

Cervical cancer screening and treatment of cervical intraepithelial neoplasia in female sex workers using “screen and treat” approach

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Objective: Female sex workers (FSWs) are at an increased risk of human immunodeficiency virus (HIV) as well as human papillomavirus (HPV) infections and thus have an increased risk of cervical intraepithelial neoplasia (CIN) and cervical cancer. We evaluated the feasibility of “screen and treat approach” for cervical cancer prevention and the performance of different screening tests among FSWs.

Methods: Women were screened using cytology, VIA (visual inspection with acetic acid), and VILI (visual inspection with Lugol’s iodine) and underwent colposcopy, biopsy, and immediate treatment using cold coagulation, if indicated, at the same visit.

Results: We screened 300 FSWs of whom 200 (66.67%) were HIV uninfected and 100 (33.34%) were HIV infected. The overall prevalence of CIN 2–3 lesions was 4.7%. But all women with CIN 2–3 lesions were HIV infected, and thus the prevalence of CIN 2–3 lesions in HIV-infected FSWs was 14/100 (14%, 95% confidence interval: 7.2–20.8). All of them screened positive by all three screening tests. Cold coagulation was well tolerated, with no appreciable side effects.

Conclusion: Cervical cancer prevention by “screen and treat” approach using VIA, followed by ablative treatment, in this high-risk group of women is feasible and can be implemented through various targeted intervention programs.

Keywords: cytology, VIA, VILI, CIN, cold coagulation, cervical cancer, HPV, FSWs

Introduction

Female sex workers (FSWs) are at an increased risk of many sexually transmitted infections, including human papillomavirus (HPV) and human immunodeficiency virus (HIV) infections. These infections interact with each other in many ways given the overlap of risk factors; thus HPV as well as HIV prevalence is very high in FSWs. A meta-analysis of 14 studies involving more than 4,000 FSWs in nine Asian countries has reported that HPV prevalence among FSWs in this region ranged from 12.8% to 84.8% and that FSWs had a nearly tenfold risk of HPV infection than women in the general population.¹

HPV-associated cancers occur at increased rates in persons infected with HIV.² The prevalence of HPV is more in HIV-infected women. They are infected with a broad range of HPV genotypes, and multiple concurrent infections are also common.³ HPV infections are more likely to persist in HIV-positive women than in HIV-negative women.^{4–6} This persistent HPV infection contributes to a higher prevalence of HPV infection among HIV-infected women, leading to higher risk of cervical intraepithelial neoplasia (CIN).^{7–9}

Prevalence of HIV in FSWs varies in different regions of the world, and it is considerably higher than in women in the general population. The overall prevalence of

HIV in FSWs in India during 2008–2009 was 4.77% (95% confidence interval [CI]: 4.60–4.94) as compared to 0.6% (95% CI: 0.52–0.67) among antenatal women who represent women at low risk of HIV.¹⁰ HIV prevalence in FSWs in certain states such as Andhra Pradesh, Maharashtra, Karnataka, Manipur, and Nagaland was >10%.¹⁰

HIV infection increases the risk of new HPV infections and decreases the rate of HPV clearance.¹¹ There is increasing evidence suggesting that HPV-infected individuals are at higher risk of acquiring HIV infection.^{12–14}

It is now well established that persistence of HPV infection is the strongest epidemiologic factor associated with cervical intraepithelial neoplasia and cancer of the cervix.^{15–20} Thus, FSWs face a dual risk and dual burden of both: HPV and HIV infections, and cervical cancer screening and treatment of CIN must be offered to all FSWs.

Cytology-based cervical cancer screening programs have not really worked well in developing countries in reducing cervical cancer incidence and mortality. Visual inspection of the cervix after application of acetic acid (VIA) is an alternative screening test which has been shown to be more sensitive than cytology in many studies in the developing regions. VIA offers an opportunity to immediately treat screen-positive women in a single visit “screen and treat” approach and has been recommended by the World Health Organization (WHO).²¹

We evaluated the feasibility of offering cervical cancer prevention programme for to this very high-risk and vulnerable population using “screen and treat” approach. We also concurrently evaluated the performance of conventional cytology, VIA, and visual inspection with Lugol’s iodine (VILI) in cervical cancer screening and the feasibility and acceptability of immediate treatment for CIN using an ablative method.

Materials and methods

The project was approved by the ethics committee of the Hirabai Cowasji Jehangir Medical Research Institute (HCJMRI) and Jehangir Clinical Development Centre, Pune, India. We conducted a cross-sectional study between October 2012 and February 2013. We contacted non-governmental organizations (NGOs) working in three high HIV-prevalent districts in Maharashtra, namely, Pune, Sangli, and Ahmednagar, and data were collected from a convenience sample of 300 FSWs. The peer educators and counselors working with these NGOs were provided with study information, and they referred willing FSWs to our designated study clinic for cervical cancer screening. FSWs between the age group of 18 and 60, willing to sign or provide a thumb impression on the informed consent form, willing to undergo study procedures,

who were nonpregnant, with no history of prolapse, no history of treatment for cervical neoplasia, and having an intact uterus were enrolled in the study.

The study was conducted at a designated cervical cancer screening clinic set up at Prayas (a non-governmental, nonprofit organization) by a collaborative effort between HCJMRI and Prayas. After a written informed consent and HIV pre-test counseling, demographic information, history regarding sexual practices, years in sex work, number of sex partners, condom use with regular partner/client, etc were collected using a structured questionnaire. Approximately 10 mL of venous blood sample was collected for HIV testing (if a documented HIV test report was not available), HBsAg testing, syphilis serology, and CD4 and HIV viral load testing (for HIV-infected FSWs only). HIV testing was done using HIV TriDot (J. Mitra & Co. Pvt. Ltd., New Delhi, India) and Instachk (Transasia Bio-Medicals Limited, Mumbai, India) for the detection of anti-HIV antibodies, and HBsAg testing was done using the One Step Cassette Style HBsAg Test (IND Diagnostic Inc., British Columbia, Canada). Syphilis testing was done using rapid plasma regain (RPR) test (Tulip, Goa, India), and if RPR was positive, a second test was performed using Instachk TP test (Transasia Bio-Medicals Limited) for confirmation. Appropriate post-test counseling was done to participants detected with HIV infection. Treatment for syphilis and other sexually transmitted infections was provided following National AIDS Control Organization’s guidelines.²²

After completing the case report forms and blood collection, a speculum examination was done with women lying down in the modified lithotomy position. A trained nurse exposed the cervix with a bivalved speculum and collected cervical specimen for cytology using a Cervex-Brush and prepared a cervical smear on a glass slide, which was fixed immediately in 95% ethanol.

Cervical cancer screening using VIA was performed by two nurses who were trained in visual screening methods, and colposcopy was done by a trained doctor using the manual developed by the International Agency for Research on Cancer (IARC), WHO.²³ The nurse applied 5% acetic acid on the cervix with a cotton swab for 1 minute. Findings were recorded as VIA negative, VIA positive (if there was an acetowhite lesion touching the squamocolumnar junction), or VIA positive (suspicious of invasive cancer).²³

Colposcopy was done on all women by a trained doctor, and the nurse independently recorded the findings of VILI when the doctor applied Lugol’s iodine as a part of colposcopic evaluation. Colposcopic findings were reported

as normal, inflammation, probable low- or high-grade precancerous lesions, or suspected invasive cancer following the IARC manual.²³ If there was a lesion suggestive of any colposcopic abnormality (low- as well as high-grade), colposcopic findings were explained to the woman and multiple punch biopsies were collected using a Tischler punch biopsy forceps. Women having lesions not involving more than three-fourths of the transformation zone and not entering into the endocervical canal, and those with fully visible squamocolumnar junction with no suspicion of an invasive cancer were treated immediately using cold coagulation. Cold coagulation (WISAP® Medical Technology GmbH, Brunnthal/Hofolding, Germany) is actually a misnomer and utilizes heat to ablate the epithelium at 105°C when applied for 45 seconds. Multiple overlapping applications of 45 seconds each were used during the same sitting without any local anesthesia to cover the entire transformation zone.

Cervical smears for cytology were stained by standard Papanicolaou staining method and the results reported by a trained cytologist using the Bethesda 2001 system of reporting cervicovaginal smears.²⁴ Cervical biopsy specimens were analyzed and the results were reported by two pathologists using CIN terminology independently and then a consensus diagnosis was reached.

Reference standard for final diagnosis

All women underwent colposcopy irrespective of the visual screening test results. If colposcopy was suggestive of any abnormality, multiple punch biopsies were obtained from the abnormal area for histopathology. Thus, the reference standard was a normal colposcopy or histopathology. We did not perform cervical biopsies for histological diagnosis on all participants to avoid unnecessary intervention; however, colposcopy was performed on all participants to minimize the bias, and colposcopy or histopathology was taken as a reference test to derive the test characteristics of various screening modalities.

Data entry was done using MS Access 2007 software, and the data were analyzed using the STATA 12.0 software. Standard formulae were used to calculate the sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) (and their exact 95% CIs) of the screening tests to detect CIN 2 and 3 lesions.

Results

We enrolled 300 FSWs in this cross-sectional study. The mean age of the participants was 33.6 (range, 21–58 years;

SD, 8.7; median, 30.5). Their demographic characteristics are presented in Table 1. Of the 300 FSWs enrolled, 196 (65.3%) were natives of Maharashtra, while 104 (34.7%) were migrants from other states (Karnataka, Andhra Pradesh, West Bengal, Uttar Pradesh, Bihar, and Orissa) who relocated to Maharashtra for sex work. Majority (273/300, 91%)

Table 1 Participant's characteristics

Characteristics	Total	
	Number	%
Total participants	300	
Geographic location		
Maharashtra	196	65.3
Other	104	34.7
Typology		
Brothel based	273	91.0
Street based	27	9.0
Age		
21–29 years	116	38.7
≥30 years	184	61.3
Literacy		
Literate	75	25.0
Illiterate	225	75.0
Smoking		
No	258	86.0
Yes	42	14.0
Tobacco use		
No	113	37.7
Yes	187	62.3
Age at first sex (years)		
≤18	241	84.3
>18	45	15.7
Duration of sex work (years)		
≤10	195	68.2
≥11	91	31.8
Frequency of male condom use with different partners		
Each and every partner/client	227	75.9
Each and every client except for regular partners	59	19.7
Occasionally	0	0.0
Rarely	1	0.3
Never	12	4.0
Total number of pregnancies		
None	69	23.0
One or more	231	77.0
Total number of miscarriages		
None	200	66.7
One or above	100	33.3
Syphilis		
Negative	270	90.0
Positive	30	10.0
HBsAg		
Negative	294	98.0
Positive	6	2.0
Final diagnosis		
Normal	282	95.3
CIN 2/3 present	14	4.7

Abbreviation: CIN, cervical intraepithelial neoplasia.

were brothel based and the remaining 9% were street based. Seventy-five percent of the sex workers had no formal education and 25% had some education. Smoking was reported by 14% of the participants, but majority (62.3%) reported tobacco chewing. Age at first sex before 18 years of age was reported by a substantial number of FSWs (241/286, 84.3%), and about 68% reported being in the occupation of sex work for less than 10 years. Three-quarters of the FSWs reported condom use with each and every partner, including regular partners, and about 20% reported condom use with all partners except with their regular partners. Majority reported at least one pregnancy (77%), and induced abortions were reported by 10% of the FSWs, with the number of maximum abortions exceeding more than eight. Of the 300 FSWs enrolled, 100 (33.3%) FSWs were HIV infected, 10% (30/300) were positive for syphilis serology, and 2% (6/300) were positive for HBsAg. We did not observe any participant characteristics that were significantly associated with CIN 2–3 lesions.

Of the 300 enrolled, 296 completed all three cervical cancer screening tests and 5 were excluded from final analysis due to unsatisfactory cytology smears. VIA was positive in 45/296 (15.2%), VILI was positive in 36/296 (12.2%), and cytology at ASC-US (atypical squamous cells of undetermined significance) threshold was positive in 66/291 (22.7%) women. Distribution of final disease status by results from different screening tests is presented in Table 2. Histopathology of cervical punch biopsies revealed CIN 1 in eleven

women, CIN 2 in five women, and CIN 3 in nine women. The overall prevalence of CIN 2–3 lesions was 4.7%. But all women with CIN 2–3 lesions were HIV infected, and thus the prevalence of CIN 2–3 lesions in HIV-infected FSWs was 14/100 (14%, 95% CI: 7.2–20.8). None of them were detected with invasive carcinoma.

Sensitivity, specificity, and PPV and NPV of VIA, VILI, and cytology (at ASC-US threshold) to detect CIN2+ lesions are presented in Table 3. Sensitivity of VIA, VILI, as well as cytology (at ASC-US threshold) was 100%. Specificity of VIA was 89%, that of VILI was 92.2%, and that of cytology was 81.2%. PPV of VIA, VILI, and cytology was 31.1%, 38.9%, and 21.2%, and NPV was 100% for all the three tests.

All FSWs with colposcopy suggestive of CIN (low-grade as well as high-grade) underwent cervical punch biopsies and were eligible for ablative treatment using cold coagulation. Of the 296 FSWs included in final analysis, 27 (9.12%) FSWs underwent cervical punch biopsies and treatment using cold coagulation. All of them accepted biopsies and treatment during the same screening visit except for one FSW, who reported to our study clinic after about 2 months following repeated counseling by the study staff and social workers of the NGO working in their area. Treatment with cold coagulation was well tolerated by all of them, and none had any appreciable side effects after treatment.

Discussion

In our study, 14% of the HIV-infected FSWs were detected with CIN 2–3 lesions; this emphasizes the need for screening and appropriate treatment of CIN in HIV-infected FSWs. There is a complex interplay between HIV and HPV infections, and FSWs constitute a very high-risk group for HIV as well as HPV infections. We concurrently evaluated the test characteristics of VIA, VILI, and cytology in detecting CIN 2–3 lesions. The sensitivity of all the three tests was 100%; however, this study was underpowered for evaluating sensitivity and NPV, and our results should be considered with caution.

It is important to note that visual screening tests, which are low-cost screening tests, did not miss any single high-grade lesion. In a pooled analysis involving about 58,000 women, cytology had the lowest sensitivity as compared to visual screening tests.²⁵ However, considering our small sample size, it is possible that this may not be the true reflection of the screening tests. In our study, the specificity of cytology was lower than those reported in the reports published earlier.²⁵ However, it is possible that a large percentage of FSWs were

Table 2 Distribution of final disease status by results from different screening tests

Test result	Final diagnosis status				Total
	Normal	CIN 1	CIN 2	CIN 3	
VIA					
Negative	249	2	0	0	251
Positive	22	9	5	9	45
Total	271	11	5	9	296
VILI					
Negative	259	1	0	0	260
Positive	12	10	5	9	36
Total	271	11	5	9	296
Cytology at ASC-US threshold					
Normal	217	8	0	0	225
Abnormal	50	2	5	9	66
Total	267	10	5	9	291
Cytology at LSIL threshold					
Normal	237	8	1	1	247
Abnormal	30	2	4	8	44
Total	267	10	5	9	291

Abbreviations: CIN, cervical intraepithelial neoplasia; VIA, visual inspection of the cervix using 3%–5% acetic acid; VILI, visual inspection using Lugol's iodine; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion.

Table 3 Accuracy of the different screening tests for detection of cervical intraepithelial neoplasia 2–3 lesions

Screening test	True positives	False positives	False negatives	True negatives	Sensitivity value (95% CI)	Specificity value (95% CI)	PPV (95% CI)	NPV (95% CI)
VIA	14	31	0	251	100 (76.8–100.0)	89.0 (84.8–92.4)	31.1 (18.2–46.6)	100 (98.5–100.0)
VILI	14	22	0	260	100 (76.8–100.0)	92.2 (88.4–100.0)	38.9 (23.1–56.5)	100 (98.6–100.0)
Cytology at ASC-US threshold	14	52	0	225	100 (76.8–100.0)	81.2 (76.1–85.7)	21.2 (12.1–33.0)	100 (98.4–100.0)
Cytology at LSIL threshold	12	32	2	245	85.7 (57.2–98.2)	88.4 (84.1–92.0)	27.3 (15.0–42.8)	99.2 (97.1–99.9)

Abbreviations: CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; VIA, visual inspection of the cervix using 3%–5% acetic acid; VILI, visual inspection using Lugol's iodine; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion.

infected with high-risk HPV, resulting in minor cytological abnormalities that could not be detected on colposcopy. Histopathology report of the cervical biopsy is the gold standard, and although colposcopy was done on all participants to minimize verification bias, we did not perform cervical biopsies on all the participants without colposcopic abnormalities due to ethical reasons. In a study conducted in Hong Kong, the prevalence of any CIN among FSWs using cytology screening was 9.7%, and poorer compliance for the follow-up visit was seen among those with an abnormal result.²⁶ This underscores the importance of the “screen and treat” approach. In spite of these limitations, our study provides important information about the feasibility of “screen and treat” strategy for preventing cervical cancer, which has been recommended by the WHO for low-resource countries.²¹

Visual screening tests provide an opportunity to treat screen-positive lesions at the same time; this is particularly important for this highly mobile population. Single-visit “screen and treat” approach was well accepted by FSWs, and thus it is feasible for various organizations providing care and support to FSWs to include cervical cancer screening in their program. Ablative treatment using cold coagulation was well tolerated and accepted by the FSWs. This method has several advantages over cryotherapy and has comparable cure rates for the treatment of all grades of CIN.²⁷

Another incidental finding of our study is about the very high rate of induced abortions in this population in spite of the high rate of reported condom use, and therefore, it is essential that FSWs are counseled and provided effective temporary contraceptive choices in addition to condom counseling for HIV prevention.

Early age of initiation of sexual activity is one of the strongest risk factors for cervical cancer,¹⁸ and majority of the sex workers in our study reported age at initiation of sex work below 18 years. The first few reports on increased risk of cervical cancers among sex workers date back to 1950s and 1960s, but to our knowledge, prevention of cervical cancer among FSWs has remained neglected. It is possible to reach this highly vulnerable population and provide comprehensive reproductive health care that includes contraception and cervical cancer screening and treatment of CIN through the targeted intervention programs. We did not find any CIN in HIV-uninfected FSWs; however, high risk of CIN among them cannot be precluded due to the small sample size of our study, and all FSWs should be offered cervical cancer screening irrespective of their HIV status.

Primary prevention of infection with high-risk HPV (HPV-16 and -18) is now possible with advancement in the

development of HPV vaccines, and these vaccines have been approved in several countries. The WHO recommends HPV vaccine for 9- to 13-year-old girls for preventing HPV-16 and -18 infections,²⁸ which are responsible for 70% of the cancers. These vaccines also provide some cross-protection^{29,30} against additional high-risk HPV types and have the potential to substantially reduce the incidence of CIN caused by these high-risk HPV types. Because of the increased risk of HIV infection in HPV-coinfected individuals, HPV vaccines may be of help in reducing HIV acquisition and may reduce HIV incidence in high HPV-prevalent populations, in addition to preventing cervical cancer, if validated in future studies.¹⁴

To conclude, cervical cancer screening and treatment of CIN using “screen and treat” strategy needs to be integrated into targeted interventions that are ongoing for prevention of HIV infection and care and support of HIV-infected FSWs. An integrated approach of HPV vaccination and screening will help in reduction of cervical cancers in this highly vulnerable population.

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Author contributions

SJ, VK, AB designed and implemented the study, interpreted the data, and prepared the manuscript; TD implemented the study and prepared the manuscript; UM analyzed the data and prepared the manuscript; YS, SG, SK and MM were involved with cytology and histology reporting, interpretation of data and preparation of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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