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Screening for Cancer in Persons Living with HIV Infection

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Abstract

Survival with human immunodeficiency virus (HIV) infection has greatly improved due to effective antiretroviral therapy (ART). As infectious complications have declined, malignancy now accounts for over one-third of deaths among people living with HIV (PLWH). Based on practices in the general population, cancer screening of PLWH can decrease both morbidity and mortality. In this article, we review and consider directed approaches for colorectal, breast, cervical and lung cancer screening. Furthermore, routine physical examinations may detect lymphomas and skin, anal and oral cancers. Comprehensive cancer prevention in PLWH should also include ART adherence, vaccination against oncogenic viruses, treatment of hepatitis viruses and smoking cessation. Cancer screening for PLWH warrants further research on safety and efficacy as well as targeted efforts to increase adherence.

Malignancies among people living with HIV

Human immunodeficiency virus (HIV) infection destroys CD4+ mononuclear cells, and can lead to severe immune deficiency and the acquired immunodeficiency syndrome (AIDS), including a high risk of the AIDS-defining malignancies – Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer. Some non-AIDS-defining cancers also occur excessively in *people living with HIV* (PLWH) relative to the general population, especially cancers related to smoking tobacco (e.g., lung cancer) and oncogenic virus co-infections (e.g., Hodgkin lymphoma [HL], anal cancer, and liver cancer). It is not clear whether the cancer risks result from immune dysfunction, higher oncogenic exposures, or both; regardless, these cancers are more common in PLWH and must be of concern to the physician.

PLWH are surviving longer through the increasing use and earlier initiation of well tolerated, effective antiretroviral therapy (ART). The median age of PLWH in the United

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ⁱhttp://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

ⁱⁱwww.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/

States (USA) today is above 50 years, placing them at growing risk of the age-related malignancies that are common in the general population. Several cohort studies of PLWH have reported that diagnoses of non-AIDS-defining cancers now outnumber AIDS-defining cancers.^{1,2} For the USA general population, consensus guidelines currently recommend screening for four cancers – cervix, colorectal, breast and lung.³ The survival benefits and adverse consequences of screening for these cancers have not been firmly established for PLWH, but benefits and risks may be assumed similar to those in the general population. Cancer screening can and should be part of routine clinical care for PLWH.⁴ While detailed regimens of HIV care are beyond the scope of this review, we advocate that PLWH regularly undergo careful, repeated physical examinations and testing for hepatitis B and C viruses (HBV, HCV) to facilitate primary or secondary cancer prevention. In addition, the following PLWH-specific factors are particularly relevant.

First, control of HIV replication with an effective and well tolerated ART regimen is the highest priority for managing an individual newly found to be HIV-infected. Thus, efficacy of a prescribed ART regimen should be determined by quantifying HIV viremia and CD4 count. ART toxicities and side effects should be assessed with clinical chemistry, hematology and a symptom checklist, in order to maximize adherence and (early) retention in care. Cancer screening should then be considered once a stable regimen has been established.

Second, while ART has reduced the epidemic rates and individual risks of KS and NHL, these cancers continue to occur at much higher rates in PLWH than in the general population.⁵ Continuing high rates of KS and NHL are mostly related to late presentation; unavailability, intolerance of, or poor adherence to ART; or residual immune perturbations. Thus, detection of KS or NHL in PLWH should signal re-evaluation for treatment failure.

Third, many PLWH come from ‘risk-taking’ population groups that have heightened risk of cancer due to certain sexual activities, sex partner selection, injection drug use, and cigarette smoking.^{6,7} PLWH include a high proportion of men who have sex with men (MSM) who may be exposed to oral or anal hr-HPV by sexual contact with numerous casual partners.^{8,9} In addition, the high prevalence of recreational drug use in PLWH may involve exposure to HBV/HCV-contaminated blood and needles or may include sex-for-drugs exchanges that broaden their exposure within a high-risk network. PLWH are also more likely to smoke and less likely to quit smoking than the general adult population.¹⁰ Therefore, excess cancers could occur even in PLWH who are immunocompetent, because tobacco carcinogens and oncogenic infections, particularly high-risk human papillomavirus (hrHPV) and HBV/HCV, can lead to cancer regardless of immune status.

Fourth, certain communities may have inadequate facilities and providers for safe and effective detection, diagnosis, and treatment of malignancies. As discussed below, this limitation is particularly problematic for cervical cancer, which is a major cause of morbidity and mortality for women in developing countries, and for anal cancer. Appropriate resources for definitive diagnosis and treatment must be assured prior to screening for cancer in any population.

The cancers of major importance for PLWH are summarized in the Key Table. While the screening approach outlined in the Key Table is generally applicable to clinically stable PLWH on effective ART, screening practices should be tailored to the individual patient's clinical and exposure history. Major open issues and screening approaches that are currently under consideration are highlighted in the Outstanding Questions Box.

Site-Specific Screening Approach

Malignancies associated with severe immune deficiency

Lymphomas—The incidence of AIDS-related non-Hodgkin lymphoma in the USA is diminished by ART, but in the early 2000s NHL was still nearly 7-fold higher in PLWH than in the general population.⁵ Moreover, it continues to be the most common malignancy in PLWH, arising largely from inadequate HIV treatment.¹¹ Hodgkin lymphoma also remains important because ART is relatively less potent in reducing AIDS-associated incidence of this malignancy.¹² Earlier diagnosis and treatment of these disorders would potentially improve patient outcomes. While there are no definitive hematologic or radiographic screening tests for lymphoma, physical examination and chest X-ray performed as part of routine care may detect lymphadenopathy that raises suspicion of malignancy. Because of the high risk of lymphoma, biopsy should be considered for a lymph node that is enlarged to at least 2 cm in diameter, persistent for at least one month, not readily explained by another condition, and especially if accompanied by systemic signs such as fever, weight loss, drenching night sweats, or elevated serum lactate dehydrogenase (LDH). Abdominal, pelvic, hepatic, splenic, or gastrointestinal lymphoma may be undetectable on physical exam and chest X-ray, but additional screening for those internal lesions is not warranted.

Kaposi sarcoma—KS is caused by infection with human herpesvirus 8 (HHV8, also known as KS-associated herpesvirus) and presents most often as red or violaceous lesions on the skin or in the oral cavity or conjunctivae. Because KS incidence is very high in PLWH,⁵ especially among sub-Saharan Africans and MSM, two populations with a high likelihood of HHV8 infection,¹³ the skin, mouth, and eyes should be carefully examined for potential lesions during routine clinical care. As with other AIDS-defining opportunistic diseases, appearance of a KS-suspicious lesion should trigger evaluation of ART failure. Biopsy for histopathologic confirmation of KS is advised if a suspicious lesion is progressing or disseminating, as KS-specific chemotherapy may be required in addition to effective ART.¹⁴ Testing for anti-HHV8 antibodies or viremia is not appropriate, as licensed assays for this infection have not been developed and clinical care would not be altered by knowledge of HHV8 status.

Cancers associated with oncogenic human papillomavirus co-infection

Several HPV vaccines are now widely used in many countries, which may be expected to greatly reduce the incidence of HPV-related cancers in years to come. However, many PLWH are beyond the currently recommended upper age for receiving HPV vaccine, generally 26 years.¹⁵ Thus, screening and treatment is still important for cervical cancer prevention for current PLWH and will remain the mainstay for the foreseeable future in populations with limited access to HPV vaccination.

Cervical Cancer—Invasive cervical cancer (ICC) is the fourth most common cancer in women worldwide,¹⁶ and many regions with the highest rates of ICC and ICC-related mortality also have the highest rates of HIV.¹⁷ The high risk of ICC in PLWH has important implications for screening practices. For example, a recent multi-cohort study of >13,000 women in the USA found that ICC risk increased with worsening immunosuppression, such that PLWH with CD4+ T-cell counts <200/ul had eight-fold greater ICC incidence than HIV-uninfected women in these same cohorts.¹⁸ Importantly, 94% of cases were in women who lacked a recent Pap test (cervical cytology), had an abnormal Pap but no follow-up colposcopy, or had evidence of pre-cancer but no treatment – all of which strongly indict inadequate screening and follow-up as a factor in these cases. Conversely, a cohort study of PLWH who had routine serial Pap testing and treatment reported very low ICC incidence, suggesting that proper surveillance and follow-up can reduce ICC morbidity and mortality in HIV-infected women.¹⁹ Indeed, recent data from the USA suggest a modest decrease in ICC incidence among HIV-infected women,²⁰ which likely reflects improving care and management.

U.S. Public Health Service (USPHS) guidelines on cervical cancer screening for HIV-infected women (available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf) have recently been updated to incorporate co-testing for hr-HPV as well as longer intervals between screening visits conditional on the test results.²¹⁻²⁴ As shown in Table 1, PLWH 30 years of age with a normal Pap result who co-test negative for hr-HPV should receive follow-up screening in three years. In contrast, if typing is conducted and HPV16 or HPV18 is detected, immediate colposcopy is warranted; women with other hr-HPV types but a normal Pap should be screened again in one year. Because HPV prevalence is very high and likely to clear spontaneously in young sexually active women, hr-HPV testing is not recommended in women <30 years of age. Regardless of age, a three-year screening interval is recommended for women who have had three consecutive normal Pap tests. While primary HPV screening (e.g., instead of Pap tests) was recently approved for use in the general population in the USA, this approach is not currently recommended for PLWH, nor is it recommended that PLWH discontinue cervical cancer screening after age 65, as in the general population. Despite negative results of HPV-cotesting, many HIV-infected women without clinically significant cervical disease are inappropriately referred to colposcopy, which is considered an unnecessary harm by USPHS standards. Thus, continued improvement in screening methods is warranted.

Resource Limited Settings—Cervical cancer risk is increased among populations with inadequate access to health services; as individuals diagnosed with HIV become engaged in appropriate care, integration of cervical cancer screening is a potential approach to reduce morbidity and mortality.²⁵ However, Pap-based screening is impractical in most resource-limited settings, because of high costs, the paucity of trained clinical and laboratory personnel, and the requirement for multiple clinical visits, sometimes with lengthy intervals awaiting laboratory results. Instead, the World Health Organization (WHO) recommends a “screen-and-treat” approach that allows for treatment soon (if not immediately) after screening with hr-HPV testing, followed by visual inspection after acetic acid application (VIA; available at <http://www.who.int/reproductivehealth/publications/cancers/>)

[screening_and_treatment_of_precancerous_lesions/en/](#)). If the HPV test is positive, VIA results are used to determine the extent of the lesions, the immediacy of treatment, and the optimal therapy (e.g., cryosurgery vs. Loop Electrosurgical Excision Procedure).²⁶ If HPV testing is unavailable, “screen-and-treat” can be based solely on VIA, although this approach is considered inferior to HPV screening. Women in the general population who have a normal VIA (or normal Pap) can be rescreened in 3-5 years, and those who are hr-HPV negative in 5 years. Although data in PLWH are limited, the main difference in recommendations for PLWH under the current WHO guidelines is that they should be rescreened 3 years following a negative hr-HPV test or normal VIA or Pap.

Anal Cancer—The incidence of anal cancer is elevated in PLWH relative to the general population,^{6,27,28} particularly in HIV-infected MSM (who account for 83% of all cases in PLWH).^{7,29-31} For several reasons, however, anal cancer screening is not currently routine even in HIV-infected MSM. Most importantly, it has not yet been established that treatment of high-grade anal intraepithelial neoplasia (hgAIN) reduces the risk of invasive anal cancer.³² To address this issue, a large multi-institutional randomized clinical trial, the ANCHOR (Anal Cancer/HSIL Outcomes Research) study, is currently enrolling 5000 PLWH with biopsy-confirmed hgAIN to compare treatment versus close observation for at least 5 years. Pending these results, a range of screening practices and treatment approaches have been adopted, with no uniform national or international recommendations for routine anal cancer screening.³³ Most proposed strategies follow a model similar to that used for ICC, namely, cytology and/or hr-HPV testing, followed by high resolution anoscopy with biopsy if indicated.³³ More than 70% of anal cancers in the general population are positive for HPV16,³⁴⁻³⁷ but anal cancers among PLWH contain a broader distribution of hrHPV types. Furthermore, even in the absence of lesions, more than two-thirds of HIV-infected MSM have anal hrHPV.³⁸ Thus, anal HPV screening will likely need to be combined with other methods, and cost effectiveness will need to be evaluated. Digital ano-rectal examination (DARE) is currently being studied as a screening approach, including self-screening.^{39,40} Farther on the horizon, serologic screening for HPV16 E6 antibodies might prove useful in some populations but has not yet been assessed in PLWH.⁴¹

It is widely agreed that anal cancer screening should not be done without the availability of referral for high resolution anoscopy, and subsequent treatment if indicated. Overall, our approach is to consider anal Pap testing or DARE only for HIV-infected MSM, assuming that the resources are in place to conduct high resolution anoscopy and follow-up treatment if indicated. We note that this type of care will not be available in most resource-limited areas, or even in many settings in developed countries.

Oral and Oropharyngeal Cancer—Squamous cell cancers at these sites have several commonalities, including three-fold higher incidence in PLWH compared to the general population, four-fold higher risk with older age (>50 years versus <40 years), and higher risks with tobacco use or lower CD4 count.^{6,7,42} However, differences between cancers of the oral cavity and cancers of the oropharynx are important, especially for prevention. HPV, especially HPV16, is a major contributor to cancer of the tonsil and other oropharyngeal sites, whereas this virus is seldom found in cancers of the oral cavity. Among PLWH, the

incidence of HPV-related cancer has been increasing, while the incidence of HPV-unrelated cancer has been decreasing.⁴² Detection of HPV16 E6 antibodies may be predictive of oropharyngeal cancer, but its utility in PLWH is unknown.⁴³ Oropharyngeal cancers are not readily detected by visual inspection, and detection of these by oral cytology has been disappointing.⁴⁴

Unlike cancers of the oropharynx, most cancers of the oral cavity are visible and therefore amenable to detection by inspection. To be protective, screening must detect and enable effective treatment of early cancers or truly precancerous lesions. Several “oral potentially malignant disorders” (OPMDs) have been recognized and associated with high risk of oral cancer.⁴⁵ These lesions include erythroplakia, leukoplakia (not to be confused with the Epstein-Barr virus-related oral hairy leukoplakia that occurs in immunocompromised PLWH), mixed red and white lesions, submucous fibrosis, and subtypes of lichen planus.^{46,47} Further, while expert opinion suggests screening for these lesions in the general population using standard visual and tactile exam (VTE)⁴⁴ followed by surgical biopsy, this approach is associated with potential morbidity.⁴⁸ Moreover, both a meta-analysis and a subsequent, large cohort study questioned the clinical utility of VTE and surgical biopsy^{49,50} Adjunctive visualization methods such as VELscope and Vizilite have shown good sensitivity but poor specificity.⁴⁹ While results with oral cytology in those with visible OPMD have been encouraging (e.g., to triage who requires biopsy), appropriate studies in the general clinic population are required, and there is a paucity of relevant data in HIV-infected individuals.

Based on sparse data, the prevalence of OPMD is probably low among PLWH in highly industrialized countries.^{51,52,53} There is insufficient evidence to recommend intensive screening approaches, particularly since randomized trials have not been conducted to assess the efficacy of surgery in preventing cancer morbidity or mortality in any population.⁵⁴ However, a community-based trial of oral examinations in India, where incidence is high in the general population, reported a 24% reduction in oral cancer mortality among tobacco and alcohol users.⁵⁵ In a study in US Medicare beneficiaries, oral cavity cancer was reported to be diagnosed at an earlier stage among people with, versus those without, a prior finding of leukoplakia.⁵⁶ Although the benefits and risks are uncertain, careful examination of the mouth with biopsy of suspicious lesions as part of routine HIV care may afford detection of cancer at a curable stage.

Cancer associated with chronic hepatitis virus co-infection

Liver cancer—Nearly all cases of liver cancer are hepatocellular carcinoma (HCC), which generally arises in cirrhosis that is the end result of chronic active infection with HBV or HCV.⁵⁷ The disease is highly lethal unless detected very early. Screening with liver ultrasonography for single, small HCC lesions has been endorsed by a panel of expert hepatologists,⁵⁸ but this approach is very controversial.^{58,59} The most recent Cochrane review identified only three randomized clinical trials that were all deemed to be at high risk of bias,⁶⁰ and the relevance of findings from HBV carriers in Asia to HCV carriers in the USA and other developed countries has been questioned.⁵⁹

Among PLWH, liver cancer risk is elevated more than 3-fold compared to the demographically adjusted general population.⁶¹ Thus, compared to the general population, the potential benefits of screening for liver cancer may be modestly higher for cirrhotic PLWH who have chronic HBV or HCV infection. However, there are no data on the sensitivity, specificity, positive/negative predictive values, or adverse consequences of screening for HCC in PLWH.⁶² HCC may be discovered in HBV/HCV co-infected PLWH during evaluation of cirrhosis,⁶³ but data are insufficient to justify screening for potentially treatable HCC. Instead, ascertainment of HBV and HCV status in all PLWH at initial presentation, followed by primary prevention through HBV vaccination and treatment of chronic HCV or HBV has low risk and high efficacy.

Other major cancers

Lung cancer—Lung cancer is the most important non-AIDS-defining cancer for PLWH. Due to its high incidence and high case-fatality rate, lung cancer accounts for about 30% of all cancer deaths and 10% of all non-HIV-associated deaths in PLWH.^{64,65} As in the general population, the disease is often locally advanced or disseminated at diagnosis. Even after adjustment for reported tobacco use, PLWH are estimated to have at least two-fold higher risk than the general population.⁶⁶⁻⁶⁸ Obviously, strong efforts to encourage smoking cessation are warranted.

With post-diagnosis survival similar in PLWH compared to the general population, early diagnosis and treatment may be beneficial. For the general population, based largely on results from the National Lung Screening Trial (NLST),⁶⁹ the United States Preventive Services Task Force (USPSTF) recommends annual low-dose computed tomography (LD-CT) for tobacco smokers ages 55-80 years with a history of at least 30 pack-years of smoking and who currently smoke or have quit within the past 15 years, provided they would be able to tolerate lung cancer surgery if indicated.⁷⁰ Whether these recommendations are appropriate for PLWH is unclear. A particular concern, which might argue against screening, is that false positive findings (e.g., due to calcified tuberculous- or fungal-related lung nodules) could in theory be more frequent in PLWH and lead to more unnecessary invasive procedures for definitive diagnosis, though there is a paucity of relevant data. Conversely, PLWH diagnosed with lung cancer tend to be younger and have lower pack-years of exposure, which would suggest that screening should be done with modified criteria.⁷¹ In a study of 442 French PLWH of median age 49.8 years who were screened with one LD-CT, there were no serious adverse events; lung cancer was found in 10 (2%), including 5 who were outside USPSTF guidelines but had early, resectable cancer.⁷² Clinicians should maintain a high index of suspicion for lung cancer in PLWH who have a history of cigarette smoking. Criteria for LD-CT screening should follow USPSTF guidelines for the general population, pending additional studies in younger and moderate-smoker PLWH to assess sensitivity, specificity, and complication rates from follow-up procedures.

Colorectal cancer—Colorectal cancer is the second leading cause of cancer death in the general population; and screening by colonoscopy or repeated fecal occult blood testing, with appropriate follow-up, markedly reduces mortality.⁷³ While colorectal cancer incidence

in PLWH is not elevated relative to the general population,⁵ aging PLWH are still at risk and require appropriate screening. However, two studies have reported that colorectal cancer screening rates in PLWH are 20% lower than in the general population.^{74,75} Increasing PLWH participation in colorectal cancer screening would be expected to improve their survival.

Breast cancer—As for colorectal cancer, the risk of female breast cancer for PLWH is similar to that observed in the general population.⁵ Compared to no screening, mammographic screening to detect early stage disease has been estimated to reduce breast cancer mortality by 15-35% and to reduce total mortality by 1%.⁷⁶ On the assumption that screening efficacy would match efficacy in the general population, biennial mammography to detect early breast cancer should be encouraged for female PLWH ages 50-74 years who are clinically stable.⁷⁷ As is true for women in general, a screening mammogram can be considered on a case-by-case basis for younger female PLWH deemed to be at exceptionally high risk by virtue of breast biopsy history or breast cancer in first-degree relatives. Unfortunately, survey data suggest that female PLWH have a substantial deficit in the use of screening mammography.⁷⁴

Prostate cancer—Potential screening modalities for prostate cancer include serologic testing for prostate specific antigen (PSA) and digital rectal examination, although these modalities either individually or combined have low sensitivity, specificity and positive predictive value. Prostate cancer is a common “incidental finding,” and there are no accepted tests or criteria to determine which asymptomatic cancers found by screening warrant aggressive treatment to avert future health problems. The value of screening in the general population is debated, with the relatively small survival benefit possibly outweighed by substantial morbidities associated with overdiagnosis and overtreatment of non-life-threatening cancers.^{78,79} Importantly, PLWH do not have increased prostate cancer incidence,⁵ but prostate cancers in PLWH do tend to present at more advanced stage and to be associated with 70% higher cancer-specific mortality.^{80,81} For PLWH who have extended life expectancy on ART, considerations for or against prostate cancer screening are the same as in the general population. American Cancer Society (ACS) guidelines support PSA screening for African American men and those with a strong family history of prostate cancer at a young age.

Melanoma and non-melanoma skin cancers—Skin examination during routine HIV care can detect not only KS but also malignant melanoma and non-melanoma skin cancers. The incidence of advanced-stage melanoma and melanoma-specific mortality are both approximately doubled in PLWH.^{80,81} Common basal and squamous cell skin cancers, as well as rare adnexal and skin appendage neoplasms, are increased nearly 3-fold, but few of these cancers are lethal.^{82,83} Particular attention should be paid to PLWH with fair complexion or history of excessive sun exposure, as these characteristics may be common in some AIDS-risk groups and are major risk factors for melanoma and other skin cancers. Suspicious skin lesions, especially those fitting the ABCDE mnemonic for suspicion of melanoma (Asymmetrical, Border irregular, Color irregular, Diameter >6mm, Enlarging)

should be excised, yielding diagnosis and potential cure. Pathologic confirmation of melanoma should trigger comprehensive clinical staging.

Concluding Remarks

In the 20 years since the introduction of ART, the burden of diseases, causes of death, and health priorities for PLWH have changed dramatically.⁸⁴ Non-AIDS malignancies have emerged as major causes of morbidity and mortality due to prolonged infection by oncogenic viruses, accumulating tobacco exposures, and population aging, although two AIDS-defining cancers, NHL and KS, remain the most common in PLWH. Accordingly, effective ART, vaccination against HPV and HBV, treatment of chronic HBV and HCV, and cessation of smoking are primary measures of cancer prevention. Screening and treatment of curable cancer represents potentially beneficial, secondary prevention. The Outstanding Questions Box highlights some of the pressing issues to address toward further reducing cancer morbidity and mortality in PLWH.

Screening programs in the general population are proven to reduce mortality from cervical cancer, colorectal cancer, breast cancer, and lung cancer. Participation in these programs may be expected to reduce cancer mortality for PLWH as well, but empirical data are needed. Quantification of screening sensitivity, specificity, and adverse event rates in so-called “bridging studies” of PLWH could energize implementation and verify favorable risk-benefit ratios for this population. Modified procedures to screen for cervical neoplasia in PLWH have already been recommended (Table 1), and modification of lung cancer screening (for younger ages and lighter smoking histories) may also be found appropriate.

A major concern is that PLWH, disproportionally poorly educated and socio-economically of low status, too often fail to get the cancer screening recommended for the general population or fail to have adequate follow-up of positive findings.^{85,86} This public health problem warrants the attention of national and community health services. Furthermore, in resource limited settings, cancer screening remains a challenging issue, not only in its implementation but also in the inability to respond to positive findings.

PLWH require clinical monitoring for ART drug toxicities and efficacy against HIV. We advocate routine physical examination by their clinical care providers, because it affords the possibility to detect KS and other skin malignancies, lymphomas, oral cancers, and anal cancer. While the efficacy of physical examination to detect cancer, as well as the adverse event rates from follow-up diagnostic procedures and treatment, are largely unknown, cancer rates and thus potential benefits are higher for PLWH than the general population. If physical examination is safe and even modestly effective for cancer screening, it could be rapidly applied to improving health care of PLWH, particularly in resource-limited settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

Acquired immune deficiency syndrome (AIDS)

Terminal stage of human immunodeficiency virus infection, manifesting as a life-threatening opportunistic infection or malignancy.

Anal Cancer/HSIL Outcomes Research study (ANCHOR)

A research study, sponsored by U.S. National Cancer Institute AIDS Malignancy Consortium, to evaluate whether detection and treatment of high-grade intraepithelial neoplasia in the anal canal effectively reduces anal cancer development with acceptably low side effects for PLWH. Results are expected in 2022.

Antiretroviral therapy (ART)

A combination of two or three licensed medications that block different stages of the human immunodeficiency virus lifecycle, allowing partial recovery of immunity but not eradication of the infection.

Bridging study

A supplemental research study designed to provide data allowing extrapolation of prior findings to a different population.

Hepatitis B virus (HBV)

A partially double-stranded DNA virus of humans that is highly infectious and primarily transmitted by direct contact with blood or other body fluids. HBV primarily targets and replicates in hepatocytes. Chronic HBV infection, manifest as persistence of HBV antigens and genome in the blood, ensues in approximately 90% of infected neonates and 10% of people infected as adults. HBV-related hepatic inflammation can progress to fibrosis, cirrhosis, and hepatocellular carcinoma.

Hepatitis C virus (HCV)

A single-stranded RNA virus of humans that is highly infectious but almost exclusively transmitted by direct contact with blood. Chronic HCV infection and hepatic inflammation persist in the majority of infected people, progressing slowly but unpredictably to fibrosis, cirrhosis, and hepatocellular carcinoma.

High-grade anal intraepithelial neoplasia (hg-AIN)

A potentially, but as yet unproven, pre-cancerous abnormality of the squamous epithelium of the anal canal.

Human herpesvirus 8 (HHV8)

A large double-stranded DNA virus of humans that is the primary cause of Kaposi sarcoma and that is also known as the Kaposi sarcoma-associated herpesvirus (KSHV). HHV8 is primarily transmitted by saliva, persists lifelong in lymphocytes, and seldom manifests as Kaposi sarcoma or another disease, except in people with AIDS or another deficiency in cell-mediated immunity.

Human immunodeficiency virus (HIV)

The human lentivirus that targets, replicates in, and progressively destroys T lymphocytes, resulting in profound deficiency in cell-mediated immunity that ultimately manifests as AIDS. HIV is primarily transmitted by sexual intercourse, blood injection or transfusion, during childbirth, or by breastfeeding. HIV's pathogenesis is greatly reduced by adherence to an effective ART regimen.

Hodgkin lymphoma (HL)

Malignancy of B lymphocytes with peak incidence rates at ages 15-35 and after age 55. Typically presents as one or more enlarged lymph nodes (especially cervical or supraclavicular) plus fevers, weight loss and night sweats. The disease often responds favorably to intensive, combination chemotherapy.

Human papilloma virus (HPV)

A small, highly diverse DNA virus usually transmitted by direct contact. Of the many HPV types that infect mucosae, four (HPV-16, -18, -31, and -45) cause nearly all cervical cancers. These are classified as high-risk HPV (hr-HPV). Licensed vaccines safely and effectively prevent nearly all hr-HPV infections.

High-grade squamous intraepithelial lesion (HSIL)

A pre-cancerous abnormality of the squamous epithelium of the cervix. HSIL can be detected by routine Pap testing (cervical cytology) and effectively treated by Loop Electrosurgical Excision Procedure or cryosurgery.

Invasive cervical cancer (ICC)

Malignancy of the epithelium of the cervix that is caused by long-term, persistent infection with high-risk HPV. Some individuals progress to pre-cancerous abnormalities (low-grade and high-grade squamous intraepithelial lesion) that may be detected by Pap testing (cervical cytology).

Kaposi sarcoma (KS)

A malignancy of mesenchymal (connective) tissue that probably originates in lymphatic endothelial cells. KS appears most often as red, purple, or darker patches or papules, especially on the skin but also on mucous membranes. KS is primarily caused by human herpesvirus 8 infection, and risk is greatly increased with HIV-, transplant-, or medication-induced deficiency of cell-mediated immunity.

Lactate dehydrogenase (LDH)

An enzyme in all cells that catalyzes the conversion of pyruvate to lactate and back again, contingent on availability of oxygen. Increased levels of LDH in serum occur with a range of conditions including myocardial infarction, hemolysis, and several malignancies including lymphomas.

Non-Hodgkin lymphoma (NHL)

A highly diverse group of approximately 80 malignancies of lymphocytes. Most NHLs associated with AIDS are diffuse large B-cell or Burkitt lymphomas. AIDS NHL is usually highly aggressive, often lethal, and frequently arises in the central nervous system and other extranodal sites. These tumors may respond to intensive, combination chemotherapy, although survival benefit is variable.

National Lung Screening Trial (NLST)

Clinical trial at 33 medical centers in the USA in which 53,454 current or recent heavy smokers, ages 55-74 years, were randomized to three annual examinations with low-dose computed tomography (LD-CT) versus conventional chest X-ray. As lung cancer was more often detected at a treatable stage, participants who were randomized to LD-CT had 20% lower mortality due to lung cancer and 8% lower mortality due to all causes.

Oral potentially malignant disorders (OPMD)

A group of potentially, but as yet unproven, pre-cancerous abnormalities of the oral mucosa including erythroplakia, leukoplakia, mixed red and white lesions, submucous fibrosis, and subtypes of lichen planus. Major risk factors are tobacco smoking, use of smokeless tobacco, and heavy alcohol consumption.

United States Preventive Services Task Force (USPSTF)

An independent panel of experts in primary care and prevention that systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services. The USPSTF is funded, staffed, and appointed by the U.S. Department of Health and Human Services.

Table 1
Recommendations for Cervical Cancer Screening for HIV-Infected Women*

HIV-Infected Women Aged <30 Years:

- If younger than age 21, known to be HIV-infected or newly diagnosed with HIV, and sexually active, screen within 1 year of onset of sexual activity regardless of mode of HIV infection.
- HIV-infected women aged 21-29 should have a Pap test following initial diagnosis.
- Pap test should be done at baseline and every 12 months.
- Some experts recommend a Pap test at 6 months after baseline test.
- If results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years.
- Co-testing (Pap test and HPV test) is not recommended.

HIV-Infected Women Aged ≥ 30 Years:

Pap Testing Only:

- Pap test should be done at baseline and every 12 months.
- Some experts recommend a Pap test at 6 months after baseline test.
- If results 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years.

Or Pap Test and HPV Co-Testing:

- Pap test and HPV co-testing should be done at baseline.
- If result of the Pap test is normal and HPV co-testing is negative, follow-up co-testing can be performed every 3 years.
- If the result of the Pap test is normal but HPV co-testing is positive, follow-up co-testing should be performed in one year.
- If the one-year follow-up Pap test is abnormal or HPV co-testing is positive, referral to colposcopy is recommended.

Or Pap Test and HPV 16 or HPV 16/18 Specified in Co-Testing:

- Pap test and HPV 16 or 16/18 co-testing should be done at baseline.
  - If result of the Pap test is normal and HPV 16 or 16/18 co-testing is negative, follow-up co-testing can be performed every 3 years.
  - If initial test or follow-up test is positive for HPV 16 or 16/18, referral to colposcopy is recommended.
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* Adapted from guidelines of the United States Public Health Service, Centers for Disease Control and Prevention, National Institutes of Health, and American Congress of Obstetrics and Gynecology.

Key Table
Malignancies potentially amenable to screening for early diagnosis and intervention in persons living with HIV (PLWH)

Malignancy	Annual No. PLWH Cases in the USA *	Method	Benefit	Risks	Common Treatment	Authors' Approach	Notes
<i>Associated with severe immune deficiency</i>							
Lymphomas, non-Hodgkin (NHL) and Hodgkin (HL)	1970	Careful lymph node exam, chest X-ray	Potential early diagnosis at lower stage	Minimal	Cytotoxic chemotherapy	Biopsy node if accompanied by other signs or symptoms that are highly suspicious of malignancy	Annual cases NHL: 1650 HL: 320
Kaposi Sarcoma (KS)	910	Careful exam of skin and conjunctivae	HIV/AIDS prognostic marker	Minimal	Consider chemotherapy; indicative of antiretroviral treatment failure, which should be investigated.	Biopsy lesion at follow-up if progression or dissemination is suspected	88% occur in men who have sex with men (MSM)
<i>Associated with oncogenic human papillomavirus (HPV) co-infection</i>							
Cervical Cancer	80	Pap test +/- high-risk (hr) HPV testing	Lower mortality with routine Pap (53-80% ↓)	Anxiety, pain, bleeding with colposcopy and biopsy	For precancer: ablation or excision.	Age 30+ yrs: Pap test alone, or Pap plus hr-HPV co-testing. Age <30 yrs: Pap test alone. See Table 1.	PLWH have high rates of invasive cancer in developing countries and of precancer in the USA.
Anal Cancer	760	Digital anal rectal exam (DARE); anal Pap test	Unproven	Anxiety, pain, bleeding with high-resolution anoscopy and biopsy.	For high-grade anal intraepithelial neoplasia (hg-AIN): ablation, cautery, infrared coagulation, laser, or cryotherapy.	Only in MSM and only if necessary diagnostic and treatment resources available; DARE or Pap test; if suspicious for malignancy, high-resolution anoscopy, possible biopsy. HPV testing not recommended.	83% occur in MSM; uncertain whether hg-AIN is a cancer precursor.
Oral and Oropharyngeal Cancer	280	Careful visual and tactile oral exam	Unproven	Anxiety, pain, bleeding with biopsy of suspect lesion	Excision, radiotherapy, chemotherapy	Biopsy lesion(s) if highly suspicious of malignancy	Suspect lesions: erythroplakia, leukoplakia, mixed red and white lesions, submucous fibrosis, lichen planus subtypes
<i>Associated with chronic hepatitis virus co-infection</i>							

Malignancy	Annual No. PLWH Cases in the USA *	Method	Benefit	Risks	Common Treatment	Authors' Approach	Notes
Liver Cancer	390	Liver sonography if cirrhosis is suspected	Inconsistent evidence for hepatitis B virus (HBV), no data for hepatitis C virus (HCV) and other etiologies	Anxiety, pain, bleeding, possible bile peritonitis or pneumothorax with biopsy of suspect lesion	Surgery, chemotherapy	Serologic screening for treatable (HCV, HBV) or preventable (HBV) infections; no cancer screening	Cancer risk reduced by prevention or effective treatment of HCV and HBV
<i>Other</i>							
Lung Cancer	840	Low-dose computed tomography (LD-CT)	Lower mortality in current and recent smokers of 30+ pack-years (20% ↓ lung cancer deaths, 8% ↓ overall)	Anxiety, pain, bleeding, possible pneumothorax with biopsy of suspect lesion	Surgery, radiotherapy, chemotherapy	Annual LD-CT as per US Preventative Services Task Force (USPSTF) criteria: assess efficacy in younger, moderate-smokers	<u>USPSTF</u> : Current or recent smoker, age 55-80 yrs, 30+ pack year smoking history, able to tolerate lung cancer surgery
Colorectal Cancer	360	Colono-scopy or annual fecal occult blood test	18,800 fewer all-cause deaths/yr in USA	Colonoscopy-related gut perforation, bleeding	Polyp excision, cancer surgery, chemotherapy	Screen age 50-75 yrs as per USPSTF	Colonoscopy repeat interval: q10 yrs if normal, q3 yrs if polyps found
Breast Cancer	180	Mammo-graphy	Lower mortality (15-35% ↓ breast cancer deaths, 1% overall)	Anxiety, pain	Surgery, hormonal therapy, chemotherapy	Biennial screen age 50-74 yrs as per USPSTF; age <50 or 75+ yrs, consult physician	
Prostate Cancer	570	Prostate specific antigen (PSA)	Inconsistent evidence of minimally reduced mortality (0.1% ↓)	Anxiety, pain, bleeding with biopsy of suspect lesion	Surgery, radiotherapy, hormone therapy	If life expectancy 10+ years, consider biennial PSA screening only for high/very high risk as per American Cancer Society (ACS) criteria (differs from USPSTF)	* ACS criteria: High risk = African-American or prostate cancer age <65 in a brother or father; Very high risk = prostate cancer age <65 in >1 brothers/father

* From Robbins HA, et al. 21