

# Cancer screening in women living with HIV infection

Women's Health  
2017, Vol. 13(3) 68–79  
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DOI: 10.1177/1745505717731970  
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## Abstract

The number of women living with HIV continues to increase. Thirty years into the AIDS epidemic, we now expect those with access to highly active antiretroviral to survive into their seventh decade of life or beyond. Increasingly, the focus of HIV care is evolving from preventing opportunistic infections and treating AIDS-defining malignancies to strategies that promote longevity. This holistic approach to care includes detection of malignancies that are associated with certain viral infections, with chronic inflammation, and with lifestyle choices. The decision to screen an HIV-infected women for cancer should include an appreciation of the individualized risk of cancer, her life expectancy, and an attempt to balance these concerns with the harms and benefits associated with specific cancer screening tests and their potential outcome. Here, we review cancer screening strategies for women living with HIV/AIDS with a focus on cancers of the lung, breast, cervix, anus, and liver.

## Keywords

cancer screening, HIV/AIDS, non-AIDS defining malignancies, women

Date received: 9 April 2017; revised: 4 August 2017; accepted: 11 August 2017

With the advent and availability of highly active antiretroviral therapy (HAART), morbidity and mortality associated with HIV infection have decreased dramatically in both resource-limited and resource-rich countries.<sup>1</sup> In 2017, HIV is best viewed through the public health lens as a chronic disease associated with unique clinical issues.

There is significant interest in long-term morbidities associated with HIV/AIDS including cardiovascular complications, endocrinopathies which can contribute to bone demineralization, potential adverse consequences of HAART, and, most relevant to this review, malignancies which occur disproportionately in this population and that pose unique clinical concerns for HIV-infected men and women. As the frequency of classically defined AIDS-defining malignancies (ADM) such as Kaposi's sarcoma, primary central nervous system lymphoma and intermediate and high-grade peripheral B cell non-Hodgkin's lymphomas wane, other non-ADM loom large and now represent a substantial health risk to people living with HIV/AIDS (PLWHA).<sup>2</sup>

Non-ADM in PLWHA are often typified by earlier age at onset, more aggressive clinical course and more advanced stage at presentation.<sup>3,4</sup> For many of these

tumors, such as lung cancer and other aero-digestive tumors, the occurrence of cancer is linked to lifestyle choices, including tobacco use and alcohol consumption.<sup>5</sup> Co-infection with other viruses including hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus (HPV) results in additive risks for liver cancer and squamous neoplasms of the head and neck, anus, and cervix.<sup>6,7</sup>

Women living with HIV/AIDS (WLWHA) continue to be affected by gynecologic and non-gynecologic malignancies at disconcerting rates.<sup>8</sup> Cervical cancer caused by HPV is a leading cause of health complications in Sub-Saharan Africa (SSA). Although initially recognized as a problematic cancer among HIV-negative men who have

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sex with men (MSM), anal cancer, also caused by HPV, is increasingly recognized as a major health concern for women.<sup>9</sup>

According to the US Centers for Disease Control and Prevention (CDC),<sup>10</sup> the number of PLWHA in the United States is increasing steadily, and by 2012, numbered 1.2 million. The highest prevalence rate of HIV is in the age group between 45 and 55 years. With aging, this population will be increasingly vulnerable to tumors whose incidence increases with aging. In women, this would include breast, lung, colon, anal, and cervical cancers.

The decision to screen WLWHA for cancer should include an assessment of individualized risk for the particular cancer, life expectancy, the harms and benefits associated with screening tests, and its potential outcome. In this article, I will review the potential cancer screening approaches for lung, liver, breast, colorectal, anal, and cervical malignancies most favored by US clinicians with a special focus on WLWHA. WLWHA are not at unique risk for uterine or ovarian cancer, and these malignancies will be discussed only briefly.

## Lung cancer

Lung cancer is the leading cause of cancer mortality for both men and women in the United States. In PLWHA, lung cancer is also the most common non-ADM, and the leading cause of death.<sup>4</sup> The number of lung cancers has doubled over the past 20 years, and the burden is seen primarily in people over the age of 50 years, which is tied to the cumulative risk of tobacco use and aging in this population.<sup>11</sup> Among WLWHA, there is a fourfold increased incidence of lung cancer compared to the general population. The reasons for this are likely multifactorial and include the carcinogenic effects of tobacco as well as the effects of chronic inflammation exacerbated by repeated and frequent pulmonary infections.<sup>12,13</sup> Patients with HIV and lung cancer tend to present at a more advanced stage of disease and more commonly with non-small cell histology compared to HIV-negative patients.<sup>14</sup> They also have a worse 5-year overall survival compared to those without HIV (9% vs 23%); those with CD4+ count greater than 200 cells/uL have a better prognosis than those with less than 200 cells/uL.<sup>15</sup> In a South African study, there was no statistical sex difference between those with and those without HIV infection.<sup>11</sup>

Initial randomized controlled studies in lung cancer screening focused on using chest radiography with or without sputum cytology and showed no impact on lung cancer mortality.<sup>16</sup> The National Lung Screening Trial (NLST) sought to compare low-dose helical chest computerized tomography (LDCT) screening with chest radiographs. Participants between the ages of 55 and 74 years, and with at least 30-pack-year history of smoking, were recruited from 33 large medical centers across the United

States.<sup>17</sup> At a median of 6.5 years of follow-up, there was a 20% relative reduction in lung cancer mortality in the LDCT group compared with the conventional chest radiograph group.

There are some potential benefits of screening high-risk PLWHA with LDCT, assuming they match the profile of those participants recruited to the NLST.<sup>18</sup> These include shifting the diagnosis of cancer from advanced disease to an earlier stage and with the promise of a better opportunity for cure. Although the NLST study participants reflected well the demographics of high-risk US smokers, it is worth emphasizing that the screening took place at major medical centers with multidisciplinary teams reviewing radiographs. These teams were also provided resources to ensure study participants were able to receive well-coordinated care. Such resources may not be available in community medical centers or in US Veterans Health Medical Centers where the use of screening LDCT has not yet been widely embraced.<sup>19</sup> In addition, the participants for the NLST were highly motivated and may not reflect the profile of WLWHA or the disparity in care that such women may face.

The downside of LDCT screening includes the cumulative effect of radiation exposure through repeated exams, surgical and medical complications associated with diagnosis, treatment for those who prove not to have malignancy, and over-diagnosis and over-treatment of lung cancers.<sup>18</sup> This may be particularly true for PLWHA with low CD4+ count, as they may be more likely to have false-positive LDCT findings because of infections or non-specific scarring from other opportunistic infections. In a recent study, asymptomatic PLWHA with CD4+ count >200 cells/uL did not show a higher rate of incidental pulmonary nodules on LDCT screening than HIV-negative controls, though they did have more lymphadenopathy than controls.<sup>20</sup>

In total, 224 HIV-infected (current or former smokers) underwent LDCT screening to assess the computer tomography (CT) detection rate for lung cancer.<sup>21</sup> None of the pulmonary nodules detected in 48 participants at baseline were diagnosed as cancer by study end, and only one cancer was detected in 678 patient-years. This may have been because of the young age of the screened population. In order for such screening efforts to be most effective, the population of WLWHA must overlap with the profile of NLST participants.

On the basis of NLST data and preliminary experience in screening PLWHA for lung cancer, it is reasonable for medical providers, who have access to high-volume and high-quality lung cancer screening and treatment centers, to discuss screening for lung cancer in WLWHA between the ages of 55 and 80 years who have at least a 30-pack-year history of smoking, continue to smoke, or who have stopped smoking in the past 15 years.

Our inexperience with lung cancer screening with LDCT emphasizes the importance of robust discussions around the potential benefits, limitations, and harms associated with lung cancer screening. Even more important is stressing the importance of stopping smoking during clinical encounters. Tobacco smoking rates among WLWHA are significant with rates nearly twofold to threefold higher than in the general population. Several studies have showed that PLWHA lose more life years to smoking than to HIV.<sup>22,23</sup> We must not view lung cancer screening as an alternative to smoke cessation.<sup>24</sup>

Although beyond the scope of this review, the British HIV Association has recently published a comprehensive review of how best to address smoking cessation efforts in PLWHA.<sup>24</sup> Included are practical methods to choose the best strategies for an individual patient and how to help the individual patient during the process. As the authors strongly point out in the light of current evidence on the efficacy and benefits of stopping smoking in PLWHA, medical care givers must make smoking cessation a major focus in the day-to-day clinical care of PLWHA.

## Breast cancer

Although the incidence of certain cancers, particularly ADMs, are inversely correlated with CD4+ count, these findings may not apply to WLWHA and diagnosed with breast cancer. Retrospective case series have failed to show a clear link between low CD4+ count and AIDS diagnosis and breast cancer. Breast cancer is the second leading cause of death in women.<sup>25</sup>

The epidemiology of breast cancer in WLWHA may be changing. During the modern HAART era, the frequency of breast cancer in WLWHA is approaching that of the general female population, where it had once been thought (paradoxically) to be much less.<sup>26</sup> The lower than expected breast cancer risk was linked to C-X-C chemokine receptor type 4 (CXCR4) binding of the HIV envelope protein to neoplastic breast cancer. Such interaction between HIV and the cancer cell was hypothesized to lead to greater frequency of apoptosis.<sup>27</sup> Perhaps more significantly, women in the pre-HAART era may have had other causes of morbidity and mortality that prevented them from being diagnosed with breast cancer or living long enough to be diagnosed with breast cancer.<sup>18</sup>

Certain clinical features may be different in WLWHA and diagnosed with breast cancer compared to the general population. Specifically, they are typically identified with breast cancer at a younger median age compared (46 vs 61 years old) to the general female population, have a greater likelihood of multifocal breast involvement, present with a more advanced stage at time of diagnosis, and have a possibly lesser response to systemic chemotherapy.<sup>26,28</sup>

The association between HIV, the immune reservoir, and the natural history of breast cancer requires further study. Among 43 WLWHA, breast cancer was inversely associated with initial stage and ranged from 100% survival for Stage I to 43% survival for Stage III and 0% survival for those with Stage IV disease.<sup>28</sup> Clearly, those women diagnosed with more advanced disease or greater degrees of immunodeficiency are less able to withstand the effects of cytotoxic chemotherapy than those with normal CD4+ counts. Overall survival still depends strongly on stage of breast cancer diagnosis, and those with earlier stage disease have a greater expectation of longevity.

Breast cancer screening modalities include mammography, screening ultrasonography, clinical and self-breast exam, breast magnetic resonance imaging, and breast tomosynthesis. Of these, mammography is the best studied and proven method to reduce mortality from breast cancer in those women deemed to be of average risk.<sup>29</sup> Harms associated with screening include over-diagnosis and subsequent over-treatment of clinically trivial disease, radiation-associated tumors, and risk of false-positive results resulting in recall, with or without biopsy, which may contribute to additional anxiety.<sup>18</sup> An additional concern includes when false-negative results occur, which could lead to a false sense of reassurance.

The central tenant for screening mammography is that early detection of breast cancer prevents late-stage disease. Despite substantial increases in the number of breast cancers that were detected in the United States from 1976 to 2008 according to an analysis extracted from Surveillance, Epidemiology, and End Results, mammography had a very modest impact on the rates of which women presented with advanced cancer.<sup>30</sup> Although it is unclear which women have been affected, the imbalance suggests that there is substantial over-diagnosis, which may account for over 30% of newly diagnosed breast cancers. The authors conservatively estimate that breast cancer was over-diagnosed in 1.3 million women in the United States in the past 30 years.

Despite controversies as to what age breast cancer screening should begin, there is widespread consensus that it should be practiced in the general female population. Application of national guidelines to WLWHA is appropriate provided prognosis conferred by HIV and other comorbidities are taken into account in the decision-making process.<sup>8,18</sup> A meta-analysis of survival data of randomized control studies from the United States, Denmark, United Kingdom, and Sweden suggests that screening for breast cancer is most appropriate for patients with a life expectancy of greater than 10 years.<sup>31</sup>

The US Preventive Service Task force (USPSTF) recommends biennial screening mammograms between ages of 50 and 74 years, and an individualized discussion for those younger than 50-years old taking into account the

**Table 1.** Recommendations for breast cancer screening mammography: USPSTF, CDC, and ACS.

Organization	40–44 years old	45–49 years old	50–54 years old	55–74 years old	Older than 75 years
USPSTF	Individualized decision to screen every 2 years	Individualized decision to screen every 2 years	Every 2 years	Every 2 years	No recommendation
CDC	Individualized decision	Individualized decision	Every 2 years	Every 2 years	No recommendation
ACS	Option to begin annual screening	Yearly	Yearly	Every 2 years with option to screen yearly. Discontinue when life expectancy is less than 10 years.	Every 2 years with option to screen yearly. Discontinue when life expectancy is less than 10 years.

USPSTF: US Preventive Services Task Force; CDC: Centers for Disease Control and Prevention; ACS: American Cancer Society.

**Table 2.** USPSTF updated recommendation on screening for colorectal cancer.

USPSTF reviewed the evidence on the effectiveness of screening methodologies looking at their effect on reducing incidence and mortality. It also evaluated testing harms and performance characteristics, and commissioned a comparative modeling study to determine ideal starting and stopping ages, as well as screening intervals. Among the findings are the following:

There is high certainty that screening for colorectal cancer in average risk, asymptomatic adults aged 50–75 years are of substantial net benefit.

Multiple screening strategies are available, with different levels of evidence to support their effectiveness, as well as unique advantages and limitations.

There are no empirical data to demonstrate that any of the reviewed strategies provide a greater net benefit.

Screening for colorectal cancer is a substantially underused preventive health strategy in the United States.

USPSTF: US Preventive Services Task Force.

harms and benefits of such screening.<sup>32</sup> The CDC recommends mammographic screening every 2 years for women between 50 and 74 years of age and further discussions with the patient and medical provider regarding screening between the ages of 40 and 49 years.<sup>33</sup> In contrast, the American Cancer Society (ACS) recommends that women with an average risk of breast cancer begin screening at age of 45 years, with annual mammography from 45 to 54 years, and biannual mammography with the opportunity to continue screening mammography as long as the women's overall health is good and as long as she has a life expectancy of 10 years or longer.<sup>34</sup> The ACS also advocates that women be given the opportunity to begin annual screening from 40 to 44 years of age.

The differences in breast cancer screening recommendations between the USPSTF, CDC, and the ACS are highlighted in Table 1. Regardless of which of these guidelines medical providers adhere to for the general female population, for WLWHA screening remains challenging with screening rates that are only a small fraction compared to those achieved in the general population.<sup>35,36</sup>

## Colorectal cancer

Globally, colorectal cancer (CRC) is the third most common cancer in men and in women and is the leading

cause of death when both genders are combined.<sup>37</sup> In two analyses, the prevalence of colonic adenomas in PLWHA was high compared to the general population; however, the relative risk of CRC in PLWHA is uncertain.<sup>38,39</sup> Conflicting information is available through various meta-analysis and cohort studies. On one hand, a prospective cohort study in PLWHA from 1992 to 2003 showed a greater incidence of CRC than in the general population (standard rate ratio 2.3).<sup>40</sup> On the other hand, a meta-analysis and a cohort study failed to show an elevated risk of CRC among PLWHA compared to age-matched controls.<sup>41,42</sup> In addition, a case series involving PLWHA and with colon cancer indicated that CRC is diagnosed at a younger age and has a more aggressive course than in the general population.<sup>43</sup> In contrast, a registry linkage study showed that the age of CRC was no different in groups infected with HIV and the general population.<sup>3</sup>

The USPSTF recommends CRC screening with intervals between screening studies depending on the modality used for cancer detection (Table 2).<sup>44</sup> These include high-sensitivity fecal occult blood testing (FOBT) annually, sigmoidoscopy every 5 years with FOBT every 3 years, or colonoscopy every 10 years in adults who are deemed at average risk for CRC beginning at age of 50 years and continuing until age of 75 years. The CDC<sup>45</sup>

also notes that earlier screening strategies may be needed if the person or close relative have had colorectal polyps or CRC, inflammatory bowel disease, familial polyposis, or Lynch syndrome.

Application of USPSTF or other national CRC screening to PLWHA is reasonable, provided prognosis conferred by HIV or other comorbidities are considered in the decision-making process, as there is a 10-year lag to observe the mortality benefit from screening (see Table 2).<sup>44</sup> Despite clear reasons to incorporate similar standards for PLWHA, both genders are less likely to undergo CRC screening than the general population. Among 205 consecutive patients interviewed at outpatient clinics with either average risk of CRC as defined by age greater than 50 years or high risk for CRC as defined by family history of colon cancer or adenomas, those who were HIV positive were significantly less likely to undergo CRC screening.<sup>46</sup> The reasons for the disparity in screening between PLWHA and the general population are likely multifactorial and include patient and physician education regarding CRC screening, lack of CRC screening guidelines which are specific for PLWHA, and health care disparities faced by both men and women who are infected with HIV and that cut across racial and economic and social divides.<sup>47</sup>

How best to bridge this divide in CRC screening for PLWHA and the general population is an area of active research. Successful strategies used in the general population may be applicable to PLWHA. A 2-year randomized controlled study found that compared to usual care, patients completed recommended screening twice as often when electronic health record linked reminders and FOBT were sent to them.<sup>48</sup> Follow-up telephone calls by medical assistants and if required, nursing assistance, each resulted in additional but smaller incremental improvements in adherence.

Evidence-based screening modalities that have led to decreased colorectal mortality include FOBT, sigmoidoscopy, and colonoscopy. The harms associated with screening for CRC are due to the invasive procedures that are used initially or in the evaluation sequence and include significant bleeding, severe abdominal pain, and cardiovascular events and rarely, bowel perforation.<sup>44</sup>

## Anal cancer

Anal cancers are composed predominantly of squamous carcinomas and are HPV-associated in 90% of instances. The little attention that anal cancer has received may be related in equal parts to the stigma surrounding this malignancy and to the rarity of this tumor in the general population where the incidence has been estimated at 1 to 2 per 100,000.<sup>49</sup> The profile of anal cancer among the public was raised considerably when the Hollywood and stage actress Farrah Fawcett went public with her personal struggles

after she had been diagnosed with invasive anal cancer and underwent surgery, radiation therapy, and also sought non-traditional treatments for this condition.

In the United States, the incidence of anal cancer is more common in women than men with a rate of 1.8 compared to 1.1, respectively, per 100,000.<sup>50</sup> In WLWHA, the incidence of invasive anal cancer is approximately 15- to 60-fold greater than the general population.<sup>51</sup> Risk factors for anal infection with HPV include cigarette smoking, presence of anal warts, and cervical HPV infection.

Survival from anal cancer significantly improves when it is diagnosed at an early stage; yet, most are diagnosed at an advanced stage when symptoms of pain, pruritus, or bleeding supervene.<sup>49</sup> An important argument for anal cancer screening in PLWHA, in addition to its increased incidence and mortality in the HIV-infected population, is the biological similarity between the cervix and the anus. Both anatomical sites include a transition zone and squamous epithelium with the propensity for HPV infection.<sup>52</sup> High-resolution anoscopy (HRA) is similar to cervical colposcopy, allowing for visualization of dysplastic lesions and the identification of suspicious lesions to biopsy.<sup>53</sup>

Screening for anal cancer is currently based on cytological detection of HPV-induced abnormalities, followed by histological confirmation and treatment of the precursor lesion, high-grade anal intraepithelial neoplasia (AIN).<sup>53</sup> Although similarities exist between cervical and anal cancer screening, outcome research into anal cancer screening is lacking.<sup>54</sup> The various techniques which are used to screen for anal cancer include digital anal rectal exam (DARE), anal Papinicolaou (Pap) test, and HRA. Anal cytology is a fair predictor of AIN with a sensitivity ranging from 61% to 93% in various studies.<sup>8</sup> HRA followed by biopsy are used as an adjunct for AIN diagnosis. Yet, there is a poor correlation between the cytological and histological grade of AIN. Cytology underestimates dysplasia grade compared with the corresponding biopsy. There are no randomized studies to establish the reliability and validity of anal cancer screening, or evidence of improved survival rates from anal cancer screening.<sup>53</sup> There also is no consensus as to who should be screened with DARE.<sup>54,55</sup> The sensitivity, specificity, negative predictive value, and quality-of-life metrics and costs associated with false-positive and false-negative DARE have not been established.

An ongoing study (NCT01946139) seeks to establish the best strategy for anal dysplasia screening in women and compares three different assays (the HPV Hybrid Capture 2 (HC2) assay; the HPV messenger ribonucleic acid (mRNA) assay (APTIMA); and the OncoHealth HPV E6/E7 oncoprotein assay) against the gold standard, biopsy-confirmed high-grade squamous intraepithelial lesion (HSIL). The results of this study should be available in 2018.

Additional barriers to more widespread anal cancer screening are the paucity of medical practitioners well trained in HRA, the challenges of getting prior authorization from Insurance carriers to pay for the procedure, and variations in interpreting anal biopsy specimens. Ironically, the CDC has supported anal cytology screening for PLWHA but have qualified this endorsement by emphasizing the need for further studies to address screening and treatment programs.<sup>56</sup>

Although no consensus guidelines exist, several financial analyses support strategies around anal cancer screening. Researchers estimated that the biennial screening of WLWHA would account for a 4.4-year increase in quality-adjusted life years (QALY) at an incremental cost effectiveness ratio of US\$34,763 per life gained compared to no screening.<sup>57</sup> Another analysis estimated that a yearly anal Pap test for HIV-infected MSM would translate to US\$16,000 per QALY gained compared to no screening.<sup>58</sup> A third study evaluated the feasibility and acceptability of anal screening among HIV seropositive men.<sup>59</sup> The high prevalence of high-risk HPV serotypes and the frequency of false-negative cytology suggested that HRA would have most clinical benefits as a primary screening strategy for anal cancer in this high-risk group. The analysis was hampered, however, by uncertainty as to how best to monitor those participants with lower grades of AIN.

A National Institute of Health (NIH) funded study will shed more light on this important area. The Anal Cancer High-Grade Squamous Intraepithelial Lesion Research Outcome (ANCHOR) Study is a Phase III randomized clinical trial for PLWHA of age 35 years and older and who have high-grade AIN not previously treated.<sup>60</sup> One-half of the study volunteers will have their high-grade AIN treated and the other half will be monitored every 6 months but not receive treatment unless they develop invasive anal cancer. The primary outcome is the time from randomization to anal cancer diagnosis. Secondary end points include incidence of adverse events subsequent to treatment and quality of life. Treatment options include imiquimod, topical fluorouracil, infrared coagulation, thermal ablation, and laser therapy.

Vaccination is also an important but underutilized strategy for anal cancer prevention with its greatest impact to be among those between the ages of 9 and 26 years. Strategies to reduce the burden of anal HPV-associated disease have been more extensively studied in men than women because of the high incidence of anal cancer in MSM.<sup>8</sup> An international study of 13,800 anogenital samples collected from women suggests that incorporation of the nine-valent HPV vaccine among young girls and women in 48 countries could lead to as much as an 86% reduction in anal cancer.<sup>61</sup>

## Cervical cancer

On a global scale, invasive cervical cancer (ICC) is both the most frequent source of new cancers in women and

the cause of the most cancer-associated fatalities in women.<sup>25</sup> In some areas of SSA, the rates of ICC are exceedingly high and approach 168/100,000 among women who receive HAART.<sup>62</sup> A disproportionate number of deaths also occur in resource-limited countries where the death rate at 17.5/100,000 is nearly threefold greater than in industrialized countries.<sup>8,25</sup> In WLWHA, in the United States, the incidence of cervical cancer is roughly 7 per 100,000 but is still 66% greater than the incidence seen among non-HIV infected women.<sup>62</sup> In a multi-cohort North American analysis between 1996 and 2010, WLWHA had a higher risk of ICC compared to HIV-negative women, and the risk increased inversely to the CD4+ count.<sup>63</sup>

Among WLWHA, ICC presents nearly 15 years earlier than in the general female population.<sup>64,65</sup> Although several studies have suggested that ICC presents at a more advanced stage among women infected with HIV, this has been difficult to clearly demonstrate because in resource-limited areas, non-HIV infected women also present with more advanced disease.<sup>8</sup> The increased incidence of advanced stage disease at diagnosis may be a reflection of the limited screening of ICC among women in general and not specifically, or solely, among WLWHA.<sup>66</sup>

Treatment of ICC requires close collaboration between the Gynecological Surgeon, Radiation Therapist and Oncologist. Treatment is particularly challenging in resource-constrained countries where fear of cancer and poor infrastructure hinders efforts at early diagnosis and treatment.<sup>65</sup> Interruptions in treatment and failure to deliver complete cancer care lead to worse outcomes, and this is particularly true for WLWHA who are not engaged in medical care and who are not receiving HAART. Although concomitant HAART may lead to a greater likelihood of completing combined chemotherapy and radiation therapy, it does not in itself lead to regression of high-grade cervical dysplasia.<sup>64,65</sup>

Current guidelines for cervical cancer screening by the USPSTF include women between 21 and 65 years old. Grade A recommendations include a Pap test every 3 years between 21 and 65 years old, or cytology with HPV testing every 5 years between 30 and 65 years old.<sup>67</sup> These recommendations do not include women with precancerous cervical lesions, in utero exposure to diethylstilbestrol, or those with immunosuppression including HIV infection.

For WLWHA, the CDC recommends cytology screening every 6 months after initial diagnosis of HIV and if both tests are normal, than annual screening.<sup>68</sup> Guidelines from the American College of Obstetricians and Gynecologists and the U.S. Preventive Services Task Force (USPFT) recommend that WLWHA should undergo cervical cytology for cancer screening twice in the first year after diagnosis of HIV infection and then annually, provided the test results are normal (Table 3).<sup>69,70</sup> Two cervical screening assessments initially are prudent

**Table 3.** Cervical cancer screening summary and recommendations.

WLWHA should undergo cervical cancer screening twice in the first year after diagnosis of HIV infection and then annually, provided the test results are normal.

Women with two consecutive normal cytological examinations should be monitored yearly with a thorough visual inspection of the anus, vulva, and vagina, as well as the cervix.

There is no consensus as to whether HPV testing should be performed routinely on HIV-infected women. HPV testing can be used to determine the frequency of subsequent cervical cancer screening in these women; women who test negative for HPV and have two negative initial cervical cytology results could undergo cytological screening yearly; while those with high-risk HPV DNA should have cervical cytology every 6 months.

Screening colposcopy should be a part of initial evaluation. The need for subsequent examinations is based upon cervical cytology results.

Source: American College of Obstetricians and Gynecologists and the USPST.

WLWHA: Women living with HIV/AIDS; HPV: human papillomavirus.

**Table 4.** ASCO HPV recommendations for cervical cancer prevention.

In all environments and independent of the resource settings, two doses of HPV vaccine are recommended for girls' ages 9 to 14 years, with an interval of at least 6 months and up to 12–15 m.

Girls who are HIV positive should receive three doses.

For maximal and enhanced resource settings:

If girls are 15 years or older and have received their first dose before age 15 years, they may complete the two-dose series;

If they have not received the first dose before age of 15 years, they should receive three doses;

In both scenarios vaccination may be given through age of 26 years.

For limited and basic resource settings: if sufficient resources remain after vaccinating girls 9–14 years, girls who received one dose may receive additional doses between ages 15 and 26 years.

Vaccination of boys: in all settings, boys may be vaccinated; if there is at least a 50% coverage in priority female target population, sufficient resources, and such vaccination is cost-effective.

ASCO: American Society of Clinical Oncology; HPV: human papillomavirus.

for HIV-infected women, since intraepithelial neoplasia is not uncommon and can develop rapidly in these women. Although the importance of cervical cancer screening is better established in this population, the vast majority of WLWHA are not receiving necessary gynecological services.<sup>52</sup> In an interview study which occurred over 4 years and encompassed 18 US states, nearly a quarter of 2417 WLWHA and who were receiving care in HIV primary clinics had not undergone ovarian and corpus uterine cancer screening over the past 1 year.<sup>71</sup>

The World Health Organization (WHO) have adopted an alternative model for screening women for ICC in resource-constrained countries, "screen and treat." This strategy uses existing screening modalities, preferably HPV testing as first line, followed by immediate treatments (e.g. cryotherapy) for identified cervical abnormalities.<sup>72</sup> However, the nexus between convenience associated with HPV testing in poorer countries and the higher cost of such tests have not yet been examined in a large-scale effort, and cost remains a considerable barrier for implementing these strategies in resource-constrained countries.<sup>73</sup>

Similar to anal cancer, ICC is a vaccine-preventable disease, but HPV vaccines remain incompletely available for PLWHA. The Advisory Committee on Immunization Practices (ACIP) recommends that all

males and females including PLWHA between the ages of 11 and 26 years receive the nine-valent HPV vaccine.<sup>74,75</sup> The CDC now recommends 11- to 12-year-olds to receive two doses of HPV vaccine rather than the previously recommended three doses to protect against cancers caused by HPV. The second dose should be given 6–12 months after the first dose.<sup>76</sup> The American Society of Clinical Oncology has also issued updated guidelines on HPV vaccination for the prevention of cervical cancer, which incorporates evidence-based recommendations stratified to four levels of resource settings: basic, limited, enhanced, and maximal (Table 4).<sup>77</sup> These levels are designed to correspond to the financial resources of a region as well as to the development of its health system, which include infrastructure, personnel, and access to services.

## Ovarian and uterine cancer

Ovarian cancers account for less than 2% of new cancer diagnoses in women. It has a high mortality because most patients present with advanced peritoneal metastases at time of diagnosis.<sup>8</sup> Among WLWHA, ovarian cancer does not seem to be associated with a greater prevalence and is not associated with onset of AIDS diagnosis or CD4+ count. The incidence and natural

history of uterine cancer among WLWHA have not been thoroughly studied. This is, in part, related to the paucity of reported cases. In a large study of 85,268 WLWHA and followed for 665,987 patient-years, only 31 cases were identified and this was less than what was expected in the general population.<sup>26</sup> In another study of WLWHA and encompassing the years between 2006 and 2011, uterine cancer accounted for 4% of cancer-specific deaths. Standardized mortality ratio of women with AIDS and uterine cancer was comparable to those without AIDS in the same study.<sup>78</sup>

In the general population, neither early recognition of symptoms nor annual pelvic exam has influenced survival. Serum cancer antigen 125 (CA-125) and transvaginal ultrasound (TVUS) have also been evaluated in several large prospective studies but without an impact on survival, although morbidity increased in screened women because of surgeries related to false-positive tests.<sup>79</sup> Efforts are underway to define best available screening strategies in high-risk groups (e.g. parity, oral contraceptive use, tubal ligation, endometriosis, and BRCA1/2 mutations) incorporating TVUS, CA-125, and annual multimodal screening.<sup>80</sup> Cancer screenings studies thus do not appear to apply to WLWHA who do not fall into these high-risk groups.

## Hepatocellular cancer

HIV-infected intravenous drug users (IVDU) have a heightened risk of HBV and HCV co-infection compared to the general population and consequently are at risk for hepatocellular cancer (HCC). Recent US data indicate that at a rate of 30 per 100,000 individuals PLWHA have a fourfold higher incidence of HCC risk than the general population.<sup>81</sup> Other possible risk factors contributing to HCC in PLWHA include immunosuppression and higher prevalence of alcoholism, non-alcoholic steatosis and diabetes.<sup>82</sup> The magnitude of this risk has remained relatively constant despite the positive hepatic impacts of HAART in minimizing progression to cirrhosis.

Both HBV and HCV cause HCC, but variations in their route of transmission means that for PLWHA and diagnosed with HCC they are more likely to have HBV, whereas as HIV-infected IVDU with HCC are more likely to have HCV. HIV aggravates the clinical outcome of viral-induced cirrhosis and liver-associated death; this is especially true at low CD4+ cell counts. Among 104 HIV-infected and 484 uninfected patients, HIV-positive patients were significantly younger than uninfected ones at HCC diagnosis and were co-infected with HCV or HCV in the great majority of cases.<sup>83</sup> CD4+ cell count at diagnosis was not independently associated with survival; but patients receiving HAART and with undetectable HIV RNA at diagnosis had a better prognosis than untreated subjects or subjects with

higher HIV viral loads. Even though, in HIV-infected patients, HCC was diagnosed mostly at an early stage (66% at Barcelona Clinic, Liver Cancer (BCLC), Stage A or B) and then amenable for potentially curative approaches, the median survival time was significantly shorter than that observed in the HIV-negative counterparts (35 vs 59 months).

The benefits associated with HCC screening interventions may include an improvement in survival if the cancer is caught at an early phase, and although non-cirrhotic patients might be eligible for surgical resections, most patients would require hepatic transplants for cure.<sup>84</sup> The downside associated with ultrasonography as a screening test include potential complications associated with liver biopsy if an abnormality is detected, as well as excess exposure to radiographs and contrast dye exposure due to a need for follow-up imaging in false-positive instances.<sup>18</sup>

Screening guidelines from the American Association for the Study of Liver Disease (AASLD) recommend liver ultrasonography twice yearly for those at high risk for HCC (see Table 4).<sup>84</sup> Controversy has followed these recommendations due to a lack of randomized controlled studies that clearly show benefit to this approach. A recent Cochrane review concluded that there was insufficient evidence grounded by randomized controlled trials to support routine screening liver ultrasounds and serum tumor marker collections of HBV surface antigen positive patients for HCC.<sup>85</sup> The review noted the high risk of bias in many of the studies they surveyed, including methodological flaws and incomplete long-term data (Table 5).

Among a large Chinese cohort, HCC screening of patients with HBV infection led to a 37% reduction in mortality by utilizing twice yearly liver ultrasound and serum alpha-fetoprotein assessments.<sup>86</sup> Although encouraging, applying HCC screening recommendations to PLWHA and co-infected with viral hepatitis is challenging and further studies are needed before nuanced recommendations can be offered to this specific population.<sup>18</sup> A recent Cochrane review concluded that there was insufficient evidence grounded by randomized controlled trials to support routine screening liver ultrasounds and serum tumor marker collections of HBV surface antigen positive patients for HCC.<sup>85</sup> The review noted the high risk of bias in many of the studies they surveyed, including methodological flaws and incomplete long-term data. Complicating available trials looking at screening for HCC is the lack of liver transplantation as a routinely available treatment option for HCC. Emerging experience with liver transplantation for PLWHA appears encouraging. Among Spanish patients with HIV and HCV co-infection, liver transplantation outcomes were similar to HIV-negative patients who underwent similar surgery.<sup>87</sup>



**Table 5.** Groups for whom HCC surveillance is recommended or in whom the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated.

Population group	Annual incidence (percentage per year) for which surveillance is considered to be cost-effective	Incidence of HCC
<b>Surveillance recommended</b>		
Asian male hepatitis B carriers over age of 40 years	0.2	0.4%–0.6% per year
Asian female hepatitis B carriers over age of 50 years	0.2	0.3%–0.6% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2–1.5	3%–8% per year
Hepatitis C cirrhosis	1.5	3%–5% per year
Stage 4 primary biliary cholangitis	1.5	3%–5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown
<b>Surveillance benefit uncertain</b>		
Hepatitis B carriers younger than 40 (males) or 50 (females) years	0.2	<0.2% per year
Hepatitis C and stage 3 fibrosis	1.5	<1.5% per year
Non-cirrhotic NAFLD	1.5	<1.5% per year

Source: Adapted from Bruix and Sherman.<sup>84</sup> Copyright©2010 John Wiley & Sons. Graphic 68371 Version 8.  
HCC: hepatocellular carcinoma; NAFLD: non-alcoholic fatty liver disease.

## Summary

Experts, professional societies, and consumer groups frequently recommend different strategies for cancer screening. Nonetheless, high-intensity screening or, in some instances, lack of screening does not equate to a higher value of care. In order for cancer screening to be effective, the American College of Physicians (ACP) defines high-value care as the delivery of services providing benefits that make their harms and costs worthwhile. Strategies designed to screen WLWHA for cancer must take into consideration the risk of the specific cancer, patient life expectancy, and the benefits and harms that can occur because of the cancer screening endeavor.

In WLWHA, experience with screening for lung cancer with LDCT is small but may be reasonable after informed shared decision-making and when access to high-quality and high-volume lung cancer screening and treatment centers exist. Breast and colon cancer screening should generally follow recommendations that are applied to the general population. Gynecologic care is a priority for WLWHA and cervical cancer screening is an important component of their routine care. Given the high burden of HPV-associated anal cancer in PLWHA, all HIV-infected adults could be offered screening as part of clinical care at specialized centers. Ultimately, the NIH-sponsored ANCHOR study will

determine the harms and benefits of this strategy. WLWHA should not undergo uterine and ovarian cancer screening due to lack of evidence of benefit coupled with increases in harm and cost. Assuming that early and aggressive treatment is available, AASLD screening recommendations with ultrasonography may be applied to at-risk WLWHA for HCC.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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