HHS Public Access

Author manuscript

Curr HIV/AIDS Rep. Author manuscript; available in PMC 2017 June 02.

Published in final edited form as:

Curr HIV/AIDS Rep. 2011 September ; 8(3): 192–199. doi:10.1007/s11904-011-0084-6.

See-and-Treat Approaches to Cervical Cancer Prevention for HIV-Infected Women

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Abstract

Cervical cancer remains the second commonest cancer among women worldwide, and more than 85% of the global burden of this disease occurs in the developing world. HIV-infected women have a higher likelihood of developing persistent high-risk human papillomavirus (HPV) infection, precancer, and invasive cervical cancer than seronegative women. Although highly effective primary and secondary prevention strategies are currently available, they remain inaccessible to the vast majority of women. Because of their simplicity and affordability, see- and-treat cervical cancer screening modalities have the potential to substantially improve women's access to cancer prevention, as well as to create much needed infrastructure for future molecular-based cervical screening and HPV vaccination programs. Additional data addressing the effectiveness of see-and-treat approaches for HIV-infected women are urgently needed. Studies informing best practice guidelines on when to start, when to stop, and how frequently to screen HIV-infected women within the see-and-treat paradigm would be of great value.

Keywords

See-and-treat; Cervical cancer; HPV; HIV; Resource-limited setting; Complications of HIV infection and treatment; HIV-infected women; Women; Cervical cancer prevention

Introduction

Despite being largely preventable, each year half a million new cases of cervical cancer are diagnosed and over 250,000 women die from invasive disease worldwide [1]. This constitutes 9% of the global burden of cancer among women [2]. The overwhelming majority of new cases and deaths occur in resource-constrained regions of developed and developing countries and result, most commonly, from limited access to screening services [3•, 4, 5].

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Disclosure No potential conflicts of interest relevant to this article were reported.

The natural history of cervical cancer is clearly understood. Persistent high-risk human papillomavirus (HPV) infection is well established as the causative agent in nearly all cases of precancer (ie, cervical intraepithelial neoplasia or CIN) and invasive cervical cancer [6–9]. It has also been repeatedly demonstrated that, compared with HIV-negative women, HIV-infected women are at higher risk of persistent genital tract HPV infection. HIV-infected women are also at higher risk of co-infection with multiple subtypes of HPV [10–13]. Epidemiologic studies have demonstrated that, among HIV-negative women, most HPV infections will clear spontaneously within a 1–2 year period [14, 15]. Conversely, less than 10% of HPV infections among HIV-infected women will resolve spontaneously within a similar period [11]. Among HIV-negative women, approximately 10% of low-grade precancers and 30–50% of high-grade precancers will progress to invasive disease without treatment [16], whereas progression of premalignant lesions appears more rapid among HIV-infected women [17]. HIV-infected women are therefore at substantial risk of precancer and invasive cervical cancer. It remains unclear whether treatment with highly active antiretroviral therapy will significantly impact the natural history of HPV infection and preinvasive cervical disease among HIV-infected women [12].

In industrialized nations, organized Pap smear-based cervical screening programs have resulted in dramatic and sustained reductions in cervical cancer incidence over the past 50 years [1]. At the same time, these countries have also experienced health care innovations resulting in improved surgical and radiotherapy treatments, which, in turn, improve cure and survival rates for invasive cervical cancer. Unfortunately, cervical cancer prevention and control programs in the developing world are rarely implemented at the national level. Pap smear-based systems required at least two—and typically three—clinical visits for women with abnormal results to obtain histological diagnosis and establish a treatment plan. This approach is costly and complex, contributing substantially to difficulties in implementation.

More recently, screen-and-treat programs have gained popularity in developing country settings [18–22]. Within the context of these programs, women are offered screening and treatment for suspected precancer lesions within a single clinic visit. Indeed, screening strategies that involve fewer follow-up visits to coordinate and execute clinical management of abnormal results have been demonstrated to be cost-effective [23]. In this paper, we review see-and-treat approaches to cervical cancer prevention, discuss treatment options for precancer, and highlight special considerations for HIV-infected women.

See-and-Treat Approaches to Cervical Cancer Prevention

Pap smear (cytology) screening has been successful in reducing the rates of cervical cancer in developed countries. However, many of the logistical prerequisites for a successful Pap smear–based program have been difficult to implement in developing countries. Cervical cytology programs require preparation of high-quality smears, trained and experienced personnel, and internal and external control mechanisms. Additionally, these programs must reach a high percentage of the population, and must have high return rates and scheduled follow-up and treatment of abnormal lesions. By contrast, see-and-treat modalities for cervical cancer screening rely on visual tests, making them simple, affordable, and scalable to primary health care facilities in settings where modern laboratory infrastructure is

unavailable or inaccessible. As the results of visual screening tests are available immediately, diagnostic colposcopy and/or treatment can also be offered at the time of screening, minimizing follow-up losses. In response to global need, three low-technology visual techniques have been developed and implemented in various settings: unaided visual inspection (VI), visual inspection with acetic acid (VIA), and visual inspection with Lugol's iodine (VILI) (Table 1).

Visually Based Cervical Screening Test

Unaided visual inspection involves pelvic examination with a speculum and light source during which inspection of the cervix is performed with the naked eye. A low-threshold positive test includes findings of cervicitis, erosion, polyps, warts, or a generally unhealthy appearing cervix. A high-threshold positive test includes the above findings in addition to evidence of bleeding on touch, bleeding erosion, ulceration, growth, or a hypertrophied, elongated cervix. However, with sensitivity rates as low as 30%, VI lacks sufficient sensitivity for use as a primary cervical screening modality [24, 25].

VIA involves a naked eye examination of the cervix following application of a dilute (3–5%) solution of acetic acid. A positive test is based on the finding of acetowhite lesions within the cervical transformation zone. Acetowhite changes result from reversible coagulation of intracellular proteins; however, they are not specific to neoplasia and may instead represent benign immature squamous metaplasia, cervical inflammation, or infection [24]. Pooled studies that included nearly 57,000 women aged 25–65 years from Burkina Faso, Congo, Guinea, India, Mali, and Niger demonstrate the sensitivity, specificity, positive predictive value, and negative predictive value for VIA to be 76.8% (95% confidence interval [CI]: 74.2–79.4%), 85.5% (95% CI: 85.2–85.8%), 9.4% (95% CI: 8.8–10.8%), and 99.5% (95% CI: 99.4–99.6%) for detecting high-grade precancer, respectively [26]. Although the specificity of VIA is inferior to Pap smear screening, several studies have demonstrated near-equivalent sensitivity of the tests.

VILI also involves a naked eye examination of the cervix. In this case, the exam is performed following the application of Lugol's iodine, which produces a dark brown or black stain in glycogen-containing epithelial cells. Mature squamous epithelium stains darkly following the application of Lugol's solution, while columnar epithelium does not stain at all. Neoplastic areas take on a yellow stain as they contain little or no glycogen. As with VIA, the yellow stain is not specific to neoplasia [24]. The pooled sensitivity, specificity, positive predictive value, and negative predictive value of VILI are 91.7% (95% CI: 89.7–93.4%), 85.4% (95% CI: 85.2–85.7%), 10.9% (95% CI: 10.2–11.6%), and 99.8% (95% CI: 99.7–99.9%), respectively [26]. These data suggest that VILI may be more sensitive than VIA. The tests appear equivalently specific. Additional data from pooled analyses of 11 African and Indian studies confirm these findings [27].

Few published studies have addressed visual screen test performance in HIV-infected women. A cross-sectional study in Nigeria compared the sensitivity and specificity of VIA and Pap smear in 205 HIV-infected women. The sensitivity of VIA was 76.0% (95% CI: 52.0–91.0%); the specificity was 83.0% (95% CI: 77.0–88.0%). The sensitivity of Pap smear was 57.0% (95% CI: 34.0–77.0%); the specificity was 95.0% (95% CI: 90.0–97.0%) [28]. A

second study conducted in India demonstrates similar findings. Sahasrabuddhe and colleagues [3•] report the sensitivity, specificity, positive predictive value, and negative predictive value for VIA as 80.0%, 82.6%, 47.6%, and 95.4%, respectively, at a threshold of CIN 2 or worse. This was compared to a sensitivity, specificity, positive predictive value, and negative predictive value of 60.5%, 59.6%, 22.4%, and 88.7% for any abnormality on cytology [3•].

In summary, visual screening tests for cervical cancer are safe, low in cost, and, with adequate training, can be performed by a variety of health care personnel. Two crosss-ectional studies suggest that VIA has improved sensitivity over Pap smear for detecting CIN 2 or worse in HIV-infected women [3•, 28]. As the results of a visual screening test are immediately available, treatment or referral can be offered with the context of a single visit, improving program effectiveness.

Treatment Options for Cervical Precancer

In developed country settings, where continued clinical follow-up is more readily assured, low-grade precancer lesions (ie, CIN 1) are typically followed with observation alone, while high-grade precancers (CIN 2/3) are treated after histological confirmation of the diagnosis. In developing country settings, histological diagnoses may not be available prior to clinical management. Instead, treatment may be offered to women on the basis of a positive screening test. Regardless of setting, cervical precancers are treated by either ablative techniques (eg, cryotherapy, laser, or cold coagulation) or excisional techniques (eg, loop electrosurgical excision procedure, also known as large loop excision of the transformation zone, laser excision, cold knife conization, or hysterectomy). No single treatment modality has been proven to have superior efficacy [29]. Conservative approaches, such as cryotherapy and loop electrosurgical excision procedure (LEEP), represent the mainstay of treatment and will be reviewed here [30–32]. Both cryotherapy and LEEP services can be seamlessly integrated within see-and-treat, cervical screening programs.

Ablative Treatment Using Cryotherapy

Cryotherapy, using nitrous oxide or carbon dioxide as refrigerant gas, is the most commonly used ablative treatment for cervical precancer. Regardless of grade, lesions that can be completely covered by the cryoprobe, those that occupy less than 75% of transformation zone, and those that do not involve the endocervical canal or contain features suspicious for invasive cancer may be treated with cryotherapy. In randomized trials that have included HIV-infected participants but not reported outcomes stratified by HIV serostatus, treatment success rates following cryotherapy are between 76% and 88% [33, 34]. Intraoperative complications are rare. Post-procedure complications—also rare—may include persistent pelvic pain, vaginal discharge, bleeding, infection, and cervical scarring [34]. Cryotherapy is simple, safe, affordable, and can be performed in first-level health care facilities by a variety of personnel, including nurses, mid-level providers, and general practitioners, making cryotherapy-based programs feasible–and scalable–in resource-limited settings [31].

Excisional Treatment Using LEEP

All precancer lesions can be treated with LEEP. The procedure may be performed under local anesthesia in the outpatient setting and involves excision of the transformation zone using a wire loop electrode powered by an electrosurgical unit. A reliable electricity supply is a prerequisite for this treatment modality. In randomized trials, treatment success rates are reported between 84% and 96% [33, 34]. Again, intraoperative complications are uncommon, but may include pain, surgical site bleeding, thermal injury to surrounding tissues, and complications resulting from anesthesia. Postprocedure complications, such as persistent pelvic pain, vaginal discharge, bleeding, infection, cervical scarring [34], and preterm birth [35, 36], occur slightly more commonly than with cryotherapy.

Failure of Cryotherapy or LEEP Treatment Among HIV-Infected Women

Persistence and/or recurrence of precancer lesions after treatment appears more common among HIV-infected women, however data are limited. In a Zimbabwean clinical trial, Chirenje and colleagues [37] followed 109 HIV-positive and 38 HIV-negative women over a 12-month period. The authors report failure rates of cryotherapy to be 40.5% among HIV-positive women and 15.8% among HIVnegative women (P=0.057). Additionally, 14% of HIVpositive women who underwent LEEP were found to have persistent or recurrent cervical precancer during the follow-up period. There were no LEEP failures among HIV-negative women. This difference was not statistically significant (P=0.328) [37]. A subsequent study combined two long-term observational cohorts in the United States, reporting findings for 170 HIV-positive and 15 HIV-negative women. In this study, persistent CIN was noted in 46% of HIV-positive women and 33% of HIV-negative women 6 months after their initial treatment by cryotherapy, LEEP, knife conization, laser ablation, or laser conization [38]. More recently, Lima and colleagues [39] reported on a cohort of 98 HIV-positive and 120 HIV-negative Brazilian women. In their study, recurrence rates of CIN were 33% among HIV-positive women and 8.4% among HIV-negative women completing 24 months of follow-up after LEEP (P<0.01) [39]. Treatment failure may also be associated with immunosuppression [40, 41], endocervical disease [40], positive margins, and HPV infection [42]. Despite the potential for higher treatment failure rates among HIV-infected women, the risk of complications following treatment with either cryotherapy or LEEP does not appear elevated over that experienced by HIV-negative women [43•, 44, 45].

Special Considerations

Target Age and Frequency of Screening

The average age at diagnosis of invasive cervical disease may be 10–15 years earlier among HIV-infected women [46], highlighting their substantial risk for high-grade precancer lesions and a shorter interval between preinvasive and invasive disease. The American College of Obstetricians and Gynecologists recommends that HIV-infected women be offered Pap smear screening twice during the first year following diagnosis and annually thereafter [47]. No definitive guidance has been outlined by international organizations such as the World Health Organization (WHO) or the International Federation of Gynecology and Obstetrics (FIGO). WHO recommends that decisions regarding when to start screening and how frequently to offer screening services be tailored according to available resources [48].

Data from mathematical modeling studies suggest a 90% reduction in lifetime risk of cancer resulting from organized 3 yearly Pap screening, an 87% decrease from 4 yearly screening, 83% from 5 yearly screening [49], and as much as 19% from screening once at age 35 [50]. However, the cost-effectiveness of Pap smear screening programs in low-income and middle-income countries has been questioned [50]. A cost-effectiveness analysis based on a Thai case study projected an 83% reduction in cervical cancer mortality from VIA screen-and-treat programs at a cost of $524 per year of life saved (YLS). The authors also project a 92% reduction in mortality from combined Pap and HPV-based screening at a cost of $1683 per YLS [5]. Finally, in a cost-effectiveness analysis, including data from India, Kenya, Peru, and South Africa, Goldie and colleagues [23] demonstrate that screening strategies based on the single-visit or two-visit approach are the most cost-effective. At age 35, a single screen with VIA or an HPV test would reduce women's lifetime risk of cervical cancer by 25%–36% at costs of less than $500 per YLS [23]. We were unable to find any English language cost-effective analyses that specifically address age and frequency of screening for HIV-infected women.

Performance of Visual Screening Tests in Menopausal Women

HIV-infected women in low-income and middle-income countries are living longer due to therapeutic advances and improved access to care and treatment services. Cervical screening policies and programs should address the unique needs of older women. Cremer and colleagues [51] compared test performance of conventional Pap smear screening and VIA in Salvadoran women over 50 years of age. Although the squamocolumnar junction was completely visible for the majority of women, age was negatively correlated with the adequacy of VIA. The sensitivity of Pap smear for detecting CIN 2 or worse was 33.3%; the sensitivity of VIA was 16.7%. Specificity was 95.2% and 99.2% for Pap smear and VIA, respectively. These differences were not statistically significant and HIV serostatus was not reported in the publication [51]. The sensitivity and specificity of both Pap smear and VIA screening reported in this Salvadoran study are substantially lower than previously reported test performance characteristics. Nonetheless, other authors have also highlighted decreased sensitivity and specificity of both Pap smear and visual screening tests in post-menopausal women [26]. Caution may also be warranted in older HIV-infected women. Published data on which to base specific recommendations are not currently available.

Overtreatment

Although VIA and VILI will identify the majority of precancer lesions in reproductive age women, these visually based tests have only moderate specificity and the resultant risk of overtreatment is largely unknown. Published data describing overtreatment in see-and-treat programs are scarce. A single-institution study from South Africa reporting on a "look and LLETZ" prevention program for patients with abnormal cytology suggests an overtreatment rate of 9.7% for HIV-positive women and 15.5% for HIV-negative women [52]. This risk of overtreatment—the potential sequelae of clinical complications coupled with unnecessary costs to health systems and individuals—should be weighed against the potential benefits of early detection and treatment of preinvasive and invasive cervical disease.

Risk of HIV Acquisition or Transmission Following Treatment

Ablative and excisional treatment procedures for cervical precancer invariably result in a transient inflammatory response in the lower genital tract. There is concern that this transient cervical inflammation and ulceration may increase women's risk of HIV acquisition or lead to increased cervicovaginal viral shedding in those infected with HIV To address risk for HIV acquisition, Denny and colleagues [53] ascertained seroconversion rates 6 and 12 months following treatment with cryotherapy in both the intervention and delayed evaluation arms of their see-and-treat trial. They report no significant differences in HIV seroconversion at either 6 or 12 months between women randomized to HPV-and-treat, VIA-and-treat, or delayed evaluation (1.8% [95% CI: 1.0–2.5%] vs 1.9% [95% CI: 1.1–2.7%] vs 2.0% [95% CI: 1.1–2.8%] at 12 months) [53].

Although highly correlated with plasma viral load, sexual transmission of HIV typically occurs through exposure to the virus in genital tract secretions [54]. In a case series of 14 HIV-infected women, Wright and colleagues [55] demonstrated a 1.0–4.4 $\log_{10}$ increase in genital tract HIV-1 RNA levels in the month that followed treatment for CIN, including three women treated with cryotherapy and eight with LEEP By 3 months, genital tract HIV shedding had returned to baseline [55]. A preliminary report describing a Kenyan cohort of 50 HIV-infected women treated with cryotherapy for CIN 2/3 indicates no statistically significant increase in genital tract viral shedding 2 and 4 weeks after treatment. Subgroup analyses were performed for 40 women receiving antiretroviral treatment and 10 women who were not receiving treatment. Among women receiving HIV treatment, the odds of detectable shedding were not increased at 2 weeks (odds ratio [OR] 1.17; 95% CI: 0.64–2.13) or 4 weeks (OR 1.29; 95% CI: 0.71–2.33) post-cryotherapy Among 10 women not receiving antiretroviral treatment, there was a nonsignificant increase in viral shedding at 2 weeks (OR 3.43; 95% CI: 0.54–21.71) but not at 4 weeks (OR 1.00; 95% CI: 0.27–3.74) [56]. No subsequent studies have adequately addressed this scientific question. In order to minimize potential risks associated with transient increases in genital tract HIV shedding, the clinical recommendation is that women abstain from vaginal intercourse for 4–8 weeks following treatment for cervical precancer.

Conclusions

It is well documented that HIV-infected women are at higher risk of HPV infection, with rates as high as 45–90% [11, 13, 57]. Not surprisingly, co-infection with multiple HPV subtypes, cytological abnormalities, and high-grade preinvasive lesions occur more frequently in these women. Although standard treatment for premalignant cervical lesions appears effective, HIV-infected women are more likely to experience persistent or recurrent cervical dysplasia [37–39]. In resource-poor settings, the complex nature of Pap smear screening has resulted in several barriers to cervical cancer control [57, 58]. To overcome these barriers, visual techniques are being used increasingly in single-visit, see-and-treat programs. Although current costs preclude implementation of HPV-based "test-and-treat" strategies, molecular screening also has the potential to greatly enhance cervical cancer prevention programs worldwide [59, 60•, 61•]. Additional data on the effectiveness of screen-and-treat interventions targeted toward HIV-infected women are needed. Finally,

primary prevention though HPV vaccination should remain a priority. The efficacy of both available HPV vaccines has been clearly demonstrated among HIV-negative women [62•, 63–65]. A recently published randomized, placebo-controlled trial confirms the safety and immunogenicity of the quadrivalent HPV vaccine in HIV-infected children [66•]. Studies to determine the efficacy of HPV vaccination among HIV-infected girls and women are currently ongoing.

Acknowledgments

Support was provided by the National Institutes of Health through the International Clinical Research Fellows Program at Vanderbilt University (R24 TW007988), as well as through a K24 award (K24 AI066884). The funding agency played no role in the preparation of this manuscript.

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Table 1

Studies of visually based cervical screening test

Reference (year)	Screening methodology	Sensitivity	Specificity	Comments
Basu et al. [25] (2002)	High-threshold positive VI	31.9%	93.3%	• This study included more than 6000 Indian women • VI was evaluated for its ability to detect CIN 2+, with colposcopically directed biopsy serving as the reference standard • HIV serostatus of women screened for cervical cancer was not reported
Sankaranarayanan et al. [26] (2004)	VIA	76.8%	85.5%	• This is a meta-analysis of pooled African and Indian studies, including more than 56,000 women
	VILI	91.7%	85.4%	• Screening tests were evaluated for their ability to detect CIN 2+, with colposcopically directed biopsy serving as the reference standard • HIV serostatus of women screened for cervical cancer was not reported
Arbyn et al. [35] (2008)	VIA	79.2%	84.7%	• This is a meta-analysis update of pooled African and Indian studies, including more than 58,000 women
	VILI	91.2%	84.5%	• Screening tests were evaluated for their ability to detect CIN 2+, with colposcopically directed biopsy serving as the reference standard • HIV serostatus of women screened for cervical cancer was not reported
Akinwuntan et al. [28] (2008)	VIA	76.0%	83.0%	• 205 HIV-infected women were enrolled in this study • VIA was evaluated for its ability to detect CIN 2+, with cervical biopsy serving as the reference standard
Sahasrabuddhe et al. [3•] (2011)	VIA	80.0%	82.6%	• 303 HIV-infected women were enrolled in this Indian study • VIA was evaluated for its ability to detect CIN 2+, with colposcopically directed biopsy serving as the reference standard

VI, visual inspection; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine.