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Immunotherapy in People With HIV and Cancer

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HIV infection alters the natural history of several cancers, in large part due to its effect on the immune system. Immune function in people living with HIV may vary from normal to highly dysfunctional and is largely dependent on the timing of initiation (and continuation) of effective antiretroviral therapy (ART). An individual's level of immune function in turn affects their cancer risk, management, and outcomes. HIV-associated lymphocytopenia and immune dysregulation permit immune evasion of oncogenic viruses and premalignant lesions and are associated with inferior outcomes in people with established cancers. Various types of immunotherapy, including monoclonal antibodies, interferon, cytokines, immunomodulatory drugs, allogeneic hematopoietic stem cell transplant, and most importantly ART have shown efficacy in HIV-related cancer. Emerging data suggest that checkpoint inhibitors targeting the PD-1/PD-L1 pathway can be safe and effective in people with HIV and cancer. Furthermore, some cancer immunotherapies may also affect HIV persistence by influencing HIV latency and HIV-specific immunity. Studying immunotherapy in people with HIV and cancer will advance clinical care of all people living with HIV and presents a unique opportunity to gain insight into mechanisms for HIV eradication.

Keywords: HIV, immunotherapy, HIV reservoir, cancer, PD-1, Kaposi sarcoma, lymphoma

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INTRODUCTION

People living with HIV (PLWH) have an elevated risk of developing cancer compared to the general population. This increased risk is partially attributable to comorbid conditions and social factors such as smoking or poorer access to preventative services. However, there is strong evidence that immunologic factors such as decreased immunologic surveillance and increased susceptibility to oncogenic viral infection play a significant role (1–5). Historically, cancers developing in the setting of HIV have been classified as AIDS-defining malignancies (ADM; cancers that, when present, confer a diagnosis of AIDS) and non-AIDS defining malignancies (NADM; cancers whose presence does not necessarily indicate AIDS) (6). Many HIV-related cancers have a viral etiology (7). These include Kaposi sarcoma (KS) [Kaposi sarcoma herpes virus (KSHV)]; cervical, anal, penile and vulvar squamous cell cancer and oropharyngeal cancers [human papilloma virus (HPV)]; B cell non-Hodgkin lymphomas (NHL) including diffuse large B-cell lymphoma, Burkitt lymphoma, plasmablastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, classic Hodgkin lymphoma, and lymphoproliferative disorders [in some cases, Epstein-Barr virus (EBV) and/or KSHV]; hepatocellular carcinoma [hepatitis B and C viruses (HBV/HCV)], and Merkel cell carcinoma [Merkel cell polyoma virus (MPV)]. In epidemiological studies of

non-Hodgkin lymphoma, Kaposi sarcoma, and anal cancer, uncontrolled HIV viremia is an independent risk factor (4, 5, 8).

The introduction of antiretroviral therapy (ART) after 1996 resulted in a reduction in the incidence of many ADMs by 75–80% (9), largely due to reduced prevalence of profound immunodeficiency. NADMs including lung cancer, Hodgkin lymphoma, anal cancer, and oropharyngeal cancer now comprise an increasing proportion of total cancers in PLWH in North America (10, 11). A similar trend has been documented in Europe, Australia (12) and the Asia-Pacific region (11, 13). This epidemiological switch in prevalence away from ADMs and virally-associated malignancies corresponds with increasing life expectancy of PLWH, increased availability of ART and promotion of viral suppression (14–16).

HIV LEADS TO PARTIALLY REVERSABLE PERTURBATION IN T-CELL FUNCTION

HIV has multiple effects on T-cell immunity that may contribute to cancer risk. Absent effective ART, uncontrolled HIV infection leads to massive depletion of HIV-infected CD4 cells and uninfected bystander CD4s in both blood and tissue (17). In the same setting, CD8 counts often rise, leading to inverted CD4/CD8 ratios that are an independent measure of immune dysfunction. Moreover, HIV and other chronic viral infections lead to increased expression of immune checkpoint proteins (such as PD-1), exhaustion markers, and impaired CD8 T cell function (18–20), causing systemic immune dysfunction and dysregulation (21). Untreated HIV perturbs not only the quantity but also the breadth of T-cell immunity. HIV leads to decreased numbers of naïve T cells, less diversity of the T-cell repertoire in the blood (22, 23), and skewing of the T-cell receptor (TCR) repertoire secondary to CD4 depletion and expansion of oligoclonal CD8 populations (24). HIV viremia is rapidly suppressed with modern ART. Immune reconstitution after initiation of ART leads to CD4 recovery and CD8 decline over time (25). The likelihood of full immune recovery improves with earlier diagnosis and a younger age at ART initiation (26), although immune recovery is often incomplete (27). The heightened pro-inflammatory state associated with both untreated and treated HIV contributes to long-term adverse outcomes (28, 29).

ONCOGENESIS IN THE SETTING OF HIV-INDUCED IMMUNE DYSFUNCTION

Immunodeficiency is an established risk factor for the development of cancer, and the underlying causes are likely many, including uncontrolled proliferation of oncogenic viruses and inadequate immune surveillance. Many oncogenic viruses have been shown to cause cancer in other immunosuppressed states, including inherited immunodeficiencies and solid-organ transplantation (30). CD4 deficiency is strongly linked to malignancy (31), independent of HIV infection (32–35). The presence, number, and functionality of CD4 T cells are important in multiple steps of the oncogenic pathway, including recognition of tumor antigens, development of effective neutralizing antibody, and cellular responses to viral pathogens, and clearance of premalignant lesions. The risk of many HIV-associated malignancies decreases with improved CD4 count on ART (9, 12, 36–39) and cancer-specific mortality correlates inversely with CD4 count (12, 40). The link between reduced CD4 count and elevated cancer risk is profound in KS and NHL (41–43), but also present in other malignancies (37). An individual's risk of cancer (and long-term immune dysfunction) is likely influenced by the CD4 nadir, perhaps indicative of a synergistic relationship between chronic inflammation and impaired immune surveillance (10, 44–49).

CD4 lymphocytopenia, ineffective CD8 response, and associated immune dysregulation lead to a reduction in immunosurveillance, a key mechanism in HIV-associated oncogenesis (21, 50). This is illustrated in the link between HIV, immune status, and cervical cancer (37). PLWH are more likely to acquire high risk HPV (51, 52), less likely to clear HPV, and more likely to progress to higher-grade forms of dysplasia (53). PLWH with lower CD4 counts are also more likely to progress from dysplasia to invasive cancer (54). In an HPV vaccine trial in adolescents with HIV, the induced antibody titer correlated positively with CD4 count (55), supporting the importance of CD4 T cells in the production of high-affinity antibodies (51), the primary correlate of protection of the HPV vaccine (56). Tissue-localizing HPV-specific CD4 and CD8 T cells are also potentially important to tumor regression (57, 58).

Immune exhaustion and T-cell senescence are prominent features of both chronic viral infections and malignancies (59). In PLWH, T-cell dysfunction is most strongly implicated in the development of EBV-related lymphomas and KS (60). In HIV-associated B cell NHL, reduced T-cell polyfunctionality and TCR diversity is associated with poorer prognosis (61). These observations, among others (62), have led to interest in remedying immune dysfunction to treat malignancy in PLWH (63).

ANTIRETROVIRAL THERAPY AND OTHER FORMS OF IMMUNOTHERAPY IN HIV-RELATED CANCER

ART is itself an effective form of immunotherapy for ADM. Improvements in ART in 1996 resulted in a decline in the incidence and severity of KS, as well as changes in its natural history (9, 64–66): the risk of death due to KS decreased at similar HIV RNA levels and CD4 count (66), suggesting that ART resulted not only in improved immune control of KSHV but also decreased immune dysregulation. ART-induced immune reconstitution results in regression of KS lesions in ∼80% of PLWH with early KS (67). However, ART alone is often insufficient in advanced KS.

Several immunotherapies have shown efficacy in KS and other HIV-related cancers (**Table 1**). Interferon alpha (IFN-α), the first true immunotherapy used in HIV-associated KS, generated a 20–40% response rate (98–100). IL-12, which enhances Th-1 type immune responses (91), has been shown to have anti-KS

TABLE 1 | Select immunotherapeutic agents used in cancers that occur at increased frequency in people with HIV and their demonstrated or hypothesized effect on measurements of the HIV reservoir.

Agent	Mechanism	Indication in cancer that is associated with HIV	Adverse events	Potential effect on HIV reservoir	References
Checkpoint inhibitors (ipilimumab nivolumab, pembrolizumab, durvalumab, etc.)	Block inhibitory T cell receptors including CTLA4, PD-1, or PD-L1, allowing T cell activation and promoting cytotoxic killing of target cells	Lung cancer, classical Hodgkin lymphoma, head and neck cancer, liver cancer	Fatigue, rash, arthralgia, pruritis, GI toxicity, asthenia, pulmonary toxicity, pyrexia, autoimmune phenomena, headache	Transient increases in unspliced HIV RNA and decreases in HIV DNA in blood, variable effects on plasma HIV RNA	(68–72)
Pomalidomide	Modulates substrate specificity of cereblon E3 Ubiquitin ligase, altering protein expression. Induces cell cycle arrest and apoptosis in plasma cell malignancies. Enhances T cell- and natural killer (NK) cell-mediated cytotoxicity, inhibits angiogenesis, modulates cytokines, and cell microenvironment	Under evaluation for KS	Thromboembolic events, teratogenicity, fatigue and asthenia, cytopenias, GI toxicity, dyspnea, back pain, pyrexia	Immune stimulation, increased killing of reservoir cells	(73–75)
Brentuximab vedotin	Monoclonal antibody drug conjugate with anti-CD30 antibody (expressed on Hodgkin Reed-Sternberg Cells) and MME (microtubule disruptor) payload	Classical Hodgkin lymphoma	Cytopenias, peripheral sensory neuropathy, fatigue, GI toxicity, pyrexia, rash, cough	Transient loss of detectable CD4 T-cell HIV RNA and reduction in plasma HIV viremia	(76, 77)
Alemtuzumab	Monoclonal antibody to CD52 (expressed on lymphocytes, monocytes, macrophages, NK cells, and some granulocytes)	Hematopoietic stem cell transplant conditioning	Infusion reaction, serious infections, cytopenias, secondary autoimmune disorders	*Ex vivo* elimination of latently-infected CD4 T cells. Evidence of decreased frequency of HIV-infected CD4 T cells *in vivo*.	(78–81)
IL-7	Modulates T cell development and maturation in the thymus. Modulates T cell homeostasis and proliferation and memory differentiation. Inhibits T cell apoptosis and promotes proliferation.	Under evaluation in combination with CD19 CAR T-cells in relapsed B-cell lymphoma	Infusion reaction, hypersensitivity	Transient increases in HIV viral load without observed clinical sequelae, as well as enhanced anti-HIV CD8 activity	(82–90)
IL-12	Promotes activation and differentiation of T lymphocytes and NK cells	Under evaluation in therapeutic vaccines for HPV associated cancers, phase 1 studies in solid tumors.	Immune activation	Latency reversal *ex vivo*	(91–93)
IL-15	Stimulates the proliferation of memory T cells and regulates their turnover. Promotes the survival of naive T cells.	Under evaluation in refractory B-cell lymphomas and solid tumors	Infusion reaction, hypersensitivity	*Ex vivo* killing of latently-infected CD4 T cells by cytotoxic CD8 T cells	(94–97)

activity in patients who are progressing despite ART (92) and is currently being developed as a tumor-targeted immunocytokine, NHS-IL12 (101). A recent trial of the immunomodulatory drug pomalidomide in 22 participants with heavily pretreated KS who were virally suppressed on ART noted an overall response rate of 60% among HIV-infected participants, which is comparable to traditional cytotoxic chemotherapy for KS. The investigators observed expansion of central memory cells and decreases in CD57+ immunosenescent T-cells (73, 74).

Despite immune dysfunction due to HIV, cancer in PLWH is often responsive to immunotherapy. Thus far, the best-studied agents are tumor-targeting monoclonal antibodies in the management of HIV-associated lymphomas. Rituximab, a monoclonal antibody to the B-cell antigen CD20 that works in part through antibody-dependent cell-mediated cytotoxicity, is associated with improved overall survival in NHL when compared to chemotherapy alone (102–104). In people with HIV-associated lymphoma, a pooled analysis of over 1,500 patients noted that rituximab improved overall survival in those with a CD4 count >50 cells/μL (105). Brentuximab vedotin, an antibody-drug conjugate directed at CD30 on Reed-Sternberg cells, has been shown to have activity in HIV-associated Hodgkin lymphoma: in a study of 6 patients with HIV and classical Hodgkin lymphoma, all achieved a complete response with minimal hematologic toxicity or infectious complications (106).

More recently, immune checkpoint inhibitors (CPIs), monoclonal antibodies to cytotoxic lymphocyte associated protein 4 (CTLA-4) or programmed cell death 1 or its ligand (PD-1 and PD-L1), have gained widespread use due to their demonstrated activity and favorable toxicity profile in many malignancies. CPIs, which function by blocking T-cell inhibitory signaling, have performed well in clinical trials of many malignancies that are common in the setting of HIV, including lymphoma, lung cancer, cervical cancer, liver cancer, and

head and neck cancers (107, 108). While nearly all these trials excluded PLWH (109), case reports and retrospective cohort studies from US and European collaborative groups have described an acceptable safety profile with the use of nivolumab, pembrolizumab, and ipilimumab in PLWH, with reported tumor responses in classical Hodgkin lymphoma, melanoma and lung cancer (68, 69, 110–116). A systematic review of CPIs in PLWH noted overall response and adverse event rates that were similar to the general population. In the subset of patients in whom viral load was measured, HIV remained suppressed in 93% of participants, and CD4 counts increased modestly. Notably, CPI use in KS was associated with an overall response rate of 63% (117). A prospective cohort study of 10 PLWH with NSCLC treated with nivolumab noted similar response rates to HIV-uninfected patients: 2 patients had a partial response, 4 had stable disease, and 4 progressed. All patients tolerated nivolumab well with no serious adverse events (70). A prospective phase 1 study of pembrolizumab in PLWH with a CD4 count >100 cells/μl and advanced cancer demonstrated evidence of safety and activity in KS, NHL, lung cancer, and liver cancer (118). A study of durvalumab in 20 aviremic PLWH with advanced solid tumors likewise reported no serious adverse events, nor evidence of HIV reactivation during durvalumab therapy (119). Ongoing studies evaluating CPIs in HIV-associated cancers include a phase 1 study of nivolumab (anti-PD-1) combined with ipilimumab (anti-CTLA-4) in relapsed classical Hodgkin lymphoma or solid tumors (NCT02408861), a phase 2 study of nivolumab in advanced non-small cell lung cancer (NCT03304093), a phase 2 study of durvalumab in advanced cancer (NCT03094286), a study of pembrolizumab as first systemic therapy in KS (NCT02595866), and intralesional nivolumab for limited cutaneous KS (NCT03316274).

CANCER IMMUNOTHERAPY AND HIV PERSISTANCE

Although HIV-infected individuals on ART may have undetectable plasma HIV RNA by standard clinical assays, a reservoir of latently HIV-infected cells (120, 121) persists from which the virus will resurface after discontinuation of ART (122). Persistence of the HIV reservoir is partly due to the inherent longevity of resting memory CD4 T cells; growing evidence suggests that its persistence is maintained by clonal expansion (123, 124). In whole genome-based studies, HIV integration favors sites of active gene transcription (125) which benefits HIV replication and establishment of latency (126, 127) and promotes pathways associated with oncogenesis (124). The HIV reservoir has been a major subject of research into a functional cure for HIV. One theory called "kick and kill" (**Figure 1**) (128, 129) proposes that HIV latency reversal in the setting of ART (meaning activation of HIV replication within a latently infected cell), can lead to increased immunogenicity of HIV infected cells, enhancement of anti-HIV immunity, and increased cell death of HIV reservoir cells.

Several immunotherapeutic agents used in the treatment of cancer may have cause HIV latency reversal and/or have a targeted effect on HIV persistence. CPIs have been proposed to have latency reversal activity. Anti-PD-1 therapy is associated with changes in CD4 count and HIV RNA (130–132), perhaps due to direct targeting of the HIV reservoir. PD-1 and CTLA-4 expression are increased in the setting of chronic HIV infection, and HIV DNA and unspliced RNA are enriched in PD-1+ cells in blood and lymph nodes of individuals with HIV on ART (133–136). Multiple case reports and prospective studies have documented transient increases in HIV transcription in CD4 cells in people with HIV-associated malignancies on ART who are treated with anti-PD-(L)1 drugs, although many of these participants later experienced decreases in plasma HIV RNA (117, 128, 129, 132, 137). In one study, 2 of 28 patients who had undetectable HIV RNA prior to CPI therapy developed detectable HIV RNA, whereas 5 of 6 patients who had detectable viremia experienced a decrease in their viral load (117). A prospective study of the effect of ipilimumab in 24 PLWH with detectable viremia and without cancer, of whom 17 were on ART, also demonstrated a range of responses: 2 participants had slight decreases in HIV RNA but 14 had slight increases. None experienced significant change in CD4 or CD8 T cell

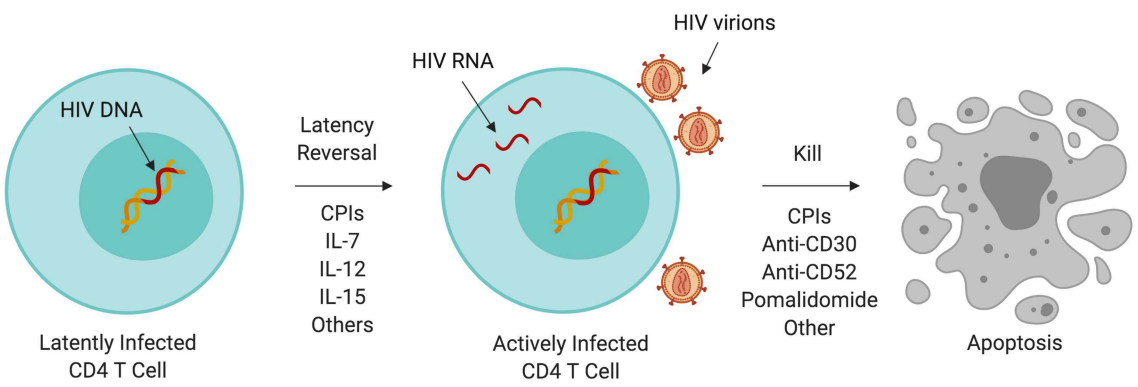

FIGURE 1 | Immunotherapy and the HIV reservoir. A variety of immunotherapeutic agents used to treat cancer may perturb the HIV reservoir through induction of latency reversal or increased cell killing. Some of these agents are being evaluated in clinical trials targeting HIV persistence. CPI, immune checkpoint inhibitor; IL, interleukin.

count (138). These observations support the activity of CPIs to produce latency reversal. Additional studies are being performed to evaluate the effects of CPIs on anti-HIV T-cell function.

The effects of anti-CD30 monoclonal antibodies on HIV latency have also been investigated. Early work in HIV demonstrated that cross-linking of CD30 on latently-infected CD4 T cells induced HIV transcription (139). More recently, brentuximab vedotin has been associated with transient loss of detectable CD4 T-cell HIV RNA and reduction in plasma HIV viremia (76). CD30 is therefore speculated to be a marker of latent, but transcriptionally-active, HIV-infected cells and a potential therapeutic target for HIV eradication (140).

Alemtuzumab is a monoclonal antibody targeting CD52, which is expressed by T cells including HIV-infected T cells, regardless of CD4 count or plasma viremia. Latently-infected CD4 T cells have been eliminated *in vitro* with alemtuzumab (78). *In vivo*, a case report of alemtuzumab in an individual with HIV and Sezary syndrome described decreased frequency but not elimination of HIV-infected CD4 T cells (79). Alemtuzumab was also part of the conditioning regimen of one of the patients with sustained HIV aviremia after HSCT (141).

T-cell growth factors, many of which are being investigated for cancer indications, have also been shown to affect the HIV reservoir. Interleukin 7 (IL-7) is a homeostatic cytokine that increases T-cell repertoire diversity through expansion of naive T cells (82) and is being investigated in several malignancies. IL-7 levels increase in HIV-associated CD4 lymphocytopenia and decrease with immune reconstitution (142). Exogenous administration of IL-7 is associated with dose-dependent increases in CD4 and CD8 T cells in PLWH on ART (143), including HIV-specific CD8 T cells (83). In patients with suppressed HIV, administration of IL-7 led to transient increases in HIV viral load without observed clinical sequelae (84), as well as enhanced anti-HIV CD8 activity. Another T-cell growth factor, IL-15, induces antigen-specific T-cell proliferation, most pronounced in the CD8 compartment (94, 95, 144, 145). IL-15 is produced during acute HIV infection (95). Stimulating NK cells with IL-15 *ex vivo* from participants with suppressed HIV on ART led to *ex vivo* killing of latently-infected CD4 T cells by cytotoxic CD8 T cells (96). Early phase studies of IL-7 and IL-15 in several malignancies are underway.

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN HIV

In 2007, an individual with HIV infection and leukemia underwent hematopoietic stem cell transplant (HSCT) in Berlin, using cells from a donor who was homozygous for CCR5-delta32, a mutation that renders CD4 cells resistant to CCR5-tropic HIV. After transplant, HIV was undetectable in blood and biopsy specimens, despite discontinuation of ART (146, 147). Recently, a second patient who underwent allogeneic HSCT for Hodgkin lymphoma using cells from a homozygous CCR5-delta32 donor and whose HIV remained undetectable 18 months after stopping ART (141) was described. Allogeneic stem cell transplant itself appears to substantially decrease the HIV reservoir. In the European IciStem cohort of PLWH on ART who underwent HSCT for hematologic malignancies from CCR5 wild-type donors with full donor engraftment and who remained on ART, 5 of 6 were found to have no detectable HIV DNA in CD4 cells from blood and tissues and no evidence of HIV in a humanized mouse viral outgrowth assay (148). However, ART interruption is required to demonstrate functional cure, and in cases of allotransplants from CCR5 wild-type donors, HSCT has failed to produce long-lasting viral suppression in the absence of ART. In an ART interruption study of 2 PLWH who underwent HSCT for hematologic malignancies from CCR5 wild-type donors and had undetectable HIV RNA for years post-transplant while on ART, both participants developed detectable viremia after ART interruption: patient A at day 84 and patient B at day 225 (149).

Given the success of allotransplants from homozygous CCR5-delta32 donors, CCR5-mutant cell products have been developed via gene editing and have been shown to be safe when infused into participants with chronic aviremic HIV. When ART was interrupted, the edited CD4 cells declined at a slower rate than endogenous CD4 cells. While these results are promising, additional work is required to develop a scalable approach to address HIV persistence on ART (150–153).

IMPROVING OUR UNDERSTANDING OF HIV-RELATED CANCER

As PLWH are living longer, cancer has become a major cause of morbidity and mortality, well above the burden faced by the general population. Although the incidence of AIDS-defining malignancies has decreased, mortality associated with NADMs is rising. Given the persistent immune abnormalities despite ART and the implications for cancer risk, immunotherapy is uniquely poised to improve outcomes in HIV-associated cancers. In order to advance our understanding, PLWH must be included in immuno-oncology studies. Recent recommendations from ASCO and the FDA provide guidance for appropriate inclusion of PLWH and cancer in clinical trials (109, 154). Furthermore, studying cancer immunotherapy in this population represents an opportunity to gain a better understanding of HIV itself. Investigation of the immunologic and viral responses to cancer immunotherapy in PLWH will lead to novel insights into HIV elimination and, above all, improve the outcomes of people with HIV and cancer.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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