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An Insight into Cervical Cancer Screening and Treatment Capacity in Sub-Saharan Africa

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Abstract

OBJECTIVE—Approximately 85% of cervical cancer cases and deaths occur in resource-constrained countries where best practices for prevention, particularly for HIV-infected women, still need to be developed. The objective of this study was to assess cervical cancer prevention capacity in select HIV clinics located in resource-constrained countries.

METHODS—A cross-sectional survey of sub-Saharan African sites of four NIH-funded HIV/AIDS networks was conducted. Sites were surveyed on the availability of cervical cancer screening and treatment among HIV-infected and HIV-uninfected women. Descriptive statistics, and chi-square or Fisher's exact test were used as appropriate.

RESULTS—Fifty-one out of 78 (65%) sites responded. Access to cervical cancer screening was reported by 49 (96%) sites. Of these sites, 39 (80%) performed screening on-site. Central African sites were less likely to have screening on-site (P= 0.02) versus other areas. Visual inspection with acetic acid (VIA) and Pap testing were the most commonly available on-site screening methods at 31 (79%) and 26 (67%) sites, respectively. High-risk HPV testing was available at 29% of sites with VIA and 50% of sites with Pap testing. Cryotherapy and radical hysterectomy were the most

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commonly available on-site treatment methods for premalignant and malignant lesions at 29 (74%) and 18 (46%) sites, respectively.

CONCLUSION—Despite limited resources, the majority of sites surveyed had the capacity to perform cervical cancer screening and treatment. The existing infrastructure of HIV clinical and research sites may provide the ideal framework for scale up of cervical cancer prevention in resource-constrained countries with a high burden of cervical dysplasia.

Keywords

HIV; cervical cancer; Pap; HPV; VIA; resource-constrained country

INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide and in 2012, there were 528,000 new cases and 266,000 deaths [1]. An estimated 85% of new cases and almost 9 out of 10 deaths from cervical cancer occur in resource-constrained regions [2]. In sub-Saharan Africa (SSA), there are more than 250 million women who are at risk of developing invasive cervical cancer (ICC) [1]. The annual incidence of ICC is 50 per 100,000 women in SSA, and in 2012, there were over 75,000 new cases reported and more than 50,000 women died from the disease [1, 3].

Cervical cancer can be prevented through comprehensive cervical cancer screening and treatment programs. According to the National Cancer Institute, the annual incidence of ICC in the United States decreased by 80% after Papanicolaou (Pap) testing was widely adopted [4]. Conversely, the incidence of ICC is expected to rise in SSA over the next 20 years due to lack of appropriate cervical cancer prevention services, including high-risk human papillomavirus (hrHPV) vaccination programs, the projected doubling of the population, and the disproportionate burden of HIV in the region [1]. Studies have consistently shown that HIV-infected women have higher prevalence and longer persistence of oncogenic hrHPV subtypes than HIV-uninfected women [5–7]. Because SSA has the highest burden of HIV infection among women, who are living longer due to the success of HIV treatment, a perfect storm has been created that is anticipated to increase the incidence of ICC [8]. However, effective and feasible screening and treatment approaches need to be developed among HIV-infected women in this region.

While Pap testing has been recommended for routine cervical cancer screening in the U.S. for over 50 years, in resource-constrained settings, it is not feasible due to high cost, and the need for cytology services, well trained experienced personnel, internal and external control mechanisms, and multiple clinic visits for the patients. Some screening guidelines have incorporated hrHPV testing (using either molecular biomarkers such as DNA and RNA or onco-proteins) into the screening process, which has shown high sensitivity [9–11]. Although the cost of hrHPV testing is decreasing, it may still be too costly in some settings. As a result, many resource-constrained settings have focused on service delivery models using alternatives to the Pap test and hrHPV testing, such as visual inspection with acetic acid (VIA) or Lugol’s solution (VILI) with same-day cryotherapy in the see-and-treat approach. Although there is some controversy around the impact of VIA on reducing ICC

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incidence and mortality, it is a cost-effective and practical tool that has been embraced by the World Health Organization for implementation in resource-constrained settings [12–15].

Furthermore, treatment algorithms for cervical dysplasia and cancer vary from region to region and the management of ICC is a major challenge due to the lack of treatment options. Recently, there have been discussions about the potential to expand existing cervical cancer prevention programs; however the current infrastructure is not well-defined [16]. The aim of this report is to describe the current capacity of cervical cancer prevention programs affiliated with NIH-funded HIV/AIDS networks that are located in SSA in anticipation of the need-based expansion of these programs.

METHODS

This was a cross-sectional survey of SSA sites affiliated with four NIH funded HIV/AIDS networks: Centers for AIDS Research (CFAR), International Epidemiologic Databases to Evaluate AIDS (IeDEA), AIDS Clinical Trials Group (ACTG) and the AIDS Malignancy Consortium (AMC). However since all responding AMC sites were also ACTG sites, for the purpose of this analysis, they are reported as ACTG sites. Other sites with more than one affiliation were categorized based on the network that they listed on the survey. While CFAR, ACTG, and AMC are large innovative HIV/AIDS research networks that support clinical trials, the IeDEA network collects data generated during the course of routine care within HIV clinics and utilizes these data to answer operational and outcomes questions related to antiretroviral rollout. The survey included questions about availability of cervical cancer screening, either on-site or through referrals, availability of treatment for premalignant and malignant lesions, and available personnel (Table 1). Respondents were asked to describe their site and were able to select more than one option. Surveys were emailed to the affiliated sites and completed by a site representative between February and December 2013. For the IeDEA sites, this study was considered part of the parent study, which received approval from the institutional review boards previously. For the other sites, the study was exempt from institutional review board review as it was considered non-human subjects research.

Statistical methods

The proportion of sites with screening and/or treatment, personnel, and methods of screening and/or treatment were calculated. Descriptive and comparative statistics were performed using SPSS v.22.0. The Pearson chi square test or Fisher’s exact test were used for categorical variables, as appropriate.

RESULTS

Fifty-one out of 78 (65%) sites that were invited to participate completed the survey (Figure 1). Among the 27 non-responding sites, 19 (70.4%) were co-located in the same country as one or more responding sites with 16 (59%) co-located in the same city. Only eight (29.6%) of the non-responding sites, representing six countries (Benin, Mali, Ethiopia, Ghana, Congo, and Mozambique), were located in countries from which no responses were

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received. The majority of the respondents were represented by IeDEA-affiliated HIV clinics (n=27 [53%]), followed by CFAR (n=14 [27%]) and ACTG (n=10 [20%]).

Clinic Type, Screening Access, Personnel

Thirty-three (65%) respondents described their site as a clinical research setting and 34 (67%) described their site as an HIV care and treatment clinic. Additional responses included 12 (24%) family planning clinics, 9 (18%) antenatal care clinics, 7 (14%) primary care clinics, and 5 (10%) other (tertiary care hospital, sexually transmitted disease clinic, or cancer center).

Of the 49 (96%) sites that had access to cervical cancer screening (Table 2), 39 (80%) had screening services on-site. Electronic medical records were utilized at 17 (44%) sites with on-site screening. Sites in Central Africa were less likely to have screening on-site compared to the other regions (4 [67%] vs. 8 [18%], P=0.02). Specifically, none of the Burundi or Rwanda sites reported on-site screening. In East Africa, 5 of the 7 Ugandan sites (71%) did not have on-site screening, and 2 of these sites did not have access to screening services elsewhere.

For the 39 sites providing on-site screening, nurses performed screening at 32 (82%) sites, including 10 (26%) sites that relied on nurses exclusively. Physicians provided screening at 25 (64%) sites, including 6 (24%) sites that relied on physicians exclusively. Clinical officers provided screening at 11 (28%) sites, and none of these sites relied on clinical officers exclusively. The remainder of the sites reported a combination of providers, including one site that reported the availability of lay health workers.

On-site Screening and Treatment Modalities

VIA was the most commonly reported screening method, which was available at 31 (79%) sites. Eleven of these 31 (35%) sites used VIA as the sole screening method. VILI was reported less commonly at 11 (28%) sites. Pap testing was the second most commonly reported screening method, which was used at 26 (67%) sites. Four of these 26 (15%) sites used Pap testing as the sole screening method. High-risk HPV testing was available at 13 (33%) sites. Neither VILI nor hrHPV DNA testing were ever used as the sole screening method. The majority of sites (62%) reported the availability of multiple screening methods. High-risk HPV testing was available at 29% of sites with VIA or VILI and 50% of sites with Pap testing. Colposcopy was only available at sites that offered Pap testing. Of the 26 sites with Pap testing, 5 (19%) had colposcopy and 4 (15%) had colposcopy with biopsy services. Sites with on-site colposcopy and biopsy services were more likely to be located in Southern Africa compared to other regions in SSA (5 [28%] vs. 0 [0%], P=0.02).

The majority of sites that offered on-site screening also had treatment available (n=36 [92%]) and some had multiple treatment options available. Cryotherapy was the most commonly reported method available to treat premalignant lesions, which was used at 29 (74%) sites. Excisional procedures, such as a loop electrosurgical excisional procedure (LEEP) and cold-knife conization, were offered at 23 (59%) and 12 (31%) sites, respectively. Of the sites that offered cryotherapy, 24 (77%) reported having either LEEP or cold-knife conization available, if needed. Radical or extended hysterectomy was the most

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commonly reported method available to treat ICC, which was used at 18 (46%) sites. Fewer sites had chemotherapy or radiation therapy at 10 (26%) and 6 (15%), respectively. Of the sites that offered radical or extended hysterectomy, 9 (50%) had chemotherapy, 5 (28%) had radiation therapy, and 4 (22%) had both chemotherapy and radiation available.

Nearly 37 (95%) sites reported on-site cervical cancer prevention programs for HIV-infected women, and 8 (22%) of these sites restricted services to HIV-infected women alone (Table 3). There were no significant differences between the screening and treatment modalities available at the sites that offered services to HIV-infected women compared to those that offered services to both HIV infected and uninfected (data not shown).

Referral Center Designation and Access

Thirty (59%) sites served as a referral center for cervical cancer screening. Of these, 26 (87%) received referrals from other HIV care and treatment programs and 20 (67%) received referrals from primary care clinics. The remainder of the referrals to the individual programs originated from family planning clinics 17 (60%), clinical research sites 17 (57%), antenatal care clinics 15 (50%), and other clinic types 8 (27%). Sites were queried on the access to referral centers for cervical cancer screening that was not available at their clinic. For the 12 (24%) sites that did not have on-site screening, 10 (83%) of their referral sites were located within the same facility or less than 10 kilometers away; and 2 (17%) sites did not have access to a referral clinic.

DISCUSSION

The majority of sites affiliated with an NIH-funded HIV/AIDS network in our study had on-site cervical cancer screening programs, and almost all had access to screening, even if screening was not available on-site. Some of these sites also served as referral centers from other treatment programs. These data show that the infrastructure for cervical cancer screening and linkages between clinics have been established in many urban areas, however there remain a few challenges.

The majority of sites with several cervical cancer screening methods available performed VIA, however many sites continue to offer Pap testing. Ideally, abnormal Pap tests are managed using colposcopy and biopsy, if needed, but most of these sites did not have an available colposcope or pathology services. A recent quality assurance program for cervical cytology and histology showed that an education program for pathologists in resource constrained settings can lead to improved diagnostic interpretations [17]. However, studies have shown that there is a shortage of pathologists in SSA, which contributes to the long interval between biopsy results and treatment [18]. Scale-up of Pap testing for many millions of women would likely create a large burden on the scant pathology services in much of SSA. Additionally, the complexity of Pap testing programs may increase the proportion of patients who do not return for treatment since multiple visits are usually necessary, which requires reliable communication with and transportation for patients. Khozaim K *et. al* reported that loss to follow-up is one of the major challenges of cervical cancer prevention programs since a third of their patients in Western Kenyan did not return for treatment [19]. Currently, a better approach is the single visit ‘screen-and-treat’ strategy

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that uses visual inspection techniques followed by cryotherapy for eligible women. However, future availability of lower-cost, point-of-care rapid hrHPV DNA testing should also be incorporated into the 'screen-and-treat' strategy to improve specificity and better identify the women with premalignant lesions who could benefit most from immediate treatment [20]. High-risk HPV testing has not been widely available to date, but a new point-of-care cartridge-based molecular diagnostic system for hrHPV is now available in SSA that requires very little laboratory infrastructure, and provides results in one hour allowing for same day test-and-treat approaches [21]. These single visit approaches decrease barriers to care, are affordable, and are sustainable, as opposed to Pap testing and colposcopy [9–11, 22–24].

In addition to screening, a successful cervical cancer prevention program requires treatment of premalignant lesions. Cryotherapy has been shown to be an effective treatment modality, regardless of HIV status, but has higher subsequent disease negative rates among HIV-uninfected women [25]. In HIV-infected women, premalignant lesions tend to be larger and involve the endocervical canal, which makes it more likely that an additional treatment method, i.e. LEEP or cold-knife conization, is needed [6, 26]. While we found that the majority of sites that offered treatment for premalignant lesions had cryotherapy, almost a quarter of these sites did not have excisional procedures like LEEP available although the sites provided care to HIV-infected women. Cervical cancer prevention sites should increase access to excisional procedures, either on-site or by referral, which will involve additional training for providers and implementation of safety and quality control measures.

Integral to cervical cancer screening programs are the skilled providers. Our survey showed that physicians performed screening at a large number of sites. However, it has been shown that nurses can successfully perform these tasks. In Zambia, which reportedly has one of the highest mortality rates from cervical cancer worldwide, one program employs trained nurses to provide digital cervicography-aided VIA (DC-VIA) with same-day cryotherapy [27]. Digital images of suspicious lesions are reviewed in real-time by gynecologists at remote tertiary care sites. Even among HIV-infected women, the sensitivity of DC-VIA to detect CIN 2/3 lesions was higher than Pap testing [28]. Thus, task shifting from physicians to nurse-led programs can lower costs and expand access without compromising effectiveness.

Furthermore, a successful cervical cancer prevention program requires treatment of malignant lesions; however, the management of ICC is a major challenge in SSA countries due to the lack of access to and varied quality of cancer treatment centers. In our survey, fewer than half of sites were able to perform radical or extended hysterectomies and an overwhelming majority did not have chemotherapy or radiation therapy. An even smaller proportion had all three options available. A 2008 review on cancer treatment in SSA noted that radiotherapy was available in only 23 of 53 countries, and that although there was a 30% increase in sites during the previous decade, this expansion occurred in countries already able to offer radiotherapy, and was not expanded to countries that did not have any access to radiation [29]. To decrease ICC deaths, adequate and appropriate treatment options must be expanded, with special attention to those countries that did not have any access previously.

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Our study has limitations. First, there may have been sampling bias. The survey was sent only to NIH-funded HIV/AIDS sites, which may have impacted the responses. For example, the high proportion of sites that offered Pap testing might be because U.S. investigators, who are accustomed to using the Pap test as the primary screening method, led these sites. Additionally, more than a third of sites that were invited to participate in the study did not respond. Besides geographic location, we do not have any additional details about these non-responding sites. It is possible that sites without cervical cancer screening did not respond, which would decrease our reported percentages of sites with on-site screening availability. Second, we did not query Ministries of Health, the private sector, or other organizations that might have robust cervical cancer prevention programs. Therefore, our results may not be indicative of the country's response to cervical cancer screening, and may not reflect the general environment. However, over half of our respondents were a part of the IeDEA network, which collects data from routine HIV clinical visits, and thus provides some insight into services offered at local healthcare facilities. Next, there might be misclassification. For example, on-site screening services might have been interpreted literally; meaning it is possible that a site could have reported not having on-site screening services, however another building on-campus might have screening services. Last, SSA is undergoing scale-up of cervical cancer screening services and our results represent status through the end of 2013.

Overall, the higher incidence and mortality of cervical cancer in developing countries can be attributed to a generalized lack of awareness, absence or poor quality of screening programs, and poor access to care, prevention and treatment. Building upon the existing infrastructure in established care delivery systems in resource-constrained settings represents an ideal framework for implementing a program to reduce cervical cancer incidence. Although we surveyed HIV programs, it is important to note that routine cervical cancer screening among the general population in many countries typically was introduced by HIV clinics. Cost containment and skilled staff who are able to perform screening and treatment are integral to the sustainability of a cervical cancer prevention program. It is possible that a coordinated network can be established that could serve as a platform to accelerate the implementation of evidence-based cancer prevention programs for HIV-infected and HIV-uninfected women. There should be a collective effort among public, private, and academic sectors to increase screening and treatment programs, determine the most effective screening algorithm, particularly for HIV-infected women, and conduct cancer research to halt the projected rise of ICC in resource-constrained settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

ACTG	AIDS Clinical Trials Group
AIDS	Acquired immunodeficiency syndrome
AMC	AIDS Malignancy Consortium
CFAR	Centers for AIDS Research
DC-VIA	Digital cervicography-aided visual inspection with acetic acid
DNA	Deoxyribonucleic acid
HIV	Human immunodeficiency virus
hrHPV	High-risk human papillomavirus
IeDEA	International Epidemiologic Databases to Evaluate AIDS
ICC	Invasive cervical cancer
LEEP	Loop electrosurgical excisional procedure
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases

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NICHD	Eunice Kennedy Shriver National Institute of Child Health & Human Development
NIH	National Institutes of Health
RNA	Ribonucleic acid
SSA	Sub-Saharan Africa
VIA	Visual inspection with acetic acid
VILI	Visual inspection with Lugol's solution

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Figure 1.

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Table 1

Survey Questions

1	What type of clinic is your program? (multiple choice: antenatal clinic, clinical research site, family planning, HIV care site, primary care clinic, other; more than one answer may be appropriate)
2	Is cervical cancer screening available to your patients (either on site or via referral)? (Yes, No)
3	If cervical cancer screening is available <u>on site</u>: • Does your program screen HIV-infected women? (Yes, No) • Does your program screen HIV-uninfected women? (Yes, No) • Does your program maintain electronic records on women screened? (Yes, No) • Cervical cancer screening is done by: (multiple choice: clinical officer, nurse, lay health worker, physician, other; more than one answer may be appropriate) • The method(s) used for cervical cancer screening are: (multiple choice: Pap, VIA, HPV DNA, VILI; more than one answer may be appropriate) • Treatments available for premalignant lesions and cervical cancer: (multiple choice: cryotherapy, conization, loop electrocautery excisional procedure [LEEP], radical hysterectomy, radiation therapy, chemotherapy, other; more than one answer may be appropriate) • Patients are referred to our facility for cervical cancer screening (Yes, No) • Patients are referred from: (multiple choice: antenatal clinic, clinical research site, family planning, HIV care site, primary care clinic, other)
4	If cervical cancer screening is available at <u>referral site</u>: • Distance to referral site

Surveys were emailed to the affiliated sites and completed by a site representative. Some questions permitted more than one answer.

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Table 2

Screening Method by Country

Site (by region and country)	No. Sites	No. On-site Screening Programs	Screening Method					No. Sites with Electronic Medical Records
			Pap	VIA	VILI	HPV	Colpo/bx	
Central Africa (n=6)								
Burundi	3	0	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Cameroon	2	2	2(100)	0(0)	0(0)	1(50)	0(0)	0(0)
Rwanda	1	0	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
East Africa (n=18)								
Kenya	6	6	5(83)	6(100)	2(33)	3(50)	0(0)	5(83)
Tanzania	5	5	1(20)	5(100)	1(20)	1(20)	0(0)	0(0)
Uganda	7	2	1(50)	2(100)	1(50)	0(0)	0(0)	0(0)
Southern Africa (n=19)								
Botswana	2	2	2(100)	1(50)	1(50)	1(50)	1(50)	1(50)
Lesotho	1	1	1(100)	1(100)	0(0)	0(0)	0(0)	1(100)
Malawi	7	7	3(43)	7(100)	2(29)	2(29)	1(14)	1(14)
South Africa	5	4	4(100)	2(50)	1(25)	2(50)	2(50)	3(75)
Zambia	2	2	0(0)	2(100)	0(0)	0(0)	(0)0	2(100)
Zimbabwe	2	2	1(50)	2(100)	0(0)	0(0)	1(50)	2(100)
West Africa (n=8)								
Burkina Faso	1	1	1(100)	1(100)	1(100)	1(100)	0(0)	1(100)
Côte d'Ivoire	2	1	1(100)	1(100)	1(100)	0(0)	0(0)	0(0)
Nigeria	2	2	2(100)	1(50)	1(50)	1(50)	0(0)	1(50)
Senegal	2	1	1(100)	0(0)	0(0)	1(100)	0(0)	0(0)
Togo	1	1	1(100)	0(0)	0(0)	0(0)	0(0)	0(0)
	51	**39**	**26(67)**	**31(79)**	**11(28)**	**13(33)**	**5(13)**	**17(44)**

Data are n(%)

Denominator is the number of on-site screening programs

Pap – Papanicolaou test, VIA -visual inspection with acetic acid, VILI - visual inspection with Lugol's solution, HPV – human papilloma virus DNA test, colpo/bx – colposcopy +/− biopsy

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Table 3

Sites with On-site Screening and Treatment Available by HIV status[#]

	HIV-infected n=37	HIV-uninfected n=29
SCREENING		
VIA	29(78)	24(83)
Pap	25(68)	19(66)
HPV DNA	13(35)	10(34)
VILI	10(27)	9(31)
Colposcopy +/− biopsy	4(11)	3(10)
TREATMENT		
None	3(8)	1(3)
Premalignant lesions		
Cryotherapy	27(73)	21(72)
LEEP	21(57)	17(59)
Conization	12(32)	10(34)
Malignant lesions		
Radical or extended hysterectomy	18(49)	16(55)
Chemotherapy	9(24)	10(34)
Radiation therapy	5(14)	5(17)

Data are n(%)

[*] Sites may report more than one screening and treatment method

[#] Sites may be included in both HIV-infected and HIV-uninfected women columns if sites report screening and treatment programs regardless of HIV status.

Pap – Papanicolaou test, VIA -visual inspection with acetic acid, VILI - visual inspection with Lugol's solution, HPV – human papilloma virus DNA test