinely offered for PWH outside childhood immunization programs.

Behavioral Risk Reduction

As noted previously, several behavioral cancer risk factors are more frequent among PWH. A systematic review evaluating smoking cessation interventions in PWH showed that the most successful approaches were tailored to the needs of PWH, including assessment of and intervention for polysubstance abuse and mental health issues, and use of cell phone-based strategies.[68] WHO recommends healthy lifestyle counseling, smoking cessation advice, healthy diet, and exercise among other modifiable factors for PWH to prevent non-communicable diseases.[69] Other factors such as exposure to UV radiation, or occupational hazards must also be considered (see **Fig. 1**).

Timely Human Immunodeficiency Virus Diagnosis and Treatment

The Strategic Timing of Antiretroviral Therapy study led to universal treatment recommendations for PWH, in part by demonstrating that the risk of cancer was higher among those who started ART with CD4 less than 350 cells per ml than for those starting with CD4 greater than 500 cells per ml.[70] PWH starting immediate ART reduced cancer risk by 64% compared to the deferred arm.[71] Current guidelines recommend that all PWH should start ART as soon as possible.[59,64,72]

Screening for Specific Cancer Sites

Cancer screening practices for PWH should address cancers with higher prevalence among PWH (cervical, anal, and liver cancer) but also cancers for which screening is recommended in the general population (breast, colon, and prostate). In **Table 3**, we have summarized current recommendations from various representative international guidelines regarding cancer screening among PWH, including recommendations extrapolated from the general population.

To provide a global perspective, we have included current guidelines and recommendations from the WHO, the United States Department of Health and Human Services, the European AIDS Clinical Society, along with representative countries from Africa, Latin America, and Asia.

As illustrated in **Table 3**, all guidelines recommend regular cervical cancer screening, with cytology still the most frequently recommended technique. Although WHO has recommended the transition to HPV DNA testing as the primary screening test for cervical cancer screening, visual inspection with acetic acid or cytology continue to be the primary screening tests in most LMIC settings,[87] although these are likely suboptimal.[88] Lack of access to cryotherapy, excision, or thermal ablation for preneoplastic lesions identified via screening is another major challenge in the control of cervical cancer in LMIC, as screening programs will have limited value if follow-up care for screen-positive women is not assured. Single-visit screen and treat approaches have, therefore, been recommended for low-resource settings.[89]

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Table 3
Representative contemporary cancer screening guidelines for people with human immunodeficiency virus across different world regions

		DHHS[64] and USPSTF[73]	EACS[59]	WHO[72,74–76]	South Africa[77–79]	Kenya[80]	Thailand[81–83]	Brazil[84,85]
Cervix	Target populations	Women >21 y	Women >21 y	Women ≥ 25 y Children and adolescents after sexual debut	All women Children and adolescents after sexual debut	Women 18–65 y	Women	Women
	Method	21–29 y: Cytology >30 y: Cytology or Cytology + HPV DNA	Cytology HPV DNA	HPV DNA Alternative: Cytology or VIA	Cytology	HPV test VIA-VILI	Cytology	Cytology
	Frequency	1–3 y	1–3 y	3–5 y	At diagnosis and every 3 y	1–2 y	During the first y and once a y	Every 6 mo during first y; yearly afterwards, if normal
Anus	Target populations	People with HIV	MSM and persons with HPV-associated dysplasia	MSM, trans and gender diverse people and other people who are more likely to engage in anal sex	Not stated	Not stated	Anal sex	Receptive anal intercourse, prior HPV or abnormal vulvar or cervical histology
	Method	DRE Cytology (only if HRA is available) HRA (specialists recommendation)	DRE Cytology HRA	Cytology Skin anal and genital examination			Cytology	DRE Cytology Anoscopy if abnormal
	Frequency	1 y	1–3 y	Not mentioned			In the first y and once a y afterwards	1 y
Liver	Target populations	HIV/HBV > 40 y HIV/HCV, in particular if cirrhosis	HBV or HCV with cirrhosis if treatment available for HCC HBV- non-cirrhotics, consider risk factors	People with cirrhosis	Not stated	Not stated	People with cirrhosis, Men> 40 y or Female > 50 y or family history of liver cancer	Cirrhosis and HBV
	Method	Ultrasound	Ultrasound (and alphafetoprotein)	Not stated			Ultrasound and alphafetoprotein (HBV) Ultrasound (HCV + cirrhosis)	Ultrasound and alphafetoprotein
	Frequency	6 mo	6 mo	Not stated			6–12 mo	6 mo
Lung	Target populations	50–80 y with history of ≥ 20 pack-ye smoking and currently smoke or have quit within the past 15 y	50–80 y with history of ≥ 20 pack-y smoking, and are current smokers or former smokers that quit within the past 15 y	Not stated	Symptom-based work-up	Not stated	Not stated	No recommendations to screen for lung cancer. However, services should have a harm reduction policy and promote tobacco cessation.
	Method	Low-dose CT	Low-dose helical CT (where local screening programs are available)	Low dose helical CT WHO supports but no guidelines.[86]	Chest x-ray			
	Frequency	1 y (stop if > 15 y	1 y	Not stated	Not			

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Table 3
(continued)

		after quitting or limited life expectancy)			applicable			
Breast	Target populations	Women (40) 50–74	Women 50–74 y	Not stated	Women >40 y	40–74 y	Women 30–70 y	Women 50–69 y
	Method	Mammography	Mammography	Mammography wherever available. Early detection programs prioritized	CBE	Mammography CBE if not available	30–70 y: BSE 40–70 y: CBE >45 y mammography	Mammography
	Frequency	2 y	1–3 y	2 y	2 y	1–2 y	2 y	2 y
Colorectal	Target populations	50–75 y (45–49 y moderate benefit)	Persons 50–75 y or with a life expectancy > 10 y	Not stated	Symptom-based work-up	40–75 y	50–70 y	50–70 y
	Method	Stool-based tests or Direct visualization tests	According to local screening program Colonoscopy FIT for occult blood, or MT-sDNA or CT colonography	Stool-based tests	Colonoscopy	FIT FOBT Colonoscopy	FIT	Stool based test or colonoscopy or sigmoidoscopy
	Frequency	Depending on method 1–10 y	Depending on method 1–10 y	Not stated	Not applicable	1 y (10 y if colonoscopy)	2 y	Not stated
Prostate	Target populations	55–69 y	Men > 50 y with a life expectancy >10 y	Not mentioned	Symptom-based work-up	Men > 40 y	Not mentioned	Not recommended
	Method	PSA (to be discussed on a individual basis)	Use of PSA controversial		DRE	PSA DRE if not available		
	Frequency	Periodic	1–2 y		Not applicable	1 y		

Guidelines or recommendations specific for PWH. Guidelines or recommendations for the general population.

Abbreviations: BSE, breast self-examination; CBE, clinical breast examination; CT, computed tomography; DHHS, United States Department of Health and Human Services; DRE, digital rectal exam; EACS, European Academy of Cancer Sciences; FIT, fecal immunochemistry test; FOBT, fecal occult blood test; HBV, hepatitis B Virus; HCV, hepatitis C Virus; HPV, Human Papilomavirus; HRA, high-resolution anoscopy; MT-sDNA, multitarget stool DNA; PSA, prostate specific antigen; USPSTF, United States Preventive Services Task Force; Via, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine; WHO, World Health Organization.

Please see Refs.[59,64,72–86]

Timely detection and treatment of anal precancerous lesions was recently shown to reduce the risk of anal cancer for PWH.[90] Recently published consensus guidelines recommend anal cancer screening for populations at high risk of anal cancer.[91]

Despite PWH experiencing a lower risk of breast, prostate, and colorectal cancers in the US, and increased mortality after cancer diagnosis for PWH, recommended screening interventions for these cancers in the general population are generally extrapolated to PWH.[92]

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Additionally, some as yet unproven cancer screening interventions might have value for PWH in certain settings. For example, skin cancer screening is not routinely recommended for the general population.[93] However, for PWH in endemic areas for KSHV or with very low CD4 counts, comprehensive skin examination for KS lesions integrated into routine HIV care might be a relatively simple and inexpensive method of reducing KS morbidity and mortality in settings with high burden. While rare in other settings, conjunctival cancer is particularly frequent in Africa with a risk 21 times higher in PWH.[94] Early-stage conjunctival lesions might be identified through routine external inspection in high-incidence settings despite not having been formally studied as a cancer screening intervention.

TREATMENT

Treatment of HIV-associated cancers is multifaceted. ART is an essential component, restoring immune function and reducing risk of infectious complications during cancer treatment. ART has enabled treatment of cancer in PWH to be similar in most instances to treatment of cancer in people without HIV, including with intensive curative-intent regimens. However, there are a few special considerations in PWH, including co-infections, drug-drug interactions (DDI), and diagnostic challenges.

Special Considerations or Departures from General Standards-of-Care

Co-management of human immunodeficiency virus and cancer

Co-management of HIV and cancer may result in better outcomes,[95] but management of HIV and cancer is often verticalized.[96,97] Greater integration of HIV and cancer care for PWH and cancer, including through physical co-location of services, can improve outcomes for PWH across the cancer prevention and treatment continuum.[55,98] For example, ART-naïve PWH whose first clinical presentation results from a new diagnosis of cancer may experience delays in initiating ART,[99] yet these delays can be successfully reduced using HIV and cancer co-management models. This is important because initiation or continuation of ART among PWH who have cancer improves cancer treatment outcomes. For example, PWH in LMIC with locally advanced cervical cancer receiving ART experience similar 5-year overall survival[100] and adverse effect rates[101] as those without HIV after curative-intent chemoradiation therapy. Similarly, PWH with lymphoma in LMICs experience significantly improved overall survival when ART is initiated soon after lymphoma diagnosis.

Supportive care

PWH receiving cancer therapies have a higher risk of opportunistic infections than HIV-negative cancer patients due to immunosuppression from both HIV and cancer therapies. As such, supportive care during cancer treatment for PWH requires careful consideration. As with PWH without cancer, prophylaxis against Pneumocystic jiroveci pneumonia and toxoplasmosis is recommended with CD4 counts less than 200 cells per uL and *Mycobacterium avium* complex prophylaxis for CD4 less than 50 cells per uL. Routine growth factor supports with granulocyte-colony stimulating factor may be indicated in some instances for PWH receiving chemotherapy even if not indicated for HIV-negative individuals, for example, with curative-intent ABVD chemotherapy for HL.[102]

Drug interactions

Older ART regimens have significant DDI, overlapping toxicities with cancer therapies, and adverse effects that precluded combination with chemotherapy. Fortunately, current ART regimens, such as those that include HIV integrase inhibitors, are well-tolerated and do not have significant DDI with common cancer therapies.[103] ART

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regimens boosted with cobicistat or ritonavir, as well as antifungals such as fluconazole, by strongly inhibiting CYP3A4, may increase toxicity of cancer chemotherapeutic agents that are metabolized by CYP3A4. This is especially well-documented with vinca alkaloid-containing treatment regimens such as ABVD for HL where neurotoxicity is worse when combined with ritonavir-based ART.[104,105] Some chemotherapeutic agents used for treatment of lung cancer (eg, platinum agents) may need to be used with caution, with close monitoring of renal function, in PWH due to potential for additive renal toxicity when combined with ART containing tenofovir. Notably, newer cancer therapies may be associated with increased risk of opportunistic infections. For example, use of the Bruton tyrosine kinase inhibitor (TKI) ibrutinib in cancer treatment has been associated with increased risk of serious infections, including invasive fungal infections such as aspergillosis.[106] This risk is higher in patients already predisposed to invasive fungal infections such as PWH.[107] Finally, for PWH receiving hematopoietic stem-cell transplants, teams will need to include experts in HIV care for close monitoring of pharmacologic interactions between post-transplant immunosuppression and ART. Important DDI between cancer therapies and ART are summarized in **Table 4** as follows.

Specific Cancers for Which Management May Depart from General Standards-of-Care

Kaposi sarcoma

ART alone may be sufficient for limited KS. In PWH with advanced stage KS, addition of chemotherapy to ART improves survival and is considered the standard-of-care.[108] Liposomal doxorubicin is commonly used as the first-line chemotherapy option and has shown efficacy in treating KS in PWH while minimizing toxicity. Paclitaxel has also shown efficacy in treating advanced KS and is also an option, although with more toxicity that liposomal doxorubicin.[109] Importantly, in the ART era, single-agent paclitaxel showed superiority to oral etoposide and bleomycin or vincristine regimens in resource-limited settings,[110] and may be preferred to liposomal doxorubicin due to lower cost.[111] Pomalidomide, an oral immunomodulatory drug, is also now approved by the US Food and Drug Administration (FDA) for KS treatment,[112] and may be particularly attractive for use in LMICs as it does not require visits to a

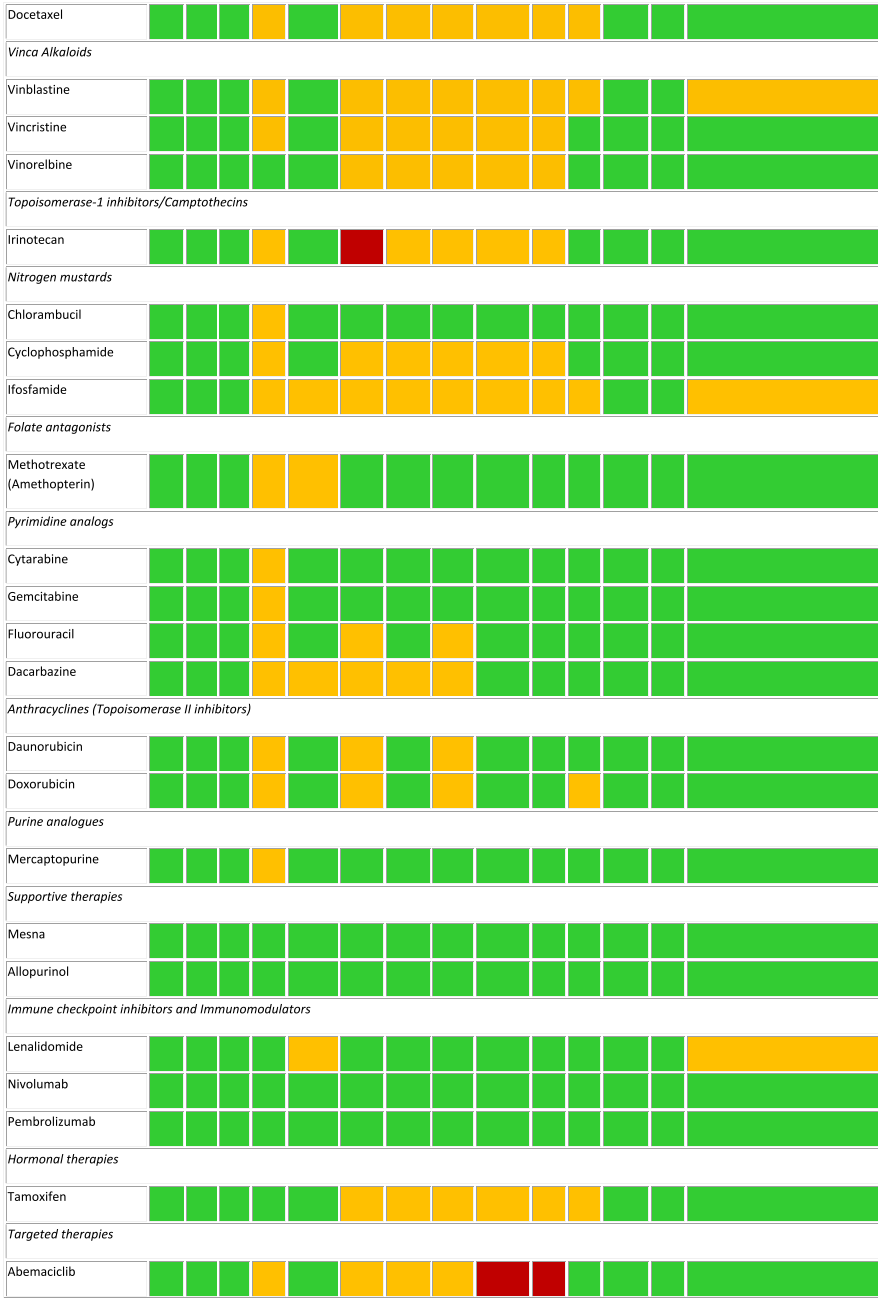
Table 4
Drug-drug interactions (DDI) between antiretroviral therapies (ART) and common cancer therapies

	NRIs				NtRTIs	PIS			NNRTIS			INSTIs		BIC/FTC/TAF
	ABC	FTC	3TC	ZDV	TDF	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	DTG	RAL	
Cancer Therapies														
Platinum analogues														
Cisplatin														
Carboplatin														
Oxaliplatin														
Taxanes														
Paclitaxel														

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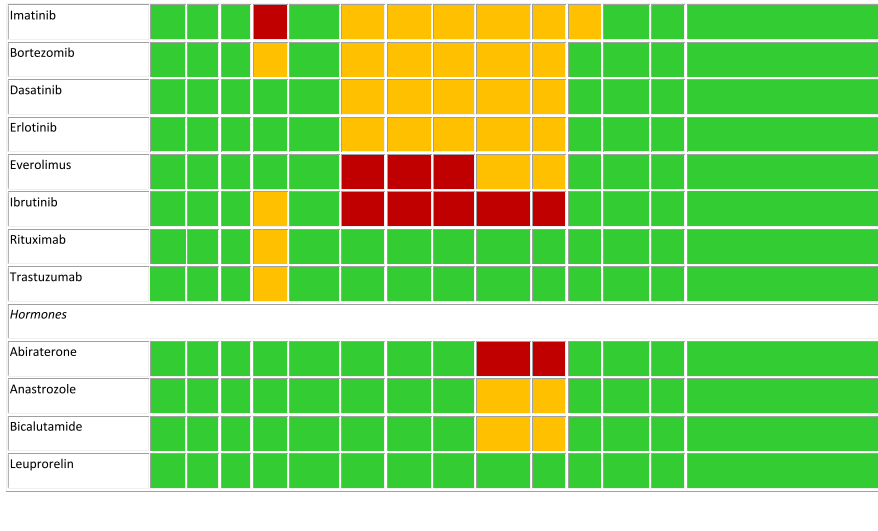
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Table 4
(continued)



Adapted and modified from WHO HIV treatment guidelines, Rudek et al., University of Liverpool hiv-druginteractions.org tool, WHO Model List of Essential Medicines.

chemotherapy clinic for intravenous infusion. Recently, immune checkpoint inhibitors (ICI) (eg, pembrolizumab) have shown promise in treating advanced KS.[113]

Hodgkin lymphoma and non-Hodgkin lymphoma

While ART has lowered the incidence of some virus-associated cancers (KS, NHL),[19] in the era of ART scale-up there has been a significant increase in the fraction of HL among all lymphomas in Africa.[114] There has also been increased incidence of HL observed in the first 3 months of ART, likely triggered by immune reconstitution.[115] HL in general is associated with declines in CD4-cell,[116] likely due to sequestration of these cells in the tumor microenvironment. In PWH, HL risk increases with low CD4 cell counts less than 100 cells per μL.[115] Therefore, consideration should be given for routine growth factor support when treating HL among PWH with regimens such as ABVD, although not typically considered for people without HIV. In addition, dose reductions may be necessary for PWH with HL who experience prolonged neutropenia with ABVD. In cases of relapsed or refractory HL, both autologous and allogeneic stem cell transplants are safe in PWH, as in people without HIV. There is an emerging role for use of immunotherapy for HL in the first and subsequent lines, although research specifically for PWH is ongoing.[117]

NHLs that occur in PWH tend to be aggressive and are often associated with EBV or KSHV, including diffuse large B-cell lymphoma, Burkitt lymphoma, primary central

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nervous system lymphoma, primary effusion lymphoma, and plasmablastic lymphoma.[118] The infusional dose-adjusted EPOCH chemotherapy regimen has demonstrated particularly good results for most aggressive systemic NHL subtypes among PWH and is the typical backbone used in clinical trials conducted by the AMC. Pembrolizumab, an ICI, has shown particular promise in treating HIV-associated NHL caused by oncogenic viruses, despite general lack of efficacy for NHL in the general population.[119] Chimeric antigen receptor T-cells (CAR-Ts) have been successfully used to treat lymphoma in PWH similar to the general population.[120]

Non-small cell lung cancer

People with HIV have higher risk of lung-cancer specific mortality and all-cause mortality than those without HIV, even adjusting for cancer stage, treatment, and health care-related factors such as treating cancer facility and type of health insurance.[121,122] The underlying mechanisms for this elevated risk are unclear.

Targeted therapies (eg, TKIs against EGFR, ALK, ROS1) have greatly improved outcomes for patients with lung cancer harboring targetable genetic alterations. Data about DDI between targeted TKI therapies for lung cancer and ART are sparse, but in general support avoidance of concomitant CYP3A4 inhibiting ARTs (eg, PIs) and the need for multidisciplinary care.[123–125]

ICI have revolutionized the treatment of lung cancer and are as safe and efficacious in PWH who are on suppressive ART as in people without HIV.[126–128]

Application of Novel Therapies

Immunotherapy, cellular therapy, and immunomodulatory drugs

Classical cancer treatments such as chemotherapy and radiotherapy are often more difficult to apply in PWH due to worsening CD4 counts, myelosuppression, and infectious risks that may result in increased treatment-related morbidity and mortality.[129] Conversely, immunotherapy shows promise in harnessing the immune system to combat both HIV and cancer without worsening immunosuppression. PWH have disproportionately higher risk of many cancers for which ICIs are currently approved. Immune checkpoints such as PD-1 and CTLA4 are upregulated in PWH as a result of persistent immune stimulation by chronic HIV infection and, in those with virus-associated cancers (eg, KS, NHL, cervical cancer, HCC), chronic viral stimulation, both of which lead to T-cell exhaustion and impairment of their killing function. ICIs are safe in PWH receiving ART with CD4 counts above 100 cells per uL.[113,128,130] In fact, among patients with advanced cancer enrolled into trials of ICIs, PWH have similar baseline CD4 counts as HIV-negative patients, and these low CD4 counts neither increase the risk of treatment-related adverse events nor lower survival after receiving immunotherapy.[127] Pembrolizumab, an ICI, has shown particular promise in treating HIV-associated NHL,[119] and KS.[113]

The immunomodulatory drug, pomalidomide, is associated with reduced downregulation or increased cell surface expression of MHC-1 in cells infected by the oncogenic viruses KSHV, HTLV-1, and EBV.[131] Pomalidomide has been shown to be particularly effective in treatment of KS, which is caused by KSHV, and is currently approved by the US FDA for this indication.[112] Ongoing studies show promise for the combination of pomalidomide with ICIs to treat virus-associated cancers in PWH.[119]

Implications and opportunities for cure of both human immunodeficiency virus and cancer

Allogeneic hematopoietic stem cell transplantation using suitable donor stem cells in PWH with hematological malignancies such as acute myeloid leukemia and HL can result in long-term remission with potential for cure of both conditions.[132,133] However,

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the logistical and cost implications make it likely unsuitable for large scale adoption. CAR-Ts have been successfully used to treat lymphoma in PWH,[120] and offer promise for targeting HIV cure.[134] Interestingly, even though CAR-Ts have revolutionized treatment of relapsed lymphoma, they were originally developed in search of HIV cure. More recently, the ICI pembrolizumab has been shown to reverse the latency of HIV and might provide insights and opportunities that are informative to ongoing HIV cure efforts.[135]

Clinical Trials

Clinical trials usually offer the best cancer treatment options.[102] However, PWH are often excluded from cancer clinical trials. The American Society of Clinical Oncology and the US National Institutes of Health (NIH) both support the inclusion of PWH in cancer clinical trials.[136,137] However, where PWH are included, there are usually arbitrary CD4 count thresholds for eligibility. Emerging research shows that among people with relapsed and refractory cancers, CD4 counts are similar between PWH and people without HIV.[138] Moreover, for those who are enrolled in clinical trials of immunotherapy, there is no significant association between low CD4 counts less than 350 cells per μL and either the proportion of adverse events or overall survival in both people with and without HIV.[127] Real-world data further show that the use of ICIs in PWH does not increase toxicity.[126] Therefore, PWH should be included in clinical trials of immunotherapy without regard to CD4 count thresholds. A recent assessment by the National Cancer Institute's Cancer Therapy Evaluation Program found that there is increasing intention to include PWH in cancer immunotherapy trials, but that actual inclusion in trial protocols remains unchanged.[139]

Reflecting this need for rigorous clinical trials to inform cancer treatment and prevention among PWH, including in LMICs where HIV-associated malignancies burden is high, it is important to note efforts like the AMC. AMC is an NIH-sponsored network to study cancer and precancer pathobiology and to evaluate new treatment and prevention approaches among PWH, first launched in 1995. Initially limited to the US, it has more recently expanded internationally to include Africa and Latin America. This consortium has contributed significantly to advancements in prevention and treatment of cancer in PWH.[140]

IMPLEMENTATION SCIENCE

Finally, as new cancer control interventions become available, implementation science enables contextual adaptation to ensure relevance and feasibility. Because different populations of PWH have cultural nuances, implementation science provides a framework for tailoring interventions in ways that respect their beliefs, attitudes, and practices. Implementation science methodologies also facilitate the systematic evaluation of barriers and facilitators to adoption of cancer control interventions, thereby enabling development of targeted strategies. Application of implementation science principles to cancer control in PWH also ensures that the perspectives and experiences of all stakeholders are considered in the design and execution of cancer control interventions. Particularly in LMICs, implementation science can allow comprehensive and coordinated cancer control efforts to effectively leverage the existing strong HIV infrastructure.

SUMMARY

The complex interplay between HIV and cancer requires a holistic approach that transcends traditional disease boundaries. Collaboration between infectious disease

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specialists, oncologists, and public health experts is paramount to comprehensively address the continued challenges posed by HIV-associated cancers even in the ART era, toward improving outcomes for PWH worldwide. (see **Table 2**)

CLINICS CARE POINTS

- Many factors contribute to a continued increased cancer risk among PWH globally, despite advancements in ART.
- Behavioral, vaccination, and screening interventions are currently available to reduce cancer risk and should be integrated into routine health care, alongside continued research and tailoring to meet the diverse needs of PWH globally.
- PWH diagnosed with cancer can often be treated similarly to people without HIV in the ART era – including with novel cancer therapies and in clinical trials – but unique treatment challenges and opportunities remain among PWH.
- Collaborative multidisciplinary efforts, leveraging implementation science, are critical for continued progress against cancer in PWH, especially in parts of the world with the greatest burden of HIV.

DISCLOSURE

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