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## Cervical Cancer Prevention in Low- and Middle-Income Countries: Feasible, Affordable, Essential

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### Abstract

The annual worldwide burden of the preventable disease cervical cancer is over 530,000 new cases and 275,000 deaths, with the majority occurring in low- and middle-income countries (LMICs), where cervical cancer screening and early treatment are uncommon. Widely used in high-income countries, Pap smear (cytology-based) screening is expensive and challenging for implementation in LMICs, where lower-cost, effective alternatives such as visual inspection with acetic acid (VIA) and rapid human papillomavirus (HPV)-based screening tests offer promise for scaling up prevention services. Integrating HPV screening with VIA in “screen-and-treat-or-refer” programs offers the dual benefits of HPV screening to maximize detection and using VIA to triage for advanced lesions/cancer, as well as a pelvic exam to address other gynecologic issues. A major issue in LMICs is co-infection with human immunodeficiency virus (HIV) and HPV, which further increases the risk for cervical cancer and marks a population with perhaps the greatest need of cervical cancer prevention. Public-private partnerships to enhance the availability of cervical cancer prevention services within HIV/AIDS care delivery platforms through initiatives such as Pink Ribbon Red Ribbon® present an historic opportunity to expand cervical cancer screening in LMICs.

### Introduction

Cervical cancer is a preventable malignancy, yet every year over 530,000 women are diagnosed with and over 275,000 women die from the disease worldwide (1). The distribution of cases and deaths is heavily weighted towards low- and middle-income countries (LMICs), which have 86% of the global cases and 88% of the total deaths (2). High-income countries have effectively integrated Pap smear-based cervical cancer screening services into both medical and public health services and have achieved reasonably high coverage rates, effectively reducing incidence and mortality over the past seven decades (3). The expanding use of effective prophylactic vaccines for preventing infection with human papillomavirus (HPV) types 16 and 18, common etiologic agents for

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cervical cancer, offers even greater promise for eventual elimination of cervical cancer as a major public health problem (4, 5). Yet, continued high rates of cervical cancer in LMICs point to the failure to bring sustainable prevention programs up to a substantial scale in these countries. This gap between scientific, clinical, and public health discovery and the implementation of service delivery showcases a significant global public health failure.

### **Unrealizable Promise of Cervical Cytology in LMICs**

George Papanicolaou invented a simple technique (cervical cytology or Pap smear) for early detection of cervical cancer by collection, smearing, and microscopic observation of desquamative cells of the cervix in 1928; the Pap smear became highly popular in higher-income nations in the 1940s (6). Cervical cytology was soon refined and adopted as a routine part of preventive care, saving millions of women's lives (7). On its face, a cytology program seems simple, yet it has multiple infrastructural and resource requirements, along with the need for awareness in the population, trained cytology technicians, and cytopathologists. With a critical lack of resources for health in general and of commitment to preventive health for women in particular, most LMICs do not have the current capacity to sustain cytology-based cervical cancer prevention programs (8). Even in venues with functioning health-care systems, there are multiple operational factors that inhibit quality, including the follow-up challenges of multiple visits for screening and later post-diagnosis therapy, inefficient recall and referral systems, inadequate resources for screening and treatment, and competing priorities in the healthcare system. Effective cervical cancer control is uncommon in resource-limited settings (9).

### **Suitable Screening and Prevention Technologies for LMICs**

The continued high incidence of cervical cancer across LMICs has prompted the development, evaluation, and adoption of innovative approaches for improving sustainable prevention efforts (Table 1). Visual inspection with acetic acid (VIA) is readily mastered by non-physician providers and has been extensively studied as an alternative screening approach to the Pap smear (10–12). VIA gives immediate results and can be linked to cryotherapy in a relatively low-cost single-visit “see-and-treat” approach. Cryotherapy-based treatment of eligible VIA-positive lesions has been shown to be safe, feasible, acceptable, and effective in treating appropriate precancerous lesions (13, 14). Patients with cryotherapy-ineligible VIA-positive precancerous lesions and visually apparent frank invasive cervical cancer can be referred to hospitals offering excisional methods for diagnosis and treatment such as loop electrosurgical excision procedure (LEEP) and hysterectomy; even if advanced cancer management by surgery and chemoradiation is unavailable, many cervical cancer cases can be prevented or remediated at early stages (15, 16). More aptly called “see-and-treat-or-refer,” this cost-effective paradigm represents a pragmatic innovation for rapidly scaling up cervical cancer prevention services in LMICs.

Visualization of lesions is not the only screening alternative to Pap smears. HPV can be detected in cervical sampling by performing a pelvic examination or through patient self-collection. HPV testing offers the most biologically compelling method of screening since virtually all cervical cancers result from chronic, persistent HPV infection (17). In comparison with other screening methods, HPV screening was superior in helping reduce both the incidence and mortality of cervical cancer in a large community-based randomized trial (18). With the ongoing development of low-cost, rapid molecular-assay technologies for HPV that are robust for field operations (19, 20), HPV-based screening has the promise to become a frontline method for cervical cancer screening to maximize detection and expand access across LMICs. Integrating HPV testing with VIA-based “see-and-treat-or-refer” platforms can combine the high accuracy of HPV DNA testing with the same-visit

benefit of triage by VIA-based screening (21–23). With innovative public-private partnerships, it can be expected that HPV screening tests would be cheap enough for widespread deployment in low-income nations.

Limited resources for disease prevention require LMIC policy makers and health care providers to evaluate the utility of individual disease control efforts through the lens of cost effectiveness (24). It is encouraging that cervical cancer prevention programs using VIA and HPV testing have “incremental cost-effectiveness ratios” (ratio of the difference between the cost of an intervention and that of the next best strategy to the change in effects due to the intervention) well below the globally accepted definitions for public health interventions judged as cost effective by public health agencies; these programs may even save money in many specific settings where costs of the illness and its treatment exceed costs of prevention (25–27). Combining HPV vaccination with cervical cancer screening can further maximize the cost effectiveness of prevention strategies for both current and future generations of at-risk populations (27, 28).

## Cervical Cancer Prevention in HIV-infected Women

The human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) epidemic has led to a historic health burden in LMICs, particularly in sub-Saharan Africa. The incidence, progression, and recurrence of cervical precancerous lesions are higher in HIV-infected than HIV-uninfected women. Before combination antiretroviral therapy (cART) became widely available, HIV-infected women did not live long enough for precancerous lesions to progress to cervical cancer (29). Given that cART has a limited or no impact on reducing cervical cancer rates (30), HIV-infected women who live longer on cART are at an increased risk of persistent HPV infection and cervical precancer progressing to cervical cancer. This scenario reminds HIV clinical service providers of the futility of a “surgery that is a success” even though the patient died.

Still, the natural course of cervical neoplastic disease in the context of HIV infection is not yet fully elucidated, particularly in relation to varying levels of immunosuppression and regimens of cART. And at a local level, HIV-HPV coinfection involves a complex interplay of pro-inflammatory cytokines and enzymatic pathways that leads to enhanced inflammatory responses in the cervicovaginal milieu (31–34). In this issue of the journal, Fitzgerald and colleagues (35) present their pilot, hypothesis-generating study suggesting that HIV is associated with increased levels of cervical cyclooxygenase-2 (COX-2) and elevated systemic prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) levels. Since PGE<sub>2</sub> can modulate chronic inflammation-mediated carcinogenesis (36), if its elevation in HIV-positive women is confirmed in larger, prospective studies, it might serve as a useful biomarker to predict the progression of persistent HPV infection to cancer in the context of both local and systemic immunosuppression in HIV-infected women. A role for anti-inflammatory drugs, including commonly used non-steroidal anti-inflammatory drugs (NSAIDs), might be conceivable for prevention of inflammation-mediated cervical cancer risk, as has been demonstrated particularly in the colorectum (37). Indeed, exogenous factors influencing cervical inflammation—e.g., intrauterine devices (38), other hormonal methods for contraception (39), concurrent sexually transmitted and other infections (40), and local inflammatory changes with use of vaginal microbicides and other topical treatments (41–43)—continue to be important for understanding why only a fraction of HPV infections persist and progress to cervical cancer. Although beyond the scope of this review, recently reported observational studies have shown an increased risk of HIV acquisition linked to HPV infection (44); might HPV be a risk factor for HIV acquisition through its local immunomodulatory impact, along with its microvascular and cervical tissue physical changes (45)?

Inflammation may also be a key factor in influencing the variable response to cryotherapy-based treatment of cervical lesions in HIV-infected women (46, 47). It is possible that cryotherapy would enhance the potential for sexual transmission of HIV by HIV-infected women, given the bleeding and inflammation caused by the procedure. Similarly, HIV acquisition by at-risk uninfected women undergoing cryotherapy may be more likely because of breached integrity of the cervicovaginal mucosae. Although recently suggested to be less likely than previously assumed (48), such risk may be influenced by local PGE<sub>2</sub>-mediated inflammatory responses. Further research is needed to evaluate this risk, and if an association with PGE<sub>2</sub> is established, local or systemic treatment by anti-inflammatory agents may augment advice about temporary abstinence and use of condoms in preventing sexual transmission or acquisition of HIV after cryotherapy.

The study by Fitzgerald and colleagues (35) is hypothesis-generating and highlights an important consideration for implementing screening strategies, particularly for HIV-infected women. Cervical cancer screening strategies that use HPV-based screening via self-collection as the first-line approach can reduce the burden of pelvic examinations for women who test HPV negative since the high negative predictive value of HPV DNA testing provides reassurance of safety against current risk for cervical cancer (49). However, an undesirable side effect of this approach is that HPV-negative women end up not receiving a detailed pelvic examination in the context of cervical cancer screening. Since resource limitations often preclude follow-up visits, this “once-in-a-lifetime” self collection-based approach for HPV-based screening, while saving costs and resources for HPV testing, may in fact represent a missed opportunity for evaluating risk for other cervical conditions in HPV-negative women, including evaluation of cervical inflammation. Therefore, we believe that it is important to emphasize the need for at least one pelvic exam when offering cervical cancer screening services for HIV-infected women, ideally accompanied by evaluation for other gynecologic conditions (including local inflammation and infection-associated changes) and appropriate treatment for sexually transmitted infections. Only a small minority of women has been screened even once in a lifetime in lower-income nations; it is therefore vital to emphasize the importance of a pelvic examination as part of routine reproductive health care services for all women and especially for those with immunosuppressive illnesses.

## Integration of Cervical Cancer Prevention Programs with HIV/AIDS Care

Cervical cancer prevention with a woman-centric approach is amenable to effective integration with other public health programs being implemented in LMICs (15, 50, 51). Since the advent of the President’s Emergency Plan for AIDS Relief (PEPFAR) in 2003, the global community has experienced a major surge in funding for prevention and treatment of HIV/AIDS and other infectious diseases in LMICs. The clinical infrastructures being created or expanded through PEPFAR, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the World Bank offer historic opportunities to integrate cervical cancer screening services with expanded HIV screening and care infrastructures. As described by the U.S. State Department, the September 2011 launch of the Pink Ribbon Red Ribbon® campaign is expanding “the availability of vital cervical cancer screening and treatment—especially for high-risk HIV-positive women—and also promot[ing] breast cancer education” (<http://www.state.gov/r/pa/prs/ps/2011/09/172244.htm>). This initiative was inspired by the success of PEPFAR-supported implementation initiatives such as our Cervical Cancer Prevention Program in Zambia (CCPPZ; refs. 15, 52). Now a routine part of public sector services, we are effectively delivering cervical cancer prevention services to HIV-infected and other at-risk women with nurses (Fig. 1) as frontline care providers (16, 53). CCPPZ has also pioneered the use of digital cervicographic adjunct to routine VIA screening, thereby achieving efficiencies in quality assurance and provider retraining, as well as providing an

opportunity for bedside patient education and feedback (53). Furthermore, digital cervicography has allowed internet and cell-phone-based clinical consultations at a distance between nurses in peripheral clinics and gynecologists located centrally, thereby allowing efficient utilization of health care manpower through a “hub and spoke” model (54). Thousands of precancerous lesions and hundreds of cancers have been treated (and deaths prevented) in this program that has now screened more than 65,000 women over five years (15).

Can HPV vaccine be helpful in HIV-infected women? Little is known about the utility of HPV vaccine in HIV-infected women, but arguments are compelling that women who are not infected with HPV types 16 or 18 may benefit from vaccination even if they are not in the lower-age target group of virginal girls (55). Many women globally are infected with oncogenic strains of HPV but not yet with types 16 or 18, suggesting that vaccine protection from the HPV types would be helpful (56–58). Of course, multivalent vaccines now in development should protect against even more oncogenic HPV types of relevance to women in LMICs. Combination prevention efforts are being advocated for HIV control in LMICs (59–64). Can we afford to do less with combining HPV vaccination and HPV screening/treatment together to maximize long-term and immediate impact (65)?

## Concluding Remarks

We are confident that affordable screening for cervical cancer is feasible and effective in LMICs (5, 11, 15, 16, 52, 53). Along with the Pink Ribbon Red Ribbon® campaign organizers, we believe it is an opportune time for expanding cancer prevention initiatives nested within ongoing public health programs in LMICs. Vertical programs, like HIV screening, also should be broadened to include cancer screening. While immunosuppressed women are of special concern, mitigation of risk through pragmatic clinical prevention services, including HPV vaccine, can be expanded to reach a wide swath of at-risk women in an implementation catchment area. A concerted push by key stakeholders—clinicians, public health professionals, researchers, politicians, policy makers, and women themselves—is needed to build on this momentum and dramatically enhance cost-effective cervical cancer screening and treatment to prevent unnecessary deaths of women in LMICs.

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**Figure 1.** A nurse conducts a cervical cancer screening examination in a public sector clinic operated by CCPZ in Lusaka, Zambia. Nurses use digital cervicography–aided VIA to provide immediate screening results and offer same-visit cryotherapy for eligible VIA-positive women, or they refer advanced lesions to a central hospital for further care.

**Table 1**

Comparison of operational aspects of currently available cervical cancer screening tests

<b>Operational aspect</b>	<b>Pap smear (cytology)</b>	<b>VIA</b>	<b>Low-cost HPV tests</b>
Cost	Moderate to high (\$10–\$25/test)	Low (< \$5/test)	Low (< \$8/test)
Provider	Cytotechnologist and cytopathologist (physician)	Nurses or mid-level providers	Lab technician
Training requirements	Substantial	Relatively modest	Relatively modest
Quality assurance	Substantial need for ensuring quality	Significant need for ensuring quality	Minimal quality assurance for processing samples
Technology ownership/copyright	Open source/public domain	Open source/public domain	Proprietary technology
Automation in results	Not possible	Not possible	Automated readout in some/ not all formats
Range of sensitivity of single test	60%–80%	50%–80%	80%–95%
Range of specificity of single test	85%–95%	70%–80%	50%–70%
Minimum number of visits	2	1	1 or 2
Linking screening and treatment	Not possible in same visit	Possible in same visit (“see-and-treat”)	Possible in same visit with high-volume screening approach
Home-based/ self testing	Not possible	Not possible	Possible
Inter-observer variation	Significant	Significant	Minimal
Reproducibility	Limited, but possible with digital imaging of slides	Limited, possible with digital cervicography	Easily achievable
Evidence of effectiveness	Declining rates in developed countries since 1940s	Results from cross-sectional studies and randomized trials	Results from cross-sectional studies and randomized trials
Clinical limitations	Sample collection on slide may be inadequate or improperly stained	Limited use in post-menopausal women and endocervical lesions	Not all detected HPV infections are clinically significant; not available widely in 2011
Other ancillary benefits	Can detect other infections on smears	Can detect other gynecological abnormalities during pelvic exam	Sample can be stored for testing by other molecular markers