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Review of Screening Guidelines for Non-AIDS-Defining Malignancies: Evolving Issues in the Era of Highly Active Antiretroviral Therapy

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Abstract

HIV-associated morbidity and mortality have declined dramatically in the era of HAART. Through direct and indirect benefits of HAART, people with HIV/AIDS are living longer, developing less AIDS-defining cancers and more cancers commonly seen in the seronegative population. Herein, we review cancer screening strategies for people living with HIV and compare and contrast them with those of the general population. The most noticeable differences occur in anal and cervical cancer screening. Although anal cancer is uncommon in the general population, it is more prevalent in men who have sex with men and people at high risk for human papillomavirus infection, especially those infected with HIV. To address this, we recommend that a digital rectal exam and a visual inspection be performed annually. In addition, an anal Pap test should be performed soon after the diagnosis of HIV infection, with follow-up testing every six months until two normal tests. Abnormal cytological results are then investigated with high-resolution anoscopy and biopsy of suspicious lesions. In screening for cervical cancer, a Pap test should be performed during the anogenital exam after initial HIV diagnosis, with a second Pap six months later, then annually if the results are normal. A colposcopy should follow an abnormal result. Human papillomavirus testing as a screening method for cervical cancer in women with HIV can also be efficacious. In lung cancer screening, preliminary data suggest that low-dose computerized tomography may play an important role, but further research is needed. Screening for breast and colon cancer should follow guidelines for the general population. Early screening for prostate cancer based on a diagnosis of HIV lacks clear benefit. **(AIDS Rev. 2012;14:3-16)**

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Key words

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Introduction

Among the most dramatic clinical observations during the early years of the AIDS epidemic was the propensity of HIV-infected people to develop cancers. AIDS-defining malignancies (ADM) include Kaposi's sarcoma (KS), intermediate and high-grade non-Hodgkin's lymphoma (NHL), primary central nervous system lymphoma, and invasive cervical cancer (ICC). Together KS, NHL and ICC made up 16% of AIDS-defining illnesses between 1992 and 1997[1]. These ADM have been associated with viral infections in addition to HIV, including human herpes virus type 8 (HHV-8) in KS[2], Epstein-Barr virus (EBV) in NHL[3], and oncogenic types of human papillomavirus (HPV) in cervical cancer[4]. Infections with these viruses are sufficient to promote neoplasia, but when coinfection with HIV occurs, their oncogenic potential is enhanced considerably[5].

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While HAART-associated immune reconstitution has contributed to a profound decline in AIDS-defining opportunistic infections and opportunistic malignancies, the reduced morbidity of HIV infection provides a longer latency period for development of non-ADM. In the pre-HAART era, non-ADM accounted for 1% of the deaths of HIV-infected patients. Currently, 13% of people with HIV die of non-ADM[6-8]. The ongoing HIV/AIDS Cancer Match Study compared the five years from 1991 to 1995 to the five years from 2001 to 2005, and found a threefold increase in the prevalence of non-ADM[9]. For people living with HIV in the HAART era, the increasing risk of dying from non-ADM can be attributed to evolving comorbidities, exposure to oncogenic viruses, substance abuse, and older age[10-13].

Herein, we will briefly discuss the epidemiology and risk factors of HIV-associated malignancies of the cervix, anus, breast, prostate, lung, and colon. Though immune reconstitution induced by HAART has helped to minimize morbidity and mortality from KS and NHL, its impact on ICC is less certain. Some studies have suggested reduced persistence and progression of cervical dysplasia[14], while others suggest HAART has no effect[15-17]. It is clear, however, that women with HIV remain at substantial risk of ICC even with HAART use[18]. With that in mind, we include it in our discussion of screening options for non-ADM.

Risk factors for malignancy

The multistage model of cancer etiology was introduced by Armitage and Doll in 1954[19]. It suggests that cancer is caused by discrete changes in a cell's genetic information. These "hits" are usually introduced by specific environmental factors rather than inherited genetic mutations, two common sources being cigarette smoke and radiation. Infectious agents can also supply hits by introducing their own genetic material into the cell[19].

The role of immunosuppression in contributing to non-ADM risk remains uncertain. In general, the risk of such cancers has not been independently associated with a low $CD4^+$ cell count[20], and it is unclear if HIV acts as a direct oncogenic agent. However, HIV may contribute to malignancy by other mechanisms. Impaired immune surveillance, dysregulation of cytokine pathways and growth factor production, chronic B-cell stimulation, and balance between cellular proliferation and differentiation may contribute to ADM and non-ADM to varying degrees[21].

Coinfection with viruses other than HIV plays a significant role in promoting malignancy in people infected with HIV. In the general population, infection with oncogenic viruses, including cytomegalovirus, EBV, hepatitis B virus (HBV), hepatitis C virus (HCV), and HPV, are important risk factors for malignancy. People with HIV may be more susceptible to successive hits due to a higher rate of infection with oncogenic viruses like HPV, especially HPV-16 and -18. In a representative study of HIV-negative women, the baseline HPV prevalence was 26%[22]; in contrast, among 634 HIV-infected women, the prevalence of HPV was 48%, of whom 94% were infected with carcinogenic HPV strains[23].

Anal HPV is highly prevalent in men who have sex with men (MSM). In one study, anal HPV DNA was identified in 93% of HIV-positive MSM and in 61% of HIV-negative MSM, with HPV-16 being the most common type[24].

The use of HAART itself continues to be investigated as a possible risk factor for malignancy. Though there have been some reports of association between some antiretroviral agents and the occurrence of cancer, a correlation has not been proven[25,26]. In an effort to minimize HAART-related adverse events, a number of studies have examined structured treatment interruptions. In the SMART study, patients were randomized to a viral suppression or a drug conservation group, with treatment interruption occurring at prespecified $CD4^+$ cell counts[27]. A higher rate of ADM and other deleterious clinical events were identified in the drug conservation cohort, while both groups had a substantial number of non-ADM[28]. Consequently, patients who now begin HAART are encouraged to continue such treatment without interruptions[29,30].

Multiple sexual partners, increased alcohol consumption, illicit drug use, cigarette smoking, and HBV and HCV coinfection also account for increasing rates of non-ADM in HIV-positive patients[31-34]. In one analysis, 70 of 71 HIV-infected lung cancer patients were active smokers with a long history of smoking[35]. Furthermore, the Swiss HIV Cohort Study (SHCS) found no lung cancers in HIV-infected patients who were nonsmokers[11].

Cancer screening strategies should be adjusted for the HIV-positive population to meet the increased risk they may have of developing certain malignancies. However, in order to be widely accepted, screening strategies in this population must comply with guidelines such as the World Health Organization's Principles and Practice of Screening for Disease[36] to show that the benefits of early diagnosis outweigh its inconveniences or deleterious effects.

Table 1. Cervical cancer screening guidelines

	HIV-negative women				HIV-positive women
Organization	**AAFP[44]**	**ACOG[45]**	**ACS[46]**	**USPSTF[47]**	**CDC[48]**
Pap testing	Pap test at least every 3 years for women who have ever had sex	Biennial Pap test (liquid or conventional) after the age of 21, or 3 years after onset of sexual activity (whichever comes last)	Annual Pap test 3 years after onset of vaginal intercourse; not later than age 21; every 2 years with liquid-based Pap test	Conventional Pap test at least every 3 years for all women within 3 years after onset of sexual activity or by age 21 years (whichever comes first)	Pap test at initial HIV diagnosis; Second test 6 months later
		If ≥ 30 years, Pap test every 3 years after 3 normal consecutive smears	If ≥ 30 years, Pap test every 2-3 years after 3 normal consecutive smears		If 2 initial tests are negative, testing should continue annually
		Discontinue at 65 years with 3 normal tests in a row and no positive test for the past 10 years	Discontinue at 70 years (if not high risk) with 3 normal tests in a row and no positive test for the past 10 years	Discontinue at age 65 years if not at high risk	
HPV testing	Insufficient evidence of new technologies and HPV testing	For women ≥ 30 years, HPV test combined with cytology no more than every 3 years	For women ≥ 30 years, HPV test combined with cytology no more than every 3 years	Insufficient evidence of new technologies and HPV testing	

AAFP: American Academy of Family Physicians; ACOG: American Congress of Obstetricians and Gynecologists; ACS: American Cancer Society; USPSTF: United States Preventive Services Task Force; CDC: Center for Disease Control; Pap: Papanicolaou; HPV: human papillomavirus.

Cervical cancer

In the early years of the AIDS epidemic, case reports included women who presented with advanced-stage cervical cancer and whose tumors were poorly responsive to conventional chemotherapy[37,38]. To highlight the increased risk of cervical cancer in this population, the Center for Disease Control (CDC), Atlanta, GA included ICC in the case definition of AIDS in 1993 and listed severe cervical dysplasia as an early symptomatic HIV condition[39].

Women with HIV have greater rates of ICC and cervical intraepithelial neoplasia (CIN) than the general population[40]. A meta-analysis by Grulich, et al.[5] calculated an ICC surveillance incidence ratio (SIR) of 5.82, while the SHCS reported SIR of 8.0 (95% CI: 2.9-17.4)[11]. The higher incidence of ICC in HIV-positive women is linked to more prevalent infection of the high-risk types of HPV than the general population[23]. Though the role of immunosuppression in relation to ICC and CIN is unclear, there is a correlation between $CD4^+$ cell counts and HPV infection[14,15]. Women with $CD4^+$ counts < 200 cells/μl, and especially those with $CD4^+$ counts < 100 cells/μl, are more commonly infected with high-risk HPV[40]. The incidence of ICC in the HAART era is similar to the pre-HAART era[41-43].

Since the introduction of the cervical Pap test in 1941, the mortality of cervical cancer has been reduced substantially. Though there is a debate about the proper age to start and end Pap testing, medical organizations agree upon the efficacy of the test. The American Academy of Family Physicians (AAFP)[44], American Congress of Obstetricians and Gynecologists (ACOG)[45], American Cancer Society (ACS)[46] and United States Preventative Services Task Force (USPSTF)[47] all have published guidelines on cervical cancer screening in the general population. They are summarized in table 1.

Screening protocols are modified to address the heightened concern of ICC in women with HIV. The CDC recommends women should undergo a liquid-based or conventional Pap test after their initial diagnosis with HIV, with a follow-up test six months later[48] (Table 1). The initial twice-per-year tests for women with HIV are especially important as CIN is common, can develop rapidly[49-51], and high-grade lesions may go undetected with a single Pap test[52]. After two normal results, further

tests should be administered annually[48]. Key guidelines support this protocol[53-56], which has been shown to be cost-effective in the USA compared to other protocols[57].

The HIV Epidemiology Research Study (HERS) followed 189 HIV-infected women over six years. Because cytology and colposcopy findings in this cohort rarely diverged, the investigators concluded that routine colposcopy was not necessary[58]. However, some studies suggest that annual or biannual cytology alone is insufficient. Among 248 HIV-infected women, 38% of all CIN would have been missed without routine colposcopy and biopsy[52]. Whether cytology alone or cytology combined with colposcopy and biopsy are more effective screening strategies needs further study. However, HIV-positive women with atypical squamous cells with possible high-grade or low-grade squamous intraepithelial lesions, squamous cell carcinoma, or atypical squamous cells of undetermined significance should undergo colposcopy and directed biopsy[59,60].

The role of HPV DNA testing for cervical cancer screening in women with HIV remains uncertain. Some studies have suggested that it has low specificity and poor predictive value[61,62]. However, in a recent South African trial that included 6,553 women between the ages of 35-65 years (of whom 956 [14.5%] were infected with HIV), participants were divided into one of two screen-and-treat groups or a control group[63]. The screening methods used for the screen-and-treat groups were HPV DNA testing (HPV-and-treat) or visual inspection with acetic acids (VIA-and-treat). Dysplastic lesions were treated with cryotherapy. In the control group, inspection and treatment were delayed six months. All women underwent colposcopy and biopsy at month 6 and, in a subset of women, at month 12, 24, and 36. The study endpoint was CIN grade 2 or higher. At 36 months, HIV-positive women had higher detected rates of CIN 2+ (14.9%) than HIV-negative women (4.6%) ($p = 0.0006$). In the HPV-and-treat group, there was a significant reduction in CIN 2+ in both HIV-positive women (RR: 0.20; 95% CI: 0.06-0.69) and HIV-negative women (RR: 0.31; 95% CI: 0.20-0.50). In the VIA-and-treat group, the reduction in CIN was less apparent. The authors concluded that the VIA test's low sensitivity was the cause for its relative failure compared to HPV testing. For every 100 women screened, HPV-and-treat could prevent 11.9 cases of CIN 2+ in HIV-positive and 3.1 cases in HIV-negative women. The VIA-and-treat would only prevent 7.4 CIN 2+ cases in HIV-positive and 1.1 cases in HIV-negative women.

Though these results are promising, further research is needed. Finding a way to distinguish the many transitory HPV infections from long-duration, cancer-causing infections would accelerate the acceptance of HPV testing as a screening tool regardless of HIV status[64].

Anal cancer

Squamous cell carcinoma of the anus (SCCA) is rare in the general population, making up only 4% of gastrointestinal malignancies. Although more women are diagnosed with SCCA than men, over the past 35 years the incidence of SCCA has increased significantly in both men and women[65]. HIV-negative and HIV-positive MSM are 20 and 40 times, respectively, more likely to be diagnosed with SCCA than the general population[66]. In HIV-seropositive women, the incidence of SCCA is 7-28 times that of the general population[37]. In a study that spanned 11 years, the incidence of non-ADM in 54,780 people with HIV was compared to the general population. The SIR for anal cancer was 78 in people infected with HIV[67]. Another study found that high-grade anal cytological abnormalities are present in 30-60% of people with HIV[68].

Like cervical cancer, SCCA is strongly associated with high-risk types of HPV, most notably 16 and 18[69]. Though anal HPV is highly prevalent in MSM, especially those infected with HIV[25], increased anal HPV infection and precursor lesions are also noted in HIV-infected people who do not practice anal sex[70].

The incidence of SCCA is increasing in the HAART era[71,72]. In the Multicenter AIDS Cohort Study (MACS), the incidence of SCCA in the HAART era was higher than in the pre-HAART era (incidence rate: 137 vs. 30 per 100,000 person years)[73]. Like high-grade cervical dysplasia, HAART use does not reliably lead to regression of high-grade precancerous anal lesions, nor does it appear to improve the clearance of anal HPV in people with HIV[74]. Recently, however, new preventative measures have been approved for the general population, which could reduce HPV infection in people with HIV.

In December 2010, the U.S. Food and Drug Administration (FDA) approved the use of the HPV vaccine Gardasil® for the prevention of anal cancer. The vaccine inoculates against HPV types 6, 11, 16, and 18, but it does not prevent development of anal precancerous lesions from HPV types already present at the time of vaccination. Thus, the vaccine has been recommended for use in both males and females between the ages of nine and 26 years, with a goal to immunize against oncogenic HPV strains before infection through sexual contact[75].

The FDA approval of Gardasil® is based on a randomized, controlled trial of 4,065 male participants

Table 2. Cervical and anal cancer prevention tips

– Smoking is a known risk factor for cervical and anal cancer
– Having multiple sexual partners increases the risk of HPV infection
– Condoms can lower the risk of HPV infection and reinfection with new types, though they are not completely protective
– Because OCP may increase HPV infection, women with multiple partners should consider a different contraceptive method or the additional use of condoms
– Women should get regular Pap smears (every 6-12 months if HIV-positive, at least every 3 years if HIV-negative)
– At-risk individuals should ask their medical provider about anal Pap smears and obtain regular anal exams
– A follow-up colposcopy or anoscopy should follow an abnormal Pap test

HPV: human papillomavirus; Pap: Papanicolaou; OCP: oral contraceptive pills. *Adapted from Aboulafia DM*[175].

aged 16-26 years. In those with either positive or negative HPV status at baseline, the vaccine was 60% more effective than placebo in the prevention of external genital warts, and 66% more effective in preventing HPV-6, -11, -16, or -18-related lesions. In the subgroup that was HPV-negative at enrollment, the vaccine was 90% more effective than placebo among HPV-6, -11, -16, or -18-related lesions[76]. Though use in HIV-positive patients was not directly addressed, preliminary findings suggest that this is a preventive strategy whose benefits may well extend to this at-risk population[77].

Early detection of anal cancer may lead to better treatment outcomes, as prognosis depends heavily on the stage at diagnosis[65,78]. Nonetheless, the value of anal cancer screening remains unproven. A randomized trial to document the value of screening for anal cancer in at-risk populations has not yet been undertaken, as the duration, size, and costs of such a trial have, up until now, been daunting[79,80]. Coupled with the uncertainty over the predictive value of cytological findings[81,82], uniform guidelines have not been established. Despite the lack of data, the potential benefits of anal cancer screening can be extrapolated from highly successful cervical cancer screening protocols[79].

In 2007, the New York State Department of Health AIDS Institute (NYSAI) was the first to issue guidelines recommending annual anal cancer screening in HIV-infected people[83]. At baseline and as a part of the annual physical exam, healthcare providers are encouraged to ask about any symptoms in the anal region (itching, bleeding, diarrhea, or pain), and perform an inspection of the perianal region and a digital rectal exam. Anal Pap tests should also be performed in three HIV-infected subgroups: MSM, women with a history of abnormal cervical or vulvar histology, and men and women with a history of anogenital warts. If the anal Pap test is abnormal, including atypical squamous cells of undetermined significance, high-resolution anoscopy and biopsy are recommended[83]. However, the cost of such a screening protocol is substantial, in the order of $70,000 per quality-adjusted life year gained[84]. Less controversial is the low-cost message that healthcare providers can provide their patients to change anogenital cancer-promoting habits[85] (Table 2).

Breast cancer

Among females, breast cancer is the most common malignancy (except for non-melanoma skin cancers) and second most common cause of cancer-related death[86]. Though men do develop breast cancer, women are about 100-times more likely than their male counterparts[86]. Unlike cervical and anal cancer, breast cancer is not attributed to infection with an oncogenic virus. The main causes are not fully understood, but important risk factors include family history and hormonal factors[87-89].

The prevalence of breast cancer in women with HIV is unclear. A Tanzanian study of cancer registry data from 1969 to 1996 showed a significant decrease in observed breast cancer cases in both men and women after the AIDS epidemic began[90]. Similar findings were reported in an Italian cancer registry study[91]. Furthermore, among 25,914 chronically immunosuppressed, HIV-negative, solid organ transplant female patients who were monitored for 1-11 years, there were only 86 cases of breast cancer compared to 114 expected cases based on data from the general population[92]. These findings lend support to the hypothesis that immunosuppression is correlated with a reduced incidence of breast cancer. In contrast, a Nordic study of 5,629 renal transplant patients showed no difference in breast cancer incidence compared to the general

Table 3. Breast cancer screening guidelines

Organization	AAFP[101]	ACOG[102]	ACS[103]	USPSTF[104]
Mammography	Mammography every 2 years for women 5074 years. Screening before 50 decided by patient	Mammography every 1-2 years for women 4049 years; then annually	Mammography annually for women ≥ 40 years	Mammography every 2 years for women 5074 years. Screening before 50 decided by patient
Clinical breast exam	Insufficient evidence for CBE	CBE annually for all women ≥ 19 years	CBE every 3 years for women 20-39 years; annually for women ≥ 40 years	Insufficient evidence for CBE
MRI considerations	Insufficient evidence for the use of MRI or digital mammography instead of film mammography		Mammography and MRI annually for women with > 20% lifetime risk	Insufficient evidence for the use of MRI or digital mammography instead of film mammography
Breast self-exam	BSE should not be taught	Optional: BSE for all women	Optional: BSE for women ≥ 20 years	BSE should not be taught

AAFP: American Academy of Family Physicians; ACOG: American Congress of Obstetricians and Gynecologists; ACS: American Cancer Society; USPSTF: United States Preventive Services Task Force; BSE: breast self-exam; CBE: clinical breast exam; MRI: magnetic resonance imaging.

population[93]. Furthermore, when Frisch, et al. found an unexpectedly low relative risk (RR) of breast cancer after AIDS diagnosis in their study of 302,834 HIV-infected adults, they surmised that it was due to an increase in medical attention around the time of AIDS diagnosis, followed by a shift to palliative care[94]. Additionally, the high mortality rate of HIV in African countries may contribute to an apparent decrease in breast cancer incidence, as many women die from AIDS-related complications before they can be diagnosed with breast cancer[95]. Further studies are needed to determine the prevalence of breast cancer in HIV-infected individuals, and whether HIV itself can protect against breast cancer on a cellular level[96].

Initial case reports of breast cancer in HIV-infected women focused on early age of onset, unusual or poorly differentiated neoplasms, increased frequency of metastases, and poor survival outcome[97]. Contemporary case series involving patients with HIV and breast cancer show survival rates similar to HIV-negative controls[98,99]. With only 46 cases of breast cancer in women with HIV reported in the literature, further study of clinical outcomes is needed[95].

Mammography is the primary screening tool for breast cancer, and randomized clinical trials have shown a clear mortality benefit in women older than 50 years. A recent study has also shown a significant benefit to screening minority group women aged 40-49 years, specifically Hispanic women. Women in this subgroup are 60% more likely to be diagnosed with ductal cancer *in situ* and 80% more likely to be diagnosed with small invasive breast tumors than their Caucasian counterparts[100]. The recommendations for the use of mammography and other screening modalities vary amongst medical societies[101-104] (Table 3). Though mammography has traditionally been the standard in screening, as many as 20% of new breast cancers are not detected on mammogram[105]. This underscores the importance that all suspicious lumps are fully evaluated, even in the context of an unremarkable mammogram. Magnetic resonance imaging (MRI) may improve upon mammography's high false-positive rate and low sensitivity to invasive cancers, especially in women with dense breasts. In a study of 687 women at high risk for breast cancer, MRI had a sensitivity of 93%, while the sensitivity of ultrasound and digital mammography were only 37 and 33%, respectively. If women at high risk are to be screened starting around age 30 years, MRI should be utilized as it is more sensitive and prevents excessive radiation exposure[106].

Breast cancer screening in women with HIV appears to be underutilized. At the Johns Hopkins University Moore Clinic, only 56% of eligible HIV-infected women were referred for mammography[107]. In another study, 2,059 HIV-positive and 569 HIV-negative women from the Women's Interagency HIV Study (WIHS) were compared with women from the National Health Insurance Survey (NHIS). The NHIS was used to simulate a sampling of the general population in regard to use of mammography. For women 40 years or older, women in the WIHS reported less screening, regardless of HIV status, than in the NHIS[108].

Table 4. Prostate cancer screening guidelines

Organization	AUA[119]	ACS[120]	USPSTF[121]
When to begin screening	PSA test should be given to well-informed men ≥ 40 years with a life expectancy of >10 years. A DRE should accompany the PSA test	Men should have a discussion with their doctor about screening starting at 50 years for average risk, 45 years for high risk*, and 40 years for very high risk† men	Insufficient evidence for screening men under 75 years
Frequency of screening	Frequency of test should be discussed with doctor and be based on the patient's individual risk factors such as race and family history	For those who are tested: PSA < 2.5 ng/ml should consider retesting biennially. PSA > 2.5 ng/ml should undergo annual testing. DRE is also optional	
When to stop screening		Men with a < 10-year life expectancy should not be tested	Men over 75 years should not be screened

AUA: American Urological Association; ACS: American Cancer Society; USPSTF: United States Preventive Services Task Force; DRE: digital rectal exam; PSA: prostate-specific antigen.
*African Americans and men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65).
†Several first-degree relatives who had prostate cancer at earlier than 65 years.

We recommend that women with HIV should be screened for breast cancer starting at the same age and with the same frequency as HIV-negative women.

Prostate cancer

Prostate cancer is the most common malignancy in men in the USA, with a lifetime risk of diagnosis at 16.4%[109]. Though its causes are unclear, risk factors include family history with a possible inherited genetic mutation, androgenic hormones, and exposure to radiation and carcinogenic chemicals[110].

Like breast cancer, the relationship between prostate cancer incidence and HIV is unclear. Among 14,000 men with AIDS living in San Francisco between the years 1990 and 2001, the SIR of prostate cancer was 1.7 compared to the general population[111]. In addition, among 4,144 HIV-infected individuals who had access to U.S. military clinics between 1988 and 2003, the reported age-adjusted incidence rate of prostate cancer was nearly twice that found in the general population[20]. However , a meta-analysis using SIR from 18 studies of non-ADM in HIV-infected individuals found substantially lower rates of prostate cancer compared to the general population (SIR: 0.69; 95% CI: 0.55, 0.86)[8]. Other similarly designed, retrospective, population-based studies have shown comparably low risk[112].

Current data include only epidemiological studies that look at the incidence of prostate cancer in an HIV-positive cohort. This is dependent on detection, and thus on digital rectal exam (DRE) and prostate-specific antigen (PSA) screening. Similar to breast cancer, reports of lower incidence of prostate cancer in HIV-positive individuals may, in part, be due to decreased screening in this group[113,114].

The most common screening modalities for prostate cancer include DRE, measurement of serum PSA, and transrectal ultrasound of the prostate. The cancers detected by a PSA test, as opposed to physical exam or presentation of symptoms, are more often at an early stage of development. However, the survival benefit from early detection has not been clearly demonstrated[109,115]. Among 9,000 Swedish men, researchers found no significant mortality benefit for men screened for prostate cancer versus treatment after clinical diagnosis[116]. Alternatively, the European Randomized Study of Screening for Prostate Cancer showed a 20% reduction in the cancer-specific mortality for screened men aged 55-69 years[117]. Alarmingly, a recent study reports men in their 70s are nearly twice as likely to have had a PSA test as men in their 50s, demonstrating that the men most likely to benefit from PSA screening are typically screened at markedly lower rates than those most unlikely to benefit[118]. Complicating matters further, the American Urology Association[119], ACS[120], and USPTF[121] have differing opinions on how and when prostate cancer screening should occur (Table 4).

Whether men with HIV should undergo more screening seems unlikely based on current evidence. Two cross-sectional studies have examined the prostate cancer

screening outcomes in older HIV-positive men[122,123]. Both studies found abnormal PSA measurements in about 3% of subjects. Yet, among 600 men, only one case of prostate cancer was identified. As the benefit of early detection of prostate cancer in the general and HIV-infected populations remains unclear, HIV-infected men should have the same discussions with their doctors about screening as the general population.

Lung cancer

Lung cancer (both small cell and non-small cell) is the second most commonly diagnosed malignancy in the USA in men and women, and it is the leading cause of cancer-related death among both sexes. Approximately 222,500 people were diagnosed with lung cancer. Among those, 157,300 died due to lung cancer in 2010[124].

Lung cancer, like prostate cancer, is strongly associated with age. Roughly 66% of people diagnosed with the disease are older than 65 years and only 3% are younger than 45 years. Men are more likely to develop the disease than women (72 per 100,000 men vs. 54 per 100,000 women) and African American men are 40% more likely to develop lung cancer than Caucasian men[124].

Approximately 20% of Americans smoke, a behavior that is accountable for about 85-90% of lung cancers. Other risk factors include radon gas exposure, asbestos inhalation, air pollution (including second-hand cigarette smoke), and inherited genetic mutations[124].

The incidence of lung cancer in people with HIV is several times higher than in the general population[125-128]. Immunosuppression associated with HIV infection may play an important role. In a recent meta-analysis of seven studies of adults with HIV/AIDS in developed countries, spanning the years 1980 to 2002, 444,172 people with HIV/AIDS were identified, of whom 1,297 were diagnosed with lung cancer. The SIR for lung cancer in people with HIV/AIDS was 2.72 (95% CI: 1.91-3.87), which is comparable to the lung cancer SIR of 2.18 (95% CI: 1.85-2.57) in immunosuppressed organ transplant recipients[5].

Lung cancer risk in the HAART era appears to have remained relatively stable when compared to the pre-HAART era[94,129]. Among 20,277 HIV-infected patients in the Kaiser Permanente registry, 54 were diagnosed with lung cancer. Compared to the general population, the RR was 1.9 (95% CI: 1.42.5)[130]. Furthermore, when Engels, et al. examined trends in cancer risk among people with AIDS in the pre- and post-HAART eras, they found a RR of lung cancer between 1980-1989 of 2.5 (95% CI: 1.9-3.3), between 1990-1995 of 3.3 (95% CI: 2.9-3.8), and between 1996-2002 of 2.6 (95% CI: 2.1-3.1)[131].

Even when adjusted for smoking, people with HIV appear to be at a greater risk for lung cancer. In a study involving 2,086 HIV-infected patients, data were modified for smoking, sex, age, and calendar period[132]. HIV infection was still associated with an increased lung cancer risk (HR: 3.6; 95% CI: 1.6-7.9). Preexisting lung disease and smoking were the major risk factors for lung cancer. Illicit drug use was not associated with increased risk, nor was $CD4^+$ cell count or HIV viral load.

Patients with HIV and lung cancer tend to be 10-15 years younger and have more advanced disease at time of cancer diagnosis than their HIV-negative lung cancer counterparts[133]. Despite their younger age at lung cancer diagnosis, HIV-infected patients also tend to have a greater cumulative pack year history of smoking[35].

The benefits of screening and early detection of lung cancer remain unproven. Several studies have investigated the benefits of routine chest radiographs (CXR) and sputum cytology to detect lung cancer at an early stage, but they have not shown such efforts lead to a difference in mortality or reduction in late-stage cancers[134,135]. The ongoing Prostate, Lung, Colon, and Ovarian Cancer Screening Trial may more definitively determine if there is a mortality benefit with CXR screening[136].

Low-dose spiral computerized tomography (LDSCT) is also being investigated as a screening tool for lung cancer. The impetus for this derives from the findings of the Early Lung Cancer Action Project which demonstrated that CT scans had accuracy and sensitivity rates six-times higher than CXR at identifying very small tumors[137]. Recently, the National Lung Screening Trial recruited 53,454 participants from 33 sites across the USA to test whether three annual screenings with a LDSCT for five years could reduce overall and disease-specific mortality compared to CXR. Participants were between the ages of 55 and 74 years, were current or former smokers who had quit within 15 years of enrollment, and had a smoking history of at least 30 pack years. In October 2010, the data and safety monitoring board stopped the trial after preliminary findings showed a 20% reduction in lung cancer mortality and a 7% reduction in overall mortality[138] in the group receiving CT screening. Despite these promising findings, it is not clear how this will influence lung cancer screening programs. The costs of CT scans are not currently covered by insurance or Medicare, and each investigation may cost more than $300. Based on current data, $90,000 (300 individuals screened) would have to be spent to prevent one death[139]. Also uncertain

is the possible risk of repeated radiation exposure and unnecessary invasive procedures as a result of a false-positive test. Among patients who were screened with LDSCT, the false-positive rate was 25%[139].

Although the benefits of lung cancer screening require further study, it is clear that healthcare providers must continue to focus on smoking cessation as a primary mortality-reducing tool. Furthermore, HIV-positive smokers may benefit from smoking cessation interventions specifically tailored to their complex range of psychiatric, social, economic, and medical needs[140,141]. Further studies of factors or interventions that can lessen the risk of continued smoking are needed.

Colorectal cancer

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the USA. The causes of CRC are not clear, but risk factors include, age, family history, adenomatous polyps, and ingestion or inhalation of carcinogenic materials, including cigarette smoke[142].

Some authors suggest a relationship between chronic HIV infection and colonic adenocarcinoma[143]. However, there is a scarcity of data regarding the prevalence of CRC in the HIV-infected population, and the data that have been published lack a clear trend. An Australian study of 8,108 HIV-infected individuals and an Italian registry study of 12,104 people living with HIV reported colon cancer SIR of 0.33 and 0.95, respectively[144,145]. Alternatively, some studies suggest that the CRC incidence is increasing in the HIV-infected population[143,146,147]. A prospective study of 2,882 patients with HIV found an incidence of 0.65 per 1,000 patient years in the pre-HAART era, which increased to 2.34 per 1,000 patient years in the HAART era[147]. Furthermore, a study of screening colonoscopy in 136 asymptomatic HIV-infected patients aged older than 50 years found the prevalence of neoplastic lesions to be significantly higher than for control subjects[148]. Additional studies are needed to properly gauge the prevalence of CRC in HIV-positive individuals compared to the general population.

There have been relatively few case reports detailing HIV-associated CRC and, therefore, little information about the natural history of the disease in HIV-infected individuals[149-153]. The few case studies that have been published suggest CRC in the setting of HIV infection tends to occur at a younger age, with more advanced disease, and is associated with a poorer outcome[143,154,155]. In the general population, diagnosis of CRC at an age of less than 40 years is rare. Yet, in a recent case series, 11 of 17 (64%) HIV-infected patients with CRC were less than 40 years of age. These individuals had no predisposing conditions that would heighten their risk[156]. In this series, right-sided colonic neoplasms were more prevalent, even after adjustment for race, sex, and age. Similar to the general population, there was a predominance of grade 2 malignancies. However, 54% were stage 4 cancers, a sharp contrast to the 19% found in the general population[156]. Most patients in this study with stage 4 cancer died within 26 months of diagnosis. This is consistent with the 8%, five-year survival rate of stage 4 cancer in the general population[157].

Factors contributing to a more aggressive clinical course of CRC in the presence of HIV infection are unclear. HAART does not likely influence tumor grade or cancer stage, but the HIV virus itself may have an effect. *In vitro* HIV transactivator, or Tat protein, promotes colorectal cell growth in a way that is perhaps analogous to how it promotes the aggressive growth of KS[158]. Furthermore, the effects of smoking should not be underestimated, as the practice has been associated with increased CRC risk[159,160]. Since a far greater proportion of people with HIV are smokers, smoking cessation is a logical step in the prevention of CRC in HIV-infected patients.

Various professional societies are in agreement that screening for CRC in average-risk individuals begin at 50 years of age[142,161-163]. Colonoscopy remains a gold standard for screening because it allows for full visual examination of the entire colon, and simultaneously offers the opportunity for biopsy and removal of suspicious lesions or polyps[164]. However, there are alternative tests that are accepted by the professional societies. They are summarized in table 5.

The mortality benefit of screening for CRC is well established. The ACS, in association with the U.S. Multi-Society Task Force, estimates that colonoscopy has the potential to prevent about 65% of CRC events. For the area of the colon within its reach, sigmoidoscopy has the ability to reduce colorectal cancer mortality by 60-80%. Regular use of fecal occult blood tests (FOBT) reduces the risk for death from CRC by approximately 15-33%. Unfortunately, only 50% of the adult population aged over 50 years has ever undergone an endoscopy and only 10% reported having a FOBT within the proper time intervals. Screening prevalence is especially low among those who are nonwhite, lack health insurance, have few years of education, and are recent immigrants[165].

Screening for CRC appears to be even more underutilized in the HIV-infected population compared to the general population. While interviewing 114 HIV-positive and 91 HIV-negative patients, Iqbal, et al. noted

Table 5. Colorectal cancer screening guidelines

Organization	ACS[142]	ACG[161]	ACOG[162]	USPSTF[163]
When to begin screening	50 years	50 years (1B)	50 years	50 years
		45 years in African Americans	45 years in African Americans	
	High risk: 40 years, or 10 years before the age of the youngest diagnosis in immediate family	High risk: 40 years, or 10 years before the age of the youngest diagnosis in immediate family		
Preventative testing options (only one should be performed)	Colonoscopy every 10 years	Colonoscopy every 10 years	Colonoscopy every 10 years	Fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults
	Flexible sigmoidoscopy every 5 years*	Flexible sigmoidoscopy every 5-10 years	Flexible sigmoidoscopy every 5 years*	
	Double-contrast barium enema every 5 years*		Double-contrast barium enema every 5 years*	Insufficient evidence for computed tomographic colonography and fecal DNA testing
	CT colonography (virtual colonoscopy) every 5 years*	CT colonography every 5 years	CT colonography every 5 years*	
Cancer detection tests (only one should be performed)	Annual gFOBT†	Annual gFOBT	Annual gFOBT	
	Annual FIT†	Annual FIT	Annual FIT*	
	Stool DNA test (sDNA)† interval unspecified	Stool DNA testing every 3 years (2B)	Stool DNA test (sDNA)* interval unspecified	
When to stop screening				75 years

ACS: American Cancer Society; ACG: American College of Gastroenterology; ACOG: American Congress of Obstetricians and Gynecologists; USPSTF: United States Preventive Services Task gFOBT: guaiac fecal-occult blood test; FIT: fecal immunochemical test.
*If the test is positive, a colonoscopy should be done.
†The multiple stool take-home test should be used. One test done by the doctor in the office is not adequate for testing. A colonoscopy should be done if this test is positive.

that those with HIV were less likely to undergo testing (18 vs. 8%; p = 0.001). Only 41% of HIV-positive subjects were up to date on their screening, compared to 67% of HIV-negative subjects. The subjects with HIV who did undergo screening were most often given FOBT as the primary screening tool (36 vs. 16.4%; p = 0.0001). The HIV-positive patients who underwent colonoscopy were more likely to have visualized lesions than their non-HIV-infected counterparts (50 vs. 23.8%; p = 0.0281)[166]. Reinhold, et al. also looked at CRC screening among 538 HIV-infected patients, of whom 56% were older than 50 years old. Despite significantly more visits to their primary care provider, HIV-infected patients were less likely to have ever had even one CRC screening compared to the general population (55.6 vs. 77.8%; p < 0.001)[167].

Additional research is needed to determine if HIV-positive individuals should be screened differently than the general population. For example, because patients in this cohort were diagnosed with CRC at an earlier age, perhaps they would have benefitted from CRC screening at an age younger than 50 years. Since many of the carcinomas reported in HIV-infected patients involve the right colon, sigmoidoscopy may not be an adequate screening tool[156]. Until more information regarding the natural history and prevalence of CRC in the HIV-infected population is available, healthcare providers should utilize CRC screening in HIV-infected individuals with the same frequency and technique as the general population.

Future research considerations

Cancers of the liver, stomach, testes, and esophagus are not routinely screened for in the general population but may be overrepresented in the HIV-infected

population. The most prevalent of these malignancies is hepatocellular cancer, which accounts for as many as 25% of non-AIDS-related deaths in HIV-infected patients[168]. This can be attributed to a 30% prevalence of HCV in the HIV-infected population, and up to 75% prevalence of HCV in HIV-infected injection drug users[34]. In a recent surveillance study, the use of twice-yearly alpha-fetoprotein and twice-yearly hepatic ultrasound in those with elevated tumor markers of current or previous HCV infection showed a reduced mortality of 37% over five years when compared to no surveillance[169].

The risk for stomach cancer is 70% higher among those with AIDS compared to the general population, and their risk of esophageal cancer is 2.7-times that of the general population[170]. Likewise, testicular cancer risk may be as much as eight-times higher in HIV-infected men than in the general population[171]. More research is needed to determine if screening for these cancers would be cost-effective in the HIV-infected population.

Another area worthy of investigation pertains to cancer prevention. Although vitamin D deficiency is often identified in HIV-infected individuals, the link between low vitamin D levels and cancers is just emerging, and the role of vitamin D supplementation to ameliorate cancer risk is uncertain[172].

Finally, the role of Patient Navigators to educate at-risk groups on the importance of cancer screening and to provide accompaniment in long-term follow-up care may have great utility in disparate communities, including those with HIV-infection[173].

Conclusion

We have witnessed great advances in the treatment of HIV/AIDS in the HAART era. With proper adherence to antiretroviral treatment, HIV infection can be controlled and infected individuals can now anticipate a near normal life expectancy[174]. However, this newly extended life span has brought with it challenges and competing causes of mortality, including non-ADM.

The prevalence of ICC[40] in women and SCCA[37,66] in men and women is greater in the HIV-infected population than in the general population. Women with HIV should be screened with a cervical Pap test shortly after the time of HIV diagnosis, with another test six months later. If both of these tests are normal, annual screening should be performed[48]. The screening guidelines for anal cancer are less widely accepted, but the benefits can be extrapolated from the success of cervical cancer screening. We endorse the guidelines initially put forth by the NYSAI[83]. In addition to healthcare providers performing an inspection of the perianal region during routine physical exam, three subgroups of HIV-infected individuals should be screened using anal Pap tests. Those groups are MSM, women with a history of abnormal cervical or vulvar histology, and men and women with a history of anogenital warts.

When screening for CRC, some have suggested that HIV-infected individuals begin evaluations before 50 years of age[156]. We favor colonoscopy instead of sigmoidoscopy as the preferred screening test because the majority of colonic lesions involve the right side of the colon, out of reach of sigmoidoscopy[156].

Despite the higher prevalence of lung cancer in the HIV-infected population[132], the benefit of screening is unproven. Furthermore, it is unclear if people with HIV are at a higher risk for breast[9095] and prostate cancer[20,94,111,112] compared to the general population. We recommend screening HIV-infected patients for these cancers using the same guidelines as the general population.

Promising new screening and prevention techniques, including LDSCT[138] for lung cancer and HPV vaccination for cervical and anal cancer prevention, are now available for the general population[76], although their impact on the natural history of these malignancies and their potential utility in the setting of HIV infection remains to be seen. Until then, the priority of healthcare providers should be to stress the importance of the cessation of cancer promoting habits, especially smoking, and compliance with current cancer screening guidelines.

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