Cervical Cancer Prevention and Control in Women Living With Human Immunodeficiency Virus

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Abstract: Despite being highly preventable, cervical cancer is the fourth most common cancer and cause of cancer death in women globally. In low-income countries, cervical cancer is often the leading cause of cancer-related morbidity and mortality. Women living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome are at a particularly high risk of cervical cancer because of an impaired immune response to human papillomavirus, the obligate cause of virtually all cervical cancers. Globally, approximately 1 in 20 cervical cancers is attributable to HIV; in sub-Saharan Africa, approximately 1 in 5 cervical cancers is due to HIV. Here, the authors provide a critical appraisal of the evidence to date on the impact of HIV disease on cervical cancer risk, describe key methodologic issues, and frame the key outstanding research questions, especially as they apply to ongoing global efforts for prevention and control of cervical cancer. Expanded efforts to integrate HIV care with cervical cancer prevention and control, and vice versa, could assist the global effort to eliminate cervical cancer as a public health problem. **CA Cancer J Clin 2021;71:505-526. © 2021 The Authors. CA: A Cancer Journal for Clinicians published by Wiley Periodicals LLC on behalf of American Cancer Society. This article has been contributed to by US Government employees and their work is in the public domain in the USA. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.**

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Cervical Cancer and HIV/AIDS as Intersecting Epidemics

Invasive cervical cancer is one of the leading causes of cancer-related morbidity and mortality in women globally. It is estimated that approximately 600,000 women are diagnosed with, and more than 300,000 women die from, cervical cancer worldwide annually.[1] A disproportionate amount of its global burden is experienced by women living in low- and middle-income countries (LMICs), where it is often the first or second leading cause of cancer cases and deaths in women.

With the discovery of an obligate causative infectious agent, high-risk human papillomavirus (HPV), elucidation of key steps in its natural history, and availability of highly effective primary and secondary prevention technologies, cervical cancer is an eminently preventable malignancy. Indeed, in countries with routine, effective cervical cancer screening and early detection programs, cervical cancer incidence and mortality rates have declined precipitously over the past one-half century.[1,2] HPV vaccines will likely lead to even further reductions in decades to come. Buoyed by rising global optimism about the possibility of reducing cervical cancer globally, the World Health Organization (WHO), with endorsement from over 194 countries, including the United States, has recently launched a global initiative to accelerate the elimination of cervical cancer as a public health problem by significant

expansion of efforts to increase HPV vaccination to 90% coverage, screening to 70% coverage in mid-adult women, and treatment to 90% of those in need of it ("90-70-90").[3-5]

Over the past 4 decades, the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) pandemic has emerged and persisted as one of the world's most serious public health, development, and economic challenges. With an estimated 37.7 million (uncertainty bound, 30.2-45.1 million) people living with HIV (PLWH) worldwide in 2020,[6] 53% of all PLWH were women and girls. HIV/AIDS disproportionally affects people in LMICs, where cervical cancer is also exceedingly common. More than two-thirds of PLWH live in sub-Saharan Africa (SSA).[7,8] Untreated HIV leads to severe impairment of the immune system, increasing the risk of developing opportunistic infections as well as infection-related cancers and other chronic comorbidities that are otherwise rare in people with normal immune function.

Since the mid-1990s, the availability of combination antiretroviral therapy (ART) for HIV has led to significant improvements in the management of HIV disease, including a partial or near-complete restoration of immunocompetence, with long-term adherence to ART regimens and retention within the HIV care continuum. Over the past 2 decades, catalyzed by generous bilateral and multilateral public sector and philanthropic initiatives (eg, The President's Emergency Plan For AIDS Relief [PEPFAR]),[9] ART has become affordable and accessible to millions of PLWH, including in some of the most resource-limited settings in SSA. This has led to dramatic increases in the lifespans of PLWH[10,11] as well as several considerably improved trajectories in the incidence of HIV-associated opportunistic infections,[12] cancers,[13-15] and comorbidities.[16] In fact, in resource-rich areas of the world, the presence of HIV infection is thought of more like a *chronic* disease compared with pre-ART times in which HIV infection often led to terminal sequalae.

Women living with HIV (WLWH) have long been recognized as having a higher risk for the acquisition, persistence, and progression of high-risk HPV and its downstream consequences, including cervical cancer. In fact, invasive cervical cancer was first included as an AIDS-defining condition (ie, a marker of clinically relevant immunosuppression) by the US Centers for Disease Control and Prevention (CDC) in 1993.[17,18] Yet, just like the wide heterogeneity seen in the incidence rates of cervical cancer among women in the general population globally, incidence rates in WLWH have also varied substantially between countries. Although incidence rates of cervical cancer in WLWH have been uniformly higher than those in women without HIV (HIV-negative women) within any given setting/geographic region, recent meta-analyses have demonstrated that the attributable fraction of cervical cancers because of HIV is much greater in LMICs than in high-income countries (HICs).[19] These differences are likely because of a combination of factors, such as a higher percentage women who are WLWH,[6] differences in the duration[20] and adherence[21] that affect the degree of immune restitution, various social determinants of health (eg, nutrition, housing, and transportation), and better access to cervical cancer screening services in HICs.[22] Yet, unlike other AIDS-defining cancers (Kaposi sarcoma and specific types non-Hodgkin lymphoma, ie, Burkitt lymphoma, immunoblastic lymphoma, and primary lymphoma of the brain),[23] which have clearly demonstrated evidence linking dramatic declines with the availability of ART over the past 3 decades,[14] cervical cancer rates have not declined by the same magnitude, and cervical cancer remains a significant comorbidity among WLWH regardless of the setting globally.

Although the relative importance of the 2 factors related to health care delivery, HIV care and cervical cancer screening services, is unclear and difficult to disentangle, their confluence likely contributes to the excessive cervical cancer burden in LMICs.

In this article, we attempt to provide a critical appraisal of the evidence to date on this topic while describing key methodologic issues inherent in studies contributing to this evidence. We also discuss the implications for clinical cancer prevention, especially as they apply to the ongoing global efforts for prevention and control of cervical cancer globally, because both the management of HIV disease and interventions for the prevention and control of cervical cancer (ie, vaccines, screening and treatment of precancerous lesions, and management of invasive cancers) can be conceived as the necessary *dual arms* of a multifocal public health strategy to reduce cervical cancer burden in WLWH.

Quantifying the Burden of Cervical Cancer in WLWH

Over the past 3 decades, there has been significant evolution in quantifying the burden of cervical cancer in WLWH by efforts using a variety of descriptive epidemiology approaches. These have included population registries/records-linkage studies that connect evidence from disparate sources, such as cancer registries, HIV registries/surveillance databases, and national death registers, as well as cohort and case-control studies from pooled databases of clinics and hospitals providing care for WLWH.

Results of 2 large meta-analyses conducted 14 years apart (2007 and 2021)[19,24] are consistent in their reporting that cervical cancer incidence remains approximately 6 times higher in WLWH compared with the general population or HIV-negative women (pooled risk estimate from the most recent meta-analysis, 6.07; 95% confidence interval [95% CI], 4.40-8.37).[19] In 2018, 5.8% (95% CI,

4.6%-7.3%) of new cervical cancer cases were diagnosed in WLWH, most of which were attributable to HIV infection (4.9%; 95% CI, 3.6%-6.4%).[19] Yet the attributable risk varies greatly across regions and countries because of the very wide variations in HIV prevalence worldwide: <5% in 122 countries and >40% in 9 southern African countries (Eswatini, Lesotho, Botswana, South Africa, Zimbabwe, Namibia, Mozambique, Zambia, and Malawi).[19] These high-burden countries also have some of the highest HIV prevalence (between 11% and 32%) in females aged 15 years or older, and ART has been available only over the past 15 years.[25-27] Other key findings from the literature on quantification of the burden include:

1. Cervical cancer incidence rates in WLWH in HICs (in contrast to those in LMICs) have declined steadily with access to ART as well as wider availability of cervical cancer screening over the past 3 decades.[13-15] The age-standardized incidence rate of cervical cancer in US WLWH is predicted to decrease from 60 per 100,000 in 2006 to 10 per 100,000 in 2030.[15]
2. Among WLWH, those with higher CD4-positive T-cell levels have a lower risk of cervical precancer and cancer.[28-30]
3. Although cervical precancer among WLWH is common, WLWH who receive regular cervical screenings have low incidence rates of invasive cervical cancer.[29,31]
4. The magnitude of the effect of precancer risk varies with differences in the use of ART regimens and precancer detection methods.[28,29]
5. For US WLWH who receive adequate cervical screening and follow-up care for positive screening results, incidence rates of cervical cancer are projected to converge with those of the general population within the next decade.[15]
6. WLWH non-White racial and ethnic subgroups in both HICs[32,33] and LMICs[34,35] experience significant health disparities because of systemic racism, differential access to health care, and/or other social determinants of health, resulting in higher risks of cervical cancer incidence and mortality compared with their White counterparts. Although these underserved groups are minorities in HICs, they are often the majority population in LMICs.

Therefore, HIV infection and the subsequent disparate care are important contributors to the unequal burden of cervical cancer in some of the lowest resource settings globally.[25-27] Prevention and control of HIV infection and improved focus on patient-centered care resources to complement efforts for prevention and control of cervical cancer will have a profound impact on reducing the burden of cervical cancer globally.

Impact of HIV and HIV Control on HPV Natural History

There are 4 key stages in the development of cervical cancer: HPV acquisition, HPV persistence, progression to cervical precancer, and development of invasive cancer.[36] In addition to factors such as age, parity, smoking status, and hormonal contraceptive use, HIV coinfection, although not causal, has a profound impact on several steps in the natural history of HPV (HPV cofactor) that increases HPV-related cancer risk in WLWH compared with HIV-negative women.

ART modifies these associations by mitigating HIV effects on the immune system. However, the evolution of ART regimens over the past 3 decades has often complicated uniform interpretations of the effect of ART across studies. Furthermore, a one-time measurement of ART status is an imperfect surrogate of adherence to ART and retention in the HIV care cascade over the long-term, which are key factors for HIV viral control and immune restitution. In addition, the development of HIV resistance to ART regimens can reduce their effectiveness for immune reconstitution despite adequate adherence.[37,38] Variations in methods to detect cervical disease status due to variability in screening and diagnostic tests (especially seen with visual screening approaches and cytologic/histopathologic interpretations) also affect the interpretation of these associations. Finally, in the context of a dynamic immune milieu with swings between relative immunosuppression and immune restoration states in WLWH, cervical HPV detection may represent reactivation of latent/quiescent infections[39] as opposed to new infections, as also observed in studies among women undergoing long-term immunosuppressive therapy after solid organ transplants.[40,41]

Notwithstanding these significant methodologic limitations, meta-analyses of the available literature suggest that WLWH have a higher risk of HPV acquisition, presumably due to shared behavioral risk of sexual transmission but also likely due to immune dysregulation (presumably because more incident HPV infections, even those destined to clear, persist long enough to be detected[42,43]), as evidenced by the inverse association between HPV acquisition risk and markers of HIV control/immune status (eg, CD4 counts).[43-45] WLWH have an approximately ≥2-fold prevalence of HPV compared with HIV-negative women.[46-52] Among WLWH, HPV prevalence was lower among those receiving ART (vs not),[51,53,54,55,56,57,58,59] on longer (vs shorter) duration of ART,[20,54] with higher (vs lower) CD4 counts,[51,54,55,56,57,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75] and with a lower HIV viral load.[58,70,71]

In multiple HPV type infections, individual HPV type infections likely act independently rather than synergistically and thus contribute additively to the cervical cancer risk. A few studies in the general population have found that multiple HPV infections with non-HPV16 types increase

the risk of cervical precancer and cancer.[76,77] WLWH are from 2-fold to 3-fold more likely to have multiple HPV infections (among HPV-positive women) compared with HIV-negative women.[47,48,49,52] Receiving ART[56] and having a lower HIV viral load[78] and/or higher CD4 counts[73,78] are associated with fewer multiple HPV infections.

HIV infection increases the likelihood of cervical HPV infection persisting and, given its persistence, progressing to precancer, and it reduces the likelihood of clearance/regression of low-grade and high-grade cervical abnormalities.[44] A recent meta-analysis[53] reported that ART was associated with reduced incidence of incident high-grade cervical abnormalities (adjusted odds ratio, 0.59), progression from low-grade to high-grade cervical abnormalities (adjusted odds ratio, 0.64), and an increased regression of cervical abnormalities (adjusted hazard ratio [HR], 1.54). Most importantly, data from 2 studies included in that meta-analysis demonstrated that ART was associated with a reduced risk (adjusted HR, 0.50) of invasive cervical cancer.[53] Likewise, low CD4 counts were strongly associated with cervical cancer risk,[79] and low CD4 counts at the time of ART initiation were also associated with an increased risk of cervical cancer.[35] Overall, the age at cervical cancer diagnosis in WLWH is approximately 5 to 10 years younger than that in HIV-negative women,[33,80,81,82,83,84] highlighting the possible role of HIV coinfection as an *accelerant* in cervical carcinogenesis.

It is less clear whether HIV infection and immune status influence the last step of HPV-related carcinogenesis: cervical precancer developing into invasive cancer. It is unethical to observe the progression of cervical precancer into cancer, as was observed tragically in the "The Unfortunate Experiment": from 1955 to 1976, New Zealand's National Women's Hospital withheld treatment from women diagnosed with cervical precancer.[85] Over the next 30 years, approximately 30% of these women with untreated cervical precancer developed cervical cancer.[85] Fortunately, no such experiment has been done among WLWH diagnosed with cervical precancer.

There are no high-quality, well powered, population-based, cross-sectional studies comparing the prevalence ratio of cervical intraepithelial neoplasia grade 3 (CIN3)/adenocarcinoma in situ (AIS) and invasive cervical cancer as a proxy for invasive potential in WLWH versus HIV-negative women. Such an approach (vs comparing between separate studies of WLWH or HIV-negative women with different methods, etc), by using statistical methods to control for the effects of differences in screening, variability of pathology diagnosis,[86] sociodemographic determinants, and behavioral and cultural factors, might provide some indication of whether there are gross differences in the invasive potential of cervical precancer according to HIV status and the degree of immune reconstitution. HPV genotyping data might provide insights into how these factors influence HPV genotype-specific invasive potential, as has been shown in a meta-analysis of data from the general population.[87] A few studies report lower CD4 counts in women diagnosed with cervical cancer versus those with precancerous abnormalities,[71,88] suggesting that immunity may play a role in this final step in cervical carcinogenesis.

Interestingly, of the few studies that have reported on stage distribution of cervical cancer, most did not find a significant difference in cancer stage at diagnosis in WLWH compared with HIV-negative women[83,89,90,91]; one study reported more stage IIIb cervical cancer in WLWH than in HIV-negative women.[92] The general lack of a difference in cancer stage distribution between WLWH and HIV-negative women may be a result of the early stage presentation of symptoms, such as postcoital bleeding in both, and/or because WLWH are generally under closer clinical surveillance than HIV-negative women.

There are some data that point to differences in the HPV type-specific natural history in WLWH compared with HIV-negative women. First, the types most commonly found in HIV-negative women, notably HPV16, are the least affected by the immune status in WLWH.[93] Second, HPV16 is less commonly detected in CIN3 diagnosed in WLWH than in HIV-negative women.[94] Finally, there is some evidence to suggest that HPV16 is somewhat less dominant in cervical cancers diagnosed in WLWH than in HIV-negative women.[95,96] Such type differences might play a role in the time to develop HPV-associated disease, because women with HPV16-related (and HPV18-related) cervical cancers diagnosed in the general population are approximately 5 years younger than women with cervical cancers related to other types.[97] These differences also could reduce the effectiveness (eg, positive predictive value) of HPV16 and HPV18 genotyping for clinical decision making, as recommended in the general population, in the management of HPV-positive WLWH.[98]

These data highlight the importance of using ART in cervical cancer risk reduction. Counterintuitively, PLWH live longer on ART,[10,11] giving them more time to develop HPV-related cancers, which may partially offset its cancer risk-reducing benefits.[99,100] This may explain the time trend of increasing cervical cancer risk in WLWH compared with HIV-negative women observed in South Africa.[101] Thus the integration of prevention strategies with the delivery of ART to WLWH will maximize the cervical cancer prevention benefits of ART, as discussed below.

Primary Prevention: Prophylactic HPV Vaccination

The discovery of high-risk HPV infections as the necessary cause of cervical cancer has led to revolutionary advances in cervical cancer prevention, including the development of

prophylactic HPV vaccines for primary prevention. Current prophylactic HPV vaccines are based on the self-assembly of recombinantly expressed L1 protein in cell lines into virus-like particles that resemble native viral capsids but without the viral genome necessary for viral replication.

First-generation HPV vaccines, Gardasil (Merck & Company, Kenilworth, New Jersey)[102] and Cervarix (GlaxoSmithKline, Rixensart, Belgium),[103] target HPV16 and HPV18 (HPV16/HPV18), which cause approximately 70% of cervical cancers. Gardasil also targets HPV6 and HPV11 (HPV6/HPV11), which are non-high-risk HPV types responsible for 90% of anogenital warts (*Condyloma acuminata*). The next-generation HPV vaccine, Gardasil 9 (Merck & Company),[104] targets HPV31, HPV33, HPV45, HPV52, and HPV58 in addition to HPV6, HPV11, HPV16, and HPV18 and is predicted to prevent approximately 90% of cervical cancers. Notably, the same types of HPV cause cervical cancer in approximately the same proportions in every region of the world, with the exception of Africa, as discussed below.[105]

Because HPV vaccination is only prophylactic and not therapeutic, the ideal timing of HPV vaccination is before sexual initiation and exposure to HPV (ie, HPV-naive women). On a population level, this can be achieved by vaccinating a few years before the population median age of sexual initiation. Because the median age of sexual initiation in many countries is typically from 15 to 17 years, the WHO recommends vaccination programs to target girls aged 9 to 13 years,[106] and the CDC recommends routine HPV vaccination for girls (and boys) aged 11 to 12 years.[107] With older cohorts of women, prophylactic vaccine is equally efficacious but less effective; ie, older age does not reduce vaccine efficacy in HPV-naive individuals but, because there are fewer HPV-naive women at older ages, overall vaccine effectiveness and cost-effectiveness of prophylactic vaccination decreases.[108-110] On the basis of immunogenicity data, the WHO[111] and the CDC[95,112] recommend 2-dose schedules for those younger than 15 years and 3-dose schedules for those aged 15 years and older for all HPV vaccines. There is increasingly strong evidence that a single dose of HPV vaccine is sufficient to confer protection equivalent to multiple doses.[113,114]

Several countries, eg, Australia,[115-121] Scotland,[122] Denmark,[123] and the United States,[124-126] were early adopters of HPV vaccination and have documented population reductions in HPV infections and HPV-related diseases and abnormalities. Australia, for example, implemented vaccination with Gardasil in 2007, shortly after its US Food and Drug Administration approval and after a public awareness campaign. Their HPV vaccination program for females achieved >70% coverage in its first year and in subsequent years.[115] Within several years after their national HPV vaccination was implemented, there was a significant decrease in anogenital warts among women and heterosexual men (because of herd protection), but not among men who have sex with men.[116] Subsequently, there have been documented decreases in the prevalence of HPV16 and HPV18 in vaccinated women,[117,118] and now in unvaccinated women (because of herd protection),[118] and in the prevalence of high-grade cervical abnormalities, first in younger women[119,120] and now in slightly older women,[121] as HPV-vaccinated cohorts have aged.[127] A meta-analysis on the impact of HPV vaccination found reductions in anogenital warts, HPV infections, and CIN grade 2 (CIN2) or more severe (CIN2+) diagnoses among girls and women and in diagnoses of anogenital warts among girls, women, boys, and men.[128] Recent reports from Finland,[127] Sweden,[129] and Denmark[130] now provide real-world evidence that HPV vaccination prevents cervical cancer.

HPV vaccination in PLWH has been well tolerated and safe and has resulted in good immune responses. One study of Gardasil[131] in children living with HIV aged 7 to 12 years reported high-seroconversion, 4-year persistent, HPV type-specific immunity[132] and immune memory cells[133] and a significant increase in, and persistence of, antibody titers (anamnestic response) after an additional booster (fourth dose).[132] A study of Gardasil in adult men living with HIV also found high seroconversion in addition to a good safety profile.[134] Another study reported a seroconversion rate similar to that of Gardasil in WLWH and HIV-negative women aged 13 to 27 years.[135]

Some studies have noted an impact of HIV disease status (CD4 counts and viral suppression) on immune responses to HPV vaccination. One study reported lower HPV seroconversion and antibody titers in young adult WLWH not taking ART compared with those taking ART.[136] Another study reported lower seroconversion and antibody titers in adult WLWH who had lower (vs higher) CD4 counts.[137] A third study reported that peak antibody titers after Gardasil vaccination were 2-fold to 3-fold higher in mid-adult WLWH with full HIV viral suppression versus those without viral suppression.[138]

Two studies have compared the immune response to Cervarix versus the response to Gardasil in adult PLWH. Both studies found that the antibody titers after Cervarix immunization were superior to those after Gardasil.[139,140] However, it remains unclear whether this difference in antibody titers translates into meaningful differences in efficacy or duration of protection.[141]

Immunogenicity studies in WLWH have been of insufficient sample size to address efficacy/effectiveness in preventing clinical disease. Studies of HPV vaccination in select PLWH at high risk of anal cancer have been limited in their effective sample size because of the high degree of anal HPV exposure (and likely misclassification of exposure) to targeted HPV genotypes before enrollment[142] and the possible reactivation of previously acquired, latent HPV infection, such that few truly incident events can be observed.

Another challenge in conducting placebo-controlled randomized clinical trials to demonstrate efficacy of HPV vaccines

is that projected effect sizes are attenuated by lower-than-expected number of endpoints in placebo-arm participants, who may be practicing lesser risky behaviors with fewer exposures during the course of thestudy (presumably with adequate counseling and awareness of risk in relatively controlled clinical trial settings). This may result in studies being stopped as per pre-defined rules for futility, as evidenced in a recent trial of Gardasil in older men (aged 27 years and older) to prevent anal HPV infectionor anal high-grade squamous intraepithelial lesions.[143] Yet, this same study suggested a signal of potential benefit for protection against oral HPV that is now under further investigation (ClinicalTrials.gov identifier NCT04255849).

Another study of Gardasil vaccination in perinatally HIV-infected versus HIV-exposed, uninfected youth reported a 5-fold higher incidence of abnormal cervical cytology among the former, suggesting that HPV vaccination is likely less effective in the context of perinatally acquired HIV infection.[144] Not surprisingly, HPV vaccination with Gardasil either before[145] or after[146] excision of high-grade cervical/anal abnormalities in persons with HIV, did not prevent recurrence of lesions,[145,146] and it seems unlikely that Gardasil 9 will either (ClinicalTrials.gov identifier NCT03284866). However, HPV vaccination should prevent newly acquired (not latent) infection by HPV vaccine-targeted types acquired posttreatment from developing into new (vs recurrence of the same, type-specific) high-grade cervical abnormalities.

A recent study compared the effectiveness of catch-up HPV vaccination (ages 13-26 years) in women with history of immunosuppression (mostly HIV) versus those without a history of immunosuppresion.[147] HPV vaccination significantly reduced the risk of CIN2+ by 19% in those without a history of immunosuppression, whereas the risk was not significantly reduced in those with such a history.

There is still a need to assess the efficacy, effectiveness, and duration and determinants of protective immunity of prophylactic HPV vaccines in PLWH. Given the immunodeficiencies related to HIV infection and the lack of defined immune correlates of protection, it is unclear whether immunogenicity, as measured by antibody or neutralizing antibody titers, is a good proxy for the efficacy and long-term effectiveness of HPV vaccines in PLWH. Some key outstanding questions for HPV vaccination in PLWH include: 1) how many doses are needed for protective immunity, and does an adjuvanted vaccine (eg, AS04 adjuvant in Cervarix) improve the protective immunity such that fewer doses are needed to achieve long-lasting, protective immunity compared with unadjuvanted HPV vaccines (eg, Gardasil); 2) does protective immunity wane; and 3) do these vaccines provide sufficiently broad coverage against the HPV types that cause cancer in PLWH?

As noted, there is some evidence to suggest that the distribution of HPV types that cause cervical cancer in WLWH is somewhat different from that in the general population/HIV-negative women such that HPV16 is somewhat less predominant in cervical precancer and cancer diagnosed in WLWH.[95,96] HPV35, a type in the same phylogenetic group (α-9) as HPV16, is particularly common in cervical cancers diagnosed among WLWH living in Africa,[95] precancers diagnosed among WLWH living in SSA and Sweden,[148] and precancers diagnosed among WLWH and HIV-negative women living in South Africa.[149] This may be due in part to viral variants of HPV35 that cause more cancer in women of African descent than in women of other ethnicities.[150] Whether there are any independent effects of HIV coinfection and African descent on the HPV type distribution in cervical cancer is uncertain given the high proportion of WLWH who are of African descent. Regardless, current HPV vaccines might be less effective in preventing cervical cancer in WLWH and/or in women of African descent than in other populations. Of note, there is already some evidence that Cervarix, which targets only HPV16 (vs HPV16, HPV31, HPV33, HPV52, and HPV58 in Gardasil 9) among α-9 types, induces some immunity, cross-protection, and herd immunity against HPV35,[151-153] including immunity in WLWH.[154]

The optimal HPV vaccination strategy for long-term protection against cervical cancer in WLWH, especially those living in LMICs, has yet and needs to be established. The US Advisory Committee on Immunization Practices recommends 3-dose HPV vaccination (at 0, 1 or 2, and 6 months) for females and males aged 9 to 26 years who have primary or secondary immunocompromising conditions.[155] However, as noted by the 2017 American Society of Clinical Oncology (ASCO) resource-stratified recommendations, HPV vaccination of WLWH is a D-level recommendation (ie, *insufficient* evidence quality, *weak* strength of recommendation).[156]

The use of more viable end points, such as short-term HPV persistence, which is strongly predictive of high-grade cervical abnormalities[157,158] and is accepted as a trial end point,[159] will increase the feasibility of studies to answer these questions. However, the use of HPV persistence as an end point must be interpreted with caution because of the possibility of reactivation of latent HPV infections, which may have obfuscated the benefits of HPV vaccination in clinical trials in adult WLWH who were previously exposed to HPV. This will be less of an issue for trials in which HPV vaccines are given before sexual initiation, at a time when the vaccines will provide the greatest benefit regardless HIV status. Nevertheless, a long-term follow-up of WLWH participants in a trial that used 6-month HPV persistence as its end point will be important to confirm the vaccine effectiveness.

If the next generation of HPV prophylactic vaccines can produce broad-spectrum immunity, either by adding a more active adjuvant than the aluminum-based adjuvant to 9 HPV types included in Gardasil 9 or by expanding the types

included with the AS04 adjuvant used with Cervarix, it will be important to establish their long-term effectiveness and the number of doses needed to achieve that protection in WLWH living in LMICs, perhaps the most vulnerable population. At least one such vaccine is under development.[160]

Secondary Prevention: Cervical Screening, Management, and Precancer Treatment

New guidelines[161] from the WHO on cervical cancer screening and treatment recommend the use of HPV DNA testing as the primary cervical cancer screening test, although visual inspection after acetic acid (VIA) and Papanicolaou (Pap) tests may continue to be used according to local guidelines in various settings when HPV DNA testing is not *operational*. These guidelines recommend HPV testing-based screening for women aged 30 to 49 years every 5 to 10 years. For WLWH, these guidelines recommend HPV testing-based screening for women aged 25 to 49 years every 3 to 5 years. These are similar to recent resource-stratified guidelines for cervical cancer screening from the ASCO that recommend screening WLWH twice as frequently using HPV testing as what is recommended for HIV-negative women and the general population within the resource strata.[162]

Studies have demonstrated unequivocally that testing for HPV DNA is more effective than Pap testing[163-166] and VIA[164] in the prevention of cervical cancer. In a cluster randomized trial of approximately 100,000 women aged 30 to 59 years living in India,[164] a single round of HPV DNA testing reduced cervical cancer-related mortality by 50% in 8 years (HR, 0.52; 95% CI, 0.33-0.83), whereas Pap testing (HR, 0.89; 95% CI, 0.62-1.27) and VIA (HR, 0.86; 95% CI, 0.60-1.25) did not reduce cancer-related mortality compared with the community control. Moreover, a negative HPV test provided approximately 4-fold greater reassurance than negative Pap and VIA results against incident cervical cancer (3.7, 15.5, and 16.0 per 100,000 person years, respectively). In a pooled analysis of 4 randomized control trials in Europe that included approximately 175,000 women aged 20 to 64 years who were assigned to either HPV or cytology,[165] HPV testing reduced the incidence of invasive cervical cancer by 40% compared with cytology (rate ratio, 0.60; 95% CI, 0.40-0.89), and a negative HPV test was 70% more reassuring against cancer than cytology (rate ratio, 0.30; 95% CI, 0.15-0.60) over a 6.5-year follow-up period.

As a result of its superior sensitivity for cervical precancer/cancer and reassurance against incident cervical cancer after a negative screen, HPV testing is increasingly being adopted, recommended, and implemented as the primary (standard-of-care) cervical screening method in HICs, including the United States, despite the preexistence of highly successful Pap screening programs.[167-169] The US Preventative Services Task Force[170] and the American Cancer Society[171] have recommended HPV testing as the acceptable and preferred option, respectively, for cervical cancer screening, and it has been endorsed by several professional medical societies, including the Society of Lower Genital Tract Diseases (formerly known as the American Society of Colposcopy and Cervical Pathology),[172] ASCO,[162] The American College of Obstetrics and Gynecology,[173] and the Society for Gynecologic Oncology.[174] Several European countries have implemented or are implementing HPV testing for cervical cancer screening.[175] Notably, HPV testing for cervical cancer screening is being recommended for LMICs.[176,177]

One important advantage of HPV testing-based screening over other screening modalities is the possibility of using self-collected cervicovaginal specimens rather than provider-collected specimens. HPV testing of self-collected specimens minimizes the reliance on clinic-based screening and overcomes barriers such as geographic inaccessibility, lack of an adequate health care provider workforce, the need for a pelvic examination, or sociocultural issues that have been historically associated with lack of screening or underscreening. A recent meta-analysis reported that there was virtually no difference in the clinical performance for the detection of cervical precancer and cancer between the 2 specimen types when a polymerase chain reaction-based HPV test (eg, GP5+/6+; cobas [Roche Molecular Systems, Pleasanton, California]; and Onclarity [Becton Dickinson, Franklin, New Jersey]) was used (relative sensitivity [vs provider-collected specimen], 0.99; 95% CI, 0.96-1.02; relative specificity [vs provider-collected specimen], 0.98; 95% CI, 0.97-0.99).[178] By comparison, there was a slight decrement in the clinical performance when a signal amplification-based HPV test (eg, Hybrid Capture 2 [Qiagen, Germantown, Maryland]) was used (relative sensitivity [vs provider-collected specimen], 0.86; 95% CI, 0.76-0.98; relative specificity [vs provider-collected specimen], 0.97; 95% CI, 0.95-0.99).[178] Women were more likely to self-collect when a kit was mailed to their home than to undergo routine screening prompted by invitation/reminder letters (relative participation, 2.33; 95% CI, 1.86-2.91).[178] However, there is a paucity of data on the comparative clinical performance and acceptability of self-collected versus provider-collected specimens for HPV testing in WLWH.

Given its clinical performance and reliability, HPV testing has significant potential for widespread adoption and scalability across LMICs, but only if robust, LMIC-ready HPV tests are made affordable and available through innovative financing and procurement mechanisms. Currently, there are 2 promising polymerase chain reaction-based HPV tests for use in LMICs, the Xpert HPV test (Cepheid, Sunnyvale, California) and the AmpFire Multiplex High Risk HPV Real Time Fluorescent Detection with HPV16/18 Genotyping (Atila BioSystems, Mountain View,

TABLE 1. Simulation of the Impact of HIV Control on Human Papillomavirus Test Performance for the Detection of Cervical Precancer and Cancer (Cervical Intraepithelial Neoplasia Grade 3 or More Severe Diagnoses [CIN3+])[a]

WLWH WITHOUT HIV CONTROL	CIN3+ (PREVALENCE: 5%)	<CIN3	TOTAL	PREDICTIVE VALUES
HPV test result				
Positive	450	4550	5000	PPV, 9.0%
Negative	50	4950	5000	NPV, 99.0%
Total	500	9500	10,000	
	Sensitivity, 90.0%	Specificity, 52.1%		

WLWH WITH HIV CONTROL	CIN3+ (PREVALENCE: 2.5%)	<CIN3	TOTAL	PREDICTIVE VALUES
HPV test result				
Positive	225	2275	2500	PPV, 9.0%
Negative	25	7475	7500	NPV, 99.7%
Total	250	9750	10,000	
	Sensitivity, 90.0%	Specificity, 76.7%		

SIMULATION OF US POPULATION FOR REFERENCE	CIN3+ (PREVALENCE: 0.5%)	<CIN3	TOTAL	PREDICTIVE VALUES
HPV test result				
Positive	45	955	1000	PPV, 4.5%
Negative	5	8995	9000	NPV, 99.9%
Total	50	9950	10,000	
	Sensitivity, 90.0%	Specificity, 90.4%		

Abbreviations: <CIN3, a diagnosis of less than grade 3 cervical intraepithelial neoplasia; CIN3+, cervical intraepithelial neoplasia grade 3 or more severe diagnoses; [CIN3+]; HPV, human papillomavirus; NPV, negative predictive value; PPV, positive predictive value; WLWH, women living with HIV.
[a]Typically, prevalence of the disease only influences PPV and NPV, not sensitivity and specificity. However because immune status influences both the prevalence of disease (ie, CIN3+) as well as the test biomarker (ie, HPV), the specificity of HPV to detect CIN3+ is indeed influenced by immune status. For this simulation, we assume: 1) the prevalence of HPV in WLWH without HIV control (eg, no antiretroviral therapy) is 50% (top), in WLWH with HIV control is 25% (middle), and the general US population of women (for reference) is 10% (bottom); 2) the prevalence of CIN3+ in WLWH without HIV control (eg, no antiretroviral therapy) is 5% (top), in WLWH with control is 2.5% (middle), and the general US population of women (for reference) is 0.5% (bottom); and 3) the sensitivity of HPV testing for cervical precancer and cancer is 90% and does not differ by immune status or HIV status.

California). The Xpert HPV test is a random-access, rapid (60 minutes), WHO-prequalified[179] HPV test run on the multianalyte GeneXpert clinical laboratory platform; however, a cost of almost $15 per test is not generally affordable for widespread use in LMICs.[180] AmpFire is an isothermal amplification HPV test but currently lacks sufficient evidence of clinical performance for regulatory approvals and adoption, and its commercial price is unknown.

HPV testing has shown similar sensitivity for high-grade cervical abnormalities among WLWH and HIV-negative women but has lower specificity because of the higher HPV prevalence, which leads to more HPV-positive women in need of follow-up care. Head-to-head comparisons have demonstrated that HPV testing is more sensitive but less specific than VIA and/or Pap testing for the detection of high-grade cervical abnormalities.[57,181,182,183,184,185,186,187] Importantly, a negative HPV test, even in WLWH, provides excellent reassurance against high-grade cervical[187-189] and anal[190] abnormalities and cancers.

HPV test specificity is influenced by HPV prevalence, which, in turn, is influenced by HIV prevalence and control, as previously discussed[191] and illustrated in Table 1. As noted above, among WLWH, HPV positivity decreases and HPV test specificity increases with a higher CD4 count,[51,54,55,56,57,60,61,62,63,64,65,66,67,68,69,70,71] ART use and duration,[51,53,54,55,56,57,58,59,192] and lower HIV viral load.[58,70,71] One study reported that national implementation of ART for PLWH in Rwanda led to a time trend of higher CD4 counts and lower HPV prevalence.[67]

Likewise, VIA and Pap test specificity is influenced by HIV infection and its control, probably as a result of their influence on HPV prevalence, as shown in one study that controlled for the presence of HPV.[193] VIA positivity is higher (and its specificity is lower) for WLWH (vs HIV-negative women)[182,194,195,196,197,198,199,200] and, among WLWH, for those with lower CD4 counts[183,201] and lack of ART use.[57] Pap test positivity is higher (and its specificity is lower) for WLWH (vs HIV-negative women)[71,202] with higher CD4 counts[71,183,193,203,204,205,206,207,208] and lower HIV viral loads.[71,205]

Therefore, although there is not consistency across all studies about which types of biomarkers[44,88] (eg, absolute CD4 count, CD4 percentage of total T-cell count, and HIV viral load) or clinical markers (eg, ART status, duration of ART use, and ART adherence measures) of HIV disease

status/immune competency are most strongly associated with the accuracy of cervical cancer screening tests, and not all studies have reported or controlled for all such markers, there is consistent evidence that HIV control in general improves cervical cancer screening test performance by improving its specificity. The implication of these data is that, with good HIV control, fewer WLWH will screen positive, which is especially important in LMICs with limited capacity and resources to manage them. Conversely, with uncontrolled HIV, the benefits versus harms of HPV testing are less certain not only because the high HPV positivity results in poor specificity, leading to overtreatment, but because of the increased burden on limited, financially strapped health care systems to manage patients who have positive results.

A secondary triage test of HPV-positive WLWH can be included to increase specificity but at the price of reducing sensitivity for high-grade cervical abnormalities as well as increasing cost, complexity, and burden on the health care system. Studies have evaluated visual triage (VIA or visual inspection with Lugol iodine),[181,184,187,209,210] cytology,[187,210,211] p16/Ki-67 dual-stain immunocytochemistry,[209] HPV genotyping/type restriction,[181,187,210,211,212,213] changing the positive cutoff point/viral load,[213] and host[214,215] and viral methylation[216] biomarkers measured from the cervical specimen. There is no consensus approach to choosing which triage test to use for HPV-positive WLWH, and the choice may depend on local capacities and which HPV test is being used for primary screening. A large study of screening and triage strategies in 5000 WLWH living in Rwanda may provide important data on triage strategies for HPV-positive WLWH.[217]

Although no studies are published on the impact of HIV control on the performance of colposcopy, it is reasonable to expect that greater HIV control will lead to fewer and smaller visible acetowhite abnormalities, like what is observed for VIA, because of fewer and better controlled prevalent HPV infections. Whether better HIV control might result in poorer colposcopic performance will likely depend on the skill of the colposcopist and their willingness to take multiple biopsies, which increases the sensitivity of colposcopic-directed diagnoses.[218,219]

The treatment of cervical cancer precursors also is affected by HIV. Treatment by any method is more likely to fail in WLWH than in HIV-negative women.[220] In HICs, the primary treatment modality is excision (loop electrosurgical excision procedure, large loop excision of the transformation zone, or cone excision) of histologically confirmed CIN2, CIN3, or AIS. Margins with disease (*positive margins*) after excision are a strong predictor of recurrent (incomplete treatment) disease in the general population[221] and also in WLWH.[220,222,223] As a result of having larger areas of abnormality, WLWH are more likely to have positive margins[224,225] and recurrence[220,224,226,227,228,229,230] than HIV-negative women. Among WLWH, a higher CD4 count,[224,231,232,233,234,235] ART before treatment,[236] and a lower HIV viral load[222] are associated with a lower risk of recurrence.

Where the capacity for excising cervical abnormalities is lacking, primarily in low-resource settings, tissue ablation by cryotherapy or thermal ablation is the primary method of treating cervical abnormalities. Tissue ablation, which potentially does less destructive damage to the cervix, may have a role in the treatment of smaller lesions or persistent HPV infection in WLWH,[237] especially within single-visit *screen-and-treat* programs that seek to improve operational efficiencies by reducing attrition. Those cervical abnormalities that cover >75% of the cervical transformation zone, that are suspicious of cancer, and/or that cannot be fully visualized are deemed ineligible for ablative treatment and are referred for excisional treatment or cancer treatment, as needed.[238]

WLWH are more likely than HIV-negative women to have an ablation-ineligible cervical abnormality,[239,240] again suggesting that WLWH have larger, harder-to-treat cervical abnormalities than HIV-negative women. Low CD4 counts[241-243] and high HIV viral loads[222] in WLWH are associated with the recurrence of cervical abnormalities after treatment. Loop electrosurgical excision procedure/large loop excision of the transformation zone has shown more efficacy in treating CIN2+ than cryotherapy in WLWH, especially in those with CD4 counts <250/mm^3, perhaps because of the size of the abnormality,[244] indirectly supporting WHO recommendations to refer larger cervical abnormalities for excisional rather than ablative therapy.[238] Although excisional treatments may be more efficacious than ablative treatments in WLWH, especially for those with uncontrolled HIV infections, the cancer prevention benefits of each must weighed carefully against their potential harms, such as preterm birth and procedural complications, especially in relation to a woman's desire to have children in the future and the ability of the health care system to manage those complications.[245,246]

Thermal ablation (thermocoagulation) is now recommended as an alternative to cryotherapy[247] and should be applied using the same WHO guidelines as cryotherapy.[238,247] However, there remains a dearth of data on the short-term and long-term effectiveness of any tissue ablative methods to treat high-grade cervical abnormalities and reduce cancer risk in WLWH.[247,248] A new clinical trial may help address these knowledge gaps.[249]

Cancer Management

The survival of WLWH with locally advanced cervical cancer (LACC) after treatment in the era of ART differs from patient outcomes that were observed at the onset of the AIDS epidemic. Cervical cancer screening is often part of the basic services provided in HIV screening and treatment

settings, resulting in the earlier detection of cancers. In addition, most patients are on ART at the time of their cervical cancer presentation and have high CD4 counts.[250] Many have been viremically HIV-suppressed on ART for several years before cancer diagnosis compared with older cohorts before increased HIV care capacity existed.[251] Also, for those who are not on ART at the time of their cervical cancer diagnosis, as part of treatment, they are all started on ART, which has led to historical differences in treatment completion, tolerability, and survival compared with historical cohorts. In prospectively followed patients with HIV-associated LACC who were treated on protocol in Zimbabwe and South Africa, concomitant chemoradiotherapy with cisplatin, at the same doses used for HIV-negative women with LACC, was well tolerated with excellent survival.[252] Furthermore, those WLWH who had LACC with the best HIV viremic control tolerated treatment better and had the best survival outcomes.[253,254]

Radiation therapy is the primary treatment for LACC, regardless of HIV status. However, because of the lack of radiation equipment, trained personnel, as well as cost differences or delays because of limited services in public-sector hospitals in LMICs, more aggressive surgical approaches have been considered. This, however, requires experienced gynecologic surgeons with expertise in radical hysterectomies and the complications that arise from these complex surgeries—personnel who are in limited supply and high demand in LMICs. Mostly retrospective investigations of the use of neoadjuvant chemotherapy to shrink the tumor to make the completion of surgery possible have been done and have shown mixed results, with no studies exclusively focusing on WLWH.[255-258] A 2003 meta-analysis found that studies with chemotherapy cycle lengths ≤14 days or cisplatin dose intensities ≥25 mg/m^2 per week showed a slight improvement in survival with neoadjuvant chemotherapy and radiation versus radiation alone, whereas longer cycle lengths or lower cisplatin dose intensities reduced survival.[257] A randomized controlled trial in India found poorer disease-free survival (HR, 1.38) but similar overall survival (HR, 1.03) for neoadjuvant chemotherapy plus surgery compared with concomitant chemoradiation.[258] A retrospective review of data from 3 northern Italian hospitals found better disease-free survival (HR, 3.95) and overall survival (HR, 5.33) for neoadjuvant chemotherapy plus surgery compared with concomitant chemoradiation.[255] None of those studies focused on WLWH or reported on the effects on WLWH in a subgroup analysis. Ethically, such an approach might present challenges in some regions of the world because additional high-risk features (eg, lymph node positivity, positive margins) might still require the need for radiation therapy.

Immunotherapies and targeted therapies have been shown to improve survival in the recurrent setting.[259-262] However, there is limited information on the role of these therapies in the setting of HIV and no information on a survival benefit in HIV. Early phase clinical trials to assess safety are underway.[263] In addition, many immunotherapies and targeted therapies might be cost prohibitive in the regions of the world that need it the most, which calls into question the ethics of studying such agents in women with HIV-associated LACC in LMICs unless some provision is made to make them available and affordable.

A recent meta-analysis of retrospective or prospective cohort studies, most of which were conducted in SSA and published between 2012 and 2018, on the chemoradiation treatment of LACC in WLWH found that: 1) 8 of 13 studies identified reported no significant differences in treatment outcomes, 2) 6 of 8 studies identified reported no significant difference in survival, 3) all 4 studies identified reported no significant differences in treatment response, and 4) all 6 studies identified reported no significant differences in toxicity between WLWH and HIV-negative women.[264] Of note, one of the 13 studies included in the meta-analysis found that there was a difference in overall survival if the WLWH group included those not on ART.[264,265] Another of the studies included in the meta-analysis commented that, with regard to the effect of HIV status on the survival of women with invasive cervical cancer, 27.5% of patients tested positive for HIV and had poorer survival compared with those who were HIV-positive, although the difference was not statistically significant.[266] A recent AIDS Malignancy Consortium feasibility study found that a high proportion of WLWH with LACC will complete concomitant chemoradiotherapy with the same cisplatin dose as, and with tolerability comparable to, that in HIV-negative women.[252] Two studies have reported that lower CD4 counts[90,253] among WLWH were associated with poorer survival from cervical cancer. Importantly, although some studies have reported worse outcomes for WLWH compared with HIV-negative women, possibly related to being immunocompromised, none of the studies have reported better outcomes for WLWH versus HIV-negative women.

Taken together, immune status, or at least HIV status, might play a role in survival from LACC. Additional investigations are needed to clarify the role of HIV status in cervical cancer management outcomes and to optimize care.

Barriers to Implementation

Although not specific to cervical cancer prevention in WLWH, there are several barriers to implementing a global cervical cancer prevention and control program in LMICs where most WLWH live. In relation to primary and secondary prevention strategies, because the burden of cervical cancer disproportionately affects the poorest countries and populations, a global procurement strategy with innovative

financing mechanisms is needed to improve the availability and affordability of HPV vaccines as well as HPV tests for cervical cancer screening. In addition, without addressing patient-specific social determinants of health care, even with effective access to primary and secondary prevention like what we see in HICs, disparities will persist. Models for reaching the lowest income countries through entities such as GAVI, the Vaccine Alliance should also spur efforts to reach GAVI-support ineligible LMICs that are also largely unable to afford these interventions because of competing priorities within overstretched health budgets.

Underlying the challenges of implementing and scaling up cervical cancer prevention, treatment, and care services for women with HIV in LMICs, especially in some of the highest burden countries in SSA, are some of the most persistent challenges that have historically affected similar vertical, disease-focused programs. In particular, the lack of availability of a specialized and trained workforce and suboptimal health care infrastructures often limit widespread, equitable, and affordable access to high-quality services such as surgery, oncology, radiation, and pathology.[267-273] Although there are ongoing efforts to address these gaps,[274-276] it is likely to be decades before these services are of sufficient quality and quantity to meet the demands of cervical cancer prevention and control in these regions as well as many other health care demands. In the meantime, cervical cancer prevention and control programs will need work within those limitations to make progress in averting cervical cancer-related morbidity and mortality.

Financing for cancer-specific services and infrastructures, especially in the public sector and with other competing disease priorities, is often a challenge for already severely constrained national health care budgets. External financing efforts, including through multilateral or bilateral donor initiatives[277,278] and philanthropic/nonprofit sector investments,[279] have been critical to augment and expand nascent efforts by in-country agencies, although ensuring the sustainability of such approaches over the long term remains an ongoing challenge.[280]

Rwanda is an illustrative example of both the successes and challenges of cervical cancer prevention and control in LMICs. In 2010, Rwanda entered public-private partnerships with Merck and Qiagen to launch a national cervical cancer prevention program of prophylactic HPV vaccination in preadolescent females and HPV testing-based screening in mid-adult women, respectively. From 2011 to 2013, Merck donated Gardasil to the Rwanda government, which launched arguably the most successful national HPV vaccination program globally, achieving a laudable >90% coverage of 12-year-old girls in its first year.[281] In contrast, the establishment of a complementary national cervical cancer screening program for mid-adult women remained unrealized, largely because of costs and the lack of health care infrastructure to provide the necessary follow-up care of screen-positive women.

Summary

HIV is an important risk factor for cervical cancer. HIV exerts its effects by acting as an HPV cofactor to increase the likelihood of viral persistence and perhaps progression and invasion.

Because cervical cancer is only one and, relatively speaking, an infrequent comorbidity of HIV infection, its prevention in itself is not a reason for HIV control. Yet, in high-burden countries, where there are the least resources and capacities to directly address the cervical cancer burden and the prevalence of HIV is often high, good HIV care might be the easiest and most cost-effective first step in cervical cancer prevention. Better HIV care through increased access to ART will reduce cervical cancer risk overall, although there might be a short-term increase in cervical cancer incidence as the result of reducing HIV-related deaths as a competing risk.[282]

Therefore, achieving the WHO goal for HIV control of "90-90-90" (ie, 90% diagnosis, 90% treated, and 90% virally suppressed) for HIV care[283] will contribute significantly to the WHO's goal of eliminating cervical cancer as a public health problem globally.[3] This is especially so in SSA, where there is a *perfect storm* of high HIV prevalence and a profound lack of preventive services, a consequence of which is that one-fifth of all cervical cancers are attributable to HIV. That is, approximately 2-fold more HIV-related cervical cancers occur in SSA than of all the cervical cancers that occur in the United States annually.[19] Given the general lack of surgical, oncology, and radiation services,[268-271] as well as incomplete reporting of cancer cases,[284] it is likely that the numbers and fractions of HIV-attributable cervical cancer-related deaths are higher still in SSA.

However, benefits of HIV care go beyond cervical cancer risk reduction and impact every step in the cervical cancer control continuum: 1) improved immune responses to prophylactic HPV vaccination, which might be important for long-term vaccine effectiveness in immunocompromised WLWH populations; 2) more effective secondary prevention through screening, diagnosis, and treatment of cervical precancer and early cancer; and 3) perhaps even tertiary prevention through better outcomes and longer survival.

Most notably, comprehensive HIV care will likely improve the clinical and cost effectiveness of secondary cervical cancer prevention by screening by: 1) reducing the number of screen-positive women who will need follow-up care because of fewer HPV infections, 2) reducing the likelihood of

HPV persistence and progression to high-grade cervical abnormalities and increasing the likelihood of regression of the latter, and 3) reducing the size of cervical abnormalities that need to be treated, making them more amenable to be treated effectively, even in low-resource settings, and less likely to recur. As noted above, positive margins after treatment are a strong predictor of recurrent disease, and larger abnormalities, which are more common in WLWH, especially in those with poorly controlled HIV infection, than in HIV-negative women, are more likely to have positive margins.

Given the call for cervical cancer elimination,[3] programs implementing cervical cancer care in areas where HIV is highly endemic should consider screening for HIV and, if positive, linkage to HIV care, which will reduce the risk of cervical cancer. If possible, cervical cancer prevention through prophylactic HPV vaccination of younger WLWH and screening of mid-adult WLWH should be integrated with their HIV care, as has been supported widely in high-burden countries in SSA through initiatives such as PEPFAR.[277,285] The introduction of cervical cancer screening with VIA into PEPFAR has proven to be effective in increasing screening rates in WLWH.[286] Efforts to mitigate HIV-related stigma[267,287] and better approaches for the prevention of attrition[288] may be necessary to optimize integration and better care for both epidemics. A meta-analysis reported widely variable low levels of knowledge, attitude, and practice of cervical cancer screening among WLWH living in SSA,[289] which will need to be overcome to implement screening in this population.

Not only does better HIV care influence cervical cancer risk, but the converse may also be true. Several studies have demonstrated that prevalent HPV infection increases the risk of HIV acquisition by approximately 2.0-fold to 2.5-fold,[290,291] perhaps as a result of the recruitment of T cells, the target cell for HIV infection, in the immune response to HPV infection. Therefore, in addition to the protection against both infections offered by barrier methods such as condoms,[292-294] and perhaps one day by topical microbicides, reducing the endemicity of HPV by primary prevention through vaccination and secondary prevention through screening and treatment may even help reduce the spread of HIV.

Several key questions and issues need to be addressed in the prevention and control of cervical cancer in WLWH. First, are prophylactic HPV vaccines efficacious in WLWH, and how do the number of doses and the type of adjuvant vaccine influence the effectiveness and duration of protection against even viral end points (eg, the prevention of incident persistent infections, recommended as an acceptable surrogate end point for vaccine trials instead of incident precancerous lesions[159])? Understanding the protective effect of HPV vaccines in WLWH will help to optimize their use in this highly vulnerable, highest risk population.

Second, what is the best screening protocol, including the optimal management, of HPV positive results for WLWH? Because the majority of WLWH live in LMICs, and specifically SSA, these screening protocols need to work in/be applicable to these settings, which have limited resources and health care infrastructure and services. Relying on pathology for cervical diagnosis to guide clinical management is not practical in many of these LMIC settings. A robust, broadly available, and affordable molecular triage method using the residual cervical specimen or, better yet, the self-collected cervicovaginal specimen has the distinct advantage of not burdening women or the health care system with an extra clinical visit and its associated costs. Artificial intelligence-based image analysis of cervical images is a promising method for the triage of HPV positive results[295-297] and treatment decisions[298] because it could remove the interrater variability inherent to visual methods due to their subjectivity. Such a methods, if validated in WLWH, might be combined with self-collection and/or rapid, affordable, point-of-care HPV testing (when it becomes available) to greatly reduce the number of clinical visits and associated costs for a cervical cancer screening algorithm for WLWH.

Finally, given the scale-up of cervical cancer screening activities, which will lead to large increases in screen-detected cervical cancers that will need care, are the current cancer treatment protocols optimized for WLWH, especially those living in LMICs? Currently, there are limited data on the comparative effectiveness of cervical cancer treatment modalities, including the management of LACC, in WLWH compared with HIV-negative women, with some, albeit inconsistent, evidence that WLWH may have poorer outcomes. Moreover, in LMICs where HIV prevalence is highest, there is a limited number of trained cancer surgeons[268] to effectively perform the radical surgery in localized tumors. Thus cancer management protocols may need to be adapted to improve outcomes. One possible adaptation is the use of neoadjuvant chemotherapy before surgery to shrink the tumor and allow for better completion of surgery. This is being used widely in many SSA settings (P. Castle, personal observation), especially in areas where radiation therapy is not routinely available, but its effectiveness and best practices need to be established to inform international recommendations.

In conclusion, a significant number of cervical cancers and related deaths (as well as other cancers and related deaths) can be averted through better, more comprehensive HIV care alone. Further reductions in cervical cancer incidence and mortality will be achieved through primary, secondary, and tertiary cervical cancer prevention services, all of which are likely be more effective because of that better HIV care. That is, "90-90-90" for HIV care will help achieve a more *effective* "90-70-90" for cervical cancer control. ■

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