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Cancer Prevention in HIV-Infected Populations

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Abstract

People living with human immunodeficiency virus (HIV) are living longer since the advent of effective combined antiretroviral therapy (cART). While cART substantially decreases the risk of developing some cancers, HIV-infected individuals remain at high risk for Kaposi sarcoma, lymphoma and several solid tumors. Currently HIV-infected patients represent an aging group, and malignancies have become a leading cause of morbidity and mortality. Tailored cancer-prevention strategies are needed for this population. In this review we describe the etiologic agents and pathogenesis of common malignancies in the setting of HIV, as well as current evidence for cancer prevention strategies and screening programs.

Introduction

There are approximately 1.2 million people living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in the United States (US) and more than 35 million HIV-infected worldwide[1]. HIV and associated immune suppression have been strongly associated with several mature B-cell lymphomas and Kaposi Sarcoma (KS) since the beginning of the AIDS epidemic. In women with HIV/AIDS, premalignant cervical lesions were also noted to be common. KS, certain non-Hodgkin lymphomas (NHL) and cervical cancer confer the diagnosis of AIDS in an HIV positive patient, and as such are referred to as AIDS defining malignancies (ADM). Over the years it has been recognized that several additional cancers occur more frequently in HIV-infected patients, such as lung cancer, hepatocellular carcinoma (HCC), anal cancer, oropharyngeal cancer, classical Hodgkin lymphoma and non-melanomatous skin cancer[2,3]. These neoplasms in HIV patients are referred to as non-AIDS defining malignancies (NADM). As the population of HIV-infected patients ages, incidental cancers not associated with HIV, such as breast, prostate and colon cancer are also increasingly seen.

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Access to combined antiretroviral therapy (cART) has markedly decreased mortality among HIV-infected patients. This is largely due to a decrease in the incidence and mortality rate of opportunistic infections (OI)[4–6]. With decreases in infectious deaths, the population with HIV is living longer, and cancer has become a leading cause of morbidity and mortality in this patient population[1,4,7,8]. Additionally, at the beginning of the HIV epidemic, the majority of malignancies in HIV-infected patients were ADM. However, over the last two decades, the epidemiology of cancer in HIV-infected patients has markedly changed[8]. The incidences of cancers that occur most frequently in advanced immunosuppression have decreased in the setting of widespread use of cART[9]. While KS and mature B-cell lymphomas remain the commonest individual cancers in this population, collectively NADM and incidental cancers[1] now comprise the majority of the cancer burden in HIV-infected populations in the US and represent a growing public health concern both in the US and globally.

Cancer is responsible for approximately one third of all deaths in people with HIV[4]. A recent study from France reported that respectively, ADM and NADM were the cause of death in 10% and 26% of HIV patients from 2000–2010[8]. Both ADM and NADM are associated with decreased 10-year overall survival in HIV-infected patients, despite the use of cART. Health care disparities compromise outcomes for patients with HIV who develop cancer[10,11]. For these reasons, prevention and early detection of malignancies in HIV-infected patients are increasingly important in the US and globally.

The majority of cancers associated with HIV are linked to co-infection with oncogenic viruses, immunologic and inflammatory factors, and environmental conditions. The commonest oncogenic viruses in this patient population include Epstein-Barr virus (EBV), Kaposi sarcoma herpes-virus (KSHV) - also called human herpes-virus 8 (HHV-8), and human papilloma virus (HPV). Co-infection with hepatitis C virus (HCV) and hepatitis B virus (HBV) increases the risk of HCC in this population. A rare viral cause of cancer is Merkel cell polyomavirus[12], which is the etiologic agent of Merkel cell carcinoma. Immune and inflammatory risk factors are closely related to HIV viremia and associated immunosuppression, and these directly and indirectly contribute to oncogenesis in several HIV-associated cancers. Further important and modifiable risk factors include cigarette smoking and sun exposure[13,14].

In this review of cancer prevention in people with HIV, we will focus on the pathogenesis of ADM and NADM most strongly associated with HIV/AIDS (Table 1). We discuss the etiologic agents and pathogenesis of the commonest malignancies in HIV-infected patients. We review the mechanism of action of individual antiretroviral agents and the evidence for prevention of several cancers through the use of cART, control of viral co-infections and associated diseases, cancer screening, vaccination use, and behavioral modification.

Etiologic Agents and Pathogenesis

Human Immunodeficiency Virus

HIV, like other retroviruses, is enveloped and contains two strands of RNA. It is a lentivirus, a type of retrovirus that mainly infects CD4+ T-cells. The HIV lifecycle depends on several

HIV encoded proteins (Figure 1). During HIV infection, viral envelope proteins gp120 and gp41 specifically bind to the CD4 receptor as well as the co-receptors CXCR4[15] or CCR5[16], which lead to fusion and entry into the cell. In the cytoplasm, HIV RNA undergoes reverse transcription by HIV-encoded reverse transcriptase (RT)[17] to form a double stranded (DS) HIV DNA, which is further processed and chaperoned to the nucleus where it is integrated into the host DNA genome by an HIV integrase[18]. HIV can then be transcribed from this pro-viral DNA, which is followed by translation of HIV polyproteins. These polyproteins undergo secondary processing by an HIV aspartic protease[19] to form mature protein components of an infectious virion. These virions are assembled and released by dying $CD4^+$ T-cells. Untreated, HIV replicates rapidly, leading to rapid turnover of $CD4^+$ T-cells[20]. It can also kill $CD4^+$ T-cells by indirect mechanisms. Several steps in the lifecycle, including fusion, reverse transcription, integrase strand transfer and protease function can be effectively targeted by a variety of agents (Figure 1, Table 2). HIV mutations are common in the setting of uncontrolled viremia, and under the pressure of a single agent HIV regimen or suboptimal antiretroviral drug concentrations, this can quickly lead to drug resistance. However, cART, generally consisting of three drugs from at least two classes leads to effective control of HIV viremia and thwarts development of resistance. HIV can also infect macrophages and related cells such as microglia, which are important additional cellular reservoirs.

The incidence of ADM is substantially increased in HIV-infected patients. This is particularly true for certain NHLs and KS, for which both HIV viremia as well as HIV-induced immunosuppression as measured by $CD4^+$ T-cell counts, are strongly correlated with incidence[21]. Several overlapping mechanisms of oncogenesis have been proposed, including decreased immune surveillance, increased activation of both the innate and acquired immune system, and possibly direct HIV effects on proliferation of certain cell populations, and possibly other mechanisms.

Untreated HIV-infection leads to decreased $CD4^+$ T-cell count. Lack of virus-specific or tumor-specific $CD4^+$ T-cells is an important mechanism for development of some tumors, especially those occurring at the lowest $CD4^+$ T-cell counts. This is best studied for EBV, KSHV and HPV specific T-cells. $CD4^+$ T-cells targeting the latency associated EBV nuclear antigen (EBNA) 1 are depleted in both systemic AIDS-related NHL[22] and AIDS-related primary central nervous system lymphoma (PCNSL)[15]. Both absolute decreases in $CD4^+$ T-cell counts and lack of KSHV-specific T-cell immunity are associated with incident KS[23]. Functional deficits such as decreased IFN-gamma production have been observed in patients with KS[23], and an immunosenescent $CD4^+$ T–cell phenotype, marked by increased populations of $CD4^+$ $CD57^+$ T-cells, is associated with KS tumorigenesis. $CD4^+$ T-cell depletion also diminishes control of carcinogenic high-risk HPV infection and is associated with cervical and anal intraepithelial neoplasia. HIV-infected patients with HPV-16 positive genital lesions can lack detectable $CD4^+$ T-cell immunity against HPV viral proteins[24].

HIV Viremia Promotes Immune Activation

In addition to defects in T-cell immunity, HIV infection is associated with chronic inflammation through different mechanisms. Immune activation in the setting of HIV

appears particularly important in the pathogenesis of AIDS-related NHLs and some KSHV-associated malignancies (discussed below). AIDS-related lymphomas are aggressive B-cell lymphomas that largely arise from germinal center or post-germinal center B-cells. Several circulating biomarkers have been correlated with B-cell activation and expansion, such as interleukin (IL)-6, IL-10, CD30, CD27 and CD23, neopterin, interferon gamma-induced protein 10 (IP-10), tumor necrosis factor alpha (TNF-alpha), and microRNA (miR2-121)[25–27]. The epidemiologic observation that elevated levels of serum free light chains are a risk factor for lymphoma in patients with HIV further supports the role of B-cell lymphoproliferation in pathogenesis[28]. Interestingly, elevated plasma levels of CXCL13, a B-cell chemokine strongly associated with NHL risk, is elevated in the setting of uncontrolled HIV viremia but decreases with cART[29], supporting one potential mechanistic role for cART in NHL prevention.

Early in infection, HIV depletes gut associated $CD4^+$ T-cells. At the same time, HIV is associated with $CD8^+$ T-cell[30], B-cell[31] and monocyte activation, which promotes an inflammatory milieu[32] and resultant decreased mucosal integrity[33]. Preferential loss of gut $CD4^+$ T_H17 cells has been posited to play an important mechanistic role in this process[34]. Interestingly, recent *in vivo* studies showed that a model retrovirus, simian immunodeficiency virus (SIV), disrupts overall microRNA (miRNA) expression and diversity of commonly expressed miRNAs in the small intestinal mucosa, perhaps contributing to epithelial barrier dysfunction in this setting[35]. Associated microbial translocation is then associated with systemic immune activation. Lipopolysaccharide (LPS), the major component of the bacterial wall of gram-negative microorganisms, is recognized by toll like receptors 2 and 4 (TLR2, TLR4) and stimulates several immune cell populations. Systemic LPS levels are increased in HIV-infected patients, especially in the setting of HIV viremia. This increase in circulating LPS occurs in conjunction with chronic stimulation of monocytes and an increase in circulating $CD8^+$ T-cells with an activated $CD38^+$ $HLA\text{-}DR^+$ phenotype (polyclonal T-cell activation) and an increase in measures of immune activation such as soluble CD14 (sCD14). $CD4^+$ T-cell depletion and immune activation are reversible with cART[36], especially when started soon after HIV infection[37]. However, gut associated lymphoid tissue abnormalities appear to improve slowly, and can persist even after years of effective cART[30]. Inflammatory biomarkers have been shown not only to correlate with HIV disease progression and poor response to cART[38], but also development of AIDS-related lymphoma[39]. For example, elevated levels of sCD14 and LPS were significantly associated respectively with a 2.7- and 3.2-fold risk for NHL, implicating gut dysfunction in lymphomagenesis. More studies are required to evaluate this as a risk factor for the development of other malignancies in HIV infected patients.

HIV is associated with chronic B-cell activation and B-cell exhaustion has been described, characterized by increased frequencies of circulating tissue-like memory B-cells[40]. Chronic stimulation of B cells from HIV viremia is partially reversed with cART; however markers of exhaustion are not completely reversed to compared to HIV-negative individuals. B-cell lymphomagenesis in the setting of HIV-associated inflammation involves chronic antigen stimulation and associated B-cell immune hyperactivation. B-cell activation may occur through LPS or other infectious antigens binding to TLR. HIV itself appears to be able to

stimulate B-cells though both CD40 and the B-cell receptor. CD40 is a membrane protein in the tumor necrosis factor (TNF) receptor family that is found on the surface of B cells, macrophages, dendritic and endothelial cells. CD40 ligand (CD40L) is found on $CD4^+$ T-cells, and the incorporation of CD40L into HIV virions may lead to B-cell activation. Additionally, HIV upregulates the Syk and Jnk pathways through the B-cell receptor. A consequence of B-cell activation in lymphatic germinal centers is upregulation of activation induced cytidine deaminase (AICD), an enzyme required for immunoglobulin (Ig) class switch recombination and somatic hypermutation[42]. However, AICD is also responsible for translocations that potentiate lymphoma development (i.e. *c-Myc/IgH*) as well as other recurrent mutations (i.e. in the promoter region of *BCL6*) that contribute to lymphomagenesis. In the setting of HIV, *c-Myc/IgH* contributes to the pathogenesis of Burkitt lymphoma[43], a large number of diffuse large B-cell lymphomas, and plasmablastic lymphoma.

Kaposi Sarcoma Herpesvirus (KSHV)

KSHV is a gamma herpesvirus that is a necessary but not sufficient etiologic agent of KS, a plasmablastic form of multicentric Castleman disease (KSHV-MCD) and primary effusion lymphoma (PEL)[44,45]. Early in the HIV/AIDS epidemic, as many as 20–30% of men who have sex with men (MSM) AIDS patients developed KS. In the cART era, the incidence of KS has decreased 84% in HIV-infected patients, which appears largely to be due to control of HIV viremia and resultant improvement in T-cell mediated immunity[46].

KSHV seroprevalence varies substantially between populations; in the general US population it is less than 5%. In contrast, it ranges from 10% to 25% in the Mediterranean area[47] and from 20% to 60% in certain regions of Africa and among MSM[48]. KSHV DNA has been detected in saliva, and saliva exchange is considered the major transmission route[49]. KSHV seroprevalence is associated with sanitation, number of sexual partners, and saliva exchange behaviors during sex or in some cultures, pre-mastication of food[49,50]. KSHV infection is also associated with other infections such as malaria and HIV[51], which may be due in part to the effect of certain infections on increasing KSHV salivary shedding[52].

In addition to its effect on KSHV transmission, an HIV encoded protein, trans-activator of transcription (tat), has also been directly implicated in KS pathogenesis. Intriguingly, *in vitro*, HIV tat appears permissive for infectivity of KSHV in cultured endothelial cells[53]. In transgenic mice models, tat induces dermal lesions similar to KS[54], and in cell culture, tat alone and synergistically with human basic fibroblast growth factor (bFGF) promotes spindle cell proliferations derived from KS lesions[55]. More recently, HIV tat was found to promote KSHV-encoded viral IL-6 (vIL-6, discussed below) induced angiogenesis and tumorigenesis *in vitro* through activation of the PI3K/PTEN/AKT/GSK-3beta signaling pathway[56]. Thus, treatment of HIV may have an additional protective effect against KSHV-associated malignancies through decreasing HIV tat.

KSHV can infect a variety of cell types, including endothelial cells, B-cells and monocytes. KSHV has a large double stranded DNA genome that encodes a number of mimics of human genes, many of which have immunologic or angiogenic properties[57]. Viral

oncogenesis is complex; KSHV-associated tumors do not appear to be driven by a single viral oncogene. Some of the better-studied KSHV-encoded oncogenes include those that encode a constitutively active transmembrane viral G-protein coupled receptor (*vGPCR*) that is a homologue of the IL-8 receptor, CXCR1[58], viral interleukin-6 (*vIL-6*) and a viral FLICE-inhibitory protein (*vFLIP*) that activates nuclear factor-κB (NF-κB) signaling by binding to the inhibitor of IκB kinase-γ[59]. More recently, miRNAs were shown to be derived from 12 precursor miRNAs (pre-miRNAs) encoded by sequences in the latency locus of the KSHV genome[60]. These miRNAs can contribute to oncogenesis by modulating cell differentiation[60], cytokine production, and immune receptor signaling[61].

Epstein-Barr-Virus (EBV)

Like KSHV, EBV is a DNA gamma herpesvirus. EBV infection is almost universal by adulthood. Acute infection can cause infectious mononucleosis, but in immune-competent hosts, the virus then generally forms an asymptomatic latent chronic infection in which the virus remains in a latent state, primarily in B cells. However, EBV is associated with several lymphomas in the setting of HIV. The malignant cells are EBV-infected in a majority of cases of AIDS-related PCNSL, immunoblastic forms of systemic diffuse large B-cell lymphoma (DLBCL) occurring at low $CD4^+$ T-cell counts, plasmablastic lymphoma, and classical Hodgkin lymphoma, as well as a proportion of Burkitt lymphoma and primary effusion lymphoma cases. EBV is also associated with rare cases of leiomyosarcoma in children with HIV.

EBV encodes several latency-associated genes that are variably expressed during primary and chronic infection, and which may contribute to lymphomagenesis. One important gene is *EBNA1*, which is expressed in all latently infected cells and can induce oxidative stress as well as promote telomere dysfunction[62]. *LMP2* is expressed in a more limited fashion but is sufficient for B-cell transformation *in vitro*. More recently, it has been recognized that EBV encodes viral miRNAs that play an important role in modifying the cellular environment through a variety of mechanisms such as inducing resistance to apoptosis, modulating the latency to lytic transition, regulating angiogenesis[63] and regulating cellular oncogenes[64].

EBV-associated lymphomas can be classified into 3 different categories based on the variable expression of EBV viral proteins and RNA, and these latency patterns provide insight into disease pathogenesis. Latency 1 tumors generally occur at relatively preserved $CD4^+$ T-cell counts. The tumor cells express EBV nuclear antigens (EBNA) 1, EBV-encoded RNA (EBER) and several microRNAs, and include monomorphic cases of DLBCL, Burkitt lymphoma, and plasmablastic lymphoma. There is overlap between Latency 1 EBV+ lymphomas and translocations involving c-*Myc* and immunoglobulin genes, mainly t(8;14) (*c-Myc/IgH)*. C-*Myc* translocations are noted in the majority of plasmablastic lymphomas, as well as Burkitt lymphoma and 25% of DLBCL, regardless of EBV status. When present, c-*Myc* translocations likely drive the high proliferative rate in these tumors. Interestingly, in EBV+ cases of Burkitt lymphoma, EBNA1 may inhibit c-Myc induced apoptosis, and thereby contribute to oncogenesis[65].

Classical Hodgkin lymphoma has latency 2 pattern. The EBV-infected Reed-Sternberg cells express EBER, EBNA1, miRNA and latent membrane protein (LMP) 2 with varying LMP1

levels. EBV-encoded genes may play a more important role in these tumors through proliferative signaling and modulation of the immune response. LMP1[66,67], a constitutively active homologue of CD40 that upregulates NF-κB signaling and IRF4 expression[68], and LMP2A that mimics B-cell receptor signaling both contribute to proliferation[69]. EBNA1 appears to influence cytokine networks by stimulating production of chemokines such as CXCL10 and CCL20[70] that attract T-regulatory cells and modulate an immunosuppressive microenvironment.

EBV type 3 latency pattern is the most immunogenic, and is characterized by the expression of all six EBV-nuclear antigens (EBNA) and all 3 LMPs. Tumors in which EBV usually expresses a type 3 latency pattern include AIDS-related PCNSL and immunoblastic DLBCL occurring at low $CD4^+$ T-cell counts. EBV-encoded gene products play an important role in the pathogenesis of these tumors. Latency 3 tumors occur at the lowest $CD4^+$ T-cell counts, and CD4+ T-cell immune reconstitution with cART is most important in prevention and treatment of this category of EBV-associated lymphomas. More recently, strong upregulation of the immune modulatory molecule, PD-L1, has been noted in EBV-associated DLBCL and classic Hodgkin lymphoma but not EBV-associated Burkitt lymphoma, supporting an association between EBV and tumor immune evasion in latency 2 and latency 3 tumors [71].

Human Papilloma Virus

Human papilloma virus (HPV) is the etiologic agent of the majority of cases of cervical cancer and anal cancer, as well as a proportion of head and neck squamous cell cancers (HNSCC) in the general population and in people with HIV. Most HPV-associated HNSCC involve the oropharynx, and a recent large case series of head and neck cancers in HIV infected individuals found that 64% of HIV oropharyngeal cases were HPV positive[72]. Rare HPV-associated malignancies include cancer of the vulva and penis. HIV infection and associated immunosuppression are associated with an increased risk for HPV associated invasive cancers in these sites[73]. High-grade squamous intraepithelial lesions (HSIL) precede the development of cervical or anal cancer, and HIV/AIDS is associated with an increased risk of HSIL[74]. Given the high prevalence of HSIL, screening for cervical cancer and possibly anal cancer is important in people with HIV.

The HPV virion contains a double-stranded, circular DNA genome covered by a capsid. HPV can infect cells of the basal layer of squamous epithelium that have been exposed due to microabrasions. The main viral capsid proteins are L1 and L2. The genome is divided into three regions: early, late and long control (LCR) or non-coding (NC). The early region contains the regulatory proteins (E1, E2, E4, E5, E6 and E7). The latter two are viral oncogenes that promote cellular proliferation and are responsible for the carcinogenesis of high-risk HPV types. Multiple HPV genotypes have been associated with HSIL and cervical cancer; these are called “high risk” genotypes. HPV-16 accounts for about 50% of cases of HSIL and cervical cancer. Other high-risk types include 18, 31, 35, 45, 51, 52 and 58[75,76]. High-risk HPV are more prevalent among HIV-infected individuals, which can also contribute to a higher prevalence of HPV-associated malignancies in this population[77].

Several factors have been proposed to explain the increased risk of HPV-related cancers in the HIV population. HIV-encoded proteins tat and gp120 disrupt the integrity of mucosal epithelium and may facilitate the penetration of HPV[78]. Persistent HPV infection and associated anal and cervical HSIL in the setting of HIV are also highly dependent on the immune status of the host and have been associated with decreases in $CD4^+$ T-cell counts and increases in HIV viral load[79]. HPV-specific immune defects, including defective $CD4^+$ T-cell response and increases in CD4+ T regulatory cells are also demonstrable in this setting[24,80]. Quantitative defects in perforin granule release by CD8+ T cells in HPV/HIV co-infected patients may further contribute to pathogenesis[81]. Polymorphisms in human genes that code for proteins targeted by E6 and E7 or those associated with IL-2 and IL-7 signaling are host factors that may further modulate HPV clearance[82,83].

It has been hypothesized that HIV-induced immune suppression enhances the risk of HPV-associated tumors by being permissive for chronic HPV infection, thus allowing premalignant lesions to accumulate genetic damage and progress through increasing dysplasia to cancer. Two HPV-encoded genes have been strongly implicated in this oncogenic process. E6 from high-risk HPV strains interacts with human E6 associated protein (E6AP), forming an E3 ubiquitin complex that targets specific proteins such as p53 for proteosomal degradation. High-risk E7 also modulates ubiquitin ligase activity, leading to degradation of the retinoblastoma tumor suppressor (pRb). Besides E6AP, E6 also interacts with and modulates the function of several other regulatory proteins, leading to suppression of apoptosis, disruption of cell adhesion and epithelial differentiation, activation of telomerase reverse transcriptase (TERT), and reduction of immune recognition through modulation of interferon responses[84,85].

Hepatitis B Virus

Hepatitis B virus (HBV) is a member of the *Hepadnaviridae* family, which infects hepatocytes and increases the risk of HCC by 5–15 fold. Co-infection with HBV is frequent in people living with HIV (PLWH) due to the common route of transmission (sexual, parenteral and perinatal). It is estimated that worldwide the prevalence of co-infection, assessed by persistent hepatitis B surface antigen (HBsAg), in HIV-infected patients is 5–25%, with higher prevalence in regions of Asia and Africa [86]. Patients with detectable HBsAg in serum for longer than 6 months are considered as having chronic hepatitis B, a condition that can lead to cirrhosis, liver failure and hepatocellular carcinoma (HCC) with significant associated morbidity and mortality. HBV-induced inflammation is believed to play a major role in the development of HCC. Uncontrolled HIV is associated with increased HBV viral load[87] and increased liver-associated mortality, especially in severely immunosuppressed patients in the pre-cART era[88]. Patients co-infected with HIV and HBV may progress more rapidly to liver disease and have a higher risk of developing HCC[89]. The risk of developing HCC is 3–8% per year in HBV-infected patients with established cirrhosis[90]. Alcohol use may further promote carcinogenesis.

The hepatitis B encoded protein X antigen (HBx) is a transactivating viral-encoded protein that is implicated in hepatocyte proliferation through its effect on the expression of a range of proto-oncogenes and microRNAs[91], such as TGF-beta, Wnt/beta-catenin, JAK/STAT,

PI3K, Ras-raf-MAPK along with inhibition of p53 and Fas-mediated apoptosis[92]. Additionally, HIV proteins (tat, gp120) may act on hepatic stellate cells (HSC) to induce inflammation and contribute to fibrosis[93]. Genomic integration of HBV is present in the majority of cases in which HBV-infection leads to HCC[94], and appears to be facilitated by DNA damage in the setting of chronic inflammation and oxidative stress. HBV integration is not sufficient for patients to develop HCC, and oncogenesis likely depends on either integration site mutagenesis (i.e. insertion near *MLL4*, *ANGPT1*, *PDGFRB* and *hTERT* genes have been reported in some HCC patients) or more generalized HBV-associated genomic instability. Secondary mutations in human genes are required in HCC, the most common being mutations in *TP53* (>30% of cases) and *CTTNB1* (20%)[95].

Hepatitis C Virus (HCV)

HCV is a single stranded RNA virus belonging to the *Flaviviridae* family. HCV co-infection rates among HIV-infected persons are estimated at 25–30%[96]. Individuals with HIV and HCV who develop HCC are often diagnosed with more advanced disease than those with HCV alone[97]. Unlike HBV, HCV is not able to integrate into the human genome. Chronic HCV infection promotes host responses that lead to inflammation, oxidative stress and associated DNA damage, steatosis and cirrhosis. These processes then contribute to the pathogenesis of HCC. The annual risk of developing HCC in HCV cirrhotic patients is around 1–7%[98]. Additionally, several HCV encoded proteins have a potential role in oncogenesis. The best studied is the HCV core protein, which is associated with induction of oxidative stress, modulation of p53, upregulation of TGF-beta, and activation of the Raf/MAPK pathway; these are but a few of the proposed mechanisms[92]. Additionally, an HCV encoded nonstructural protein; NS5A promotes cell survival through activation of PI3-kinase/akt [99] and stabilization of beta-catenin[100]. As with HBV-associated HCC, secondary mutations are required[95]. HCV infection is also associated with several forms of NHL, including marginal zone lymphoma, diffuse large B-cell lymphoma, and lymphoplasmacytic lymphoma[101].

Smoking

Tobacco smoke contains more than 60 known carcinogens, including polycystic hydrocarbons (PAHs) and nitrosamines[102], which cause DNA adducts. These in turn lead to mutations in *TP53*, *RAS* and other genes in lung cancer[103]. Tobacco-induced promoter hypermethylation is an early epigenetic event that is implicated in lung carcinogenesis[104]. In addition to being a carcinogen, tobacco smoke may have tumor promoter effects by triggering and maintaining chronic inflammation through modulation of inflammatory signaling[105,106]. For example, the nicotine-derived nitrosamine ketone (NKK) is implicated in IL-6 upregulation and lung cancer tumorigenesis through gp130 pathways[107]. Smoking is a modifiable risk factor for cancer. Patients at risk for HIV have relatively high rates of smoking compared to the general population, and over 70–85% of some HIV-infected populations smoke[108]. Smoking increases the risk of several important cancers affecting people with HIV, including lung, head and neck, esophageal, stomach, pancreatic, liver, anal and cervical cancers.

Lung cancer risk is increased by approximately 5-fold in people with HIV, and in most large studies, HIV remains an independent risk factor for lung cancer even after correcting for smoking[109]. Lung cancer is the most common NADM in the cART era, representing a leading cause of morbidity and mortality[110]. Aging of the HIV-infected population contributes to the increasing burden of lung cancer. However, the median age of diagnosis of lung cancer in HIV-infected people is 10–15 years younger than that in HIV uninfected patients[111]. Even when adjusted for the different age distributions of the underlying populations, age at diagnosis is 4 years younger in HIV-infected versus uninfected individuals[112]. Increasing evidence suggests chronic inflammation as well as immunosuppression play important roles in lung carcinogenesis, and these factors may be of particular mechanistic importance in people with HIV[106,113,114]. A large study in non-HIV patients showed that elevated serum levels of IL-8 and C-reactive protein (CRP) were associated with lung cancer, after adjustment for cigarette smoking[115]. The evidence regarding the degree of immunosuppression (based on $CD4^+$ T-cell counts) as a risk factor for lung cancer is controversial. Several studies showed that the degree and duration of immunodeficiency and low $CD4^+$ T-cell counts (< 200–500/mm^3) is associated with lung cancer risk[116,117], whereas others failed to come to the same conclusion when adjusted for smoking and age[108,118,119].

HIV-infected patients are at an approximately 2–4 fold increased risk of developing both HPV-associated and HPV-unassociated head and neck squamous cell carcinomas (HNSCC)[120] compared to the general population. Collectively, head and neck cancers are the fourth commonest NADMs. Like lung cancer, laryngeal cancer occurs at younger ages in people with HIV[112]. In addition to smoking, risk factors for the development of (HNSCC) include alcohol, older age, and in some cases HPV[72]. The role of HIV in the pathogenesis of HNSCC is not completely clear; however reduced $CD4^+$ T-cell count is an important risk factor suggesting that HIV-associated immunosuppression is a contributory factor, especially for those cases associated with HPV[9,72,108,121].

A modest but significant increased risk of esophageal (both adenocarcinoma and squamous) and stomach cancers has been noted in US patients with HIV, with the highest risk seen in upper esophageal squamous cell carcinoma[9,122]. Age is an important risk factor in this patient population. Additional studies are required to determine whether this elevated risk is independent of tobacco or alcohol or is related to any specific infectious agents such as *H. pylori*. Pancreatic cancer risk is also increased in the setting of HIV[9], and mortality appears substantially increased, even in the setting of HIV control and relatively preserved $CD4^+$ T-cell counts[123]. In addition to cigarette smoking, a well-established risk factor for pancreatic cancer in the general population is chronic inflammation (pancreatitis)[124]. Interestingly, HIV/AIDS has been associated with increased risk of pancreatitis. Major risk factors in this population include low $CD4^+$ T-cell count, opportunistic infections, specific medications, and female gender[125]. While some older antiretroviral nucleoside reverse transcriptase inhibitors, as well as pentamidine used for prophylaxis and treatment of *Pneumocystis* pneumonia, are also associated with pancreatitis, the risk of pancreatitis is substantially lower with current antiretroviral drugs[125,126]. A potential role of inflammation in pancreatic cancer in people with HIV requires further study.

Sun exposure

HIV-infected patients have an increased risk of developing non-melanoma skin cancer (NMSC) (approximately 2-fold higher than the general population; cumulative risk 6%), most commonly squamous cell and basal cell carcinomas[3]. Interestingly, risk is lower than that of immunosuppressed transplant patients (cumulative risk 30–70%)[127–129], and HIV-associated NMSC is not strongly associated with $CD4^+$ T-cell counts [129,130]. Major risk factors for both basal cell and squamous cell carcinoma of the skin in HIV-infected patients appear to be more similar to those in the HIV-negative counterpart, and include fair skin, aging, a positive family history, and cumulative sun exposure[129,131,132]. In the US, NMSC are most common in white/non-Hispanics, and recurrent NMSC is common[129,133]. Ultraviolet-B (UVB) radiation induced DNA damage, from which mutations arise, likely plays a central role. In general, HPV does not appear to have an etiologic role in non-anogenital SCC of the skin in HIV-infected patients, although HPV-association has been noted in some cases[132,134]. HIV patients are also at a higher risk of developing Merkel cell carcinoma, which is a virally-associated skin cancer caused by Merkel cell polyomavirus[135,136], and immunosuppression likely plays an etiologic role in this uncommon tumor[137].

HIV-infected patients also have an increased risk of developing melanoma, even after adjusting for ethnicity and race[14,127]. While immunodeficiency, immunosenescence and increased inflammation or increased medical surveillance possibly increase risk, behavioral factors associated with UVB induced DNA damage, such as use of tanning beds and excessive sun exposure likely are major contributors [138,139].

Cancer prevention interventions

Antiretroviral therapy

The introduction of cART in 1996, and its broad availability led to decreased infectious mortality, as well as a decrease in incidence and mortality from Kaposi sarcoma, systemic NHL and AIDS-related PCNSL[1,46,140]. In the US, it is estimated that KS incidence decreased by 84%, and non-Hodgkin lymphoma incidence decreased by 57%. To a large extent, $CD4^+$ T-cells are the best predictor of KS and NHL risk, especially for lymphoma histologies such as PCNSL, which are mostly closely associated with the degree of immunosuppression. Large cohort studies also show that cumulative HIV viremia is independently associated with increased risk and cART with a decreased risk for developing these ADMs[116,141,142], while time on cART appears to be protective[143].

Prevention of KS and NHL with cART has also been demonstrated in a randomized controlled trial. The Strategies for Management of Antiretroviral Therapy (SMART) study randomized patients with HIV and a $CD4^+$ T-cell count greater than 350 cells/mL to continuous cART or a $CD4^+$ T cell-guided ART, where cART was given when $CD4^+$ T-cell count was less than 250 cells/mL and stopped once over 350 cells/mL[144,145]. The ADM rate was significantly higher in the $CD4^+$ T-cell guided therapy (driven by lower $CD4^+$ T-cell counts and higher viral load). Other outcomes were also improved in the continuous therapy arm, and provided Level 1 evidence for using higher $CD4^+$ T-cell count thresholds for

initiating cART in HIV-infected patients. A subset analysis from the same study found that elevated interleukin-6 (IL-6) levels and other inflammatory biomarkers on the continuous cART arm were associated with increased risk of cancer[16].

While decreases in KS and NHL have been substantial, the incidences of these malignancies remain markedly increased compared to the general population. Estimates of the percent of HIV-infected patients with controlled HIV viremia on cART is generally less than 50%. Many HIV-infected patients are still not receiving cART either because they are not aware they have HIV or because they are not engaged in appropriate medical care. It is estimated that 18% of HIV-infected patients in the US are unaware of their diagnosis[146] Improved testing in high risk patient populations, as well as methods to increase adherence to prescribed cART, are required. Potential further prevention may be possible with implementation of programs designed to increase HIV diagnosis, improve linkage and retention in care, and increase adherence. (Figure 2) Furthermore, recent modification of treatment guidelines to include patients with higher $CD4^+$ T-cell counts should lead to a larger proportion of the HIV-infected population on cART. Prevention of KS and lymphoma through increasing availability of cART is particularly important in sub-Saharan Africa, where KSHV seroprevalance is increased in both men and women, there is a large burden of these ADM, and chemotherapy treatment options are more limited.

A preventive effect of cART was less readily apparent in the initial epidemiologic studies evaluating other types of cancers. Indeed in the cART era, the burden of many NADM increased[9,46,110], in part due to demographic changes in the underlying population such as decreased infectious mortality, aging of the HIV-infected population, and in the case of classical Hodgkin lymphoma, a very high incidence noted during the first year on cART[147]. Nonetheless, several lines of emerging evidence suggest a potential protective effect of long-term cART against a broader range of pre-malignant lesions and malignancies.

Importantly, cART and associated immune reconstitution decrease the risk of pre-malignant cervical and anal HPV-associated HSIL among HIV-infected individuals[148]. Indeed, well-controlled HIV viremia is associated with half of the risk of developing cervical or anal HSIL after adjusting for $CD4^+$ T-cell counts[149]. This effect may lead to decreased progression of some HSIL to invasive cancers.

With increased experience of large populations of patients on long-term cART, evidence supporting a role for cART in preventing cervical cancer and certain other NADM is growing. Importantly, large cohort studies consistently show an increased risk for both ADM and NADM in patients with low $CD4^+$ T-cell counts (<350–500 cells/mm^3)[116,117,141,150]. Therefore maintenance of T-cell immunity with cART could potentially play an important preventative role, especially when cART is initiated earlier in the natural history of infection. The effect of cART on cancer incidence is likely to be heterogeneous across cancer types. While some studies show no decreased risk of NADM as a whole for patients on cART[139,141,143], a few large studies have identified HIV viremia as an independent risk factor for cervical cancer and anal cancer[149,151,152], while others have found time on cART (or controlled HIV viremia) associated with decreased risk of certain non-virally associated NADM (largely lung cancer)[153], as well as classical Hodgkin

lymphoma[147] and anal cancer[152]. Differences between studies may depend in part on the definition of HIV viremia, with percent time with undetectable HIV a more sensitive measure of cART effect than single measurements of HIV viremia. Follow-up time also appears important, as decreasing incidence for certain cancers may become apparent only after 5 or more years[110,147].

Screening for HPV-associated malignancies

Cervical Cancer Screening—The incidence of cervical cancer in the United States has been reported at 8 cases per 100,000 women per year in the general population, and as high as 26 per 100,000 HIV-infected women[154]. HIV-infected women have an increased incidence of pre-malignant lesions, including low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL) and cancers[155]. In addition to that, women with HIV have higher recurrence rates of cervical HSIL following treatment[156]. Current guidelines note that HIV-infected women require more intense surveillance for cervical cancer than the general population.

Currently, the U.S. Preventive Services Task Force (USPSTF) recommends cervical cancer screening in the general population with periodic cervical cytopathology, or Pap testing, every 3 years for women ages 21 (or 1 year after start of sexual activity, whatever comes first) to 65, or every 5 years after testing negative for HPV screening[157]. Women who test positive for HIV should start the screening upon diagnosis. The recommended frequency of screening in HIV-infected women is every 6 months in the first year of diagnosis, and annually thereafter, provided cervical cytology tests are normal[158]. Abnormal findings should be followed up with colposcopy following standard guidelines that include visual inspection with acetic acid (VIA), and treatment of abnormal areas with cryotherapy, laser or conization using loop electrosurgical procedure (LEEP). Compared to women not on cART, women on cART have a decreased incidence of precancerous cervical lesions, increased regression of existing precancerous lesions, decreased recurrence, and increased clearance of oncogenic HPV[159,160]. Indeed, there is emerging evidence from a cohort of women with relatively preserved $CD4^+$ T-cell counts in the Women's Interagency HIV Study (WIHS) that HIV infected women with a baseline normal Pap test and negative oncogenic HPV-PCR have rates of subsequent HSIL or cervical cancer that are comparable to the general population[161]. Nonetheless, currently, the US Department of Health and Human Services (DHHS) Guidelines recommend yearly testing in women with HIV. The integrated use of HPV testing remains controversial, and should not be used in women with abnormal pap tests. Participation in cervical cancer screening programs is low in HIV infected patients with low educational level, depressive symptoms, substance abuse, younger age and smoking, and efforts to increase screening are required[162].

In order to decrease cervical cancer incidence in resource-limited settings that do not have established Pap testing programs, "screen and treat" approaches have been evaluated. These strategies utilize VIA or HPV testing to evaluate for the presence of premalignant conditions. When a positive VIA is found or detection of oncogenic HPV is noted, cryotherapy can be applied immediately, offering the opportunity to patients of being screened and treated in a single visit without the need for cytopathology services,

colposcopy or biopsy[163,164]. Both VIA and treat and HPV and treat have been shown to decrease incidence of HSIL at 12 months[165]. Additional implementation strategies that optimize resources include prioritizing screening of women aged 30–49 years and prioritizing the number of woman tested rather than intensive surveillance in smaller numbers of women[157].

Anal Cancer Screening—Anal cancer incidence in HIV-infected MSM is 46 per 100,000, substantially higher than that of the general population[166]. Women with HIV also have a higher incidence of anal HPV infection compared to HIV negative women[167]. Risk factors for anal HSIL and associated progression to anal cancer include high-risk HPV infection (most commonly serotype 16) and low CD4+ counts[139,168]. Based on cervical cancer screening models, routine periodic cytologic examination of anal mucosa with treatment of premalignant lesions is being evaluated in HIV-infected patients to potentially reduce the incidence of anal cancer[169]. Anal Pap testing demonstrating abnormal cytology is generally followed up with high-resolution anoscopy. While there is no standard therapy, treatment decisions are generally based on the location and grade of the lesion. Current options for HSIL include local treatment with topical immune modulators (e.g., imiquimod)[170], topical antiviral agents (e.g., cidofovir)[171] or ablative procedures using electrocautery, laser or infrared coagulation[172] or surgery. It should be noted, however, that while plausible, treatment of anal dysplasia has not been shown to prevent anal cancer, and current therapies are associated with local morbidity and a high incidence of recurrence. An NCI-funded Anal Cancer/HSIL Outcomes Research Study (ANCHOR) is currently enrolling patients with HIV to undergo anal Pap testing and then be randomized to either therapy (topical or ablative) versus observation to determine whether treatment of HSIL prevents anal cancer in HIV-infected patients and to inform the best practice for anal cancer prevention.

HPV Vaccine

Immunization with HPV virus-like particles composed of the L1 viral protein can induce neutralizing antibodies against HPV[173]. Antibody responses are directed against type-specific L1 particles of the specific types of HPV utilized in the vaccine, although there is some evidence of development of cross-type neutralizing antibodies[174]. Currently, there are three vaccines available, a bivalent HPV vaccine (HPV2, Cervarix™), a quadrivalent HPV vaccine (HPV4, Guardasil™) and a nonavalent HPV vaccine (HPV9, Gardasil 9)[175], which are prescribed as a series of three injections over 6 months. All protect against HPV 16 and 18. HPV4 also protects against HPV 6 and 11, which cause genital warts, while HPV9 protects against additional oncogenic strains 31, 33, 45, 52 and 58. Vaccines have almost a 100% prevention rate against HPV 16 and 18 infections in non-HIV infected patients and are effective in preventing anogenital diseases, including cervical HSIL[176]. The HPV4 vaccine has demonstrated efficacy in decreasing anal intraepithelial neoplasia (AIN) by 54.2% in HIV-uninfected MSM ages 16–26, supporting the potential importance of this approach in reducing the risk of anal canal cancer[177].

Females are recommended to be vaccinated with HPV2, HPV4 or HPV9 at age 11 or 12; and immunization may begin as early as nine years of age[178,179]. Males are recommended to

be vaccinated with HPV4 or HPV9 starting at the same age. For those not vaccinated earlier, it is recommended for females through age 26 and for males through age 21, although males can be vaccinated trough age 26. Immunization is thought to be most effective in patients never infected with HPV; hence the optimal time of vaccination is prior to sexual debut. For MSM, including HIV infected patients, the recommendation is to consider vaccination with HPV4 or HPV9 through 26 years of age if not previously vaccinated or for individuals who have not completed the 3-dose series[180]. At the current time, uptake of the HPV vaccine in the US is relatively poor. Vaccination coverage among adolescents ages 13 to 17 was 57.3% for girls and 34.6% for boys in 2013[181]. A role for HPV vaccine in older subjects is less well established. There is some evidence suggesting HPV4 may have efficacy in the prevention of recurrent anal HSIL in HIV-uninfected MSM older than 18[182].

HPV vaccines appear to have reasonably comparable immunogenicity in HIV-infected populations, including children with preserved T-cell function [183], HIV infected women[184] or men[185] on cART with $CD4^+$ T-cell counts >200 cells/mm^3, and a cohort of HIV infected women in Africa (98% with $CD4^+$ T-cell counts > 200 cells/mm^3)[186]. Immunogenicity appears slightly inferior in HIV viremic patients and those with $CD4^+$ T-cell counts less than 200 cells/mm^3 [187]. The Department of Health and Human Services (DHHS) guidelines support use of HPV vaccination in HIV-infected individuals ages 13–26.

Hepatocellular Carcinoma Prevention and Early Detection

Chronic HBV co-infection is more common in HIV-infected patients in the US, and perhaps more importantly, in some parts of sub-Saharan Africa. Furthermore, HIV infection increases the risk of chronic HBV infection[87,188]. HIV/HBV co-infection was associated with increased liver–related mortality in the pre-cART era compared to infection with either virus alone, especially in patients with decreased $CD4^+$ T-cell counts[88]. Universal HBV vaccination of infants is currently recommended by the World Health Organization (WHO), and implementation has been shown to reduce the risk of infection by more than 70%[189]. However, many adults have not received HBV vaccination. Therefore, HIV infected patients should be tested for HBsAg, along with antibodies to HBsAg (anti-HBsAg) and hepatitis B core antigen (anti-HBc) to distinguish between infection and immunity[190]. In HIV-infected patients lacking serological markers of immunity, vaccination is recommended. Not all HIV infected patients will develop a positive response to the HBV vaccine, and lack of antibody response to HBV vaccination correlates with low $CD4^+$ T-cell counts, HIV viremia, and HCV co-infection. Increasing the number of HBV injections can improve the response rate in HIV-infected persons, as well as increasing the dose from 20 mcg to 40 mcg per dose[191]. Patients with established co-infection should have HBV DNA viral load and liver function assessed. They should also be started on cART regimens that include agents active against HBV, including lamivudine, emtricitabine, and/or tenofovir, regardless of $CD4^+$ T-cell counts[192].

Additionally, approximately one third of HIV-infected patients are co-infected with HCV. Therefore, all HIV-positive persons should also be screened for HCV at time of HIV diagnosis and annually thereafter[192]. Sensitivity of HCV serology is suboptimal in HIV-infected patients, with 13% of seronegative patients having evidence of HCV upon RNA

testing. Therefore, HCV RNA testing is advised in HCV seronegative patients with a history of intravenous drug use, liver function test abnormalities, and/or thrombocytopenia[193]. Re-infection rates after successful treatment are also high and continuous screening is advisable in some patient populations[194]. HCV-induced cirrhosis is a well-established risk factor for HCC development, including in the setting of HIV[195]. In studies performed in the pre-cART era, co-infection of HIV and HCV increased the risk of liver fibrosis and cirrhosis[196], while cART decreased progression to cirrhosis in HIV/HCV co-infected patients[197]. Decreased $CD4^+$ T-cell count (< 200–500 cells/mm^3) has been associated with risk for HCC in several small studies[198,199], and confirmed in a large retrospective study involving 8,563 veterans co-infected with HIV and HCV. The risk of HCC in co-infected patients was increased compared to patients infected with HCV only. A low $CD4^+$ T-cell count (<200 cells/mm^3) and having cirrhosis were also significantly associated with an increased HCC risk[200]. These studies raise the hypothesis that the use of cART with consequent increase in $CD4^+$ T-cell count and decrease in cirrhosis may be beneficial in preventing HCC. Cumulative HIV viremia has recently been associated with HCC, but this effect was no longer significant after correcting for cirrhosis [152], suggesting cART is most beneficial before cirrhosis develops.

In HIV-infected patients with detectable HCV RNA, HCV therapy decreases liver-related events[197] and is generally indicated. Until recently, HCV treatment with pegylated interferon-alfa and ribavirin has been the standard therapy for co-infected patients[201]. However, new interferon-free regimens employing direct-acting anti-HCV agents have been shown to be highly effective and less toxic than interferon-based regimens, and initial studies of HCV suggest they may be safe and effective in patients with HIV[202]. Treating clinicians should be aware of the rapidly changing armamentarium of FDA approved drugs for treatment of HCV.

Despite concerns for potential lead and length time bias, as well as marginal cost-effectiveness; surveillance for HCC in high-risk patients is still recommended by some professional organizations and is widely applied[203], with the goal of early detection and treatment of small HCC tumors. For HBV carriers, the risk of HCC is not always associated with the development of cirrhosis, whereas the same does not hold true for HCV. Currently surveillance is recommended in cirrhotic HBV carriers, Asian HBV carriers (men over age 40 and women over age 50), HBV carriers with a family history of HCC and HCV, and cirrhotic patients[203]. It is reasonable to enter patients with HIV and either HBV and/or HCV into HCC surveillance programs if they meet these criteria for high risk. Periodic (6 monthly) liver ultrasound is usually employed to evaluate for nodules. Abnormal findings should be further evaluated by a 4-phase multi-detector computed tomography or a dynamic contrast enhanced magnetic resonance imaging. Specific findings on imaging are highly suggestive of HCC, and equivocal cases require a liver biopsy[203].

Smoking cessation interventions

Integration of smoking cessation intervention into the care of patients with HIV is extraordinarily important, as HIV-infected smokers on effective cART lose more life-years to smoking than to HIV complications[204]. Smoking cessation interventions are likely to

decrease the risk of most of the major NADM and have additional health benefits. The most important intervention to increase smoking cessation rates is the assessment and discussion of the topic between patients and health care providers[205]. Smoking cessation programs tailored to HIV infected patients have also proven to be effective in achieving this goal[206,207]. Patients with HIV often face significant barriers to cessation that must be recognized and addressed in order to improve the chances of successful abstinence. Such factors include low socioeconomic status, poor access to care and lack of social support, psychiatric disorders, substance and alcohol abuse and low autonomous motivation[208]. Patients and physicians may find themselves busier dealing with managing HIV/AIDS infectious and associated complications than focusing on smoking cessation and other forms of preventive care[209]. Motivational interviewing techniques with or without nicotine replacement support significantly reduce smoking rates[210]. Interventions that include multiple strategies through a longer period of time and that are specifically tailored to this patient population will likely yield a higher rate of smoking cessation[211]. For example cell-phone interviews with counseling and assessment of smoking status[212] have been proposed. Varenicline tartrate, a medication indicated as an aid to smoking cessation treatment was evaluated in a HIV-infected cohort of patients on cART. Most frequently reported adverse events (AEs) were nausea (33%), abnormal dreams (31%), affect lability (19%) and insomnia (19%)[213].

Although no grade 3 or 4 AEs were reported, the high frequency of side effects reported might preclude routine use of this medication in HIV patients.

Lung Cancer Screening

The National Lung Cancer Screening Trial showed that low-dose computerized tomography (CT) compared to chest X-ray for early lung cancer detection in patients aged 55–74 with 30+ year smoking histories increased the diagnosis of earlier staged tumors, and improved overall survival[214,215]. However, the low-dose CT is associated with a high rate of false positive findings, especially in patients with $CD4^+$ T-cell counts less than 200 cells/mm^3 who may have other pulmonary disease[216], and the specificity of lung cancer screening using low-dose CT in such patients may pose additional challenges. In a prospective lung screening study of 224 HIV-infected patients with a median age of 48 years, median 34 pack-year history, and median $CD4^+$ T-cell count of 400 cells/mm^3 (range 217–568), only one lung cancer was found on incident screening with annual low-dose CT for up to 4 years[217]. Possible explanations for the low rate of lung cancer diagnosis include the lower age of the cohort, selection bias of recruiting “healthier” HIV patients and higher $CD4^+$ T-cell counts. At the present time there is no solid evidence to back up the use of annual low-dose CT chest screening specifically in patients infected with HIV, although consideration of screening for patients over 55 years of age with a 30+ pack-year smoking history is reasonable, extrapolating from the HIV-uninfected population[215]. For lung cancer screening in HIV-infected populations, definition of appropriate characteristics of patients to include in screening, test characteristics and cost-effectiveness all require further evaluation[218].

Skin cancer prevention

The risk for developing most skin cancers appears to be related largely to exposure to ultraviolet (UV) light and patient-specific characteristics (age, ethnicity and skin type). It is therefore reasonable to counsel HIV-infected patients on UV avoidance (excessive sun exposure, avoiding tanning beds) and the use of sunscreen, although these interventions have not been formally studied in HIV-infected populations. Due to the higher recurrence rates of SCC in one study, it may be also advisable to develop a close monitoring schedule after resection of NMSC in HIV-infected patients[133].

Aspirin

In persons not infected with HIV, there is strong evidence that long-term (3 or more years) of low dose aspirin use reduces the incidence of cancer. Protective effects are best established for gastrointestinal cancers[219,220]. While aspirin has not been evaluated for cancer prevention in people with HIV, it has been studied in this population for modulation of cardiovascular risk. HIV patients have a higher risk of cardiovascular disease than the general population[221,222]. In addition to traditional cardiovascular risk factors, low CD4+ counts and increased inflammation are biomarkers of risk in people with HIV. Specific antiretrovirals may further modulate risk[223–227]. Interestingly, a pilot study in patients with HIV demonstrated that HIV infected subjects as compared to controls, have increased platelet activation. After treatment with aspirin, HIV patients exhibited decreased markers of T-cell and monocyte activation[228]. Given the effects of aspirin on immune activation, as well as the effect of aspirin in preventing some common cancers, further evaluation of the effect of aspirin in preventing cancer in this patient population is warranted. Aspirin use for the prevention of cardiovascular outcomes appears to be lower among many HIV-infected populations than that of the general population. There are currently no specific recommendations for aspirin prophylaxis in HIV-infected individuals. This said, given the high risk of cardiovascular events in this population; the evidence that aspirin can prevent certain types of cancer and the lack of recommendations to not use aspirin; it is reasonable to follow guidelines for the use of aspirin prevention of cardiovascular disease in the general population. Like smoking prevention, long-term low-dose aspirin use may have a more global benefit on health that may include cancer prevention.

Other cancer prevention for incidental cancers

HIV-infected patients are increasingly at risk for developing incidental cancers not associated with HIV infection. It is thus important that they also participate in generally recommended strategies to prevent and screen for cancers, including routine screening for colon cancer and breast cancer. There is emerging evidence that weight control and exercise may reduce the incidence of certain cancers, such as colon, breast, and pancreatic cancer, and this should also be encouraged. Clinicians should be alert for new developments in this area.

Future directions

Anti-inflammatory and immune modulatory approaches

Medical interventions that modulate inflammation may hold particular potential for preventing cancers in HIV-infected patients. Current and planned studies are evaluating strategies that may modulate immune activation in patients with HIV, using agents that may be of particular interest for cancer prevention in this patient population. One example is an ongoing double-blind randomized study of aspirin or placebo with a primary outcome to evaluate changes in sCD14, a marker of immune activation (clinicaltrials.gov NCT02155985). HMG-CoA reductase inhibitors (or statins) are also known to have anti-inflammatory and *in vitro* antineoplastic properties, such as promoting cell cycle arrest, inducing apoptosis and blocking c-Myc-induced lymphomagenesis, among others [229]. Mechanistic studies have shown that the addition of rosuvastatin to tenofovir/emtricitabine and efavirenz decreased the serum mean levels of C-reactive protein and tumor necrosis factor alpha (TNF-a) when compared to anti-retroviral drugs alone[20]. Interestingly, a case-control study that evaluated HIV-positive patients with and without NHL found that the use of statins was associated with a lower risk of AIDS-related NHL[230]. A large randomized prospective study in HIV-infected patients, but no cardiovascular indications for statins, is planned comparing pitavistatin combined with cART versus cART alone to primarily evaluate cardiovascular outcomes. However, this trial will also explore incident cancers and may provide additional insights for cancer prevention in HIV-infected patients. Additional immune modulatory agents may also have cancer preventative effects in specific populations [231].

Novel anti-viral approaches

The majority of HIV-associated tumors are caused by other viruses, and this may provide opportunities for developing of additional anti-viral preventive measures in the future. One potential approach would be to develop effective vaccines for EBV, KSHV, HCV, or Merkel cell polyomavirus. For example, a recombinant EBV gp350 vaccine has been developed. While it did not prevent EBV infection in a phase 2 trial, it was found to prevent the development of mononucleosis[232]. Studies evaluating the use of the anti-gp350 vaccine to modulate of the natural history of EBV lymphoproliferations and prevent EBV-associated tumors, especially Burkitt lymphoma, have been proposed. It is unclear whether vaccine development is economically feasible for KSHV or Merkel cell polyoma virus.

For KSHV-associated malignancies, other anti-viral approaches are attractive. One approach would involve decreasing the transmission of KSHV. KSHV prevalence varies widely among populations. The main route of transmission of KSHV is by saliva, in contrast to other herpesviruses[233]. Practices that are associated with KSHV transmission include pre-mastication of food given to infants in resource-poor countries, deep kissing, and use of saliva as a lubricant for anal intercourse. It is thus possible that public health measures might be developed to reduce KSHV transmission by these routes.

Additionally, several antiviral drugs are somewhat effective against KSHV replication. In one study performed in the pre-cART era, the administration of systemic ganciclovir for

AIDS-associated cytomegalovirus retinitis was found to reduce the incidence of KS[234]. While chronic ganciclovir is too toxic to be used for cancer prevention, other drugs with anti-KSHV effect may be developed that could be used as preventive therapy. Interestingly, nelfinavir, an HIV protease inhibitor, has recently been shown to inhibit replication of KSHV *in vitro*[235]. Furthermore, some HIV protease inhibitors may have anti-angiogenic or anti-tumor properties that may help prevent KS[236] and perhaps other tumors as well. While most epidemiologic studies have not demonstrated superiority of protease inhibitor (PI)-based cART over other regimens in preventing KS[237,238], a recent large Veteran's Affair cohort study did show that ritonavir-boosted PI-based cART could reduce the incidence of KS, even after correcting for cumulative HIV viremia and $CD4^+$ T-cell counts[167]. Differences in studies may be based on the time exposed to a PI-based regimen. Given the need for cART in patients with HIV, further evaluation of the effects of PI-based regimens on prevention of KS and perhaps other malignancies are important, and may inform future guidelines for "what to start" in some HIV infected populations at increased risk of developing cancer.

Conclusion

The initial decrease in ADM after cART was introduced led to an optimism that HIV-associated cancer would become much less of a clinical problem. In fact, the opposite has happened; cancer is now the leading cause of death among HIV-infected patients in a number of studies and it is vital that we consider means for effective prevention. Substantial progress has already been made on several fronts, such as decreased incidence of cancers occurring at low $CD4^+$ T-cell counts with rollout of cART and the development of an effective HPV vaccine and effective antiviral therapy for HBV and HCV. At the same time, many challenges persist, and further improvements in cancer prevention appear highly feasible. Therefore prevention of cancer in HIV-infected patients remains a critically important area for public health interventions and future research.

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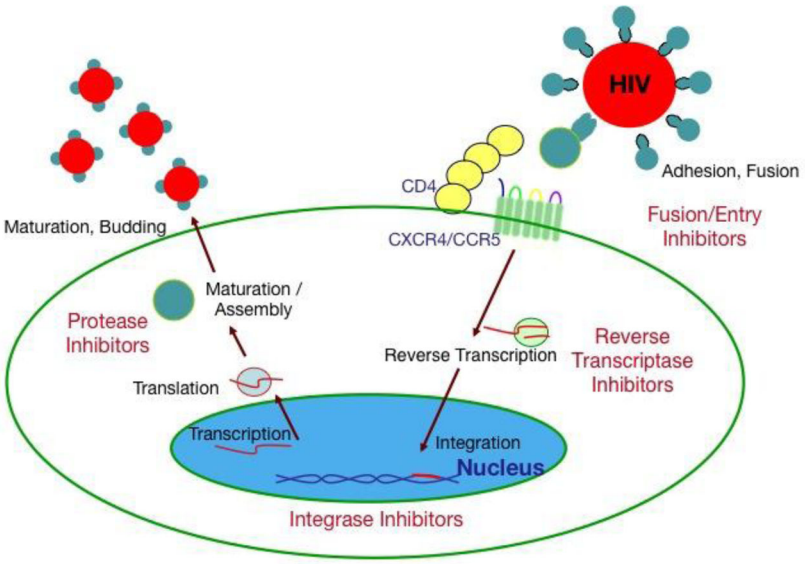

Figure 1. HIV lifecycle and steps targeted by antiretroviral therapy

Current agents target human immunodeficiency virus (HIV) cell surface interactions that inhibit HIV – entry, or target HIV-encoded enzymes that are required for reverse transcription, integration, or protease activity. CD4- cluster of differentiation 4; CXCR4- chemokine receptor type 4; chemokine receptor type 5

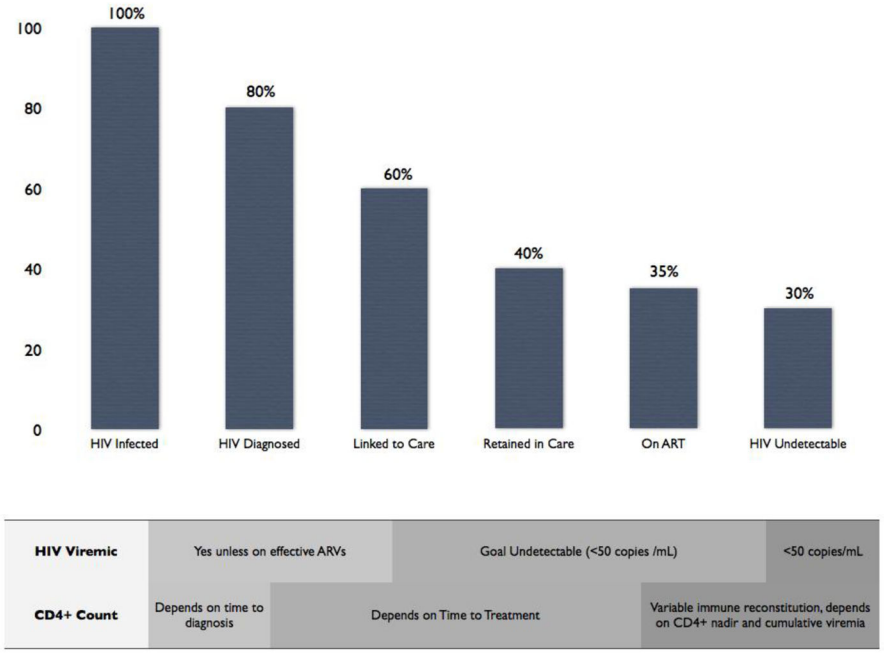

Figure 2. Gaps in implementation of combination antiretroviral therapy

Populations infected with HIV are heterogeneous in terms of time with uncontrolled HIV viremia, extent of immune depletion, and time on antiretroviral therapy (cART). Globally, percent of HIV-infected patients on cART varies between countries and is increasing over time. Presented data is based on 2011 United States estimates. Further cancer prevention through increased cART coverage is likely achievable. Considerations regarding effects of timing of initiation of cART on cancer risk factors are noted.

Table 1

Common Malignancies in People with HIV in the cART Era

Malignancy	Standard Incidence Ratio* (HIV only / AIDS)	Incidence in HIV (per 100,000 person-years)	Estimated % of all cancers† 2004–2007 in HIV/AIDS in US	Viral Associations	Smoking Association
AIDS-Defining Malignancies					
Non-Hodgkin lymphoma					
Systemic	10–15 / 30–60	>153¥	25.9%	EBV, KSHV	−
Primary CNS lymphoma	250 / 1,020	27	3%	EBV	−
Kaposi sarcoma	1,300 / 3,640	110	18.5%	KSHV	Inverse relation
Cervical cancer	2.9 / 5.3	47	2.4%	HPV	+
Non-AIDS Defining Malignancies					
Lung cancer	2.6 / 2.6	78	10%	−	+
Anal cancer	9.2 / 20	59	5.7%	HPV	+
Classic Hodgkin lymphoma	5.6 / 14	33	4.4%	EBV	−
Oropharyngeal carcinoma	1.7 / 2.1	22	2.5%	HPV	+
Hepatocellular carcinoma	2.7 / 3.3	32	2.3%	HBV, HCV	+
Non-melanomatous skin cancer					
Basal cell	1.8/2.5	1197	−		−
Squamous cell	1.6/4.2	405	−	? HPV (not established)	+

*Standard incidence ratio of patients in cohorts with 1) HIV but not AIDS and 2) AIDS compared to the general United States population

†Excluding non-melanomatous skin cancers

¥153 Includes diffuse large B-cell lymphoma and Burkitt lymphoma, but not other rarer histologies

Table 2

United States Food and Drug Administration approved targeted antiretroviral agents for the control of HIV

Class	Mechanism of action	Mechanism of resistance*	Specific agents
Fusion/Entry Inhibitors	Synthetic peptide corresponding to a region of the HIV envelope protein, gp41. Inhibits gp41-mediated virus entry.	HIV mutations leading to amino acid substitutions in positions 36–38 in HIV gp41.	Enfuvirtide (T20)
	Imidazopyridine CCR5 ligand that alters conformation of extracellular loops (host targeted antiviral). Inhibits HIV binding and fusion to CCR5; active against CCR5-tropic HIV-1.	HIV cell entry through CXCR4 co-receptors. HIV gp120 V3 loop mutations leading to HIV binding to CCR5.	Maraviroc
Nucloside Reverse Transcriptase inhibitors (NRTIs)	Deoxynucleoside analogue, active metabolites are competitive substrate inhibitors, incorporation by HIV reverse transcriptase leads to chain termination.	HIV reverse transcriptase (RT) inhibitors' mutations that lead to discrimination against select triphosphate derivatives of NRTIs (i.e. M184V interferes with binding to lamivudine or emtricitibine triphosphate). Acquisition of thymidine analogue resistance mutations in RT that allow for excision of 3′ chain terminators (mechanism for zidovudine, stavudine, and tenofovir resistance).	dTTP competitors: • Stavudine • Zidovudine dCTP competitors: • Emtricitabine • Lamivudine dATP competitor: • Didanosine dGTP competitor: • Abacavir • Tenofovir
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Direct inhibitors of HIV reverse transcriptase through interaction with p66 subunit of HIV-1 reverse transcriptase.	Mutations in the NNRTI binding pocket (i.e. K103N) of HIV-1 reverse transcriptase that inhibit or modify interactions with NNRTIs.	• Efavirenz • Etravirine • Nevirapine • Rilpivirine
Integrase Strand Transfer Inhibitors (INSTIs)	Interfaces with HIV- Integrase catalytic core domain as well as divalent cationic co- factors (Mg^{2+} or Mn^{2+}), inhibiting the catalytic activity required for transfer of HIV cDNA.	Mutations in HIV-1 Integrase catalytic core domain (especially Q148H and N155H) that affect INSTI interactions. Q148H plus secondary HIV integrase mutations increase INSTI resistance.	• Dolutegravir • Elvitegravir • Raltegravir
Protease Inhibitors (PI)	Bind to Asp residues in the protease binding site, inhibiting the proteolytic cleavage of HIV polypeptides required for viral maturation and assembly. Darunavir also inhibits protease dimerization.	Mutations in the HIV protease that lead to a conformational change and lower affinity for PI in relation to other HIV polyprotein substrates. Most major mutations occur at the HIV protease catalytic site (i.e. V82F/I84V double mutation), although distal site mutations may also lead to resistance, notably L90M occurs at the PI dimerization interface.	Peptomimetics: • Atazanavir • Indinavir • Lopinavir • Ritonavir • Saquinavir Non-peptidic: • Darunavir • Fosamprenavir • Nelfinavir • Tipranavir

Specific mutations do not necessarily lead to cross-resistance for an entire class of antiretroviral agents, and are sometimes agent specific. Some anti-retroviral agents have been designed to address common mechanisms of resistance noted in the same class. Selection of effective antiviral therapy in patients with resistant HIV generally requires expert input from infectious disease physicians and pharmacologists.