



Cervical Cancer Screening in HIV-Positive Women in India: Why, When and How?

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Abstracts

Background Cervical cancer is an AIDS-defining illness, and HIV-positive women are at high risk. The present study aimed to determine the magnitude of the problem, compare the performance of screening tests and assess factors affecting participation.

Methods HIV-positive women aged 30–59 years attend the anti-retroviral therapy (ART) clinics were screened by conventional Pap, HPV testing (Hybrid Capture 2) and visual inspection with acetic acid (VIA). A cohort of HIV-negative women from the community matched for age and parity were screened similarly. Screen-positive women underwent colposcopy and biopsy. Factors affecting participation were assessed.

Results Pap, VIA and HPV were positive in 48 (23.8%), 65 (32.2%) and 76 (37.6%) subjects, respectively, among HIV-positive women, and in 12 (5.9%), 10 (4.9%) and 12 (5.9%) subjects, respectively, among HIV-negative women. CIN2+ was present in 12 (6.4%) HIV-positive women and in 1 (0.5%) HIV-negative woman ($p = < 0.004$). Sensitivity of HPV, Pap and VIA for detection of CIN2+ lesions was 91.7%, 75.0% and 75.0%, respectively; specificity was 68.4%, 83.9% and 72.5%, respectively. Lack of availability of screening facilities in the ART clinic and long waiting times were a strong deterrent to participation among HIV-positive women.

Conclusions There was higher prevalence of HPV infection and CIN2+ lesions in HIV-positive women. VIA showed equivalent sensitivity to Pap and could be a good substitute in low resource settings. Setting up cervical screening services in ART clinics and sensitising physicians can improve outcomes among these women.

Keywords HIV · Pap · CIN · VIA · Colposcopy · Cervical cancer · Barriers · Screening

Introduction

Women infected with the human immunodeficiency virus (HIV) have a higher prevalence, more persistence and less regression of human papillomavirus (HPV) infection, with greater viral load and higher likelihood of infection with multiple genotypes [1]. Areas of the world which have been worst hit by HIV and acquired immunodeficiency syndrome (AIDS) show a high prevalence of HPV infection and thus of cervical cancer [2]. Cervical cancer is considered an AIDS-defining illness; [3] hence, regular screening is recommended for early detection of pre-invasive and invasive disease [4, 5]. This is even more relevant in the era of antiretroviral therapy (ART), which is able to increase life expectancy of HIV-infected patients but does not prevent persistent HPV infection [6]. Women infected with HIV remain at high risk of cervical cancer with the associated

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morbidity and mortality, even if they survive the scourge of other dreadful conditions associated with AIDS.

According to the World Health Organisation (WHO) 2018 data, 37.9 million people, including 18.2 million women, were living with HIV globally in 2018 [7]. In India, the estimated HIV prevalence was 0.22%, which equates to approximately 2.1 million adults, including 0.9 million women living with HIV/AIDS [8].

The present study was carried out in HIV-positive women attending the ART clinic at a tertiary care hospital, in order to determine the prevalence of HPV infection and cervical neoplasia, and assess cervical cancer awareness and performance of various screening methods, as well as understand the barriers to screening. A cohort of HIV-negative women from an urban resettlement area of Delhi who were similarly screened formed the comparison group.

Materials and Methods

This cross-sectional study was carried out from March 2014 to July 2015. Ethical approval was obtained from the Institutional Ethics Committee. Informed written consent was taken from all women. Sample size was calculated based on reported prevalence of HPV infection of 26% and abnormal Pap smear of 20% in HIV patients. To estimate HPV prevalence among HIV-infected women at hospital set-up, it was presumed that it varied between 20 and 32% (a 6% absolute difference). The required sample with 95% confidence was found to be 200. HIV-positive women aged 30–59 years attending the antiretroviral therapy (ART) Clinic in the Department of Medicine, and HIV-negative women of similar age and parity from an urban community in Delhi were invited to participate in the study. Exclusion criteria were: prior hysterectomy or surgical procedures on cervix, pregnancy, unwilling to participate in the study. Eligible women were referred to the Colposcopy Clinic in the Department of Obstetrics and Gynaecology. A study proforma was completed with detailed history, including socio-demographic parameters, and reproductive history; for HIV-positive women: risk factors and mode of contracting HIV, antiretroviral therapy (ART) status, cluster of differentiation (CD) 4 count at diagnosis and at recruitment into the study. Complete physical examination was done followed by per speculum and pelvic examination.

Pap smear was obtained using an Ayre's spatula and cytobrush and reported using Bethesda terminology. For HPV test, the Digene brush and specimen collection tube were used. HPV testing was done by the Digene Hybrid Capture 2 (HC2) test (Qiagen Inc, Germany). Visual inspection with acetic acid (VIA) was performed and reported according to the International Agency for Research on Cancer (IARC) criteria [9].

Criteria for test positivity were as follows: Pap smear: ASCUS (Atypical squamous cells of undetermined significance) and above; HPV positive: sample RLU ≥ 1 pg/mL (ratio of sample RLU and positive control RLU 1.0): or VIA positive. Women positive on any of the above tests underwent colposcopy using a proMIS COLpro222DX-OZ view digital video colposcope. Colposcopy lesions were graded using the Swede score, and biopsy was taken from all abnormal areas. When no abnormality was found, four-quadrant biopsies were taken from the squamocolumnar junction. The final reference diagnosis was based on histopathology and classified into five classes—normal/inflammatory, cervical intraepithelial neoplasia (CIN) 1, CIN2, CIN3 and invasive cancer. Threshold defining disease was presence of lesions \geq CIN2. Subjects with CIN2 and CIN3 underwent loop electrosurgical excision procedure (LEEP). Those found to have cervical cancer were clinically staged and appropriately managed. Subjects found to be negative on all four screening procedures were considered to be normal and advised routine yearly cytological screening.

Data were analysed using Statistical Product Service Solutions (SPSS) software IBM version 19.0. Mean values were compared using analysis of variance (ANOVA). Frequency distributions were compared using Chi-square/Fisher's exact test as appropriate. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each test were calculated. Kappa statistics were computed to see the correlation between two screening tests. A probability value (*p* value) of < 0.05 was considered for statistical significance. Biopsy results or colposcopy results, where biopsy was not indicated, were used as the reference standard for measuring true disease, thereby adjusting for verification bias.

Results

A total of 202 HIV-positive women and 202 HIV-negative women for whom results of Pap smear, HPV and VIA were available were evaluated in the study. The comparison of socio-demographic characteristics between HIV-positive and HIV-negative women is shown in Table 1. Comparison of different socio-demographic characteristics and HIV-related factors to final diagnosis is shown in Table 2. Among HIV-positive women, the mean age was 36 years, with 158 (78.2%) aged 30–40 years; 59 (29.2%) women had received no formal education; the majority 106 (52.5%) were from the middle; and 78 (38.6%) were from the lower socioeconomic strata. Most women ($n = 133$, 70.4%) were married, 51 (27.0%) were widowed, and 5 (2.6%) were divorced. The age at first coitus was < 18 years in 66 (31.7%) subjects. Parity was ≥ 3 in 87 (43.1%). Barrier contraception was used by 102 (50.5%) subjects. Partner was HIV positive in 174

Table 1 Comparison of socio-demographic variables between HIV-positive and HIV-negative women

| Socio-demographic variable | HIV-positive (<i>n</i> = 202) | HIV-negative (<i>n</i> = 202) | |
|----------------------------|--------------------------------|--------------------------------|-----|
| Age (years)* | 30–39 | 145 | 145 |
| | 40–49 | 46 | 43 |
| | 50–59 | 11 | 14 |
| Parity* | < 3 | 114 | 117 |
| | ≥ 3 | 88 | 85 |
| Education* | Uneducated | 59 | 38 |
| | Educated | 143 | 164 |
| Occupation | Unemployed | 135 | 9 |
| | Employed | 67 | 193 |
| Marital status | Married | 143 | 189 |
| | Unmarried | 0 | 0 |
| | Widowed/separated/divorced | 59 | 13 |
| Socioeconomic status | Upper class | 2 | 17 |
| | Middle class | 191 | 106 |
| | Lower class | 9 | 79 |

*statistically not significant

Table 2 Comparison of different socio-demographic characteristics and HIV-related factors to final diagnosis

| Characteristics | Final diagnosis | | | | | |
|---------------------------------------------------------------|----------------------------------------------|--------------------------------|-------------------------------|-------------------------------|-------------------------------------|------------|
| | Chronic cervicitis (<i>n</i> = 130) No. (%) | CIN 1 (<i>n</i> = 44) No. (%) | CIN 2 (<i>n</i> = 3) No. (%) | CIN 3 (<i>n</i> = 6) No. (%) | Invasive Ca (<i>n</i> = 3) No. (%) | |
| Age (years) (NS) | 30–40 | 100 (76.9%) | 38 (86.3%) | 3 (100.0%) | 4 (66.7%) | 2 (66.7%) |
| | 41–50 | 27 (20.7%) | 5 (11.4%) | 0 (0.0%) | 2 (33.3%) | 0 (0.0%) |
| | 51–59 | 3 (2.3%) | 1 (2.3%) | 0 (0.0%) | 0 (0.0%) | 1 (33.3%) |
| Parity (NS) | < 5 | 124 (95.4%) | 41 (93.2%) | 2 (66.7%) | 5 (83.3%) | 3 (100.0%) |
| | > 5 | 6 (4.6%) | 3 (6.8%) | 1 (33.3%) | 1 (16.7%) | 0 (0.0%) |
| Socioeconomic status (NS) | Upper | 15 (11.5%) | 2 (4.5%) | 0 (0.0%) | 1 (16.7%) | 0 (0.0%) |
| | Middle | 66 (50.8%) | 27 (61.4%) | 2 (66.7%) | 2 (33.3%) | 1 (33.3%) |
| | Lower | 49 (37.7%) | 15 (34.1%) | 1 (33.3%) | 3 (50.0%) | 2 (66.7%) |
| Educational status* | Uneducated | 39 (30.0%) | 11 (25.0%) | 1 (33.3%) | 4 (66.7%) | 3 (100.0%) |
| | Educated | 91 (70.0%) | 33 (75.0%) | 2 (66.7%) | 2 (33.3%) | 0 (0.0%) |
| ART status (NS) | on ART | 121 (93.1%) | 41 (93.2%) | 3 (100.0%) | 6 (100.0%) | 2 (66.7%) |
| Duration of HIV illness (NS) | ≤ 5 years | 80 (61.5%) | 25 (56.8%) | 3 (100.0%) | 2 (33.3%) | 2 (66.7%) |
| | > 5 years | 50 (38.5%) | 19 (43.2%) | 0 (0.0%) | 4 (66.7%) | 1 (33.3%) |
| Duration of ART (NS) | ≤ 5 years | 93 (71.5%) | 35 (79.5%) | 3 (100.0%) | 3 (50.0%) | 2 (66.7%) |
| | > 5 years | 37 (28.5%) | 9 (20.5%) | 0 (0.0%) | 3 (50.0%) | 1 (33.3%) |
| CD4 count (cells/mm ³) at diagnosis of HIV* | ≤ 200 | 32 (24.6%) | 41 (93.2%) | 2 (66.7%) | 4 (66.7%) | 2 (66.7%) |
| | > 200 | 98 (75.4%) | 3 (6.8%) | 1 (33.3%) | 2 (33.3%) | 1 (33.3%) |
| CD4 count (cells/mm ³) at recruitment into study* | ≤ 200 | 5 (3.8%) | 5 (11.4%) | 2 (66.7%) | 1 (16.7%) | 0 (0.0%) |
| | > 200 | 125 (96.2%) | 39 (88.6%) | 1 (33.3%) | 5 (83.3%) | 3 (100.0%) |
| Age at first coitus (years)* | < 18 | 40 (30.8%) | 9 (20.5%) | 3 (100.0%) | 1 (16.7%) | 2 (66.7%) |
| | ≥ 18 | 90 (69.2%) | 35 (79.5%) | 0 (0.0%) | 5 (83.3%) | 1 (33.3%) |

NS, not significant

**p* value < 0.05—significant result

(86.1%) subjects. Diagnosis of HIV-positive was made within the last 5 years in 120 (59.4%) subjects. The mean CD4 counts at diagnosis of HIV was 303 cells/mm³ (range 0–1388 cells/mm³). The mean CD4 count at recruitment was 305 cells/mm³ (range 39–1493 cells/mm³); 147 (72.8%) subjects were on triple drug ART, most of them for 1–5 years.

The screening process of the study is shown in Fig. 1. Among HIV-positive subjects, ASCUS or worse cytology was reported in 48 (23.8%) subjects, with high-grade squamous intraepithelial lesion (HSIL) in 9 (4.5%) subjects. High-risk HPV (hrHPV) infection was detected in 76 (37.6%) subjects; the rate of VIA positivity was 65 (32.2%). Prevalence of CIN2+ lesions was 6.4% ($n=12$). Among HIV-negative group, Pap, VIA and HPV were positive in 12 (5.9%), 10 (4.9%) and 12 (5.9%) subjects, respectively. High-grade CIN was seen in only 1 (0.5%) subject. The difference was statistically significant ($p < 0.004$). CIN2+ lesions among HIV-positive women were most common among 30–40 years age ($n=9$, 75%). CIN2+ lesions were significantly more frequent among uneducated patients ($p=0.03$); 6 (50%) cases were seen in subjects with age at first intercourse < 18 years ($p=0.02$). There was no correlation with parity.

There was a significant inverse correlation between CIN2+ and CD4 counts, both at diagnosis of HIV and at recruitment into study ($p=0.01$ and 0.03 , respectively), (Table 2). The duration of HIV infection was not significantly related to diagnosis of CIN2+ (6.1% if < 5 years vs. 6.5% if > 5 years). The duration of ART was less than 5 years (mean 3.6, range 1–10 years) in 8 (66.7%) of CIN2+ cases.

Out of 202 HIV-positive subjects, 115 (56.9%) subjects were positive by any test, of which 13 (11.3%) were lost to follow-up. Reasons for non-compliance among women who were loss to follow-up were as follows: different locations of ART and Colposcopy Clinics ($n=5$, 8.7%), increased waiting time in hospital due to policy of first performing colposcopy for seronegative patients ($n=6$, 4.6%) and perception of stigmatisation ($n=2$, 1.5%).

To avoid bias, every 10th woman among 87 screen-negative women ($n=8$) underwent colposcopy, and all were found to be normal ($n=8$).

Out of 102 subjects who underwent colposcopy, biopsy was reported to be inadequate in 3 cases. Thus, the final analysis was performed on 186 patients (87 screen negative and 99 screen positive): normal $n=133$ (70.4%); CIN1 $n=44$ (23.3%); CIN2 $n=3$ (1.6%); CIN3 $n=6$ (3.2%); and invasive carcinoma $n=3$ (1.6%). Table 3 shows the comparison of screening results with final diagnosis. On Pap smear, 2 (16.7%) CIN2+ cases were normal and 3 (25%) CIN2+ cases were VIA negative, whereas only one positive case (invasive cancer) was missed by HPV DNA test. Out of 12 biopsy positive cases, colposcopy detected all cases of CIN2+.

The test performance of different screening tests for detection of CIN2+ lesions among HIV-positive women is shown in Table 4. Positive Pap smear (ASCUS+ cytology), VIA and HPV were found to be significantly associated with high-grade CIN on histopathology ($p=0.01$, 0.02 and 0.01 , respectively), with sensitivity 75.0%, 75.0% and 91.7%, respectively, and specificity 83.9%, 72.5% and 68.4%, respectively. Whereas Pap smear has best positive likelihood ratio, HPV test negative gives best negative likelihood ratio.

Comparison of screening test results and final diagnosis on histopathology between HIV-positive and HIV-negative women is shown in Fig. 2.

Discussion

Cancer cervix is an AIDS-defining condition, and annual screening is recommended in HIV-positive women [3, 4]. The Federation of Obstetrics and Gynaecological Societies of India (FOGSI) recommends that in limited resource settings, while VIA is advised every five years in normal women, it is advised three-yearly in HIV-positive women up to age 50 years, bearing in mind that this is an additive factor which can increase the incidence of cervical neoplasia [5]. New HIV diagnoses have shown a fall of 27% over the last 7 years, increasing coverage by ART (56%) [8], and better understanding of disease process has increased the life expectancy. Nevertheless in 2017, it was estimated that there were 0.9 million women living with HIV/AIDS in India [8]. These women should be the first target population for universal screening, but while attendance at ART clinics has increased, cervical screening is lagging. Firstly, this facility is not available at ART centres. Secondly, there is poor awareness as the need to participate in screening programmes is not emphasised in busy clinics.

During the course of this study, we encountered a number of non-technical challenges that impeded the process of cervical screening in this population. The first was persuading women to visit the Gynaecology OPD after their ART Clinic appointment. Many had a fatalistic attitude towards life after the diagnosis of HIV/AIDS. Others did not want to go to a different clinic after having spent time at the ART Clinic, CD4 tests, documentation, etc. Some could not understand where to go, and an attendant had to be provided to guide them. There were a large proportion of widows, with limited income and lack of social support to take care of children in their absence. They had to wait since the Colposcopy Clinic had a policy to take HIV-positive cases at the end of the list. This increased the perception of stigma in addition to time lost. Only when these barriers were addressed did the participation improve. However, the main thrust to recruitment came when the ART physicians counselled them

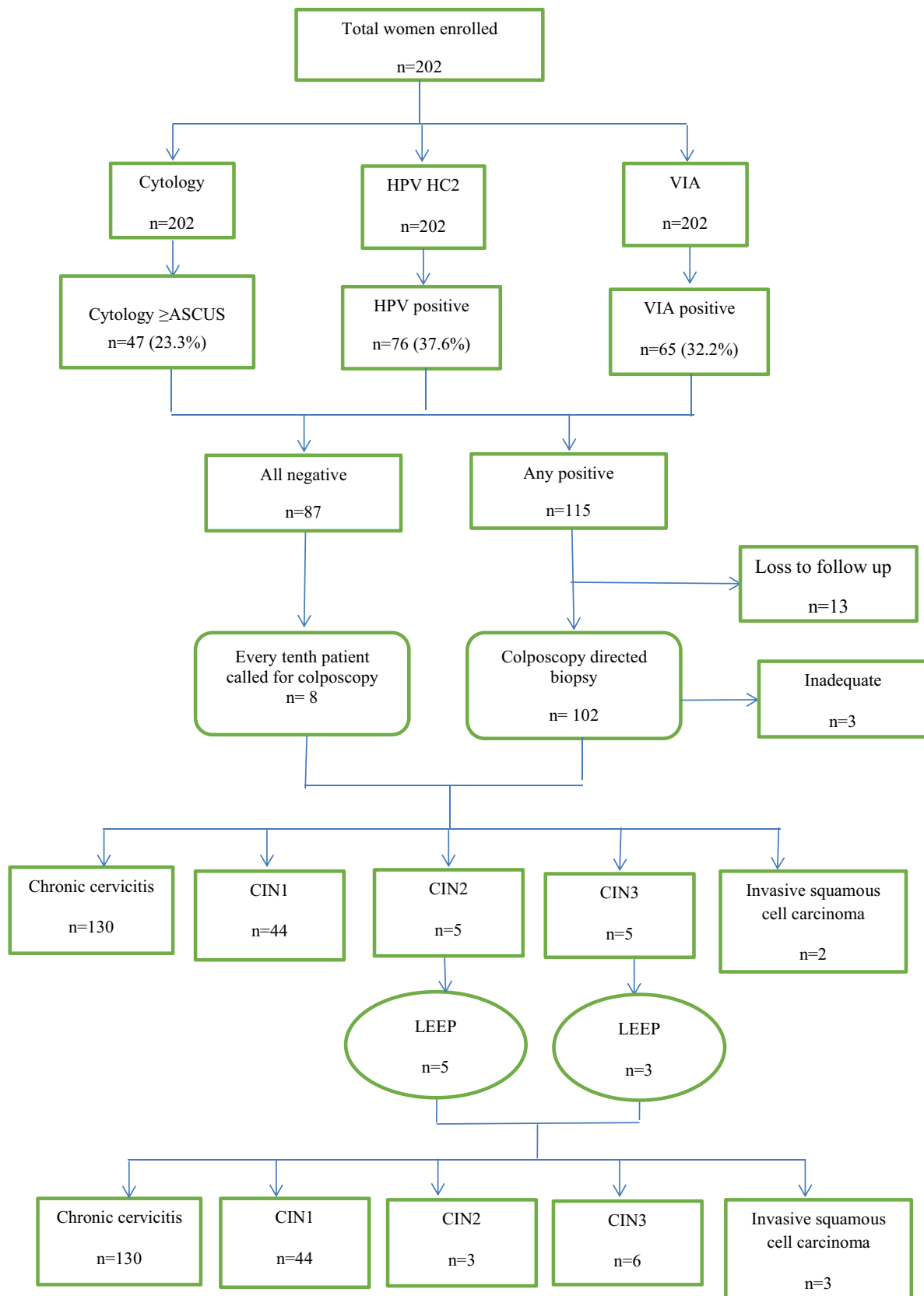


Fig. 1 Screening process of the study

Table 3 Comparison of results of different screening tests with final diagnosis among HIV-positive and HIV-negative women

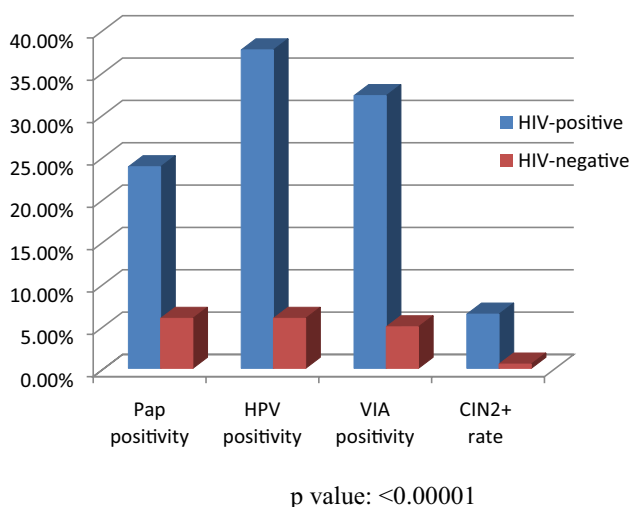
| Screening test | Final diagnosis | | | | | | | | | |
|--------------------------------|------------------------|------------------------|-----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|-----------------------|
| | Chronic cervicitis | | | | | | | | | |
| | CIN 1 | | CIN 2 | | CIN 3 | | Invasive Ca | | Invasive Ca | |
| | HIV + N = 130 no(%) | HIV - N = 199 no(%) | HIV + N = 44 no(%) | HIV - N = 2 no(%) | HIV + N = 3 no(%) | HIV - N = 0 no(%) | HIV + N = 6 no(%) | HIV - N = 1 no(%) | HIV + N = 3 no(%) | HIV - N = 0 no (%) |
| <i>Pap smear*</i> | | | | | | | | | | |
| Normal | 104 (80.0) | 171 (86%) | 26 (59.0%) | 2 (100%) | 1 (33.3%) | 0 (0.0%) | 1 (16.7%) | 1 (100%) | 0 (0.0%) | 0 (0.0%) |
| Scant | 14 (10.8) | 16 (8%) | 2 (4.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| ASCUS | 7 (5.4%) | 7 (3.5%) | 8 (18.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| ASC-H | 1 (0.8%) | 0 (0.0%) | 1 (2.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| LSIL | 3 (2.3%) | 5 (2.5%) | 5 (11.4%) | 0 (0.0%) | 1 (33.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| HSIL | 1 (0.8%) | 0 (0.0%) | 2 (4.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (50.0%) | 0 (0.0%) | 3 (100.0%) | 0 (0.0%) |
| Invasive Carci- noma | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (33.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| <i>VIA *</i> | | | | | | | | | | |
| Positive | 23 (17.7%) | 9 (4.5%) | 24 (54.5%) | 1 (50%) | 2 (66.7%) | 0 (0.0%) | 4 (66.7%) | 0 (0.0%) | 3 (100.0%) | 0 (0.0%) |
| Negative | 107 (82.3%) | 190 (95.5%) | 20 (45.5%) | 1 (50%) | 1 (33.3%) | 0 (0.0%) | 2 (33.3%) | 1 (100%) | 0 (0.0%) | 0 (0.0%) |
| <i>HPV DNA *</i> | | | | | | | | | | |
| < 1 RLU | 105 (80.7%) | 189 (95%) | 15 (34.1%) | 1 (50%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (100%) | 1 (33.3%) | 0 (0.0%) |
| 1-10 RLU | 13 (10.0%) | 4 (2%) | 12 (27.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (16.7%) | 0 (0.0%) | 1 (33.3%) | 0 (0.0%) |
| 11-100 RLU | 8 (6.2%) | 1 (0.5%) | 5 (11.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (33.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| > 100 RLU | 4 (3.0%) | 5 (2.5%) | 12 (27.3%) | 1 (50%) | 3 (100.0%) | 0 (0.0%) | 3 (50.0%) | 0 (0.0%) | 1 (33.3%) | 0 (0.0%) |
| <i>Colposcopy Swede score*</i> | | | | | | | | | | |
| Nil | 91 (70.0%) | 186 (93.5%) | 0 (0.0%) | 1 (50%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 0-4 | 39 (30.0%) | 11 (5.5%) | 40 (90.9%) | 1 (50%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 5-7 | 0 (0.0%) | 2 (1.0%) | 4 (6.8%) | 0 (0.0%) | 2 (66.7%) | 0 (0.0%) | 3 (50.0%) | 1 (100%) | 1 (33.3%) | 0 (0.0%) |
| 8-10 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (33.3%) | 0 (0.0%) | 3 (50.0%) | 0 (0.0%) | 2 (66.7%) | 0 (0.0%) |

NS, not significant; RLU, relative light units
* p value < 0.05—significant result

Table 4 Test performance of all screening tests for detecting CIN2+ in HIV-positive women

| Screening test | Percentage referral to colposcopy (%) | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | PPV (%) (95% CI) | NPV (%) (95% CI) | Diagnostic accuracy (95% CI) | LR of positive test (95% CI) | LR of negative test (95% CI) |
|---------------------------|---------------------------------------|--------------------------|--------------------------|------------------|------------------|------------------------------|------------------------------|------------------------------|
| Pap smear (\geq ASCUS) | 25.8 | 75.0 (42.8–94.5) | 83.9 (77.6–89.0) | 24.3 (11.8–41.2) | 97.9 (94.2–99.6) | 83.3 (77.3–88.0) | 4.7 (4.0–5.4) | 0.3 (0.2–0.6) |
| HPV DNA | 37.7 | 91.7 (64.6–98.5) | 68.4 (61.2–74.8) | 16.7 (9.6–27.4) | 99.2 (95.4–99.9) | 69.9 (62.9–76.0) | 2.9 (2.8–3.1) | 0.1 (0.0–0.9) |
| VIA | 32.2 | 75.0 (42.8–94.5) | 72.5 (65.3–79.0) | 15.8 (7.5–27.9) | 97.7 (93.4–99.5) | 72.7 (65.9–78.6) | 2.7 (2.4–3.1) | 0.4 (0.2–0.7) |

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; CI, confidence interval

**Fig. 2** Comparison of screening test results and final diagnosis on histopathology between HIV-positive and HIV-negative women

that participating in the cervical screening programme was important and essential.

Studies on HIV-positive women in India have shown higher prevalence of HPV infection than in the general population [10]. Joshi et al. in a cross-sectional study on 1109 HIV-infected women reported hrHPV prevalence of 41.0% [11]. In the present study, hrHPV infection was seen in 37.6% subjects as compared to 5.9% in HIV-negative women and background prevalence of HPV infection in the general population is reported to be 6.6% [12]. Abnormal Pap in HIV-positive women has been reported to be 8.1% (88/1081) by Joshi et al. [11] and 38.3% (116/303) by Sahasrabudhe et al. [13]. In our study, abnormal Pap was seen in 23.8% of HIV-positive and 5.9% of HIV-negative women which is 4 times higher [14]. Abnormal Pap was seen in 5.9% of HIV-negative women which corresponds to the prevalence in general population. VIA positivity (32.2%) was similar to studies Joshi et al. and Sahasrabudhe et al. [11, 13].

The prevalence of high-grade neoplasia (CIN2, CIN3) or invasive cancer in the general population is estimated to be <math><1\%</math> [15]. In our study, prevalence of CIN2+ lesions among HIV-negative was 0.5% and among HIV-positive was 6.4%.

Prevalence of CIN2+ lesions was significantly related to low CD4 counts at the time of diagnosis of HIV ($p=0.026$) as well as at recruitment into the study ($p=<0.05$), which is similar to results reported by Zhang et al. and Memiah et al. [16, 17]. Singh et al. in their case-control study comparing CIN lesions in HIV-positive and -negative women showed increased incidence (15.9%) of cervical lesions in seropositive women, with further increased risk if CD4 count was less than 500 cells/mm³ [18].

Primary HPV screening is now considered to be the best strategy for cervical cancer screening. However, since many HIV-positive women harbour HPV infection owing to poor immune clearance, it is debated whether this will prove to be the case in this special population [5]. In a study by Bhatla et al., sensitivity of HPV in general population was 85.7% and specificity 89.7% [19]. In the present study, HPV testing had the highest sensitivity (90.9%) for detection of CIN2+ disease, but lowest specificity (68%) and diagnostic accuracy (69.4%), reflecting the high prevalence of HPV in these women. Pap smear had good sensitivity (75%), the best specificity (83.9%), diagnostic accuracy (83.3%) and lowest referral to colposcopy (23.8%) among all the tests. Since the sensitivity of testing by both Pap and VIA was the same, VIA can be a good substitute for Pap in low resource settings, but a way to triage these patients and reduce referral, e.g. using portable colposcopes and telemedicine, will need to be determined [20].

Out of 5 cases with CIN2, only 3 underwent LEEP, while 2 were lost to follow-up. Following a screen-and-treat policy and facilitating rapid testing would probably decrease the attrition of eligible cases. There are concerns that in HIV-positive women there may be increased shedding of the virus in women who undergo cervical procedures [21]. Women

need to be advised appropriate precautions of abstinence or barrier contraception.

The possible solutions to existing barriers include educating patients when they are diagnosed with HIV/AIDS regarding associated ailments and ways to prevent them. This can be done by displaying such information at prominent locations in clinics, providing patient information leaflets, materials in electronic formats through internet or mobile phones, and formulating a plan for arranging cervical screening facilities in the ART clinics. Health workers can be trained to provide basic screening services. Ideally, a colposcopy facility at the ART clinic should be set up, but coordinating with existing colposcopy clinics to reduce patient waiting time will help to improve participation and compliance. Importantly, physicians at ART centres should be repeatedly sensitized and reminded of the need for cervical cancer screening in this high-risk population.

Conclusion

HIV-positive women are a special high-risk group who should be offered a one-stop solution at ART centres including counselling, medication, CD4 testing, cervical cancer screening and follow-up. Primary HPV screening which is now an accepted to be the best strategy may not be ideal with lowered specificity and high referral rates. Pap smear or VIA can serve as good screening tools in these special groups depending on the resource availability.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and Animal Rights Research involves human participants.

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